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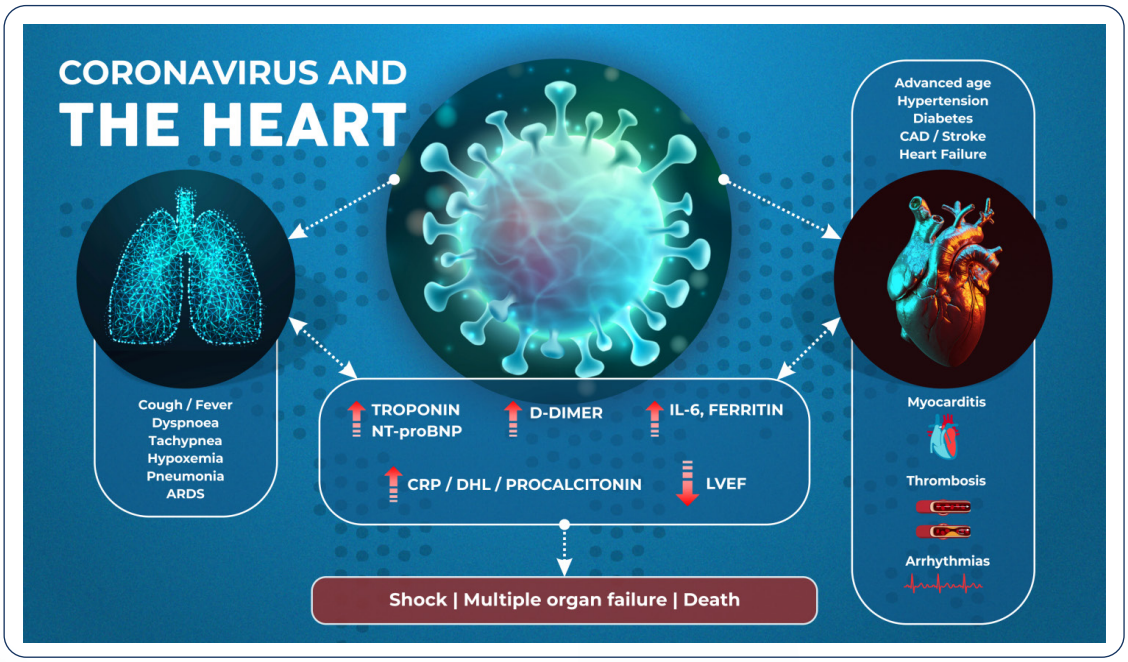

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Journal of Brazilian Society of Cardiology

JOURNAL OF BRAZILIAN SOCIETY OF CARDIOLOGY - Published since 1943

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Address: Av. Marechal Câmara, 160 - 3º andar - Sala 330
20020-907 • Centro • Rio de Janeiro, RJ • Brasil
Phone.: (21) 3478-2700
E-mail: arquivos@cardiol.br
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Pandemonium During the Pandemic: What is the Role of Health and Science Professionals?

André d'Avila,[1] Marco F. Vidal Melo,[2] Renato D. Lopes[3]

Serviço de Arritmia Cardíaca, Hospital SOS Cardio,[1] Florianópolis, SC – Brazil

Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Harvard Medical School,[2] Boston, MA – USA

Division of Cardiology, Duke Clinical Research Institute, Duke University School of Medicine,[3] Durham, NC – USA

The behavior of Brazilian sports commentators during the recent COVID-19 pandemic is noteworthy. Day after day, despite social distancing, they continued their television broadcasts to help ease their viewers' discomfort. For hours, they discussed past games, current problems and the future of the sport. At no time, however, did they make comments on topics outside of their area of expertise. Although they most certainly had an opinion on the seriousness of COVID-19, the merits of social distancing or use of medications popularized by many without scientific evidence, they restricted their commentary to their areas of expertise – sports!

What has been hard to understand is the insistence of some physicians to provide opinions on unsubstantiated interventions for the treatment of COVID-19. Some simply choose medical proselytism. Others may not appreciate the need for proper scientific investigation. Many prefer to omit themselves from any debate. However, the most perplexing type of attitude is simply a reactionary behavior related to the fear of the unknown that is, the combination of desperation and need to provide care for patients, and bombardment of information from social media may bias many doctors to embrace any potential redemptive treatment. Unfortunately, the only disease treated with this approach is the anxiety shared by doctors and their patients.

In this bleak scenario full of uncertainties, mismatched information, lack of leadership, and a raging torrent of assertions in social media can transform claims into truth (or at least into expectations), however absurd they may be. Unfortunately, disregarding strict scientific methods, using an alibi of trying to help, creates an atmosphere of confusion and increases the risk of those who implement such statements.

The scientific and ethical rigor of research as a whole, and particularly in the medical field, has benefited thousands of patients around the world through careful research carried out under the guidance of the Declaration of Helsinki from 1964. The basic principle of the Declaration is respect for the individuals (who must consent to participate in the research protocol), as the individual's interests precede that of science and society. However, if the patient's interest is imposed then one logically will ask how is it possible to justify randomization given the fears patients or physicians may have with the possibility of having "bad luck" and being allocated to a control group, perhaps a placebo, when the alternative is perceived to be a hope for cure?

The answer to this question requires understanding and acceptance of the scientific method. Although several ideas appear effective during preliminary stages, only objective demonstration of efficacy beyond mere chance merits acceptance. In that regard, a control group is indispensable to achieve this as it allows determination of the benefit/risk ratio ("equipoise") of the intervention. While participation in a control group may be met with disappointment from some patients and physicians, it must be remembered that individuals who participate in clinical trials in general do better than those who do not participate in such studies, even when allocated to control or placebo groups. Thus a logical and safe way to treat a patient when an answer to a clinical question is not available is to include them in a clinical trial as these patients will be offered the best possible treatment, under direct supervision, while advancing science.

The history of medicine is full of examples of treatments considered by experts as "absolutely effective" that clinical trials proved to be futile and even harmful. In cardiology, cases of futility and harm are numerous and even striking. The use of antiarrhythmic drugs to prevent sudden death in patients with ventricular extrasystoles after acute myocardial infarction (AMI), magnesium to reduce the infarcted area and beta-blockers in vasovagal syncope are examples of the huge difference between expectation (perceived "common sense") and the actual effect resulting in a therapeutic upheaval.

In the current situation of COVID-19, supposedly miraculous therapies (including supratherapeutic doses of vitamins [C, D, and zinc], macrolides, chloroquine and its derivatives, corticosteroids, antivirals and other medications) have been tested in clinical trials for other viruses including HIV, Ebola and H1N1 and, despite the expectations of efficacy in these conditions, none were shown to be safe or effective. While it may be assumed that the effect of some of these interventions might work differently in the current Covid pandemic, these beliefs will need to be evaluated with scientific rigor that the urgency and gravity of the situation entails.

Unfortunately, most recommendations of interventions to fight COVID-19 are based in pseudo-evidence. The study that popularized hydroxychloroquine[1] (*the one cited by Donald Trump as having "a real chance to be one of*

Keywords

Coronavirus; COVID-19; Pandemics; Hydroxychloroquine/effects medication; Azythromicine/adverse effects; Drug Approval; Ethics Committees, Research; Social Media.

Mailing Address: Andre d'Avila •
Hospital SOS Cardio - Serviço de Arritmia Cardíaca - SC 401.121.
Postal Code 88030-000, Florianópolis, SC – Brazil
E-mail: andredavila@mac.com

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the biggest game changers in the history of medicine") is scientifically ludicrous. The authors of the study investigated whether patients with COVID-19 would have a better outcome with hydroxychloroquine. To that end, it would have been mandatory that two similar groups of patients would exist with only one receiving the drug. As simple as this seems, that is not what happened. In addition to the different drugs administered, the groups were from different hospitals, were of different ages, had different clinical conditions and received different additional treatments. Most notably, these patients had different viral loads. How is one to isolate the effect hydroxychloroquine when such marked differences are present? On top of that, four patients who died or went to the intensive care unit (ICU) who received hydroxychloroquine were eliminated from the results suggesting that for some investigators death may be less relevant than the detection of a virus in the nasopharynx. Finally, the sample size was very small not allowing any possible effect from the treatment to be defined.

While it is disappointing when a study fails to answer the proposed question, it is worse when it creates social upheaval. This article was peer-reviewed by colleagues and by an editor who could have avoided consequences of this publication had they acted responsibly. A pandemic does not justify forgetting science as mistakes create false hopes that may potentially put lives at risk.

There has been variable interpretation of these data by the medical community throughout the world. Whereas many believe that the use of chloroquine is justifiable, that stance is far from unanimous. Many health care workers diagnosed with COVID-19 agreed to participate in randomized clinical trials to help create high-quality data that may potentially benefit thousands of people. It is remarkable that the medical community would band together as subjects in a clinical trial to generate data for a disease they are helping the public fight! This is the correct decision. Only properly designed and executed clinical studies conducted by professionals, hospitals and medical societies globally, and led by experts in clinical research, can offer accurate answers. The medical fraternity has a duty to free us from the setbacks created by the failure to understand scientific methods. "Common sense" and our collective mood cannot justify methodological errors which in turn may adversely impact thousands of lives. Physicians are expected to do what they best do - act in the light of ethics, pragmatically, based on the best that science can offer. Let us be genuine specialists when high-quality scientific data is available. After all, truth always prevails, and science is the tool that most rapidly draws us closer to it. As doctors and scientists, our role is to abate the gap between assumptions and reasoned conclusions as this will benefit patients and the population that yearns for answers provided by medical science.

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Hypertension in Workers: The Role of Physical Activity and its Different Dimensions

Uelito Everaldo Souza Ribeiro Junior[1] *and Rita de Cassia Pereira Fernandes*[2]

Universidade Federal da Bahia - Programa de Pós-Graduação em Saúde, Ambiente e Trabalho,1 Salvador, BA - Brazil

Universidade Federal da Bahia - Faculdade de Medicina da Bahia,2 Salvador, BA – Brazil

Abstract

Background: Physical activity, each type in its own manner, whether occupational, domestic or leisure, can play a significant role regarding high blood pressure (HBP). However, practicing physical activity only at leisure time, or in specific situations, can be insufficient to achieve the effective control of HBP.

Objective: To analyze the isolated and cumulative effect of different types of physical activity and the prevalence of HBP among workers.

Methods: A cross-sectional study with 1,070 Urban Cleaning and Footwear Industry workers in Bahia, who answered a survey, conducted by an interviewer on sociodemographic, occupational, lifestyle and hypertensive morbidity aspects. Weight, height, waist circumference and blood pressure were measured. Case of HBP: Systolic blood pressure ≥140 or diastolic blood pressure ≥90, or regular treatment for HBP. The occupational, domestic and leisure aspects of Physical Activity were studied. A multivariate analysis with Cox Regression was performed for cross-sectional studies.

Results: The prevalence of HBP was 24%, being 37% among workers aged between 35-44 years, and 51% among workers aged between 45-54 years. The multivariate model showed that workers who were active in one form of physical activity only or no forms had 62% higher BP levels and that these levels were 25% higher among workers who were active in two out of three physical activity forms. Being a male, being older (> 31 years old) and being overweight were characteristics associated with HBP, with prevalence ratios of 1.62, 2.10 and 2.26, respectively.

Conclusions: There was a cumulative effect of the form of physical activity on the occurrence of HBP. Classifying active subjects at work or at home as inactive persons by relying only on the leisure form can lead to methodological errors. (Arq Bras Cardiol. 2020; 114(5):755-761)

Keywords: Hypertension; Workers; Urban Cleaning Service; Motor Activity; Anthropometry; Physical Exerton; Work; Socioeconomic Factors; Life Style.

Introduction

High blood pressure (HBP) is a chronic disease defined by blood pressure levels greater than or equal to 140/90 mmHg and represents one of the risk factors for cardiovascular diseases. On the other hand, it is known that insufficient or lack of physical activity (PA) is a modifiable risk factor for this condition.[1,2]

Every movement produced by skeletal muscles that generates energy greater than the resting state is considered PA. An active person is an individual who practices at least 30 minutes of moderate-intensity PA five days a week. This does not include leisure only; on the contrary, the literature emphasizes the importance of approaching PA in different forms: leisure (PA-L), occupational (PA-O), domestic (PA-D) and displacement.[3,4]

Mailing Address: Uelito Everaldo Souza Ribeiro Junior •
Universidade Federal da Bahia - Programa de Pós-Graduação em Saúde, Ambiente e Trabalho - Largo do Terreiro de Jesus, s/n. Postal Code 40110-060, Centro Histórico Salvador, BA – Brazil
E-mail: jr.vdgm@hotmail.com, ritafernandes@ufba.br
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Brazil, a signatory to the World Health Organization's Plan for the Prevention of Noncommunicable Chronic Diseases, committed to a 25% relative reduction in the prevalence of HBP and a 10% reduction in insufficient PA by the year 2025. This challenge highlights the relevance of HBP as a health problem.[5,6]

Although a negative association between PA and HBP has been observed - more physically active people have lower HBP prevalence - there is a recent interest in the role of PA forms. In this sense, evidence about the forms has shown that individuals who are active at their work, leisure time and also practice sports have lower prevalence of HBP;[7] in addition, the lack of PA-O and PA-L significantly increases the risk of HBP.[8] However, occupational physical activities, considered strenuous, have also been associated with higher prevalence of hypertension, but this positive association of higher PA-O with hypertension has been attributed by some researchers to the role of unvalued confounders, such as psychological demands.[9-11] In addition, the so-called "PA paradox" has been discussed, according to which the benefits of leisure activity could be minimized by high levels of PA-O.[12-14] Therefore, there are confluences and gaps regarding the role of the different PA forms on the occurrence of HBP.

Thus, the objective of this study was to verify how forms of PA (PA-O, PA-L and PA-D) are associated with the occurrence of HBP, both alone and cumulatively.

Method

Study design and population

A cross-sectional study with Footwear Industry workers (n=446) and Urban Cleaning workers (n=624), totaling 1,070 subjects. In both survey clusters, the response rate was 97%. The sampling plan in the Footwear Industry was a stratified random sample proportional to the gender and number of workers from each of the two factories in the countryside of Bahia; in Urban Cleaning, a census was carried out at the municipal company in Salvador. Data collection was carried out in 2012 and 2010. As an inclusion criterion, all workers interviewed should be employed during data collection, which was conducted by a trained team of health and safety professionals and students of the physical therapy program. Everyone was aware of the need to clarify any aspects about the questions in order to obtain the most reliable answers possible. The interviews were carried out in each participating company, during regular working days, in a reserved place, ensuring the workers' privacy.

Survey

The survey carried out by the interviewer included questions about sociodemographic factors, job characteristics and life habits. The sociodemographic factors asked were gender, age, marital status, schooling, color or race, and if the interviewed worker had any children. Job characteristics: physical demands, evaluated through the handling of loads (lifting, pushing and pulling); psychosocial aspects of work, measured using the Job Content Questionnaire (JCQ), an instrument that measures the forms of the Demand-Control Model;[15] working hours and time of service in the company studied. Life habits: current or previous smoker and frequency of alcohol use. Direct measurements of Blood Pressure (BP), weight, height and waist circumference were performed.

Dependent variable

The dependent variable is HBP, defined by two measures of BP: the first at the beginning of the interview, with subjects sitting for five minutes before the start of the survey, and the second upon completion of the survey, as carried out by the interviewer, with a mean interval of 20 minutes between these measurements. A duly calibrated aneroid sphygmomanometer and stethoscope were used. The measurements were performed according to the recommendations of the Sixth Brazilian Guidelines on High Blood Pressure. Cases of hypertension were considered as those with systolic blood pressure ≥ 140 and/or diastolic blood pressure ≥ 90, and subjects undergoing regular treatment for hypertension. The information was divided into two groups, classifying subjects as those who did and those who did not show a hypertensive condition.

Main independent variable

The main independent variable is PA in three forms: occupational (PA-O), domestic (PA-D) and leisure (PA-L).

The level of PA-O was obtained through the worker's self-report on his physical demands of load handling (lifting, pushing and pulling), using a 0-5 scale, where 0 meant no exposure (never) and 5 meant maximum exposure (all the time). The three variables were summed, with the resulting value divided by three, to calculate the mean of the scores. Those workers who reached score ≤ 2 (less active) were considered exposed, whereas the non-exposed ones had scores ranging from 3 to 5 (more active).

For the PA-L, the following question was asked, "What do you do when you're not working at home or at work?", with four answer options: (I) Talk to family or friends, read the newspaper or a magazine, watch TV, go to church; (II) Hike, fish, maintain the garden or the yard; (III) Run, exercise, swim, play a ball game, ride a bicycle; (IV) Train for a competition. Individuals with "I" and "II" responses were considered, therefore, to have lower PA-L levels, i.e., the exposed ones; and those who responded positively to "III" and "IV" were considered active in leisure, i.e., the non-exposed ones.

In the PA-D domain, workers were questioned about weekly hours devoted to domestic work. They were classified as exposed and non-exposed, absence and presence of hours dedicated to housework, respectively.

In the multivariate analysis, the main variable PA was used, subdividing the three forms into three strata. Workers who had high PA levels in the three forms, i.e., active at leisure, at work and at home, were considered non-exposed, and two strata of exposure were used: the first one included active individuals in two forms; and the second, individuals who were inactive or active in only one form.

Covariables

For the age variable, those workers who were older than the median age were considered to be exposed. Color or race was stratified into "non-black", which included White, Brown, Asian and Indigenous, classified as non-exposed, whereas Black individuals were classified as exposed. As for schooling, the exposed ones were those who had not completed High School. For marital status, those who had a stable partner were exposed, even if they were not formally married.

The variable "type of workday" consists of rotating shifts (exposed groups) and business hours (non-exposed groups). For the psychosocial aspects of work, psychological demand and job control questions, from the JCQ, were used. Exposed individuals were those who had high demand and low control over their work. For the time of service variable, those exposed were the ones with values above the median.

An individual who smokes or used to smoke was considered exposed. For "alcohol use frequency", those who consumed alcohol more than once a week were classified as exposed.

The anthropometric indicator used to verify the association with HBP in the multivariate analysis was Body Mass Index (BMI), calculated from subjects' direct height and weight measurements. Excess weight was considered present above the cut-off point of ≥ 25 kg/m^2, and those were the exposed ones, including, therefore, those who were overweight and obese.[16]

Statistical analysis

All variables went through a descriptive analysis and their frequencies were verified. For continuous variables, measures of central tendency, dispersion and position were provided. The HBP prevalence ratio, according to the independent variables, were was initially calculated in the univariate analysis. In the multivariate analysis, the covariables entered the block models, and PA was considered as a main independent variable with three strata: active in the three forms, active in two forms, and inactive or active in one form. The reference group consisted of active individuals in the three PA forms. The selection of covariables for entry into the multivariate models was based on the theoretical and biological plausibility, and on the gross association strength of the univariate analysis. The Cox regression model was used for cross-sectional studies.[17] Interaction was tested using an additive model of the three PA forms for the occurrence of HBP.

The study population, consisting of a pool of surveys, is not random. Thus, the analyses did not use statistical inference; on the contrary, the final model in the multivariate analysis is presented with all the selected variables, with their respective association measures (Prevalence Ratios). For this reason, they are all kept in the final model. Thus, in this study, procedures compatible with the non-random nature of the population investigated were used, according to an extensive literature on the subject.[18,19] All analyses were done using the Statistical Package for the Social Sciences (SPSS) software, version 24.0.

Biases

In order to minimize the effect of healthy workers, selected workers who were on medical leave were invited to participate, except when the leave was maternity-related or was due to an injury allegedly unrelated to occupational exposure. In this case, the next one on the list would be selected instead. Information biases were minimized with clarifications being provided to workers. The surveys would be under the responsibility of the Federal University of Bahia, so that it would be impossible for both companies and managers to access individual information.

Aspects of research ethics

This study was submitted to the Research Ethics Committee of the Federal University of Bahia and approved under opinion No. 1,621,917. Subjects were notified about the objectives of the research and all participants signed an Informed Consent Form.

Results

A total of 1,070 workers were studied, of which 842 (78.7%) were men. The prevalence of HBP was 24%. Workers who did not complete High School made up 46% of the population, 82% had stable partners, 63% had daily working hours with shift schedules. Those who smoke or have smoked accounted for 26%, and 42% of the population consumed alcohol more than once a week. Overweight was present in 43% of the subjects. In PA variables, 47% and 61% of the population had low PA-O and PA-L levels, respectively; 28% were not involved in PA-D. Age and BMI had the greatest factor associated with HBP in the univariate analysis (PR = 2.9 and PR = 2.8, respectively). The following also had strong association: gender (PR = 1.95), PA-D (PR = 1.62) and type of workday (PR = 1.60) (Table 1).

The prevalence of HBP by age range was: <35 years (n = 713 individuals) 16% of HBP, 35-44 years (n = 262) 37%, 45-54 years (n = 81) 51%, and for > 54 years (n = 7) individuals, the prevalence was 43%. The frequency of HBP for each one of the PA strata was: 16% for individuals who were active in the three forms, 39% for those who were active in two forms, and 45% for individuals who were inactive or active in only one form (data not shown).

Table 2 shows the multivariate analysis, with the main independent variable, PA, in its combinations. Model 1 shows the gross association between PA and HBP. In model 2, the main independent variable is adjusted by sociodemographic variables. And in model 3, an additional adjustment is made for lifestyle variables, when an adjustment of 11% in the main association is observed. The entry of occupational variables in model 4 practically did not change the PR of the main association. Active individuals in two of the three forms, and inactive or active individuals in only one form of PA had a PR of 1.25 and 1.62, respectively. Overweight (PR: 2.26), age > 31 years (PR: 2.10) and male gender (PR: 1.62) covariables maintained their association with HBP in the final model. No interaction was found in the additive model between the three forms of PA for the occurrence of HBP.

Discussion

PA accumulation in PA-O, PA-D and PA-L forms can lead to HBP improvements. Being active in one or none of the three forms of PA demonstrated a greater positive association with the outcome: 62% more HBP compared to those who are active in the three forms. These findings contribute to the literature on the role of insufficient PA as a modifiable risk factor for HBP and calls into question the isolated role of PA-L as a strategy to control this condition.

Regarding color or race, the strong miscegenation of the population in Bahia can represent a limitation to investigate its association with HBP. As described by other authors,[20] the probable homogenization of ethnical groups, due to strong miscegenation, should play a role in the result, which revealed an almost equal prevalence of HBP among the "black" and "non-black" groups in this population.[21,22] According to this explanatory hypothesis, a multicenter HBP study which, in addition to including servers from the Federal University of Bahia also included servers from five other institutions in different states in Brazil,[23] found a strong association of this variable with HBP, whose prevalence was higher among Black people, followed by Brown people, with the lowest prevalence among Caucasians.

The association of HBP with age and gender was very consistent with the literature.[11,23-26] The studied population was composed of 79% young men, with a mean age of 32 years. Men in this stage of life are seen to have higher

Table 1 - Factors associated with high blood pressure in Urban Cleaning and Footwear Industry Workers

Variable	Frequency N	%	Prevalence (%)	PR*
HBP				
yes	256	23.8		
no	812	76.2		
Gender				
male	228	21.3	13.6	1
famale	842	78.7	26.6	1.95
Age				
≤ 31 year	575	53.9	12.7	1
> 31 year	491	46.1	36.9	2.90
Color or race				
Non-black	578	54.2	24.0	1
Black	489	45.8	23.8	0.99
Schooling				
≥ high school	576	54	22.5	1
< high school	490	46	25.6	1.14
hade a stable partner				
no	188	17.6	23.5	1
yes	880	82.4	23.9	1.02
Higt-demand work				
non-exposed	714	68.7	23.4	1
exposed	326	31.3	25.6	1.09
time of service				
≤3 year	506	47.4	19.4	1
>3 year	562	52.6	27.8	1.43
Type of workday				
business hours	392	36.7	17.3	1
rotating shift	676	63.3	27.6	1.59
Smokes or used to smoke				
no	779	74.3	21	1
yes	270	25.7	31.1	1.48
frequency of alcohol use				
≤ 1 once a week	616	58.4	18.7	1
> 1 once a week	438	41.6	28.8	1.44
Excess weight				
no	612	57.4	13.5	1
yes	455	42.6	37.4	2.775
PA occupational				
high	567	53.1	22.0	1
low	501	46.9	25.9	1.18
PA leisure				
high	413	38.7	20.9	1
low	655	61.3	25.7	1.23
PA domestic				
yes	761	71.7	20.3	1
no	300	28.3	33	1.62

** PR: prevalence ratio; HBP: high blood pressure; PA: physical activity.*

Table 2 – Prevalence ratios between PA, combining the three forms, and systemic hypertension, in models adjusted for sociodemographic, lifestyle and occupational variables

Variable	mod 1* PR	mod 2* PR	mod 3* PR	MOD 4* PR
PA				
active in 3 dimensions	1.00	1.00	1.00	1.00
active in 2 dimensions	1.22	1.26	1.24	1.25
inactive or active in 1 dimensions	1.76	1.80	1.60	1.62
Gender				
male		1	1	1
famale		1.94	1.66	1.62
Age				
≤ 31 year		1	1	1
> 31 year		2.63	2.22	2.10
Excessive weight				
no			1	1
yes			2.24	2.26
Smokes or used to smoke				
no			1	1
yes			1.11	1.11
frequency of alcohol use				
≤ 1 once a week			1	1
> 1 once a week			1.18	1.18
Type of workday				
business hours				1
rotating shift				1.05
time of service				
≤3 year				1
>3 year				1.17

** MOD 1: gross association; MOD 2: adjusted for gender and age; MOD 3: adjusted for overweight, currently smoking or smoked in the past and frequency of alcohol use; MOD 4: adjusted for type of workday and working hours; PR: prevalence ratio; PA: physical activity.*

prevalence of HBP than women.[1] Studies that show a higher prevalence among women are based on self-report or populations in higher age groups, in which the female gender shows higher values than the male gender with greater prevalence.[27] As for studies based on self-reporting,[1] the predominance of HBP among women may be due to the fact that women are more likely than men to seek out health care and, consequently, greater knowledge of their hypertensive condition is available.

In Brazil, in 2016, the prevalence of HBP was increasing with age, and among those aged between 35 and 44 years, the prevalence was 19.1%.[1] In a comparison with the results of this study, a prevalence of 37% was found in the age group of 35 to 44 years; therefore, among those studied here, HBP was higher than the national average. In comparison with Chor et al.,[23] who studied university servers, the age strata of this study with workers had higher prevalence rates.

Overweight workers had 2.3 times the prevalence of HBP compared to those who were not overweight. This result is consistent with other studies, demonstrating the association of HBP with greater body density.[28,29] The other variables that were associated in the univariate stage had their associations with HBP greatly reduced in the multivariate analysis.

The main independent variable was consistently associated with HBP in the multivariate analysis, showing a cumulative effect of low PA in the three forms regarding the prevalence of HBP.

The independent association between occupational physical activity (PA-O) and HBP was explored through

analyses that included PA-O, both with a duration scale and an intensity scale of load handling. The most active workers in this form were more effectively protected against HBP, even with age, gender and overweight adjustments. Motivation for these analyses with PA-O levels was based on the recent literature discussion about the "paradoxical effect" of PA-O on blood pressure.[30] According to researchers, individuals subjected to high PA-O levels would have a higher risk of HBP.[14,31] It is possible that occupations that demand the use of large muscle groups, such as garbage collection, although they may exhibit physical fatigue, do not seem to show association with HA, as proposed in the paradoxical effect. In this study, active work was always protective against this condition, particularly when associated with PA-D and PA-L.

Although PA-L is deemed to be one of the main non-pharmacological treatments for HBP,[32-34] according to the present study, PA-L alone may not compensate for insufficient PA for the purposes of effective HBP control. Being active in only one form and inactive in the other two forms showed a positive association with HBP.

Few studies explore PA-D alone. The data on this form of PA do not seem to show an association with HBP. Nevertheless, when combined with the practice of PA in other forms, PA-D can produce beneficial effects on HBP control.

Although the present study showed the cumulative effect of low PA in its different forms as a risk factor for HBP, no interaction was found between these forms (not even in the additive model). A similar fact was observed in another study, which also revealed a cumulative effect of different forms of PA, but no interaction among them.[7] Interaction analysis to explore sedentary behavior and/or time spent in front of the TV in determining chronic diseases in adults seems to be a promising approach.[35]

In addition to PA accumulation in the different forms being a protective factor, accumulation during the various stages of life can further improve health indicators.[36]

In this study, PA levels were obtained from self-report and not measured directly through cardiac monitors, accelerometers, pedometers and frequency meters. Despite the tendency to consider direct measures more valid than self-reporting, the first have been questioned as the gold standard in Occupational Epidemiology. Due to their cost and instrument calibration requirements, direct measurements are usually obtained from short time sampling and, in the case of PA-O, during a small sample of the workday schedule. This is particularly relevant in studies with populations whose occupational activities involve high variability over the course of a workday, since this factor may limit the validity of direct measurements. In other words, direct measurements that sample a small proportion of the workday may not be representative of the whole working day.[37]

In the cross-sectional study design, the main bias is the prevalence. Therefore, reverse causality cannot be ruled out, i.e., it is not possible to determine whether the higher prevalence of HBP among less active individuals is due to a sedentary life or whether they were already hypertensive before moving on to a more sedentary life. However, since HBP is a chronic disease, treatment can ensure its control, but not its cure. Thus, this type of bias can be minimized, and cross-section may be an appropriate option for study design. The study population is predominantly composed of young workers, but the results obtained and described for the prevalence of HBP among the different age groups allow for comparisons with other populations, provided that each age group is observed.

Conclusion

This study showed that lower activity levels in the different forms of PA was a risk factor associated with HBP in this population. Since other studies demonstrate a similar line of evidence, the results of this study can be considered valid. From these studies, it was considered that the investigation of PA, a modifiable factor in the occurrence of HBP, cannot waive its different forms, otherwise it would imply a methodological error when classifying subjects who are active at work or at home as inactive individuals, based on the form of leisure. Interventions should be planned in the occupational environment, so workers have the opportunity to express what HBP means for themselves, and get access to study results in order to stimulate changes in habits and to increase the role of workers in electing active leisure activities and highlighting the importance of PA-O. New research should enhance the study of PA in order to bring new evidence on its role in HBP.

Author contributions

Conception and design of the research and Statistical analysis: Ribeiro Junior UES, Fernandes RCP; Acquisition of data and critical revision of the manuscript for intellectual content: Fernandes RCP; Analysis and interpretation of the data and writing of the manuscript: Ribeiro Junior UES.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Influence of Physical Activity on Arterial Hypertension in Workers

Cláudio L. Pereira da Cunha[1]

Universidade Federal do Paraná (UFPR),1 Curitiba, PR – Brazil

Short Editorial related to the article: Hypertension in Workers: The Role of Physical Activity and its Different Dimensions

Regular physical activity (PA) is one of the most important factors for the primary prevention of arterial hypertension (AH) and for improving the long-term survival of these patients.[1] Its benefits extend beyond AH, also providing improvements to patients with coronary artery disease, diabetes, dyslipidemia, kidney dysfunction, depression, obstructive pulmonary disease, and osteoarthritis, among others.[1]

"Physical activity" literally refers to any movement of the body; however, in epidemiological studies that assess its health context, it is related to activities that produce substantial increases in oxygen (O_2) consumption. PA can be performed both at work and during leisure and recreation, with all modalities being used to study the effects of PA on cardiovascular health.[2] The PA developed to improve health or to obtain performance benefits is considered "exercise".[2]

The exercises are classified as "aerobic" and "resistance" exercises. Aerobic exercises primarily stress the O_2 transportation system and include activities such as walking, running, swimming and cycling. Resistance exercises, in turn, stress the muscular skeletal system, such as weightlifting; they can be dynamic or static exercises (isometric). Training with exercises that are performed repeatedly can improve the cardiovascular system performance (training with aerobic exercises) or the muscular skeletal system (training with resistance exercises).[3] Such divisions of the types of PA are relatively arbitrary, considering the exercises have predominant but not absolute aerobic or resistance components. The aerobic activity of running, for instance, also improves the muscular strength of the legs, while the resistance weightlifting exercise also involves the participation of the O_2 delivery system, an aerobic component.[4]

The aerobic training reduces the casual blood pressure (BP) in pre-hypertensive and hypertensive individuals. Moreover, it reduces BP during wakefulness in hypertensive patients and decreases BP in situations of physical, mental and psychological stress.[5] Aerobic training is recommended as the preferred form of exercise for the prevention and treatment of AH, with a class of recommendation I, level of evidence A, in the 7th Brazilian Guideline of Arterial Hypertension.[5] In addition to aerobic fitness, other components of physical fitness are associated with the prognosis; studies with muscle strength and power have also shown associations with mortality. The guidelines recommend the regular and combined practice of aerobic and resistance exercises.[6,7]

The PA can be performed at work, in displacement, during housework or during leisure practices.[8] There is no consensus about the health benefits that each of these types of PA can provide, what contribution each type can offer or even what harms they can determine.[8,9]

In this issue of the *Arquivos Brasileiros de Cardiologia*, Ribeiro Jr. and Fernandes[10] analyze the cumulative effect of different types of PA on the workers' AH. They studied 1,070 participants who worked for two companies with quite different physical requirements: 624 workers in urban cleaning and 446 in the shoe industry. The PA was evaluated in all workers in the different modalities: occupational (OPA), domestic (DPA) and leisure (LPA). The occurrence of AH was analyzed considering as the main variable the number of PA modalities that the worker performed (OPA, DPA and/or LPA), and it was concluded that there was a cumulative effect of the different types of PA in the protection against AH.

This research[10] includes professional classes that characterize very well opposite behaviors in relation to the degree of OPA, involving a large number of manual workers employed in urban cleaning and others who are not very active in the conventional manufacturing industry. However, PA in displacement, which is more easily analyzed and frequently estimated in such studies,[8] was not evaluated, and DPA, present in the real world but more difficult to quantify, was included, notably in this population sample with almost 80% of male individuals. In the multivariate analysis, PA was evaluated in the three modalities (OPA, DPA and LPA), and the workers active in the three types of PA comprised the first group, those active in two modalities comprised another group and, the third consisted of workers who were inactive or active in only one type of PA. This division is liable to criticism: for instance, not impossible in the real world, an employee of the shoe factory (little OPA), little involved in DPA, but who performs 1 hour of exercise 5 times a week (300 minutes a week), would be classified as belonging to the third group (active in only one PA modality, together with the inactive ones).[10]

The contribution of OPA to AH control is defended by most researchers,[2,8,11] but it is not a consensus opinion.[9,12,13] Several epidemiological studies have shown that the risk of cardiovascular disease and death can increase with OPA.[12] These contrasting effects of PA on health have been called the "physical activity paradox" in health.[9] The increased risk in OPA has been demonstrated more frequently in workers with low income, low cardiorespiratory fitness and pre-existing diseases, such as AH and coronary disease.[13] Holtermann et

Keywords

Hypertension; Exercise; Risk Factors; Physical Activity; Epidemiology; Workers; Urban Cleaning.

Mailing Address: Cláudio L. Pereira da Cunha •
Universidade Federal do Paraná - Clinica Médica - Rua Olavo Bilac, 181.
Postal Code 80440-040, Curitiba, PR – Brazil
E-mail: cpcunha@cardiol.br

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al.[9] indicate that some differences between LPA and OPA may justify the difference in the observed results, including: 1) OPA with very low intensity and very long duration to improve physical fitness and cardiovascular health; 2) OPA with weightlifting or static postures, which can increase BP; 3) OPA performed without sufficient recovery time; 4) OPA performed with little control by the worker; and 5) OPA that increases inflammation levels. The wrong type of PA can be harmful to health, both in the context of OPA and LPA.[13] Therefore, too much mechanical force can cause a musculoskeletal injury, a too frequent activity can lead to exhaustion and too much time in the standing position can facilitate the appearance of varicose veins in the lower limbs. In contrast, too little strength can cause bone and muscle loss, infrequent exercises can cause cardiorespiratory deconditioning or cardiometabolic health alteration.[13] Thus, the benefits of physical activity, both at work and during leisure, are only manifested when the several aspects of PA are well adjusted, calibrated. The different dimensions of PA (intensity, duration, frequency of postures and different movements) affect different body systems and functions (aerobic capacity, muscle strength, movements, balance, coordination). All these aspects of PA at work should lead to the meeting of one's "perfect point", so that their effect in health promotion can occur.[13]

In conclusion, PA is beneficial to health and helps to control BP, mainly through the practice of aerobic exercises, but also with resistance exercises. The cumulative effect of different types of PA, as studied by Ribeiro Jr. & Fernandes,[10] contributes to the protection against AH. The OPA should be evaluated carefully and in details, aiming to find optimal physical activity situations, so they can be used for health benefits, and not as a harmful mechanism for the worker.

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Validity Evidence of the Brazilian Version of the Florida Shock Anxiety Scale for Patients with Implantable Cardioverter Defibrillators

Katia Regina Silva,[1] Roberto Costa,[1] Giovanna Regina Garcia de Oliveira Melo,[1] Flávio Rebustini,[2] Marcos Sidney Benedetto,[1] Marcia Mitie Nagumo,[1] Samuel F. Sears[3]

Instituto do Coração (InCor) - Faculdade de Medicina da Universidade de São Paulo,[1] São Paulo, SP – Brazil

Universidade de São Paulo - Escola de Artes, Ciências e Humanidades,[2] São Paulo, SP - Brazil

East Carolina University - Department of Psychology and Cardiovascular Sciences Greenville,[3] North Carolina – USA

Abstract

Background: In spite of proven effectiveness of implantable cardioverter defibrillators (ICDs), shock therapy delivered by the device may result in increased levels of anxiety and depression, leading to deleterious effects on quality of life.

Objective: To carry out the translation, cross-cultural adaptation and validation of the *Florida Shock Anxiety Scale* (FSAS) scale into Brazilian Portuguese.

Methods: In this psychometric study, construct validity was performed by exploratory (EFA) and confirmatory (CFA) factor analyses, and by item response theory (IRT). The adjustment indexes of the CFA were: Robust Mean-Scaled Chi Square/df NNFI, CFI (Comparative Fit Index), GFI (Goodness Fit Index), AGFI (Adjusted Goodness Fit Index), RMSEA (Root Mean Square Error of Approximation) and RMSR (Root Mean Square of Residuals). Reliability was evaluated through Cronbach's Alpha, McDonald's Omega and Greatest Lower Bound (GLB). The analyses were carried out with the programs SPSS 23 and Factor 10.8.01. A 5 percent significance level was used.

Results: The final Portuguese version of the FSAS was administered to 151 ICD patients, with a mean age of 55.7 ± 14.1 years, and predominantly male. The parallel analysis indicated that the FSAS is unidimensional, with an explained variance of 64.4%. The correlations ranged from 0.31 to 0.77, factor loadings from 0.67 to 0.86, and communalities from 0.46 to 0.74. The adjustment indexes of the CFA were above the quality threshold. Satisfactory reliability evidence was provided by the FSAS.

Conclusions: The FSAS-Br showed consistent validity and reliability evidence. Therefore, it can be used in ICD patients in Brazil. (Arq Bras Cardiol. 2020; 114(5):764-772)

Keywords: Implantable defibrillator, Shock therapies, Arrhythmias, Anxiety, Psychometric.

Introduction

Nowadays, there are no doubts regarding the role of the implantable cardioverter defibrillator (ICD) for prevention of sudden cardiac death, especially among patients with ventricular dysfunction and arrhythmogenic genetic diseases.[1-3] Due to its proven efficacy in identifying and correcting potentially lethal ventricular tachyarrhythmias, the number of ICD implantations has increased significantly worldwide, and more than 250,000 procedures are performed every year.[4]

The primary purpose of ICD is to correct potentially fatal ventricular arrhythmias by delivering low- or high-energy therapy. Low-energy therapy, known as antitachycardia pacing or antitachycardia pacing (ATP), is a painless method. High-energy therapy delivers shocks of up to 40 J which, in spite of causing major discomfort, usually occur after the patient has lost consciousness, since they are applied about 15 seconds after the initiation of ventricular fibrillation or fast ventricular tachyarrhythmia. In undesirable situations, such as arrhythmias resistant to overstimulation, or in electrical storm, high-energy discharges can occur in awake patients.[3,5,6]

It is estimated that the chances of ICD patients will need appropriate electric shocks for primary prevention of sudden cardiac death varies between 2 and 15% per year.[5-8] On the other hand, when the ICD is used for secondary prevention, the incidence of shock therapies may vary between 35 and 53%, within the first year after implantation.[5-8] Despite the high level of technological sophistication of ICDs, unfortunately, there is the risk that the patient may receive inappropriate shock deliveries as a result of erroneous discrimination between supraventricular and ventricular tachyarrhythmias. On these occasions, the sensation reported is a painful and distressing experience.[9-14]

Mailing Address: Katia Regina Silva •
Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo - Unidade de Estimulação Elétrica e Marcapasso - Dr. Enéas de Carvalho Aguiar, 44. Postal Code 05403-900, São Paulo, SP – Brazil
E-mail: katia.regina@incor.usp.br
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ICD patients live with the expectation that, at any moment, the device will deliver shock therapies to interrupt ventricular arrhythmias resulting from their heart disease. Thus, although they recognize the benefits of the treatment, some patients may present with anxiety, depression, mood disorders, post-traumatic stress disorder, as well as fear that the device will not operate in crucial situations.[9-14] On the other hand, ICD implantation has been reported to provide the patient with a great sense of safety, considering the device's capacity to interrupt unexpected episodes of potentially fatal ventricular arrhythmias.[10-14]

In face of the concern about the deleterious effects of ICD on psychosocial adaptation, an scale was specifically developed to assess the level of anxiety related to the presence of ICD and to the shocks delivered by the device, for use both in clinical practice and in the context of scientific research.[15,16] The Florida Shock Anxiety Scale (FSAS) quickly achieved wide international acceptance, and has been translated and validated in several countries (Netherlands,[17] Denmark,[18] Poland,[19] China,[20] Norway,[21] Turkey[22]), with consistent results.

Objectives

The purpose of the present study was to assess the psychometric properties of the Brazilian version of the FSAS for ICD patients.

Methods

Study design

This study was conducted in a high-complexity cardiology hospital and it was approved by that hospital's Committee of Ethics in Research. All subjects signed a free and informed consent form.

Study location and ethical aspects

This was a psychometric study of cross-cultural adaptation and validation of the FSAS.

The Florida Shock Anxiety Scale (FSAS)

The FSAS was developed in 2006 in the United States to provide a quantitative measure of ICD shock-related anxiety. The instrument consists of 10 items, with five response options ("not at all","rarely","some of the time","most of the time","all the time"), corresponding to a 5-point Likert scale.[15,16]

Questions are related to patients' fear or anxiety caused by the expectation that the device may deliver shock therapies and to the behavioral changes (not engaging in physical exercise or in sexual activity, or not getting angry or upset, for instance) to avoid the occurrence of ICD therapies.

The FSAS total score is determined by the sum of all items, with a maximum score of 50 points. The higher the score, the higher the anxiety level. The items receiving three points or more should be considered the most critical aspects.[17,18] The instrument can be self-administered or administered by interview.

Stage 1 – Translation and cross-cultural adaptation of the instrument

The cross-cultural adaptation process of the FSAS followed international guidelines and included five stages: (1) Translation by two independent translators; (2) Synthesis of the translations; (3) Back-translation; (4) Harmonization of the translations by the expert committee; (5) Pretest with the target population; (6) Pretest review and final translation.[23-25] The expert committee was composed by professionals of the area of artificial cardiac stimulation and by nurses.

The translation of the original instrument into Portuguese was performed by two independent Brazilian translators, proficient both in the Portuguese and English languages. In this stage, the translations produced by the two independent translators (T_1 and T_2) were reconciled into one version ($T_{1\text{-}2}$), after discussion with the expert committee. Working from the final version and blind to the original version, two bilingual teachers carried out the back-translations (RT_1 and RT_2). The aim of this stage was to measure the semantic and idiomatic consistency of the translations produced in the first stage. Finally, a new meeting was held with the expert committee to review all the cross-cultural adaptation process and undertake the harmonization across versions, thus obtaining the pre-final version of the instrument (Figure 1).

The pretest version was administered in a convenience sample of 20 ICD patients, aged between 18 and 80 years, All patients were recruited during an outpatient cardiovascular clinic appointment, and were at least 6 months postimplant. The pretest was conducted to identify and correct possible translation problems. Following self-completion of the instrument, a clarifying interview was held to verify the existence of irrelevant or hardly understandable items, as well as to measure the understanding of each item of the instrument. It was established that the translation would be reviewed or reformulated if less than 80% of the participants were able to understand the items.

Stage 2 – construct validation of the FSAS

The final Portuguese version of the FSAS was administered to a convenience sample of 151 participants with the following characteristics: (1) adults, aged between 18 and 80 years, of both sexes and with any education level; (2) ICD implanted for more than 6 months; (3) capable of understanding and answering the questionnaire used in the study; (4) having agreed to participate in the study by signing the informed consent form. We did not include in the study patients presenting at least one of the following situations: (1) indication for cardiac transplantation; (2) ongoing pregnancy; (3) malignant neoplasia.

Patients were selected consecutively, during outpatient care or by visits to the inpatient unit of our institution. Individuals who met the eligibility criteria were invited to answer the FSAS questionnaire. At the same time, demographic, clinical and ICD data were collected by using electronic case report forms developed in REDCap[26] (Research Electronic Data Capture) hosted at the hospital's server.

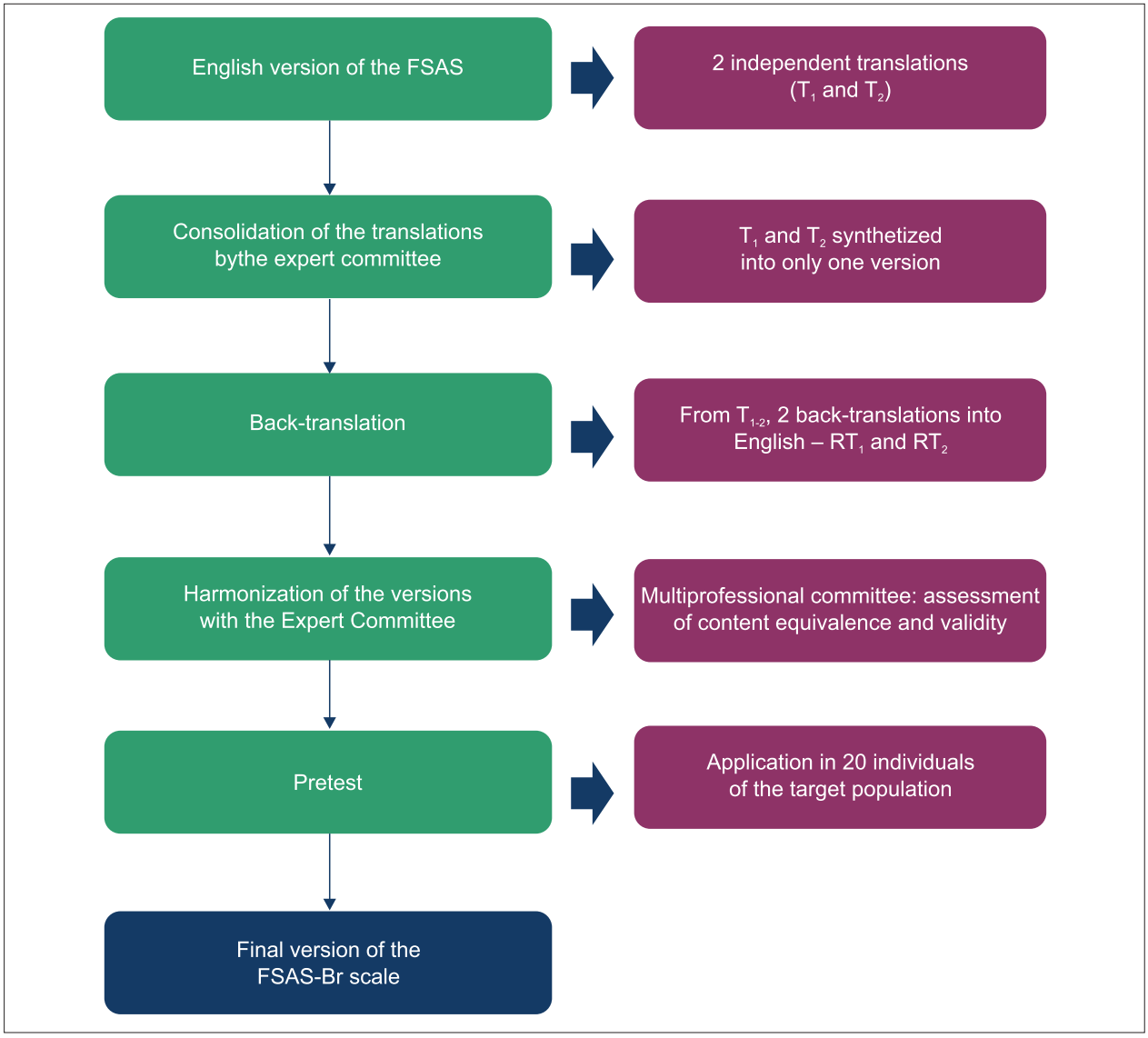

Figure 1 – *Cross-cultural adaptation process of the FSAS instrument*

Sample size

Sample size determination for psychometric studies is usually calculated based on the number of items of the instrument. Some studies have demonstrated that a ratio of 20:1 or greater, that is, 20 participants per item would be ideal. However, ratios of 10:1 are sufficient to allow for adequate analysis. Thus, a minimum sample number of 150 patients was established.[25]

Statistical Analysis

Descriptive analysis

Detailed descriptive analysis was performed, using measures of central tendency (mean, standard deviation, median, trimmed average, confidence intervals and interquartile interval). The Kolmogorov-Smirnov (KS) test was used to test the normality of each item in the questionnaire, whereas the Mardia test was employed to assess multivariate normality.

All analyses were performed using SPSS 23 statistical package software and Factor 10.8.01, adopting a level of significance of 5%.

Construct validity and dimensionality

In this study, we conducted an exploratory factor analysis (EFA) and a confirmation factor analysis (CFA) to verify the dimensionality of the FSAS in its Portuguese version.

The dimensionality testing was performed using Robust Parallel Analysis (RPA) through the Optimal implementation of Parallel Analysis (PA) with minimum rank factor analysis (MRFA), which minimizes the common variance of residuals.[27,28] The robustness of the test was determined

from the association of a bootstrap with sample extrapolation to 5,000. Factor extraction was done initially with Robust Unweighted Least Squares (RULS), which reduces the matrix of residuals.[29]

Item Response Theory

Item discrimination index was used (a), which measures the association strength between the item and the latent variable, and whose interpretation is similar to factor loading in the exploratory factor analysis.

Quality parameters of the translated and adapted versions of the FSAS

To adequate the items and the models, the following criteria were taken into account: the explained variance of the model (60 to 70%), factor loading values (> 0.50), communalities (> 0.40) and item discrimination, and collinearity and multicollinearity problems (factor loads ranging from 0.80 to 0.85).

Indices of adjustment obtained in the Confirmatory Factor Analysis

The model adjustment indices and their respective expected values were: Robust Mean-Scaled Chi Square/df NNFI (Non-Normed Fit Index > 0.93), CFI (Comparative Fit Index > 0.94), GFI (Goodness Fit Index > 0.95), AGFI (Adjusted Goodness Fit Index > 0.93), RMSEA (Root Mean Square Error of Approximation < 0.07) and RMSR (Root Mean Square of Residuals < 0.08).[29-31]

Reliability

Three indicators were adopted to assess the reliability of the Brazilian version of the FSAS questionnaire: Coefficient Alpha ("Cronbach's Alpha"), Omega and the Greatest Lower Bound (GLB).

Results

The final version of the FSAS

The stages of the translation and cross-cultural adaptation resulted in similar versions of the FSAS instrument. The synthesis of the translations was quite concise and combined the most coherent elements of each translation. The back-translations confirmed the good quality of the translations and the synthesis process carried out in the initial stages.

A total of 20 ICD patients, with a mean of age 55.6 ± 6.8 years, took part in the pretest. Of these, 50% were female, 50% were white and 30% had studied up to High School. All participants reported that the items were relevant, easy to understand and that the response options were clear. No modifications in the instrument were required. Table 1 shows the instrument items in its English and Portuguese versions.

Psychometric properties of the FSAS

Population composition

In this stage of the study, 151 ICD patients, with a mean of 55.7±14.1 years (range, 19- 80 years), were included. There was a male sex predominance, which corresponded to 64% of the cases. Most patients were white (85.4%) and 49% had attended Middle School (Table 2).

Among the cardiac diseases, there was a predominance of Chagas disease, which was present in 30.5% of the cases, followed by ischemic cardiomyopathy in 25.2%. Brugada syndrome and congenital long-QT syndrome (LQTS) were identified in 4.6 and 3.3% of patients, respectively.

Baseline assessment showed that most patients were in the New York Heart Association (NYHA) functional classes I (37.1%) and II (47.7%). Left ventricular function was determined by bidimensional transthoracic echocardiography and ranged from 18 to 77%, with a median of 35%.

Only 29.1% of the patients did not present any associated comorbidities. Dyslipidemia and arterial hypertension were the most frequent comorbidities, being present in 51.4% and 49.5% of patients, respectively. Atrial fibrillation was present in 27.1% of the individuals studied (Table 2).

As expected, 80.1% of the indications for ICD were r secondary prophylaxis of sudden cardiac death. In Brazil, due to lack of resources, ICD implantation is still underused for primary prophylaxis of sudden cardiac death.

Descriptive analysis of the FSAS items

Through descriptive analysis of the instrument items, it was possible to identify that normality of distribution was violated, indicating, therefore, the need for polychoric correlation, instead of Pearson's correlation coefficient.

The means of the instrument items ranged from 1.5 to 2.9. The FSAS average score was 22.8 ± 11.1, with a median of 20 points and variation of 10 to 50 points. There was no impact of extreme values on the mean (Table 3).

Construct validity and dimensionality of the FSAS

The values obtained from the Kaiser-Meyer-Olkin index (KMO= 0.88), the Bartlett's sphericity test (X^2= 565.5, df= 45; p<0.001) and the matrix determinant (0.0206 (p<0.0001)) revealed a significant correlation between the items, which confirmed the adequacy of the EFA.

The parallel analysis indicated the existence of only one dimension for the instrument. Moreover, this item set can explain 64.4% of latent variable (above the values recommended in the literature).[29-31] The eigenvalue criteria also indicated only one dimension, with a an eigenvalue of of 6.08. The fact that the instrument was unidimensional waived requirements for methods of matrix factor rotation. Unidimensionality indicated the use of the normal-ogive graded response IRT model, which is more adequate for a unidimensional polytomous model.[31]

Table 1 – Original and Brazilian version of the Florida Shock Anxiety Scale (FSAS-Br) instrument

Item	Original Instrument	Brazilian version: FSAS-Br
1	I am scared to exercise because it may increase my heart rate and cause my device to fire.	Eu tenho medo de fazer exercícios físicos porque isso pode aumentar meus batimentos cardíacos e fazer o meu CDI me aplicar um choque.
2	I am afraid of being alone when the ICD fires and I need help.	Eu tenho medo de estar sozinho e precisar de ajuda quando o CDI me aplicar um choque.
3	I do not get angry or upset because it may cause my ICD to fire.	Eu não posso ficar nervoso ou chateado porque isso pode fazer o CDI me aplicar um choque.
4	It bothers me that I do not know when the ICD will fire.	Me sinto preocupado por não saber quando o CDI vai me aplicar um choque.
5	I worry about the ICD not firing sometime when it should.	Eu me preocupo com a possibilidade do CDI não funcionar quando eu precisar.
6	I am afraid to touch others for fear I'll shock them if the ICD fires.	Eu tenho medo de tocar nas pessoas e dar um choque nelas caso o CDI dispare.
7	I worry about the ICD firing and creating a scene.	Eu me preocupo sobre a possibilidade de assustar as pessoas quando o CDI me aplicar um choque.
8	When I notice my heart beating rapidly, I worry that the ICD will fire.	Quando eu percebo que meu coração bate mais rápido, eu fico preocupado que o CDI vai me aplicar um choque.
9	I have unwanted thoughts of my ICD firing.	Eu penso o tempo todo que a qualquer momento o CDI pode me aplicar um choque.
10	I do not engage in sexual activities because it may cause my ICD to fire.	Eu não tenho relações sexuais porque isso pode fazer o CDI me aplicar um choque.
	Response options 1 - Not at all 2 - Rarely 3 - Some of the time 4 - Most of the time	Opções de resposta 1 - Nunca 2 - Quase nunca 3 - Algumas vezes 4 - Na maioria das vezes

Table 4 presents the factor loads, which ranged from 0.67 to 0.86, representing excellent levels of adherence of the items to the latent variable, greater than the minimum criterion of 0.50, with no evidence of multicollinearity. The unidimensionality ruled out the possibility of cross-loading. Communalities varied between 0.46 and 0.74, with all the items above the threshold of 0.40. For item discrimination (a), the values ranged from 0.91 to 1.71, also indicating good adherence to the latent variable and corroborating the data obtained from factor loading.

The CFA revealed good adjustment to the unidimensional model, with values similar to those recommended by the literature: Robust Mean and Variance-Adjusted Chi Square X^2/ df (35) = 40.40; p < 0.243; NNFI= 0.997; CFI= 0,997; GFI= 0.986; AGFI= 0.982. The residual indicators were at good levels (RMSEA= 0.032; RMSR= 0.077), showing little difference between the original matrix and the matrix generated from factor loadings.[31]

Reliability of the FSAS-Br

Satisfactory reliability evidence was provided by the FSAS-Br scale, with a Cronbach's alpha coefficient of 0.92, a McDonald's Omega coefficient of 0.92 and GLB of 0.98.

Discussion

In the present study, we described the translation and cross-cultural adaptation process of a brief scale designed to provide a quantitative measure of ICD shock-related anxiety, folllowing international methodological standards.[23-25] The final translation of the FSAS into Brazilian Portuguese (FSAS-Br) presented conceptual, semantic, cultural and measurement equivalences compared to the original items in English.[15,16]

Efforts were made to include patients with different sociodemographic profiles and various types of underlying heart diseases to ensure heterogeneous representation, aiming at providing the best calibration of the items. Thus, patients with different ICD types (ventricular, atrioventricular or associated with cardiac resynchronization therapy) were included, as well as patients with indications for primary or secondary prophylaxis of sudden cardiac death. Notwithstanding, the most common kinds of heart disease among these patients' profiles have also been contemplated, with expressive prevalence of Chagas Disease, ischemic and hypertrophic cardiomyopathy.

In the international scenario, the FSAS scale has been widely used in different scenarios, since it presents good sensitivity to identify the level of ICD shock-related anxiety and requires reduced time for completion.[15-22] Thus, it is important to highlight that the FSAS was not designed to assess relevant aspects of adaptation to the device and its real impact on quality of life, which makes it necessary to use other instruments to complement the assessment of these patients.

Table 2 – Demographic and clinical profile of the study participants

Characteristics	
Male sex	64.0%
Age (years)	55.7 ± 14.1
White	85.4%
Education	
Higher Education	14.8%
High School	34.9%
Middle School	49.0%
Illiterate	1.3%
Marital Status	
Married	64.9%
Single	14.6%
Divorced	7.9%
Widow	6.6%
Stable union	6.0%
Structural Heart Disease	
Chagas Disease	30.5%
Ischemic Cardiomyopathy	25.2%
Hypertrophic Cardiomyopathy	14.6%
Dilated Cardiomyopathy	13.2%
Brugada syndrome	4.6%
Congenital Long QT Syndrome	3.3%
Right Ventricular Arrhythmogenic Dysplasia	2.6%
Others	5.9%
New York Heart Association Functional Class	
I	37.1%
II	47.7%
III	11.3%
IV	4.0%
Left Ventricular Ejection Fraction (Echocardiography)	41.2 ± 15.6
Comorbidities	
None	29.1%
Hypertension	49.5%
Coronary Artery Disease	15.9%
Diabetes	20.6%
Atrial Fibrillation	27.1%
Chronic Kidney Disease	6.5%
Dislipidemia	51.4%
Charlson comorbidity index	1.3 ± 1.0
Use of medication	
ACEI/ARB	72.7%
Beta blockers	85.4%
Diuretics	50.7%
Antiarrhythmic drugs	58.9%
Platelet antiaggregants	31.8%
Oral anticoagulants	27.8%
ICD indication	
Primary prevention of sudden cardiac death	19.9%
Secondary prevention of sudden cardiac death	80.1%
ICD Type	
Ventricular ICD	41.1%
Atrioventricular ICD	46.4%
Cardiac resynchronization ICD	12.6%
Time of ICD implantation (years)	6.7 ± 4.4
ICD therapies	
Received shock therapies	60.3%
Never received shock therapies	39.7%

ARB: angiotensin receptor blocker; ACEI: angiotensin-converting enzyme inhibitor.

In this sense, the authors who had created the FSAS developed another instrument, the Florida Patient Acceptance Survey (FPAS),[32] which aims at assessing the psychosocial adjustment of ICD patients. The results of the cross-cultural adaptation and validation process of the FPAS into Portuguese will be published in due course.

Evidence of validity of an instrument has been recommended by the scientific community as a way to check whether the instrument actually and accurately measures the latent variable of interest. In addition, it is important to analyze whether the instrument factor structure is adequately represented by its dimensionality, that is, the number of dimensions that make up the instrument of assessment.[27-31] In the original publication of the FSAS, the authors claim that the instrument was bidimensional, presenting two dimensions: Consequence (composed of 7 items) and Trigger (composed of 3 items).[15] This model was not reproducible to the Brazilian version, because all analyses performed in this study supported the FSAS-Br scale unidimensionality. Revisiting the study by Kuhl et at.,[15] it is important to highlight that the sample was constituted by only 72 participants, which may have had an impact on the results of the psychometric analyses.

Afterwards, the psychometric properties of the FSAS were evaluated, with a sample of 443 participants.[16] The CFA showed that the two previously identified dimensions were highly related to a second-order factor ("Shock anxiety"). In other words, the two dimensions identified previously could have been better explained by their association to a common factor, namely the "shock-related anxiety" dimension. Due to these results, the authors recommended that the total scale score may be more clinically useful, instead of subdividing it into the two dimensios described before. These results corroborate the factor structure identified in our study.

Reliability assessment of the FSAS-Br scale revealed the accuracy of the Brazilian version, which was confirmed by

Table 3 – Descriptive analysis of the FSAS-Br items

Item	Average	SD	Inferior threshold	Superior threshold	5 % trimmed average	Median	Range	IQR	Asymmetry	Kurtosis	KS	Sig.
1	2.95	1.86	2.66	3.25	2.95	3.00	4.00	4.00	0.12	-4.80	0.29	0.01
2	2.46	1.72	2.19	2.74	2.40	1.00	4.00	4.00	2.84	-3.67	0.33	0.01
3	2.26	1.69	1,99	2,53	2,18	1,00	4,00	3,00	4,06	-2,90	0,37	0,01
4	2,47	1,69	2,20	2,74	2,41	1,00	4,00	3,00	2,63	-3,69	0,33	0,01
5	2,43	1,62	2,17	2,69	2,37	2,00	4.00	3.00	2.97	-3.21	0.30	0.01
6	1.54	1.25	1.34	1.74	1.38	1.00	4.00	0.00	10.81	7.67	0.48	0.01
7	2.36	1.68	2.09	2.63	2.29	1.00	4.00	3.00	3.34	-3.30	0.34	0.01
8	2.74	1.72	2.47	3.02	2.71	3.00	4.00	4.00	1.30	-4.14	0.28	0.01
9	2.07	1.59	1.81	2.32	1.96	1.00	4.00	2.00	5.37	-1.56	0.39	0.01
10	1.54	1.24	1.34	1.74	1.37	1.00	4.00	0.00	10.87	7.84	0.49	0.01

Table 4 – Construct validity of the FSAS-Br: factor loading, communalities and item description

Item	Factor loading	Communalities (h^2)	Item description (a)
1	0.76	0.58	1.17
2	0.77	0.60	1.22
3	0.76	0.59	1.19
4	0.81	0.65	1.37
5	0.68	0.46	0.93
6	0.71	0.50	1.00
7	0.67	0.46	0.91
8	0.73	0.53	1.05
9	0.86	0.74	1.71
10	0.74	0.55	1.11

adequate values of Cronbach's alpha, McDonald's Omega and GLB. The adoption of these three indications aimed to increase the accuracy of interpretation, since the Cronbach's coefficient alpha is affected by the nature of data distribution and by sample size. Besides, its values may be increased by extensive scales, parallel and/or redundant elements or limited coverage of the construct under analysis, decreasing the reliability of the measurement.[33]

In general, the results observed in the present study showed that the instrument is reliable and valid for application in Brazil, meeting the quality requirements for patient-reported outcome measurements.

Study limitations

Although the population studied is larger than the samples of several other studies which have used the FSAS, further studies with more robust samples are crucial for the consolidation of its validity and for attesting its stability in the various possible scenarios and profiles of ICD patients.

Further studies, evaluating the association of the FSAS-Br scores with the occurrence of ICD shock therapies and other clinic parameters will be useful to identify factors which may be associated with increased anxiety levels and, therefore, allow for the establishment of specific and personalized interventions for these patients.

Conclusions

The FSAS-Br instrument presented consistent validity and reliability evidence and, therefore, its use can be recommended for the ICD population in Brazil, both in clinical practice and in scientific research.

Author contributions

Conception and design of the research: Silva KR, Costa R; Acquisition of data: Melo GRGO, Benedetto MS; Analysis and interpretation of the data: Silva KR, Rebustini F; Statistical analysis: Rebustini F; Obtaining financing and writing of the manuscript: Silva KR; Critical revision of the manuscript for intellectual content: Costa R, Rebustini F, Nagumo MM, Sears SF.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the CAPPesq under the protocol number CAAE:54522516.2.000.0068. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Florida Shock Anxiety Scale for Patients with Implantable Cardioverter-Defibrillator - Appreciating the Psychosocial Aspects

Eduardo Arrais Rocha[1,2] *and Ieda Prata Costa*[1]

Faculdade de Medicina da Universidade Federal do Ceará – Cardiologia, Fortaleza, CE – Brazil

Centro de Arritmia do Ceará, Fortaleza, CE – Brazil

Short Editorial related to the article: Validity Evidence of the Brazilian Version of the Florida Shock Anxiety Scale for Patients with Implantable Cardioverter Defibrillators

The published study provides an important scale, already in its Brazilian Portuguese version and that has been validated for our population, which allows assessing the level of anxiety related to the presence of the Implantable Cardioverter-Defibrillator (ICD) and the shocks applied by the device.[1]

This scale, as well emphasized in the study by Silva et al.,[1] was not designed to assess aspects of the patient's adaptation to the ICD, or even its impacts on patient quality of life, and there is another scale that is appropriate for this purpose, such as the FPAS - Florida Patient Acceptance Survey.[2]

The article reminds us of the importance of appreciating the psychosocial aspects of patients with an ICD that are often relegated to a secondary plan. Several articles have demonstrated the negative impact that the presence of the ICD, even without therapies, can have on these patients' lives.[3-5]

However, we know about the undeniable clinical benefits they bring in different clinical contexts.[6] Therefore, a psychosocial approach should be part of the arrhythmia and pacemaker outpatient clinics, considering we now have a tool for such analysis available in our country.

Manzoni et al.[7] analyzed sixty studies and assessed the level of anxiety, depression, health-related quality of life, post-traumatic stress syndrome and psychiatric disorders in patients with ICD. They concluded there is a large methodological heterogeneity in the psychological tests used.

This has made data analysis difficult and, consequently, has hindered strategies to reduce this impact. Several factors can influence the degree of anxiety and are not fully addressed in these studies, such as the different demographic characteristics, the pre-implantation clinical and psychological status and the number of shocks, whether appropriate or not.[7]

A subanalysis of the MADIT-RIT study, which used the FSAS (Florida Shock Anxiety Scale) scale, concluded that >2 appropriate or inappropriate shocks and a higher number of inappropriate Anti-Tachycardia Pacing (ATP) episodes were associated with a greater degree of anxiety, during a 9-month follow-up. Therefore, it has been suggested that changes in the ICD programming may alter the degree of anxiety by reducing the number of inappropriate shocks and ATPs.[8]

Another relevant topic concerns the care with the ICD programming. The Specialty Societies have publications suggesting the ideal form of programming, according to each manufacturer. The implementation of these recommendations must be carried out in an attempt to minimize shock therapies, which can increase the degree of anxiety and be associated with a worse prognosis.[9,10]

The valorization of therapies with ATP (anti-tachycardia stimulation), the increase in time or the programming of a higher number of beats for the detection of sustained ventricular arrhythmias are extremely important.

The programming of patients with Chagas cardiopathy is not possible, as seen in other pathologies, as they have a greater number of therapies, in different detection zones, with different clinical implications, therefore deserving a more individualized and specialized approach in referral centers.

The correct programming of ventricular arrhythmia discrimination functions, in relation to supraventricular arrhythmias, or even for the identification of noises that may trigger inappropriate therapies, deserve special attention. We know there are several manufacturers with certain peculiarities in their programming, which are mandatory for the specialist's knowledge. The choice of the device that has the longest battery life, preventing early battery change, is also an important factor in the context of psychosocial protection.

Finally, we congratulate the authors for their important contribution to the topic in the national scenario and for the scientific thoroughness adopted in the study. The implementation of this scale, translated and validated by Silva et al. to analyze the degree of specific anxiety in patients with ICDs will help in the psychosocial treatment of these patients.

Keywords

Defibrillators, Implantable; Quality of Life; Psychosocial Impact; Anxiety; Psychophysiologic Disorders.

Mailing Address: Eduardo Arrais Rocha •
Faculdade de Medicina da Universidade Federal do Ceara – Cardiologia - Rua Capitão Francisco Pedro, 1290. Postal Code 60430-160, Fortaleza, CE – Brazil
E-mail: eduardoa@cardiol.br

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Original Article

Risk of Atrial Fibrillation after Ablation of Cavotricuspid Isthmus-Dependent Atrial Flutter: Is Combined Ablation of Atrial Fibrillation Worthwhile?

Isabella Bianco,[1] Gabriel Odozynski da Silva,[2] Alexander Romeno Janner Dal Forno,[2] Helcio Garcia Nascimento,[2] Andrei Lewandowski,[2] Elayne Pereira,[1] André d'Avila[2]

Universidade do Sul de Santa Catarina,[1] Palhoça, SC - Brazil

Hospital SOS Cardio,[2] Florianópolis, SC – Brazil

Abstract

Background: Simultaneous ablation of atrial fibrillation (AF) and cavotricuspid isthmus (CTI)-dependent atrial flutter can be performed when both arrythmias had been recorded before the procedure. However, the best approach has not been defined in case of patients referred for ablation with CTI-dependent atrial flutter, without history of AF.

Objectives: To assess the prevalence and to identify predictors of the first episode of AF after ablation of CTI-dependent atrial flutter in patients without history of AF.

Methods: Retrospective cohort of patients with CTI-dependent atrial flutter without history of AF undergoing catheter ablation. Clinical characteristics were compared between patients who developed AF and those who did not have AF after the procedure. Significance level was set at 5%. In the analysis of predicting factors, the primary outcome was occurrence of AF after CTI-dependent atrial flutter ablation.

Results: Of a total of 227 patients undergoing ablation of CTI-dependent atrial flutter (110 with history of AF and 33 without adequate follow-up), 84 were included, and 45 (53.6%) developed post-ablation AF. The HATCH and CHA2DS2-VASC scores were not different between the groups. Recurrence rate of CTI-dependent atrial flutter and complication rate were 11.5% and 1.2%, respectively, after ablation.

Conclusions: Although ablation of CTI-dependent atrial flutter is a safe and effective procedure, 50% of the patients developed AF after the procedure. However, the role of combined ablation (CTI-dependent atrial flutter plus AF) aiming at preventing AF is still uncertain. (Arq Bras Cardiol. 2020; 114(5):775-782)

Keywords: Arrhythmias, Cardiac; Atrial Flutter; Conduction; Radiofrequency Ablation; Isthmus Cavo-Tricuspid; Arial Fibrillation/prevention

Introduction

Cavotricuspid isthmus (CTI)-dependent atrial flutter is a common cardiac arrhythmia, safely and effectively treated by radiofrequency ablation with success and complication rates of 92-97% and 0.5-2.6%,[1-4] respectively. In this group of patients, those presenting atrial fibrillation (AF) before flutter ablation have an AF recurrence rate of 30-50% in the first 30 months[5,6] and of up to 82% in the following 90 months.[7,8] It has been suggested that AF and CTI-dependent atrial flutter are manifestations of the same atrial disease, and thus are associated with each other. For this reason, it has been advocated that patients with common atrial flutter, and history of AF, should benefit from simultaneous ablation of AF and atrial flutter during the first procedure, reducing the risk and costs of treatment when a second procedure is needed.

The objective of our study was to assess the prevalence and to identify predictors of AF after ablation of CTI-dependent atrial flutter in a group of patients with no history of AF before flutter ablation. Ideally, if a risk profile for FA following CTI-dependent atrial flutter could be determined, a combined approach, including ablation of both arrhythmias, could be suggested in patients with atrial flutter and no history of AF.[6,9-11]

Methods

Study design and participants

This was a cross-sectional study that evaluated patients of both sexes aged 18 years or older, undergoing ablation of CTI-dependent atrial flutter between 2017 and 2018 at SOS Cardio Hospital in the city of Florianopolis, Brazil, and at Institute of Cardiology of Santa Catarina in the city of São Jose, Brazil, with a follow-up of one year or longer, without history of AF

Mailing Address: Isabella Bianco •
Universidade do Sul de Santa Catarina - Avenida Pedra Branca, 25. Postal Code 88137-270, Palhoça, SC – Brazil
E-mail: isabellabianco97@hotmail.com
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on electrocardiogram before ablation. Therefore, patients with electrocardiographic documentation of AF before ablation of CTI-dependent atrial flutter were excluded. The flowchart of patients' inclusion and exclusion is illustrated in Figure 1.

This study was approved by the Ethics Committee of Universidade do Sul de Santa Catarina (Unisul) (approval number 79539517.1.0000.5369). All procedures involved in this study was conducted according the Helsinki Declaration, 1975, updated in 2013, and the 466 resolution of the Brazilian National Health Council (December 2012).

Data collection

The patients included in the study, with diagnosis of CTI-dependent atrial flutter, undergoing catheter ablation, were followed for the occurrence of AF after the index procedure. Recurrence of CTI-dependent atrial flutter and occurrence of AF were confirmed by data collected from medical records – electrocardiogram, 24-hour Holter monitoring, routine consultations, emergency services and ablation procedures.

Protocol of CTI-dependent atrial flutter ablation

Ablation of CTI-dependent atrial flutter was performed under general anesthesia. Two punctures were made in the right femoral vein, with placement of a decapolar deflectable 8mm ablation catheter. Ablation was then performed (60W at 60oC for up to 2 minutes), started near the tricuspid valve towards the inferior vena cava at six o'clock in a left-anterior oblique position, until interruption of the atrial flutter. When arrythmia was interrupted, double atrial potentials were observed on the ablation line, with periods of at least 100 milliseconds during continuous pacemaking of coronary sinus and lateral atrial wall for confirmation of bidirectional block and conclusion of the procedure. Patients were kept in observation for 24 hours after the procedure and instructed to consult their assistant physicians after hospital discharge.

Statistical analysis

Clinical data and procedures were compared between the groups of patients with and without atrial flutter after the ablation procedure. A convenience (non-probabilistic) sample was used, according to inclusion and exclusion criteria, and time of follow-up.

Continuous variables were described as mean and standard deviation and compared using the unpaired, two-tailed Student's t-test, according to normality of data distribution, assessed by the Shapiro-Wilk test. Categorical variables were described as absolute numbers and percentages and compared using the chi-square test of the Fisher's exact test. Significance level was set at 5%. The Kaplan-Meier curve was used for analysis of recurrence rate during the follow-up period (truncation at 24 months). Predictive factors were assessed by logistic regression, with occurrence and non-occurrence of AF following atrial flutter ablation as outcomes. All variables associated with a $p<0.20$ in the univariate logistic regression analysis were included in the multivariate model for final adjustment.

No selection was applied in the multivariate models. Statistical analysis was performed using the IBM SPSS Statistics software, version 22.0.

Results

Patients

Atrial flutter ablation was performed in 227 patients between 2017 and 2018 at two centers in Santa Catarina, Brazil. Of these, 110 patients had a history of AF and 33 patients did not have enough clinical data. Therefore, 84 patients without history of AF before CTI-dependent atrial flutter ablation were enrolled in the study. During a mean follow-up of 26±18 months, 45 (53.6%) had AF after ablation. Table 1 summarizes clinical characteristics of patients with and without AF after ablation of CTI-dependent atrial flutter ablation.

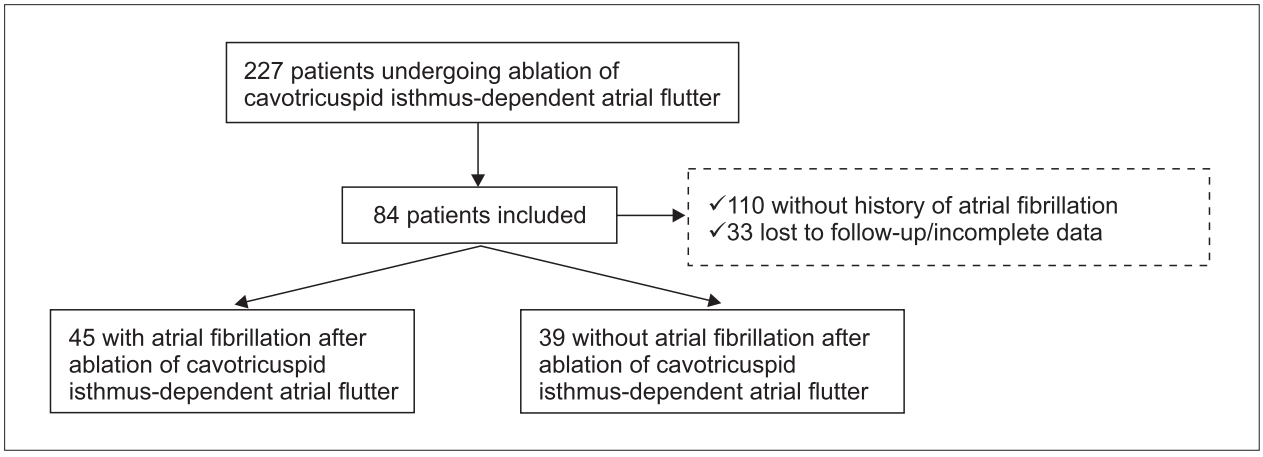

Figure 1 – *Flowchart of inclusion and exclusion of patients undergoing ablation of cavotricuspid isthmus-dependent atrial flutter categorized by occurrence of atrial fibrillation after the procedure.*

Table 1 – Characteristics of patients undergoing ablation of atrial flutter, categorized according to occurrence of atrial fibrillation during the follow-up period

Variables	Occurrence of atrial fibrillation (n = 45)	Non-occurrence of atrial fibrillation (n = 39)	p-value
Age (years)	68.0 ± 12	66.4 ± 15	0.59
Sex (male)	33 (73.2)	27 (69.2)	0.43
Body mass index	28.9 ± 4	29.7 ± 4.2	0.72
LVEF (%)	51.7 ± 14	54.8 ± 18	0.62
Left atrial diameter (mm)	41.2 ± 7.8	42.2 ± 7.3	0.97
Comorbidities			
History of renal failure	11 (24.4)	3 (7.2)	0.03
Dyslipidemia	13 (28.9)	9 (23.1)	0.36
Heart failure	12 (26.7)	12 (30.8)	0.43
Hypertension	32 (72.1)	22 (56.4)	0.12
Diabetes mellitus	8 (17.8)	10 (25.6)	0.27
Vascular disease	16 (35.6)	9 (23.1)	0.15
Previous stroke/TIA	7 (15.6)	4 (10.3)	0.35
Medications			
OAC	23 (51.1)	21 (53.8)	0.33
AAD	23 (51.1)	14 (35.9)	0.11
Scores			
HATCH	1 (1-3)	1 (0-3)	0.41
CHA_2DS_2-VASC	3 (2-4)	3 (1-4)	0.42

*Data expressed as mean ± standard deviation (age, body mass index, LVEF, left atrial diameter); or absolute and relative frequency; LVEF: left ventricular ejection fraction; TIA: transient ischemic attack; OAC: oral anticoagulants; AAD: antiarrhythmic drugs; Student's t-test for independent samples; *p-value indicates statistically significant differences at a level of 5%*

Mean age was 68±12 years in the group with AF and 66.4±15 years in the group without AF (p=0.59). In both groups, most patients were male (73.2% in the group with AF and 69.2% in the group without AF, p=0.43). Mean BMI was 28.9 ± 4 kg/m² in the group with AF and 29.7 ± 4.2 kg/m² in the group without AF (p = 0.72).

Comorbidities were similar in both groups. History of renal failure and systemic arterial hypertension was more common in the group with AF (24.4% vs. 7.2% [p = 0.03] and 72.1% vs. x 56.4% [p = 0.12]). There was no difference between the groups regarding other comorbidities such as dyslipidemia, congestive heart failure, diabetes mellitus, vascular disease, stroke/transient ischemic attack, use of anticoagulants or antiarrhythmic drugs.

Efficacy and safety of procedures

Recurrence rate of CTI-dependent atrial flutter was 11.5%. Table 2 summarizes the results of the procedure and the complication rate. There was rupture and embolization of the curved tip of the transseptal sheath used for stabilization of the ablation catheter (complication rate of 1.2%), that was lodged in the distal branch of the left pulmonary artery and was successfully removed without surgical intervention.

Table 2 – Efficacy and safety of ablation of cavotricuspid isthmus-dependent atrial flutter for treatment of common atrial flutter in 84 patients

Event	n (%)
Occurrence of post-ablation AF	45 (53.6)
Recurrence of atrial flutter	10 (11.5)
Complications	1 (1.2)

AF: atrial fibrillation.

The Kaplan-Meier curve (Figure 2) illustrates the occurrence rate of AF of 53.6% after ablation of CTI-dependent atrial flutter. The occurrence was more common in the first year after the procedure.

Predictors of AF after ablation of CTI-dependent atrial flutter

The univariate analysis revealed statistically significant predictors for the occurrence of AF after ablation of CTI-dependent atrial flutter. The variables history of renal failure (OR = 3.88 [95%CI 0.99-15.1] p = 0.05) and systemic arterial hypertension (OR = 2.15 [95%CI 0.86-5.39] p = 0.10) were included in the multivariate models, but did not show statistical significance after adjustment of the model

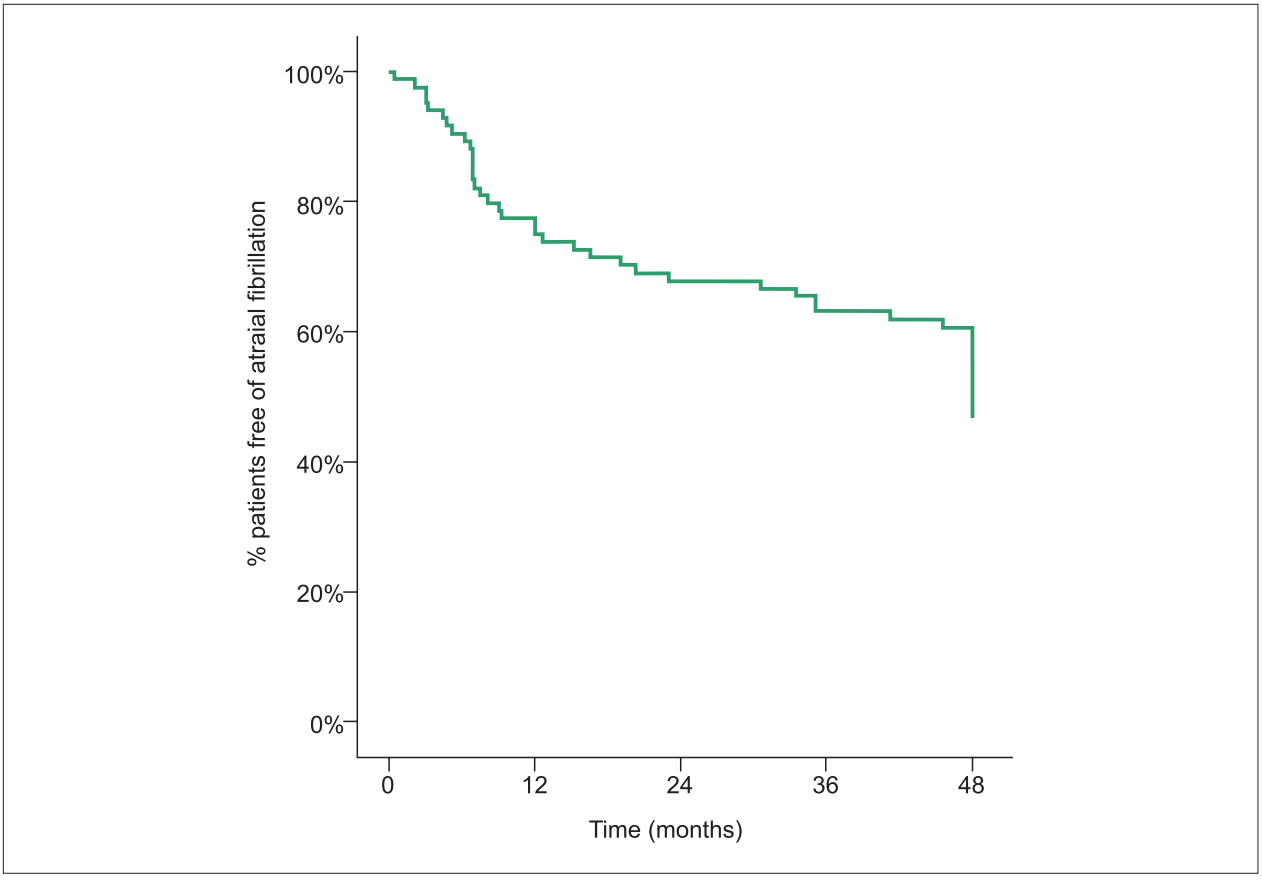

Figure 2 – *Kaplan-Meier analysis of occurrence of atrial fibrillation after ablation of cavotricuspid isthmus-dependent atrial flutter.*

Table 3 – Univariate and multivariate analysis of clinical variables for occurrence of atrial fibrillation after ablation of cavotricuspid isthmus-dependent atrial flutter

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Age	1.01	0.98-1.04	0.38	-	-	-
Sex	0.84	0.32-2.18	0.73	-	-	-
Body mass index	0.96	0.85-1.08	0.57	-	-	-
Left atrial diameter	0.97	0.90-1.04	0.42	-	-	-
LVEF	0.99	0.96-1.02	0.82	-	-	-
History of renal failure	3.88	0.99-15.1	0.05	3.12	0.89-14.2	0.10
CHF	0.66	0.25-1.73	0.40	-	-	-
SAH	2.15	0.86-5.39	0.10	1.98	0.78-5.04	0.15
Diabetes mellitus	0.59	0.20-1.73	0.34	-	-	-
Vascular disease	1.19	0.47-3.05	0.70	-	-	-
OAC	1.32	0.56-3.13	0.51	-	-	-
AAD	0.68	0.28-1.63	0.39	-	-	-

*LVEF: left ventricular ejection fraction; CHF: congestive heart failure; SAH: systemic arterial hypertension; OAC: oral anticoagulants; AAD: antiarrhythmic drugs. *p-value indicates statistically significant differences at a level of 5%*

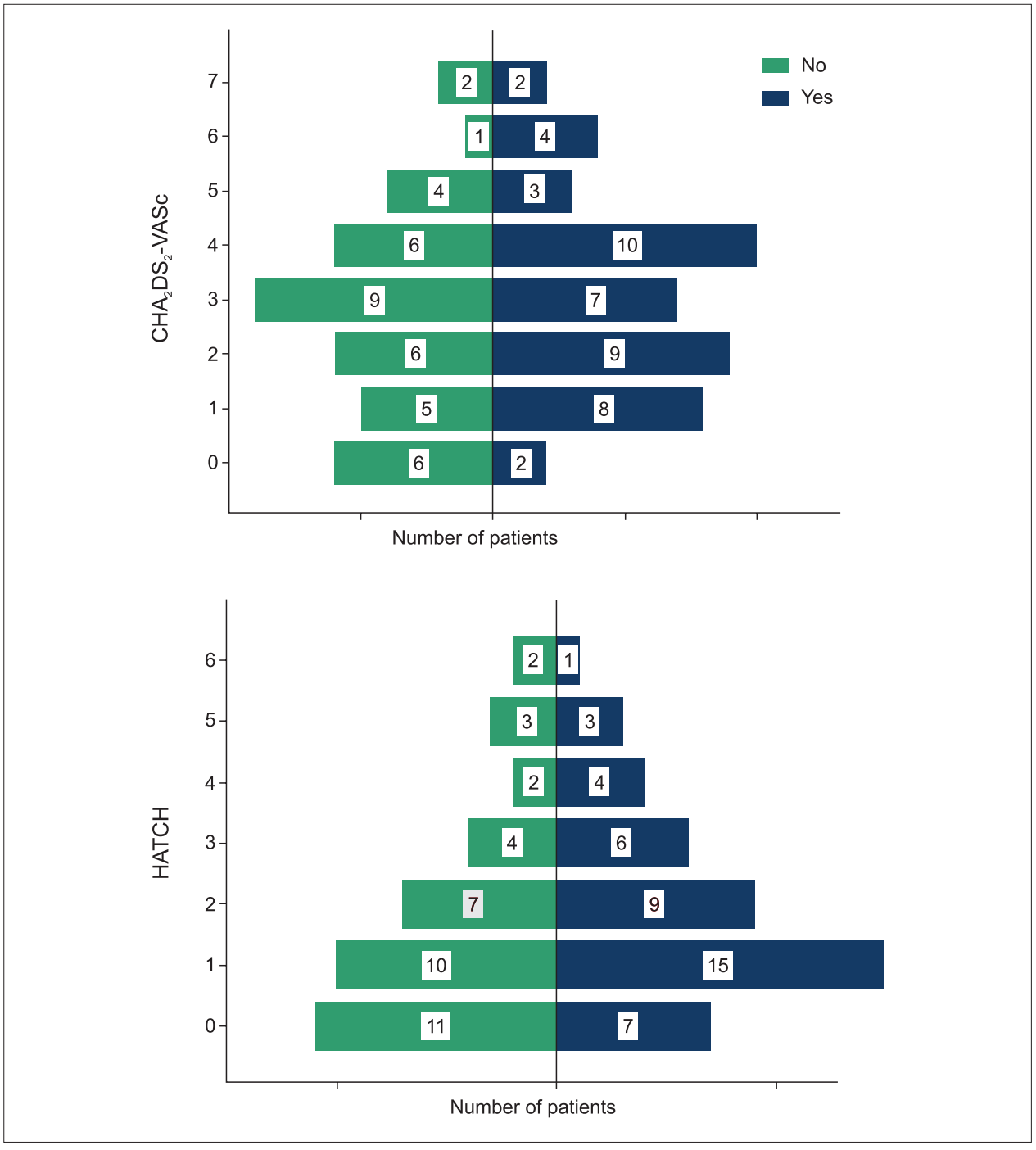

Figure 3 – *Distribution of HATCH and CHA_2DS_2-VASC scores according to the occurrence (yes/no) of atrial fibrillation after ablation of cavotricuspid isthmus-dependent atrial flutter.*

(Table 3). Figure 3 shows the distribution of the HATCH and CHA_2DS_2-VASC scores according to the occurrence or not of AF after CTI-dependent atrial flutter ablation. No difference was found between the two groups. Distribution of the HATCH score values by occurrence or not of AF after ablation was 1 (1-3) in the group with AF and 1 (0-3) in the group without AF. Distribution of the CHA_2DS_2-VASC score values was 3 (2-4) and 3 (1-4) in patients with and without AF, respectively.

Discussion

The main findings of the present study were (1) ablation of CTI-dependent atrial flutter is an effective and safe procedure, with low complication rates (1.2%); (2) AF is a frequently occurring complication (53.6%) in patients without history of AF; and (3) no criterion or predictive score for AF after ablation of CTI-dependent atrial flutter was identified.

Ablation of CTI-dependent atrial flutter by radiofrequency

Ablation of arrhythmogenic circuits of CTI-dependent atrial flutter using radiofrequency is associated with high success rates, superior to the exclusive use of antiarrhythmic drugs.[9,12] Among the known side effects, in case of recurrence of CTI-dependent atrial flutter, the use of antiarrhythmic drugs like propafenone may facilitate the atrioventricular conduction and increase ventricular response, with possible hemodynamic instability. Besides, the quality of life of patients treated with antiarrhythmic drugs is not improved, and 63% of patients require readmission.[13] Therefore, radiofrequency ablation is recommended as the treatment of choice for CTI-dependent atrial flutter.

In a recent meta-analysis, Pérez et al.[1] reported a recurrence rate of CTI-dependent atrial flutter of 10.6%, similar to that found in the present study, and complication rates of up to 2.6%.[1,3] Patients with CTI-dependent atrial flutter undergoing successful ablation showed lower mortality and lower risk of stroke and thromboembolic events, compared with patients treated only with drug therapy.[3]

In the present study, we found recurrence rate of CTI-dependent atrial flutter of 11.5% and complication rate of 1.2%. No patient had embolic event or pericardial effusion, and no patient died despite the long period of follow-up of the study sample.

Occurrence of AF after ablation of CTI-dependent atrial flutter

In our study, recurrence rate of AF after ablation of CTI-dependent atrial flutter was 53.6%. This is of clinical significance, due to the high risk of thromboembolic events associated with this arrhythmia, particularly stroke. The presence of AF is associated with 4-5 times greater risk of developing ischemic stroke. Stroke caused by AF has been associated with higher mortality and more severe functional deficits.[14,15] Thus, patients with AF are not only at greater risk of developing stroke, but also of having more severe disease, with more debilitating complications. In a study on patients undergoing ablation of CTI-dependent atrial flutter, the incidence of stroke during a mean follow-up of 40 months after the procedure was four times greater than the general population, and the only risk factor identified was occurrence of AF after ablation of CTI-dependent atrial flutter.[16] For this reason, considering the high incidence of AF in this population, discontinuation of oral anticoagulation may expose them to the risk of thromboembolic events and hence should be considered individually, considering the CHA2DS2-VASC score of the patient with atrial flutter, just as with patients with AF.[17]

Therefore, a significant number of patients remains symptomatic due to the development of AF after CTI-dependent atrial flutter ablation. A second ablation procedure may be then necessary for the control of AF. Although isolation of pulmonary veins by radiofrequency ablation (required in the treatment of AF) is a more complex procedure, with higher costs and risks compared with CTI-dependent atrial flutter ablation, an alternative may be to treat both arrhythmias using a combined procedure, thus avoiding a second intervention.[9,11]

Is it worth to perform isolation of the pulmonary veins simultaneously with ablation of CTI-dependent atrial flutter in patients with history of AF?

In the ablation of CTI-dependent atrial flutter procedure, the electrophysiologist makes an ablation line in the cavo-tricuspid isthmus area, to prevent or block the macroreentrant circuit in the right atrium. In this case, the access of the ablation catheters to the right atrium occurs exclusively by puncture of the femoral veins. Ablation of AF ablation, in turn, is a more complex and time-taking procedure that requires the access to the left atrium by transseptal puncture (passage of the catheters from the right to the left atrium by puncture of the interatrial septum) for electrical isolation of the pulmonary veins, generally responsible for the triggering of AF. The REDUCE AF study, involving 216 patients, showed that combined ablation of CTI-dependent atrial flutter plus AF resulted in a longer arrhythmia- free interval compared with the CTI-dependent atrial flutter ablation alone, especially in >55 age patients. In this subgroup of patients, the number needed to treat (NNT) was seven, with an absolute risk reduction in AF occurrence of 14%.[11]

Using a cost-effectiveness analysis, a Canadian study proposed that the combined ablation (CTI-dependent atrial flutter plus AF) does not provide financial and risk benefit. With an incidence rate of AF of up to 33%, the mean cost of performing the procedures separately was lower than the combined strategy. In addition, when performed alone, the mean risk of ablation of CTI-dependent atrial flutter is lower, since the risk of AF ablation exceeds the risk of CTI-dependent atrial flutter ablation by 25% or more. One should consider, however, that risk, cost and complication rates vary regionally, like the incidence of AF after ablation of CTI-dependent atrial flutter, which was twice greater than that predicted in cost-effectiveness studies. Also, cost-effectiveness analysis usually does not consider the negative long-term impact of embolic events in patients with new onset AF. In the state of Santa Catarina, the mean cost of hospitalization due to cardioembolic stroke with AF reaches BRL 40,539 per patient.[18] Thus, the risks and costs involved in the combined ablation procedure (CTI-dependent atrial flutter and AF) would not be justifiable in short term; instead, long-term studies

investigating the benefits of combined procedures in patients without history of AF are needed.[19] It is worth highlighting that the choice for the combined therapy is always made for patients with CTI-dependent atrial flutter and history of AF.

Predicting factor for AF

In the present study, none of the variables or scores analyzed was able to predict the occurrence of AF after ablation of CTI-dependent atrial flutter in the study population. The literature about predictors for the occurrence of AF is inconclusive. Different studies have described clinical variables such as comorbidities, previous history of AF, duration of atrial flutter,[20] echocardiographic and electrocardiographic variables as predictors of AF.[6,10,21-23] On the other hand, Chinitz et al.,[5] in a study with 254 patients undergoing ablation of CTI-dependent atrial flutter, followed-up for a mean of 30 ± 22 months, did not find any predictors for AF, even among those more commonly associated with arrhythmia, corroborating our findings.

The HATCH score has been proposed to predict the progression of AF from paroxysmal to persistent AF. In sub-analyses, the HATCH was useful in predicting the occurrence of AF in asymptomatic patients. In our analysis, no difference was observed between the groups in the occurrence of AF after ablation of CTI-dependent atrial flutter according to the HATCH score.[24] In addiction to predicting the risk of stroke in patients with AF, the CHA_2DS_2-VASC score is known to be used for prediction of morbidity and mortality in different clinical settings. However, in the present study, the score did not show statistically significance in predicting AF after ablation CTI-dependent atrial flutter.

Limitations

The first limitation of the study is its retrospective nature. Second, the limited sample size may have prevented the detection of significant differences between the two groups (AF vs. non-AF) and identify predicting variables of AF after invasive treatment for CTI-dependent atrial flutter. Finally, we did not monitor asymptomatic arrythmias after ablation of CTI-dependent atrial flutter, and hence the real incidence of AF may have been underestimated.

Conclusions

In our study, ablation of CTI-dependent atrial flutter was an effective and safe procedure. There was a high incidence of AF after the ablation procedure, even in patients without history of AF, and regardless of clinical characteristics of the patients. There is not enough evidence to recommend combined ablation for treatment of atrial flutter aiming at preventing the occurrence of AF. Studies with longer follow up are needed to determine the real benefits of simultaneous ablation.

Author contributions

Conception and design of the research: Bianco I, Silva GO, Pereira E, d'Avila A; Acquisition of data and obtaining financing: Bianco I; Analysis and interpretation of the data: Bianco I, Silva GO, d'Avila A; Statistical analysis: Bianco I, Silva GO; Writing of the manuscript: Bianco I, Pereira E, d'Avila A; Critical revision of the manuscript for intellectual content: Bianco I, Silva GO, Dal Forno ARJ, Nascimento HG, Lewandowski A, Pereira E, d'Avila A.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Unisul under the protocol number 2.412.219. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

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Short Editorial: Risk of Atrial Fibrillation after Ablation of Cavotricuspid Isthmus-Dependent Atrial Flutter: Is Combined Ablation of Atrial Fibrillation Worthwhile?

Alvaro Valentim Lima Sarabanda[1,2]

Instituto de Cardiologia do Distrito Federal,[1] *Brasília, DF – Brazil*

Fundação Universitária de Cardiologia (FUC),[2] *Brasília, DF – Brazil*

Short Editorial related to the article: Risk of Atrial Fibrillation after Ablation of Cavotricuspid Isthmus-Dependent Atrial Flutter: Is Combined Ablation of Atrial Fibrillation Worthwhile?

Cavotricuspid isthmus (CTI)-dependent atrial flutter (AFL) is a common cardiac arrhythmia that can cause significant symptoms and is associated with an increased risk of stroke and the development or worsening of heart failure. The anatomic/electrophysiological substrate underlying AFL is a combination of slow conduction in the isthmus of atrial tissue between the tricuspid annulus and the inferior vena cava and conduction block along the crista terminalis and Eustachian ridge, enabling the emergence and perpetuation of a macro-reentrant circuit in the right atrium.[1,2]

Because of the well-defined anatomic/electrophysiological substrate and the unsatisfactory results of antiarrhythmic drug therapy in treating AFL, radiofrequency catheter ablation, by means of creating a linear lesion from the tricuspid annulus to the inferior vena cava (cavotricuspid isthmus) under fluoroscopic and electrocardiographic guidance, is an established interventional procedure, with a low risk of complications (1% or less) and success rates over 90%.[1,2]

Although acutely highly successful, a significant number of patients with successful (CTI)-dependent AFL ablation will develop atrial fibrillation (AF) during the follow-up period.[1,3-5] Rather than proarrhythmia, it has been suggested that the occurrence of new AF reflects manifestation of the same atrial disease that predisposes patients to both arrhythmias.[6] Thus, elimination of the CTI-dependent AFL circuit does not prevent new AF. This effect has been reported in multiple studies examining the emergence of atrial arrhythmias, including AF, following CTI ablation for AFL.[1,3-5]

In this issue of the *Arquivos Brasileiros de Cardiologia*, Bianco et al.[7] explore the incidence and predictors of AF following ablation of AFL. They present a series of 84 patients without any prior history of AF undergoing catheter ablation of CTI-dependent AFL, with data analyzed retrospectively. There was only one periprocedural complication (1.2%), an embolization of the tip of the long sheath used for stabilization of the 8mm tip ablation catheter, which was successfully removed without surgical intervention. During a mean follow-up of 26±18 months, 10 (11.5%) patients had recurrence of AFL and 45 (53.6%) had a first episode of AF. However, no predictive variables for the occurrence of AF were identified in the clinical follow-up.[7]

The study of Bianco et al.[7] is in agreement with previous studies of patients undergoing CTI-dependent AFL ablation.[1,3-5] However, the question raised by the authors is whether we should perform a concomitant AF ablation in patients undergoing CTI-dependent AFL ablation without history of AF. As highlighted by Bianco et al.,[7] the emergence of AF after ablation of CTI-dependent AFL has great clinical relevance due to the high risk of thromboembolic events associated with AF, particularly stroke. The presence of AF is associated with 4-5 times greater risk of developing ischemic stroke. In a study including patients undergoing ablation of CTI-dependent AFL, the incidence of stroke over a mean follow-up of 40 months was four times greater than the general population.[8] For this reason, considering the high incidence of AF in this population, discontinuation of oral anticoagulation may expose them to the risk of thromboembolic events and hence should be considered individually, considering the CHA2DS2-VASC score of the patient with FLA, just as with patients with AF.[2,9]

In addition, a significant number of patients remains symptomatic due to the emergence of AF following CTI-dependent AFL ablation. A second ablation procedure may then be necessary to control AF. Therefore, the question arises whether we should perform concomitant PVI in patients undergoing CTI-dependent AFL ablation, even before AF has ever occurred (10-12). Although AF ablation, by means of pulmonary vein isolation (PVI), is a more complex procedure, involving transseptal punctures, more extensive atrial ablation and use of three-dimensional mapping equipment, with higher costs and risks compared with CTI-dependent AFL ablation, an alternative strategy may be to treat both arrhythmias in a single ablation procedure, thus avoiding a second intervention.[7]

In this context, recent data suggest that prophylactic PVI can be an effective strategy for preventing new AF in patients undergoing CTI-dependent AFL ablation.[10-12] The PREVENT AF I Study included 50 patients with CTI-dependent AFL without any prior history of AF, and randomized them in 1:1 fashion between CTI ablation alone versus CTI ablation plus cryoballoon PVI (CTI+PVI).[10] New-onset AF occurred in 52% of CTI ablation alone versus 12% with CTI+PVI group over

Keywords

Arrhythmias, Cardiac; Atrial Flutter; Conduction; Radiofrequency Ablation; Isthmus Cavo-Tricuspid; Atrial Fibrillation/prevention and control.

Mailing Address: Alvaro Valentim Lima Sarabanda •
Instituto de Cardiologia do Distrito Federal - SQSW 301 BL F AP 508.
Postal Code 70673106, Brasília, DF – Brazil
E-mail: saraband@uol.com.br

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1-year follow-up (p=0.003). Subsequently, Romanov et al.[11] presented the extended (3-year) outcomes of the PREVENT AF I Study. There was a highly significant improvement in freedom from any atrial tachyarrhythmia in the CTI+PVI group compared with the CTI ablation only group (48% vs. 20%, P=0.01). Of note, there were no adverse events in the CTI+PVI group, but 2 strokes occurred in the CTI-only group during follow-up. In this study, a multivariate analysis identified male gender and age over 55 as factors that predicted atrial arrhythmias during follow-up. Additionally, the REDUCE AF study[12] randomized 216 patients with lone AFL to CTI+PVI versus CTI ablation alone, and found a reduction in subsequent AF with prophylactic PVI, but at the cost of significantly longer procedure and fluoroscopy times. In *post hoc* analysis, all of the benefit was confined to those patients over 55 years of age, in agreement with the findings of Romanov et al.[11]

More recently, Gula et al.[13] conducted a cost-effectiveness analysis comparing the strategy of combined prophylactic PVI plus CTI versus sequential approach with separate procedures, i.e., waiting for AF to occur before undergoing PVI. Making plausible projections on AF occurrence and PVI success rates, as well as risks and costs of the procedures, the authors found that the combined approach with prophylactic PVI conferred higher risk and higher cost than the sequential approach during follow-up. However, one should consider the limitations of this study, and perhaps a strategy of combined prophylactic PVI plus CTI would have more favorable risk/benefit ratio if applied more selectively to patients at highest risk for developing AF during follow-up.

In this context, as have been acknowledged by Bianco et al.,[7] a significant limitation of their study was the limited size of the study population which may have prevented the identification of predictors for development of AF after CTI ablation. As recognized by the authors,[7] if a risk profile for the occurrence of AF following CTI-dependent AFL ablation could be determined, a combined approach, including ablation of both arrhythmias, could be prophylactically indicated in patients at higher risk for developing AF.

In summary, the study of Bianco et al.[7] provides further evidence that CTI-dependent AFL ablation is a safe and effective procedure, but solves just part of the clinical problem of the patient presenting with isolated AFL, since the occurrence of AF after CTI ablation is frequently observed. However, with regard to the issue highlighted by the authors,[7] there is still insufficient evidence to recommend combined ablation for treatment of AFL aiming at preventing the occurrence of AF. Prospective studies with a larger number of patients and longer follow-up will are needed to assess the benefits of the simultaneous ablation.

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Short Editorial

Knowledge about the Disease and the Practice of Physical Activity in Children and Adolescents with Congenital Heart Disease

Elisandra Furlan de Lima Campos,[1] Lisiane Perin,[1] Melina Assmann,[1] Fernanda Lucchese,[1] Lucia Campos Pellanda[1,2]

Programa de Pós-Graduação em Ciências da Saúde: Cardiologia. Instituto de Cardiologia do Rio Grande do Sul – Fundação Universitária de Cardiologia,[1] Porto Alegre, RS – Brazil

Departamento de Saúde Coletiva – Universidade Federal de Ciências da Saúde de Porto Alegre,[2] Porto Alegre, RS – Brazil

Abstract

Background: Knowledge about the disease itself can be important for self-care in patients with several problems and comprehends information about the diagnosis up to the most important clinical implications.

Objective: To identify the level of knowledge of children and adolescents with congenital heart disease (CHD) about their illness, and to analyze the association between the level of knowledge and the practice of physical activity.

Methods: Cross-sectional study with 335 patients with CHD, aged 8 to 13 years, followed at a referral pediatric cardiology service in Southern Brazil. Patients were interviewed regarding their knowledge about CHD and a review of medical records was performed to obtain details on heart disease and procedures. A significance level $p<0.05$ was used.

Results: More than 50% of the children and adolescents did not know how to say the name of their disease or explain it. After adjusted OR (AOR), cyanotic patients in comparison to acyanotic ones (AOR: 2.29; 95%CI: 1.76-6.71; $p = 0.019$); children with lower level of schooling (AOR: 2.20; 95%CI: 1.81-5.86; $p = 0.025$); and those who did not practice physical activity (AOR: 1.88; 95%CI: 1.09-3.45; $p = 0.011$) showed potential for incorrect answers or did not know their disease.

Conclusion: Cyanotic children and adolescents, with a lower level of schooling and who did not practice physical activity, had little knowledge about their disease. It is necessary to develop educational intervention strategies to increase knowledge and change behavior in physical activity promotion, according to the CHD complexity. (Arq Bras Cardiol. 2020; 114(5):786-792)

Keywords: Heart Defects, Congenital/physiopathology; Cyanosis; Child, Adolescents; Health Information Systems; Physical Activity.

Introduction

Knowledge of the disease itself is an important factor for self-care in patients with congenital heart disease (CHD)[1] and ranges from information about the diagnosis to the most important clinical implications.[2] CHD is responsible for 0.8–1.2% of all congenital defects and has a prevalence of approximately 5.8 per 1,000 individuals.[3] The incidence of CHD in Brazil is estimated at around 26,000 new cases per year.[4]

To minimize the risk of complications and improve health status, patients are expected to adopt certain health behaviors, such as physical activity, healthy eating and oral hygiene practices.[5] However, the complexity of heart diseases and the recurring concept of the need for physical restriction generate doubts among parents and health professionals about the adequate levels of physical activity for children and adolescents with CHD.[6] Moreover, the guidelines change over time, after the heart disease repair.[7] Therefore, often the family or the patients themselves restrict physical activities without this representing medical advice.

Few studies have been performed on the specific knowledge of diseases such as CHD in children, adolescents or adults. Therefore, there are information gaps in different age groups and most studies have a small number of patients that allows the extrapolation of results.[5,8-11] Therefore, identifying the levels of the knowledge of a child with CHD about their disease can allow better planning of health education programs that will contribute to minimize doubts regarding the practice of physical activity (PA) and improve adherence to treatment. Thus, the aim of this study was to identify the level of knowledge of children and adolescents with CHD about their disease, and to analyze the association between the level of knowledge and the practice of physical activity.

Mailing Address: Elisandra Furlan de Lima Campos •
Instituto de Cardiologia do Rio Grande do Sul / Fundação Universitária de Cardiologia - Avenida Princesa Isabel, 370 / 3º andar. Postal Code 90620-000, Porto Alegre, RS - Brazil
E-mail: elysfurlan013@gmail.com
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Methods

This is a cross-sectional study that included children and adolescents with CHD, aged between 8 and 13 years, followed at the Pediatric Outpatient Clinic of Instituto de Cardiologia do Rio Grande do Sul, carried out from February 2017 to February 2018. The study protocol was approved by the Research Ethics Committee of Fundação Universitária, and all participants and parents/guardians signed the Free and Informed Consent (FIC) form and Term of Assent (TA).

Patients were included consecutively for one year, from the list of medical appointments scheduled during the study period. Patients with Down Syndrome, Noonan Syndrome, Charge Syndrome, autism, arrhythmias and syndromes that compromise the understanding of their disease were excluded. The age range of the participants was checked on the outpatient clinic agenda. After inclusion by age, the respective medical records were analyzed to confirm the presence of CHD (Figure 1).

The children's interviews were carried out in the waiting room of the outpatient clinic, where the objectives and study protocol were explained to the patients and their parents/guardians. Data collection was carried out by the same interviewer (EFLC), who was informally dressed, and lasted between 6 and 20 minutes.

A semi-structured questionnaire was developed, based on the Leuven Knowledge Questionnaire for Congenital Heart Disease (LKQCHD)[6] about knowledge of CHD. Sociodemographic and clinical data, such as previous hospitalizations, hemodynamic and surgical procedures, were extracted from the patient's medical record. Information on the age at which the diagnosis of CHD was obtained was obtained directly from the parents or guardians, so that the CHDs were classified as minimal lesions (ML), acyanotic without implications (ASI), acyanotic with implications (AWI) and cyanotic (CY).[11] The children and adolescents were asked to explain, in their own words, what they understood about their disease. The content analysis of the explanatory responses of children and adolescents regarding the knowledge of their disease was carried out by two physicians specialized in pediatric cardiology (M.A. and L.C.P.) and, subsequently, the level of knowledge was classified into 4 groups: Correct (C), Partially Correct (P/C), Incorrect (IN) and Doesn't Know (DK).

To assess the level of physical activity, the Typical Physical Activity and Food Intake Day (DAFA) instrument was partially used. We used the part of physical activity that illustrates 11 types of physical activities in three different intensities. The overall level of physical activity was determined by adding the scores of the activities that the assessed individuals reported performing on most days of the week. Three different weights were assigned aiming to weigh the activities indicated by the patients: weight one for light intensity activities, weight three for moderate intensity activities and weight nine for vigorous intensity activities. The score can reach up to 143 points, indicating children who are less active, intermediate or more active.[12,13] Based on quartiles limits [median of 25.0 (1st - 3rd quartile: 16.0 - 36.0)], the DAFA scores were classified into three categories: extremely low DAFA, scores ≤ 16.0, intermediate scores, around the median 16.0<DAFA≤ 36.0 and extremely high scores, DAFA>36.0.

The sample calculation was performed using the WinPepi® program version 11.1914. The proportion of 50% of children with some type of knowledge about their disease was considered, with a statistical power of 90% and 5% margin of error. Therefore, the sample was estimated at 325 patients. During the study development, after the inclusion of 335 patients, it was verified that the scheduled patients had already been evaluated and there were no new inclusions in the outpatient clinic.

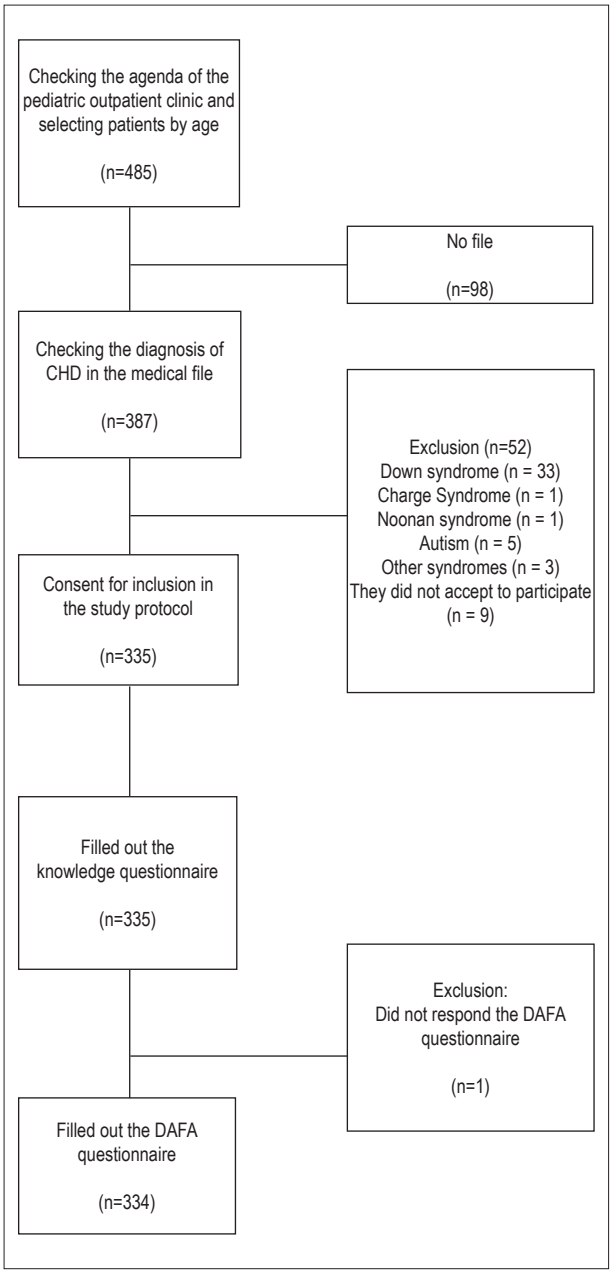

Figure 1– *Flowchart. CHD: congenital heart disease; DAFA: Typical Physical Activity and Food Intake Day.*

Statistical analysis

Categorical variables were described as absolute numbers and percentages, and the continuous variables as means and standard deviations. The Kolmogorov-Smirnov test was used in the distribution of continuous variables, where p >0.05 indicated symmetric data.

To identify the factors related to the prevalence of IN/DK knowledge, a bivariate analysis was used with Pearson's Chi-square test complemented by the measure of crude Odds Ratio (OR) effect.[15] To verify the existence of differences between knowledge about CHD at different levels of physical activity, the One-way Analysis of Variance test with Sheffé *post hoc* test was performed.

To assess the influence of the studied variables on the level of knowledge IN/DK, the Poisson regression model was used. In the composition of the model, the variables that obtained significance ≤ 0.200 in the unadjusted bivariate analysis were considered. In the adjusted analysis, the backward-stepwise method was used. Only variables associated with a p value <0.05[16] remained in the final model. A significance level of 5% was adopted for statistical decision criteria. The tests were performed with the software Statistical Package for Social Sciences 20.0 (SPSS Inc., Chicago, IL, USA, 2011) for Windows.

Results

The results presented herein are related to a sample of 335 children with CHD divided into three independent groups, according to the level of knowledge about the disease. Table 1 shows the overall sample characterization according to the classification about CHD knowledge. There was a predominance of the male gender (51.9%); age 10 years (21.2%), mean age of 10.5 ± 1.68 years; schooling between 4th and 5th grades (40.6%); acyanotic individuals with implications (55.5%); children who were hospitalized (67.2%); children not treated with surgical procedure (60%) and children practicing PA (90.1%). The DAFA instrument showed scores ranging from 2.0 to 92.0 points, with an average of 27.6 ± 14.2, median of 25.0 (1st - 3rd quartile: 16.0 - 36.0) points. Considering the PA level indicated by the instrument, it was verified through the quartiles that the low active cases had DAFA scores ≤ 16.0 points, while the highly active ones had scores ≥ 36.0 points.

Regarding the comparison of the children's profile variables in relation to the knowledge level about CHD, there was a significant difference between the age groups (p = 0.033), level of schooling (p = 0.009), CHD classification (p<0.001), hospitalization (p = 0.044), surgical procedure (p = 0.015) and PA practice (p = 0.015). There was no significant difference (p = 0.285) between the level of PA assessed by DAFA with knowledge about CHD.

According to Table 2, regarding the adjusted OR, the greatest univariate effects indicated that patients with a lower level of schooling (pre-school, 1st, 2nd and 3rd grades) were 2.20 (95% CI: 1, 81-5.86) times more likely to answer incorrectly or did not know how to answer when compared to patients with a higher level of schooling, 8th grade (p = 0.025). Regarding the classification of CHD, cyanotic patients were 2.29 (95% CI: 1.76-6.71) times more likely to answer incorrectly or did not know how to answer when compared to acyanotic patients with implications (p = 0.019). As for the practice of physical activity, patients who did not practice were 1.88 (95% CI: 1.09 3.34) times more likely to answer incorrectly or did not know how to answer when compared to patients who practiced PA (p = 0.011).

Discussion

The present study highlights the fact that most children and adolescents with CHD who participated in the interviews did not know how to say the name of their disease or explain it in their own words. Few studies have assessed the level of knowledge with the classification of heart disease or PA practice. The studies available in the scientific literature are difficult to standardize due to several methodological issues, including the absence of a validated questionnaire for children.

In a descriptive study, most adolescents (54%) did not know the name of their heart defect compared to most of their parents (78%), who in turn knew the name of their child's heart defect correctly. However, only 24% of adolescents and 30% of parents were able to correctly locate the defective lesions on a heart diagram.[17]

A study found that patients with mild CHD had more incorrect answers in a questionnaire about their disease, compared to patients with moderate CHD (p <0.001).[9] This finding differs from that found in the present study, in which cyanotic children answered incorrectly in relation to those with minimal lesions.

A possible explanation for this is that patients who belonged to the disease group with less complex malformation and with minimal hemodynamic implications, would understand and explain their disease more easily, when compared to patients with cyanotic diseases, of which explanations are more complex. In turn, specific types of CHD have been associated with significant differences in the average Intellectual Quotient (IQ).[18] Children with cyanotic disease tend to have lower average IQs than children with acyanotic CHD,[19] which was not assessed in this study.

After the implementation of a structured education program for adolescents and adults with CHD, a study found that an average total score of knowledge in the group that received educational intervention (57%) was significantly higher compared to the control group (43%) (p<0.001). However, only 24 patients (11%) in the intervention group achieved the objective proposed by the educational program. After adjusting for the patient's age, level of schooling and disease complexity, the multivariate linear regression analysis showed that the provision of structured education for CHD was an independent determinant of higher levels of knowledge (p <0.001). Therefore, adolescents and adults with a higher level of schooling and higher disease complexity were significantly correlated with greater knowledge about their disease (p <0.001).[20]

The practice of PA was associated with greater knowledge, and this may have occurred because children like to practice PA and/or parents are concerned about and questioned the limits

Table 1– Overall characterization of the sample according to the classification for knowledge

Variables	Total[A] (n=335)		Knowledge about congenital heart disease[B]						p*
			Correct / Partial (n=148)		Incorrect (n=62)		Does not know (n=125)		
	n	%	n	%	n	%	n	%	
Gender									0.367*
Male	174	51.9	77	47.8	26	16.1	58	36.0	
Female	161	48.1	71	40.8	36	20.7	67	38.5	
Age									0.033*
8	48	14.3	12	25.0	11	22.9	25	52.1	
9	60	17.9	27	45.0	9	15.0	24	40.0	
10	71	21.2	39	54.9	10	14.1	22	31.0	
11	48	14.3	20	41.7	06	12.5	22	45.8	
12	50	14.9	22	44.0	09	18.0	19	38.0	
13	58	17.3	28	48.3	17	29.3	13	22.4	
Level of schooling (year)									0.009*
Preschool, 1st, 2nd, 3rd	89	26.6	27	30.3	17	19.1	45	50.6	
4th, 5th	136	40.6	63	46.3	23	16.9	50	36.8	
6th	43	12.8	22	51.2	8	18.6	13	30.2	
7th	48	14.3	29	60.4	8	16.7	11	22.9	
8th	19	5.7	7	36.8	6	31.6	6	31.6	
CHD classification									<0.001*
ML/ASI	81	24.2	37	45.7	11	13.6	33	40.7	
AWI	186	55.5	97	52.2	27	14.5	62	33.3	
CY	68	22.7	14	20.6	24	35.3	30	44.1	
Hospitalization									0.044*
Yes	225	67.2	110	48.9	39	17.3	76	33.8	
No	110	32.8	38	34.5	23	20.9	49	44.5	
Surgical procedure									0.015*
Yes	134	40	48	35.8	24	17.9	62	46.3	
No	201	60	100	49.8	38	18.9	63	31.3	
Physical activity									0.015*
Yes	302	90.1	141	46.7	53	17.2	109	36.1	
No	33	9.9	7	21.2	10	30.3	16	48.5	
DAFA [Mean±SD]	27.6±14.2		28.9±13.8		26.1±12.8		27.6±14.2		0.285¥

*A: Percentages obtained for the total sample; B: Percentages obtained based on each category of responses; * Pearson's Chi-square test; ** Classification of CHD: Minimal lesions (ML); Acyanotic without implications (ASI); acyanotic with implications (AWI) (surgery/hemodynamics); Cyanotic (CY); ¥: Analysis of variance (One-way) - Sheffè Post-hoc test.*

of PA to the medical team. Moreover, children could also have received more information about the condition of their heart problem. Another alternative interpretation was that the children with more knowledge felt safer to practice physical activity.

In the European Society Recommendations for children with CHD, there is provision for encouraging the patient to practice PA and describing the indications and their intensities for each type of lesion.[6] Likewise, a study reports that the patient's ability to locate the heart defect on a diagram and knowledge about physical restrictions were strongly correlated with knowledge about sports, both of which were higher in male patients.[10] In contrast, another study showed that 38% of adolescents and 52% of parents knew about CHD and the endorsement to participate in competitive sports.[17]

Table 2 – Prevalence for Incorrect/Doesn't know knowledge of disease, crude and adjusted analysis on representative dependent variables in the study

Variables	Incorrect / Doesn't Know Knowledge (n=187)		*Odds ratio*[C]		*Adjusted Odds ratio*[D]	
	n	%	OR (IC95%)	p	$_{adj}$OR (IC95%)	p*
Age						
8	36	19.3	2.71(1.18 – 6.21)		2.84 (1.44-8.56)	
9	33	17.6	1.10 (0.54 –2.27)		1.22 (1.09-2.88)	
10	32	17.1	0.74 (0.37 –1.48)	0.418	0.98 (0.55-1.66)	0.068
11	28	15.0	1.26 (0.59 –2.73)		1.17 (0.89-2.67)	
12	28	15.0	1.11 (0.52 –2.37)		1.09 (0.66-1.99)	
13	30	16.0	1.0		1.0	
Level of schooling (year)						
Preschool, 1st, 2nd, 3rd	62	33.2	1.34 (0.48 – 3.77)		2.20 (1.81 – 5.86)	
4th, 5th	73	39.0	0.78 (0.25 –1.82)	0.589	2.19 (1.60 – 6.21)	0.025
6th	21	11.2	0.56 (0.18 –1.69)		1.69 (1.19 – 2.49)	
7th	19	10.2	0.38 (0.13 –1.14)		0.46 (0.14 – 1.55)	
8th	12	6.4	1.0		1.0	
CHD classification						
ML/ASI	44	23.5	1.0	0.026	1.0	
AWI	89	47.6	0.77 (0.46 – 1.30)		0.63 (0.31- 1.27)	0.019
CY	54	28.9	3.24 (1.56 – 6.75)		2.29 (1.76 - 6.71)	
Children who were hospitalized						
Yes	115	61.5	1.15 (0.92-1.49)	0.182	1.09 (0.64-1.36)	0.287
No	72	38.5	1.0		1.0	
Children treated with surgical procedure						
Yes	86	46.0	1.0	0.013	1.0	0.355
No	101	54.0	1.77 (1.13-2.78)		1.22 (0.85 – 1.87)	
Practiced physical activity						
Yes	162	86.6	1.0	0.009	1.0	0.011
No	26	13.9	2.20 (1.13-4.29)		1.88 (1.09 – 3.45)	

*C: crude odds ratio to estimate the risk of Incorrect/Doesn't know knowledge in relation to the grouped categories Incorrect/Doesn't know knowledge. D: Adjusted Odds ratio to estimate the risk of Incorrect/Doesn't know knowledge, in relation to the grouped categories Incorrect/Don't know knowledge adjusted for the variables present in the model. Classification of CHD: Minimal lesions (ML); acyanotic without implications (ASI); acyanotic with implications (AWI) (surgery/hemodynamics); Cyanotic (CY). * Pearson's Chi-square test*

Lower levels of physical exercise have been associated with an increased incidence of disabilities and diseases, including hypertension, obesity and diabetes. In contrast, high levels of physical exercise are associated with greater musculoskeletal fitness and less risk of physical disability and development of diseases.[21] However, in cases of CHD, it is important to consider that there is a lot of variability regarding the level of PA allowed according to the disease, the type of correction and the presence of sequelae. The interaction between CHD and acquired cardiovascular risk factors can have summing effects for the future. There are indications that acquired comorbidities are likely to be harmful. It is important to emphasize that the modification of knowledge, behavior and lifestyle, as well as the correct treatment, should start early with a focus on continuous cardiovascular care.[22]

The study had the possible memory bias as a limitation, which may have affected the accuracy of the answers.

Conclusion

Cyanotic children and adolescents, with a lower level of education and who did not practice physical activity, had little knowledge about their disease. It is necessary to develop educational intervention strategies to increase knowledge

and change behaviors regarding physical activity promotion, according to the CHD complexity.

Author contributions

Conception and design of the research: Campos E, Pellanda L; Acquisition of data e writing of the manuscript: Campos E; Analysis and interpretation of the data: Campos E, Perin L, Assmann M, Lucchese F, Pellanda L; Statistical analysis: Campos E, Perin L, Lucchese F, Pellanda L; Obtaining financing and critical revision of the manuscript for intellectual content: Pellanda, LC.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the ICFUC under the protocol number 5174/15. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Short Editorial

Physical Activity Knowledge and Levels among Children with Congenital Heart Disease

Adilson Marques[1,2] *and Bruna Gouveia*[3,4]

CIPER, Faculdade de Motricidade Humana, Universidade de Lisboa,[1] *Lisboa - Portugal*
ISAMB, Faculdade de Medicina, Universidade de Lisboa,[2] *Lisboa - Portugal*
Instituto de Administração da Saúde, IP-RAM,[3] *Ilha da Madeira - Portugal*
Interactive Technologies Institute, LARSyS,[4] *Lisboa – Portugal*

Short editorial related to the article: Knowledge about the Disease and the Practice of Physical Activity in Children and Adolescents with Congenital Heart Disease

The benefits of physical activity are well documented. Among children and adolescents, physical activity improves cardiovascular, bone and metabolic health, fitness levels, weight status, and sleep.[1] Also, there is evidence of the cognitive, psychological and social benefits of physical activity.[1] The health benefits of physical activity are transversal to all children, including those living with a chronic disease, such as congenital heart disease (CHD), preventing comorbidities, while improving quality of life.[2,3]

The importance of physical activity for children with CHD has been documented for a long time.[4] Engagement in physical activity is of high importance for children with CHD because they are at risk of developing other cardiovascular and metabolic diseases,[3,5] increasing signs of depression and anxiety.[6] In addition, when present, these health problems can be mitigated by an active lifestyle.[1-3]

Although the health benefits of physical activity are well recognized, evidence shows that some children with CHD do not practice enough physical activity to achieve the recommended levels,[7] and activity declines and sedentary behaviors increase with age in both genders.[5] Furthermore, levels of physical activity of children with CHD are lower than those in healthy children.[8] Therefore, it is important to identify the factors associated with lower levels of physical activity.

Despite the importance of physical activity for the health of children with CHD, physical activity is not considered a target value.[9] Because most parents put their attention on academic achievement towards a desired career, physical activity seems to be less important. Thus, the available time is used for schoolwork. Additionally, parents think that physical activity is not meaningful in comparison to the broad range of other activities that are available for children with CHD.[9] For several parents, physical activity has a limited role in the rehabilitation process, so they tend to overprotect their children against some physical activity practices.[9,10] Besides that, it is assumed that children with CHD are responsible for engaging in risk-reducing behaviors, and physical activity is considered a potential risk for some people. These conceptions contribute to the individualist discourses of healthism,[10] and children and parents assume that physical activity might be important, but it is not so important since it can jeopardize the academic achievement or the health status. In light of these beliefs, it would be interesting to analyze the knowledge of children with CHD about physical activity.

Campos et al.[11] performed a study aimed at identifying the levels of knowledge of children and adolescents with CHD about their disease and to analyze the association between the levels of knowledge and the practice of physical activity. It is an interesting study performed in a carefully selected sample of children and adolescents with CHD. Data were self-reported, but for this particular study, self-report was the most appropriate method for assessing the children's and the adolescents' physical activity knowledge and levels. From the results, it was observed that many children and adolescents had difficulties describing their disease. Almost half of the children and adolescents did not know the name of their heart defect, and only 24% correctly located the lesions on a heart diagram. These results should be a matter of concern because, without the correct knowledge of the health problem, many counterproductive actions can be taken. Regarding the physical activity, the most active children and adolescents showed greater knowledge about the disease. The study design did not allow an understanding of the association between knowledge and physical activity practice. Nonetheless, the authors provide some potential and reasonable explanations. Perhaps, the parents of children or adolescents who enjoy physical activity are concerned about the effects of physical activity on their children's health. For this reason, they consult doctors for more information about physical activity and CHD. As a result, by questioning the limitations of physical activity, parents and children or adolescents get more information about the disease and understand the health effects of physical activity. Consequently, children and adolescents with more knowledge feel safer to engage in physical activity regularly. The results of the association between knowledge and physical activity levels are partly supported by previous investigations.[12] It is clear that knowledge is important and supports the decision-making process.

Models of communication and changing behaviors suggest that knowledge about a behavior plays a significant role in persuading people to change their habits, and knowledge is

Keywords

Heart Defects, Congenital; Comorbidity; Children; Adolescents; Exercise/ Physical Activity; Knowledge; Physical Conditioning; Quality of Life

Mailing Address: Adilson Marques •
Universidade de Lisboa Faculdade de Motricidade Humana - Estrada da Costa Cruz Quebrada -- Please Select (only U.S. / Can / Aus) 1499-002 – Portugal
E-mail: amarques@fmh.ulisboa.pt

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required for people to make health decisions.[13] Therefore, it can be conjectured that knowledge of physical activity guidelines can be a step towards behavioral change, with respect to adopting and/or maintaining an active lifestyle. Studies have supported this assumption, showing that knowledge of health-related physical activity is linked with increased physical activity among children, adolescents, and young adults.[14] The results of the present study,[11] and other previously performed studies,[12,14] highlight the importance of educational programs to increase knowledge about health. Providing the physical activity recommendation message, especially among young people, might increase the physical activity levels.

However, research developed in a variety of patients[15] suggests that providing knowledge, materials and professional support is not sufficient for patients to accomplish changes regarding healthy behaviors. Therefore, alternative strategies should be considered. Strategies based on self-monitoring of behaviors, risk communication and the use of social support seem to be the most effective for behavioral changes.

Present evidence suggest that physical activity recommendations for children with CHD have been widely implemented and medical doctors' and health professionals' advice have been given regarding the potential health benefits of physical activity for people with CHD, including children. Moreover, and perhaps the most important, this also means that the message of the importance of physical activity[3] has been well accepted. This is important because, among children with CHD, physical activity is not related to an increased risk of adverse events, and particular restrictions only apply to situations with specific medical issues.[3]

For children and adolescents with CHD, physical activity is even more important due to the decreased levels of physical fitness that often occur because of the time they might have to spend at the hospital. Physical activity, mainly from moderate to vigorous intensity, is independently associated with better quality of life, improved physical fitness, and better body composition in children with CHD.[1-3]

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Original Article

HEART, TIMI, and GRACE Scores for Prediction of 30-Day Major Adverse Cardiovascular Events in the Era of High-Sensitivity Troponin

Felipe Torralba,[1] Alberto Navarro,[1] Juan Castellanos-de la Hoz,[1] Carlos Ortiz,[1] Alberth Botero,[1] Freddy Alarcón,[1] Nicolas Isaza,[1] Daniel Isaza[1]

Fundacion Cardioinfantil Instituto de Cardiologia,[1] Bogota Cundinamarca – Colombia

Abstract

Background: Multiple scoring systems have been designed to calculate the risk of major adverse cardiovascular events (MACE) in patients with chest pain. There is no data on whether the HEART score outperforms TIMI and GRACE in the prediction of MACE, especially in the era of high-sensitivity troponin assay and in an exclusively Latin-American population.

Objective: To compare the performance of the HEART, TIMI, and GRACE scores for predicting major cardiovascular events at 30 days of follow-up, in patients who consult for chest pain in the emergency department.

Methods: HEART, TIMI, and GRACE scores were analyzed in 519 patients with chest pain at the emergency department. The primary endpoint was the occurrence of MACE within 30 days. The performance of the HEART score was compared with the TIMI and GRACE scores using the DeLong test with p values of 0.05 considered statistically significant.

Results: A total of 224 patients (43%) had MACE at 30 days. The C statistic for the HEART, TIMI, and GRACE score was 0.937, 0.844, and 0.797 respectively ($p < 0.0001$). A HEART score of 3 or less had a sensitivity of 99.5% and a negative predictive value of 99% to classify low risk patients correctly; both values were higher than those obtained by the other scores.

Conclusion: The HEART score more effectively predicts cardiovascular events at 30 days of follow-up compared to the other scores. High-sensitivity troponins maintain this score's previously demonstrated superiority. This score offers more precise identification of low-risk patients. (Arq Bras Cardiol. 2020; 114(5):795-802)

Keywords: Cardiovascular Diseases/mortality; Chest Pain; Myocardial Infarction; Forecasting Risk Assessment; Risk Factors; Troponin; Myocardial Ischemia.

Introduction

Chest pain is one of the most common complaints in patients presenting to the emergency department, with approximately 15 million patient visits in the United States and Europe.[1] It is estimated that 55% of these patients have a non-cardiac cause for chest pain and only one fifth are definitively diagnosed with acute coronary syndromes.[1,2] Approximately 85% of patients with chest pain are admitted, in spite of the fact that up to 60% of cases could be managed in the outpatient setting.[3]

In Colombia, cardiovascular diseases are also a cause of high mortality; among these, ischemic heart disease was the main cause in the previous decade, accounting for 49.5% of the total in this group.[4,5] The annual cost of treatment for patients with chest pain of non-cardiac cause can be as high as 8 billion dollars in the USA and approximately 3.9 billion dollars in Colombia.[6] These expenses originate primarily from daily bed costs and radiological and laboratory studies.[2,7,8] This significant economic impact has driven efforts to develop alternatives that enable more efficient use of resources, particularly in countries with limited health budgets.[3,8,9]

The development of a tool to accurately determine the risk of major adverse cardiovascular events (MACE) in these patients is essential, and scoring systems such as TIMI and GRACE have been designed to address this problem.[10,11] More recently, the HEART score was created, being the first one prospectively designed to predict MACE.[12-14]

The HEART score has outperformed the TIMI and GRACE scores in Asian, European, and North American populations.[11,15] This study aimed to compare the accuracy of these scores for predicting MACE in a group of Latin-American patients with chest pain who presented to a cardiovascular reference center. To the best of our knowledge, this is the first prospective study of this nature.

Methods

This is a prospective observational study of diagnostic tests carried out in the Fundación Cardioinfantil, located in Bogotá, Colombia. It is a high-complexity hospital specialized

Mailing Address: Felipe Torralba •
Fundacion Cardioinfantil Instituto de Cardiologia - ak19#128b66 402
Bogota, Cundinamarca, 111121 – Colombia
E-mail: feliptorr1@gmail.com
Manuscript received March 22, 2019, revised manuscript June 02, 2019, accepted July 17, 2019

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in cardiovascular medicine, with a monthly average of 9,000 emergency consultations, 15% of which correspond to cardiovascular emergencies.

Patients over 18 years of age who presented at the emergency department with acute chest pain between August 2017 and February 2018 were included in the study. According to the institutional protocol, patients were evaluated by the cardiologist; electrocardiography was performed, and high sensitivity troponin I (hsTnI) was measured, initially and 3 hours later if needed, using ARCHITECT STAT assay (Abbot, Lake Bluff, IL, USA).

Acute myocardial infarction (AMI) was diagnosed when hsTnI values were greater than 0.026 ng/mL (reference value 0.0 – 0.026 ng/ml). In this case, patients were admitted for in-hospital care, coronary arteriography, and either percutaneous or surgical revascularization. When values were negative, but pain was considered of intermediate or high probability, the patients were admitted for further evaluation with a non-invasive stratification strategy.

Patients with myocardial infarction with ST elevation and non-cardiac causes of chest pain, such as pneumonia, trauma, or psychogenic pain, were excluded from this study.

The HEART, TIMI, and GRACE risk scores were calculated for this group of patients at the time of consultation.

Risk Scores

The methods for calculating the GRACE, TIMI, and HEART scores have been described in previous articles and are briefly summarized below.[14,16,17] The score calculations were performed using the information documented in the electronic medical record, the first electrocardiogram upon presentation, and the first laboratory values measured, including troponin measurement with the hsTnI assay.

The HEART score consists of the following 5 categorical variables: the patient's medical history, electrocardiogram, age, risk factors for coronary heart disease, and troponin. Each variable has a maximum value of 2 points adding up to a maximum score of 10, which indicates a patient with maximum risk. The GRACE score consists of the following 5 categorical variables: age, heart rate, blood pressure, creatinine, and Killip class; and the following 3 nominal variables: cardiac arrest, ST-segment deviation, and troponin elevation. Each item is assigned a value, and the sum of these values determines the risk of MACE. Finally, the TIMI score consists of the following 7 dichotomous nominal variables: age over 65 years, more than 3 risk factors for coronary artery disease, significant coronary artery stenosis, symptoms of severe angina, ST-segment deviation, use of aspirin in the last week, and elevation of troponin. The maximum TIMI score is 7, with higher scores indicating higher risks.

Ethics

The study was carried out in accordance with the principles laid out in the Declaration of Helsinki of the World Medical Association, the Nuremberg Code, and the World Health Organization International Ethical Guidelines for research involving humans, as well as domestic regulations related to basic health care. The study received approval from the ethics and research committee of the Fundación Cardioinfantil, and the patients included in the study provided their informed consent.

Data management

The data included demographic information of the patients, as well as information on clinical history, laboratory values, electrocardiographic findings, and vital signs.

Laboratory values included creatinine and hsTnI, which are the assays currently applied in the institutional protocol.

The attending cardiologist evaluated the 12-lead electrocardiogram according to the guidelines of the American Heart Association.[18] If necessary, the exam was submitted to a second blinded attending cardiologist for evaluation.

An encrypted database was created to which only the authors of the study had access, and an algorithm was developed for the automatic calculation of the risk scores.

Follow-up

Follow-up was performed at 30 days, reviewing the electronic medical record and employing a telephone survey. A structured format was applied with 4 clear questions regarding the occurrence of major cardiovascular events (death, myocardial infarction, surgical revascularization, or percutaneous revascularization), to determine the presence of the primary outcome.

Outcomes

The diagnosis of AMI was made when troponin values rose above the 99th percentile of reference values (hsTnI > 0.026 ng/mL), and evidence of myocardial ischemia was documented on electrocardiogram. We applied the criteria described by the third universal definition of AMI, which was valid at the time the protocol was written.[19] We also defined ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), and signs of ischemia according to the guidelines validated at the time of protocol design.[20]

Percutaneous revascularization was defined as any intervention through a catheter in the coronary arteries, and surgical revascularization was defined as any cardiac surgery in which coronary artery grafts were made. MACE were defined as death from any cause, myocardial infarction, and surgical or percutaneous myocardial revascularization. Follow up was completed 30 days after admission to the emergency department.

Statistical analysis

We calculated a sample of 550 patients, to obtain 185 MACE using Simel and Samsa's method of maximum sensitivity,[21] in order to yield a power of 80% and a confidence interval of 95% with an alpha error of 5%. For each score, the best cutoff point was calculated using the Youden index,[22] considering p values of 0.05 significant. Subsequently, the C statistic, the positive and negative likelihood ratio (LR), sensitivity, and specificity were calculated. Then, the LR was calculated for each risk stratum. The difference between LR was calculated using the test for adequate binomial proportions (Chi-square test and Fisher's exact test), considering p values of 0.05 significant.

The area under the curve for each test was calculated and compared using the nonparametric DeLong test ($p = 0.05$), and, finally, a calibration test was also made for each score to compare expected and actual major cardiovascular events in the study population, according to the calibration belt method described by Finazzi S, et al.[23] from the Italian Group for the Evaluation of Interventions in Intensive Care Medicine (GiViTi).[23]

Analysis was carried out using the statistical program R, version 3.3.3 (the R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients were recruited between August 2017 and February 2018. The present study's patient flow is shown in Figure 1.

A total of 519 patients were included in the analysis, with a follow-up period of 30 days. Baseline patient characteristics are shown in Table 1. MACE were confirmed in 224 patients within the first 30 days of follow-up, with a total of 351 events (AMI, revascularization, or death). These account for a MACE incidence of 43% and an average of 1.56 MACE per patient with the primary outcome. NSTEMI was diagnosed in 194 patients. Of these patients, 108 underwent percutaneous revascularization; 46 underwent surgical revascularization, and 3 died.

HEART, GRACE, and TIMI score comparison

Risk stratification for each score is shown in Table 2. Based on the HEART score, patients in the low, intermediate, and high risk groups had 3.1%, 46.2%, and 93.7% incidence of MACE, respectively. The MACE rate in the low-risk group calculated according to the HEART score was lower than that of the low-risk groups calculated by the other two scores.

A HEART score ≤ 3 had a sensitivity of 99.5% and a negative predictive value (NPV) of 99% to predict MACE in the low risk category (Table 3). Both parameters were higher than those obtained with the other scores for the low risk MACE group (TIMI: sensitivity 90%, NPV 89.9%; GRACE: sensitivity 70%, NPV 77.8%).

The ROC curves for each score are shown in Figure 2. The C statistic for the HEART score was 0.937, which was higher than the other two scores, and a statistically significant difference was found using the nonparametric DeLong test ($p < 0.0001$).

Finally, the GiViTi calibration belt test was used to compare expected and observed results (Figure 3), showing adequate calibration of the HEART score for patients with low MACE risk.[20]

Discussion

We found that the HEART score for patients with chest pain is a reliable tool for predicting major cardiovascular outcomes based on the patients' description of symptoms, clinical record data, electrocardiographic findings, and initial hsTnI value. It is readily applicable; it does not require computerized calculations, and it has been validated by international multicenter studies in multiple populations.[10,11,14,15]

Conversely, the GRACE score is a model for predicting mortality in patients with acute coronary syndrome that has been adequately validated, but the fact that it must be calculated electronically limits its applicability.[17] Similarly, the TIMI score was designed to determine the need for aggressive therapy in patients with acute coronary syndrome, allowing the calculation of risk through the use of dichotomous variables without weighing the variables or taking patient's clinical presentation into account.[16]

The results of this study are favorable for the HEART score, with a C statistic value of 0.93, which indicates an excellent ability to predict the risk of patients with chest pain, compared to the TIMI and GRACE scores. This is consistent with what was previously reported by Six et al.,[10] Sakamoto et al.,[11] Backus et al.,[15] and confirming that low scores on the HEART[24] scale are very accurate for ruling out the occurrence of MACE in low-risk patients with a 30-day follow up.[10,11,15,24]

Our study had a MACE incidence of 43%, which is higher than the 13% and 36% reported in the literature.[11,15] This high rate of MACE might be due to the institution's distinction as a referral center for cardiovascular disease, which leads to a higher than average number of patients with intermediate and high risks of coronary heart disease. Additionally, the exclusive use of hsTnI during this study might explain a higher rate of MACE detection than previously reported. However, despite higher rates of MACE, irrespective of risk status, the HEART score maintained its predictive precision, outperforming both the TIMI and GRACE scores.

With regards to the sensitivity and the NPV of the tests, we found that the C statistic was higher for the HEART score when using a cutoff of 3 points, which is the limit for the low-risk category. Both the sensitivity and NPV are close to 100%, and they are significantly higher than the sensitivity and NPV of the other two scores. Based on these results it can be concluded that a HEART score below 3 identifies patients that can safely be managed with a conservative strategy with high certainty, given that the risk of adverse cardiovascular outcomes is low.

Additionally, according to the GiViTi belt method, it is observed that there is adequate calibration between expected and observed outcomes for the low-risk group in the HEART score, as opposed to the low-risk groups in the two other scores analyzed. This supports the potential use of the HEART score as a first line score to stratify risk in patients with chest pain of suspected cardiac origin. Additionally, given its ease of application and adequate validation, it can be a valuable tool to enhance decision making and proper distribution of resources. This has been demonstrated by Mahler et al.,[12] with the use of the "HEART pathway," which combines the application of this score with troponin testing upon presentation and 3 hours later. This pathway led to a significant reduction of unnecessary tests and a shorter total hospital stay.[12,25]

To the best of our knowledge, no other studies have reported the performance of risk scores conducted in the era of hsTnI in an exclusively Latin-American population. The prospective nature of the study strengthens the findings. Therefore, these results serve as a validation of previous findings regarding the HEART score, and they should motivate further multicentric projects with larger populations. Also, we believe that these results should expand the use of the HEART score as a valuable tool that aims to facilitate decision making in a challenging patient population.

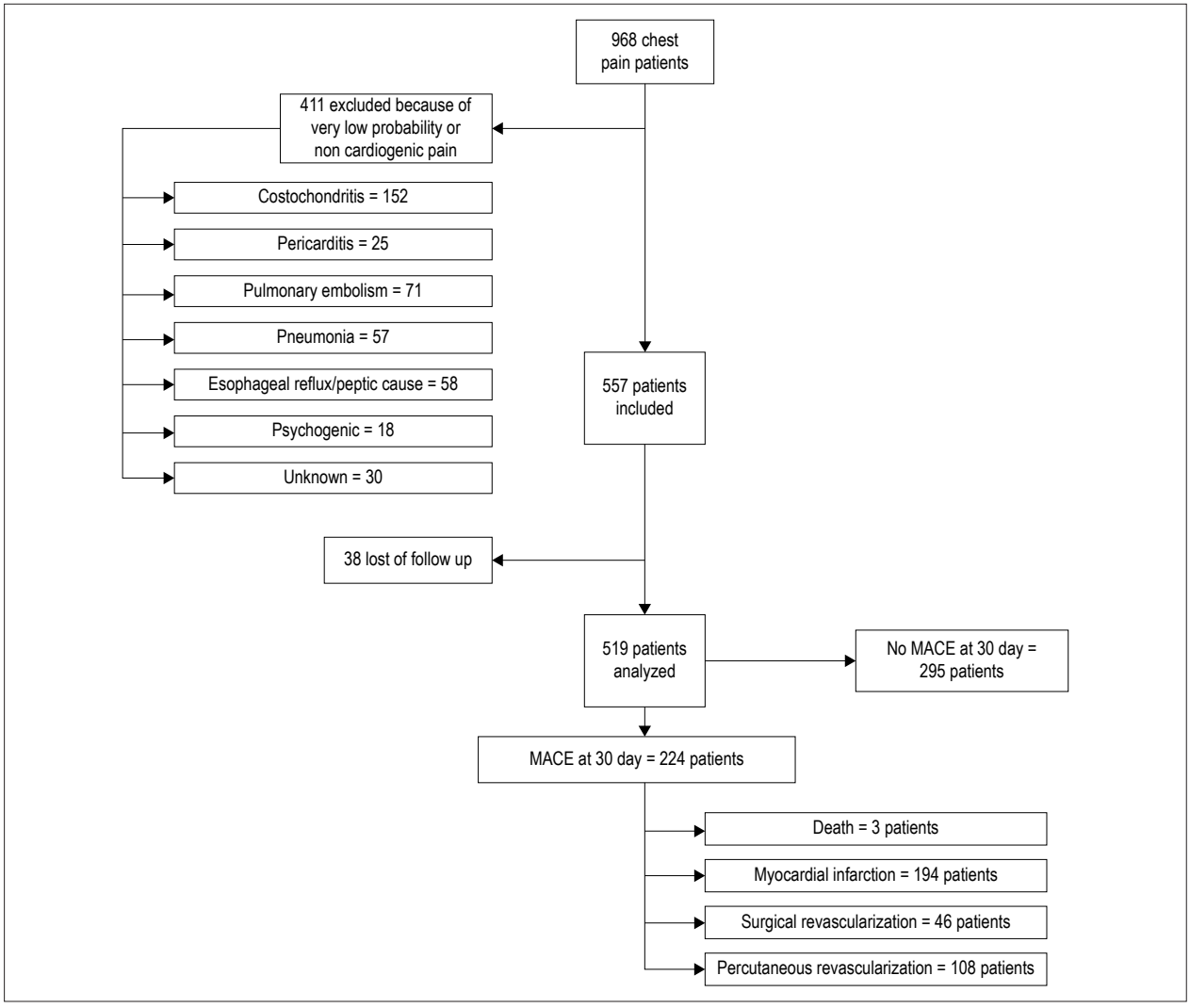

Figure 1 – *Patients of the study.*

Limitations

The TIMI and GRACE score were developed as tools to quantify risk in patients with an established diagnosis of acute coronary syndrome, whereas the HEART score was designed to assess patients with chest pain. However, despite the difference in their initial objective, in real-world clinical practice they have been used interchangeably. Furthermore, previous studies have compared the scores for risk assessment of chest pain in emergency settings.

This research protocol was carried out in a single specialized center, which may not accurately reflect the behavior of other populations in centers with different levels of complexity or in different regions or countries. Therefore, new studies with larger, multicentric populations will be required in the future to enhance the applicability of these findings.

Although the sample size was smaller than initially calculated, the fact that a greater number of MACE (n = 224) was obtained in the analyzed group of 519 patients made it possible to calculate an adequate power greater than 80%.

Additionally, different factors may affect score applicability, as patients may not always provide accurate clinical history, and therefore risk factors may not be adequately reported. Electrocardiographic changes and troponin elevations may be non-significant in the early stages of myocardial infarction, or they may be falsely elevated by other disorders such as chronic kidney disease, heart failure, arrhythmias, tachycardia, and sepsis, among others.

Finally, the follow-up information is based on the data provided by patients and their family members, which could limit the reliability of the data. Although the information is based on a structured format with 4 clear questions, it may be subject to misinterpretation.

Conclusions

We found that the HEART score was more effective in predicting MACE at 30 days of follow up compared to the TIMI and GRACE scores in the era of hsTnI in an exclusively Latin-American population with chest pain of suspected cardiac origin at a high complexity cardiovascular center.

Table 1 – Population characteristics of patients with and without cardiovascular events at 30 days

	Population (n = 519)	MACE (n = 224)	No MACE (n = 295)
Average age (%)	64.31 (12.11%)	66.9 (11.69%)	62.3 (13.7%)
Male sex, n (%)	291 (56.06%)	207 (59.5%)	84 (40.5%)
Without cardiovascular risk factors (BMI > 30, smoker, DM2, family coronary artery disease, age < 55 years, hypertension, hypercholesterolemia)	64 (12.3%)	40 (40%)	24 (60%)
1 – 2 risk factors	348 (67%)	247 (70.97%)	101 (29.02%)
3 or more risk factors	98 (18.8%)	74 (75.5%)	24 (24.5%)
Previous coronary heart disease as the only factor	84 (16.1%)	61 (72.6%)	23 (27.3%)

BMI: body mass index; DM2: diabetes mellitus type 2.

Table 2 – Occurrence of MACE (AMI, percutaneous revascularization, surgical revascularization, or death) according to risk groups

HEART score	Patients (n)	MACE (n)	MACE (%)
Low (0 - 3)	194	6	3.1
Intermediate (4 – 6)	182	84	46.2
High (7 – 10)	143	134	93.7
TIMI score			
Low (1 – 2)	336	21	10.1
Intermediate (3 – 4)	130	119	55.6
High (5 – 7)	53	84	86.6
GRACE score			
Low (< 88)	183	65	22.2
Intermediate (89 – 118)	165	88	60.7
High (> 118)	171	71	87.7

** Total MACE = 351. † MACE per patient: 351 MACE / 224 patients = 1.56 MACE / patient.*

Table 3 – Operative characteristics for the HEART, TIMI, and GRACE scores

	HEART score ≤ 3 (CI 95%)	TIMI score ≤ 2 (CI 95%)	GRACE score ≤ 108 (CI 95%)
SENS	99.5% (97 – 99.9)	90% (86 - 94)	70.9% (64.5 – 76.8)
SPEC	36.6% (31.1 – 42.4)	63% (57.5 – 68.8)	77.2% (72 – 81.9)
NPV	99% (95 - 99)	89.9% (85 – 91.9)	77.8% (72.3 – 82.3)
PPV	54% (48 - 97)	65.2% (59.6 – 75.6)	70.3% (64 - 76)
LR (+)	1.57 (1.4 – 1.7)	2.47 (2.1 – 2.8)	3.125 (2.4 – 3.9)
LR (−)	0.012 (0.001 – 0.08)	0.147 (0.09 – 0.22)	0.375 (0.3 – 0.4)

** SENS: sensitivity; SPEC: specificity; NPV: negative predictive value; PPV: positive predictive value; LR: likelihood ratio.*

The use of hsTnI maintained the previously demonstrated superior performance of the HEART score compared to the TIMI and GRACE scores.

The HEART score allows for more accurate differentiation of patients with low risks of presenting major cardiovascular events, which will enable physicians to opt for earlier discharge and which may allow savings in hours of in-hospital stay and unnecessary diagnostic tests. This could lead to better care for patients and more efficient distribution of healthcare system resources.

Author contributions

Conception and design of the research: Torralba F, Navarro A, Ortiz C; Acquisition of data: Torralba F, Navarro A, Botero A, Alarcón F; Analysis and interpretation of the data: Torralba F, Castellanos JC, Botero A, Alarcón F, Isaza N, Isaza D;

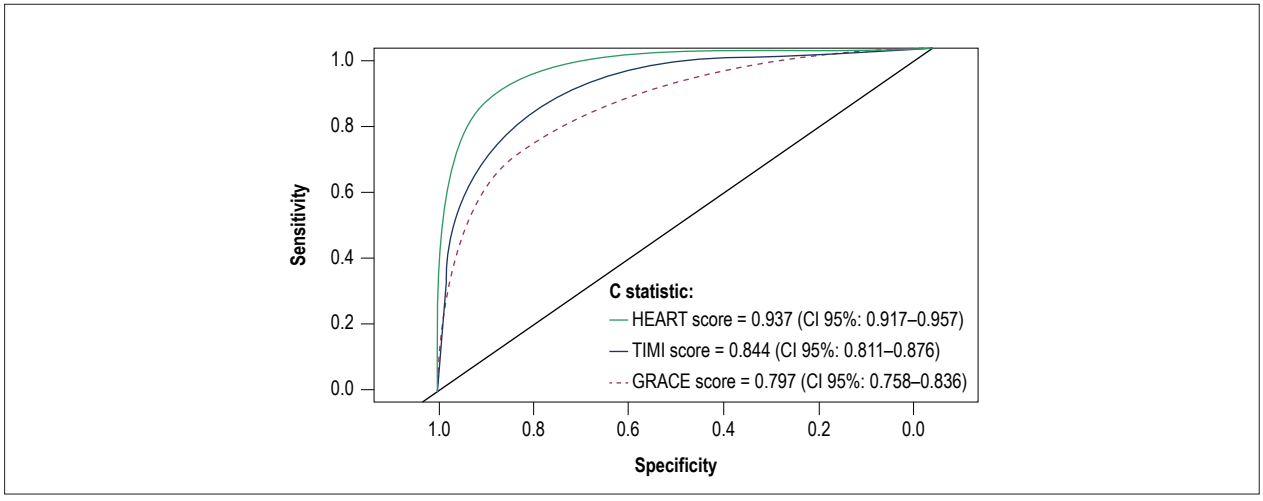

Figure 2 – *ROC curves for the HEART, TIMI and GRACE scores.*

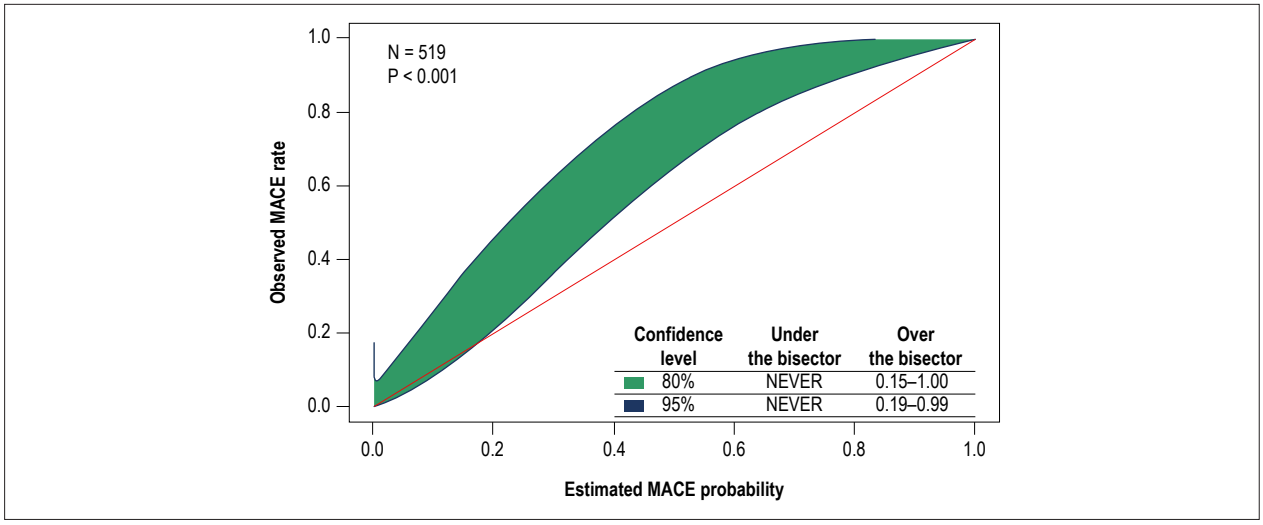

Figure 3 – *Calibration belt test for HEART score*

Statistical analysis: Castellanos JC; Writing of the manuscript: Torralba F, Navarro A, Ortiz C, Isaza N, Isaza D; Critical revision of the manuscript for intellectual content: Torralba F, Navarro A, Castellanos JC, Ortiz C, Isaza N, Isaza D.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Fundación Cardioinfantil under the protocol number 20-2017. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Comparison of HEART, TIMI and GRACE Scores for Predicting Major Adverse Cardiovascular Events in the Era of High-Sensitivity Assay for Troponin I

Gabriel Porto Soares[1,2,3]

Universidade Federal do Rio de Janeiro (UFRJ),[1] *Rio de Janeiro, RJ – Brazil*

Universidade de Vassouras,[2] *Vassouras, RJ – Brazil*

Centro Universitário de Valença (UNIFAA),[3] *Valença, RJ – Brazil*

Short Editorial related to the article: HEART, TIMI, and GRACE Scores for Prediction of 30-Day Major Adverse Cardiovascular Events in the Era of High-Sensitivity Troponin

Diseases of the circulatory system predominate as the leading cause of death in the world; among cardiovascular diseases, ischemic heart diseases are the first group of causes. Ischemic heart disease (IHD) is the leading global cause of death, accounting for more than 9 million deaths in 2016, according to estimates from the World Health Organization (WHO).[1] Mortality from IHD in Western countries has decreased dramatically over the past few decades, with a greater focus on primary prevention and better diagnosis and treatment of IHD. However, developing countries present new challenges for public health[2] — this scenario is reproduced in Latin America. In this study,[3] carried out in Colombia, the mortality rate from IHD was 150 deaths per 100,000 inhabitants in 2015, representing the main cause of deaths in that country.[4]

Developing scores capable of predicting death from the diseases responsible for the largest share of deaths in the world has always been among the objectives of cardiologists. The question "How likely is this patient with acute IHD to die?" is made, whether consciously or not, every time there is a diagnostic possibility of acute myocardial infarction (AMI) with or without ST-segment elevation or unstable angina.

The search for variables capable of predicting deaths or unfavorable outcomes — assigning mathematical models of probability in the short or medium term to these set of variables — has led to the development of scores, with more organization and reliability in the early 2000s. It started with TIMI (Thrombolysis In Myocardial Infarction Risk Score), for prognosis and therapeutic decision in patients with unstable angina and AMI without ST-segment elevation.[5] Then, the GRACE score (Global Registry of Acute Coronary Events), as a predictor of hospital mortality in patients with acute coronary syndromes. The third score used in this comparison was developed in the Netherlands in 2007 and consists of five variables, forming the HEART mnemonic (**h**istory, **E**CG, **A**GE, **r**isk factors and **t**roponin).

Keywords

Acute Coronary Syndrome; Propensity Score; Probability; Risk Factors; Case-Control Studies; Troponin/adverse effects.

Mailing Address: Gabriel Porto Soares •
Praça Sebastião de Lacerda, 15. Postal Code 27700-000, Centro, Vassouras, RJ - Brazil
E-mail: gp.soares@yahoo.com.br

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Below, in Table 1, the variables and predictions of the three types of scores are compared. Note that three variables are common among them: age, electrocardiographic abnormality and the presence of positivity in myocardial necrosis markers, especially troponin I. This demonstrates that these three variables are independent indicators of mortality and unfavorable outcomes in any type of acute coronary syndrome. The GRACE score does not take into account the presence of risk factors or clinical history data, but, among the three, it is the one that contains the greatest number of hemodynamic variables: systolic pressure, heart rate and Killip classification. One variable of the TIMI score must be incomplete in most cases, as it assesses the presence of previous coronary stenosis; therefore, previous coronary angiography scan is required. TIMI is the only one that also considers any use of previous antiplatelet therapy. In the GRACE score, the variable "creatinine" may be missing in the initial evaluation in the emergency room, as it will depend on the timing of this scan.

The three scores were constructed to predict death at different intervals — 14 days at TIMI; hospital death and in 1 year at GRACE; in 6 weeks for HEART. It is worth mentioning that, in the comparative study by Torralba et al.,[3] the interval of outcome evaluation was 30 days. Another point to be criticized is that, in the GRACE score, the predicted outcome is death and, in such study, the outcomes death, AMI, surgical or percutaneous coronary artery bypass grafting for the three scores were analyzed, probably reducing the sensitivity of the GRACE score, as outcomes not included in the mathematical predictive model of the score were analyzed. Several authors have compared different predictive scores for acute coronary disease, demonstrating superior performance of the HEART[8-10] score compared to the other scores.

In the HEART score, it is easier to obtain the variables, as these are objective and present at the patient's first appointment; scoring of 0 to 2 to each of the variables is simpler and does not require any calculators or apps. These facts certainly contribute to the better performance in high-sensitivity prediction of major cardiac events compared to TIMI and GRACE. We must still consider that the performance of the three scores was quite satisfactory for predicting events, since even GRACE, which proved to be the least sensitive one, was the one with the best specificity compared to the other two.

All scores play their role when well performed, well applied and well interpreted — noting that they are mathematical values capable of making extrapolated predictions for population groups and do not substitute the individualized assessment of each patient with acute coronary syndrome.

Table 1 – Comparison of variables and predictions of outcomes of the TIMI, GRACE and HEART scores

Risk Scores		
TIMI	**GRACE**	**HEART**
Age	Age	Age
ST deviation	ST deviation	ECG: ST deviation — nonspecific disorder, repolarization or LBBB — normal
+ markers	+ markers	Troponin 3 ×, 1 to 3 ×, normal
Risk factors < 3 or > 3		RF > 3 or atherosclerosis, 1 or 2 RF, without RF
Chest pain in 24 hours		Clinical history
	Heart rate	
	Systolic blood pressure	
	Killip	
Coronary stenosis >50%		
Acetylsalicylic acid: 7 days		
	Creatinine	
	Cardiac arrest	
Prediction of Outcomes		
TIMI	**GRACE**	**HEART**
14-day prediction: death, reinfarction, emergency coronary artery bypass grafting	Prediction of mortality at admission and for 1 year	Prediction for 6 weeks of death, surgical or percutaneous coronary artery bypass grafting and AMI

ECG: electrocardiography; LBBB: left bundle branch block; RF: risk factor; AMI: acute myocardial infarction.

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Review Article

The Heart and COVID-19: What Cardiologists Need to Know

Isabela Bispo Santos da Silva Costa,[1,2] Cristina Salvadori Bittar,[1,2] Stephanie Itala Rizk,[1,2] Antônio Everaldo de Araújo Filho,[1] Karen Alcântara Queiroz Santos,[1] Theuran Inahja Vicente Machado,[1] Fernanda Thereza de Almeida Andrade,[1] Thalita Barbosa González,[1] Andrea Nataly Galarza Arévalo,[1] Juliano Pinheiro de Almeida,[1] Fernando Bacal,[2] Gláucia Maria Moraes de Oliveira,[3] Marcus Vinícius Guimarães de Lacerda,[4] Silvio Henrique Barberato,[5,6] Antonio Carlos Palandri Chagas,[2,7] Carlos Eduardo Rochitte,[2,8] José Antonio Franchini Ramires,[2] Roberto Kalil Filho,[2] Ludhmila Abrahão Hajjar[1,2]

Universidade de São Paulo - Instituto do Câncer do Estado de São Paulo,[1] São Paulo, SP - Brazil

Universidade de São Paulo Instituto do Coração,[2] São Paulo, SP - Brazil

Universidade Federal do Rio de Janeiro – Cardiologia,[3] Rio de Janeiro, RJ - Brazil

Fundação de Medicina Tropical Doutor Heitor Vieira Dourado,[4] Manaus, AM - Brazil

CardioEco Centro de Diagnóstico Cardiovascular,[5] Curitiba, PR - Brazil

Quanta Diagnóstico – Ecocardiografia,[6] Curitiba, PR - Brazil

Faculdade de Medicina da Fundação do ABC,[7] Santo André, SP - Brazil

Hospital do Coração,[8] São Paulo, SP – Brazil

Abstract

In face of the pandemic of the novel coronavirus disease 2019 (COVID-19), the management of patients with cardiovascular risk factors and/or disease is challenging. The cardiovascular complications evidenced in patients with COVID-19 derive from several mechanisms, ranging from direct viral injury to complications secondary to the inflammatory and thrombotic responses to the infection. The proper care of patients with COVID-19 requires special attention to the cardiovascular system aimed at better outcomes.

Introduction

Currently the world faces the pandemic of the novel coronavirus disease 2019 (COVID-19), which emerged in December 2019 in the city of Wuhan, province of Hubei, in China.[1,2] The initial cases were described as pneumonia that rapidly progressed to acute respiratory distress syndrome (ARDS).

This novel virus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is the seventh coronavirus identified so far and differs from the other coronaviruses that cause common cold and mild pneumonia (229E, OC43, NL63 and HKU1). The SARS-CoV-2 is similar to the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV), responsible for the infections occurring in China in 2002-2003 and in the Middle East in 2012, respectively.[1,2] Despite the phylogenetic similarities between SARS-CoV-2 and the zoonotic coronaviruses that caused SARS and MERS, the SARS-CoV-2 spread is much higher, contributing to an infection dissemination ten times faster than that of the SARS-CoV.[2-4] The basic reproduction number (R0) of COVID-19 is 2.78, meaning that, on average, each individual infected can transmit the disease to three others.[5] A study recently published in *Science* has stated, by use of a mathematical model, that 85% of the COVID-19 transmissions occur from asymptomatic individuals.[6]

Because of its fast dissemination, COVID-19 was declared a pandemic by the World Health Organization (WHO) on March 11, 2020.[4] At the current time, COVID-19 affects more than 181 countries and the number of cases keeps increasing exponentially. Up to April 2, 2020, 1,015,403 cases and 53,030 deaths had been registered around the world, yielding a lethality of 5.2%. Up to that same date, 8,044 confirmed cases and 324 deaths had been registered in Brazil, with a mortality of 4%. Initial Brazilian data have shown 90% of the deaths occurring among individuals aged over 60 years and 84% of the patients with at least one comorbidity, 51% with cardiovascular disease (CVD) and 37.7% with diabetes.[7]

The analysis of 44,672 confirmed cases of COVID-19 in Wuhan has evidenced an overall case-fatality rate of 2.3%; however, among those with preexisting comorbidities, the case-fatality rate was higher: 10.5% for CVD, 7.3% for diabetes and 6% for hypertension.[8] In addition, cardiovascular complications due to COVID-19, such as myocardial injury (20% of the cases), arrhythmias (16%), myocarditis (10%), heart failure (HF) and shock (up to 5% of the cases), have been reported.[9-11]

This review was aimed at aiding healthcare professionals (clinicians, emergencists, cardiologists and intensivists) involved in the care of patients with COVID-19, proposing an

Keywords

Coronavirus; COVID-19; Cardiovascular Diseases/complications; Heart/physiopathology; Pandemics; Respiratory Distress Syndrome, Adult; Risk Factors; Patient Care.

Mailing Adddress: Ludhmila Abrahão Hajjar •
Universidade de São Paulo Instituto do Câncer do Estado de São Paulo – Av. Dr. Arnaldo, 251. CEP 01246-000, São Paulo, SP – Brazil
E-mail: ludhmila@usp.br
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algorithm of cardiovascular assessment for the early detection of complications, in addition to recommending protocols to treat cardiovascular complications in those patients.

Complications of COVID-19 on the cardiovascular system

Recent data of the COVID-19 pandemic have shown that the virus can affect the cardiovascular system with several manifestations, such as myocardial injury, HF, Takotsubo syndrome (TS), arrhythmias, myocarditis and shock.[4,11-14] The damage due to COVID-19 to the cardiovascular system is probably multifactorial and can result from an imbalance between high metabolic demand and low cardiac reserve, systemic inflammation and thrombogenesis, in addition to direct cardiac damage from the virus.[13] This damage to the cardiovascular system occurs mainly in patients with cardiovascular risk factors (advanced age, hypertension and diabetes) or preexisting CVD.[10,11] Figure 1 summarizes the inflammatory response to the viral infection, which leads to damage to the cardiovascular system and lungs, with elevation in the levels of d-dimer, procalcitonin, C-reactive protein, ferritin, troponin and NT-proBNP, culminating in cardiovascular complications and death.

The systemic inflammatory response to SARS-CoV-2 is accompanied by higher concentrations of cytokines related to injury to the cardiovascular system.[15] The increase in troponin levels is accompanied by an elevation in other inflammatory markers, such as d-dimer, ferritin, interleukin 6 (IL-6), lactate dehydrogenase (LDH), C-reactive protein, procalcitonin and leukocyte count.[1,11] Zhou et al. have shown higher levels of d-dimer, IL-6, ferritin and LDH, as well as lymphopenia, in patients who died, suggesting that those inflammatory markers might have prognostic implications. A d-dimer level at admission greater than 1μg/mL was an independent predictor of mortality in that population.[12] In addition to elevated inflammatory markers, patients with COVID-19 show increased BNP or NT-proBNP levels, markers of myocardial dysfunction. Patients with myocardial injury showed higher NT-proBNP levels, with positive linear correlation.[10,11] This finding reinforces that those with myocardial injury are prone to cardiac function impairment.[10]

A meta-analysis with four studies, including 341 COVID-19 patients, has reported significantly higher troponin I levels in patients with severe disease as compared to those with non-severe disease.[16] Patients with myocardial injury more often required admission to the intensive care unit (ICU) (22.2% vs. 2.0%), had a higher incidence of HF (52% vs 12%) and a higher death rate (59% vs. 1%).[1,9] Shi et al., assessing 416 hospitalized patients with COVID-19, have reported that myocardial injury, defined as troponin levels above the 99th-percentile upper reference limit, is a frequent complication (19.7%) in those patients, being associated with increased mortality and ARDS.[11] On multivariate analysis, myocardial injury and ARDS were independent predictors of mortality (HR

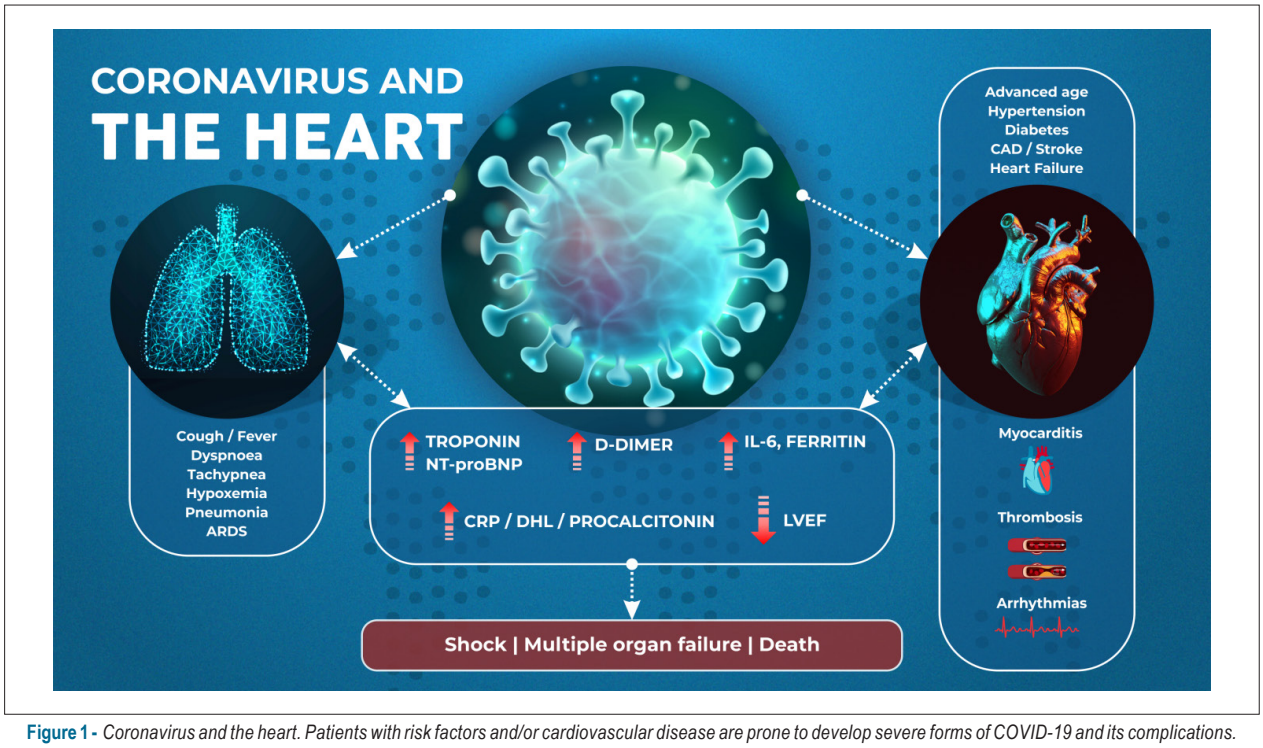

Figure 1 - *Coronavirus and the heart. Patients with risk factors and/or cardiovascular disease are prone to develop severe forms of COVID-19 and its complications. Pulmonary impairment manifests initially as an influenza syndrome (cough and fever), progressing to pneumonia (dyspnea, hypoxemia, tachypnea) and, in some cases, to ARDS. Host response to the virus leads to systemic inflammation findings, with elevation of markers of inflammation (CRP, procalcitonin, d-dimer, IL-6, ferritin, LDH) and of myocardial injury / cardiac dysfunction (troponin/NT-proBNP), which predisposes to acute heart failure, myocarditis, thrombosis and arrhythmias. Cardiovascular complications hinder the host response to the virus, leading to shock, failure of multiple organs and death.*
CAD: coronary artery disease; LDH: lactate dehydrogenase; LVEF: left ventricular ejection fraction; CRP: C-reactive protein; IL-6: interleukin-6; ARDS: acute respiratory distress syndrome.

4.26 and 7.89, respectively).[11] In a recent study, Guo et al. have reported elevated troponin levels in 27.8% of 187 patients with COVID-19. Among patients without CVD and with normal troponin levels, mortality was 7.6%; among patients with CVD and normal troponin levels, mortality was 13.3%; among patients without CVD and with elevated troponin levels, mortality was 37.5%; and among patients with CVD and elevated troponin levels, mortality was 69.4%. There was a strong correlation between high troponin levels and increased C-reactive protein and NT-proBNP levels. Patients with increased troponin levels had a higher incidence of ventricular arrhythmias and higher need for mechanical ventilation.[10]

Cardiovascular complications, such as HF, myocarditis, acute myocardial infarction, shock and arrhythmias, are also frequent in patients with myocardial injury. In a cohort with 150 patients, 7% of them developed irreversible myocardial damage and HF, associated with significant elevations in troponin levels.[17] Malignant arrhythmias (ventricular tachycardia with degeneration to ventricular fibrillation or hemodynamic instability) have been most frequently observed in individuals with troponin elevation (11.5% vs 5.2%).[10] Patients with severe COVID-19 can rapidly develop important cardiovascular impairment, shock and failure of multiple organs. In two Chinese cohorts of hospitalized patients with COVID-19, up to 20% developed the severe form of disease with shock.[9,12]

Myocarditis can be related to acute HF in patients with COVID-19. Cases of COVID-19-related myocarditis have been described, with fulminant myocarditis, rapid progression and significant ventricular dysfunction, associated with diffuse myocardial edema. Those patients had electrocardiographic changes and troponin elevation.[14,18,19] Although TS has not been directly linked to COVID-19, some cases of ventricular dysfunction in COVID-19 patients might be attributed to that syndrome, which is a frequent complication in individuals with exacerbated systemic inflammatory response, in whom the stress and severity of the viral infection trigger the TS.[20]

Interaction of SARS-CoV-2 with angiotensin-converting enzyme-2

Some studies have suggested that the damage to the cardiovascular system secondary to SARS-CoV-2 can be linked to the angiotensin-converting enzyme-2 (ACE2),[13,15] which is related to the immune system and present in high concentration in the lungs and heart. The ACE2 down-regulates the angiotensin-renin system by inactivating angiotensin-2, and ACE2 might have a protective role against the development of respiratory failure and its progression. SARS-CoV-2 has four main structural proteins: spike (S), nucleocapsid (N), membrane (M), and envelope (E) proteins. The coronavirus spike protein binds to the

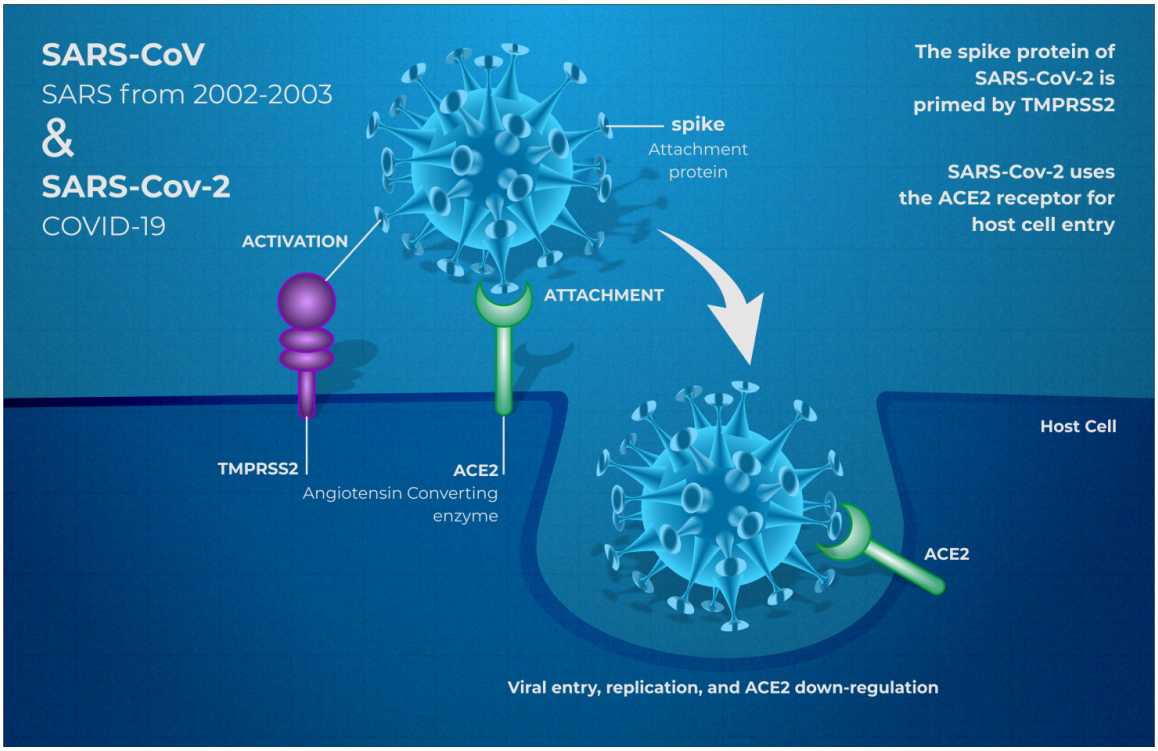

Figure 2 - *The SARS-CoV-2, via its surface spike protein, binds to the human ACE2 receptor after spike protein activation by TMPRSS2. SARS-CoV: severe acute respiratory syndrome coronavirus; SARS-COV-2: severe acute respiratory syndrome coronavirus 2; COVID-19: coronavirus disease 2019; ACE2: angiotensin-converting enzyme-2; TMPRSS2: transmembrane protease serine-2.*

ACE2 receptor and the virus enters the host cell (Figure 2), where ACE2 inactivation occurs, favoring pulmonary damage. Because of the high ACE2 concentrations in the heart, potentially severe damage to the cardiovascular system can occur.[13,21]

Patients with preexisting CVD apparently have increased serum levels of ACE2, which might contribute to the more severe manifestations in that population.[22-24] Similarly, individuals with hypertension would have a higher ACE2 expression secondary to the use of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB), which would potentially increase the susceptibility to SARS-CoV-2 infection.[4] However, current studies on humans have some limitations: a) assessment of a small number of individuals using those drugs, and b) the advanced age of a large part of the patients assessed, which is an important confounder, because advanced age increases the susceptibility to infection and is the major factor of poor prognosis.[25]

It is worth noting that, despite substantial structural homology between ACE2 and ACE, their enzyme active sites are distinct, and, as a result, ACE inhibitors in clinical use do not directly affect ACE2 activity. In addition, that enzyme plays a well-known role in the recovery of ventricular function of patients with myocardial injury, because it inhibits angiotensin II activity.[26] On the other hand, angiotensin II has been suggested to account for the cardiac injury by the coronavirus, and the administration of recombinant ACE2 would normalize angiotensin II levels. Studies with recombinant ACE2 and losartan are being conducted.[25]

The current recommendation is that ACEI and ARB should be continued in patients on regular use of those drugs, because of the clear benefit of blood pressure control and mortality decrease in those with HF, as evidenced in randomized studies.[27,28] In the severe forms of COVID-19, hemodynamic stability and renal function should be assessed individually before deciding on the continuation or withdrawal of the drugs.

Cardiovascular disease as a risk for the severe form of COVID-19

Patients with cardiovascular risk factors (advanced age, hypertension and diabetes), as well as those with CVD (coronary artery disease, cardiomyopathies and cerebrovascular disease), have susceptibility to the severe form of COVID-19 and cardiovascular complications, being classified as a risk group. Approximately 80% of the patients with the severe form of COVID-19 have a comorbidity.[29] Table 1 summarizes the major studies that characterize the clinical comorbidities of patients with COVID-19.[9-12,17,29-32]

A recent meta-analysis including eight studies from China, with 46,248 infected individuals, has shown that the most prevalent comorbidities were hypertension (17 ± 7%), diabetes mellitus (8 ± 6%) and CVD (5 ± 4%). Wang et al., assessing only hospitalized patients with COVID-19, have reported a higher prevalence of hypertension (31.2%), CVD (19.6%) and diabetes (10.1%),[9] emphasizing that individuals with those comorbidities have the most severe form of COVID-19, usually requiring hospitalization. These patients more often had hypoxemia and need for ICU admission.[9,30] Likewise, advanced age is related to the severe form of disease. In those studies, the median age has ranged from 42 to 64 years,[11,30] being higher in severely ill patients (64 vs 51.5).[29] In addition, patients admitted to ICU and those with hypoxemia were older.[9,30]

Cardiovascular complications were also frequent among patients from the risk group. Those with CVD had troponin elevation and higher rates of shock and arrhythmias.[10-12] Guo et al., assessing a cohort with 187 patients, have observed that those with myocardial injury had a high prevalence of hypertension (63%vs 28%), diabetes (30.8% vs 8.9%), coronary artery disease (32.7% vs 3%) and HF (15.4% vs 0%), and were older (median age, 71.4 years).[10]

In a cohort of 191 patients, Zhou et al. have assessed the characteristics of the deceased ones as compared to those of the discharged ones. In that cohort, the deceased patients had a higher prevalence of hypertension (48%), diabetes (31%) and CVD (24%). Advanced age was an independent predictor of mortality.[12] Mortality rate increases with increasing age as follows: 1.3% in patients aged 50-59 years; 3.6% in patients aged 60-69 years; 8% in patients aged 70-79 years; and 14.8% in patients aged 80 years and older.[31] Population studies have reported an overall mortality rate of 6% in patients with hypertension, 7.3% in patients with diabetes and 10.5% in patients with CVD.[33]

Patients with cancer have a higher risk for COVID-19 because of their impaired defense and their sequelae from the antineoplastic treatment. In China, among the confirmed cases of COVID-19, the prevalence of cancer has ranged from 1% to 7%, which is higher than the overall incidence of cancer in that country (0.2% - 201.7/100,000 individuals).[2,10,34] Patients with cancer more often developed the severe form of COVID-19 as compared to those without cancer (39% vs 8%).[35] Of the patients with cancer submitted to recent chemotherapy or surgery, 75% developed severe disease as compared to 43% of those with no recent treatment.[35]

Algorithm of cardiovascular assessment

Although not formally, cardiovascular assessment of patients with suspected or confirmed SARS-CoV-2 infection is recommended in the following situations: a) preexisting CVD or cardiovascular risk factors; b) cardiovascular signs and symptoms (dyspnea, shock, chest pain, electrocardiographic alterations or increased cardiac area); c) alterations on biomarkers, such as d-dimer, troponin, NT-proBNP and ferritin; and d) need for hospitalization. Those with CVD are prone to experience myocardial injury after SARS-CoV-2 infection, in addition to being at a higher risk of death.[10] Cardiologists should be part of the team caring for critical patients, aiding in clinical discussions and treatment.

The initial cardiovascular assessment should comprise clinical history, physical examination, troponin levels, and electrocardiogram (ECG). Troponin levels above the 99th-percentile upper reference limit and acute alterations on ECG support the identification of patients at higher cardiovascular

Table 1 - Summary of the clinical characteristics of the major studies on COVID-19

Author	N	Type	Age (years)	Comorbidities	Major findings
Huang et al. 2020[17]	41	Prospective	49 (41-58)	- DM: 8 (20%) - AH: 6 (15%) - CVD: 6 (15%) - COPD: 1 (2%) - Cancer: 1 (2%)	- 13 (32%) ICU admissions - 5 (12%) MI, and 4 (31%) to the ICU - 3 (7%) shock and 12 (29%) ARDS - Mortality: 6 (15%)
Wang et al. 2020[30]	69	Retrospective	42 (35-62)	- AH: 9 (13%) - CVD: 8 (12%) - DM: 7 (10%) - COPD: 4 (6%) - Cancer: 4 (6%)	- Hospitalizations: 44 (65.7%) - Mortality: 5 (7.5%) - Patients with DM, AH and CVD more often had hypoxemia ($SatO_2$ < 90%) - MI not assessed
Chen et al. 2020[31]	99	Retrospective	55 (21-82)	- CVD: 40 (40%) - DM: 12 (12%) - Cancer: 1 (1%)	- 57 (58%) hospitalizations, 17 (17%) ARDS, 4 (4%) shock - Mortality: 11 (11%) - Of the deceased, 63% were > 60 years and 33% had AH
Wang et al. 2020[9]	138	Retrospective	56 (42-68)	- AH: 43 (31.2%) - CVD: 20 (14.5%) - DM: 14 (10.1%) - Cancer: 10 (7.2%) - Stroke: 7 (5.1%)	- 36 (26%) ICU admissions, high prevalence of risk factors - 12 (8.7%) shock, 23 (16.7%) arrhythmias, 27 (19.6%) ARDS, and 10 (7.2%) MI - Mortality: 6 (4.3%)
Zhang et al. 2020[29]	140	Retrospective	57 (20–83)	- AH: 42 (30%) - DM: 17 (12.1%) - CAD: 7 (5%) - Arrhythmias: 5 (3.6%)	- Comparing severe x non-severe groups: median age 64 vs 51.5, p < 0.001 comorbidities 79.3% vs 53.7%, p = 0.002 d-dimer 0.4 vs 0.2, p<0.001
Guo et al. 2020[10]	187	Retrospective	58.5 (±14.7)	- AH: 61 (32.6%) - CAD: 21 (11.2%) - HF: 8 (4.3%) - DM: 28 (15%) - COPD: 4 (2.1%) - Cancer: 13 (7%)	- 52 (27.8%) MI - Comparing normal tropo x high tropo: AH: 27% vs 63.5%, p 0.001 CAD: 3% vs 32.7%, p <0.001 HF: 0% vs 15.4%, p <0.001 - 43 deaths, 31 (59.6%) in the MI group - Mortality: 13.3% CVD without MI, and 69.4% CVD with MI
Zhou et al 2020[12]	191	Retrospective	56 (46-67)	- AH: 58 (30%) - DM: 36 (19%) - CAD: 15 (8%) - COPD: 6 (3%) - Cancer: 2(1%)	- MI: 24/145 (17%), greater in patients who died (22.2 [5.6-83.1] vs 3.0 [1.1-5.5], p <0.001) - HF 44 (23%), shock 38 (20%), ARDS 59 (31%) - 54 (28%) deaths, 67% with comorbidities
Shi et al. 2020[11]	416	Prospective	64 (21-95)	- AH: 127 (30.5%) - DM: 60 (14.4%) - CAD: 44 (10.6%) - Stroke: 22 (5.3%) - HF: 17 (4.1%) - Cancer: 9 (2.2%)	- 82 (19.7%) MI - High prevalence of AH, DM, CAD and HF in patients with MI - MI was related to higher mortality: (42 of 82 [51.2%] vs 15 of 334 [4.5%]; p < .001) - MI was associated with ARDS: (48 of 82 [58.5%] vs 49 of 334 [14.7%]; p < .001)
Guan et al. 2020[32]	1099	Retrospective	47 (35-58)	- COPD: 12 (1.1%) - DM: 81 (7.4%) - AH: 165 (15%) - CAD: 27 (2.5%) - Stroke: 15 (1.4%) - Câncer: 10 (0.9%)	- Severely-ill patients: AH 41 (23.7%) - High CK-MB 90/657 (13.7%) - 12 (1.1%) shock, 37 (3.4%) ARDS, 1029 (93.6%) hospitalizations, 55 (5%) ICU admissions - Mortality: 15 (1.4%)

DM, diabetes mellitus; AH, arterial hypertension; CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; HF, heart failure; MI, myocardial injury; tropo, troponin; ARDS, acute respiratory distress syndrome; ICU, intensive care unit.

risk and might contribute to the decision making on hospital admission and case management. Figure 3 shows the flowchart for cardiovascular assessment in COVID-19 cases.

The ECG can identify malignant cardiac arrhythmias, defined as sustained ventricular tachycardia inducing hemodynamic instability or ventricular fibrillation. Alterations in repolarization suggesting acute ischemia have been reported, mainly in patients with myocarditis.[14,18]

The ECG plays an important role in the QTc interval monitoring of patients on hydroxychloroquine (HCQ) and azithromycin. Both drugs have been linked to QT interval prolongation. The combination of both drugs and the presence of fluid and electrolyte imbalance in patients with COVID-19 require QTc interval monitoring. In-patients should undergo an ECG 2-3 hours after the second dose of HCQ and daily thereafter. If QTc increases by >60ms or absolute

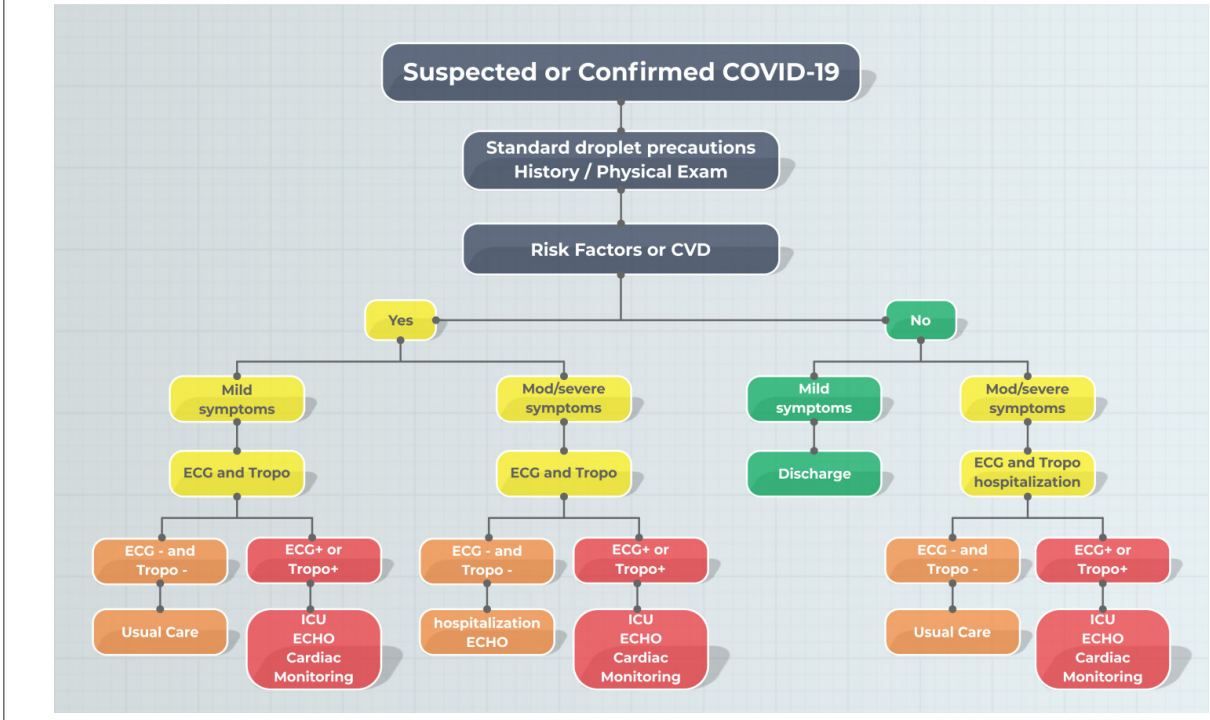

Figure 3 - *Flowchart for cardiac assessment of patients with suspected COVID-19. *Advanced age, coronary artery disease, cerebrovascular disease, arterial hypertension, diabetes mellitus, cardiomyopathy or arrhythmia. COVID-19: Coronavirus disease 2019; CVD: cardiovascular disease; ECG +: supraventricular or ventricular tachycardia, new repolarization changes suggestive of acute ischemia; ECG -: electrocardiogram without acute changes; ECHO: echocardiogram; mod: moderate; Tropo +: troponin levels above the 99th-percentile upper reference limit; Tropo -: troponin levels below the 99th-percentile; ICU: intensive care unit.*

QTc >500ms (or >530-550ms if QRS >120ms), azithromycin should be discontinued or the HCQ dose, reduced, and ECG performed daily. If the ECG changes remain, the risk/benefit of maintaining the medication should be reevaluated. For outpatients, who may be less at risk for complications from QT interval prolongation, baseline ECG should be acquired 2-3 hours after initiating HCQ and on day 3 of therapy. If QTc increases by >30-60ms or absolute QTc >500ms (or >530-550ms if QRS >120ms), consider discontinuing therapy.[36]

Transthoracic echocardiogram should be the initial choice for assessing cardiac function in those patients, and ideally performed at the emergency department by use of the point-of-care or dynamic method. Transthoracic echocardiogram can show systolic and/or diastolic left ventricular impairment and provides hemodynamic information to support the management of patients, in addition to enabling the diagnosis of pericardial changes. It should be considered for all risk groups or those requiring hospitalization. Patients with ventricular dysfunction are more likely to need mechanical ventilation and be of worse prognosis.[13] Critical patients should be followed up with daily echocardiogram, as well as strict assessment of hemodynamic parameters and biventricular function. In addition, the detection of ventricular dysfunction is an indication for invasive hemodynamic monitoring and will guide the treatment with inotropic and/or circulatory support. In critical cases, dynamic echocardiogram should be acquired daily and at every hemodynamic change.

Magnetic resonance imaging should be considered in stable patients and can support the differential diagnosis of ventricular dysfunction etiology, which might be related to myocarditis or stress-induced systolic dysfunction. The diagnosis of myocarditis follows the classic criteria already validated for other viral etiologies, in which myocardial edema and non-ischemic myocardial late enhancement can be observed.[37-39]

Management of the patient with COVID-19

Initial approach and intensive support. The mean time of symptom onset is 4-5 days, and 97.5% of contaminated individuals will have symptoms in up to 11.5 days from exposure.[32] Most patients (81%) have mild symptoms, the most common being fever (88%) and cough (67.7%). Other less frequent are diarrhea, myalgia, headache and runny nose. Approximately 20% of the patients with COVID-19 will have the severe form, with dyspnea, tachypnea, oxygen saturation ≤93%, and pulmonary infiltrate, while 5% will have the critical form of COVID-19, with signs of shock and respiratory failure.[1,40] Most of asymptomatic or olygosymptomatic clinically stable patients require no hospitalization, which is mandatory for those with severe symptoms and unfavorable evolution.

The initial assessment of patients with COVID-19 should include: ECG, arterial blood gas analysis with lactate level, d-dimer, complete blood count, kidney and liver function tests, clotting factors, troponin, creatine phosphokinase, ferritin, LDH, IL-6 and electrolytes (sodium, magnesium, potassium, and calcium). Chest radiography should be performed and chest computed tomography (CT) considered in some cases. Computed tomography evidences abnormalities in 85% of the patients, and 75% of them show bilateral pulmonary involvement, commonly characterized as ground-glass opacifications and subpleural and peripheral consolidations.[41] Those with indication for hospitalization should undergo echocardiography in the emergency department or within the first hours from hospital admission.

The clinical course of COVID-19 is variable and potentially severe, because 3.4% of the patients progress to ARDS,[32] a proportion that increases in the cohorts of those hospitalized with the disease (19.6%) and among those with myocardial injury (58.5%).[9,11] Acute respiratory distress syndrome is defined based on the Berlin criteria: acute onset of pulmonary damage, bilateral pulmonary opacities on chest radiography, and pulmonary edema. The ARDS Berlin Definition stratifies the severity of pulmonary damage based on the relation between partial pressure of arterial oxygen (PaO_2) and fraction of inspired oxygen (FiO_2), acquired in a positive-end expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) $\geq$ 5 cm H_2O. The ARDS is considered severe when PaO_2/FiO_2 is <100.[42]

Mechanical ventilation is recommended in the presence of hypoxemia despite oxygen supply. Protective mechanical ventilation strategies should be used, with tidal volume of 6 mL/kg, plateau pressure < 30 cm H_2O, and PEEP adjusted according to FiO_2. Patients usually have good pulmonary compliance despite severe hypoxemia. For patients with ARDS and $PaO_2/FiO_2 \leq 150$, prone position should be considered, and, in case of significant patient-ventilator dyssynchrony, neuromuscular block can be performed.[43]

Hemodynamic monitoring should be cogitated in all ICU patients with signs of shock. Minimally invasive hemodynamic monitoring and continuous cardiac output monitoring should be considered in association with dynamic echocardiography and analysis of tissue hypoperfusion markers, such as clinical parameters, arterial lactate levels, deltaPCO_2, and base excess. In the presence of shock, norepinephrine is the drug of choice, and the addition of vasopressin is recommended if increasing doses of noradrenaline are necessary for hemodynamic optimization.[44] If cardiac dysfunction occurs, dobutamine should be added.[44] Norepinephrine should be immediately initiated, even in a peripheral access, preventing prolonged hypotension, which yields high mortality.

Extracorporeal membrane oxygenation (ECMO) might be necessary for patients with acute respiratory failure refractory to initial measures.[45,46] At first, venovenous ECMO is indicated for recovery of pulmonary function.[46,47] When associated with significant cardiovascular impairment in patients with severe ventricular dysfunction and/or cardiogenic shock, venoarterial ECMO might be considered.[48] ECMO should be initiated before the installation of failure of multiple organs.[49]

Specific treatment. At the present time, the treatment of critically ill patients is based on supportive measures for organic dysfunctions. Since the beginning of the pandemic, an effective antiviral treatment for COVID-19 has been sought. In China and Italy, in severe cases and in an individualized manner depending on the institution, drugs like chloroquine (CQ) or HCQ, lopinavir/ritonavir, remdesivir and favipiravir have been used. Remdesivir and favipiravir are broad-spectrum antiviral agents, whose efficacy and safety for the management of patients with COVID-19 are being assessed in randomized clinical trials.[50] A recent randomized and controlled study has shown that the lopinavir/ritonavir combination, used in the management of HIV infection, is ineffective against the SARS-CoV-2 infection.[50]

Chloroquine diphosphate and HCQ sulfate are well-known useful drugs to treat malaria and autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus. In experimental studies, CQ and HCQ have shown to act against SARS-CoV-2, by interfering with ACE2 glycosylation, thus reducing the efficiency of the binding between ACE2 of host cells and the coronavirus surface protein. In addition, those drugs act by increasing the pH of endosomes and lysosomes, thus preventing virus/host cell fusion and subsequent viral replication. Moreover, HCQ prevents the presentation of viral antigens to T cells and inhibits the transcription of proinflammatory genes, hindering the release of cytokines. Thus, in experimental studies, CQ and HCQ have prevented viral entry into the cell and replication, as well as attenuated the inflammatory response. In China, a study has shown that CQ was linked to a higher percentage of clinical and virological cure, being then adopted for the treatment of COVID-19 in that country. A small study has reported that HCQ, regardless of combination with azithromycin, reduced the SARS-CoV-2 RNA detection on respiratory tract swab samples, but that study has not assessed clinical outcomes.[51-53]

The major side effects of CQ and HCQ are gastrointestinal intolerance (nauseas and vomit) and, in the long-term use, retinopathy, maculopathy and cardiomyopathy. Other common side effects of those drugs are total atrioventricular block, bundle-branch block, cardiac arrhythmias, hypotension, *torsades de pointes*, T-wave inversion, ventricular fibrillation, and ventricular tachycardia, which are even more frequent with their prolonged use and in the presence of liver and kidney dysfunction. On March 10, 2020, the *Journal of Critical Care* has published a systematic review on the efficacy and safety of CQ for the treatment of COVID-19, including one narrative letter, expert consensus paper, one editorial, one *in-vitro* study, two national guideline documents, and the description of 23 ongoing clinical trials in China.[54] On March 21, 2020, the president of the United States urged the FDA to quickly approve CQ and HCQ for the treatment of COVID-19. However, the FDA currently recommends the compassionate drug use until scientific evidence on the efficacy of CQ, HCQ and azithromycin for the treatment of COVID-19 is available.

On March 23, 2020, two studies conducted in Brazil were approved by the Brazilian Committee on Ethics in Research (CONEP): a) a phase IIb study to assess the efficacy and safety of CQ diphosphate in the treatment of patients hospitalized with SARS-CoV-2: a double-blind, randomized, clinical

trial – a multicenter study with 440 patients proposed by the Teaching and Research Board of Fiocruz Amazonas – that has included 50 patients so far; and b) an assessment of the safety and clinical efficacy of HCQ in association with azithromycin for patients with SARS-CoV-2 pneumonia – a multicenter study with 400 patients proposed by the Brazilian Israeli Beneficent Society Albert Einstein – waiting to start recruiting.

Since March 25, 2020, the Brazilian Ministry of Health has adopted that drug as an adjuvant for the treatment exclusively of the severe forms of COVID-19, while also maintaining the other supportive measures. The indication considers that there is no other effective specific treatment available at the present time and that the recommendation can be modified at any time, depending on new evidence. On March 31, 2020, in a preprint study, without peer review, a Chinese group showed the superior efficacy of HCQ for mild pneumonia in 62 patients assessed (with a control group).[55] That should be confirmed in a study with higher sample power and stricter methodology. Other drugs being analyzed are glucocorticoids, immunoglobulins, interferon, and tocilizumab.

Cardiopulmonary resuscitation. When patients with COVID-19 have a cardiorespiratory arrest, special care should be taken, with special attention to airway management, because of the higher risk of contamination of healthcare workers performing aerosol-generating procedures.[56,57] All healthcare professionals in contact with patients with COVID-19 should follow the local and national orientations for infection control and use of personal protective equipment, which should be readily available.[58,59]

SARS-CoV-2 infected patients at risk for acute deterioration or cardiac arrest should be identified early, as should those for whom a 'do not attempt cardiopulmonary resuscitation' applies, and that should be based on local guidelines.[58]

Hypoxia is the most probable cause of cardiorespiratory arrest among patients with COVID-19; however, all causes should be taken into account (hypoglycemia, acidosis, coronary thrombosis). The algorithms already validated should be applied according to the identification of shockable and non-shockable rhythms.[56,57] Airway should be manipulated by experienced and skilled professionals. Healthcare professionals caring for patients with COVID-19, including physicians, nurses and physical therapists, are at higher risk of infection.[60,61] Aerosol-generating procedures, such as non-invasive ventilation, high-flow nasal cannula therapy, and bag-valve-mask or bag-tracheal-tube ventilation, pose a particularly high risk.[62]

Bag-valve-mask or bag-tracheal-tube ventilation should be avoided, because of its elevated risk of aerosolization and contamination of the team; moreover, that type of ventilation has not proven to be superior to the mechanical one.[56] If bag-valve-mask ventilation is necessary, the mask should be properly sealed, which requires more than one professional. In addition, the use of filters between the mask and the bag is mandatory. For those patients, the establishment of advanced airway should be prioritized and conducted by skilled individuals.[56] If intubation fails or is impossible, other devices should be used, such as laryngeal tube or mask, to enable closed-circuit mechanical ventilation until definite access to airway is obtained, by either tracheal intubation or cricothyroidostomy.[57]

In case of cardiorespiratory arrest of patients on mechanical ventilation, to prevent aerosol contamination from cardiopulmonary resuscitation maneuvers and ventilation, the patient should remain connected to the mechanical ventilator in a closed-circuit system, maintaining FiO_2 at 100%, asynchronous mode, and respiratory rate of 10-12 bpm (Figure 4).[56]

Thrombosis prevention and management

The literature provides suggestive evidence that the exacerbated systemic inflammatory response present in COVID-19 causes endothelial dysfunction and increased procoagulant activity, which, in association with lower oxygen supply, might contribute to coronary plaque instability or to thrombus formation on a ruptured coronary plaque, and, thus, to plaque vulnerability.[10,11,63] It is worth noting the importance of the differential diagnosis of obstructive coronary artery disease from type II myocardial infarction.[64] Patients with COVID-19 can present with acute coronary syndrome due to a mismatch in myocardial oxygen supply and demand, being diagnosed with type II myocardial infarction. The cases should be analyzed individually, because a large part should be managed conservatively, considering that 7% of the patients with COVID-19 and acute coronary syndrome might have type II myocardial infarction or myocarditis.[64]

The approach to acute coronary syndrome in patients with COVID-19 should consider the availability of local resources, such as structured catheterization laboratories, coronary care unit and/or ICU beds, and adequacy of the environment to the protective measures against SARS-CoV-2.[64] A Chinese report has suggested that thrombolysis should be the first-choice therapy for patients with COVID-19. That is a controversial recommendation, especially where primary angioplasty can be performed, respecting all the safety rules for protection of healthcare professionals and hospital environment (personal protective equipment, negative pressure room, proper cleaning).[64]

The treatment of cardiovascular complications should be based on the ideal and careful use of the therapies recommended in the guidelines. Therapy with ACEI, ARB, beta-blockers, antiplatelet agents and statins should abide by the recommendations in the guidelines, respecting the contraindications related to hemodynamic stability and presence of other organic dysfunctions.[21]

Patients with COVID-19 are at a higher risk of venous thromboembolism, because of their prolonged physical inactivity and their abnormal coagulation parameters.[4] The use of non-pharmacological prophylaxis strategies is recommended for all in-patients with COVID-19. Pharmacological strategies should be considered, such as the use of unfractionated or low-molecular-weight heparin, taking into account the latter's contraindications and the patient's creatinine clearance. Venous thromboembolism should be suspected based on clinical criteria, in situations such as maintenance of high d-dimer levels and refractory hypoxemia, or in the presence of echocardiographic signs of pulmonary hypertension and right ventricular dysfunction.

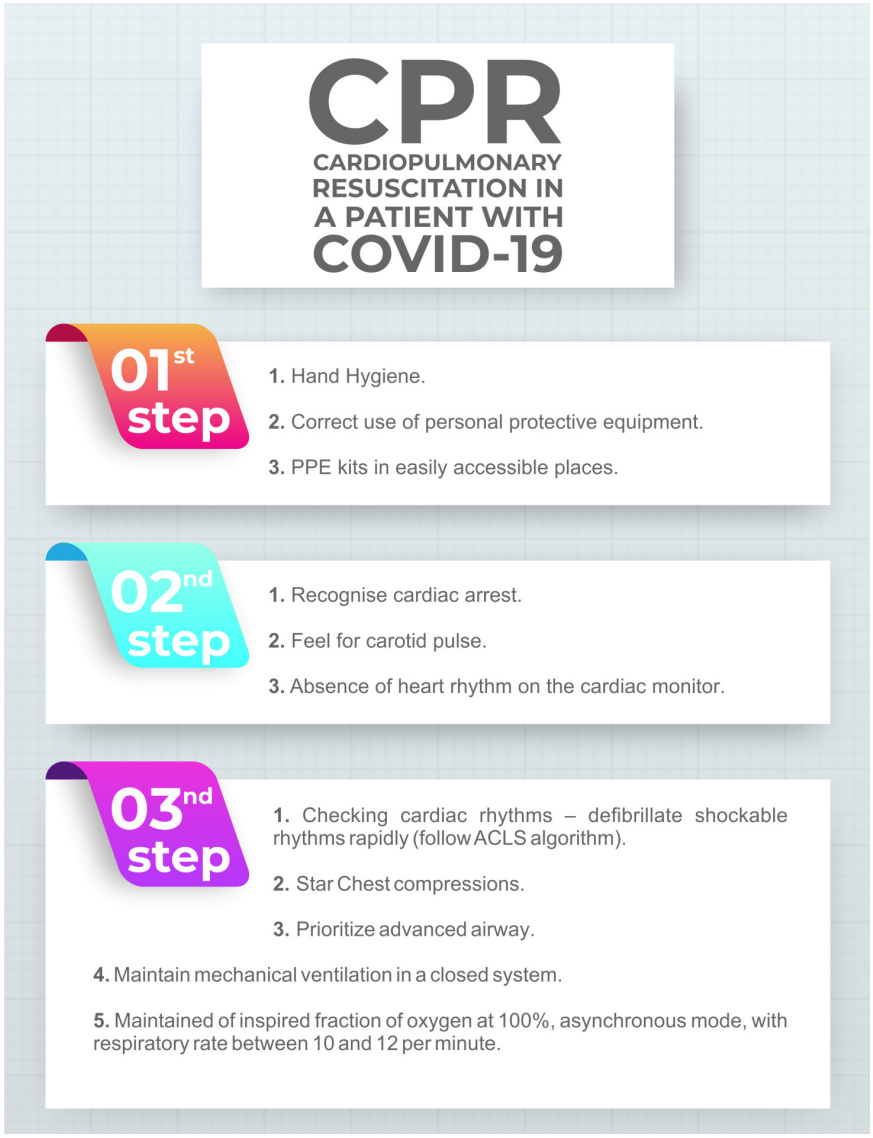

Figure 4 - *Cardiopulmonary resuscitation of patients with COVID-19. CRA: cardiorespiratory arrest; COVID-19: Coronavirus disease 2019; PPE: personal protective equipment; ACLS: Advanced Cardiovascular Life Support; FiO_2: fraction of inspired oxygen; RR: respiratory rate.*

Telemedicine and cardiology

Because of the exponential viral spread, social distancing has been determined as a key-factor to reduce the speed of spread by reducing person-to-person contact. The use of information technology, thus, is mandatory as an emergency response to environmental issues or biological risks. Telehealth enables remote triage, supports the diagnosis of diseases, and ensures access to routine care during an infectious disease outbreak.[65]

In 2019, the Brazilian Medical Board published a decree defining telemedicine as the technology-mediated practice of medicine aimed at health care, education, research, prevention of diseases and injuries, and health promotion, regulating that practice. The Brazilian Society of Cardiology has issued a guideline on telemedicine applied to cardiology, also named telecardiology. Telecardiology by acting in health promotion, disease prevention, diagnosis, treatment and rehabilitation, which impact the quality of life, can be considered an important ally of the health system, be it public, supplementary or private, to promote quality integral health care. The implementation of telecardiology is important to primary and specialized health care.[66] In cardiology, telemedicine can be useful to control risk factors, such as blood pressure and diabetes mellitus, to improve the lipid profile, to reduce weight, and to increase the success rate of smoking cessation programs.[66]

At the current stage of pandemic control, telemedicine became a useful tool, especially for patients at high risk, reducing the exposure to SARS-CoV-2 and helping control comorbidities. On March 19, 2020, the Brazilian Medical Board, in accordance

with the Brazilian Ministry of Health, recognized the possibility and ethical character of telemedicine regarding teleguidance, teleconsultation, and telemonitoring.[67]

General recommendations

• Intensify the care and preventive measures against the novel coronavirus infection in the population with CVD.

• Patients with CVD should be managed according to current guidelines, ensuring the best treatment available for chronic illnesses.

• It is essential that patients with CVD maintain strict adherence to proper diet, regular sleep and physical activity, avoiding tobacco and alcohol consumption.

• It is important to update vaccines. This includes the pneumococcal vaccine, because of the increased risk of bacterial infection secondary to SARS-CoV-2, and the influenza vaccine, indicated for patients with CVD.

• Outpatient appointments as well as elective tests and procedures should be postponed if clinical discretion determines they are not essential and if not performing them neither increases the risk of events nor hinders the clinical management of an underlying CVD. Telemedicine should be used to help patient's follow-up.

• The number of healthcare professionals taking part in ward rounds for patients should be reduced, and online discussion should be implemented.

Conclusions

COVID-19 is potentially severe and has a high spread rate. Current data available are mainly derived from retrospective studies and should be cautiously interpreted. However, current evidence already shows the need to pay special attention to patients at risk and the importance of the proper management of cardiovascular complications, with rapid identification and implementation of adequate treatment.

Author contributions

Conception and design of the research: Costa IBSS, Bacal F, Oliveira GMM, Lacerda MVG, Barberato SH, Chagas ACP, Rochitte CE, Ramires JAF,Kalil Filho R, Hajjar LA; Acquisition of data and Writing of the manuscript: Costa IBSS, Bittar CS, Rizk SI, Everaldo Filho A, Queiroz KA, Machado TIV, Andrade FTA, Arévalo ANG, González TB, Almeida JP; Analysis and interpretation of the data: Costa IBSS, Bittar CS, Rizk SI, Everaldo Filho A, Queiroz KA, Machado TIV, Andrade FTA, Lopes MACQ, Arévalo ANG, González TB, Almeida JP; Critical revision of the manuscript for intellectual content: Costa IBSS, Lopes MACQ, Bacal F, Oliveira GMM, Lacerda MVG, Barberato SH, Chagas ACP, Rochitte CE, Ramires JAF,Kalil Filho R, Hajjar LA.

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This article does not contain any studies with human participants or animals performed by any of the authors.

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Review Article

The Effect of Coronavirus Disease 2019 on Cardiovascular Diseases

Lutfu Askin,[1] *Okan Tanrıverdi,*[1] *Husna Sengul Askin*[2]

Adiyaman Universitesi Egitim ve Arastirma Hastanesi – Cardiology,[1] *Adıyaman, Centry – Turkey*

Adiyaman Universitesi Egitim ve Arastirma Hastanesi – Infectious Disease,[2] *Adıyaman, Centry – Turkey*

Abstract

Coronavirus disease 2019 (COVID-19) is a global pandemic affecting the world, seen in more than 1,300,000 patients. COVID-19 acts through the angiotensin-converting enzyme 2 (ACE2) receptor. Cardiovascular comorbidities are more common with COVID-19, and nearly 10% of cases develop myocarditis (22% of critical patients). Further research is needed to continue or discontinue ACE inhibitors and angiotensin receptor blockers, which are essential in hypertension and heart failure in COVID-19. Intensive research is promising for the treatment and prevention of COVID-19.

Introduction

Coronavirus disease 2019 (COVID-19) has been characterized as a global pandemic. As of March 28, 2020, there were infected patients in 167 countries worldwide and more than 1,300,000 cases with approximately 69,780 deaths.[1] The outbreak originated in China, and the number of cases outside China has exceeded the number of cases in China. It is increasing steadily as of March 28, 2020. Furthermore, the number of deaths in Italy now exceeds three times the total number in China. COVID-19 interacts with the cardiovascular system and increases morbidity and mortality by causing myocardial dysfunction in patients with previous cardiovascular comorbidities.

COVID-19 causes severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). In its single-chain envelope structure, the RNA virus is the seventh known human coronavirus. SARS-CoV-2 differs from the coronaviruses that caused zoonotic severe acute respiratory syndrome coronavirus (SARS-CoV)[2] in 2002 and middle east respiratory syndrome coronavirus (MERS-CoV)[3] in 2012. SARS-CoV-2 is thought to have 89% to 96% nucleotide similarity with bat coronaviruses and to be caused by bats, similar to other coronaviruses.[4] Like SARS-CoV-1 and MERS, SARS-CoV-2 can pass from bats to an intermediate host (possibly a Malayan pangolin sharing 91% nucleotide identity) and then to humans.[5]

SARS-CoV-2 binds to the human angiotensin-converting enzyme 2 (ACE2) receptor (Figure 1) after activation of the spike protein by transmembrane protease, serine 2 (TMPRSS2).[6] ACE2 is mainly expressed in the lung (type II alveolar cells),[7] and this appears to be the dominant access site. ACE2 is highly released in the heart in cases of excessive activation of the renin-angiotensin system, such as hypertension (HT), congestive heart failure (CHF), and atherosclerosis.[8] In addition to its cardiac effects, ACE2 is expressed in the lung, intestinal epithelium, vascular endothelium, and kidneys, which is one of the causes of multiple organ failure in SARS-CoV-2 infection.[8,9] Evidence for the association of COVID-19 with morbidity and mortality is growing in cardiovascular diseases (CVD). In this review, we aimed to share up-to-date data on COVID-19, which spreads very rapidly.

COVID-19 in CVD

CVD was a common comorbidity in SARS and MERS infections before COVID-19. The prevalence of diabetes mellitus (DM) and CVD in SARS was 11% and 8%, respectively, and the presence of both comorbidities had a twelve-fold risk of death.[10] DM and HT were common in approximately 50% of MERS cases.[11] The presence of cardiovascular comorbidities also applies to COVID-19, and its importance increases in more severe cases. In Wuhan, 30% of infected patients (48% of survivors) had HT; 19% had DM (31% of survivors), and 8% had KVH (13% of survivors).[12] In a cohort of 138 patients with COVID-19, cardiovascular comorbidities were similarly

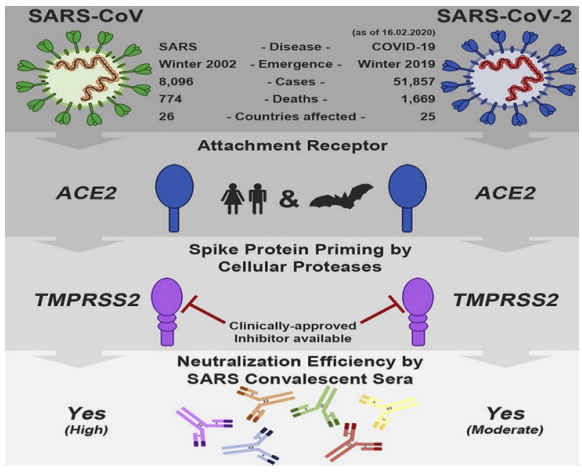

Figure 1 – *SARS-CoV-2 receptor interaction.*

Keywords

Coronavirus; COVID 19; Cardiovascular Diseases/complications; Comorbidity; Hypertension;Heart Failure; Myocarditis; Acute Respiratory Syndrome; Pandemic; Mortality; Hospitalization; Critical Care.

Mailing Address: Lutfu Askin •
Adiyaman Universitesi Egitim ve Arastirma Hastanesi – Cardiology - Adıyaman Eğitim Ve Araştırma Hastanesi Kardiyoloji Bölümü Adıyaman Centry 2230 – Turkey
E-mail: lutfuaskin23@gmail.com
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common (46% overall, 72% in intensive care patients). Of these, 31% had HT (58% in intensive care patients); 15% had CVD (25% in intensive care patients), and 10% had DM (22% intensive care patients).[13]

In a cohort analysis of 1,099 outpatients and inpatients, 24% had some comorbidity (58% among intubation or death); 15% had HT (36% among intubation or death); 7.4% had DM (27% among intubation or death), and 2.5% had KVH (9% among those with intubation or death).[14] The Chinese National Health Commission reported that 35% of patients diagnosed with COVID-19 had HT, and 17% had coronary heart disease.[15] A metaanalysis in China showed that, in 46,248 infected patients, the most common comorbidity was HT.[16] The possible mechanism of these associations is considered to be more common in people with advanced age, impaired immune system, high ACE2 levels, or predisposition to CVD. Another study conducted in China indicated that the most common comorbidity seen in patients who died from COVID-19 was CVD with 10.5% (Figure 2).[17]

COVID-19 and myocardial damage

Myocardial damage, with increased cardiac biomarkers, was among the first cases in China. In a study with 138 patients with COVID-19 in Wuhan, cardiac damage with high sensitivity Troponin I (hs-cTnI) and ECG or echocardiographic abnormalities were generally present in 7.2% of patients and 22% of patients in need of intensive care.[13] The Chinese national health report stated that approximately 12% of patients without CVD have increased troponin levels or arrest rates during hospitalization.[15] Hs-cTnI, in particular, was above the 99th percentile upper reference limit in 46% of survivors.[12]

Initial results show that there are two myocardial damage patterns with COVID-19. One study showed that on the fourth day following the onset of symptoms, the median hs-cTnI level in survivors was 8.8 pg/mL and 2.5 pg/mL in those who died. During follow-up, mean hs-cTnI between survivors did not change significantly (2.5 – 4.4 pg/mL), but on the seventh day, hs-cTnI values were 24.7 pg/mL; 55.7 pg/mL on the 13th day; 134.5 pg/mL on the 19th day, and 290.6 pg/mL on the 22nd day. In particular, average time from onset of symptoms to death was 18.5 days (IQR 15 – 20 days).[12]

The increased hs-cTnI level was associated with other inflammatory biomarkers (D-dimer, ferritin, interleukin-6 [IL-6], lactate dehydrogenase). This was the reason for the cytokine storm or secondary hemophagocytosis. Viral myocarditis or stress cardiomyopathy is mostly reported in the cases who mostly present with cardiac symptoms. Recently, a case with chest pain with ST-segment elevation on ECG but normal coronaries was reported. The patient had reduced ejection fraction (EF) (27%), increased left ventricular diameters, and high cardiac biomarkers (troponin T > 10 ng/mL, NT-proBNP > 21,000 pg/mL).[18] Intravenous immunoglobulin and steroids improved his cardiac capacity within three weeks.

In another report from China, a 63-year-old male with no cardiac history had severe respiratory symptoms, enlarged left ventricle (LVEDD 6.1 cm), and fulminant myocarditis with reduced EF. He had higher troponin-I (> 11 ng/mL) and NT-proBNP (> 22,000 pg/ml) levels. Extracorporeal membrane oxygenation and intravenous immunoglobulin, steroids, antiviral treatment regimens were applied because of the cardiogenic shock situation. Ventricular function improved significantly within 2 weeks.[19]

Glucocorticoid therapy is not recommended by the world health organization because the effect of this therapy is still uncertain.[20,21] China's national report also reported that symptoms might be palpitations and chest pain rarely.[15] Limited data showed a lower incidence of fulminant myocarditis and

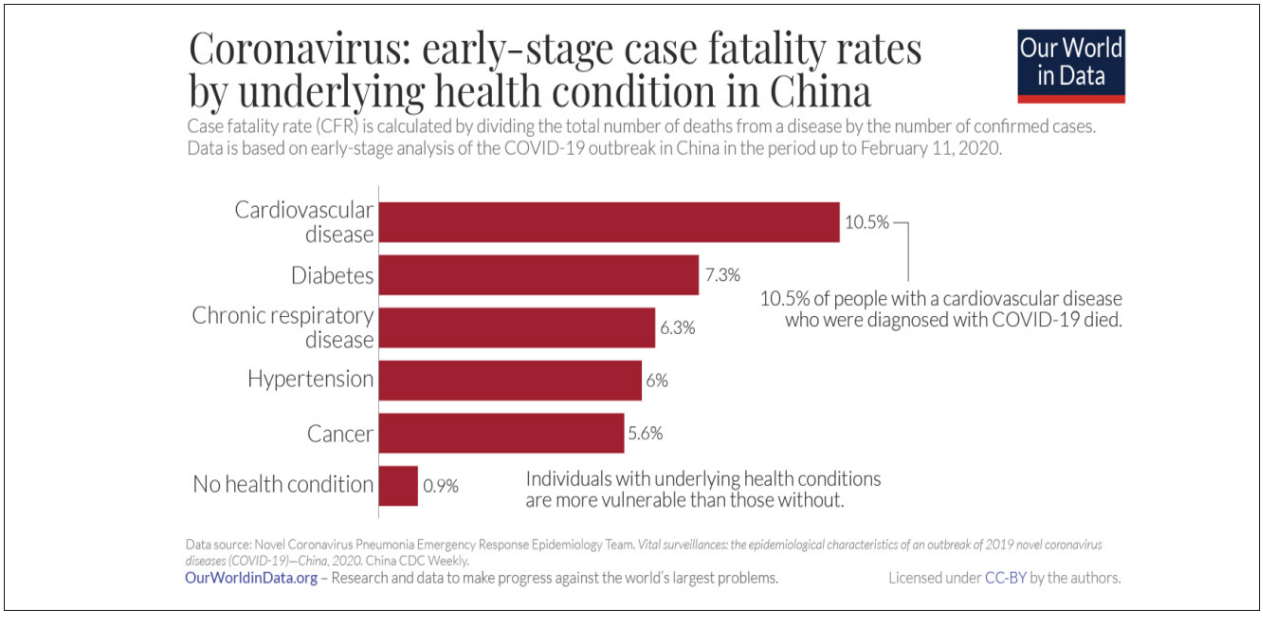

Figure 2 – *Comorbidity rates in patients who died from COVID-19 in China.*

cardiogenic shock. However, the rate of recovery and treatment is not yet at a systematic level.

The exact mechanism of COVID-19's cardiac involvement is still under investigation. A potential mechanism is ACE2-mediated direct myocardial involvement. It was observed that a myocardial infection due to ACE2 was also triggered by SARS-CoV pulmonary infection developed by in murine model.[22] During the Toronto SARS epidemic, SARS-CoV viral RNA was detected in 35% of autopsies.[23] Other possible mechanisms of cardiac involvement related to[21] COVID-19 are cytokine storm induced by an imbalanced response between T helper cell subtypes and excess intracellular calcium inducing hypoxic cardiomyocyte apoptosis.[12]

The role of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

ACE2 is an ACE homolog that converts angiotensin II to angiotensin 1-7, thereby reducing vasoconstriction mediated by the renin-angiotensin system. Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) use is common in CVD (HT, coronary artery disease [CAD], CHF, and DM). There are conflicting data from studies showing that these drugs increase ACE2 levels.[24,25] SARS-CoV-2 binds to ACE2 in order to gain entry into cells. However, ACE2 has a protective role against acute lung injury.

In a murine model, binding of the SARS-CoV spike protein to ACE2 is the reason for ACE2 downregulation, increased angiotensin II levels, pulmonary vascular permeability, pulmonary edema, and impaired lung function. However, treatment with recombinant ACE2[26] and losartan[27] reduced the degree of lung injury. Studies are currently underway in patients with COVID-19 due to the potential to reduce lung damage with losartan.[28] Currently, no recommendations have been reported on the continuation or discontinuation of ACEi, ARB or other renin-angiotensin-aldosterone system (RAAS) antagonists. Due to the lack of evidence about the harms of RAAS antagonists, RAAS therapy will continue in COVID-19.[29]

Peng et al.[30] reported that patients with COVID-19 and CVD had a higher risk of mortality. Critical patients also had low lymphocyte counts and high body mass index (BMI). ACEI/ARB usage does not affect morbidity and mortality in COVID-19 patients with CVD. Aggravating causes of death include fulminant inflammation, lactic acid accumulation, and thrombotic events.

COVID-19 has caused great damage to the health and economic situation of China. How to deal with aortic diseases has become a serious problem in this situation. Rapid diagnosis, safe and effective transportation, implementation of the interventional procedure, protection of the vascular surgery team, postoperative management, and follow-up of such patients are urgent problems for patients. More studies are needed to minimize complications in vascular diseases, critical emergencies in vascular surgery and even manage routine vascular diseases with COVID-19. [31]

Drug Therapy and COVID-19: Cardiovascular Effects

Antiviral Therapy

Ribavirin and remdesivir are two agents that bind to the active site on RNA-dependent RNA polymerases on SARS-CoV2.[32] However, lopinavir/ritonavir inhibits the replication of the RNA virus and proves to have a synergistic effect with ribavirin.[33] Clinical trials are currently researching ribavirin and lopinavir/ritonavir for COVID19, and these antivirals were used as components of hepatitis C and HIV treatment for years.[34,35]

Ribavirin does not characteristically have direct cardiovascular toxicity. However, lopinavir/ritonavir may cause QT prolongation in patients with long QT.[35] Both ribavirin and lopinavir/ritonavir have the potential to affect the anticoagulant dose.[36] Ribavirin affects warfarin doses. It may be necessary to avoid CYP3A-mediated drugs such as rivaroxaban and apixaban with lopinavir/ritonavir treatment.[37,38]

Lopinavir/ritonavir may also influence the activity of P2P12 inhibitors through CYP3A4 inhibition, lead to decreased serum concentrations of clopidogrel and prasugrel active metabolites, and increase serum concentrations of ticagrelor. In the United States and Canada, it is not recommended to use such drugs with ticagrelor due to the excessive risk of bleeding.[39,40]

On the contrary, clopidogrel may not always provide adequate platelet inhibition in the simultaneous administration of lopinavir/ritonavir.[41,42] Prasugrel may be preferable to other P2Y12 inhibitors during lopinavir/ritonavir therapy. However, it is contraindicated in cases such as a history of stroke or TIA, low BMI, or active pathological bleeding. A test-guided approach with alternative antiplatelet agents may be considered. Details about switching P2Y12 inhibitors have already been determined.[43] cangrelor metabolism is independent of hepatic function, so drug interaction is not expected.[44] HMG-CoA reductase inhibitors (statins) also have the potential to interact with the lopinavir/ritonavir combination. Co-administration may cause myopathy due to high statin levels. Lovastatin and simvastatin are contraindicated for co-administration with lopinavir/ritonavir due to the risk of rhabdomyolysis. Other statins, including atorvastatin and rosuvastatin, should be administered in the lowest possible dose, and they should not exceed the maximum dose indicated with lopinavir/ritonavir.[35]

Remdesivir is a research drug previously evaluated during the Ebola epidemic and currently studied in patients with COVID-19. Although extensive cardiovascular toxicities and drug interactions have not yet been reported, preliminary assessment of this drug during the Ebola epidemic noted the development of hypotension and subsequent cardiac arrest in one patient (out of a total of 175 patients).[45]

Other therapies

In addition to antiviral drugs, a large number of immunomodulators and secondary drugs are being investigated to prevent complications from COVID-19. Chloroquine, used as an antimalarial agent, blocks virus infection by increasing the endosomal pH required for virus/cell fusion and stops SARS-CoV2 activity in vitro.[46,47] Chloroquine and hydroxychloroquine act toxic to cardiac myocytes. Risk factors include prolonged exposure (> 3 months), higher weight-based dose, pre-existing heart disease, and kidney failure. Chloroquine cardiac toxicity occurs as restrictive or dilated cardiomyopathy or conduction abnormalities that are thought to be due to intracellular

inhibition of lysosomal enzymes in myocytes.[48]

Furthermore, due to the effects of chloroquine on CYP2D6 inhibition, beta-blockers (such as metoprolol, carvedilol, propranolol, or labetalol) metabolized via CYP2D6 may cause increased drug concentration that requires careful monitoring of heart rate and blood pressure changes. Finally, both agents are associated with the risk of conditional torsade de pointes in patients with electrolyte abnormalities or in combination with agents that prolong QT. Short-term exposure to these agents as expected in the treatment of COVID-19 poses a lower risk for these dose-dependent side effects.[49]

COVID-19 cases complicated by severe acute respiratory distress syndrome (ARDS) are currently treated by methylprednisolone.[50] This steroid cause fluid retention, electrolyte irregularity, and hypertension, and it also interacts with warfarin through an unknown mechanism. Clinicians advise observing these drug interactions. Finally, severe COVID-19 may create difficulties in the application of routine cardiovascular medications; for this reason, patients at a risk of ischemic heart disease or heart failure may worsen.[47]

Other recently published studies

Recent studies provide promising information for treatment and follow-up of COVID-19. Diaz et al.[51] showed that ACEi and ARB therapy increased the number of ACE2 receptors in experimental animals. ACE2 receptors serve as binding sites for SARS-CoV-2 virions in the lungs. This increase can produce serious disease outcomes. COVID-19 can suppress cardiac functions and cause myocardial damage. History of CAD and increased levels of cTnI are two major independent markers that affect clinical evolution of patients with COVID-19.[52]

In HT and DM, ACE2 enhancing drugs pose a risk for serious COVID-19 infection, so ACEi and ARB therapy require close monitoring. As calcium channel blockers (CCBs) have not been shown to affect ACE2 expression or activity, they may be an alternative therapy in COVID-19 patients.[53] Age, presence of underlying diseases, secondary infection, and high inflammatory indicators in the blood are determinants of mortality in COVID-19. COVID-19 mortality develops due to virus-activated "cytokine storm syndrome" or fulminant myocarditis.[54]

Previous cardiovascular metabolic history may further increase the severity of COVID-19 and greatly affect the prognosis of COVID-19. On the other hand, a marked increase in myocardial damage is observed in patients with COVID-19.[55] Recent studies have focused on the beneficial effect of chloroquine, an antimalarial drug, which is effective on the treatment of patients with SARS-CoV-2. Due to previous experiments with chloroquine in the field of antiviral research, the scientific community is more concerned with the treatment of chloroquine[56] Among cases of COVID-19, patients with comorbidities have worse clinical results than those without comorbidities. More comorbidity is associated with worse clinical outcomes.[57]

Recognizing acute myocarditis as a complication associated with COVID-19 is important for close follow-up of patients affected by COVID-19 and increased knowledge of public health officials about this type of complication. Clinical surveillance and laboratory tests, including troponin levels, are essential for proper identification of COVID-19 and reduction of transmission. More studies are needed to determine the effectiveness of corticosteroids in suppressing the myocardial inflammatory response. It cannot be denied that antiviral drugs or chloroquine can contribute to the recovery of patients with COVID-19.[58]

Myocardial injury has fatal consequences for COVID-19. Patients with a history of CAD without myocardial damage have relatively better prognosis. Myocardial damage triggers cardiac dysfunction and arrhythmias. Inflammation is one of the possible causes of myocardial injury. Closer follow-up and multiple treatment regimens should be considered for patients with a high risk of myocardial injury.[59] Cardiac damage has been common among patients hospitalized with COVID-19, and it is closely related to the risk of in-hospital mortality. More research is needed to clarify the mechanism of cardiac injury, and complications should be carefully monitored in COVID-19 management.[60]

Chen et al.[61] observed that the elderly, male patients, and/or patients with high ACE2 expression-related diseases had worse prognosis when exposed to COVID-19. With preclinical evidence, renin-angiotension system blockade was thought to alleviate COVID-19. Multicentre studies are needed to test the hypothesis before making recommendations on potentially essential drugs.[62]

Conclusion

SARS-CoV-2 causing COVID-19 is a global pandemic problem. KVH is more common in COVID-19 patients. Morbidity and mortality rate is high in these patients. Whether CVD is an independent risk or whether it is mediated by other factors (e.g. age) has not been clarified yet. Myocardial damage occurred in more than a quarter of critical cases. Clinical ACEi and ARB medications do not present problems according to the current evidence. Research is currently promising in terms of treatment.

Author contributions

Conception and design of the research: L.A., O.T., H.S.A. ; Acquisition of data: L.A., O.T., H.S.A. ; Analysis and interpretation of the data: L.A., O.T., H.S.A. ; Writing of the manuscript: L.A., O.T., H.S.A. ; Critical revision of the manuscript for intellectual content: L.A., O.T., H.S.A.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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This article does not contain any studies with human participants or animals performed by any of the authors.

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COVID-19: Updated Data and its Relation to the Cardiovascular System

Filipe Ferrari[1]

Graduate Program in Cardiology and Cardiovascular Sciences, Universidade Federal do Rio Grande do Sul, Hospital de Clínicas de Porto Alegre, Porto Alegre,[1] *RS – Brazil*

Abstract

In December 2019, a new human coronavirus, called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or coronavirus disease 2019 (COVID-19) by the World Health Organization, emerged in the city of Wuhan, China. Spreading globally, it is now considered pandemic, with approximately 3 million cases worldwide at the end of April. Its symptoms include fever, cough, and headache, but the main one is shortness of breath. In turn, it is believed that there is a relationship between COVID-19 and damage to the heart muscle, and hypertensive and diabetic patients, for example, seem to have worse prognosis. Therefore, COVID-19 may worsen in individuals with underlying adverse conditions, and a not negligible number of patients hospitalized with this virus had cardiovascular or cerebrovascular diseases. Systemic inflammatory response and immune system disorders during disease progression may be behind this association. In addition, the virus uses angiotensin-converting enzyme (ACE) receptors, more precisely ACE2, to penetrate the cell; therefore, the use of ACE inhibitor drugs and angiotensin receptor blockers could cause an increase in these receptors, thus facilitating the entry of the virus into the cell. There is, however, no scientific evidence to support the interruption of these drugs. Since they are fundamental for certain chronic diseases, the risk and benefit of their withdrawal in this scenario should be carefully weighed. Finally, cardiologists and health professionals should be aware of the risks of infection and protect themselves as much as possible, sleeping properly and avoiding long working hours.

Introduction

In December 2019, in the city of Wuhan, China, there was an explosion of cases of pneumonia caused by a novel coronavirus, called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),[1] identified as the agent that causes the disease called coronavirus disease 2019 (COVID-19), which is the name officially adopted by the World Health Organization. COVID-19 is a condition that can affect the lungs, respiratory tract, and others systems. Phylogenetic data imply a zoonotic origin,[2] and it has been shown that the transmission of the virus occurs from person to person. It has been detected in sputum, saliva, throat and nasopharyngeal swabs.[3] Therefore, it can spread through small droplets released from the nose and mouth of infected individuals. Some of the most observed symptoms are fever, fatigue, dry cough, upper airway congestion, sputum production, myalgia/arthralgia with lymphopenia, and prolonged prothrombin time.[4] However, one of the main symptoms may be shortness of breath.

Although evidence on the specific effects of COVID-19 on the cardiovascular system is still little-known, there are reports of arrhythmias, acute cardiac injury, tachycardia, and a high burden of concomitant cardiovascular disease in infected individuals, particularly in those with higher comorbidities and risk factors who require more intensive care.[5]

Diagnosis of SARS-CoV-2 can be made by electron microscopy morphology, but the method currently considered the gold standard is detection of nucleic acid in nasal swab, throat samples, or other respiratory tract samples by real time polymerase chain reaction (PCR), which is later confirmed by next generation sequencing.[6]

Finally, it should be noted that the best treatment is still prevention, and simple measures such as washing hands with soap, using alcohol gel, and disinfecting surfaces such as cell phones play an essential role in reducing the spread of the virus.

Epidemiology

Adults and the Elderly

More recent data indicate that by April 23 the number of confirmed cases of COVID-19 exceeded 2,700,000 worldwide.[7] On January 30, 2020, 9,976 cases of COVID-19 had been reported in at least 21 countries.[8] One month later, 83,652 cases were confirmed, with 2,791 deaths (3.4% mortality).[9] Cases were reported in 24 countries on 5 continents.[10] In Brazil, specifically, by March 3, 488 suspected cases had been registered, in 23 states.[11] In addition, as of April 23, approximately 49,500 cases and 3,313 deaths had been confirmed by COVID-19 in Brazil.[12] In Italy, on February 20, a young man in the Lombardy Region was hospitalized with an atypical pneumonia that later proved to be COVID-19. In the following 24 hours, there were 36 more cases, none of which had been in contact with the first patient or anyone known to have COVID-19.[13] Unfortunately, despite aggressive containment efforts, the disease continues to spread and the number of affected patients is increasing. The fatality rate is not low, and it is dominated by elderly patients.[12] Therefore, special attention should also be given to this population.

Keywords

Coronavirus; COVID 19; Acute Respiratory Syndrome; cardiovascular Diseases/complications; Myocarditis; Infectious Diseases; Risk Factors/prevention and control.

Mailing Address: Filipe Ferrari •
Universidade Federal do Rio Grande do Sul - Rua Mariana Prezzi, 617, 43B. Postal Code 95034460, Caxias do Sul, RS - Brazil
E-mail: ferrari.filipe88@gmail.com
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By April 23, the world had already registered 2,707,356 cases of COVID-19, including 83,880 cases in China. Of the 190,743 deaths from the disease as of April 23, 4,636 occurred in China. Europe had registered 1,193,276 cases, with 114,259 deaths,[7] making it the region with the largest 24-hour increase in new infections. Several regions have also registered their first cases, including Somalia, Benin, Liberia, and the Bahamas.[14]

There are uncertainties about the estimates of the true number of infected people, which is crucial to determine the severity of infection and the incidence of mild or asymptomatic cases, as well as their possible transmission.[15]

Children

Epidemiological factors of COVID-19 among children are scarce. Dong et al.[16] through a retrospective analysis of children with a mean age of 7 years included in the Chinese Center for Disease Control and Prevention from January 16 to February 8, 2020, found that there were 731 confirmed cases in the laboratory and 1,412 suspected cases. Importantly, more than 90% of these individuals were asymptomatic or had only mild or moderate symptoms. These data draw attention to the fact that not only adults and the elderly, but also children of any age are susceptible to COVID-19. Therefore, attention and care should be directed to the entire population, without distinction.

COVID-19 and the Cardiovascular System

Respiratory infections and influenza can play an important role in the short-term increase of risk of myocardial infarction and ischemic stroke.[17] SARS-CoV-2 has a pathogenicity that can increase damage to the myocardium caused by this viral infection. The data suggest that acute cardiac injury, shock, and arrhythmia were present in 7.2%, 8.7%, and 16.7% of patients, respectively, and their prevalence was higher among patients requiring intensive care.[10] Based on the fact that the virus can cause damage to the cardiovascular system, careful attention should be given to cardiovascular protection during treatment of COVID-19.[18] In fact, cardiovascular disease and hypertension have been associated with an increased case fatality rate of COVID-19 in China.[19]

Myocardial injury associated with SARS-CoV-2 was reported in 5 of the first 41 patients diagnosed with COVID-19 in Wuhan, who had high-sensitivity cardiac troponin I levels > 28 pg/ml.[20] In another study, conducted in 2019, Panhwar et al.[21] observed that concomitant infection by influenza increased risks in hospitalized patients with heart failure. In a survey of 25 patients who had recovered from SARS-CoV-1 infection, almost half of them had changes in the cardiovascular system, and 60% had glucose metabolism disorders.[22] Another study included 1,099 patients with confirmed COVID-19, 173 of whom had severe disease, with comorbidities of hypertension (23.7%), diabetes mellitus (16.2%), coronary diseases (5.8%), and cerebrovascular disease (2.3%).[23]

When evaluating data from 138 patients hospitalized for COVID-19 in China, the median time between the first symptom and dyspnea was 5 days, and 7 days between the first symptom and hospital admission. Computed tomography of the chest showed bilateral patchy shadows or ground glass opacity in the lungs of all patients. Approximately 90% of patients received antiviral therapy with oseltamivir, and more than 60% received antibacterial therapy with moxifloxacin. Thirty-six patients were transferred to the intensive care unit due to complications, including acute respiratory distress syndrome (61.1%), arrhythmia (44.4%), and shock (30.6%). Patients who required intensive care were older and more likely to have underlying comorbidities, as well as dyspnea. On February 3, 34% were discharged and 6 died, representing an overall mortality of 4.3%.[10]

In COVID-19 patients, the incidence of cardiovascular symptoms is high, due to systemic inflammatory response and immune system disorders during disease progression. Patients with underlying cardiovascular disease who are infected by COVID-19 may then have worse prognosis. Special attention should, therefore, be given to cardiovascular protection during treatment for COVID-19.

Angiotensin-Converting Enzyme Receptors and Angiotensin Receptor Blockers

COVID-19 uses angiotensin-converting enzyme (ACE) receptors, more precisely ACE2, to penetrate the cell. It has thus been hypothesized that the use of ACE inhibitors and angiotensin receptor blockers (ARB) could increase these receptors, facilitating the penetration of the virus.[24]

In a note, the Brazilian Society of Cardiology recently emphasized data on the importance of the use of drugs such as ACE inhibitors and ARB, as there is no clear evidence to support the association between therapy with these drugs and worsening prognosis of the disease.[25] It is thus recommended that physicians carefully evaluate the risk-benefit balance before suspending drugs, given that they are fundamental pillars for management of chronic diseases, such as hypertension and heart failure. Likewise, patients should not interrupt their use indiscriminately without first consulting their physicians.

Final considerations

Coronavirus is a family of viruses that cause respiratory infections. COVID-19 is a serious disease, which requires special care. Individuals who present fever, cough, and shortness of breath should seek medical service. Contrary to what many may believe, COVID-19 is not a disease restricted to older adults; young people and children can also become infected. However, older patients who have cardiovascular disease and are infected with COVID-19 may have worse prognosis. Frequent hand washing, use of alcohol gel, covering the nose with the inside of the arm, and avoiding crowded environments can play an important role in reducing the spread of the virus and aggravation of the disease, especially in patients with cardiovascular disease.

Author contributions

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Physical Exercise in Patients with Heart Disease and in the General Population in Times of Coronavirus

Ricardo Stein[1]

Universidade Federal do Rio Grande do Sul,[1] Porto Alegre, RS – Brazil

I will begin this text without speaking about exercise. I want to emphasize that individuals with chronic diseases, such as hypertension, heart failure, different types of myocardiopathy, and some forms of arrhythmia are at an increased risk of fatal outcomes after contracting SARS-COV-2 and developing the infection denominated COVID-19. In the same manner, those who have undergone mechanical or surgical revascularization, individuals with prosthetic valves (whether biological or metallic), pacemakers, implanted defibrillators, or other devices, as well as those with some forms of congenital heart disease are also part of a higher risk group.[1]

First point: The patients described above are definitely at a higher risk and they are part of the risk group regardless of age.*

*Note: Like individuals with heart disease, the elderly, immunosuppressed patients, and individuals with some chronic diseases, such as diabetes and pulmonary disease, are also at an increased risk of being infected.

- This raises the question, "Regarding exercise in individuals with heart disease and in the general population, how should we proceed? There is a consensus that regular practice of physical exercise should continue, even in isolation at home; this position is clear among cardiologists, exercise physicians, and other specialists. Naturally, on one hand this may seem difficult, but, on the other, the increase in available time will do away with the excuse that "I don't have time." The week continues to be made up of 168 hours. Is it not possible to dedicate five half-hour periods, at least, to some type of exercise at home?

Second point: Exercising at home is indicated for the following two reasons: a) It follows the main criterion of care against SARS-COV-2 infection that causes COVID-19; b) it is healthy.

- This, however, brings up another question: If I feel well, why can't I exercise in the street, in public squares, in gyms, or in condominiums? If we think in individual terms, going out or running on the condominium treadmill does not appear to be problematic. However, social and epidemiological reasoning indicates that the chance of there being a crowd increases and this goes against specialists' recommendations. Imagine if everyone decided to go to the sidewalk next to the beach or to the park to jog at the same time… It would be wonderful… for the virus!!!

Third point: In the risk-benefit ratio, specialists recommend not leaving home to exercise during this pandemic moment.

- Another question seems important to me: If I have signs and/or symptoms, should I exercise? No!!! Exercise should not be practiced in the presence of signs and/or symptoms, neither in this nor in any other situation of infection. The best thing to do is rest until you have fully recovered.

Fourth point: If you are symptomatic, do not exercise, not even at home. After you have recovered, return to practicing as indicated.

- Another relevant point deals with previous history of exercise. It would be great if everyone were physically active and inactivity were a minor issue. Some people think that because they are active or athletic they are immune to SARS-COV-2. Not at all!!! High performance athletes have already contracted COVID-19 and recovered or are in recovery; some have even been hospitalized.

Fifth point: Active or athletic individuals should follow the same precautions as the rest of the population, as they are at the same risk of contracting the disease as any other human being.

- Many of us had childhoods filled with physical activity. We played hula hoop, jump rope, hopscotch, and hide and seek, as well as other games that we still remember and that remind us a time with no pandemics but that will inexorably never return. Faced with the current scenario, why not take advantage of this time with your children; reiterating: make the most of this time with your children, which was something many of us could not imagine was possible a few weeks ago!!! Drag them out of bed or off the sofa; encourage them to give WhatsApp, games, and Netflix a break. Go play!!!

Sixth point: *Return to the past*. Encourage your children to be less sedentary. According to the World Health Organization, it is ideal that adults dedicate 150 minutes to exercise weekly and that younger individuals exercise for at least 300 minutes weekly.[2] In short, integration of the family promotes the family's own health.

- Not all physical activity is exercise, but all exercise is a form of physical activity. There are countless examples, sweeping, ironing, cleaning and/or vacuuming, gardening,

Keywords

Coronavirus; COVID-19; Exercise; Physical Activity; Life Style; Sedentarism; Cardiovascular Diseases; Risk Factors; Healthy Diet; Residence

Mailing Address: Ricardo Stein •
Rua Ramiro Barcelos, 2350 - Serviço de Fisiatria/Térreo.
Postal Code 90035-903, Porto Alegre, RS – Brazil
E-mail: kuqui.r@gmail.com
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working in the yard, going up and down the stairs (with precaution if the stairs in an apartment building are being used by other residents at the same time), and others.[2]

Seventh point: Intensify physical activity at home on a daily-to-day basis. You and your family will have a more active, healthier, and more productive lifestyle.

- Sexual activity is a form of physical exercise/activity. For many, it is the most pleasurable one. In times of isolation-coronavirus, this is a general concern. We certainly do not have scientific data, but logic leads us to think that distancing should come before desire, that common sense should be more prevalent than the pleasure principle.

Eighth point: Unfortunately, it is recommended that sexual activity involving hugging, touching, kissing, and penetration be avoided (in the scenario of occasional sexual activity, of course). Masturbation, the use of vibrators and erotic toys is not contraindicated. If objects are to be shared, it seems to me that they should be washed with water and soap and/or 70% alcohol gel (this is merely an intuitive deduction, given that there are no studies testing hypotheses on this subject).

- Readers of the Archives, regarding this theme, it would certainly be possible to list several other points, but it seems to me that at the end of these indications what is most important is to emphasize that physical inactivity in a treacherous enemy. Its effects typically do not manifest in an acute manner as is the case with SARS-COV-2, whose effects need to be combated with emergency health measures based on the best scientific evidence. In turn, by negatively affecting the cardiovascular, respiratory, metabolic, muscular, and immune systems, physical inactivity is also very harmful. In conclusion, the previous eight points were written in order to provoke reflection that at this moment we must live within the confines imposed by this new global order that is restrictive, but not limiting.

Author contributions

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COVID-19 and Hypercoagulable State: A New Therapeutic Perspective

Jorge Henrique Paiter Nascimento,[1] Bruno Ferraz de Oliveira Gomes,[1,2] Plínio Resende do Carmo Júnior,[1] João Luiz Fernandes Petriz,[2,3] Stephanie Itala Rizk,[4,5] Isabela Bispo Santos da Silva Costa,[6] Marcus Vinicius Guimarães Lacerda,[7] Fernando Bacal,[8] Ludhmila Abrahão Hajjar,[9] Gláucia Maria Moraes de Oliveira[1]

Universidade Federal do Rio de Janeiro – Cardiologia,[1] Rio de Janeiro, RJ - Brazil
Rede D'Or São Luiz – Cardiologia[2] Rio de Janeiro, RJ - Brazil
Hospital Barra D'Or – Cardiologia,[3] Rio de Janeiro, RJ - Brazil
Universidade de São Paulo Instituto do Câncer do Estado de São Paulo,[4] São Paulo, SP - Brazil
Universidade de São Paulo Instituto do Coração,[5] São Paulo, SP - Brazil
Hospital Sírio-Libanês - Instituto Sírio Libanês de Ensino e Pesquisa,[6] São Paulo, SP - Brazil
Fundação de Medicina Tropical Dr Heitor Vieira Dourado,[7] Manaus, AM - Brazil
Universidade de São Paulo Faculdade de Medicina Hospital das Clínicas Instituto do Coração,[8] São Paulo, SP - Brazil
Intituto de Coração – Cardiopneumologia,[9] São Paulo, SP – Brasil

The novel coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is responsible for the outbreak of the viral pneumonia identified for the first time in the Chinese city of Wuhan at the end of 2019. The outbreak has expanded rapidly, affecting 184 countries. The experience acquired in past months identified different clinical presentations with varied severity, ranging from asymptomatic infection to death due to multiple organic dysfunction. The World Health Organization (WHO) has recently defined the complex process of the SARS-CoV-2 infection as novel coronavirus disease 2019 (COVID-19).

COVID-19, whose notification grows fast in different countries, currently affects more than one million people worldwide according to the WHO, which has characterized the infection as a pandemic.[1] As of April 29, 2020, Brazil had registered 73,235 confirmed cases of COVID-19 and 5,083 deaths, with a case-fatality rate of 6,9%.[2] Hospitalization is necessary in up to 20% of the patients infected by SARS-CoV-2, and 5% to 10% of them require admission to the intensive care unit because of the need for hemodynamic and/or ventilatory support.[3-7] The mortality rate ranges from 0.8% to 12% depending on the country, and this difference might result from multiple factors, of which the healthcare system structure stands out.[8-11] Patients with the moderate and severe forms of the disease had manifestations mainly of the respiratory system involvement, with clinical findings ranging from mild pneumonia to acute respiratory distress syndrome (ARDS).[7,11-13]

Keywords

COVID-2019; Betacoronavirus; Catastrophic Illness; Viral, Pneumonia; Pandemics; Coronavirus Infections; Complications, Cardiovasculares; Thrombophilia; Anticoagulants/therapeutic use.

Mailing Address: Gláucia Maria Moraes de Oliveira •
Universidade Federal do Rio de Janeiro – Cardiologia - Universidade Federal do Rio de Janeiro Rua Visconde de Pirajá, 330 Sala 1114. Postal Code 21941-901, Rio de Janeiro, RJ – Brazil
E-mail: glauciamoraesoliveira@gmail.com
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Complications usually occur between the 7th and 12th day of disease.[3,14] The most severe clinical manifestation, ARDS, is characterized by hypoxemia, bilateral pulmonary infiltrate, and variable phenotypic presentations, such as 'normal lung compliance and low potential for lung recruitment' and 'low lung compliance and high potential for lung recruitment'. From 20% to 30% of the patients have cardiovascular complications, such as myocardial ischemia, acute coronary syndrome, myocarditis, arrhythmias, heart failure and shock. Kidney failure occurs in 30-50% of critically ill patients infected by SARS-CoV-2, 30% of whom require renal replacement therapy.[14-17]

The SARS-CoV-2 enters the cell via the angiotensin-converting enzyme 2 (ACE2) receptor present in the alveoli. The severe form of the infection is characterized by an intense immune-inflammatory response, evidenced by the presence of neutrophils, lymphocytes, monocytes and macrophages.18 Minimally invasive autopsies have revealed diffuse alveolar damage, hyaline membrane formation and interstitial mononuclear inflammatory infiltrate, with microcirculatory thrombosis.[17] High serum levels of pro-inflammatory cytokines (interleukins 1 and 6, tumor necrosis factor and interferon-γ), known as "cytokine storm", have been reported in those patients.

Thrombosis and damage to extrapulmonary organs have been observed without the confirmed presence of the virus in those sites, which led to the assumption that SARS-CoV-2 infection involves intense inflammatory response with a hypercoagulable state and ischemia, aggravated by hypoxemia.[17,19,20] In Brazil, preliminary findings of minimally invasive autopsies performed at the São Paulo Medical School have shown similar results to those from China.[21]

When elevated, D-dimer, a product of fibrin degradation, has been associated with a higher mortality rate.[22] Expert opinion, based on clinical experience and analysis of a few descriptive studies, highlights the role of the hypercoagulable state on the pathophysiology of COVID-19, supported by the progressive increase in D-dimer levels as the disease worsens. The phase in which ARDS develops and the radiographic pattern worsens is marked by the significant elevation of D-dimer. The most severe cases develop myocardial injury and disseminated intravascular coagulation (DIC).[23,24]

Systemic inflammatory response in patients with infection can result in endothelial damage, with a consequent increase in thrombin generation and a reduction in endogenous fibrinolysis.[25,26] This prothrombotic state is called sepsis-induced coagulopathy (SIC) and precedes DIC.[27,28] The several mechanisms involved in SIC act simultaneously towards a pro-hemostatic state. Apparently, inflammatory cytokines are the most important factors mediating that coagulation system disorder during sepsis.

Evidence has shown a bidirectional relationship between inflammation and coagulation, in which inflammation activates coagulation, and coagulation heightens inflammatory activity (Figure 1).[29-32] Platelets play a central role in the development of coagulation abnormalities in sepsis and they can be activated directly by pro-inflammatory mediators, such as platelet activating factors, as well as by the thrombin generated. Platelet activation can also stimulate the formation of fibrin via an alternative mechanism. The expression of P-selectin in platelet membrane not only mediates the adhesion of platelets to leukocytes and endothelial cells, but also increases the tissue factor expression in monocytes. Under normal circumstances, the activation of coagulation is controlled by three important physiological anticoagulant pathways: the antithrombin system, the activated C-protein system, and the tissue-factor pathway inhibitor. In sepsis, all three pathways are dysfunctional. Amidst all this coagulation system imbalance, endogenous fibrinolysis is largely reduced.

According to the criteria established by the International Society on Thrombosis and Hemostasis (ISTH), better clinical outcomes can be identified in patients with SIC on anticoagulant therapy.[27,28] The use of anticoagulants, mainly in critically ill patients, is not free from risk and might be related to severe hemorrhagic complications. Thus, the indication of anticoagulants should be personalized, respecting thrombotic and hemorrhagic risk profiles.

Hemophagocytic syndrome (HPS) is characterized by a systemic inflammatory response triggered by the inappropriate activation and proliferation of lymphocytes, which activate macrophages and histiocytes, resulting in phagocytosis of hematological cells. The disease is associated with a large

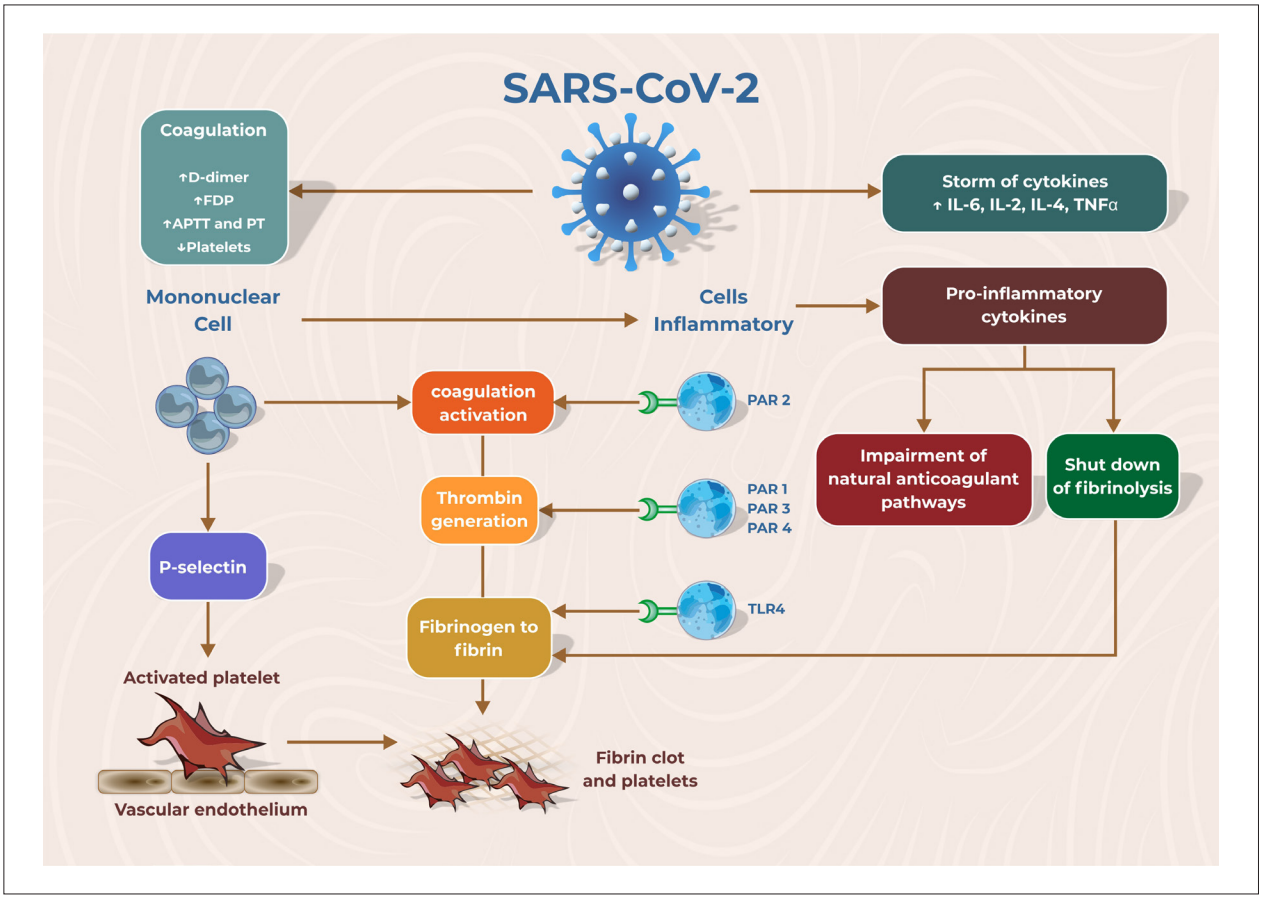

Figure 1 – *The novel coronavirus, SARS-CoV-2, activates the inflammatory and thrombotic process. The disease it causes is associated with an increase in inflammatory cytokines (cytokine storm) and coagulation disorders, with predisposition to thrombus formation. Mononuclear cells interact with activated platelets and the coagulation cascade, which activate inflammatory cells by binding thrombin and tissue factor with specific protease activated receptors and by binding fibrin to Toll-like receptor 4. The activation of inflammatory cells results in the release of pro-inflammatory cytokines, leading to impairment of the natural coagulation pathways and shut down of fibrinolysis. PAR: protease-activated receptor; TLR4: Toll-like receptor 4; aPTT: activated partial thromboplastin time; PT: prothrombin time; IL: interleukin; TNFα: tumor necrosis factor-α. Figure adapted from Levi M, van der Poll T.*[25]

production of inflammatory cytokines. The initial clinical findings of HPS are marked by those of the systemic inflammatory response syndrome. As HPS develops, the following might be observed: neurological findings, liver function changes, DIC, hepatosplenomegaly, pancytopenia, and high ferritin levels. Those findings can be triggered by infections, such as COVID-19, which shows, in some cases, a large release of cytokines, mainly interleukin 6, in association with systemic inflammatory response and DIC. Such conditions should be considered based on clinical and laboratory findings, and an early therapeutic approach should be defined to reverse them.[28]

SARS-CoV-2 infection, in its most severe presentation, marked by organic dysfunction, such as acute respiratory failure, meets the diagnostic criteria for sepsis.[33] Recent observational studies have correlated the hypercoagulable state with the severe form of COVID-19, in which SIC and/or DIC seem to be present in most fatal cases.[3,21-23,34] The reduction in oxygen arterial pressure found in critical patients contributes directly and indirectly to the development of ischemic syndrome.[35] In line of this, results suggest that the prothrombotic pathophysiology already described in sepsis might be related to intrinsic aspects of the novel coronavirus, and, thus, the beneficial potential of the use of anticoagulants in selected groups of patients should be analyzed individually. A retrospective study conducted in the hospital of Tongji (Wuhan, China) has reported lower mortality in patients with severe COVID-19 who had used anticoagulants, unfractionated heparin or low-molecular weight heparin (LMWH), with a SIC score of ≥ 4 and/or very high D-dimer (> 6 times the upper limit of reference range).[36]

Anticoagulant therapy in patients with severe COVID-19 and signs of SIC and/or very high D-dimer in association with other biomarkers of severity, in the absence of contraindication to anticoagulation, can be considered a therapeutic strategy for SARS-CoV-2 infection, based on expert consensus and a few retrospective studies. Moreover, that strategy requires the use of strict institutional protocols that enable surveillance and rapid intervention if complications occur. Figure 2 shows the algorithm to assess thrombogenesis in patients with COVID-19, as well as a suggestion of treatment. However, data are still insufficient to determine important aspects for the elaboration of a therapeutic plan, such as the best drug choice, its dosage and administration time schedule, as well as the duration of treatment.

Further studies, mainly prospective, are required to better support the indication of anticoagulation for critical patients infected by the novel coronavirus. The possible benefit from attenuating the hypercoagulable state should be balanced against the risk of bleeding. Anticoagulant therapy might be more beneficial when initiated in the pre-thrombotic stage and not in advanced

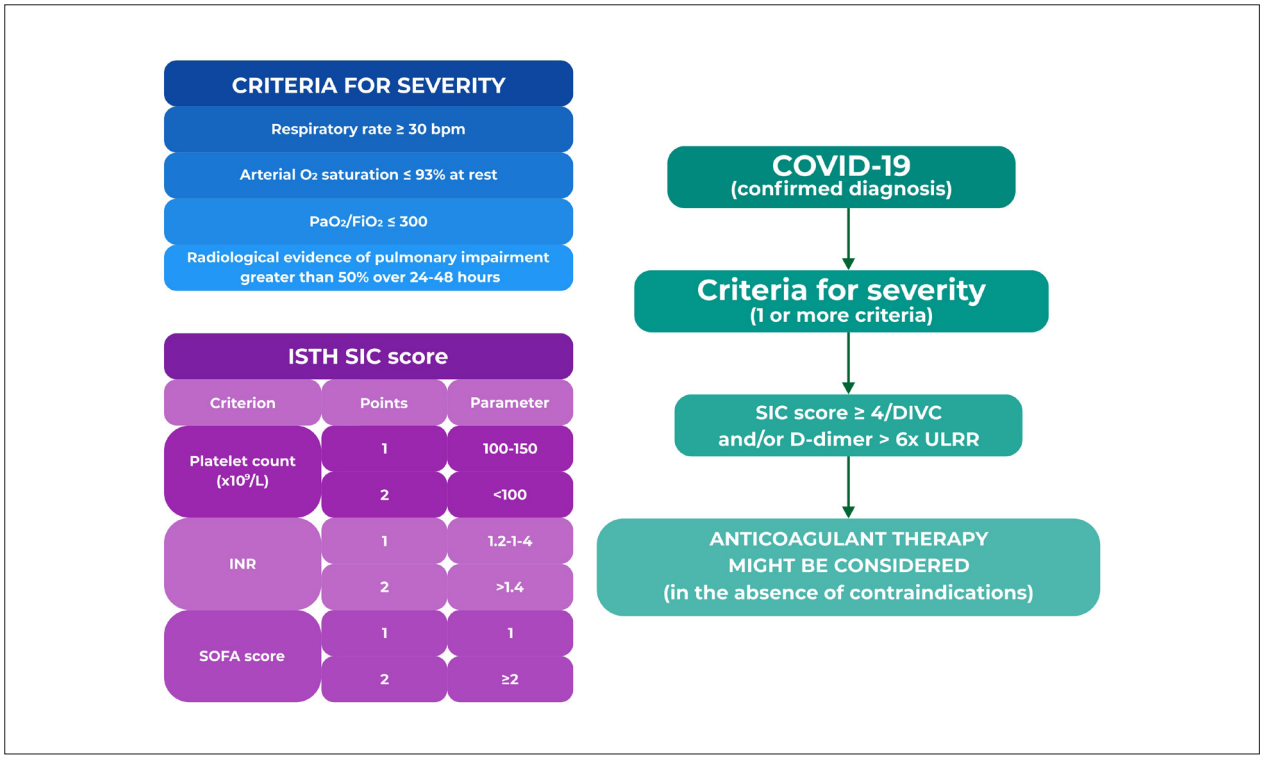

Figure 2 – *The diagnosis of COVID-19 should be confirmed according to the World Health Organization recommendations.37 Patients with the severe form of that disease8,38 in addition to a sepsis-induced coagulopathy score ≥ 4 or disseminated intravascular coagulation and/or D-dimer levels > 6 times the upper limit of reference range might benefit from anticoagulant therapy. INR, international normalized ratio; SIC, sepsis-induced coagulopathy; ISTH, International Society on Thrombosis and Hemostasis; SOFA, sequential organ failure assessment; DIVC, disseminated intravascular coagulation; ULRR, upper limit of reference range.*

phases, when the risk of bleeding is higher. If deciding to use anticoagulation, LMWH should be chosen for stable patients with normal creatinine clearance (dose of 1 mg/kg, 12/12h, subcutaneous). In case of shock or creatinine clearance below 50 mL/min/m², intravenous heparin (18 IU/kg/h) should be used, aiming at an activated partial thromboplastin time between 1.5 and 1.8. However, there is no evidence to support the wide use of the therapeutic dose of heparin in COVID-19.

In conclusion, the pathophysiology of COVID-19 involves activation of the inflammatory response and induction of the thrombotic system. Currently, the expert consensus suggests anticoagulant treatment for patients with the pro-coagulant phenotype (high D-dimer, prolongation of prothrombin time and increased plasma levels of fibrin fragments). Further studies are required to confirm the real role of anticoagulation to prevent COVID-19 complications.

Author contributions

Conception and design of the research and Critical revision of the manuscript for intellectual content: Nascimento JHP, Gomes BFO, Resende P, Petriz JLF, Rizk SI, Costa IBSS, Lacerda MVG, Bacal F, Hajjar LA, Oliveira GMM; Acquisition of data: Nascimento JHP, Gomes BFO, Resende P, Petriz JLF, Costa IBSS, Lacerda MVG, Bacal F, Hajjar LA, Oliveira GMM; Analysis and interpretation of the data: Nascimento JHP, Gomes BFO, Resende P, Petriz JLF, Rizk SI, Costa IBSS, Hajjar LA, Oliveira GMM; Statistical analysis: Nascimento JHP, Gomes BFO, Resende P, Petriz JLF, Oliveira GMM; Obtaining financing: Lacerda MVG; Writing of the manuscript: Nascimento JHP, Gomes BFO, Resende P, Petriz JLF, Lacerda MVG, Bacal F, Oliveira GMM.

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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Cardiovascular Implications in Patients Infected with Covid-19 and the Importance of Social Isolation to Reduce Dissemination of the Disease

Juliana Alves Costa,[1] *Juliana de Almeida Silveira,*[1] *Sara Cristine Marques dos Santos,*[1] *Patrícia Pereira Nogueira*[1]
Universidade de Vassouras – Cardiologia,1 Rio de Janeiro, RJ – Brazil

Abstract

Respiratory symptoms, especially the development of severe acute respiratory distress syndrome, dominate the discussion and initial concerns of the population and health professionals. However, the cardiovascular system is greatly affected by these conditions and is often responsible for complications and mortality of these patients. In order to show the cardiovascular implications in patients infected with COVID-19 and the importance of social isolation as an alternative to curb the spread of the disease, a literature review was carried out based on 37 articles, in English, Portuguese and Spanish, available on Scielo and PubMed. The findings showed that cardiac complications associated with COVID-19 infection are similar to those produced by: severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and influenza. However, COVID-19 has a much greater and faster contamination and, unlike influenza, there is no vaccine or treatment available yet. In view of this, social isolation becomes a tool that can reduce and flatten the curve of cases and thus protect the people at higher risk, decreasing the chances of serious conditions related to the disease, potential deaths and the collapse of the country's health system.

Introduction

Coronavirus is a virus belonging to the *Coronaviridae* family, causing simple flu to diseases that can cause greater risks to the population's health. The novel coronavirus, which caused the 2020 pandemic, received the name SARS-CoV-2 by the World Health Organization (WHO), and the disease it causes has the name: COVID-19.[1] It was first detected in December 2019 in Wuhan, China. However, due to its high dissemination power, several countries confirmed the presence of allochthonous cases in mid-January 2020. In Brazil, the first case was confirmed on February 26, 2020.[2,3]

Keywords

Coronavirus; COVID-19; Infecções por Coronavirus/prevention and control; Social Isolation; Diseases Dissemination.

Mailing Address: Juliana Alves Alves Costa •
Universidade de Vassouras - Cardiologia
Av. Expedicionário Osvaldo de Almeida Ramos, 280. Postal Code 27700-000, Centro, Vassouras, RJ - Brazil
E-mail: jujuh.ac@hotmail.com
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Until the appearance of SARS-CoV-2, two other epidemics caused by coronavirus were described: SARS-CoV-1, which causes severe acute respiratory syndrome (SARS), in 2002; and MERS-CoV, which caused the Middle East respiratory syndrome (MERS), in 2012.[4] The pathophysiology of SARS-CoV-2 was similar to that of SARS-CoV-1, as they present acute lung injuries due to the aggressive inflammation initiated by viral replication. SARS-CoV-2 infection can cause increased secretion of pro-inflammatory interleukins and interferon-gamma (IFN-γ) that cause lung damage.[5]

Brazil, like other countries, is going through the process of demographic transition that has the aging of the population as its main effect. Thus, diseases of the circulatory system appear as the main cause of mortality in the population. By associating this information with recent studies of cardiovascular implications and their worsening by SARS-CoV-2, it is evident that prevention and control measures that reduce risks of contamination and infection are important tools in the reduction of severe cases of the disease and potential deaths.

This article relates the current pandemic of COVID-19 with the cardiovascular implications, showing the importance of social isolation as a measure to prevent and control the spread of the disease and preserve the country's Health System.

Material and methods

Literature review based on 37 articles, in English, Portuguese and Spanish, available on Scielo and PubMed, referring to the cardiovascular implications in patients infected with Covid-19, the importance of social isolation as a measure of prevention and control of disease spread and preservation of the country's health system.

Overview of COVID-19

The COVID-19 pandemic, as well as previous epidemics of other coronaviruses (SARS and MERS) and the 2009 pandemic (H1N1), have serious consequences for the health, economic and social models of the entire world population.

Although demographic transition occurs differently from country to country, in general, is characterized by an increase in the elderly population compared to other age groups, as it grows about 4% per year. Factors such as reduced fertility, reduced infant mortality and general mortality, improvements in health care for the population, technological development with regard to the diagnosis and treatment of diseases also corroborate the current demographic scenario.[6]

Concomitantly with the increase in the number of elderly people, there is an epidemiological transition, with an increase in the proportion of circulatory diseases, diabetes mellitus,

neoplasms, diseases due to external causes and diseases of the respiratory system.[7] Studies show that a higher frequency of comorbidities is commonly related to older age.

The mortality rate of COVID-19 can be nine times higher among people with some chronic disease compared to that of patients without any pre-existing pathology. Data provided by the World Health Organization (WHO) in February show that in the group of infected people without comorbidities, only 1.4% died. Among patients with some cardiovascular disease, for example, the rate reached 13.2%. Considering all infected patients, lethality was 3.8%, but it is worth mentioning that, due to the progress of the pandemic, new statistical data has been added to the studies.

The severe form of the disease was observed in older patients[8,9] who had a more significant number of comorbid conditions compared to non-severe patients. These findings suggest that age and associated comorbidities may be one of the risk factors for critically ill patients. Besides, the elderly and immunosuppressed patients may manifest atypical symptoms and other forms of presentation, including mild, moderate and severe pneumonia and, in more severe cases, severe acute respiratory syndrome, sepsis, septic shock and death.[4]

In a case report of 138 patients hospitalized with COVID-19, 16.7% of patients developed arrhythmia and 7.2% suffered acute cardiac injury, in addition to other complications related to COVID-19. Published reports indicate cases of acute onset heart failure, myocardial infarction, myocarditis and cardiac arrest.[10] Moreover, cases of myocardial damage, with increased troponin I, acute cardiac damage, shock and arrhythmia, were found.[11,12]

In the acute phase of severe viral conditions, not only in COVID-19, but also in other Coronavirus illnesses, the patient may present tachycardia, hypotension, bradycardia, arrhythmias and sudden death. Abnormal findings on electrocardiograms and increased troponin signal myocardial involvement in the form of myocarditis.[11,12]

Cohort studies published to date show rates of acute heart failure, shock and arrhythmia of 7.2%, 8.7% and 16.7%, respectively. Cardiovascular involvement is due to a mismatch between the increased metabolic/inflammatory demand triggered by the virus and reduced cardiac reserve. The inflammatory state makes the environment more prone to thrombotic phenomena. Therefore, the recommendation has been that patients' chronic medications should be maintained, with their withdrawal/replacement being assessed on an individual level and in accordance with the guidelines in force so far. It is worth noting that new recommendations may emerge as new studies in progress come out.[13,14]

Chronic diseases, such as hypertension, diabetes, diseases of the respiratory system, cardiovascular diseases and their conditions of susceptibility, share some standardized states with infectious diseases, such as pro-inflammatory state and the attenuation of innate immune response. Diabetes, for example, occurs partly because the accumulation of innate immune cells activated in metabolic tissues leads to the release of inflammatory mediators, especially IL-1β and TNFα, which promote insulin resistance and damage to β cells.[15] Moreover, metabolic disorders can lead to depression of the immune function, impairing the function of macrophages and lymphocytes,[16] which can make individuals more susceptible to complications and aggravations of COVID-19.[9]

Many of the older patients who become seriously ill have evidence of underlying diseases, such as cardiovascular diseases, liver diseases, kidney diseases or malignant tumors.[17-19] These patients usually die from their original comorbidities. Therefore, the accurate assessment of all original comorbidities of individuals with COVID-19 must be rigorously analyzed and considered from an individualized therapeutic perspective.

Other studies add that the respiratory failure aggravated by SARS-CoV-2 occurs due to massive alveolar damage. This virus is capable of infecting human respiratory epithelial cells through an interaction between the viral S protein and the angiotensin-converting enzyme 2 receptor in human cells. Although there is evidence in the literature that the presence of severe lung infections can affect the long-term prognosis of individuals with heart diseases, there is no data to confirm that patients recovered from COVID-19 infection will experience long-term effects.[20,21]

Thus, not only capable of causing pneumonia, COVID-19 can also cause damage to other organs, and patients end up dying from multiple organ failure, shock, acute respiratory distress syndrome, heart failure, arrhythmias and kidney failure.[22] Potential injuries to multiple organs and their protection and prevention should be monitored in the treatment of COVID-19.[23] In these critical patients, the necessary protective measures include mechanical ventilation, glucocorticoids, antivirals, symptomatic treatments and shock therapy.

Another important factor would be the approach to estimating the transmissibility of a virus by calculating its reproductive number (R0), which represents a measure of its attack rate, that is, it translates the number of secondary infections that occur from an infected individual in a susceptible population. Preliminary studies pointed out that this new coronavirus, responsible for COVID-19, would be associated with R0 rates of 1.5 to 3.5, with the most recent data suggesting an R0 of 4.08 (i.e., for each case, on average , there would be four new infected individuals).[7]

As it has a high potential for dissemination1 and, knowing that it is an RNA virus, enveloped and contaminated by respiratory droplets or contact, hygiene measures must be improved and put into practice. These are: washing our hands with soap and water to destroy the morphological structure of the virus, using 70% alcohol-based hand sanitizer, covering our mouth when coughing or sneezing to prevent viral particles from spreading through the environment, avoiding crowds and staying in a well-ventilated area.[3,4]

According to the literature, the average incubation period for coronavirus is 5 days, with intervals that can be as long as 12 days. Preliminary data for SARS-CoV-2 suggest that transmission may occur even without the appearance of signs and symptoms.[4,5]

When there are no complications, the symptoms consist of fever, dry cough and tiredness. Runny nose and nasal congestion, sore throat and diarrhea may also occur. Furthermore, most of those infected are asymptomatic (about

80%) and recover without requiring any special treatment, while 1/6 of the patients can progress severely, with breathing issues.[24,25]

In view of the current situation, it is extremely important for the population to act conscientiously and stay at home, whether symptomatic or not, with the aim of reducing the number of infected people and delaying the disseminated community transmission, so that the public health system may be able to serve everyone.[26] Otherwise, the exponential growth of the disease may break the health system, leading to the death of the most fragile ones. Those who need to hang around in public places, due to work or force majeure, should take preventive measures.[27]

Slowing down the spread of the virus so that the number of cases spreads over time instead of having peaks in the beginning is one of the ways to flatten the epidemic curve and prevent the public health system from collapsing and, as a consequence, many people end up dying (Figure 1). Controlled disease transmission reduces pressure on the health system and increases the capacity of taking care not only of patients infected with coronavirus, but also those requiring medical care due to other illnesses.

Staying at home is intended to provide a means of precaution to reduce the risk of transmitting respiratory infections, such as that caused by the coronavirus (COVID-19). These special precautions prevent the contact of respiratory secretions of a person who may be infected with the coronavirus from coming into contact with others.[19] People who have tested positive for the said virus or are under suspicion should remain at home. Ideally, the individual should be alone in a bedroom or in a room that may temporarily serve as a bedroom, with a private bathroom if possible.[28,29] The bedroom doors should be closed all the time, but the windows should be open so that the area may stay well ventilated. The patient should only leave this isolated room if necessary.[30-32]

Therefore, social isolation and preventive measures are necessary to prevent, mainly, that the elderly get infected and worsen preexisting diseases, complicating their health situation and leading to signs and symptoms that can often be fatal.[33,34] When a disease spreads quickly, services are overcrowded, there are not enough beds, masks, doctors, ventilators and other equipment for those in need, and this is not only for COVID-19, but for any other illness that requires the patients to seek health care. The system must be prevented from collapsing.[35]

Final considerations

There is consensus among the authors that the group at higher risk for developing the most severe form, which may lead to death, includes the elderly and individuals who have the most prevalent comorbidities, including cardiovascular diseases.[36]

The crucial thing is not the severity of the disease itself, but the ability to care for all those infected when they need it. The more the transmission curve is flattened over time, the less the burden on the health system and the greater the likelihood that it will meet the epidemic demand — which highlights

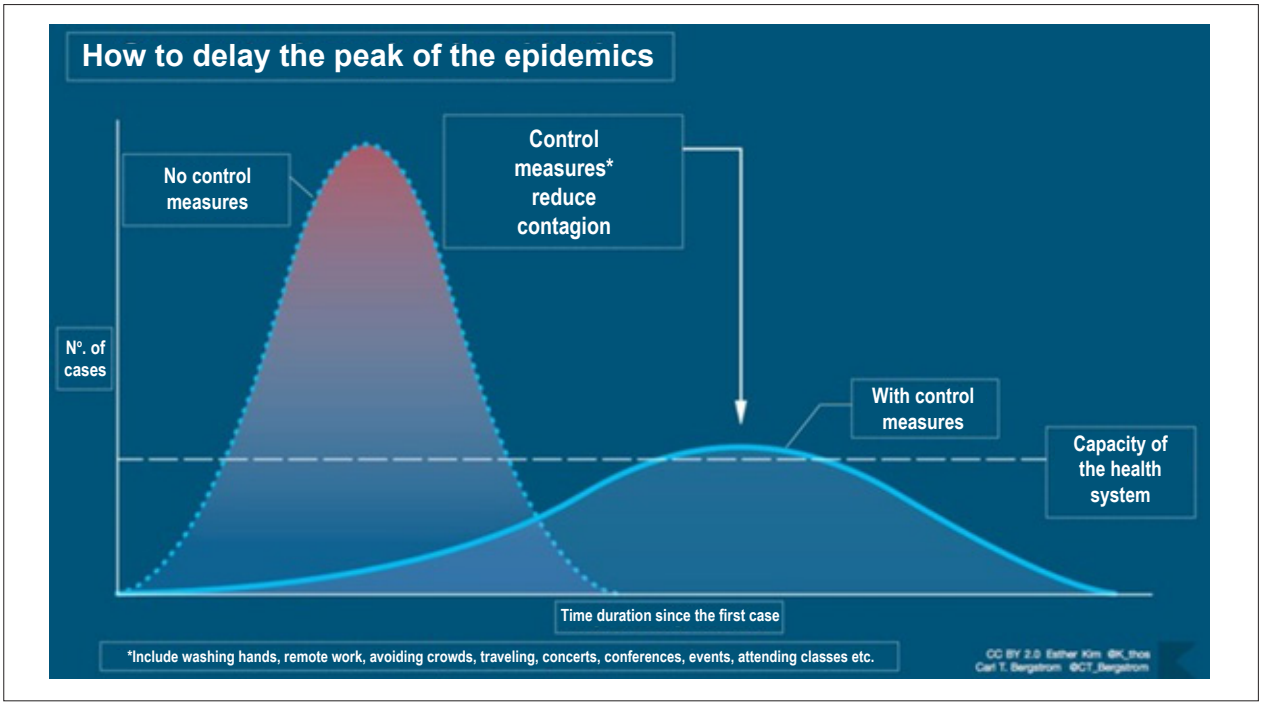

Figura 1 – *Virus spread curve.*

the importance of social isolation as a measure for preventing and controlling the spread of the disease and preserving the country's health system.

Author contributions

Conception and design of the research: Costa JA; Acquisition of data and Analysis and interpretation of the data: Costa JA, Silveira JA, Santos SCM; Writing of the manuscript: Costa JA, Silveira JA, Costa JA, Silveira JA, Santos SCM, Nogueira PP; Critical revision of the manuscript for intellectual content: Nogueira PP.

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Coronavirus and the Heart | A Case Report on the Evolution of COVID-19 Associated with Cardiological Evolution

Arthur Rente[1,2] *Delcio Uezato Junior,*[2] *Karina Margareth Kunyoshi Uezato*[2]

Hospital Municipal de Emergências Albert Sabin – Emergência,[1] *São Caetano, SP – Brazil*

Beneficência Portuguesa de São Caetano do Sul – Cardiologia,[2] *São Caetano, SP – Brazil*

Introduction

Beginning on December 31, 2019, in China, the coronavirus (Sars-Cov-2)[1] has been the target of studies in the most diverse medical fields, with cardiology as one of the major pillars of evolution.

Chronic diseases such as hypertension, diabetes mellitus and coronary artery disease dramatically increase the negative outcome of infected patients. According to data from the American College of Cardiology (ACC), in this profile of the general population, hospitalization levels resulting from COVID-19 hit 50%[2]

Due to infectious abnormalities resulting from infection, chronic comorbidities that until then were stabilized may tend to decompensate due to changes in O_2 supply and demand, among other factors of physiological responses to septic conditions.[3]

It is known that, previously, other pandemics of viral etiology, such as SARS and MERS, involved acute myocarditis with a tragic outcome from the cardiological point of view, and COVID-19 may be a source of acute myocarditis.[4]

According to data from the Brazilian Society of Cardiology (SBC), in March 2020, cardiovascular impairment related to the novel coronavirus has the following outcomes: arrhythmias (16%), myocardial ischemia (10%), myocarditis (7.2%) and shock (1–2%).[5]

Objective

Case report of a patient with diabetes mellitus who contracted the novel coronavirus in community, evolved with cardiac disorders and died.

Methods

The information included in this clinical case description derived from reviews of medical records, interviews with the medical team, diagnostic imaging tests and literature reviews.

Keywords

Cardiovascular Diseases; Coronavirus; COVID 19; Myocarditis/complications; Respiratory Insufficiency.

Mailing Address: Arthur Rente •
Hospital Municipal de Emergências Albert Sabin – Emergência -
Rua Aurélia, 101. Postal Code 09551340, São Caetano, SP – Brazil
E-mail: arthurfelipe3@gmail.com
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Case Report

R.S.C., 33 years old, sought the emergency service at a municipal emergency hospital in São Caetano do Sul, state of São Paulo, on March 12, 2020, with unverified fever, body pain and wet cough for 3 days. The patient was evaluated by the emergency duty manager, where he was physically examined but presented no abnormalities, was medicated, presented symptoms, showed improvement and was discharged.

On March 14, 2020, the patient returned to the emergency room reporting dry cough, dyspnea and fever (39 degrees — measured in the early morning). Denied congestion or rhinorrhea. Chest radiography (Figure 1) was performed and the medical prescription was amoxicillin + clavulanate 875/125 mg every 12 hours. The patient was later discharged.

On March 16, 2020, the patient returned with worsened sensation of dyspnea, no improvement of adynamia and increased dry cough; the fever had ceased, but the patient presented severe sweating. On physical examination, the patient progressed with decreased bilateral breath sounds.

A new chest X-ray was performed (Figure 2), which presented intense worsening, radiopacity bilaterally pronounced in lung fields, with supplementation of O_2 by a nasal catheter, with slight improvement.

The emergency room team requested a place in the ward to clarify diagnosis and treatment.

On March 16, 2020, the patient was received at the emergency hospital ward and history-taking was performed (as described below).

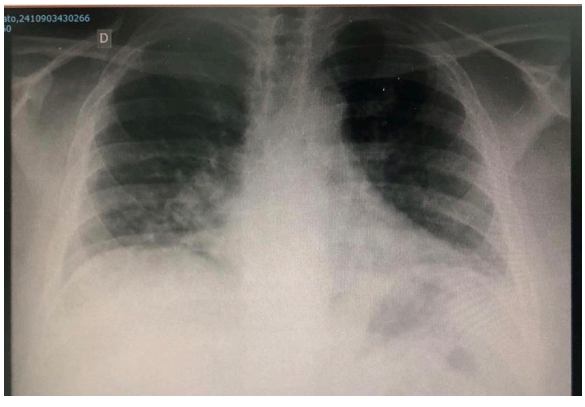

Figure 1 – *Chest radiography at first visit.*

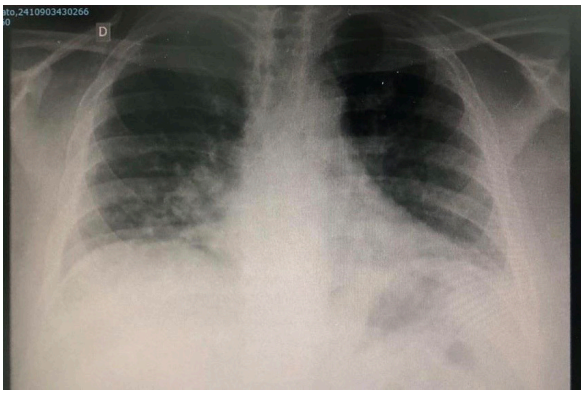

Figure 2 – *Chest radiography referring to the second appointment.*

Patient admitted to the ward with wet cough, fever for 4 days, taking amoxicillin + clavulanate for 2 days without improvement; no travel abroad or contact with anyone with symptoms of COVID-19.

Diabetes with personal history, but not regular treatment.

Admission to the ward. Glasgow 15, eupneic in O_2 catheter, acyanotic. Two-stroke regular heart rhythm; heart rate: 90 bpm; blood pressure: 120 x 70 mmHg. Globally decreased vesicular murmur with sparse diffuse snores. Chest radiography, radiopacity bilaterally pronounced in the lung fields.

Laboratory tests on March 16, 2020: Hb: 15,5; leukocytes: 16,150 mil; band cells: 323; Vhs: 23; Na: 135; K: 4.3; urea: 2; creatinine: 0,6; CRP: 23,6; blood glucose: 344.

Diagnostic hypothesis of pneumonia and decompensated diabetes was suggested.

Request for chest tomography, respiratory isolation, COVID-19 investigation (swab and CRP).

Piperacillin + tazobactan 4.5 mg every 6 hours was initiated, dextro-transposition.

On March 17, 2020, the patient evolved with general malaise, fever (38.3 °C), refractory to medication; 85% desaturation in O_2 3L/min; tachycardia, 104 bpm; tachypneic; 84 ipm; blood pressure: 120x70 mmHg.

Tachycardiac heart rhythm with muffled heart sounds, chest pain, jugular venous distension with signs of diastolic dysfunction.

Vesicular murmur with crackles all across the right hemithorax.

On March 17, 2020, electrocardiography presented no signs of ischemia.

Laboratory tests on March 17, 2020: Hb: 14,2; hT: 41%; leukocytosis: 15.030; platelets: 143 mil; CRP: 25; urea: 36; creatinine: 0.60; Na: 135; K: 4.2.

Hypothesis of pulmonary focus sepsis; viral etiology. The patient opted for a definitive airway with orotracheal intubation.

Blood pressure: 154x91 mmHg; HR: 48; bpm sat O_2: 82%; FiO_2: 100%; Peep: 12 bpm; controlled blood pressure:

Due to hemodynamic instability, the patient was kept in the emergency room waiting for a place in the intensive care unit (ICU). Computed tomography (CT) of the chest (Figures 3 to 6) revealed selective intubation of the right mainstem bronchus; extensive ground-glass opacity in both lungs, affecting all lobes predominantly in the lower lobes, which present consolidations with air bronchograms, suggesting inflammation/infection. Viral etiology cannot be ruled out. Presence of myocardial edema secondary to an inflammatory process associated with myocardial wall thickening with a slight increase in the cardiac area.

New successful orotracheal intubation, antibiotic therapy and measures for acute respiratory failure maintained.

On March 18, 2020, the patient developed general malaise — tachycardia, sedated, tachydyspneic (Ramsey 6), on mechanical ventilation.

Tachycardiac cardiac rhythm, with hypophonesis of b1 and b3 in outline, presence of jugular venous distension, edema on lower limbs 1/4+.

Vesicular murmur with diffuse snores.

Observation for acute myocarditis + pulmonary focus sepsis was initiated.

Antibiotic therapy associated with hemodynamic monitoring was maintained if necessary; initiation of vasoactive drug.

ICU spot was provided at Hospital das Clínicas (HC) de São Paulo, but the patient died on admission due to respiratory failure — COVID-19.

Relevant findings:

On March 17, 2020, additional tests presented the following findings:

- Quantitative troponin: 0.49 ng/dl
- D-dimer: 0.1 mg/L
- Venous lactate: 2.0 mmol/L
- Rapid HIV test: negative

Oropharyngeal swab (rapid test for COVID-19) was performed on March 17, 2020 and tested negative; however, it is clear that the specificity of nasal swab is around 63%, so it is used in the first screening.

The gold standard test for detecting COVID-19 consists of collecting in vivo or post-mortem CRP samples (2019-nCoV CRP), which tested positive (collected on March 19, 2020 — post-mortem). The tests performed in the state of São Paulo — sourced from the Brazilian public health system (SUS) — were analyzed by Instituto Adolfo Lutz Central, completing diagnosis of infection with the novel coronavirus.

Discussion

In view of the current pandemic and a disease still under investigation, we cannot rule out infection among young people and children, especially those with chronic conditions. Reports of clinical experience demonstrate that many patients aged 20 to 40 are being infected by the novel coronavirus, developing multiple comorbidities associated with the infection.

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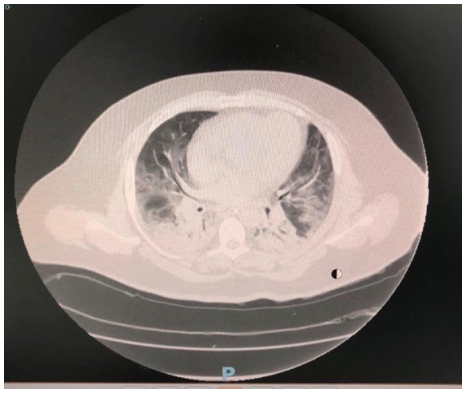

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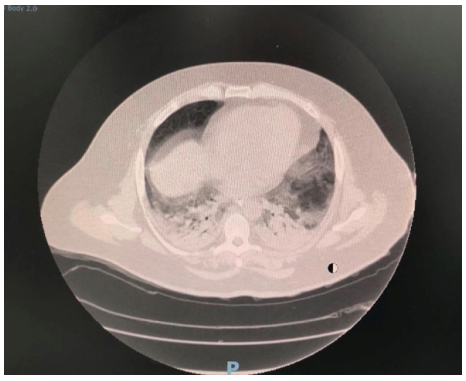

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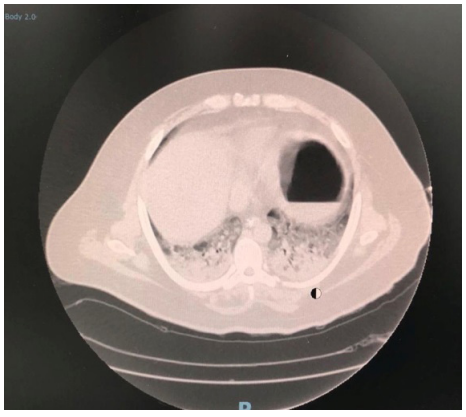

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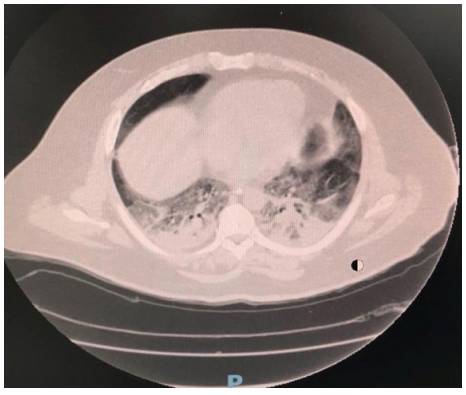

Figures 3 to 6 – *Chest tomography in pulmonary window with standard ground-glass involvement.*

Cardiac involvement, which leads to acute heart failure, has been identified as one of the major sources of secondary complications, with reserved outcome, without specific therapy, except for the classic follow-up of acute heart failure as recommended in our guidelines, in addition to control of the focus of infection.

Conclusion

The cardiovascular outcome is a real possibility in the clinical experience of the novel coronavirus pandemic, requiring monitoring and follow-up of acute heart failure.[6]

Clinical signs should always guide us to consider these possibilities, in addition to keeping an eye for myocarditis.

Complementary tests such as CT and chest radiography are useful for investigation, and echocardiography can facilitate management. It is worth noting that it is not often available in emergency care units in order to have its operator-dependent results.

Due to the severity of the patients' conditions (mostly under mechanical ventilation), cardiac resonance imaging is not of great value as it cannot be performed.[6]

We corroborate the need for history-taking and thorough clinical/cardiological evaluation of such patient profile in order to minimize unfavorable outcomes.

Author contributions

Conception and design of the research, Acquisition of data and Critical revision of the manuscript for intellectual content: Rente A, Uezato Junior D, Uezato KMK; Analysis and interpretation of the data: Uezato Junior D, Uezato KMK; Writing of the manuscript: Rente A.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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Novel Coronavirus Pneumonia and Cardiomyopathy: A Case Report

Mustafa Ahmet Huyut[1]

Yeni Yuzyil University – Cardiology,[1] *Istanbul – Turkey*

A clustering of pneumonia was first recorded in Wuhan, Hubei, China in December 2019.[1] A coronavirus has been established as the pathogen responsible for the disease, and has since been called Severe Acute Coronavirus Syndrome-2 (SARS-CoV-2). The disease triggered by SARS-CoV-2 is called COVID-19, which has spread worldwide since then. Figures tend to climb in Europe, and the extent of COVID-19 lethality cannot be correctly measured. In older patients, lethality appears to be particularly higher when compared to seasonal influenza.[2] CT is very helpful in COVID-19 diagnosis.[3] Also, TTE examination is a very important tool to asses LVEF. Previous studies reported that the real-time polymerase chain reaction (RT-PCR) was the current gold standard for COVID-19 diagnosis.[3] But in some cases, the CT sensitivity is higher than that of RT-PCR.[4] We report a confirmed case of COVID-19 pneumonia in a 59-year-old female. We found a mild decrease in LVEF without troponin-I elevation, which might be considered as cardiomyopathy due to the increased cytokine release in COVID-19. To the best of our knowledge, this is the first report in the literature demonstrating the association between TTE and CT images in COVID-19, and we found that the worsening in the TTE findings is in line with the progression of CT images.

Case report

A 59-year-old female had had fever for 4 days, after catching a cold. One day before visiting the hospital, she had fever and cough, but no chest tightness, chest pain, chills, nausea and vomiting or diarrhea. She did not feel better after receiving antifebrile agents. Then, she was admitted to our outpatient clinic in BHT Clinic Tema Hospital. Four days before, the patient had had contact with her relative who had traveled from Europe. In her previous medical history, bariatric surgery had been performed 3 years before and she had still type II diabetes mellitus, hyperlipidemia, and hypertension as pre-existing conditions. She was hospitalized in our hospital on March/20/2020, and still had fever after admission, with the highest temperature of 39.5 °C, heart rate of 119 beats per minute; the electrocardiography was consistent with sinus tachycardia and QTc was calculated at 0.398 seconds, blood pressure at 94/60 mmHg, and conspicuous tachypnea with a respiratory rate of 24/min with sufficient oxygenation (95% ambient air saturation). The identification of 2019 novel coronavirus (2019-nCoV) in RT-PCR was positive from a throat swab. The risk of simultaneous contamination with other respiratory viruses and other pathogens were negative for the throat swab. The CT characteristics of the patient were similar to the case series reported by Pan et al.[5] (Figure 1: A-B). Laboratory results showed leukopenia, with 4.1×10^9/L, lymphopenia with 0.8×10^9/L, an only slightly increased CRP level, with 18.4 mg/L and a low procalcitonin level, with 0.01 ng/mL. The patient underwent a TTE examination with a 3.5-MHz transducer (Vivid-7 GE Medical System, Horten, Norway). Examinations and measurements were performed according to the recommendations of the American Echocardiography Unit. Simpson's method was used to calculate LVEF.[6] At the admission, LVEF was calculated at 65%, with normal TTE findings.

The patient was isolated, and initiated nasal high flow therapy for respiratory insufficiency and treated with the antiviral drug (oseltamivir, 75mg/capsule, 1 capsule each time, twice a day, for 5-days), antibiotic (azithromycin, 500mg/tablet on the first day, and after that, 250mg/tablet, once a day for 4-days), antipyretic (paracetamol 1gr/100 mL, twice a day), mucolytic (N-acetylcysteine ampule, 300mg/3ml intravenous (IV), twice a day), anticoagulant (enoxaparin 4000 anti-Xa IU/0,4 mL, once a day), corticosteroid (methylprednisolone, 40mg intravenous (IV), once a day, for 5 days), proton-pump inhibitor (esomeprazole ampule, 40 mg IV, once a day), and antimalarial drug (hydroxychloroquine sulfate 200mg/tablet, 400 mg/tablet twice a day on the first day, and after that, 200mg/tablet twice a day, for 6-days). After 5 days of the treatment, the patient's temperature dropped to normal and the symptoms disappeared. However, on day 6, a repeated CT was consistent with increasing expansion of the GGOs and progressed to which are called "crazy paving consolidations" (Figure 1: C-D). Moreover, LVEF was calculated at 52%, but the troponin-I level was still normal. Due to the CT scan results and TTE findings, we added favipiravir to the treatment (200mg/tablet on the first day, 1600mg/tablet twice a day, and 600mg/tablet, twice a day for 4 days) instead of oseltamivir. On day 12, a repeated CT showed that the previous consolidations and GGOs in both lungs were mostly absorbed, leaving some fibrous lesions that may indicate residual organizing pneumonia (Figure 1: E-F). Also, LVEF was calculated at 65% and a repeated RT-PCR was negative and the patient was discharged. No other follow-up CT examinations were performed.

The infection is primarily spread through respiratory droplets. Fever and dry cough are the primary clinical signs of COVID-19 in patients, accompanied by body aches or

Keywords

Cardiovascular Diseases/complications; Coronavirus; COVID-19; Myocarditis; Cardiomyopathies; Infectious Diseases; Acute Respiratory Syndrome; Pneumonia; Echocardiography/methods; Tomography, X-Ray Computed/methods; Hospitalization.

Mailing Address: Mustafa Ahmet Huyut •
Yeni Yuzyil University – Cardiology - Merkez Mahallesi, Çukurçeşme Caddesi, 51 34245 Gaziosmanpaşa, Istanbul – Turkey
E-mail: ahuyut@yahoo.com
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exhaustion and most patients were aged between 40 and 60 years-old. Also, in some cases headache and hemoptysis and diarrhea may occur. Moreover, severe patients may progress to ARDS and intubation may be required in certain patients.[1] The clinical signs of COVID-19 are the same as those of normal upper respiratory tract infections, but the chest CT shows certain details.[5] However, it is difficult to distinguish COVID-19 from other viral pneumonia based on CT findings alone. It is still necessary to clarify and define the epidemiological history, and it should be diagnosed by RT-PCR. Acute myocarditis is a documented risk of viral infections, such as influenza. Clinical presentation ranges from asymptomatic to fulminant myocarditis, which may contribute to severe hemodynamic instability.[7] Previous autopsy-based studies on fatal cases showed that during the 1957 Asian influenza pandemic and during the Spanish influenza pandemic, 39.4% and 48% complication rates of focal to diffuse myocarditis were recorded, respectively.[8] These deadly incidents of myocarditis showed both severe pneumonia and multiple organ involvement. As a consequence, myocarditis is expected to be a fatal risk in a pandemic influenza outbreak. Miura et al.[9] also found a viral antigen in the myocardium with immunohistochemical staining of the autopsied heart.[9] Bowles et al.[10] evaluated endomyocardial biopsy samples from 624 patients and objectively identified myocarditis utilizing PCR for different viral genes. Of the 239 samples tested positive for viral genes, adenovirus was found in 142 samples, enterovirus in 85 samples and influenza A in just five (0.8%) samples.[10] Thus, although the pathogenesis of COVID-19-associated cardiomyopathy or myocarditis remains unclear, the literature suggests that endothelial dysfunction may have an important role in the pathogenesis of myocarditis and cardiomyopathy. Electron microscopic findings of the heart from a murine influenza myocarditis model showed many infiltrating lymphocytes directly attached to the cardiac myocytes, and proinflammatory cytokines in the pathogenesis of acute myocarditis.[7-9] The over-release of cytokines in COVID-19 is already known.[1-2]

We hypothesized that cytokines such as TNF-α, IL-1, IL-6, IL-8, IL-10, which are known to have cardio-depressant

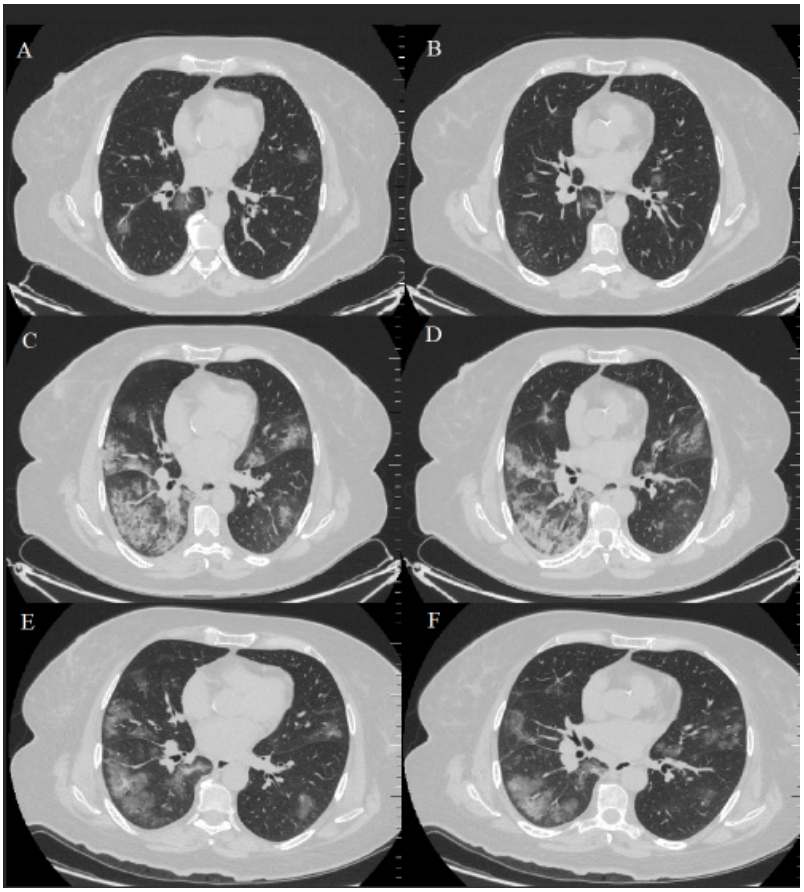

Figure 1 – *Axial CT images. **(A-B)**: At admission, CT shows the bilateral presence of mild GGOs in the parenchyma. **(C-D)**: On day 6, a repeated CT was consistent with increasing expansion of the GGOs and progressed consolidations, which are called crazy paving consolidations. **(E-F)**: On day 12, a repeated CT showed that the previous consolidations and GGOs in both lungs were mostly absorbed, leaving fibrous lesions that may indicate residual organizing pneumonia. CT: computer tomography, GGOs: ground-glass opacities.*

effects, and endogenous and exogenous catecholamines, which play important role in sepsis, may also trigger the cardio-depressant effect in COVID-19. Also, we considered that the cardiomyopathy might be reversible by clearing cytokines from the circulation during recovery. Previous studies have also demonstrated that inhibiting trypsin-mediated viral replication and downregulation of matrix metalloproteinases and cytokines, significantly improved the cardiac functions of mice infected with influenza A virus.[7-9] According to these findings, we have to promptly identify critically-ill patients and treat them as soon as possible, to avoid fatal complications. We need to use all kinds of diagnostic tools and treatment options during the follow-up. Especially, TTE may be the cheapest and the easiest way to follow-up these patients. However, there is still no specific drug for the treatment of COVID-19 patients. Based on the experience of the treatment of SARS and MERS, some drugs such as hydroxychloroquine, azithromycin, oseltamivir, lopinavir-ritonavir, remdesivir, and favipiravir might have positive effects on COVID-19 patients.[1]

In conclusion, our patient did not experience myocarditis, because there was no troponin-I increase, but we believe she might experience cardiomyopathy due to the over-release of cytokines. In our case, cardiomyopathy and COVID-19 were treated with hydroxychloroquine, methylprednisolone, azithromycin, and finally with favipiravir. However, the curative effects of these medications have not yet been proven, and still need further researches.

Author contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Statistical analysis, Obtaining financing, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Huyut MA

Potential Conflict of Interest

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Left and Right Internal Mammary Artery Angioplasties in a 3-year-old Patient with Kawasaki Disease and Failed Coronary Artery Bypass Graft Surgery

René Hameau,[1] Daniel Springmuller,[1] Francisco Garay,[1] Alberto Fuensalida,[1] Gonzalo Martinez[1]
Hospital Clinico Universidad Catolica, Santiago - Chile

A 3 years and 5 months old boy with a history of Kawasaki disease diagnosed at 6 months of age and a previous Non-ST myocardial infarction (NSTEMI) underwent Coronary Artery Bypass Graft (CABG) surgery due to a large perfusion defect and moderate systolic dysfunction on Single-photon emission computed tomography (SPECT) (Figure 1A) and a coronary angiogram showing a partially thrombosed giant aneurysm on the Right coronary artery (RCA) and a complete occlusion of the proximal Left anterior descending artery (LAD) (Figures 1B-C). A Left internal mammary artery (LIMA) graft to LAD and a free Right internal mammary artery (RIMA) to Posterior descending artery (PDA) anastomosis of RCA was performed.

Three months later, SPECT showed a 16% left ventricle (LV) ischemia. Coronary angiography revealed a severe lesion at the RIMA to PDA distal anastomosis and a complete occlusion at the distal LIMA (Supplemental Figure S1). Ad-hoc percutaneous intervention was decided. A 5F JR3.5 guiding catheter was used to selectively engage the RIMA. A Runthrough wire (Terumo Corporation, Tokyo, Japan) was advanced and Plain old balloon angioplasty (POBA) was performed with 1.25 x 12 and 1.5 x 15 semi-compliant balloons, achieving a favorable result (Figure 2-A). Subsequently, the JR3.5 guide was positioned in the left subclavian, from which the Runthrough wire was advanced into the LIMA, followed by a 1.8F Finecross microcatheter (Terumo Corporation, Tokyo, Japan), which allowed crossing the entire occlusion. Thereafter, due to the inability to selectively engage the LIMA, all contrast media injections were performed through the microcatheter.

Keywords

Heart Defects; Congenital/complications; Kawasaki Disease/complications; Myocardial Revascularization/surgery; Heart Aneurysm/surgery; Percutaneous Coronary Intervention/methods; Thrombolytic Therapy/methods

Mailing Address: Gonzalo Martinez Rodriguez •
Hospital Clinico Universidad Catolica - Marcoleta 367. 8320000, Santiago – Chile
E-mail: gmartinezr@med.puc.cl
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Several balloon angioplasties have resulted in significant residual stenosis, thus a 2.0 x12 Zotarolimus-eluting stent was successfully deployed (Figure 2-B). At a 3-month follow-up, SPECT showed no significant ischemia, confirming optimal post-procedural results (Figure 3-C).

The risks of major adverse cardiovascular events can reach up to 48% in pediatric patients with giant coronary aneurysms due to Kawasaki disease.1 Percutaneous coronary intervention (PCI), CABG and systemic thrombolysis have been used,2 yet no reports of re-intervention after CABG are available. PCI in this setting is complex due to technical difficulties, limited experience and the need to adapt adult devices to small children. Multidisciplinary assessment and intervention (encompassing adult and pediatric specialists) are key for procedural success.

Author contributions

Conception and design of the research: Davanzo RH, Martinez G; Acquisition of data: Davanzo RH, Garay F, Alarcon AF, Martinez G; Analysis and interpretation of the data: Springmuller D, Garay F, Alarcon AF; Writing of the manuscript: Davanzo RH, Springmuller D, Martinez G; Critical revision of the manuscript for intellectual content: Davanzo RH, Springmuller D, Garay F, Alarcon AF, Martinez G.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Image

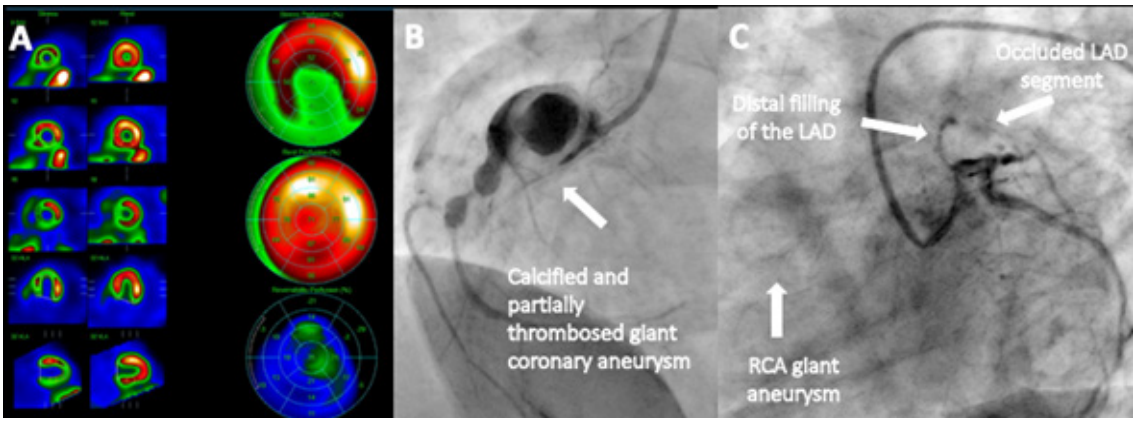

Figure 1 – *A) SPECT showing 45% area of LV ischemia; B) RCA; C) Left coronary artery.*

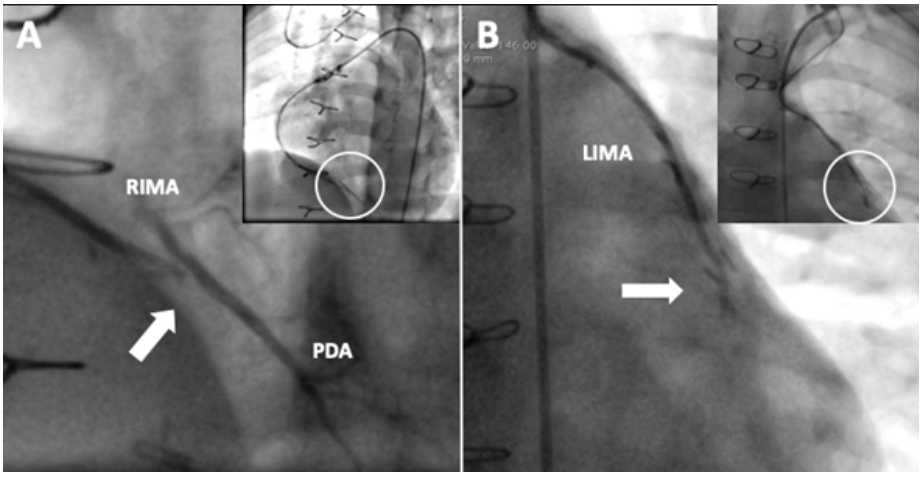

Figure 2 – *A) Severe stenosis at the distal RIMA to PDA anastomosis; B) Total LIMA occlusion.*

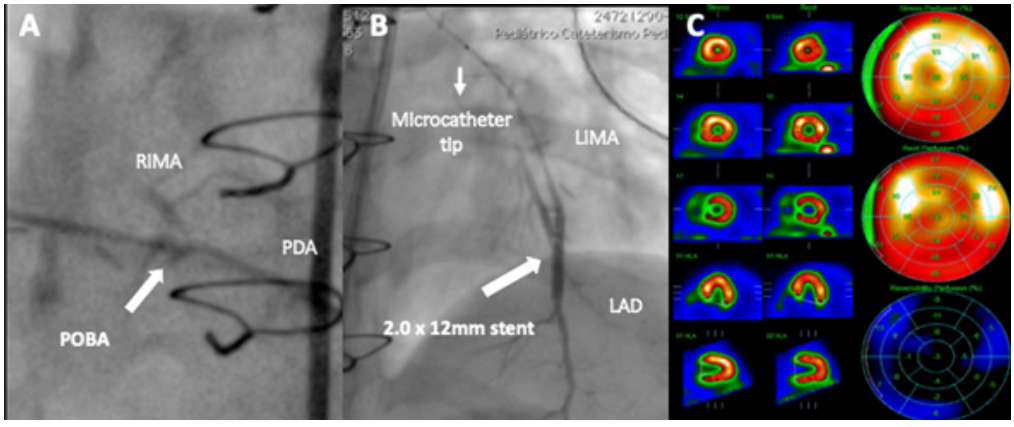

Figure 3 – *Post-procedural results. A) POBA to RIMA-PDA; B) Stenting to LIMA-LAD; C) Follow-up SPECT with mild perfusion defect.*

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Brazilian Cardiology Society Statement for Management of Pregnancy and Family Planning in Women with Heart Disease – 2020

Development: Department of Women's Cardiology of the Brazilian Society of Cardiology

Norms and Guidelines Council: Brivaldo Markman Filho, Antonio Carlos Sobral Sousa, Aurora Felice Castro Issa, Bruno Ramos Nascimento, Harry Correa Filho, Marcelo Luiz Campos Vieira

Norms and Guidelines Coordinator: Brivaldo Markman Filho

Coordenadoras do Posicionamento: Walkiria Samuel Avila, Elizabeth Regina Giunco Alexandre, Marildes Luiza de Castro

Comitê de Redação: Alexandre Jorge Gomes de Lucena, Celi Marques-Santos, Claudia Maria Vilas Freire, Eduardo Giusti Rossi, Elizabeth Regina Giunco Alexandre, Felipe Favorette Campanharo, Ivan Romero Rivera, Maria Elizabeth Navegantes Caetano Costa, Maria Alayde Mendonça Rivera, Marildes Luiza de Castro, Regina Coeli Marques de Carvalho, Walkiria Samuel Avila

Colaboradores: Alexandre Abzaid, Antonio Fernandes Moron, Auristela Isabel de Oliveira Ramos, Carlos Japhet da Mata Albuquerque, Claudine Maia Alves Feio, Daniel Born, Fábio Bruno da Silva, Fernando Souza Nani, Flavio Tarasoutchi, José de Ribamar Costa Junior, José Xavier de Melo Filho, Leila Katz, Maria Cristina Costa Almeida, Max Grinberg, Melania Maria Ramos de Amorim, Nilson Roberto de Melo, Orlando Otávio de Medeiros, Pablo Maria Alberto Pomerantzeff, Sérgio Luiz Navarro Braga, Sonia Conde Cristino, Tania Leme da Rocha Martinez, Tatiana de Carvalho Andreuci Torres Leal

Autores do Posicionamento: *Walkiria Samuel Avila,[1] Elizabeth Regina Giunco Alexandre,[2] Marildes Luiza de Castro,[3] Alexandre Jorge Gomes de Lucena,[4] Celi Marques-Santos,[5,6] Claudia Maria Vilas Freire,[7] Eduardo Giusti Rossi,[1] Felipe Favorette Campanharo,[8,9] Ivan Romero Rivera,[10] Maria Elizabeth Navegantes Caetano Costa,[11,12,13] Maria Alayde Mendonça Rivera,[10] Regina Coeli Marques de Carvalho,[14] Alexandre Abzaid,[1] Antonio Fernandes Moron,[8] Auristela Isabel de Oliveira Ramos,[15] Carlos Japhet da Mata Albuquerque,[17,18,19,20] Claudine Maia Alves Feio,[21] Daniel Born,[8] Fábio Bruno da Silva,[15] Fernando Souza Nani,[1] Flavio Tarasoutchi,[1] José de Ribamar Costa Junior,[2,15] José Xavier de Melo Filho,[22] Leila Katz,[17] Maria Cristina Costa Almeida,[23] Max Grinberg,[1] Melania Maria Ramos de Amorim,[17] Nilson Roberto de Melo,[24] Orlando Otávio de Medeiros,[25] Pablo Maria Alberto Pomerantzeff,[1] Sérgio Luiz Navarro Braga,[15] Sonia Conde Cristino,[13] Tania Leme da Rocha Martinez,[26] Tatiana de Carvalho Andreuci Torres Leal[1]*

Instituto do Coração (Incor) do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP),1 São Paulo, SP – Brazil
Hospital do Coração (HCor),[2] São Paulo, SP – Brazil
Hospital das Clínicas da Faculdade de Medicina da Universidade Federal de Minas gerais (UFMG),[3] Belo Horizonte, MG – Brazil
Hospital Agamenom Magalhães,[4] Recife, PE – Brazil
Universidade Tiradentes,[5] Aracaju, SE – Brazil
Hospital São Lucas, Rede D'Or Aracaju,[6] Aracaju, SE – Brazil
Universidade Federal de Minas Gerais (UFMG),[7] Belo Horizonte, MG – Brazil
Universidade Federal de São Paulo (UNIFESP), Escola Paulista de Medicina (EPM),[8] São Paulo, SP – Brazil
Hospital Israelita Albert Einstein,[9] São Paulo, SP – Brazil
Universidade Federal de Alagoas,[10] Maceió, AL – Brazil
Cardio Diagnóstico,[11] Belém, PA – Brazil
Centro Universitário Metropolitano da Amazônia (UNIFAMAZ),[12] Belém, PA – Brazil
Centro Universitário do Estado Pará (CESUPA),[13] Belém, PA – Brazil
Secretaria de Saúde do Estado do Ceará,[14] Fortaleza, CE – Brazil
Instituto Dante Pazzanese de Cardiologia,[15] São Paulo, SP – Brazil
Hospital Metropolitano Oeste Pelópitas Silveira,[16] Recife, PE – Brazil

DOI: https://doi.org/10.36660/abc.20200406

Instituto de Medicina Integral Professor Fernando Figueira (IMIP),[17] Recife, PE – Brazil
Hospital Barão de Lucena,[18] Recife, PE – Brazil
Hospital EMCOR,[19] Recife, PE – Brazil
Diagnósticos do Coração LTDA,[20] Recife, PE – Brazil
Universidade Federal do Pará,[21] Belém, PA – Brazil
UDI Hospital, Rede D'Or,[22] São Luís, MA – Brazil
Centro Universitário de Belo Horizonte,[23] Belo Horizonte, MG – Brazil
Departamento de Obstetrícia e Ginecologia da Faculdade de Medicina da Universidade de São Paulo (USP),[24] São Paulo, SP – Brazil
Ministério da Saúde,[25] Brasília, DF – Brazil
Universidade de São Paulo (USP),[26] São Paulo, SP – Brazil

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Note: These statements are for information purposes and should not replace the clinical judgment of a physician, who must ultimately determine the appropriate treatment for each patient.

Correspondence:
Sociedade Brasileira de Cardiologia – Av. Marechal Câmara, 360/330 – Centro – Rio de Janeiro – Postal Code: 20020-907.
E-mail: diretrizes@cardiol.br

Statement

Declaration of potential conflict of interests of authors/collaborators of the Brazilian Cardiology Society Statement for Management of Pregnancy and Family Planning in Women with Heart Disease – 2020
If, within the last 3 years, the author/collaborator of the statement:

Names of statement collaborators	Participated in clinical and/or experimental studies sponsored by pharmaceutical or equipment companies related to this statement	Spoke at events or activities sponsored by industry related to this statement	Was (is) a member of a board of advisors or a board of directors of a pharmaceutical or equipment industry	Participated in normative committees of scientific research sponsored by industry	Received personal or institutional funding from industry	Wrote scientific papers in journals sponsored by industry	Owns stocks in industry
Alexandre Abzaid	No	No	No	Boston Scientific, Medtronic, Edwards, Elixir	No	No	No
Alexandre Jorge Gomes de Lucena	No	No	No	No	No	No	No
Antonio Fernandes Moron	No	No	No	No	No	No	No
Auristela Isabel de Oliveira Ramos	No	No	No	No	No	No	No
Carlos Japhet da Matta Albuquerque	No	No	No	No	No	No	No
Celi Marques-Santos	No	No	No	No	No	No	No
Cláudia Maria Vilas Freire	No	No	No	No	No	No	No
Claudine Maia Alves Feio	No	No	No	No	No	No	No
Daniel Born	No	No	No	No	No	No	No
Eduardo Giusti Rossi	No	No	No	No	No	No	No
Elizabeth Regina Giunco Alexandre	No	No	No	No	Novo Nordisk, Servier, AstraZeneca	No	No
Fábio Bruno da Silva	No	No	No	No	No	No	No
Felipe Favorette Campanharo	No	No	No	No	No	No	No
Fernando Souza Nani	No	CSL Behring	No	No	No	No	No
Flavio Tarasoutchi	No	No	No	No	No	No	No
Ivan Romero Rivera	No	No	No	No	No	No	No
José de Ribamar Costa Junior	No	No	No	No	No	No	No
José Xavier de Melo Filho	No	No	No	No	Servier, Novartis	No	No
Leila Katz	No	No	No	No	No	No	No
Maria Alayde Mendonça Rivera	No	No	No	No	No	No	No
Maria Cristina Costa Almeida	No	No	No	No	No	No	No
Maria Elizabeth Navegantes Caetano Costa	No	No	No	No	Biolab, Pfizer, Boehringer	No	Speak, Biolab, Bouehringer
Marildes Luiza de Castro	No	No	No	No	No	No	No
Max Grinberg	No	No	No	No	No	No	No
Melania Maria Ramos de Amorim	No	No	No	No	No	No	No
Nilson Roberto de Melo	No	No	No	No	No	No	No
Orlando Otávio de Medeiros	No	No	No	No	No	No	No
Pablo Maria Alberto Pomerantzeff	No	No	No	No	No	No	No
Regina Coeli Marques de Carvalho	No	No	No	No	No	No	No
Sérgio Luiz Navarro Braga	No	No	No	No	No	No	No
Sonia Conde Cristino	No	No	No	No	No	No	No
Tania Leme da Rocha Martinez	No	No	No	No	No	No	No
Tatiana de Carvalho Andreuci Torres Leal	No	No	No	No	No	No	No
Walkiria Samuel Avila	No	No	No	No	No	No	No

Content

Statement

1. Introduction

The Women's Cardiology Department (DCM, acronym in Portuguese) presents this document, composed in accordance with the norms established by the Brazilian Cardiology Society (SBC, acronym in Portuguese), with the aim of discussing the most prevalent cardiovascular diseases that affect women during the pregnancy and for which substantial evidence or randomized clinical trials do not exist.

In 1999, with the support of the SBC, what was at that time the Department of Heart Disease and Pregnancy published the First Consensus on Heart Disease and Pregnancy, which was groundbreaking worldwide. It drew attention to the evolution of gestation in women with heart disease, at a time when the prevailing maxim was "Women with heart disease should not get pregnant because maternal mortality is prohibitive." After 10 years had passed, the experience of the department that has gone on to become the DCM made it necessary to reconsider the restrictions on pregnancy in women with heart disease. For this reason, in 2009, SBC Guidelines for Pregnancy in Women with Heart Disease published the therapeutic strategies available at that time, in a specific and adequate management of clinical situations.

Two decades after the first publication, the DCM validates its dedication by publishing the First Statement for Management of Pregnancy and Family Planning in Women with Heart Disease, which is the result of the experience and work of specialists who write protocols that contribute to therapeutic decisions during the gestational period, as well as counseling for pregnancy and contraception for women with heart disease.

A country's maternal mortality rate is one of the most sensitive indicators of its population's living conditions, and it especially reflects the quality of healthcare provided to women during prenatal care. Although the rates continue to be higher than what was estimated for this millennium, over the past three decades Brazil has registered an important reduction in the rate of maternal mortality due to complications during the pregnancy and postpartum time.

Occurring in 4% of gestations, heart disease in itself continues to be the main non-obstetric cause of maternal mortality worldwide. Nonetheless, cardiology's advancements in improving diagnostic methods and therapeutic alternatives have promoted significant change in prognosis of cardiovascular diseases and in the characteristics of heart diseases that occur during reproductive age. This has made better life expectancy and quality of life possible for women with heart disease, thus encouraging maternity and promoting safer pregnancies with lower risks.

Medicine is increasingly individualizing the approach to diverse diseases, especially in relation to gender, given that the female organism differs greatly from the male one, especially during the pregnancy-postpartum cycle.

The updating of this document fulfills the universal responsibility regarding improving maternal-fetal prognosis. It is, thus, undeniable that the DCM's accumulated experience contributes to the establishment of protocols that guide therapeutic practice during pregnancy, to the counseling of future pregnancies, to improvements in life expectancy with quality, and to the reduction in maternal mortality due to heart disease.

In consonance with the international literature, this document discusses new concepts of heart disease *versus* pregnancy, including the following: maternal risk stratification based on the recommendations of the World Health Organization (WHO); aspects of arterial hypertension; reinforcing interdisciplinary approaches, with the participation of a heart team; therapeutic proposals for complications; changes in the classification of maternal-fetal risks with respect to drugs used during pregnancy and breastfeeding; and contraception.

The objectives of this publication are to standardize routine and to divulge yet another tool that will be useful in daily clinical practice. The DCM hopes that the recommendations included in this document will have positive impact throughout Brazil and that they will contribute to better treatment and consequent reduction of cardiovascular risks in childbearing women with heart disease.

2. General Considerations

2.1. Physiological Adaptation to Pregnancy, Labor and Delivery

Interaction between the embryo and the maternal uterus provokes intrinsic hormonal stimulation in the organism and alterations in the physiology of the cardiovascular system, which are fundamental to the adequate development of pregnancy.[1] These changes, however, lead to a hemodynamic overload that may reveal previously unrecognized heart diseases or aggravate the functional state of underlying heart diseases. For this reason, it is fundamental to comprehend the hemodynamic, blood coagulation, and respiratory modifications that occur during the pregnancy, labor and delivery in order to understand the maternal clinical condition, to predict risks of gestation, and to evaluate fetal health.

2.1.1. Hemodynamic Modifications (Table 1)

Cardiac output, which is calculated by the product of systolic volume and heart rate, progressively increases, on average, 40% higher than preconception values, beginning of the first trimester of gestation, reaching the greatest increasing in onset of third trimester and tending to reduce at the term of pregnancy[2] (Figure 1). The magnitude of the increase in cardiac output varies individually, and it is 15% greater in multiple pregnancies. Plasma volume is principal responsible for the increase in cardiac output during the first half of gestation. From that moment onwards, heart rate, which does not usually exceed 100 beats per minute (bpm), plays an important role in this increase until the term of pregnancy.

The disproportion between increased plasma volume and the production of red blood cells results in haemoglobin dilution or physiological anemia of pregnancy. This is most evident during the end of the second trimester, when plasma volume reaches its peak in relation to the volume of blood cells. When the renal function is normal, blood volume and others elements return to preconception values on account of diuresis, eight weeks after delivery, while hemoglobin begins to increase on the third postpartum day.[2,3]

At the term of pregnancy, blood volume is estimated at 100 ml/kg, almost two times higher than the value of 65 to 70 ml/kg found in women who are not pregnant. Erythrocyte mass begins to increase between the eighth and tenth week of pregnancy, induced by the elevation of plasma erythropoietin.

The hormonal mechanisms of the hypervolemia during pregnancy include increasing levels of estrogen and progesterone, which increases renin levels, causing retention of sodium and total body water; prolactin; placental lactogen; prostaglandins; and the growth hormone.

After the second half of pregnancy, variations may be observed in resting cardiac output consequential to the position adopted by pregnant women. The change from dorsal decubitus to left lateral, for instance, produces an approximately 22% increase in cardiac output, an

Table 1 – Hemodynamic alterations during gestation

Parameter	Alteration
Cardiac output	Increased 30% to 50% (2l/min)
Heart rate	Increased 15% to 20% (15 bpm)
Blood volume	Increased 20% to 30% (1.8 l)
Average arterial pressure	Reduced at least 5%
Systemic vascular resistance	Reduced 20% to 30% (320 dynes-s/cm5)
Pulmonary vascular resistance	Reduced 30% (40 dynes-s/cm5)
Central venous pressure	Unaltered
Lower limb venous pressure	Increased 15%

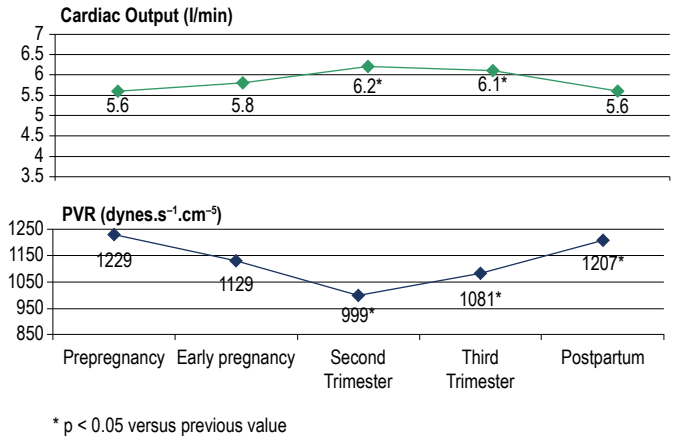

Figure 1 – *Variation in cardiac output and peripheral vascular resistance (PVR) during and after pregnancy. Adapted from Sanghavi and Rutheford, 2014.*[3]

approximately 6% reduction in heart rate, and a 27% increase in systolic volume. Compression of the inferior vena cava by the enlarged uterus in the supine position provokes what is known as supine hypotensive syndrome, which may manifest with dizziness and/or syncope.[4]

During pregnancy, a reduction occurs in plasma colloid osmotic pressure in approximately 12% to 18% of cases, as a consequence of the drop in circulating albumin concentrations, which are observed in lower levels during week 24 of pregnancy. This decline prompts edema in lower limbs, and it predisposes pregnant and parturient women who have received excessive intravenous crystalloid infusion to pulmonary congestion.[5]

The decrease in peripheral vascular resistance during the beginning of pregnancy is not limited to the uterine plexus, and it has a greater magnitude than the concomitant elevation in cardiac output. During the second half of pregnancy, resistance reaches its lowest values, at the moment when cardiac output reaches its maximum values (Figure 1).[6] Arteriolar dilation during pregnancy has been attributed to estrogenic components, prolactin, and increased levels of circulating prostaglandin (PGE2 and PGI2), a substance that is responsible for reducing vascular response to exogenous angiotensin.

A decrease in prostaglandin synthesis or an increase in its metabolism may result in increased vascular responsiveness to angiotensin II, a characteristic that has been observed in pregnant women who develop hypertension. Progesterone and its metabolites also appear to participate in modulation of vascular response to angiotensin II during pregnancy. It has recently been demonstrated that alterations in vascular tone during pregnancy may be partly attributed to changes in the synthesis of endothelium-derived vasoactive substances, especially endothelin, which is theoretically capable of mediating prostaglandin synthesis, and to the reduction in nitric oxide, which has been related to vasodilation during pregnancy.[7]

It is worth emphasizing that, during pregnancy, the arterial system undergoes remodeling in order to accommodate increased blood volume. Estrogen promotes collagen deposition in the middle layer of the large and medium arteries; circulating elastase favors rupture of the elastic lamina and weakening of the middle layer of vessel walls; and relaxin, an insulin-like growth factor hormone (detected in the plasma), causes a reduction in collagen synthesis. All of these factors explain the predisposition to artery dissection during pregnancy.

Systemic arterial pressure (SAP) decreases from the beginning to the middle of pregnancy,[8] particularly at the expense of diastolic pressure, and it subsequently rises to pre-gestation values as the term approaches (Figure 2). SAP rises during uterine contractions, especially during the second stage of delivery.

A clinical picture of orthostatic hypotension may occasionally occur, secondary to reduced venous return when a pregnant woman is in the supine position, with a consequent drop in cardiac output. Considering pulmonary output equal to aortic output in normal adults, changes in pulmonary vascular resistance are parallel to those in systemic vascular resistance.[9] Recent studies have challenged this "dogma," showing a tendency toward increased arterial pressure in women with body mass index (BMI) > 25 kg/m^2 and women who were obese prior to gestation.[2]

Normal labor is associated with significant hemodynamic alterations, due to anxiety, exertion, pain, uterine contractions, maternal posture (left lateral *versus* supine), uterine involution, and bleeding. During labor, blood from the uterine sinusoids is released into systemic circulation with each contraction, increasing the preload by about 500 ml of blood, which leads to increased cardiac output and blood pressure. Thus, during the second stage of labor, cardiac output is around 50% higher in relation to pre-delivery, and, during fetal expulsion, it is 60% to 80% higher than pre-gestational levels. This abrupt change in cardiac output is transient. It remains elevated during the immediate postpartum period, and it is not accompanied by variations in arterial pressure. During normal delivery, around 400 ml of blood are lost. In cesarean section, blood loss may be greater, namely, around 800 ml. After the delivery, a sudden increase occurs in venous return, due to "auto transfusion"

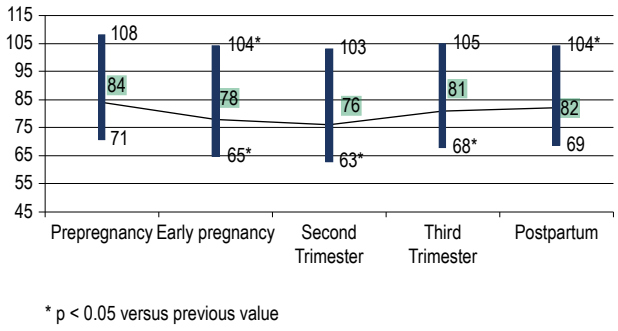

Figure 2 – *Variation in systemic arterial pressure during the pregnancy-postpartum cycle. Adapted from Sanghavi and Rutheford, 2014.*[3]

of the uterine plexus, decompression in the flow of the inferior vena cava, and reduction in venous system capacity. In addition to this, peripheral vascular resistance is increased by sustained contraction of the uterus, occluding the vessels that open on the maternal placenta surface. The continuous "auto transfusion" that occurs during 24 to 72 hours after delivery represents a high risk of pulmonary congestion in women with heart disease.[10]

Cardiovascular effects during delivery are also influenced by the eventual occurrence of infection, hemorrhage, and use of anesthetics drugs.[11]

In general, the patterns of alteration in maternal blood volume during labor, the expulsion period, and the postpartum period are described by the following phases:

1. Blood concentration during labor, varying with the degree of uterine activity and maternal dehydration;
2. Reduced blood volume during and immediately after delivery, proportional to blood lose volume;
3. Immediate, transient elevation in blood volume following placental clearance, attributed to fluid inflow into the intravascular territory, due to uterine emptying;
4. Slight elevation in blood volume between the second and third days after delivey, secondary to the transient increase in aldosterone secretion;
5. Reduced plasma volume one week after delivery, in a manner that maternal systolic volume may present a slight drop during this period, returning to normal within a short term.

2.1.2 Modifications in Blood Coagulation

During pregnancy, activation occurs in the synthesis of coagulation factors II, VII, VIII, IX, and X and fibrinogen, as well as a reduction of endogenous anticoagulants (especially antithrombin and protein S), all of which are determinants of the state of hypercoagulability, which is characteristic of a healthy pregnancy.[12] These modifications occur progressively after the first trimester of gestation, with shortening of prothrombin, partial thromboplastin, and thrombin times, favoring the weakening of the anticoagulant function.[13] Considering these mechanisms, in conjunction with the mechanical compression of the venous plexus on the lower limbs by the gravid uterus, the characteristic predisposition to thromboembolism during pregnancy is justified. (Figure 3).

2.1.3. Respiratory Changes (Figure 4)

Oxygen consumption increases by around 50%, especially during the last 2 trimesters of gestation, and this is not proportional to maternal weight gain. Weight gain during gestation includes not only fetal metabolic activity, but also the weight of amniotic fluid and the increase of fluid in maternal tissues, both of which are considered metabolically inert. During labor, oxygen consumption increases by 250 to 750 ml/min with each contraction.[14]

The normal respiratory tract undergoes modifications during pregnancy, which induce respiratory alkalosis, with higher arterial oxygen partial pressure (PaO_2) and lower arterial carbon dioxide partial pressure ($PaCO_2$), in comparison with the non-pregnant state. Lower $PaCO_2$ favors a diffusion gradient that facilitates the fetus' ability to eliminate products of aerobic metabolism.[3]

Increased minute ventilation is accompanied by an increase in tidal volume, without modifying respiratory rate. Maternal hyperventilation is considered to be a protective mechanism for the fetus against the detrimental effects of excessive tissue CO_2 concentration, at the same time that PaO_2 increases to 100 mmHg.

Modifications in the chest occur with uterine enlargement and diaphragm elevation. Thoracic circumference increases by around 5 to 7 cm; the substernal angle widens, and vertical diameter decreases. These modifications are accompanied by alterations in the distribution of air throughout the diverse pulmonary compartments.

Histological examination of the upper respiratory tract mucosa during pregnancy reveals: hyperemia, glandular hyperactivity, increased phagocytic activity, and increased mucopolysaccharide content. Nasal congestion and epistaxis, which are frequent during gestation, are possibly caused by these changes.[15] Airway and respiratory function is preserved during pregnancy, as reflected by an unchanged forced expiratory volume in one second (FEV1) and an unchanged ratio of FEV1 to forced vital capacity (FVC).[15]

The 25% reduction in lung functional residual capacity (FRC) is associated with a similar increase in inspiratory capacity (IC). Consequently, vital capacity (VC) does not show any modifications during pregnancy.

The decrease in FRC to 300 ml during pregnancy is not accompanied by increased airway resistance, which, on the

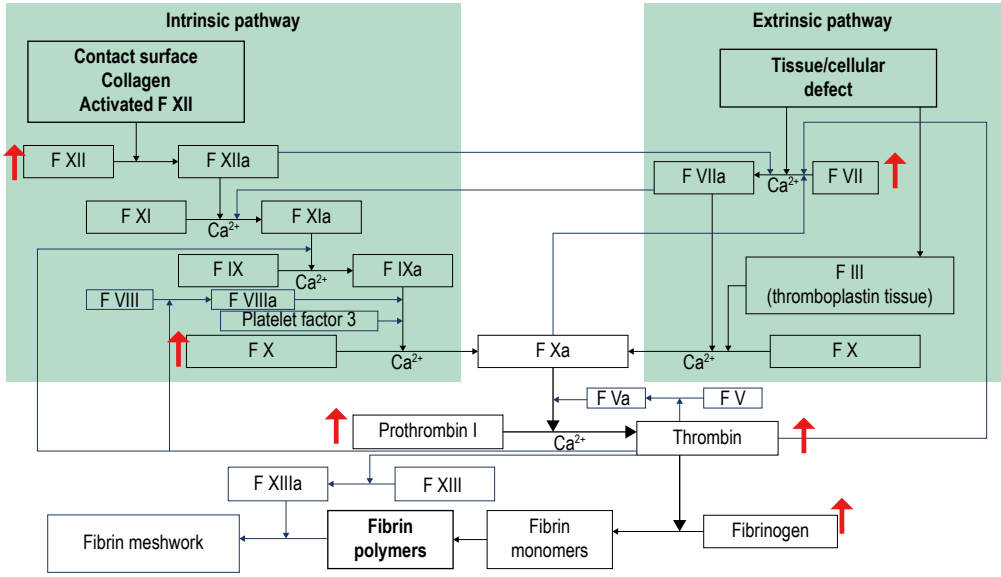

Figure 3 – *Activation of coagulation factors during pregnancy. F: factor. Adapted from Bremme et al., 2003.*[12]

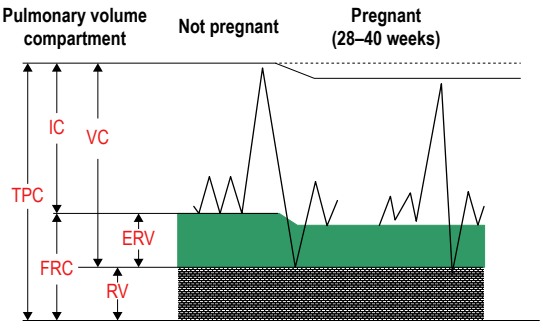

Figure 4 – *Respiratory changes during pregnancy. ERV: expiratory reserve volume; FRC: functional residual capacity; IC: inspiratory capacity; RV: residual volume; TPC: total pulmonary capacity; VC: vital capacity. Adapted from Hegewald and Crapo, 2011.*[16]

contrary, undergoes a significant reduction, possibly due to relaxation of smooth muscle tone secondary to hormonal action. This reduction serves to decrease work of breathing.

With hyperventilation, an increase in PaO_2 occurs, and the hemoglobin dissociation curve shifts to the right. Normal blood gases in pregnant women should have a pH between 7.40 and 7.47, $PaCO_2$ between 30 and 32, and a slight increase in PaO_2. Respiratory alkalosis is partially offset by increased renal excretion of bicarbonate, which maintains serum levels of HCO_3 between 18 and 21 mEq/L (a baseline deficit of 3 to 4 mEq/L). The decrease in pulmonary FRC and the increase in oxygen consumption reduce the maternal oxygen reserve, which, in the event of respiratory failure, represents a state of alert for adopting early measures of respiratory or ventilatory support, in order to avoid harm to the fetus or the mother.[16]

The mechanism behind dyspnea during normal pregnancy is not completely clear. Hyperventilation induced by progesterone is probably at least partially responsible, perhaps due to the elevation of ventilation above the level necessary to meet the increased metabolic demand.

2.1.4. Structural Vascular Changes

Hormonal changes during pregnancy may alter the structure of the vascular, resulting in weakening of the arterial walls. Estrogen influences abnormal collagen deposition inside the middle layer of the large and medium arteries. Circulating elastase may provoke a rupture of the elastic lamina and weakening of the middle layer of vessel walls. In addition to this, relaxin, an insulin-like growth factor hormone (detected in the plasma), causes a redction in the synthesis of collagen and predisposes pregnant women to artery dissection.[17]

2.1.5. Key Points

Knowledge regarding physiological modifications related to the pregnancy and postpartum period is fundamental to clinical practice for management of pregnancy and risk stratification of women with heart disease.

2.2. Maternal and Fetal Assessment

2.2.1. Maternal Clinical Evaluation

2.2.1.1. Anamnesis and Physical Examination

Initial clinical investigation of pregnant women with heart disease requires questions about family history with respect to genetically transmittable heart diseases. Family history of the following stand out: premature sudden death, cardiomyopathy, congenital heart disease, Marfan syndrome, long QT syndrome, catecholaminergic ventricular tachycardia (VT), and Brugada syndrome.

Physiological modifications during pregnancy influence the evaluation of cardiovascular status, and specialized knowledge is required to differentiate between healthy and unhealthy patients (Table 2).

Complaints of shortness of breath (hyperventilation), easy fatigue, decreased functional exercise capacity, and basal crackles that disappear with coughing or deep breathing are symptoms that arise with uterine growth and its mechanical effect on diaphragm compression, especially toward the end of gestation. In addition to this, peripheral edema and varicose veins are frequent during later stages of gestation. Systemic arterial pulse is characterized by a rapid increase and a rapid collapse ("small battering ram") starting with the first trimester.

During chest palpation, cardiac ictus is noted to be shifted to the left, anterior, and rotated in the direction of a transverse position to the extent that the uterus enlarges. As a result, the apical impulse is shifted to the fourth intercostal space, laterally to the hemiclavicular line. The left ventricular impulse is relatively hyperdynamic, but it is not sustained; the right ventricle may be palpable, because, like the left ventricle, it supports a greater volume of blood, which is ejected against relatively low resistance. As pregnancy advances, enlargement of the breasts and the abdomen makes precise heart palpation difficult and at times impossible.[18]

The changes in auscultation that accompany normal gestation begin at the end of the first trimester and generally subside within one week of delivery. Higher basal heart rate, higher precordial heart sounds, split first and second sounds in the third trimester, and systolic ejection murmurs (as high as grade 2/6) above the pulmonary and tricuspid areas are regularly detected during cardiac auscultation. The third sound may be present in the majority of pregnant women; the fourth heart sound is rarely heard, and it is, in general, pathological. Venous hum is almost universal in healthy women during normal gestation, and it is most audible over the right sternal border. The hum is attributable to an increase in venous return. Breast murmur (systolic or continuous) is audible over the anterior thorax at the end of gestation, and it is peculiar to pregnancy due to increased mammary blood flow. It is especially common after childbirth in breastfeeding women.[20]

Diastolic murmurs are not common in normal gestations. When they occur, they may reflect an increase in flow through the tricuspid or mitral valve or physiological dilatation of the pulmonary artery. Alternatively, these murmurs may represent a pathological condition, requiring investigation with further examinations.[20]

Table 2 – Clinical evaluation of normal pregnant women

Symptoms	Signs
Diminished physical exercise capacity	Hyperventilation
Dyspnea	Limb edema
Fatigue	Distention of neck veins
Palpitation	Pulmonary base crackles
Dizziness	Ictus cordis shifted to the left
Orthopnea	Palpable right ventricular impulse
Swelling in the legs	Pulmonary trunk impulse

Adapted from Davies et al., 2007.[19]

The hyperdynamic state of pregnancy may manifest with episodes of tachycardia, and baseline resting heart rate may oscillate around 90 bpm. Bradycardias are rare; when they occur, more detailed investigation is necessary. Sinus rhythm should be prevalent among pregnant women, but the presence of supraventricular or ventricular extrasystoles is very common.

When measuring pregnant women's blood pressure, the fourth Korotkoff sound is accepted as diagnosis of diastolic pressure. After this point, the sounds begin to change, and it is not easily reproducible at times. For this reason, it is fundamental to measure arterial pressure in the left lateral decubitus position using a standardized method. Arterial hypotension is a common finding during the first trimester, continuing until week 22 to 24, with arterial pressure returning to pre-pregnancy levels near the term of pregnancy.

2.2.1.2. Key Points

- Detailed anamnesis considering current and past symptoms;
- Family history;
- Detailed physical examination to differentiate between normal and heart disease.

2.2.2. Fetal and Obstetric Evaluation

Obstetrical and perinatal complications are significantly greater in women with heart disease – the leading cause of maternal death during the pregnancy-postpartum cycle. The lack of healthcare protocols for pregnant women with heart disease and fragile multidisciplinary interaction contribute to these poor outcomes in pregnancy. Within this scenario, it is necessary to develop healthcare protocols aligned with prevention and treatment of complications during pregnancy, delivery, and the postpartum period, for pregnant women with cardiac disease. The Heart Disease and Pregnancy Service of the Obstetrics Department of Universidaddse Federal de São Paulo, in this document, have proposed a protocol presented in Figure 5.

The care plan includes the following: preparation and readiness for delivery at a reference hospital; routine compliance on the part of anticoagulated patients and patients in premature labor; prevention of postpartum hemorrhage (PPH); and infective endocarditis (IE) prophylaxis.

The principal maternal factors that affect fetal growth and development are low cardiac output (heart failure [HF] and

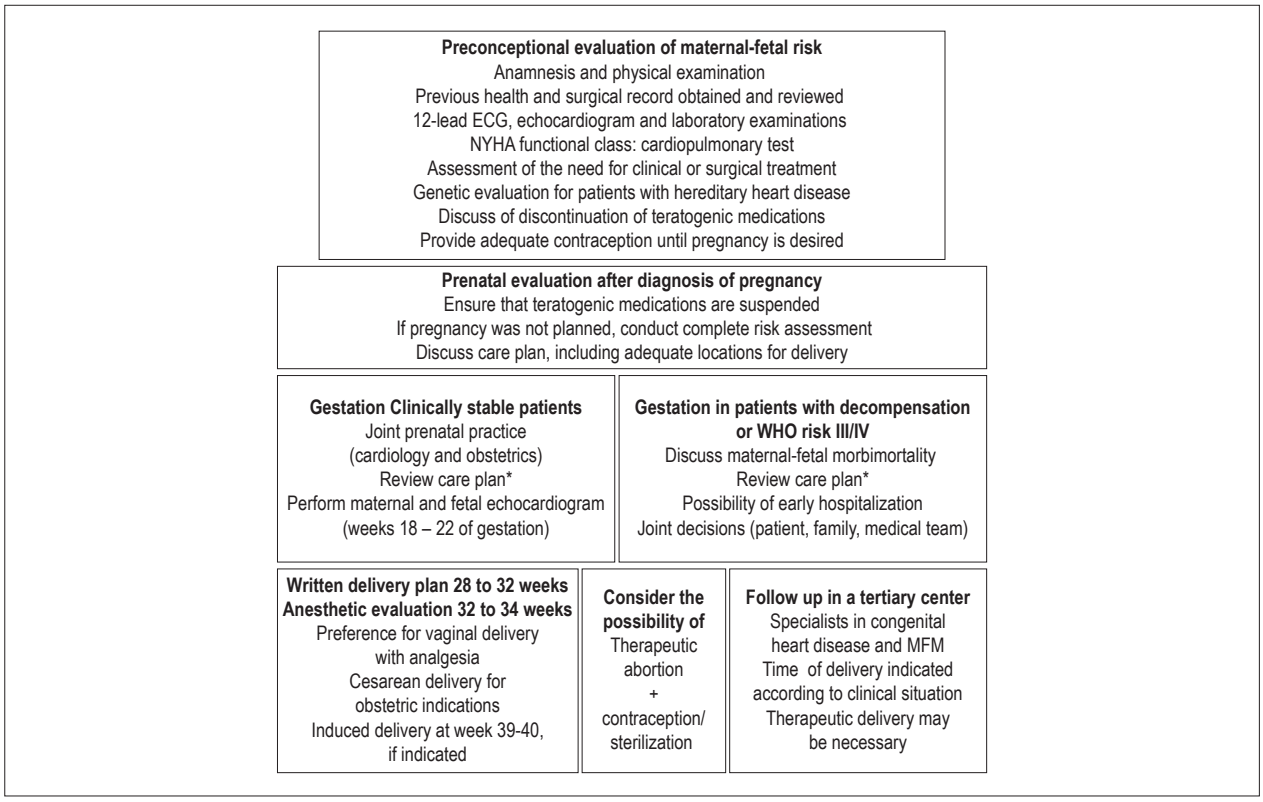

Figure 5 – *Evaluation and practice for women with cardiovascular disease. ECG: electrocardiography; MFM: Maternal-fetal medicine; NYHA: New York Heart Association; WHO: World Health Organization.*

obstructive cardiac lesions), hypoxemia (pulmonary hypertension [PH] or cyanotic heart disease), medication use (anicoagulants, beta-blockers, diuretics, or antiarrhythmics), heredity (genetic transmission), maternal infections (by *Trypanosoma cruzi* [*T. cruzi*]), and obstetric complications (Table 3).

Fetal consequences include greater frequency of prematurity, intrauterine growth restriction (IUGR), miscarriages, cardiac and non-cardiac anomalies, and death. Maternal clinical complications associated with low cardiac output lead to a greater frequency of low birth weight –, with an average weight 300 g lower when compared to pregnancies that progressed without complications – and Apgar score less than 7.[21]

Maternal hypoxemia in women with cyanotic heart disease increases fetal risk, even though there is a compensation mechanism to facilitate fetal oxygen delivery. Most newborns with maternal hypoxemia are small for gestational age and premature. A higher frequency of miscarriages has also been observed, proportional to the elevated hematocrit and maternal hemoglobin levels.

Anticoagulant use during pregnancy causes expressed fetal loss. It is estimated that the incidence of spontaneous abortion during the first trimester is 28.6% *versus* 9.2% in pregnant women using warfarin *versus* heparin, respectively.[22] Sodium warfarin, when used during the first trimester, causes fetal warfarin syndrome in 5% to 10% of cases. This occurs between the sixth and ninth week of gestation[23] (Table 4). The incidence is variable, as, in many cases, the syndrome may not be identified from the clinical point of view; according to geneticists' evaluation, however, the frequency is much higher. The risk of warfarin syndrome, when compared to the general population, is OR 3.86 (1.86-8.00- IC 95%). For these reasons, these children should receive detailed genetic evaluation during early childhood, and their scholar development should be followed.

Newborns whose mothers have used amiodarone, sotalol, angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), or other medications during gestation should receive specific assessment of these drug-related abnormalities during the neonatal period. For patients who have been previously operated or who have undergone previous blood transfusion, it is essential to investigate hepatitis B and human immunodeficiency virus (HIV) infections, given that the use of drugs for these conditions may decrease vertical transmission.

The frequency of fetal evaluation should be decided by the obstetrician according to case severity and the parameters to be evaluated. Severe patients, including those with New York Heart Association (NYHA) functional class (FC) III/IV, severe obstructive valve disease, cyanotic heart disease, complex congenital heart disease, and PH, may require fetal reassessment by ultrasound, as often as weekly. Fetal Doppler of uterine arteries during the second trimester aims to predict preeclampsia. This includes evaluation of the umbilical, middle cerebral, and uterine arteries, the cerebroplacental ratio, and the ductus venosus (Table 5).

Table 3 – Predictors of neonatal events in pregnant women with heart disease.

NYHA functional class III/IV
Cyanosis
Obstructive cardiac lesions
Tobacco use
Hypoxemia – oxygen saturation < 90%
Need for permanent anticoagulation
Abnormal uteroplacental blood flow – by Doppler scan
Maternal infections (*by Trypanosoma cruzi*, human immunodeficiency virus, or toxoplasmosis)
Parents with congenital heart disease
Medication use during pregnancy (ACEI, ARB, or beta-blockers)
Obstetric complications – arterial hypertension, gestational diabetes

ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blockers; NYHA: New York Heart Association.

Table 4 – Fetal warfarin syndrome[23]

Affected bones/cartilage (chondrodysplasia punctata)
Hypoplasia of extremities (dwarfism and bone dystrophy) Optical defects: blindness, optic atrophy, microphthalmia
Central nervous system: mental retardation, deafness
Intrauterine growth restriction
Scoliosis
Congenital heart disease
Death

During fetal ultrasound evaluation, it is important to estimate gestational age, vitality, morphology, amniotic fluid volume, and fetal growth profile. In the event that an abnormality is detected, evaluation should be complemented by more specific examinations, such as fetal Doppler, fetal biophysical profile, and fetal echocardiography (echo).[24] The latter should be performed routinely, always after week 20, when there are maternal or fetal indications. Maternal indications are diabetes mellitus, a parent with congenital heart disease, maternal infection related to teratogenicity (rubella, cytomegalovirus, HIV), Chagas disease and toxoplasmosis (related to cardiomyopathy or fetal myocarditis), maternal age > 35 years, phenylketonuria, connective tissue disease (most associated with fetal atrioventricular block), and exposure to teratogenic agents. Fetal indications for complementary evaluation include findings of other abnormalities on morphological study, chromosomal disease, and fetal arrhythmias.

2.2.2.1. Key Points

- Perinatal morbimortality is higher in newborns whose mothers have heart disease, in comparison with the general population;
- Multiple maternal factors are associated with the higher incidence of fetal loss, malformations, IUGR, and prematurity;
- Obstetricians and neonatologists must be attentive to neonatal complications related to maternal heart disease.

2.3. Complementary Cardiovascular Assessment

2.3.1. Electrocardiography

Electrocardiography (ECG) is the first method used for diagnostic confirmation in clinical cardiology practice. The criteria for performing ECG in pregnant women are the same as those defined for the general population; it should not, however, be part of routine prenatal screening for heart disease. ECG should serve as evaluation and follow up for pregnant women with previous heart disease and for investigation of arrhythmias.[25]

Physiological changes during gestation should be considered in the interpretation of the ECG record. The following stand out: electrical axis slightly shifted to the left; T-wave inversion in the DIII, V1, V2, and, at times, V3 leads; prominent q wave in the inferior and anterolateral walls; increased P-wave duration and prolonged QT interval.[26] Measurements of P-wave duration and QT interval during the 3 trimesters of pregnancy have shown prolongation of the P wave during the second trimester, followed by a plateau, as well as prolongation of the maximum QT interval at the term of the gestation.[27]

ST-segment depression may be observed in 25% to 47% of pregnant women during cesarean delivery or 30 minutes afterwards, regardless of the type of anesthesia utilized. No alterations suggestive of ischemia have been observed during vaginal birth in healthy pregnant women.[26,27]

2.3.2. Echocardiography

Echo is the examination of choice for diagnostic investigation of most heart diseases, owing to its easy use, the absence of maternal-fetal risks, and lower costs when compared to other methods. Indications are the same as those for the general population,[28] for initial diagnosis when heart disease is suspected, for risk stratification by

Table 5 – Fetal procedures

First trimester ultrasound (establish gestational age)
Second trimester ultrasound (analysis of fetal morphology)
Doppler ultrasound of uterine arteries to predict preeclampsia
Fetal Doppler ultrasound starting at week 26 (biweekly or weekly in severe cases)
Fetal echocardiography (pregnant women with congenital heart disease): week 20
Third trimester ultrasound (fetal growth profile and fetal biophysical profile) biweekly starting at week 26 in severe cases

measurement of ejection fraction or global longitudinal strain, and for determining clinical therapeutic practice or percutaneous or surgical intervention in cases with important stenoses in mitral and aortic valves.

Pregnancy hypervolemia may cause slight dilatation of the cardiac chambers (up to 20% in the right chambers and 10% to 12% in the left chambers), mild mitral and tricuspid valve reflux, appearance of minimal physiological transvalvular gradients, and increase in prior valve gradients, as in obstructive lesions of the heart.[29]

Transesophageal echo is relatively safe, and its conventional indications continue to apply;[29] the risk of vomiting and aspiration mainly increases after week 20 of gestation. This requires the presence of an anesthetist, who will assist in selecting the most appropriate sedation, in controlling ventilation, and in fetal monitoring during the procedure.

During the final periods of gestation, small pericardial effusions may be perceived as a consequence of excessive hydrosaline retention, which disappears during the postpartum period. These effusions are not pathologically significant, and they are usually asymptomatic; they do, however, require reevaluation 6 weeks after delivery.

Fetal echo may be used to detect congenital heart disease, and it may be performed transvaginal beginning with week 12 of gestation and transabdominally beginning with week 18. Although the main indication for fetal echo is the presence of an alteration in the routine ultrasound examination, some maternal indications are important, including pre-gestational diabetes mellitus or diabetes identified during the first trimester of gestation, phenylketonuria, systemic lupus erythematosus (SLE), and Sjögren syndrome with positive anti-SSA and/or anti-SSB antibodies.[30] In these cases, both the presence of fetal complete atrioventricular block during a previous gestation and neonatal SLE increase the possibility of fetal involvement during a subsequent gestation, or, at times, alteration in fetal cardiac rhythm determines better maternal evaluation for investigating autoantibodies.

Other indications are cases of assisted reproduction, maternal congenital heart disease, infections such as rubella during the first trimester of gestation, or other viruses, when there is a suspicion of associated fetal myocarditis or pericarditis. Less precise indications refer to maternal medication use during the first trimester of gestation, such as anticonvulsive drugs, lithium, ACEI, retinoic acid, vitamin A, paroxetine, and non-hormonal anti-inflammatory drugs, due to risks of both fetal malformation and ductal constriction.[31]

2.3.3. Ambulatory Blood Pressure Monitoring

Ambulatory blood pressure monitoring (ABPM) is considered a safe examination. It is mainly indicated for identification of early arterial hypertension, which occurs during the first 20 weeks of gestation. It is estimated that approximately one third of pregnant women present white coat hypertension, almost half of whom may develop true arterial hypertension which requires treatment.[32]

Blood pressure monitoring during different trimesters has shown conflicting results regarding pressure behavior, and it has little utility for identifying pregnant women who develop late hypertension or even for predicting adverse events in hypertensive patients. Reference values are the same as those used for the general population, and there are no studies which recommend routine use of ABPM for diagnosing or monitoring blood pressure as a substitute for conventional measurement with a tensiometer.[33]

2.3.4. 24-hour Holter Monitoring

Holter monitoring is mainly used for detecting or stratifying arrhythmias during gestation. It is mainly indicated for investigation of palpitation, unexplained syncope, or pre-syncope, or, less frequently, investigation of neurological events in whose etiology atrial fibrillation (AF) may be implicated.[34]

Holter monitoring is an examination method for identifying and characterizing arrhythmias as simple or complex and symptomatic or asymptomatic, which is fundamental information for practice during pregnancy. It is particularly indicated for investigating paroxysmal AF, other tachyarrhythmias, symptomatic sinus bradyarrhythmias, and different degrees of atrioventricular block. Holter is also of great value for evaluation of patients with a pacemaker or an implantable cardioverter-defibrillator (ICD) when symptoms such as palpitation, syncope, or pre-syncope occur, or when there is suspicion of device command failure.

2.3.5. Exercise Test

The main indication for ergometric test during gestation would be investigation of ischemic coronary disease. Performance of a submaximal test, reaching 80% of maximum expected heart rate, seems to be a safe method during gestation, but the lack of studies does not make it possible to validate its indication for defining ischemic disease. For this reason, there are no recommendations for performing exercise tes during gestation to investigate ischemic coronary disease. In the same manner, the use of stress with dobutamine should be contraindicated during pregnancy.

In contrast, during preconception, abnormal chronotropic response identified on ergometric test in women with heart disease seems to be predictive of adverse events during future pregnancies. In the same line of investigation, ergospirometry test is valid for evaluation of myocardial reserve, especially in women with congenital heart disease.[35]

2.3.6. Key Points

- ECG and echo should be indicated when heart disease is suspected;
- Fetal echo is indicated for congenital heart disease or when fetal involvement is assumed due to maternal disease;
- 24-hour Holter monitor assists in identification and stratification of cardiac arrhythmias;
- The main indication for ABPM is identification of "early" arterial hypertension, which occurs during the first 20 of gestation;
- Exercice testing is not indicated for investigation of ischemic coronary disease during gestation;
- Ergospirometry testing assess to risk stratification for women with heart disease when planning gestation.

2.4. Ionizing Imaging Cardiovascular Assessment

The use of ionizing imaging diagnosis in adult with heart disease corresponds to 12% of all examinations to which these patients are exposed[36] and to 40% of the total dose of radiation which they will receive during their lifetime.[37] For this reason, they are a cause of concern regarding the safety of examinations that emit radiation during pregnancy and lactation.

Measurements of ionizing radiation may be in sieverts (Sv), which express the equivalent dose of radiation in the tissue, or in gray (Gy), which indicate total radiation dose. Sv is the measure of greatest biological significance.[38]

There are two biological effects of radiation, namely, the deterministic effect, which leads to cell death when the maximum recommended dose of radiation is exceeded and which becomes evident after a few days, weeks, or months of the procedure (cataract, leukopenia, anemia, sterility, and others); and the stochastic effect, which causes cellular transformation with random alteration in single-cell DNA (deoxyribonucleic acid) that continues to reproduce. When the damage occurs in germ cells, genetic or hereditary effects may occur. There is no dose threshold, and damage may be caused by a minimal radiation dose. Moreover, the effects are difficult to measure experimentally due to the long latency period. The main examples include cancer (leukemia from 5 to 7 years, solid tumors from 5 to 10 years or more) and genetic effects. It has been verified that stochastic effects are highest in children and higher in women than in men, and they are reduced by 50% among octogenarian men.[39]

During pregnancy, the biological effects of radiation on the embryo depend on dose and gestational age, and they may be divided into the following 4 categories: intrauterine death, malformations, growth and developmental disorders, and mutagenic and carcinogenic effects.[40,41]

It is accepted that the non-carcinogenic risk, which includes miscarriage and malformations, is insignificant at doses below 50 mGy, in comparison with other risks of pregnancy. In contrast, it is estimated[42] that doses above 100 mGy present potential effects on the fetus/embryo in accordance with gestational age, such as fetal death when exposure occurs between the first and second week of gestation; severe abnormalities in the central nervous system (hydrocephalus, microcephaly, and mental retardation) between weeks 3 and 15; mental retardation, microcephaly, and fetal growth restriction between weeks 16 and 30; following week 32 of gestation, teratogenic effects are absent, but there continues to be an increased risk of developing malignancy during childhood and adulthood. Indication for interrupting gestation may be considered in cases of radiation doses between 100 and 500 mGy, based on individual circumstances, such as maternal malignant diseases that require serial imaging during gestation, interventional procedures, or radiation therapy.[43]

Accordingly, it is important to remember that the natural incidence of congenital anomalies in the general population generally varies between 0.5% and 5%, and exposure to a radiation dose of 10 mGy is associated with 0.5%, 0.4%, and 0.1% probabilities of malformations, microcephaly, and mental retardation, respectively.[41] In this line of investigation, studies have demonstrated that uterine exposure to even low radiation doses (20 mGy) increases the risk of cancer during childhood and the occurrence of leukemia, by a factor of 1.5 to 2.0, when compared to the natural incidence of these diseases.[43] The main radiological methods and the doses of radiation absorbed by the fetus, the patient, and the breasts (during lactation) are shown in Table 6.

It is necessary to remember that no single radiological examination exposes the fetus to doses above 250 mGy, which could occur as a result of a combination of examinations or during the course of a treatment that is essential to the mother.

When they do not directly involve the uterus or direct abdominal exposure, fluoroscopy, radiography, cardiac catheterization, and interventional radiology result in radiation doses that are not very significant to the fetus. Accordingly, it is necessary to consider strategies[44] that may reduce radiation, at times by around 30% to 65%. The following stand out: use of lead protectors on the abdomen, X-ray beam collimation in the area of interest, use of permanently calibrated and measured equipment, preference for digital radiography, and reduction of fluoroscopy time and number of images acquired. Furthermore, enlargements should be carried out using a lower number of images and exposures.

In nuclear scintigraphy examinations, fetal ionizing radiation exposure comes from accumulated radioactivity in the maternal organism and from radiopharmaceutical transport and diffusion through the placenta.[45] Ventilation/perfusion (V/Q) scintigraphy is the most frequent scintigraphy imaging method with reduced maternal dose, compared to computed tomography pulmonary angiography (CTPA). CTPA, however, provides lower doses when the fetus is still small and farther from the field of view or the thorax.

Table 6 – Radiation doses associated with radiological examinations

Modality	Fetal dose (mGy)	Maternal dose (mSv)	Breast dose (mGy)
Tomography			
Pulmonary angiography	0.01 to 0.66	2.7 to 40	8 to 70
Abdomen and pelvis	13 to 25	3 to 45	–
Angiography of thoracic and abdominal aorta, with or without contrast agent	6.7 to 56	4 to 68	16 to 130
Coronary artery angiography	0.1 to 3	7 to 39	10 to 90
Simple abdomen and pelvis computed tomography	10 to 11	3 to 10	–
Nuclear medicine			
Low-dose perfusion scintigraphy	0.1 to 0.5	0.6 to 1.0	0.1 to 0.3
V/Q scintigraphy	0.1 to 0.8	1.2 to 2.8	0.2 to 0.7
Myocardial viability PET with ^{18}F-FDG	6.8 to 8.1	7	–
Myocardial perfusion with ^{99m}Tc-sestamibi	17	11.4 to 14.8	–
Myocardial perfusion with ^{99m}Tc-tetrofosmin	8.45	9.3 to 11.6	–
Radiography			
Mammography, 2 positions	0.001 to 0.01	0.1 to 0.7	3
Thorax radiography, 2 positions	0.0005 to 0.01	0.06 to 0.29	< 0.4
Abdominal radiography	0.1 to 0.3	0.01 to 1.1	–

FDG: fluorodeoxyglucose; PET: positron emission tomography; V/Q: ventilation/perfusion. Note: Estimated doses vary according to protocol, radiotracer, dosage, dose calculation method, and patient-dependent factors (e.g. body weight and tissue percentage of the mammary gland).

V/Q scintigraphy and CTPA are efficacious for diagnosing pulmonary embolism during pregnancy, although CTPA demonstrates advantages for identifying other pulmonary diseases. When clinical suspicion of pulmonary embolism exists, simple chest X-ray and bilateral lower limb Doppler ultrasound are considered to be the initial examinations for guiding indication for V/Q scintigraphy, which should be preferable to CTPA when both are available.[45] Pharmacological stress with the use of vasodilators, either adenosine or dipyridamole, is not recommended during gestation, owing to the risks resulting from orthostatic hypotension.

2.4.1. Administration of Contrast Agents

Iodinated contrast agents do not present any teratogenic effects, and they may be used orally or intravenously in cases where examination information is important for immediate management; otherwise, the examination should be postponed until after delivery.[46] This is due to the fact that fetal thyroid maturation begins at week 12, and it functions minimally at week 20 of gestation. There is, thus, a concern that iodinated contrast agents might induce development of hypothyroidism, even though, over the past 3 decades, there have been no reports of this occurring in this situation. In cases of allergic reaction to the contrast, phenylephrine and corticosteroids may be used safely. In preventive situations, prednisone and dexamethasone should be considered, given that most of these agents are metabolized in the placenta before reaching the fetus. There are, however, case reports of fetal adrenal suppression with corticosteroid use, and methylprednisone has been correlated to cleft lip when used before 10 weeks of gestation.[43]

More recently, multislice tomography, with multiple rows of detectors, has been used, providing undeniable advantages, especially related to speed and definition in abdominal and angiographic studies (CT angiography). These benefits, however, have been accompanied by a significant increase in absorbed radiation doses in abdominal organs of around 90% to 180%, when compared to helical devices with a single row of detectors. At the same time that multislice technology is consolidated as an extremely useful tool for thoracic-abdominal studies, it is necessary to invest in optimizing and adjusting protocols with the aim of controlling and limiting emitted radiation dose, especially during gestation.

2.4.2. Nuclear Magnetic Resonance

Cardiac magnetic resonance (CMR) is advisable in cases where other non-invasive methods have not been sufficient to define diagnosis, and it is preferable to imaging examinations that emit ionizing radiation. Exposure during the first trimester of gestation has not been associated with harmful effects to fetuses or children during early childhood.

Evidence regarding the use of gadolinium contrast during pregnancy is controversial. Gadolinium (Gd+3) is a paramagnetic metal ion whose pharmacological behavior in the organism is similar to that of iodinated contrast medium, i.e., it acts as an extracellular agent, rapidly spreading from the intravascular compartment to the interstitial space. No mutation or teratogenic effects have been documented following inadvertent administration of gadolinium-based contrast media during pregnancy. Nevertheless, depending on the dose, its use appears to be associated with greater risks of rheumatic, inflammatory, and infiltrative cutaneous manifestations, in addition to fetal loss.[47]

In its free form, the gadolinium ion is neurotoxic; its bond to a chelating agent, however, forms a stable complex, thus protecting the organism from adverse effects. Gadolinium chelates cross the placental barrier, and they may accumulate in the amniotic cavity; nonetheless, some studies have shown that only 0.01% of the dose is present in fetal circulation 4 hours after contrast administration, and only traces are detected after 24 hours.

During lactation, both iodinated contrast agents and gadolinium have low lipid solubility, and their concentration in breast milk is lower than 1% and 0.04%, respectively.[46] For this reason, the American Academy of Pediatrics and the WHO recommend not suspending lactation.

Obtaining patients' informed consent and clarifying the inherent risks of tests that are necessary for medical practice are essential measures that should be part of the interdisciplinary decision to indicate radiation examination during gestation, which involves the obstetrician and the radiology team.

2.4.3. Key Points

- Indication for a radiological examination should consider the real benefit for determining therapeutic practice during pregnancy and the impossibility of substitution with an alternative radiation-free method (ultrasound, echo, and magnetic resonance);
- The radiologist is the professional who is most prepared to evaluate the best diagnostic option in a given clinical situation, ensuring the safety of the pregnant woman and the fetus;
- Radiological examinations should be performed in institutions that are able to guarantee the adoption of effective protection measures and that have modern equipment that is regularly calibrated and measured;
- CMR is a complementary examination for defining diagnosis of heart disease. It is safe during gestation. Nevertheless, the use of gadolinium should be avoided;
- The need for an examination with radiation demands interdisciplinary discussion involving a radiologist, a cardiologist, and an obstetrician, in addition to the patient's informed consent.

2.5. Cardiovascular Drugs during Pregnancy and Breastfeeding

Requirement of pharmacological therapy is very frequent during pregnancy and lactation.[48] It is estimated 34% of pregnant women with heart disease use cardiovascular medications, with the following distribution: beta-blockers (22%), antiplatelet drugs (8%), diuretics (7%), ACEI (2.8%), and statins (0.5%).[49] In this series, the prevalence of adverse events to the fetus, especially IUGR, was twice as high when compared to the women who did not take medication.[50]

It is estimated that 10% to 15% of women with heart disease present cardiac complications that lead to medication treatment during gestation like systemic arterial hypertension (SAH), cardiac arrhythmias, HF, and thromboembolism.[51,52] However, prescription drugs during pregnancy requires basic knowledge of pharmacokinetics and drug classification for maternal and fetal safety during pregnancy and lactation.

The pharmacokinetics of medications are influenced by the physiological changes of pregnancy, often leading to a reduction in drug plasma concentration such that any dose adjustments should be considered to achieve therapeutic efficacy.[53] Table 7 summarizes[54] the aspects deserve the following considerations:

- Absorption of orally administered drugs is reduced due to delayed intestinal motility.[55] Besides, the use of antacids and iron as a supplement appears to induce drug chelation at increased gastric pH, resulting in reduced drug bioavailability;[56]
- The volume of drug distribution is increased during pregnancy due to plasma volume expansion contributing to a reduction in peak drug concentration;[57]
- Liver metabolism is accelerated during pregnancy because liver perfusion is greater. This means that the fraction of the drug removed from the liver circulation is increased such that drugs such as propranolol, nitroglycerine, and verapamil are extracted faster from the systemic circulation.[54] Drugs such as warfarin, which do not depend on flow but on liver activity and plasma free fraction are not influenced their concentration during pregnancy. On the other hand, nifedipine and metoprolol plasma levels are reduced in pregnancy due to increased enzyme catalytic activity;[58]
- 85% increase in renal blood flow compared to pre-gestational levels.[59,60] However, a tubular function is variable, with a reduction in uric acid excretion and glucose absorption, and an increase in protein excretion.[61]

As for safety, most drug studies in pregnancy are performed on animals and have little applicability because the effects are generally species-specific. Human studies are almost always retrospective and include small series. Pregnant women, except in rare circumstances, are excluded from large clinical trials. Thus, the medical literature on drugs in pregnancy has, for the most part, questionable scientific evidence.

In 1979, the Food and Drug Administration (FDA)[62] introduced the classification of drugs according to categories A through X, which are widely used in daily practice.[55] This classification labeled drugs according to animal and female studies in categories that they ranged from drugs that did not pose a risk to the fetus (category A) to teratogenic ones (category X).

In 2015, the classification (A, B, C, D, and X) was replaced by the so-called Pregnancy and Lactation Labeling Rule (PLLR),[63] which is currently being accepted more. It provides a descriptive summary and detailed information on animal studies and clinical trials, as outlined in Table 8.

2.5.1. Antihypertensive Drugs (Table 9)

Nifedipine: hypotensive and tocolytic action; not teratogenic. May require shortening of intake range or higher dose due to CYP3A4-mediated accelerated hepatic metabolism. Increased hypotension with concomitant magnesium sulfate use.[64-66]

Table 7 – Pharmacokinetics during pregnancy

Decreased absorption	Delayed intestinal motility
Increased distribution volume	Reduced peak concentration of hydrophilic and lipophilic drugs and half-life variations
Increased hepatic metabolism	Reduced plasma concentration of drugs that pass through the liver
Increased renal clearance	Reduced plasma concentration of drugs with renal excretion. Tubular absorption/excretion function is variable

Adapted from Feghali et al., 2015.[54]

Table 8 – Pregnancy and Lactation Labeling Rule – Food and Drug Administration

Required information
Related to pregnancy: Risk of medication use, compatibility with lactation, reproductive potential in men and women, information about pregnancy tests and contraceptive use
Risk summary: Systemic absorption of the drug during pregnancy, labeled data from studies in humans and animals and adverse fetal outcomes, including fetal loss and malformation
Contraindicated during pregnancy: Structural anomaly, embryopathy or fetal and neonatal mortality, functional impairment (multiple organ toxicity), growth alterations, retardation, or prematurity
Clinical considerations: Essential guidelines for prescription considering dose adjustments during pregnancy and postpartum, associated maternal disease and/or risk of fetal embryopathy, adverse maternal and fetal reactions, and effects of medication during labor and delivery
Additional data: Information from studies in humans and animals that support previously presented declarations of risk
Pregnancy exposure registry: Information for healthcare professionals, with toll-free telephone number for obtaining information about the registry
• Data
• Human
• Animal

Table 9 – Effects of antihypertensive drug use during pregnancy and lactation

Drugs	Used during pregnancy	Maternal-fetal effects	Lactation
ACEI and ARB	No	Dysgenesis and renal insufficiency Congenital cardiovascular and neurological malformation	Compatible (captopril, enalapril, losartan)
Amlodipine	Yes	Non-teratogenic Limited data in humans	Probably compatible
Atenolol	No	IUGR Bradycardia and fetal hypoglycemia	Compatible, but with caution (safer options)
Metoprolol succinate	Yes	Low birth weight and IUGR Bradycardia and fetal hypoglycemia	Compatible, but with caution (effects of the beta-blocker on the newborn)
Nifedipine	Yes	Probably low risk during all phases of gestation	Compatible
Methyldopa	Yes	Probably low risk during all phases of gestation	Compatible
Clonidine	Yes	Probably low risk during all phases of gestation	Compatible
Verapamil	Yes	Probably low risk during all phases of gestation	Compatible
Sodium nitroprusside	Yes – risk of fetal cyanide exposure	Congenital malformations have not been described Cyanide accumulation	Not compatible
Furosemide	Yes	Reduced amniotic fluid	Compatible*
Hydrochlorothiazide	Yes	No evidence of teratogenicity Risk of hypovolemia	Compatible*
Hydralazine	Yes	Neonatal thrombocytopenia and lupus-like syndrome	Compatible
Spironolactone	No (antiandrogenic activity)	No evidence of teratogenicity Antiandrogenic activity (feminization of male fetus)	Not recommended

ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blockers; IUGR: intrauterine growth restriction.

Methyldopa (β2-adrenergic receptor agonist): Non-teratogenic, considered safe and effective in the treatment of gestational hypertensive disease with favorable outcomes in primary and secondary outcomes such as blood pressure control, fetal growth, and prematurity. Warning maternal effects such as postural hypotension, lupus-like syndrome, depression, nasal congestion, drowsiness, and liver toxicity have been reported in 1% of treated cases.[67,68]

Hydralazine: direct arteriolar vasodilator for oral or intravenous use in hypertensive emergencies. Adverse effects are maternal symptoms of "like" lupus and fetal thrombocytopenia.[69]

Clonidine: alpha-2 agonist has divergent hemodynamic effect in reducing vascular resistance versus reduction in cardiac output, and the consequent impact on fetal growth. Abrupt suspension may cause rebound hypertension. It is not teratogenic. It is available transdermal.[70]

Diuretics are indicated in hypervolemia and HF; however, the reduction in plasma volume, cardiac output, and placental flow is the major restriction on diuretic use during pregnancy. Its use during pregnancy has not been related to detrimental effects to the fetus. Furosemide is the most commonly used, while hydrochlorothiazide has been related to lower birth weight, jaundice, and neonatal thrombocytopenia.[71]

Beta-blocker: atenolol is not recommended because its use is associated with IUGR and low birth weight newborns.[71]

Amlodipine: may be considered second-line treatment without reference to being teratogenic when used in the first trimester of pregnancy.[71]

ACEI, ARB, direct renin inhibitors and aldosterone antagonists are contraindicated in pregnancy and should not be prescribed in women who wish to become pregnant. These medications cause renal dysgenesis, oligohydramnios, renal failure, IUGR, neonatal anuria, and fetal death, particularly in the second and third trimesters of pregnancy.[72] However, ACE inhibitors may be used in lactation. Aldosterone antagonists have antiandrogenic effects on the male fetus and are contraindicated in lactation.[52,73]

2.5.2. Antiarrhythmic Drugs (Table 10)

Adenosine: nucleoside with a half-life of seconds. It is safe, but adverse effects include bradyarrhythmias, dyspnea, chest pain and flushing.[74,75]

Beta-blockers: These are the most commonly used drugs during pregnancy. They are not teratogenic. Controlled studies show a higher frequency of neonatal bradycardia and hypoglycemia, as well as a higher risk of prematurity and small newborns for gestational age.[76-78]

Atenolol: hydrophilic with renal elimination, is contraindicated by the high risk of IUGR.[79,80] **Propranolol** is safe; however, depending on the dose, IUGR, hypoglycemia, polycythemia, and hyperbilirubinemia may occur.[81] **Metoprolol** is well tolerated, with high clearance in the second half of pregnancy. Succinate is safer than tartrate because doses are lower and maybe fractionated.[82,83] Sotalol is associated with point torsades due to QT interval prolongation. **Sotalol** is higher in breast milk and should be suspended during lactation. In cases of lactation maintenance, electrocardiographic control should be performed in the mother and the newborn. According to ESC Guidelines, 2018,[52] sotalol was contraindicated in pregnancy and lactation because of the risk of sudden maternal-fetal death. The proposal is a replacement for propafenone or flecainide. However, the restriction on the use of sotalol during pregnancy and lactation is still controversial, as the results in controlling complex arrhythmias have been satisfactory in the practice of the specialists. Although there are no adequate studies, sotalol appears to be safer compared to amiodarone.[84-85]

Amiodarone: lipophilic, accumulates in skeletal muscle and adipose tissue, with half-life from weeks to months. Warning effects are thyroid dysfunction (causing neonatal hypothyroidism in 17 to 25% of cases) and impaired neurological development. Should be contraindicated in pregnancy.[86-87]

Lidocaine: more studied as an anesthetic agent than antiarrhythmic. Sixty percent of it is bound to plasma protein and rapidly entering the maternal circulation and placenta. It may lead to depression of the fetal central nervous system when used at high doses.[73,88]

Propafenone: recommended for the prevention of supraventricular tachycardia in patients with Wolff Parkinson White syndrome, atrial tachycardia and atrial fibrillation refractory to nodal blocking agents.[52]

Procainamide: associated with maternal lupus syndrome.[89]

2.5.3. Drugs in Heart Failure (Table 11)

Carvedilol: There is a lack of studies. It is the first choice of cardioselective beta-blocker. It is not teratogenic and has not been associated with IUGR.[90]

Bisoprolol: Not associated with an increased risk of miscarriage or fetal malformation when used in the first trimester of pregnancy. However, IUGR cannot be ruled out during prolonged use throughout pregnancy.[52,78]

Hydralazine: A drug that replaces ACEI and ARB.[52]

Nitrates: Not routinely used and not teratogenic. Low maternal tolerance due to hypotension and headache.[52]

Sacubitril / valsartan: is contraindicated during pregnancy and although there are no studies on human milk excretion, there is no recommendation for use during breast-feeding.

Ivabradine: Animal studies show its association with malformation, bradycardia and altered fetal growth.

2.5.4. Antiplatelet (Table 12)

Aspirin: It is safe at low doses at any stage of pregnancy.[52,91,92] Not teratogenic, risk of maternal and fetal bleeding. Should be discontinued five days before delivery.[52,93,94]

Clopidogrel: There are no studies to ensure its use during pregnancy. It does not appear to be teratogenic. The use of clopidogrel should be recommended in very specific cases, as discontinuation of clopidogrel may impair the treatment of the disease for which it is indicated.[93,94]

Table 10 – Effects of the use of antiarrhythmic drugs during pregnancy and lactation

Drugs	Used during pregnancy	Maternal-fetal effects	Lactation
Lidocaine	Yes	Non-teratogenic; in high doses, respiratory depression and fetal acidosis have been described	Compatible
Propafenone	Yes	No data during the first trimester; no complications during the other trimesters	Probably compatible
Propranolol	Yes	Low birth weight and IUGR Bradycardia and fetal hypoglycemia	Compatible, but with caution (effects of the beta-blocker on the newborn)
Sotalol	No	Low weight, IUGR, torsades de pointes when associated with hypomagnesemia	No
Amiodarone	No	Fetal hypo- and hyperthyroidism, low birth weight, long QT	No

IUGR: intrauterine growth restriction.

Table 11 – Effects of heart failure treatment during pregnancy and lactation

Drugs	Used during pregnancy	Maternal-fetal effects	Lactation
Isosorbide mononitrate	Yes	Headache, hypotension, non-teratogenic	Compatible
Hydralazine	Yes	Neonatal thrombocytopenia and lupus-like syndrome	Compatible
Carvedilol	Yes	Low birth weight and IUGR Bradycardia and fetal hypoglycemia	Compatible
Metoprolol succinate	Yes	Low birth weight and IUGR Bradycardia and fetal hypoglycemia	Compatible, but with caution (effects of the beta-blocker on the newborn)
Bisoprolol	No Risk/benefit	Low birth weight and IUGR Bradycardia and fetal hypoglycemia	Compatible (effects of the beta-blocker on the newborn)
Digoxin	Yes	Non-teratogenic	Compatible
Dobutamine	Yes	Non-teratogenic in animals	Probably compatible
Milrinone	No Risk/benefit	Risk in animals No evidence in humans	Probably compatible
Sacubutril/valsartan	No	The same as ARB; inadequate data on sacubitril	No
Ivabradine	No	Cardiac defects in animals IUGR Bradycardia in newborns	No

ARB: angiotensin receptor blockers; IUGR: intrauterine growth restriction.

2.5.5. Thrombolytics (Table 13)

They do not cross the placental barrier but are at risk of maternal bleeding.[52]

2.5.6. Anticoagulants (Table 14)

When used in the first trimester, causes fetal warfarin syndrome in 5 to 10% of cases.[95] The incidence is variable because the syndrome from the clinical view can often be inconspicuous, although in the opinion of geneticists. , its frequency is much higher. The risk of spontaneous abortion (less than 20 weeks of gestation) is almost 30% and that of stillbirth (more than 20 weeks of gestation) is 10%, both caused by warfarin poisoning.[96] Maternal hemorrhage in delivery patients warfarin is serious; more severe, however, is neonatal intracranial hemorrhage and its sequelae.[96,97] For patients on oral anticoagulants who undergo premature labor, cesarean section is indicated.

The hypothesis that doses of less than 5 mg warfarin may cause a lower risk of embryopathy[52] is not supported by appropriate studies to guide anticoagulation guidance in the first trimester of pregnancy. The teratogenic property of a drug is understood to be independent of its dose. Recent reports have shown the occurrence of embryopathy even at doses below 5 mg warfarin.[98,99] It is concluded that it is "good practice" that the warfarin dose is adequate in pursuit of the therapeutic goal, controlled by the index. International Standardized Study (INR) and individualized for each clinical situation.

Heparin: does not cross the placental barrier. Table 15 presents the advantages of low molecular weight heparin (LMWH) over unfractionated heparin (UFH). Both are associated with a 10 to 15% risk of miscarriages due to

Table 12 – Effects of antiplatelet use during pregnancy and lactation

Drugs	May be used during pregnancy	Maternal-fetal observations and effects	Lactation
Aspirin	Yes	Hemorrhage	Compatible
Clopidogrel	Yes (benefit greater than risk)	Hemorrhage	Probably compatible
Prasugrel	No Risk/benefit	No evidence in humans	Probably compatible
Ticagrelor	No Risk/benefit	No evidence in humans	Probably compatible
Ticlopidine	No	Thrombocytopenia, neutropenia	No
Tirofiban	Yes (benefit greater than risk)	Hemorrhage	Compatible
Abciximab	Yes (benefit greater than risk)	Hemorrhage	Compatible
Epifibatide	Yes (benefit greater than risk)	Hemorrhage	Compatible

Table 13 – Effects of thrombolytic drug use during pregnancy and lactation

Drugs	May be used during pregnancy	Maternal-fetal observations and effects	Lactation
Streptokinase	Yes (benefit greater than risk)	Risk of hemorrhage	Compatible
Tenecteplase	Yes (benefit greater than risk)	Risk of hemorrhage	Compatible
Alteplase	Yes (benefit greater than risk)	Risk of hemorrhage	Compatible
Urokinase	Yes	Proteinase inhibitors in the placenta inactivate urokinase	Compatible

Table 14 – Effects of anticoagulant use during pregnancy and lactation.

Drugs	May be used during pregnancy	Maternal-fetal observations and effects	Lactation
Warfarin	No Risk/benefit	Warfarin syndrome during the first trimester, other congenital and neurological anomalies during the other trimesters	Compatible
Heparin	Yes	Thrombocytopenia	Compatible
Enoxaparin	Yes		Compatible
Fondaparinux	Yes	Various reviews suggest safety during pregnancy	Compatible
Apixaban	No	Low risk in animals, evidence does not support safety in humans	No
Dabigatran	No	Moderate risk in animals, evidence does not support safety in humans	No
Rivaroxiban	No	Low risk in animals, evidence does not support safety in humans	No

placental bleeding.[100] Permanent use of UFH during pregnancy presents maternal risks such as bleeding (2%); osteoporosis (30%); spontaneous fractures (2%) and thrombocytopenia (5 to 15%)[101] However, it appears that these adverse effects are minor with LMWH. Control of UFH anticoagulation should be daily, according to activated partial thromboplastin time (TTPA), with a target of 1.5 to 2 times greater than baseline. Control of LMWH should be weekly according to therapeutic values between 0.6 and 1.2 IU/ml of anti Xa factor in patients with mechanical valve prostheses.

Anticoagulation is still a therapeutic challenge. It requires knowledge of the risk of thrombosis for each clinical situation and the side effects of anticoagulants at various moments of the pregnancy-puerperal cycle. The fact is that when there is an indication of anticoagulation, pregnancy should not influence the accuracy and conventional goals. Fondaparinux has proven to be a safe alternative when heparins are not tolerated.[52,102]

New oral anticoagulants (NOACS): There is no data available on exposed pregnant women. These drugs should not be used during pregnancy.

2.5.7. Hypolipidemic Agents (Table 16)

The first choice is cholestyramine, considered the safest.[103] Statins do not appear to be teratogenic. Its correlation with congenital anomalies is not clear; however, due to the lack of studies, its use should be discouraged during pregnancy and should be discontinued at conception.[104-106] Gemfibrozil, fenofibrate and ezetimibe are considered to have teratogenic potential.[73]

Table 15 – Comparison between unfractionated heparin and low molecular weight heparin

Peculiarities	UFH	LMWH
Molecular weight	12,000 to 14,000	4,000 to 6,000
Anticoagulant action	Thrombin and Xa	Xa
Bioavailability	30%	100%
Half-life following application	45 to 60 min	12 h
Absorption following SC injection	Variable	100%
Thrombocytopenia	27%	0%
Monitoring	APTT	Anti-Xa factor
Cost	Low	High
Control frequency	Higher	Lower
Control	1.5 to 2 × baseline	7 to 12 u/ml

APTT: activated partial thromboplastin time; LMWH: low molecular weight heparin; SC: subcutaneous; UFH: unfractionated heparin. Adapted from Ginsberg et al., 2003.[100]

Table 16 – Effects of hypolipidemic agent use during pregnancy and lactation

Drugs	Used during pregnancy	Maternal-fetal effects	Lactation
Statins	No	Low risk of teratogenicity and toxicity	No
Fibrates	No	Teratogenicity in animals, with no evidence in humans	No
Ezetimibe	No	Low risk in animals, current evidence does not support use during gestation	No
Alirocumab	No	Low risk in animals, current evidence does not support use during gestation	No
Cholestyramine	Yes	Possible reduction in vitamin absorption	Probably compatible

The treatment of **pulmonary arterial hypertension** (PAH) will be discussed in topic 3.6.3. Drugs released for use during pregnancy include:[73,107]

- Prostaglandins: epoprostenol, treprostinil, Iloprost;
- Phosphodiesterase 5 inhibitors: sildenafil and tadalafil;
- Calcium channel blockers (BCC): diltiazem and nifedipine;
- Nitric oxide: via inhalation.

Contraindicated drugs during pregnancy are:[73,107]

- Endothelin receptor antagonists: bosentan, ambrisentan, and macitentan;
- Guanylate cyclase stimulators: riociguat.

2.5.8. Key Points

The basic recommendations for prescribing medications during pregnancy, when possible, are:

- Considerer pharmacokinetics of drugs during pregnancy, before prescription;
- Prescribe when treatment is indicated, and its benefit outweighs the potential risk;
- Guide to the prescription by the PLLR classification;
- Avoid medication in the first trimester of pregnancy;
- Use the lowest dose, as long as it is effective, for the shortest time, and, fractionate the daily dose;
- Use drugs that are already widely accepted and safe in pregnancy;
- Consider that drugs with molecular weight less than 1,500 Da cross the placenta and reach fetal circulation;
- Guide preconception for women who make permanent use of medicines;
- Consider that the priority of treatment is maternal, but obstetric and fetal risks should be considered.

2.6. Practice Recommendations during Pregnancy

2.6.1. Lifestyle

Pregnancy is an ideal moment for lifestyle change. This is because pregnant women, owing to concerns about their children's health, are motivated to improve unhealthy habits, for example, quitting smoking and alcoholism, consuming a more balanced diet, or controlling weight.

Tobacco use is related to complications such as placenta praevia, premature placental detachment, low fetal weight, and prematurity, even in passive smokers.[108] Consumption of alcoholic beverages should be avoided, because it can cause fetal growth retardation, as well as abnormalities in the face and the central nervous system.[109]

Pregnancy in women with heart disease should be accompanied by a multidisciplinary team. Consultations with

a cardiologist should be monthly during the first half of gestation, biweekly following week 21, and weekly until delivery, and they must respect constant interaction with an obstetrician, which ensures the best practice during the various stages of gestation.

These routines should, however, be adjusted according to case severity. Accordingly, pregnant women who permanently use anticoagulants are recommended to undergo weekly evaluation for clinical and laboratory control. Women with WHO class IV heart disease should be hospitalized during the third trimester of gestation for clinical stabilization and delivery planning. In addition, care should be recommended regarding diet, physical activity, sleep quality, and reduced stress and workload, depending on the patient's profession and heart disease. Furthermore, review and adjustment of continuously used medications, as well as suspension or replacement of drugs that are harmful to the fetus, are practices that should take place before conception, i.e., during the pregnancy planning phase.

2.6.2. Physical Activity

During pregnancies without complications, the benefits of physical activity are unquestionable. They include improved physical resistance and cardiorespiratory function; reduced stress, anxiety, and risk of comorbidities related to sedentarism; and weight gain.[110,111] Nevertheless, the American College of Obstetricians and Gynecologists contraindicates exercise during pregnancy in patients with heart disease with hemodynamic repercussions, patients classified as WHO risk III or IV, and in cases of preeclampsia, pregnancy-induced hypertension, severe anemia, and restrictive pulmonary disease.[112]

2.6.3. Diet

A balanced diet provides nutrients that are essential to fetal development, and it prevents complications related to weight loss in pregnant women. Obesity is associated with miscarriage, newborns with low birth weight, macrosomia, gestational diabetes, thromboembolism, and gestational hypertension, whereas malnutrition is linked to low birth weight and perinatal death.[113] Notwithstanding an adequate diet, nutritional goals also require oral supplementation, as shown in Table 17. Consumption of foods rich in folic acid and supplementation with doses of 1 to 5 mg daily before conception and during the first trimester prevent neural tube defects in 72% of cases.[114] Calcium supplementation (≥ 1 g daily) is associated with a significant decrease in the risk of preeclampsia (especially in women with low calcium consumption), as well as a decrease in prematurity and the occurrence of the composite outcome of "maternal death or severe morbidity."[115] The WHO recommends 1.5 to 2 g of calcium daily for pregnant women with low calcium consumption in their diets.

Fish consumption is the main source of non-occupational maternal exposure to methylmercury, which is found in all fish tissues and is absorbed in over 95%. Notwithstanding the risk of mercury poisoning, cohort studies have shown that greater maternal consumption of fish during the prenatal period was associated with better neurological development in newborns[116] and that moderate consumption (up to 3 meals weekly) before week 22 of gestation was linked to reduced repeat prematurity. However, a recent systematic review and meta-analysis of randomized trials did not show statistical significance for the effect of long chain polyunsaturated fatty acids (n-3 PUFA) on reducing prematurity or any other fetal defects, such as neurological, cognitive, or visual acuity development.[117,118]

Regarding caffeine consumption, given the lack of adequate studies, it is recommended to limit consumption to less than 200 mg daily.[119] It is important to emphasize that coffee, which the main source of caffeine in many countries, contains 50% to 70% more caffeine than tea and other products. It is accepted that there is a theoretical relationship between caffeine and arrhythmogenesis, especially in women with heart disease.

Saline consumption, with no significant restrictions on salt, is generally recommended, especially close to delivery. However, pregnant women with risk of HF should be instructed to consume of 3 to 4 g of sodium chloride daily, without adding salt to food after cooking and avoiding salty items. Diets with 2 g of sodium daily should be restricted to more severe cases (NYHA FC III/IV), in addition to instructions regarding water restriction in these cases.

2.6.4. Professional Activity

Currently, most pregnant women work until one month before delivery, and only a small percentage suspend their professional activities earlier. The risk of developing complications is not related to work activity or to the psychosocial stress of work.[120] However, demands and working conditions should be evaluated individually in women with limiting heart disease or obstetric situations, such as preeclampsia and IUGR. Changes or adaptations in work activities, reduced stress at work, or increased rest and relaxation periods are often beneficial measures, especially if the condition worsens or limiting symptoms appear.

Pregnant women with symptomatic heart disease or heart disease with hemodynamic repercussion should rest at home from the beginning of the third trimester of pregnancy, or be it, week 28 of gestation. During this phase, cardiac reserve limited by heart disease is insufficient to adapt to maximum hemodynamic changes, thus favoring the occurrence of HF, arrhythmias, IUGR, and prematurity.

Under pregnancy protection laws, all women are entitled to at least 6 leaves to perform examinations and consultations, proven by a medical certificate, for the time necessary to perform the procedures, as specified by the certificate.[121]

2.6.5. Key Points

- Prenatal care for women with heart disease is multidisciplinary, with regular consultations with a cardiologist. Frequency should be in accordance with disease severity and/or possible complications;
- Lifestyle orientations should be individualized in accordance with cardiac risk, as classified by the WHO;
- Pregnant women should be made aware of diet, weight control, physical activity restrictions, and controlling

Table 17 – Dietary recommendations during gestation

Daily caloric ingestion – 340 to 450 additional kcal	2,200 to 2,900 kcal daily
Additional dietary supplements	
Folic acid	1 to 5 mg daily, preconception
Iron	27 mg > week 20
Calcium	250 to 1,000 mg daily
Folic acid	0.4 mg; 0.6 mg during the second and third trimesters
Iodine	150 mcg daily
Vitamin D	200 to 600 IU
Vitamins A, E, C, B and Zinc	Variable quantities, second and third trimesters

stress at work. Measures such as ceasing tobacco use, ceasing consumption of alcoholic beverages, and consuming caffeine moderately are essential during the prenatal period;

- Nutritional orientations include controlled calorie intake and a balanced and nutrient-rich diet, avoiding consumption of industrialized products and undercooked and poorly washed foods;
- Supplementation of essential vitamins and minerals should be a part of the prenatal routine for women with heart disease.

2.7. Management of Delivery and Postpartum Period

The interdisciplinary view of delivery and the postpartum period in women with heart disease should consider clinical and obstetric evolution during pregnancy and the functional status preceding delivery. Programming delivery in women with heart disease requires prior hemodynamic stabilization; screening for possible intercurrences such as infection, anemia, arterial hypertension, and arrhythmias; and adjustment of cardiovascular therapy.

From the obstetric point of view, the following are mandatory: discussion with a cardiologist and an anesthetist regarding timing and route of delivery, maternal-fetal monitoring during labor, and special attention to water balance. Accordingly, pregnant women with WHO class III/IV heart disease require assistance in tertiary hospitals with possibility of transfer to intensive care unit (ICU) during the postpartum period.

The labor team for women with heart disease should be prepared to prevent and treat the main complications during the intrapartum and postpartum period. The most frequent cardiac complications that stand out are HF, acute pulmonary edema, arrhythmias, thromboembolism, and dissection of the aorta, while preeclampsia, hemorrhage, and infections are included among obstetric complications.

2.7.1. Practice during Delivery

The general consensus is that route of delivery should be indicated by the obstetrician. However, in patients considered WHO risk I/II[122] with favorable clinical and hemodynamic conditions, spontaneous delivery at term of gestation is recommended. The consensus regarding type of delivery is based on the opinion of specialists, who believe that vaginal delivery is more advantageous, because it is associated with less blood loss, quicker recovery, and lower risk of thrombosis and infection. For this reason, it is the preferred type of delivery for women with heart disease whose clinical pictures are stable and uncomplicated.

Regarding cesarean delivery, its indication for patients with heart disease varies between 21% and 55%, worldwide.[123] Available Brazilian data indicate that the rate of cesarean delivery in the general population is around 52%, and, according to the Brazilian Network for Surveillance of SevereMaternal Morbidity, the rate reached 76% among women with heart disease.[124] There is no plausible clinical justification or explanation for such a high rate.

The rate of cesarean deliveries reflects the level of access to this intervention and its use; the task of defining the "desirable" rate in a given population, however, continues to pose a great challenge, as this number would adhere to medical indications, while avoiding "unnecessary" cesarean sections.

The European Registry of Pregnancy and Cardiac Disease has shown that the frequency of scheduled vaginal delivery was 69%; among cesarean deliveries, 44% had cardiac indication.[52] In its conclusions, the registry showed that, in terms of maternal results, programmed cesarean section showed no benefits over vaginal birth, and it was associated with worse fetal evolution.[125]

Maternal indications for cesarean delivery include very specific clinical situations, such as labor in patients under oral anticoagulation, diseases with increased aortic diameters (WHO risk III/IV), severe coarctation of the aorta, Takayasu arteritis, dissection of the aorta, PAH, acute HF, peripartum cardiomyopathy (PPCM) with severe HF, or other clinical situations in which maternal condition is critical.[52]

Although it is controversial, there are recommendations for assisted delivery, either by vacuum extraction or forceps, in situations where there are real maternal-fetal benefits to shortening the active phase of the second stage of labor and the efforts of a prolonged expulsive period. The recumbent left lateral position is recommended to avoid compression of the aorta and the inferior vena cava by the gravid uterus, thus favoring better maternal venous return and facilitating effort during the expulsive period.

Basic monitoring during delivery includes non-invasive blood pressure measurement, pulse oximetry, and continuous electrocardiography, in addition to fetal monitoring (auscultation of fetal heartbeats by Doppler sonar every 15 minutes during the first stage and every 5 minutes during the second stage, or continuous cardiotocography). The need for additional monitoring should be determined on a case-by-base basis. Excessive fluid infusion should be restricted in order to avoid excessive hydration and pulmonary congestion.

The benefits of analgesia for preventing arterial hypertension and tachycardia and reducing cardiac stress are unquestionable. A safe and effective way to reduce anxiety during this moment is with humanized delivery care, i.e., authorizing the presence of a companion chosen by the parturient and allowing her to ambulate freely and to choose the most comfortable position during labor.

Delivery in patients under oral anticoagulation should be scheduled from week 37 of gestation. Patients with high thrombotic risks need to use UFH around 36 hours before delivery, and the infusion should be interrupted 4 to 6 hours before birth and reintroduced 6 afterward, with APTT control. In cases with low thrombotic risks, LMWH is used until the day before delivery, and the night dose should be omitted if induced delivery or cesarean section is scheduled for the following morning. Regional block is possible in cases where 24 hours have elapsed since the last dose.

Induction of delivery should be considered at week 40 of gestation in all women with heart disease, because the benefits of this practice outweigh the eventual risks.[126] Mode of induction mainly depends on evaluation of the uterine cervix and fetal vitality. Both misoprostol (PGE1)[127] and dinoprostone (PGE2) are recommended for preparing the uterine cervix. The Krause method (balloon), amniotomy, and oxytocin infusion are also considered safe.[128]

In contrast, inhibition of premature labor should be considered with great caution and even contraindicated in women with heart disease. The degree of prematurity should be weighed with the risks of tocolysis and corticosteroid therapy, given that both may lead to complications, such as severe HF and cardiac arrhythmias.

When indicated, tocolysis should be maintained for 48 hours, which is sufficient time for the action of the corticoid, with the aim of reducing the occurrence of respiratory distress syndrome, peri- and intraventricular hemorrhage, and necrotizing enterocolitis in the newborn. The drugs used for inhibition, such as nifedipine, may induce hypotension, and they are synergistic when used in conjunction with magnesium sulfate. Terbutaline has intense beta-mimetic effect, and it may lead to maternal HF. In this situation, atosiban, a competitive oxytocin receptor antagonist, has been the safest tocolytic agent, when used in intravenous infusion of about 400 ml of solution (0.9% saline solution, Ringer lactate solution, or 5% glucose solution) for 48 hours (approximately 200 ml/24 h).

2.7.2. Practice during the Postpartum Period

Maternal care should be intensified during the postpartum period, and preventive measures for the main complications (HF, PPH, and thromboembolism) should be part of high-risk maternity hospitals' protocols.

Maternal blood volume undergoes significant variations during the immediate postpartum period, due either to increased venous return following placental clearance or to estimated blood loss, which is as high as 500 ml in vaginal delivery and 1000 ml in cesarean delivery (as defined by the WHO and the Pan American Health Organization). The impact of these maternal hemodynamic oscillations explains the occurrence of severe complications, such as HF, acute pulmonary edema, and cardiogenic shock. Negligence regarding hemodynamic oscillations during the postpartum period is, in part, responsible for maternal mortality; for this reason, it is mandatory for patients with severe heart disease, even when they are stable, to remain in the ICU 24 to 48 hours after delivery for effective hemodynamic monitoring.

PPH is equally important; it occurs in approximately 10% of vaginal deliveries, and it is considered severe in approximately 3%. In women with heart disease, the incidence of PPH reaches 21%, and it is related to cesarean delivery, assisted delivery with forceps, general anesthesia, and use of heparin before delivery.[129] The increase in maternal morbidity due to transfusion, infection, and thromboembolism is, in fact, the leading cause of death in women with heart disease.

For this reason, all maternity hospitals should have specific conduct protocols for preventing and treating PPH, including the use of uterotonic drugs, which are recommended during the third phase in both types of delivery, in order to prevent PPH.

Oxytocin is the recommended drug, given its benefit in preventing hemorrhage; it should be administered intramuscularly, at a dose of 10 IU for vaginal or cesarean delivery. Intravenous administration is also an option, especially during cesarean delivery, in doses of ≤ 5 IU and slow infusion (> 30 seconds) every 3 minutes, up to 3 infusions. Intravenous prophylaxis should be associated with continuous-infusion maintenance dose.

Misoprostol (600 to 1,000 μg) may be used safely for both prophylaxis and treatment of PPH, but oxytocin administered via bolus should be avoided due to the risk of hypotension. Ergometrine and methylergometrine should be avoided due to their association with coronary vasoconstriction and SAH.

It is accepted that there is a high risk of thrombosis during the postpartum period; therefore, measures such as early ambulation, which more feasible with vaginal delivery, and heparin anticoagulation should be recommended within the first 48 hours after delivery. Nevertheless, thromboembolism prevention should be individualized, and it will be discussed subsequently.

When there is an indication for definitive sterilization, bilateral salpingectomy may be performed via infraumbilical incision during the first 48 to 72 hours following vaginal birth. Generally speaking, discussions about contraception should take place before discharge from the maternity hospital.

2.7.3. Key Points

- Multidisciplinary assistance during delivery and the postpartum period should take the following into consideration: risk stratification of heart disease and elaboration of protocols for prevention and treatment of HF, PPH, infection, and thromboembolism;

- Assistance during delivery and the postpartum period should take place at a high-risk maternity hospital;
- Spontaneous vaginal delivery at term is recommended for most women with heart disease;
- Maternal indications for cesarean delivery are the following: severe HF, aortic disease with significant dilatation, severe obstructions of the left heart, severe forms of PH, and ventricular dysfunction;
- Cesarean delivery is indicated in patients who have gone into spontaneous labor while using oral anticoagulants (vitamin K antagonists) or who have suspended them for a period of less than 15 days;
- Delivery in patients under oral anticoagulation should be scheduled from week 37 of gestation, with adjustments to anticoagulation, using heparin as an intra-delivery "bridge";
- Indications for preparing the cervix and inducing delivery are misoprostol (PGE1) and dinoprostone (PGE2);
- Indications for inhibiting labor are, initially, contraindicated. In exceptional cases, atosiban is the indicated tocolytic agent;
- It is mandatory for maternity hospitals to have a specific protocol for preventing and treating PPH;
- Women with severe heart disease should remain in the ICU for a 24- to 48-hour period following delivery;
- Contraception should be discussed before discharge from the maternity hospital;
- There should be awareness that the postpartum period is as important and risky as pregnancy;
- Breastfeeding should always be encouraged.

2.8. Obstetrical Anesthesia

Obstetric anesthesia plays a fundamental role in reducing maternal-fetal morbi-mortality,[130] especially in pregnant women with heart disease. The complexity of heart disease requires the involvement of an anesthesiologist in multidisciplinary discussions during prenatal planning and the intrapartum and postpartum periods.

Frequency of evaluations should be individualized according to the risk of the heart disease and the patient's clinical situation. In general, evaluation should take place trimesterly in patients in WHO risk class II and in 2- to 4-week intervals in patients in WHO classes III and IV.[131] Formal planning should be discussed between weeks 32 and 34 of gestation by the whole team,[132] so that the patient will be admitted to delivery with consolidated advice. This assists in the flow of attendance, and it reduces team stress during emergencies and the chance of negative outcomes.

The anesthesia team will have an opportunity to get to know the evolution of the gestation and its eventual complications, to adjust medications when selecting anesthesia and analgesia, and to make it possible for the patient to interact with greater clarity in understanding the conduct adopted during the intrapartum period. It is important not to neglect the risks of airway management and aspiration of gastric contents, adjustments of eventual medications, and administration of uterotonic drugs during the intrapartum period.

The current indication for pregnant women with heart disease is vaginal delivery with neuraxial analgesia. This type of anesthesia is more efficacious for controlling pain during labor analgesia than other techniques, such as the use of systemic opioids or inhaled nitrous oxide.[133,134] When effective, spinal analgesia decreases circulating endogenous catecholamines, considering that partial sympathectomy induced by the effect of local anesthesia on the neuroaxis leads to decreased systemic vascular resistance and alterations in heart rate related to sympathetic block and cardiac reflexes.

During cesarean delivery, neuraxial analgesia has become prominent for managing pregnant women with heart disease, due to the growing expertise of anesthesiologists in using spinal block techniques that allow for better measurement of anesthesia in a gradual manner, thus decreasing hemodynamic impact.[135] World literature demonstrates rates above 60% in elective cesarean deliveries performed with neuraxial block; this number is lower in emergency deliveries, in which case general anesthesia is chosen due to the complexity of factors to be evaluated for decision making.[136,137]

Among the neuraxial techniques most used for pregnant women with heart disease, both of the following stand out:

- Sequential epidural anesthesia;
- Sequential combined spinal-epidural anesthesia, with low dose in the spinal component.

These techniques are called "sequential," because they allow the installation and cephalic progression of the sympathetic block to be performed gradually, preventing sudden installation with its cardiovascular repercussions. Small doses of local anesthesia associated with opioids are initially used, and additional supplements are performed through the epidural catheter until T6 sensory level is reached.[138]

In cases with contraindications to the use of neuraxial block for cesarean section, general anesthesia should be performed. The main objective of managing and planning with this anesthesia is to minimize the deleterious hemodynamic effects of systemic anesthetics and the hypertensive response to laryngoscopy, which is the reflex to sudden, exacerbated sympathetic stimulation. In this scenario, preanesthesia evaluation contributes to the identification of dural anomalies and severe scoliosis, which are common in Marfan, Loeys-Dietz, and Ehlers-Danlos syndromes.

Fast-acting drugs with short half-lives are used in doses adapted to maternal hemodynamics, in order to attenuate sympathetic responses to laryngoscopy, avoid large blood pressure variations, and prevent increased heart rate. Opioids such as alfentanil or remifentanil, as well as the use of other classes of drugs, may be useful for managing this. In adequate doses, short-acting beta-blockers and local anesthetics, such as esmolol and lidocaine, respectively, may be presented as good options. Additionally, in some circumstances, the use of inducers, such as ketamine and etomidate, may be a better option than propofol, which has higher cardiodepressive potential when used in bolus or in unadjusted doses.

When maintaining general anesthesia, it is necessary to pay attention to the potential negative inotropism of inhaled anesthetics and the decrease in systemic vascular resistance,

which also occur with venous anesthetics. Dose-dependent uterine hypotonia, related to the use of inhaled anesthetics, may also occur, with greater potential for bleeding.[139,140]

In cases where general anesthesia has been utilized, a good plan for postoperative analgesia should be performed with the objective of reducing circulating catecholamines. In these cases, there are some options, including spinal options or epidural analgesia, abdominal wall block (transversus abdominis block and lumbar block), or use of systemic analgesia.

2.8.1. Fasting

For elective cesarean delivery, it is recommended to fast from solids for 6 to 8 hours, depending on the fat content ingested and on eventual anatomical or physiological alterations that cause longer delay in gastric emptying. Clear liquids may be consumed up to 2 hours before surgery. Pharmacological prophylaxis for aspiration of gastric contents is recommended, with non-particulate antacids, H_2 receptor antagonists, and dopaminergic antagonists. During labor, women with low risks may consume moderate quantities of clear liquids,[141] such as water, tea, gelatin, and isotonic beverages.

In the event of maternal hemodynamic instability, the team should maintain the mother's fast until it is safe to reintroduce liquids. Delivery analgesia and proximity to the second phase of labor are points that clearly exemplify this practice, given the possibility of hemodynamic instability and bleeding, respectively. In the most severe cases or when faced with a greater probability of cesarean delivery, the patient should continue fasting.

2.8.2. Anticoagulation and Neuraxial Block

It is estimated that spinal hematoma occurs in 1:200.000 to 1:250.000[142,143] deliveries. Although rare, it is a severe event; therefore, strategies should be taken to prevent it. Current recommendations consider that doses of anticoagulants and prior period of suspension are parameters for ensuring safe neuraxial anesthesia. This is the case for patients receiving a single anticoagulant, weighing more than 40 kg, with normal renal function, and without any other conditions that would contraindicate neuraxial block.[144] In summary, the recommendations are hereafter explained.

2.8.3. Unfractionated Heparin (Subcutaneous)[144]

- Low dose (5,000 IU, 2 to 3 times daily): Wait 4 to 6 hours, with normal APTT or undetectable anti-Xa factor;
- Intermediate dose (7,500 to 10,000 IU, 2 times daily; up to 20,000 IU daily): Wait 12 hours or more, with normal APTT or undetectable anti-Xa factor;
- High dose (More than 10,000 IU per dose; more than 20,000 IU daily): Wait 24 hours or more, with normal APTT or undetectable anti-Xa factor.

2.8.4. Low Molecular Weight Heparin (Subcutaneous)[144]

- Prophylactic dose (enoxaparin 40 mg or deltaparin 5,000 IU, once daily): Wait 12 hours or more;
- Therapeutic dose (enoxaparin 1 mg/kg, twice daily or deltaparin 120 IU/kg, twice daily, or 200 IU/kg, single dose): Wait 24 hours.

Any anticoagulation regimes different from those mentioned above should be evaluated and individualized by the team, taking not only the risk of spinal hematoma into consideration, but also the thromboembolic risks, fasting time, maternal-fetal conditions, and the evaluation of predictors of difficult intubation for general anesthesia.

Time period for reinitiating anticoagulation should mandatorily include the participation of the anesthesiologist in cases where the approach is neuraxial. Reintroduction of anticoagulation should be individualized, because there are technical conditions for performing spinal or epidural anesthesia that interfere with the practice of reintroducing anticoagulation.

2.8.5. Hemodynamic Monitoring

The use of invasive monitoring in high-risk patients should be necessary, with the objective of reducing time between recognition of hemodynamic deterioration and their respective treatments. Before performing neuraxial block and inducing general anesthesia in patients in WHO-risks II/IV, invasive blood pressure (IBP) monitoring may be fundamental to a better outcome.[140]

Lack of validation of the use of non-invasive methods for monitoring cardiac output during delivery in women with heart disease makes it possible to individualize cases and indicate the utilization of invasive methods, such as central venous catheter (CVC) and pulmonary artery catheter (PAC). Nevertheless, the information obtained may be imprecise due to the complexity of the heart disease, in addition to the risk of inducing arrhythmias and other risks of complications. For this reason, there is low adherence to these forms of monitoring. In cases of cesarean delivery with general anesthesia, intermittent transthoracic echo and transesophageal echo have gained prominence as options for monitoring, and they may assist in the evaluation of ventricular function and filling.[140]

2.8.6. Intrapartum Uterotonic Drugs

The most used uterotonic drug during the peripartum period is oxytocin, which has an immediate effect on systemic vascular resistance, when administered in high doses or rapid transfusion. These regimes should be avoided for all pregnant women, especially in those with heart disease. The infusion of 2 IU of the drug for 10 minutes appears to be effective and not to have significant cardiovascular effects in pregnant women with heart disease.[135] In general, it is possible to maintain an infusion of 2 to 5 IU for an interval of 15 to 30 minutes with low cardiovascular effects. Ergot derivatives induce smooth muscle contraction with vasoconstriction and consequent hypertension. Misoprostol may cause hyperthermia and tremors, and it results in increased oxygen consumption, which is harmful at times, especially in women with severe heart disease.

The rule that is most commonly used by anesthetists for oxytocin administration in patients without comorbidities is controversial, namely, the "rule of 3s," consisting of 3 IU, every 3 minutes, up to 3 times, whereas an infusion of oxytocin at 2 IU for 10 minutes appears to be too slow.[139,142]

2.8.7. Postpartum

Follow up of pregnant women with intermediate to high risks should take place in the ICU for 24 to 48 hours. This observation period is important, keeping in mind that most deaths occur during the postpartum period. Inadequate monitoring and inappropriate blood volume management may lead to cardiovascular dysfunction.[140]

2.8.8. Key Points

- Anesthesia planning for delivery in women with heart disease should be discussed with a multidisciplinary team between weeks 32 and 34 of gestation;
- The indication for pregnant women with heart disease is vaginal delivery with neuraxial analgesia;
- In cases of cesarean delivery, neuraxial analgesia has gained prominence, when using spinal block techniques;
- General anesthesia is indicated in cases of severe heart disease;
- Anesthesia should be individualized in patients under anticoagulation;
- Maternal monitoring is indispensable during delivery and during the immediate postpartum period.

3. Assessment and Management of Specific Heart Diseases

3.1. Valvular heart disease

In Brazil, rheumatic disease is the most frequent cause of heart disease during pregnancy, with an estimated incidence of 50% in relation to other heart diseases.[145] Rheumatic fever is an episode from early childhood and/or adolescence, the onset of the clinical phase coincides with fertile age in women.

Cardiovascular adaptation of heart valve diseases to the increase in cardiac output directly influences flow through the heart valves, with functional worsening of stenotic lesions. On the other hand, the drop in peripheral vascular resistance reduces the volume of regurgitation in insufficient valves. For these reasons, the evolution of stenotic lesions is generally worse, and it is correlated to the anatomical degree of the valve lesion, whereas, in patients with regurgitation, it is related to the condition of ventricular function.[146]

These initial considerations assist in risk stratification of valve disease, both for adequate family planning counseling and care during gestation. Accordingly, the classification elaborated by WHO was adapted for pregnancy in women with heart valve disease.

The WHO considers that patients classified as I and II present acceptable or low risks that do not impose serious restrictions to gestation, whereas risk III would make pregnancy inadvisable, and risk IV would contraindicate it.[147] In this position paper, women with heart valve disease are classified in the following manner: risk I, acceptable; risks II and III, intermediate; and risk IV, high risk to pregnancy (Table 18).

It is worth adding that a high-risk situation in heart valve disease does not fulfill the criteria for indicating interruption of gestation (therapeutic abortion), given that these patients may be treated by either surgical or percutaneous intervention following the embryogenesis phase.

During family planning, evaluation of heart valve disease should establish etiological, anatomical, and functional diagnosis and investigate the presence of unfavorable factors that are part of the natural history of heart valve disease and previous surgical correction.[148] These factors modify maternal prognosis, and they do not depend on structural cardiac injury per se; the following deserve special emphasis:

- AF;
- PH;
- Ventricular dysfunction;
- Associated aortic diseases;
- History of HF, thromboembolism, or infectious endocarditis (IE).

Cardiovascular evaluation before gestation should be assess the history, physical examination, and subsidiary tests that support in classification of risk of pregnancy, such as the following:

- ECG: evaluates rhythm and heart chamber overload;
- Echo: informs the type and severity of heart valve disease, degree of ventricular dilatation, presence of ventricular dysfunction, PH, and associated defects;
- CMR: useful when heart valve disease is associated with aortic disease;
- Ergometric test: valid for estimating functional capacity and arterial pressure in severe aortic stenosis in asymptomatic patients and when there is a dissociation between symptoms and the anatomical degree of mitral stenosis, indicated only during pregnancy planning;
- Biomarkers: a controversial application in heart valve disease.
- The recommendations put forth by Brazilian[149,150] and International[151] Guidelines for practice during family planning and pregnancy in cases of acquired, congenital, and prosthetic heart valve disease are shown in Tables 19 to 22.

3.1.1. General Considerations for Treatment

Moderate restrictions on salt and physical activity, weight gain control (not exceeding 10 kg), and iron supplementation after week 20 of gestation are initial recommendations, taking care to rule out factors such as anemia, infection, hyperthyroidism, and cardiac arrhythmias. Prevention of rheumatic attacks should be maintained with 1,200,000 IU benzathine penicillin every 21 days or, for patients who are allergic to penicillin, 500 mg erythromycin stearate every 12 hours. Sulfadiazine is contraindicated. Prevention of IE for delivery is done with 2 g intravenous ampicillin associated with 1.5 mg/kg intramuscular gentamicin (with a maximum dose of 120 mg) 1 hour before delivery. The safety and efficacy of pharmacological treatment requires periodic dose adjustments.

Before conception, drugs with recognized teratogenic effects should be substituted. In women with mitral stenosis, the use of propranolol or metoprolol in doses that do not exceed 80 and 75 mg, respectively, stand out for preventing

Table 18 – Risk classification for heart valve disease during pregnancy.

High risk	Intermediate risk	Acceptable risk
Severe mitral stenosis	BPV with moderate dysfunction	Mild heart valve disease
Severe aortic stenosis		
Stenotic/calcified BPV	Severe pulmonary stenosis	BPV without dysfunction
MPV with dysfunction		
Heart valve disease + significant PH (PAP ≥ 50 mmHg)	MPV Mitral MPV > risk of aortic MPV	Heart valve disease + LVEF normal
Aortic insufficiency + aortic disease	Aortic insufficiency + aortic disease	
Marfan syndrome (AAD > 45 mm)	Marfan syndrome (AAD between 40 and 45 mm)	Heart valve disease without unfavorable factors
Bicuspid aortic valve (AAD > 50 mm)	Bicuspid aortic valve (AAD 45 to 50 mm)	
Heart valve disease + LVEF < 35%	Patient requires use of anticoagulants	

AAD: ascending aorta diameter; BPV: bioprosthetic valve; LVEF: left ventricular ejection fraction left ventricular ejection fraction; MPV: mechanical prosthetic valve; PAP: pulmonary artery pressure; PH: pulmonary hypertension. Severe mitral and aortic stenosis are considered mitral valve area ≤ 1.0 cm^2 and aortic valve area < 1.0 cm^2, respectively.

and controlling pulmonary congestion, always paying attention to perinatal side effects, such as hypoglycemia, hyperbilirubinemia, and polycythemia, which have not been verified in these recommended doses.

Acute AF should be promptly reversed by electric cardioversion in women with mitral heart valve disease, given that this procedure is considered harmless to the fetus, and it has the advantage of avoiding use of drugs at levels that are, at times, toxic. Additionally, atrial or ventricular ectopic beats and asymptomatic atrial tachycardia do not require the use of antiarrhythmic drugs. In order to control heart rate in patients with permanent AF, beta-blockers, or non-dihydropyridine calcium channel blocker (CCB) should be considered, in addition to anticoagulation.

The need for intervention in heart valve disease during gestation is due to cases that are refractory to clinical treatment. Percutaneous procedures should be preferable to cardiopulmonary bypass (CPB) surgery. In aortic stenosis, balloon catheter valvuloplasty (BCV) has been indicated for heart valve disease whose etiology is congenital or in attempts to save the mother's life in extremely severe cases. In mitral stenosis, it requires the absence of thrombi in the left atrium, at most mild mitral insufficiency, and Wilkins echocardiographic score ≤ 8.[149]

3.1.2. Key Points

- Stenotic valve lesion leads to more complications than regurgitation;
- NYHA FC I/II in stenotic lesions do not guarantee good maternal evolution;
- Complicating factors significantly increase the risk of heart valve disease;
- Percutaneous intervention should be considered before gestation in women with severe mitral and aortic stenosis, even in asymptomatic patients;
- Pregnancy does not change the criteria for indicating BCV;
- Pharmacological treatment of complications during gestation should be considered as the first therapeutic option;
- Prophylaxis of rheumatic disease should be maintained throughout gestation;
- Postpartum consultation, in addition to maternal clinical examination and evaluation of the baby's health, includes medication adjustments, lactation stimulation, and contraceptive counseling.

3.1.3. Valve Prosthesis

The prevalence of rheumatic disease in Brazil and the growing number of patients with congenital heart disease who require valve replacement have led to an increase in women with valve prostheses in childbearing age. One favorable factor, in this age range, is left ventricular performance, which is generally preserved.

From the hemodynamic point of view, valve prostheses improve functional capacity and promote clinical evolution during pregnancy. Biological prostheses have attributes that are favorable to evolution of pregnancy, as they do not require anticoagulation, and they are considered WHO-risk II. Nevertheless, they have limited durability, with the possibility of short-term reoperation, including during pregnancy.

Bioprosthetic valve (BPV) dysfunction due to calcification has poor evolution, and it leads to pulmonary congestion and low cardiac output, both of which are refractory to clinical treatment, in addition to causing a high risk of sudden death (WHO-risk IV). The occurrence of BPV calcification during pregnancy makes surgical indication for valve replacement mandatory, regardless of gestational age.[152]

In contrast, gestation in women with mechanical valve prostheses (MPV) is considered WHO risk III. The risk of thrombosis due to maternal hypercoagulability and difficulties with long-term anticoagulation are associated with a variable incidence of embolic accidents, spontaneous abortion, warfarin embryopathy, and maternal and neonatal hemorrhagic phenomena.[96]

Table 19 – Recommendations for clinical practice in acquired and congenital native valve disease.[149,150]

Heart valve disease	Preconception counseling	Gestation		
		Maternal risk	Fetal risk	Intervention
Severe rheumatic mitral stenosis	FC ≥ II **or** asymptomatic + PH > 50 mmHg **or** AF recent onset **consider** BCV or CPB	Increased risk **if** • HF • AF Death < 3%	Prematurity 20% to 30% IUGR 5% to 20% Stillbirth Increases with maternal FC III/IV	Beta-blocker diuretic Anticoagulation if AF **if** Refractory FC III/IV **consider** BCV or CPB
Severe rheumatic aortic stenosis congenital (bicuspid) degenerative	Symptomatic **or** asymptomatic + altered ET **or** EF < 50% **or** AVA < 0.7 cm^2 average gradient > 60 mmHg **or** Bicuspid valve + AAD > 45 mm **consider** VCP or CPB	Increased risk HF - 10% Arrhythmia 3% to 25% Syncope Sudden death	Complications - 25% Prematurity IUGR Low birth weight Stillbirth	Rest diuretics with criterion **If** AF beta-blocker or CCB Anticoagulation Severe HF or syncope **consider** BCV or CPB
Mitral insufficiency Significant rheumatic degenerative valve prolapse	FC ≥ II **or** Complicated asymptomatic + EF ≤ 60% + SPAP ≥ 50 mmHg + LVSD ≥ 40 mm **consider** CPB (plasty or prosthesis)	HF AF Risk increases with EF < 35%	Low risk	Diuretic hydralazine digoxin **If** refractory HF **consider** CPB or "mitraclip"
Significant rheumatic aortic insufficiency congenital (bicuspid) degenerative	Symptomatic FC ≥ II **or** Unfavorable factors EF < 50% LVDD > 70 mm (75 if rheumatic) LVSD > 50 mm (55 if rheumatic) **consider** **CPB** **If** Bicuspid valve isolated AAD > 45 mm **consider** Proximal aortic intervention	Low risk Asymptomatic normal EF FC > II or EF < 35% HF and/or AF	Low risk	Diuretic hydralazine digoxin **If** refractory HF **consider** **If** Bicuspid valve AAD > 45 mm **consider** Proximal aortic intervention

AAD: aorta diameter; AF: atrial fibrillation; AoS: aortic stenosis; AVA: aortic valve area; AVM: mitral valve area; BCV: balloon catheter valvuloplasty; CCB: calcium channel blocker; CPB: cardiac surgery with cardiopulmonary bypass; echo: echocardiography; EF: echocardiographic ejection fraction; ET: ergometric test; FC: functional class; HF: heart failure; IUGR: intrauterine growth restriction; LVDD: left ventricular diastolic diameter; LVSD: left ventricular systolic diameter; ME: mitral stenosis; NYHA: New York Heart Association; PH: pulmonary hypertension; SPAP: systolic pulmonary artery pressure. Severe mitral and aortic stenosis are considered MVA ≤ 1.0 cm^2 and AVA < 1.0 cm^2, respectively.

It is estimated that the probability of pregnancy to be maternal-fetal free of events is 58.3% for BPV and 46.9% for MPV[96,153] and no differences in mortality rates for both prosthesis types, were observed . Although it is controversial, BPV may be considered the more adequate form of replacement for women of fertile age, except in adolescent patients, where premature calcification of BPV would favor the choice of MPV.

The following factors are related to prognosis of pregnancy:

- Prosthesis functional status;
- Cardiac rhythm (AF);
- Ventricular dysfunction;
- NYHA FC;
- Prior incidence of IE, HF, or thromboembolism.

3.1.4. Maternal Risk

Women with MPV present an estimated risk of 5% for valve thrombosis during gestation; maternal mortality varies between 9% and 20% associated with thromboembolic complications.[96] This incidence of thrombosis in MPV varies according to the anticoagulation regime, but it is signicantly higher during heparin use[154-157] The incidence of thromboembolism with

Table 20 – Recommendations for clinical practice in congenital or acquired heart valve disease due to infectious endocarditis[149,150]

Heart valve disease	Preconception counseling intervention	Gestation		
		Maternal risk	Fetal risk	Intervention
Structural TI *Ebstein anomaly*	Severe symptomatic TI Significant RV dilatation/dysfunction **consider** conservative surgery (plasty) **or** BPV implant	Moderate/severe lesions Right HF Supraventricular arrhythmias	Low risk	Diuretic Digoxin **If** Severe right HF **consider** conservative surgery (plasty) BPV implant
Severe pulmonary stenosis	Effort dyspnea/fatigue Hypoxemia Atypical angina Right HF (secondary TI) BCV or CPB	Syncope Right HF Atrial arrhythmia Hypoxemia	Low risk	**If** Hypoxia/severe HF **Consider** BCV

BCV: balloon catheter valvuloplasty; BPV bioprosthetic valve; CPB: cardiopulmonary bypass; HF: heart failure; IE: infectious endocarditis; TI: tricuspid insufficiency.

Table 21 – Valve prosthesis with normal function and risks to gestation

Biological prosthesis with normal EF		Mechanical prosthesis with normal EF	
Maternal risk	**Fetal risk**	**Maternal risk**	**Fetal results**
Patient does not require anticoagulation Low risk	Low risk	**Patient requires anticoagulation** Intermediate risk	High risk Warfarin embryopathy Miscarriage Prematurity Stillbirth Perinatal Hemorrhage
		Anticoagulation favors Hemorrhage Systemic embolism **If** Prosthesis thrombosis **consider** Emergency treatment Thrombolysis or CPB	

CPB: cardiopulmonary bypass; EF: ejection fraction.

LMWH is due to fluctuations in anti-Xa factor that occur over 24 hours,[158] even with the therapeutic value (0.6 to 1.2 IU/ml) during peak action 4 hours after application,[159] resulting in a suboptimal anticoagulation level. Regarding UFH, prolonged use is associated with thrombocytopenia and osteoporosis;[154,155] its efficacy is inferior to that of LMWH, and its subcutaneous use for anticoagulation practice has been prohibited. Owing to the high incidence of thromboembolism with heparins (UFH and LMWH), there is a tendency to prioritize the use of warfarin throughout the entire pregnancy, as it is believed to be safer for maternal-fetal outcomes.[154-157]

3.1.5. Fetal Risks

In all anticoagulation regimes, the obstetric risks of hemorrhage, placental abruption, prematurity and fetal death are very high.[155-157] The warfarin cross the placental barrier, it is teratogenic when used in the first trimester of pregnancy and causes embryopathy in 0,6 a 10% of cases,[160] even at doses less than 5 mg.[161-163]

The anticoagulation regime for women with MPV who wish to become pregnant or who are in the course of gestation during the first consultation continues to be controversial. Factors that should be taken into consideration when deciding on the best anticoagulation treatment include the patients' preferences, the attending physician's expertise, and availability of adequate coagulation control.

Recommendations for preventing thromboembolism in mechanical prostheses intend to meet to the ideal requirements of a position based on documentation in the literature and on the authors' experience, in a manner that is effective for the reality which different healthcare services face. It is understood that permanent anticoagulation should be divided into five different stages, including preconception, each trimester, and the postpartum period, as explained hereafter.

First Stage: Preconception. Patient/couple awareness. Advice regarding early diagnosis of pregnancy. Patients in pregnancy planning should receive clarification regarding the need to maintain anticoagulation, the regimes available, and their risks during all phases of gestation, childbirth, and the

Table 22 – Clinical practice in prostheses with dysfunction during gestation[149,150]

Biological prosthesis		Mechanical prosthesis	
Maternal risk	**Fetal risk**	**Maternal risk**	**Fetal risk**
Dysfunction with predominance of insufficiency, FC I/II and normal EF Pharmacological measures	Low risk	Dysfunction with mild to moderate "paravalvular" insufficiency without significant hemolysis or severe HF **consider** Pharmacological measures for HF and anemia **If** Severe insufficiency or significant hemolysis **consider** Intervention If symptomatic HF and/or hemolysis **consider** Percutaneous paravalvular leak closure by means of a plug device **or** CPB (high risk of relapse)	High fetal risk if CPB
Dysfunction with predominance of valve stenosis with calcification (mitral, aortic, or tricuspid) Risks of severe HF, shock, sudden death **Always consider** **Emergency** Percutaneous implant **or** new transapical valve-in-valve* BPV **or** CPB	High fetal risk Fetal loss Prematurity Stillbirth	Aortic or mitral MPV stenosis due to intravalvular endothelial growth – "Pannus": Need for intervention is rare If indicated, **consider** CPB MPV stenosis (generally aortic) "mismatch" Need for intervention is rare If indicated, **consider** CPB	High fetal risk if CPB

BCV: balloon catheter valvuloplasty; BPV: bioprosthetic valve; CPB: cardiopulmonary bypass; HF: heart failure; MPV: mechanical prosthesis.

postpartum period. In order to achieve this, frank dialogue with the couple is fundamental. Counseling also includes information regarding the importance of early diagnosis of pregnancy in order to reduce the occurrence of embryopathy. During this consultation, the patient receives an examination request for chorionic gonadotropin beta dosage, which should be taken at the first sign of delayed menstruation.

Second Stage: First trimester. Anticoagulant substitution (avoiding teratogenesis). Substituting warfarin with heparin makes it possible to reconcile the benefits of preventing maternal thrombosis and the harmful effects of embryopathy. During this period, there are different options, which are shown in Figure 6. The first choice is to use LMWH, which requires weekly anti-Xa factor control. If this option is not available, intravenous UFH is indicated between the sixth and ninth week of gestation. In patients whose first medical consultation takes place after week 6 of gestational, warfarin should not be suspended. In these cases, the couple should be informed regarding the possibility of embryopathy and that the risks of substituting with heparin are no longer justified.

Third Period: Second and third trimesters. Resuming oral anticoagulant, and anticoagulation control. Resuming warfarin use is justified by the assumption that shortening the use of heparin reduces adverse effects to the mother and leads to a lower risk of embryopathy. The proposal is to maintain warfarin doses in accordance with pre-gestation goals, with weekly or biweekly INR control. Reintroduction of warfarin should follow the dynamics of transition, or be it, simultaneous with subcutaneous LMWH or intravenous UFH until INR target value has been reached (Figure 6).

Fourth Stage: Delivery planning. Consider hospitalization, redirect to parenteral anticoagulation, control anticoagulation and plan delivery. Hospitalization should be scheduled at week 36 of gestation for use of subcutaneous LMWH or intravenous UFH in therapeutic doses (Table 23). Route of delivery must be discussed with the obstetrician; vaginal delivery is considered safer due to the fact that there is less bleeding and to the advantages of analgesic techniques. In cases of premature delivery under anticoagulation, route of delivery is cesarean, and the use of prothrombin complex concentrate may be considered.

Fifth Stage: The postpartum period. Reintroduction of oral anticoagulation and hospital discharge. Six hours after delivery, in the absence of maternal complications, intravenous UFH or subcutaneous LMWH may be reintroduced in therapeutic doses. Warfarin should be prescribed 48 hours after delivery, following the dynamic of transition, in conjunction with heparin, until INR value reaches 2.0, at which point the patient is discharged from the hospital.

3.1.6. Key Points

- BPV do not require anticoagulation, except in patients with AF or previous thromboembolic accident;
- Pregnancy does not influence structural degeneration of BPV;
- Calcified, stenotic BPV are indicated for surgery regardless of gestational age;
- MPV require anticoagulation with permanent adjustments seeking to meet conventional goals;

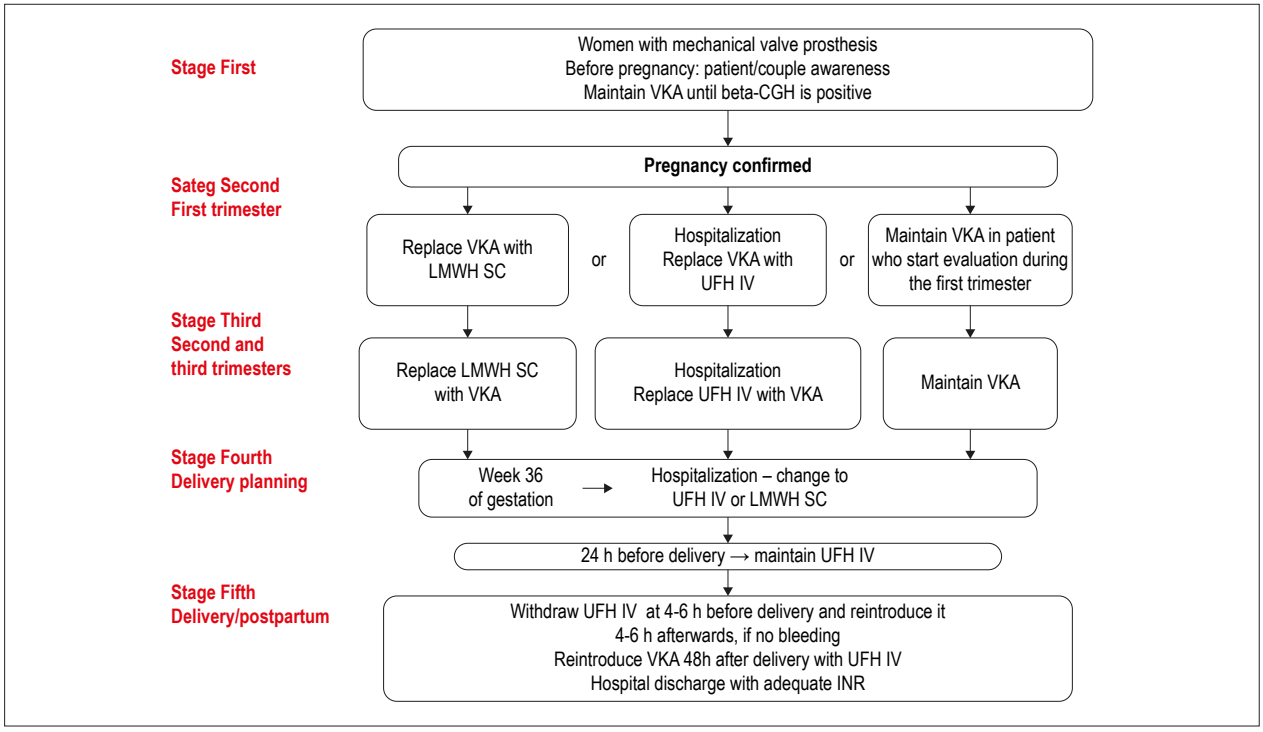

Figure 6 – *Recommendations for anticoagulation in patients with mechanical valve prostheses during gestation. CGH: chorionic gonadotropin hormone; INR: international normalized ratios; LMWH SC: subcutaneous low molecular weight heparin; UFH IV: intravenous unfractionated heparin; VKA: vitamin K antagonists. LMWH SC every 12 hours = 1 mg/kg/dose; UFH IV = 18 IU/kg/h. Dose targets and controls: LMWH SC = anti-Xa factor between 0.6 and 1.2 U/ml, weekly; UFH IV APTT: 2 times normal value, daily; VKA = INR 2.5 to 3.5, biweekly.*

- MPV thrombosis requires immediate intervention with a thrombolytic agent or emergency surgery with CPB, regardless of gestational age;
- Choice of BPV as a preferable substitute for a woman who plans pregnancy, considering that it does not requires anticoagulation and the future perspective of percutaneous valve-in-valve replacement;
- Percutaneous valve-in-valve procedures require a specialized center with a heart team and resources for valve and arterial tomography, 3-dimensional esophageal echo, and an interventional hemodynamic and surgery team on standby;
- Patients with MPV should be referred to tertiary services and reference centers in valve disease for follow up during pregnancy;
- Permanent anticoagulation in patients with mechanical prostheses or mitral valve disease with AF should follow the algorithm which divides the pregnancy and postpartum into five stages;
- Notwithstanding adequate and effective anticoagulation control at all times, there are still uncertainties regarding the success of pregnancy in women with MPV;
- A multidisciplinary team should discuss choice of valve prosthesis and prospects for future pregnancy together with the patient.

3.2. Congenital Heart Disease

Advances in clinical and surgical cardiology treatments have demonstrated that a progressively higher number of women with congenital heart disease are able to reach childbearing age[164] then they wish to become pregnant with a great likelihood of successful maternal-fetal outcome.[165]

In Brazil, a growing tendency has been observed in the percent of pregnant women with congenital heart disease, similar to European countries. They are considered the second-leading indirect cause of maternal mortality, accounting for up to 20% of deaths due to heart disease.[166]

Preconception assessment risk should be based on following variables: (1) time of heart disease diagnosis; (2) prior palliative or corrective surgery; (3) NYHA functional class; (4) laboratorial tests such as: hematocrit, hemoglobin, oxygen saturation, natriuretic peptide values; and liver and thyroid function tests.

Structural and functional diagnosis is defined by electrocardiography, transthoracic echo, magnetic resonance and cardiopulmonary testing.

The WHO classification has been very well accepted as a parameter for evaluating maternal-fetal risk according to structural cardiac injury. In addition to this classification, there are clinical conditions that are predicted over the natural history of congenital heart disease (which modify the prognosis of pregnancy and are independent of structural cardiac injury), which are shown in Table 24.

Table 23 – Recommendations for anticoagulation dose and control in patients with mechanical prostheses during pregnancy

Gestational age(week)	Anticoagulant	Control
Between 6th and 9th	LMWH 1.0 mg/kg SC every 12 hours UFH IV 18 IU/kg/h infusion pump (< 30,000 IU IV)	AntiXa: 0.6 to 1.2 U/ml APTT 1.5 to 2.0 times/NV
12th to 36th	Warfarin according to INR	Aortic INR between 2.5 and 3.0 Mitral INR between 3.0 and 3.5
After week 36th until delivery	LMWH 1.0 mg/kg SC every 12 hours UFH IV 18 IU/kg/h infusion pump (< 30,000 IU IV)	AntiXa: 0.6 to 1.2 U/ml APTT 1.5 to 2.0 times/NV
The postpartum period	LMWH 1.0 mg/kg SC every 12 hours UFH IV 18 IU/kg/h infusion pump (< 30,000 IU IV) Warfarin reaching target INR for hospital discharge	AntiXa: 0.6 to 1.2 U/ml APTT 1.5 to 2.0 times/NV INR between 2.0 and 2.5

APTT: activated partial thromboplastin time; INR: international normalized ratio; IU: international units; IV: intravenous; LMWH: low molecular weight heparin; NV: normal value; SC: subcutaneous; UFH: unfractionated heparin.

Table 24 – Factors associated with maternal prognosis in congenital heart disease

Pulmonary arterial hypertension
Cyanosis
Severe obstructive lesions
Ventricular dysfunction
Permanent anticoagulation requirement
Symptomatic patients indicated for intervention in heart disease

Eisenmenger syndrome: It is considered to have a high risk for maternal death, which reaches 50% during the pregnancy e postpartum.[167] Pulmonary arterial disease restricts circulatory adaptation to the variations in cardiac output and to the drop in peripheral vascular resistance during pregnancy and postpartum period. This leads to the main complications that cause death, such as HF, hypoxia crises, and arrhythmias. The risk during the postpartum period is as high as during gestation, due to hemorrhage and thromboembolism.[168] Patients with Eisenmenger syndrome appear to be predisposed to thrombocytopenia, deficiency in vitamin K-dependent coagulation factors, and bleeding. The fetal risks of spontaneous abortion, prematurity, and perinatal mortality are proportional to the degree of cyanosis.

Cyanosis: Almost 30% of patients with cyanotic congenital heart disease, whether or not they undergo previous surgery, present complications during gestation, such as: HF, systemic-pulmonary thrombosis, arrhythmias, and hypoxemia, are presumptive. The degree of arterial oxygen saturation is a prognostic factor for maternal-fetal survival, and the hypoxia has a significant correlation with maternal death, spontaneous abortion, and perinatal death.[169] The indication of phlebotomy in maternal erythrocytosis is only been performed with hematocrit above 65% in patients with symptoms of headache, fatigue, visual or cognitive impairment, and myalgia. Fetal outcome, including miscarriage, prematurity, and perinatal death, is related to the degree of arterial oxygen saturation. It is estimated that oxygen saturation < 85% is associated with only 12% live newborns.[170]

HF: dyspnea is a clinical parameter used to aid practice and estimate prognosis of congenital heart disease, however, have limitations when applied to pregnancy. Dyspnea may be consequence of hypoxemia or pulmonary congestion, which is related to congenital heart disease involving the left heart.[52]

Cardiac arrhythmias: Frequent in adults with congenital heart disease, arrhythmias are the result of sequelae of cardiac defects such as ventricular dysfunction, myocardial hypertrophy, fibrosis or surgical injure, conduction tissue trauma, and the presence of endocardial grafts.

Previous intervention of pregnancy: Surgical or percutaneous correction of congenital heart disease is associated with better maternal-fetal prognoses in comparison with patients who have not undergone operation for heart disease. The eventual need for intervention should be taken into account before conception.

3.2.1. Pregnancy Management

Giving continuity to preconception evaluation, initial prenatal visit should include (1) history; (2) type of corrective or palliative surgery; (3) immediate or late postoperative evolution; (4) current clinical and functional situation; and (5) periodic laboratory examinations (hematocrit, hemoglobin, oxygen saturation, and natriuretic peptide).[171]

Attending during gestation, delivery, and the postpartum period for patients with congenital heart disease should rely on a team of specialists, a tertiary hospital, and periodic attendance. It is worthwhile to recall that the hereditary nature of congenital heart disease makes routine fetal echo necessary from the second trimester of gestation on.[171]

Pregnant women classified as WHO risks III/IV should receive advice regarding routine hospitalization starting between 28 and 32 weeks of gestation, for compensation of maternal condition, continuous fetal monitoring, therapy adjustment, and delivery planning. Decisions regarding the management of delivery and anesthesia should be made jointly, in accordance with the mother's clinical situation and fetal vitality and maturity.

Congenital heart diseases associated with PH: It is recommended the interruption of pregnancy in women with

PH and Eisenmenger syndrome during the first trimester of gestation. Nonetheless, when the patient decides to continue with the pregnancy, the multidisciplinary team should follow the protocols[172] that include hospitalization after week 28 of gestation, enoxaparin (LMWH) use in a prophylactic dose (1 mg/kg daily), and oxygen therapy (supplemental oxygen for saturation below 92%) are essential measures for controlling hypotension, hypoxemia, and metabolic acidosis.

Specific vasodilators, such as phosphodiesterase inhibitors (sildenafil), may lead to arterial hypotension, and they should be indicated individually in accordance with clinical situation and maternal tolerance.[173,174] Sildenafil or other phosphodiesterase inhibitors have been used, as well as the eventual addition of prostaglandins when symptoms persist. Endothelin receptor antagonists should be suspended during pregnancy.[175,176]

Full-dose or prophylactic LMWH should be considered as substitute of warfarin during the first trimester and after 36th week of gestation for patients whose already using it before conception (Figure 6). The antiplatelet agents (such as aspirin) or LMWH should be prescribed with great caution, because patients with PH present a high risk of hemoptysis and thrombocytopenia.

Congenital heart diseases with obstructive structural lesions: Patients with severe left ventricular outflow tract obstructions should be advised to surgical or percutaneous correction previous of gestation. If the patient is, however, already pregnant, the triad of symptoms (HF, angina pectoris, and syncope) percutaneous or surgical intervention should be considered, even during gestation.[171] In patients with severe valve pulmonary stenosis whose present heart failure, the percutaneous balloon valvuloplasty is indicated, and it is safest during the second trimester of pregnancy, when the embryogenesis phase has passed; the fetal thyroid is still inactive, and the uterus still has a small volume, allowing for greater distance between the ionizing radiation and the conceptus during the procedure.

Cyanotic heart diseases without pulmonary hypertension: General measures include restricting physical activity, supplementing oxygen, and preventing venous stasis due to the known risk of paradoxical embolism. The use of LMWH in prophylactic doses is recommended, because thromboembolism is one of the main complications. Iron supplementation may be used, depending on polycythemia, similarly to Eisenmenger syndrome.[175,176]

Heart disease with shunt without pulmonary hypertension: Atrial septal defect (ASD) is well tolerated during pregnancy and is considered WHO- risk I.[177] Arrhythmias, which are generally supraventricular, are common and they may be controlled with digoxin, beta-blockers (propranolol or metoprolol), or CCB (verapamil) in fractionated low doses. Patients with uncorrected ASD are considered to present a risk of thromboembolism, which may suggest that LMWH should be used. Although it is not routine, symptomatic patients with left-right flow and hemodynamic instability may benefit from percutaneous closure of this defect.

Patients with small or operated interventricular communication (VSD) tolerate pregnancy well and are considered WHO-risk I, especially when ventricular function is normal.

The evolution of atrioventricular septal or canal defects that have not been corrected depends on the magnitude of valve regurgitation and the size of communication between chambers. It is considered WHO- risk I. The most frequent complications are arrhythmias, pulmonary congestion, and HF in patients with ventricular dysfunction. Treatment includes use of digoxin, diuretics (furosemide), vasodilators (hydralazine), or beta-blockers (carvedilol).

Coarctation of the aorta: Pregnancy is tolerated in patients with corrected coarctation of the aorta, which is considered WHO-risk II.[178,179] Nonetheless, in when it has not been corrected prior to conception, there are associated complications which lead to high risks to pregnancy, such as arterial hypertension with the additional risk of preeclampsia, aortic aneurysm, dissection of the aorta, and rupture of cerebral aneurysm, which goes on to become WHO-risk IV. It is fundamental to control arterial pressure, using conventional therapy.

Tetralogy of Fallot: Tetralogy of Fallot is the most common cyanotic heart disease in adults, and patients whose have undergone corrected surgery they tolerate pregnancy very well. In this group, risk factors are right ventricular dysfunction and pulmonary insufficiency, which adequately adapt to pregnancy in most cases.[179] The current practice of replacing the pulmonary valve in the population of patients with significant right ventricular dilatation has contributed to an increasing contingent of pregnant women with pulmonary biological prostheses. Cardiac arrhythmias are common events during the late postoperative period but do not compromise obstetric and fetal outcomes.[180] Experience with unoperated tetralogy of Fallot is very limited, and it should follow the recommendations for cyanotic heart diseases.

Ebstein anomaly: Prognosis for pregnant women with Ebstein anomaly is related to the presence or absence of cyanosis and HF. Hemodynamic instability is associated with tricuspid insufficiency or right ventricular dysfunction. Pregnancy should be planned following surgical correction in symptomatic patients with HF or cyanosis. Pre-excitation syndrome is commonly associated with the anomaly, and arrhythmias may be a complicating factor during gestation, even in patients who have undergone operation.[181]

Transposition of the great arteries (TGA): In cases of dextro-TGA, late evolution following atrial (Senning or Mustard procedure) or arterial (Jatene surgery) switch has been positive, and pregnancy is well tolerated.[182] The presence of right ventricular dysfunction or significant tricuspid insufficiency is an important factor for poor prognosis and restricting pregnancy.[175] Practice for treating complications should follow conventional recommendations. In cases with levo-TGA, also known as ventriculoarterial and atrioventricular discordance or ventricular inversion, evolution of pregnancy depends on FC, systemic right ventricular function, arrhythmias, and associated lesions.[183] In adults, the main concern is ventricular dysfunction.[184] For these young women, pregnancy should be advised against.

Fontan procedure: Successful gestations have been reported in patients who have undergone Fontan surgery, although there is a risk if Fontan circulation is not adequate,

at which point the consequent complications of low cardiac output, arrhythmia, or hepatic disease arise;[185] these cases are considered WHO risk III. Pregnancy is not advised for patients whose arterial oxygen saturation is lower than 85% or patients with severe atrioventricular insufficiency, depressed ventricular function, or enteric protein loss; these cases are considered WHO-risk IV. Practice is to treat and prevent HF, arrhythmias, and thromboembolism. Obstetric and fetal evolution in patients who have undergone the Fontan procedure is uncertain and complicated due to the high incidence of spontaneous abortion, prematurity, small for gestational age newborns, and neonatal death. There is also a high risk of PPH, which is peculiar to this clinical situation.[185,186]

Heredity: Children of mothers with congenital heart disease have a higher risk of presenting congenital cardiac lesions, which vary according to the type of maternal defect and which are not necessarily the same as the maternal structural lesion. Fetal echo is used to detect the recurrence of congenital heart disease, which is around 2.7% to 10% of cases.[187] It has been verified that there are genetic syndromes associated which specific defects, such as IAC in Holt-Oram syndrome, conotruncal anomaly in DiGeorge syndrome, among others, which are transmissible. These data reinforce the recommendation for fetal echo as part of the prenatal routine for the group of women with hereditary congenital heart disease.

3.2.2. Key Points

- Pregnancy planning requires determination of structural and functional diagnosis of heart disease based on laboratory and imaging examinations;
- Preconception counseling should be based on WHO risk classification;
- The presence of PH, cyanosis, arrhythmias, ventricular dysfunction, previous thromboembolic events, or HF adds risks to the WHO categories;
- When indicated, surgical or percutaneous intervention should be performed before conception;
- Pregnant women with WHO risk III/IV should be referred for specialized care in tertiary centers with the support of a Pregnancy Heart Team;
- Heredity of congenital heart disease requires the performance of fetal echo as well as genetic and preconception counseling.

3.3. Cardiomyopathies

Cardiomyopathies are cardiac muscle diseases that structurally and functionally compromise the heart in the absence of coronary artery disease, arterial hypertension, or valvular or congenital heart disease, which would justify the observed myocardial abnormality. According to phenotype, cardiomyopathies are classified as hypertrophic, dilated, restrictive, arrhythmogenic right ventricular, and non-compaction.[188] This classification is fundamental for risk assessment and estimating prognosis of gestation, regardless of probable etiology. PPCM will be discussed subsequently.

A retrospective study on cardiomyopathies during gestation has shown a 35% incidence of complications with 11% maternal mortality, data which are related to the form and the degree of myocardial impairment.[189,190] WHO risks III/IV includes cardiomyopathies with reduced left ventricular ejection fraction (LVEF) below 30%, with manifestations of HF, PH, and complex arrhythmias.[52]

HF is the main complication, especially after the second trimester of gestation and during labor. During the immediate postpartum period, which is as sensitive as gestation, the following recommendations should be followed: caution with the use of oxytocic drugs; moderation when infusing fluids during the intrapartum period; attention to PPH, pain control, and infection prevention; and transfer to the ICU within the first 24 to 48 hours after delivery.

3.3.1. Dilated Cardiomyopathy

Approximately 50% of cases of dilated cardiomyopathy are idiopathic, and 20% to 35% are hereditary; genetic mutations have been identified in almost 40%.[191] The following acquired causes stand out: viral myocarditis (coxsackievirus, parvovirus, echovirus, adenovirus), H1N1, Epstein-Barr virus, and other causes related to drug use.

During family planning, when the patient intends to become pregnant, the following are recommended: (1) adjustments to maternal therapy regarding HF control, considering that essential drugs which are contraindicated during pregnancy (ACEI, ARB, neprilysin inhibitors, spirolactone, ivabradine) should be substituted; (2) patient awareness of the possible immediate and long-term impact of pregnancy on heart disease; (3) genetic counseling, given that the disease is associated with autosomal dominant inheritance, followed by autosomal recessive inheritance, and to X-chromosome linked diseases.[191]

3.3.2. Hypertrophic Cardiomyopathy

Global prevalence of hypertrophic cardiomyopathy (HCM) is around 0.02% to 0.2% of the population,[192] and it was estimated at 0.015% in a cohort study of pregnant women with heart disease.[145] Pregnancy constitutes a potential risk for women with HCM; its prognosis, however, is still uncertain.

The great variation in the rate of cardiovascular complications during pregnancy, estimated between 5% and 40%, has been attributed to the heterogeneity of the phenotype of this heart disease.[193-195] Although they are often asymptomatic, the most frequent complaints of pregnant women with HCM are chest pain, dyspnea, syncope, and palpitation. The factors associated with worse prognosis for pregnancy are history of HF, ventricular arrhythmia, and sudden death in the family. Complications during pregnancy result from left ventricular outflow tract obstruction, diastolic dysfunction, and myocardial ischemia.

Among the most frequent arrhythmias, the following stand out: atrial extrasystoles, sustained supraventricular tachyarrhythmias, and AF, which favor maternal hemodynamic instability. From the obstetric point of view, the most frequent complications are spontaneous abortion in approximately 20% of cases and low birth weight in 10%.[193-195]

Another important issue is the risk of transmitting the disease to the fetus, because HCM is an autosomal dominant Mendelian trait, which is also caused by mutations that encode the components of the cardiac sarcomere.[196] The complexity of this disease still does not allow for determination of its true incidence in apparently healthy newborns who do not present abnormalities on 2-dimensional echo. In most cases, echo during the neonatal period does not identify HCM because myocardial hypertrophy occurs over the course of development, only becoming apparent after adolescence. Nonetheless, it is worth highlighting that the disease's obstructive form and family history of sudden cardiac death (SCD) are risk factors for early manifestation of hypertrophy in children.[131,197]

Genetic study of asymptomatic children and adolescents with family history of HCM may identify "healthy" carriers of the mutation. There are, however, important obstacles to the clinical application of this investigation, such as genetic plurality, low frequency of the mutation responsible in the diseased population, difficulties in techniques for identifying the pathogenic mutation, and high costs.

In symptomatic patients, initial pharmacological treatment is with the use beta-blockers, propranolol, or metoprolol succinate, which may or may not be associated with CCB, such as verapamil.[52] Association of these drugs requires caution with respect to maternal tolerance, arterial pressure, and fetal vitality. The use of prostaglandins to induce delivery is not advisable, due to their vasodilating effects. Vaginal delivery is considered to be safe, whereas cesarean delivery is reserved for special situations. Epidural or spinal anesthesia should be contraindicated in severe obstructive forms.

During pregnancy planning in patients with arrhythmias that are difficult to control pharmacologically, it is necessary to consider discussing the possibility of percutaneous intervention with an electrophysiologist. Examples include radiofrequency ablation in cases of complex and/or symptomatic tachycardias or even ICD in patients included in conventional class IA recommendations.

3.3.3. Arrhythmogenic Right Ventricular Dysplasia

Arrhythmogenic right ventricular dysplasia is a hereditary, autosomal dominant cardiomyopathy, with reduced penetrance and variable expressivity. For these reasons, genetic counseling is mandatory.

Pregnancy is well tolerated in women with this disease, but patients with preexisting biventricular disease have a higher risk of developing HF as pregnancy progresses.[198] Symptom control and prevention are done with beta-blockers (propranolol, metoprolol succinate). In the event that they are necessary, antiarrhythmic drugs should be maintained, respecting fetal toxicity limits. If indicated, ICD implantation should preferably take place before gestation.[199]

3.3.4. Non-compaction Cardiomyopathy

The non-compacted myocardium is characterized by distinctly trabeculated myocardial morphology. It is a family disease in up to 60% of cases, with autosomal dominant inheritance. Its prevalence is unknown, and evidence regarding practice during pregnancy is limited.[200] The clinical picture is highly variable, ranging from asymptomatic patients to patients with refractory HF and severe arrhythmias. There is no specific treatment for non-compaction cardiomyopathy, and therapeutic conduct should be supported by experience with other cardiomyopathies. The risk of thromboembolism, however, is considered to be greater due to the myocardial morphology in itself, which justifies permanent anticoagulation during gestation.

3.3.5. Restrictive Cardiomyopathy

Idiopathic restrictive cardiomyopathy is characterized by non-hypertrophic, non-dilated ventricles, with diastolic dysfunction, resulting in atrial dilatation. It may be idiopathic or associated with other diseases, such as amyloidosis, endomyocardial fibrosis, sarcoidosis, and hemochromatosis. Scarcity of experience in the literature, limited and controversial therapy, and frequently severe clinical evolution are factors which make pregnancy unadvisable.

3.3.6. Key Points

- Women with cardiomyopathy should participate in family planning, including genetic counseling;
- Risk stratification for subsequent pregnancies should consider the functional and structural status of the cardiomyopathy;
- Children of women with HCM, even when they are apparently healthy, should receive differentiated follow up until adolescence;
- Therapeutic optimization should follow conventional guidelines, considering classical drug contraindications during gestation;
- Permanent anticoagulation should be practiced in pregnant women with noncompaction or dilated cardiomyopathy, intracavitary thrombus, or prior embolic event;
- Genetic studies are promising for changing prognosis in cardiomyopathies.

3.3.7. Peripartum Cardiomyopathy

PMFC is defined as an idiopathic form of cardiomyopathy that manifests with HF secondary to left ventricular systolic dysfunction, with LVEF (< 45%), which occurs in late pregnancy or months after delivery or miscarriage, when none other cause of HF has been found.[201]

The pathophysiology of PPCC, not yet fully understood, is based on hypotheses that suggest hormonal, inflammatory, autoimmune, infectious, genetic and environmental mechanisms.[201] New concepts on etiopathogenesis have been presented, involving oxidative stress, angiogenic imbalance, and prolactin in the genesis of PPCM.[202,203]

The most recent studies show that PPCM is triggered by increased oxidative stress in pregnancy,[204] in combination with lower expression of angiogenesis regulators. Oxidative cleavage of prolactin by cathepsin D, the major endoprotease responsible for the generation of adenohypophyseal vasoinibins, generates an antiangiogenic subfragment,

prolactin 16kDa, with apoptotic and proinflammatory properties. The 16kDa prolactin in endothelial cells suppresses vasodilation depends on nitric oxide (ON) and angiogenesis. In addition, the endothelial cell secretes microparticle exosomes (microRNAs), specifically miRNA (miRNA), which, when absorbed by cardiomyocytes, interferes with their cellular metabolism and, consequently, leads to cellular apoptosis.[205,206] MicroRNA-146a is a highly specific marker for the diagnosis of CMPP[207] Prolactin blockade by bromocriptine or cabergoline, a dopamine-D2 receptor agonist, has shown promising results in therapy and recovery of myocardial function in PPCM.[207-211]

The main risk factors for PPCM are hypertensive pregnancy syndromes[212] (gestational hypertension, preeclampsia, eclampsia or HELLP syndrome), chronic hypertension, multiple pregnancies, obesity, smoking, pre-diabetes and diabetes mellitus, advanced age or adolescence and prolonged use of beta agonists.[213]

Mortality rates may be lower than 5%, or they may be as high as 50% of cases. The causes of maternal death are HF, ventricular arrhythmia, and thromboembolism, which mainly occur during the first 6 months of the disease until the first postpartum year (late maternal death), which may lead to underreporting of the disease.[214,215]

The main clinical manifestations are progressive or sudden dyspnea with acute pulmonary edema or cardiogenic shock. Cardiac arrest, severe arrhythmias or thromboembolic events [stroke, mesenteric ischemia or acute myocardial infarction (AMI)] and cardiogenic shock as the first manifestation of the disease are not uncommon.[216]

The diagnosis of PPCM should always be considered when cardiac decompensation occurs in the last months of pregnancy or the months following delivery in previously healthy women.[201] The diagnosis of PPCM is by exclusion and should have differential diagnosis with myocarditis, acute myocardial infarction, pulmonary thromboembolism (PTE), severe preeclampsia, amniotic fluid embolism, pre-existing cardiomyopathies, Takotsubo syndrome, congenital or valvular preexisting disease, and systemic infections. Do not value the symptoms, such as exertion, chest pain, or fatigue, which usually occur in late pregnancy and postpartum, contribute to delay in the diagnosis of PPMC , and consequently, a worse prognosis and less chance of recovery of myocardial systolic function.[201,215,217,222]

Complementary examinations include the following:[201]

- ECG: in most cases presents nonspecific changes in ventricular repolarization, sinus tachycardia or ventricular arrhythmias. Normal ECG does not exclude the diagnosis of PPCM;
- Chest X-ray: The most frequent alterations are cardiomegaly, redistribution of blood flow the pulmonary apices, and "butterfly" pattern;
- Biomarkers: Natriuretic peptides (B-type natriuretic peptide [BNP] / or NT-proBNP) are valid markers in HF investigation because, when elevated, they help establish the diagnosis and, when normal, exclude the diagnosis. BNP level is not significantly elevated in pregnancy and postpartum, the significant increase in BNP or NT-proBNP levels in pregnancy can diagnose PPCM; reference values for HF diagnosis are NT-proBNP > 300 pg/ml and BNP > 100 pg/ml; BNP has a good predictive value for persistent left ventricular systolic dysfunction after delivery and is correlated with left ventricle echocardiographic parameters;
- Troponins: Troponin may be slightly elevated in PPCM; have predictive value for persistence of ventricular dysfunction 6 months after the onset of the disease;
- Transthoracic Doppler echocardiography is the "gold standard" examination for diagnosing PPCM. Left ventricular hypokinesis findings predominate, with LVEF below 45% and may present with regurgitation of the atrioventricular valves and pericardial effusion. LVEF below 30% and final left ventricular diastolic diameter > 60 mm are correlated with worse maternal prognosis;
- CMR provides information on the degree of myocardial involvement and should be considered for estimation of prognosis and treatment in the late course of the disease;
- Coronary cineangiography and myocardial biopsy are not indicated for diagnosing PPCM.

Time to diagnose PPCM is crucial for patient survival. The immediate goals in acute treatment are to stabilize the hemodynamic state, providing symptomatic relief and ensuring maternal and fetal well-being. Emergency physicians should be aware of PPCM in the differential diagnosis of dyspnea in pregnancy-related emergencies and play a role in early diagnosis. Care should be provided by a multidisciplinary team including cardiologists, intensivists, obstetricians, neonatologists, anesthetists and cardiac surgeons. For rapid diagnosis and decision making in all pregnant women with acute heart failure, a pre-specified management algorithm and the establishment of a multidisciplinary team is crucial.[221,222]

The pharmacological treatment of PPCM[218,219] follows the guidelines of HF with reduced echocardiographic ejection fraction (EF). Beta-blockers, preferably β1-selective (carvedilol, bisoprolol, and metoprolol), are initiation with low doses associated with loop diuretics; digoxin may be considered in heart rate control indicated at initially low doses associated with loop diuretics; digoxin may be considered in heart rate control. It is important emphasis that ACEI, ARB, sacubitril/valsartan, ivabradine, spironolactone, and warfarin are contraindicated during gestation, but they may be considered during lactation. Is recommend anticoagulation with heparin to avoid cardio-embolic complications in patients with LVEF ≤ 35% with LMWH or oral anticoagulation at least in prophylactic dose.

The use of bromocriptine (ergot alkaloid) and cabergoline (dopamine D2 receptor agonist) has shown satisfactory results in the immediate response and late recovery of PPCM ventricular dysfunction.[208-211] The eventual contraindication to the use of these medications should also be weighed. If bromocriptine is not available, cabergoline may be used as an alternative to bromocriptine. As thromboembolic events have been reported during the use of bromocriptine (albeit mostly at higher dosages), bromocriptine treatment should always be accompanied by anticoagulation at least in prophylactic dosages heparin; full doses of heparin (fractional/unfractionated) is mandatory in the presence of intracardiac

thrombus or systemic embolism, as well as in paroxysmal or persistent AF.[222] The proposed schedule shows that safe doses with good tolerance and efficacy are 2.5 mg twice daily for 2 weeks, followed by 2.5 mg once daily for 6 weeks for bromocriptine; and 1 mg single dose for cabergoline for its prolonged effect from 14 to 21 days.[218-219] The abbreviation **BOARD** has been proposed for chronic treatment of patients with PPCM following delivery. The abbreviation stands for **B**romocriptine, **O**ptimization of HF therapy, **A**nticoagulation, Vaso**R**elaxants, and **D**iuretics.[218]

Bromocriptine treatment must always be accompanied by anticoagulation with heparin (LMWH or UFH), at least in prophylactic dosages; in patients with intracardiac thrombus detected by imaging or evidence of systemic embolism, as ell as in patients with paroxysmal or persistent atrial fibrillation.[222]

Regarding the non-pharmacological treatment of PPCM, ICD, cardiac resynchronization, ventricular assist devices, and cardiac transplantation are considered.[220-222] ICD has been considered for primary prevention of sudden death, following guidelines for patients with ventricular EF below 35%. Wearable defibrillator cardioverter is an alternative during the first months following diagnosis with PPCM, considering that most of these patients recover ventricular function 6 months after the acute phase of the disease.

Cardiac resynchronization may be proposed 6 months after the onset of the disease, in accordance with conventional indication criteria, or be it, advanced HF, NYHA FC III-IV with optimized treatment, sinus rhythm, EF below 35%, QRS > 150 ms, or QRS > 120 ms with desynchronization on echo or magnetic resonance.

Left ventricular assist devices may be an option in critically severe patients as a "bridge to transplant" or a "bridge to recovery." Cardiac transplant is indicated in approximately 10% of PPCM cases in patients who do not recover after 12 months with mechanical circulatory support.

During long-term clinical follow-up, the following recommendations should be followed:[221]

1. If the cardiac function does not improve, maintain beta-blocker, ACEI or ARB; spironolactone if EF < 40%, ivabradine if heart rate > 75 bpm, with a maximum dose of beta-blocker (reaching heart rate < 60 bpm); diuretics if there is edema / pulmonary congestion;
2. If ventricular function shows complete and sustained recovery, supported by bi-annual echocardiographic follow-up, maintain pharmacological treatment (beta-blocker, ACEI, spironolactone) for at least 6 months and diuretics only if there are symptoms of congestion or lower limb edema; during the period between 6 and 12 months thereafter, discontinue spironolactone and ivabradine (if in use), but continue beta-blocker and ACEI/ARB for at least 6 months following discontinuation of spironolactone; after 12 months, gradually reduce and discontinue ACEI/ARB, and maintain beta-blocker for 6 more months; after 18 months, suspension of the beta-blocker is controversial, because some studies claim that it should be maintained for at least 5 years;
3. Advising against subsequent pregnancy in patients who have completely recovered left ventricular systolic function following PPCM is controversial, giving that there is no conclusive evidence supporting this advice in medical practice.[218]

The following points resume recommendations for practice in cases of acute HF:[208,222]

1. Transcutaneous monitoring of oxygen saturation;
2. Oxygen therapy: oxygen saturation < 90% (pulse oximetry); PaO_2 < 60 mmHg (arterial-blood gas test);
3. Endotracheal intubation performed in acute respiratory insufficiency with hypoxemia (PaO_2 < 60 mmHg), hypercapnia ($PaCO_2$ > 50 mmHg), and acidosis (pH < 7.35);
4. Diuretics if there are signs of congestion (furosemide, 20 to 40 mg) in an intermittent bolus or a continuous infusion;
5. Vasodilators if SAP > 110 mmHg; intravenous nitroglycerin, at an initial dose of 10 to 20 μg/min, up to a maximum of 200 μg/min;
6. Inotropic agents (dobutamine, dopamine, levosimendan, phosphodiesterase III (PDE III) inhibitors in hypotensive patients (SBP < 90 mmHg) and/or signs of low cardiac output; experimental evidence and clinical experience suggest that catecholamines such as dobutamine are less favorable in patients with PPCM due to metabolic impairment levosimendan can be considered as the preferred inotropic agent, with continuous infusion of 0.1 μg/kg/h for 24 h without an initial bolus dose for patients with severe PPCM; if levosimendan is not available, dobutamine is the other option, while adrenaline should be avoided.
7. Vasopressor agents for cardiogenic shock; noradrenaline should be the first-line vasopressor.
8. Anticoagulation with full-dose LMWH, provided there are no contraindications;
9. Mechanical circulatory support as a "bridge to decision" for cardiac transplantation.

3.3.7.1. Key Points

- The etiopathogenesis of PPCM has yet to be fully clarified;
- Immediate diagnosis and treatment at the onset of symptoms are fundamental to ventricular recovery;
- The use of prolactin inhibitors (bromocriptine or cabergoline), combined with optimized treatment for HF is differential for the recovery of ventricular function;
- Approximately 50% of patients with PPCM recover myocardial function within 6-month period with therapy for HF;
- Even if ventricular function is recovered, follow up should be periodic for at least 5 to 10 years, following diagnosis;
- As a result of the lack of evidence regarding the actual recurrence of PPCM during subsequent gestations, there is no justification for advising against conception in patients who have truly recovered ventricular function;
- Patients with PPCM who have received transplantation have an immediate and late postoperative prognosis like that of patients with other forms of dilated cardiomyopathy.

3.4. Ischemic Heart Disease

Ischemic heart disease (IHD) is not common during pregnancy; most publications consider acute coronary syndrome rather than stable ischemic disease.[223] Data from the WHO have shown that the rate of acute infarction is 3.34 events per 100,000 pregnancies, it being most frequent during the third trimester of gestation.[224] The incidence of infarction without ST-segment elevation is higher during gestation.[52]

Risk factors for IHD during gestation are maternal age (over 40 years old; for each year of life, there is a 20% increase in the risk of infarction), family history of premature coronary disease, tobacco use, arterial hypertension, dyslipidemia, and diabetes mellitus.[52]

Additional risk factors include preeclampsia, thrombophilia, postpartum infection, cocaine use, multiparity, autoimmune diseases, aortic valve stenosis/aortic valve prosthesis thrombosis, mitral stenosis, and PPH.[52]

The etiology of IHD during gestation differs from the general population. In a contemporary review,[225] the mechanisms related to infarction were identified with following incidences: spontaneous coronary artery dissection (43%), atherosclerosis (27%), coronary thrombosis (17%), normal arteries on angiography (9%), vasospasm (2%), and Takotsubo syndrome (2%).

Spontaneous coronary artery dissection is the most common cause of AMI during gestation and the postpartum period, with a prevalence of around 1.81 events per 100,000 pregnancies, occurring most frequently during the third trimester. The outcome of dissection associated with pregnancy appears to have a worse prognosis than dissection unrelated to pregnancy.[226]

Demographic variables and associated comorbidities include the following: black race, chronic hypertension, gestational hypertension, preeclampsia, lipid abnormalities, chronic depression, migraine, advanced maternal age, first delivery, and infertility treatment.[226]

The etiology of coronary dissection has yet to be made clear, but it appears to be related to degradation and weakening of arterial walls, as a consequence of the influence of hormones during gestation. The most common maternal complications described are cardiogenic shock (24%), ventricular fibrillation (VF) (16%), and mechanical support (28%), which result in hospital death in 4% of cases.[226]

Atherosclerosis: IHD caused by atherosclerosis is linked to the presence of classic risk factors and to those referred to as emerging risk factors, including gestational hypertensive disease, gestational diabetes, history of premature delivery, autoimmune diseases (lupus erythematosus, rheumatoid arthritis, scleroderma), treatment with thorax radiotherapy/chemotherapy, and depression/general anxiety.[227]

Thrombosis: Coronary thrombosis, in the absence of atherosclerosis, is more probable due to hypercoagulability during pregnancy, and it may result in paradoxical embolization.

Normal arteries: Mechanisms of AMI with normal coronary arteries continue to be unclear; they include transitory coronary spasm (increased vascular reactivity and/or use of ergotamine derivatives) or undetected coronary dissection, reflecting the limitations of the diagnosis.[52]

Vasospasm: It may be spontaneous or induced by drugs, hypertensive syndromes during pregnancy, increased vascular reactivity to angiotensin II and norepinephrine, endothelial dysfunction, or renin release by the gravid uterus. Vasospasm may be induced by routine obstetric drugs, such as beta-agonists (terbutaline, salbutamol), inhibition of premature labor, ergot derivatives for labor induction or PPH prevention, and bromocriptine, indicated for inhibiting lactation.[227]

Other causes: coronary artery aneurysm related to Kawasaki disease.[52]

Diagnosis of AMI is not influenced by the status of pregnancy, and it includes symptoms (dyspnea and chest pain), laboratory examinations (increased troponin), ECG (specific and classic alterations of AMI), and echo (alterations in segmental wall contractility). Differential diagnosis of AMI during pregnancy should be done with pulmonary embolism, amniotic fluid embolism, dissection of the aorta, PPCM, and myocarditis. Additional examinations for diagnosis risk stratification and treatment of AMI include scintigraphy, magnetic resonance, and coronary angiography.

Patients with acute coronary syndrome should receive defined diagnosis and treatment before delivery. Therefore, in cases with chest pain or suspected acute ischemic disease, we are in favor of indicating coronary angiography, which, in addition to concluding diagnosis, increases the chance of treating the artery "responsible" for the acute ischemic condition. The risks of angiography are relatively low in relation to the benefits for planning delivery and anesthesia in these patients.

Treatment for AMI during pregnancy is similar to that of the general population, including revascularization techniques. In cases of coronary dissection, clinical treatment has been the first choice. Percutaneous or surgical intervention is reserved for cases with left coronary trunk involvement or proximal anterior descending lesion.[226] The most frequent complications are HF and cardiogenic shock (38%), arrhythmias (12%), recurring angina and reinfarction (20%), maternal mortality (7%), and fetal death (7%).[52] Clinical practice for cardiogenic shock and cardiorespiratory arrest follows conventional guidelines, with the strategy of emergency delivery in cases with fetal viability.[52]

Pharmacological treatment of AMI is similar to that recommended for the general population. Aspirin is safe in low doses;[92] there is, however, little information regarding P2Y12 inhibitors.[73] Clopidogrel is approved for use, but it should be suspended 7 days before delivery. There is no evidence on the benefits of using this medication for coronary dissection; additionally, glycoprotein IIb/IIIa inhibitors, bivalirudin, prasugrel, and ticagrelor are not recommended.[73] The use of beta-blockers, excluding atenolol, has already been established for acute coronary syndrome. Recombinant tissue plasminogen activator (TPA) does not cross the placenta, but it may induce hemorrhagic complications (subplacental bleeding).[52] Benefits of short-term heparinization probably outweigh the risk of hemorrhagic complications.

Patients with previous IHD may receive approval for subsequent pregnancy if there are no residual ischemia

or signs of ventricular dysfunction. There are no high-quality data defining how much time pregnancy should be delayed following acute coronary syndrome. However, the recommendation of 12 months seems reasonable; it should be individualized according to comorbidities, cardiovascular status, and need for medical therapy.

3.4.1. Key Points

- The growing incidence of IHD during pregnancy is due to higher maternal age and the growing presence of risk factors;
- The incidence of AMI without ST-segment elevation is higher during pregnancy, and the anterior descending artery is the most affected;
- The clinical picture of coronary artery dissection seems to be more severe during gestation, in comparison with the general population;
- Coronary vasospasm may occur as a consequence of obstetric medications;
- Symptoms, ECG, elevated serum troponin, and alterations on echo define diagnosis of acute coronary syndrome;
- Coronary cineangiography should be indicated to define diagnosis and make percutaneous treatment possible;
- Treatment follows the general rules, with eventual restrictions on gestation;

3.5. Dyslipidemia

3.5.1. Lipid Changes

During pregnancy, a substantial increase occurs in plasma concentration of lipoproteins, as result of the increase in circulating estrogen and progesterone. Triglycerides increase 2- or 3-fold in relation to pre-gestational values, reaching their peak by the end of gestation, with a progressive return to baseline values at the end of the postpartum period. In the same manner, there is a progressive increase in total cholesterol levels, corresponding to 2- to 5-fold before pregnancy values. Their decrease is slightly slower than that of triglycerides, and they may take longer than 6 weeks after delivery to normalize.[228]

Lipoprotein fractions also present qualitative increase of high density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c) and amount of triglycerides. The HDL-c has slightly different behavior from total cholesterol and triglycerides, because it raises a progressive values at 24th week, of 50% in comparison with preconception period. Subsequently, it presents a drop, equivalent to 15% higher than pre-gestational values until the end of pregnancy.[228] LDL-c levels increase in synchronization with total cholesterol. However, they showed decrease and may fall after the eighth week postpartum.

The factor responsible for these alterations in lipoproteins is the hormone estrogen. The drop in HDL-c after week 24 is understood by the increase in plasma concentration of insulin, which represents an increase in insulin resistance. It is, therefore possible to conclude that HDL-c levels are more related to estrogen levels during the first phase of gestation and to insulin during the second phase. It isrecommended that lipid profile test by postponed to, at least, 4 to 6 weeks after gestation, especially in women without previous alterations.

In an update to the Brazilian Guidelines on Dyslipidemia and Atherosclerosis Prevention, the recommendations for women of fertile age with dyslipidemia include dietary orientation and adoption of a healthy lifestyle, in addition to weight control, physical activity, and ceasing tobacco use.[229] Therapy with statins should be avoided in women of fertile age who plan to become pregnant (class II-A; C).

Gestational hypertriglyceridemia occurs to meet maternal energy demands, as a precursor of hormones for the placenta and to provide cholesterol and essential fatty acids to the fetus. Statin therapy should not be indicated for pregnant women in the second and third trimester or in breastfeeding women (class III-C). This contraindication is due to reports of teratogenicity, although the information available in the literature is inconclusive.[104]

Fibrates, ezetimibe, niacin, cholesterolamine and omega-3 are considered to be drugs without contraindication, but cholesterolamine is the only one whose safety has been established. Fibrates may be used in cases of very severe hypertriglyceridemia (plasma level of triglyceride > 1,000 mg/dL), with risk/benefit analysis for pregnant women (high maternal and fetal mortality due to acute pancreatitis). However, dietary control should be the treatment of choice for pregnant women (class IIA; C); in extreme cases, apheresis may be recommended.[230]

Regarding omega-3 fatty acids, pregnant and breastfeeding women should advised to introduce omega-3-rich fish, from deep water and with low mercury levels, into their diets. Salmon, mackerel, herring, sardines, tuna and trout are recommended. There are no studies on supplementation (capsules) and phytosterols during gestation.

Genetic dyslipidemias should be considered, both hypertriglyceridemia with frequent pancreatic complications and familial hypercholesterolemia. Apheresis is a special therapeutic approach to these severe circumstances; in familial cases, selective LDL-apheresis is used.[231]

Until recently it was accepted that dyslipidemia during pregnancy should be considered physiological, to the extent that lipid profile testing is not part of the prenatal routine. Recently, however, fatty striae have been described in the aorta of dyslipidemic mother fetuses. Based on these observations, it has been suggested that maternal cardiometabolic dysfunction may not only contribute to long-term maternal effects, but it may also lead to a risk of atherosclerosis in future generations. These considerations suggest that diagnosis and treatment of dyslipidemias should be performed prior to conception, and they should continue during gestation and the postpartum period.[232]

3.5.2. Key Points

- Increases occur in triglycerides and cholesterol during pregnancy;
- The use of statins is not recommended, although there is some controversy regarding their teratogenic effects;
- Maternal dyslipidemia may induce fetal atherosclerosis and atherosclerosis in future generations.

3.6. Other Diseases

3.6.1. Takayasu Arteritis

Takayasu arteritis is a chronic, idiopathic vasculitis that predominantly affects the aorta and its main branches, coronary arteries, and the pulmonary artery. The resulting inflammatory process causes narrowing, occlusion, and aneurysm in the affected branches.[233] Etiology of the disease is unknown, but several studies have demonstrated an association with human leukocyte antigens, suggesting a predisposition to the immune-mediated process.[234]

3.6.1.1. Prevalence

Takayasu arteritis is a rare disease, with growing rates of prevalence. The highest rates occur in Japan, with 100 to 200 new cases annually. Women are more affected, in 80% to 90% of cases; the onset of the disease occurs between 10 and 40 years of age, overlapping with the fertile period of life, and gestation demands special attention. It is the most frequently observed form of vasculitis during pregnancy, precisely because it appears in young patients.[235] Maternal immune activation during pregnancy may influence the course of the disease and impair maternal and fetal outcome.[236]

3.6.1.2. Prognosis

Pregnancy in patients with Takayasu arteritis has an uncertain prognosis. Although the majority of gestations are successful, the incidence of severe hypertension and preeclampsia is 40% higher, when compared to 8% in the general population. Obstetric complications, such as premature delivery and stillbirth, are foreseen.[235] Patients with renal artery and abdominal aorta involvement more frequently have complications of preeclampsia and IUGR.[235]

The rarest maternal complications, which are, however, very severe, are aortic aneurysm, stroke, HF, aortic insufficiency, myocardial infarction, and dissection of the aorta.[235] Other, more common complications include progression of renal insufficiency, anemia, thrombocytopenia, and elevated inflammatory markers.[235]

3.6.1.3. Treatment

Treatment of vasculitis during pregnancy is conventional, excluding three teratogenic medications, namely, methotrexate, mycophenolate and cyclophosphamide.[236] Other medications are considered compatible with gestation. It is preferable to use immunosuppressive drugs to control active vasculitis, reserving prednisone for a short-duration regime in moderate doses during the acute phase or in cases where the disease worsens. Treatment may be initiated before conception and maintained during pregnancy and lactation.[237]

Tumor necrosis factor inhibitors may be continued during the preconception, pregnancy and lactation. These inhibitors, when their composition is based on immunoglobulin G (IgG), cross the placenta from 16th of gestation with a progressive increase in transference nearby term of gestation. Therefore, these drugs should not be administered after 30th week of gestation, but they should be reintroduced in the postpartum period.[238]

3.6.1.4. Key Points

- Pregnancy is allowed when disease is in remission, because vasculitis has severe prognosis;
- Treatment with corticosteroids and immunosuppressive drugs (azathioprine, cyclosporine, and tacrolimus) improves maternal-fetal evolution;
- In cases of systemic vasculitis, seeing that the risk of thromboembolic events is elevated, prevention with aspirin or LMWH should be considered;
- Takayasu arteritis should always be considered in differential diagnosis of arterial hypertension during pregnancy;
- Contraception should be efficacious and safe during treatment with high doses of cytotoxic drugs.

3.6.2. Kawasaki Disease

Kawasaki disease is a systemic vasculitis of unknown etiology that occurs in children up to 5 years of age, with Asian prevalence and a male predominance of 1.5 para 1. During the acute phase, inflammatory involvement of coronary arteries results in clinical outcomes and provokes aneurysm formations in 15% to 25% of untreated children. It is one of the main causes of heart disease acquired during childhood.[239]

Coronary artery aneurysms may be detected early on echo and loss of laminar flow in these arteries may favor clot formation.

Disease prognosis is related to presence and size of coronary artery aneurysms. Small aneurysms have favorable prognosis, with low risk of myocardial ischemic events. In contrast, large and giant aneurysms (internal diameter > 8 mm) present a high risk of thrombosis and, consequently, myocardial infarction, arrhythmias, and sudden death.[240]

Lack of diagnosis and treatment during the acute phase in childhood has contributed to the finding of women with vascular sequelae of Kawasaki disease during fertile age and pregnancy.[241,242] The influence of the hypercoagulable and hyperkinetic states inherent to pregnancy, delivery, and the postpartum period represents a potential risk of severe events, such as thrombosis, myocardial infarction, and sudden death, throughout the natural history of women with complicated Kawasaki disease with coronary aneurysms. In addition to this, pregnancy, *per se*, favors the risk of coronary artery rupture and/or dissection, as a result of specific changes in the artery walls, which include fragmentation of reticular fibers, reduction of mucopolysaccharides and loss of normal elastic fibers ripple.

In keeping with this logic, it is accepted that the state of hypercoagulability during pregnancy and the postpartum period requires permanent anticoagulation. Therefore, low-dose aspirin (80 mg daily) up 36th week of gestation combined with anticoagulation, should be considered. LMWH is recommended during the first trimester and after week 36 of gestation, with low doses of warfarin in the interval between these 2 periods. In the literature, there is a lack of data regarding targets for prevention; nonetheless, the consensus is that INR around 2 is safe and presumably efficacious.

Previous myocardial infarction increases the risk of gestation, and ventricular function is a determining factor for

maternal evolution. Beta-blocker (propranolol or metoprolol succinate) use in low doses favors lower oxygen consumption, as a function of less cardiac work.

3.6.2.1. Preconception Evaluation

In risk stratification for future pregnancy, the presence of coronary artery aneurysm, myocardial ischemia, and ventricular dysfunction should be considered.

3.6.2.2. Key Points

- Existence of moderate coronary aneurysm (> 3 mm and < 6 mm) in one or more arteries indicates permanent use of low doses of aspirin;
- Giant (> 8 mm) or multiple aneurysms, in addition to aspirin, require association with an anticoagulant;
- In cases of myocardial ischemia, association of aspirin, an anticoagulant, and/or CCB is recommended.

3.6.3. Pulmonary Hypertension

PH is a physiopathological condition that leads to debilitating symptoms and lower life expectancy, caused by compromised pulmonary circulation. It is defined as average resting pulmonary artery pressure (PAP) ≥ 25 mmHg, measured by right heart catheterization. It is a progressive disease, predominant in the female sex, and it may occur during the reproductive period. In general, it leads to right ventricular insufficiency with a risk of death during pregnancy, but especially during the postpartum period.[243,244]

Pregnancy in women with PH is considered high risk and maternal and the neonatal complications rate achieve 50 to 70% respectively, and it has been associated with mortality rates reaching nearly 30%.[245] In view of this, pregnancy is contraindicated.

Physiological changes of pregnancy, especially the decreased peripheral vascular resistance, increased cardiac output, and hypercoagulability, are reasons for maternal hemodynamic instability. In addition to this, there is the activity of sex hormones, such as beta-estradiol, progesterone, and testosterone, in pulmonary circulation; on one hand, they attenuate pulmonary vasoconstriction, and, on the other hand, they activate angiogenic factors that stimulate the proliferation of smooth muscle cells in pulmonary vasculature, predisposing them to reverse vascular remodeling.

This physiopathological complexity of PH during gestation may be resumed in a single primary aspect, namely, the compensatory physiological vasodilatory response of pulmonary vasculature, which becomes decreased or absent, leading to a significant increase in pulmonary pressure and resistance. The inability of the pulmonary vascular bed to accommodate increased cardiac output results in significant disproportion in right ventricular afterload and failure.[246]

The classification of PH was simplistic, divided into two groups: primary and secondary, according to identification of risk factors. However, since 1998, the WHO has proposed modifications to the classification of PH in order to allow different types of the disease to be grouped based on their physiopathology, response to treatment, and prognosis[247] (Table 25). It is worth remembering that, in this classification, the term PAH is described as a subgroup of PH, characterized by left ventricular filling pressure < 15 mmHg and pulmonary vascular resistance > 3 Wood units.

Regarding diagnosis of PH, symptoms such as dyspnea, chest pain, lower limb edema, palpitation, and dry cough may be attributed to pregnancy, but the presence of syncope attributes more severity to the disease.[248] ECG and chest X-ray show right chamber overload. Transthoracic echo estimates PAP, evaluates right ventricular function, and identifies other structural heart diseases, making it possible to classify the type of PH. Definitive diagnosis is done by means of right heart catheterization and pressure measurements.[246,247]

Family planning in patients with PH includes advising against pregnancy by clarifying the maternal and fetal risks, as well as the choice of an efficacious and safe means of contraception. There is no evidence to date regarding a pulmonary arterial pressure level (cutoff point) for determining prognosis for a future pregnancy.

However, the pregnancy outcome is very different when subgroups for classification of PH are taken into consideration.[248] It is worth emphasizing that patients included in category 2 (Table 25), such as those with mitral stenosis, aortic stenosis, and cardiomyopathies, receive different treatment and counseling than patients included in the other categories.

For this reason, risk stratification according to category and treatment strategy for pregnancy should receive interdisciplinary support in a tertiary hospital that has specialists in PH, so that the best practice may be adopted.

Excluding pregnant women included in category 2, the first proposal over the course of the first trimester in patients with PAH is to interrupt pregnancy, with an emphasis on clarifying the risks of maintaining pregnancy and those of therapeutic abortion procedure. In the event that the patient does not accept this advice, the following practice is currently recommended:[249]

1. Weekly interdisciplinary consultation starting at week 16 of gestation;
2. Individualized pharmacological therapy for PH;
3. Periodic evaluation of ECG, echo, and BNP during the second and third trimesters;
4. Hospitalization starting at week 28 for therapy with intermittent oxygen in accordance with arterial oxygen saturation, anticoagulation, maternal-fetal monitoring, and delivery planning;
5. Route of delivery is indicated by the obstetrician;
6. General anesthesia is preferable;
7. Anesthesia with blocks (epidural or spinal anesthesia) is contraindicated.

Recommended pharmacological therapy is use of prostacyclins and their analogues and type 5 phosphodiesterase inhibitors, which seem to be safe during gestation. CCB are a safe and efficacious alternative for the subgroup of patients who present documented vasoreactivity and NYHA FC I/II without severe ventricular dysfunction; nevertheless, it is necessary to be attentive to their negative inotropic effects, in addition to arterial hypotension, which may limit their use.[250,251]

Table 25 – Classification of pulmonary arterial hypertension

Category 1	Idiopathic
	Hereditary
	Induced by drugs and toxins: anorectic agents, chemotherapy, serotonin reuptake inhibitors, cocaine
	Associated with congenital heart disease, collagen disease, HIV infection, portal hypertension, schistosomiasis
	Pulmonary capillary hemangiomas or veno-occlusive pulmonary disease
	Persistent pulmonary hypertension in the newborn
Category 2 - Pulmonary hypertension due to left heart disease	Diastolic dysfunction
	Systolic dysfunction
	Valve disease
	Congenital/acquired left heart obstruction and outflow tract obstruction and congenital cardiomyopathies
Category 3 - Pulmonary hypertension due to pulmonary disease and/or hypoxemia	Chronic obstructive pulmonary disease
	Interstitial pulmonary disease
	Pulmonary diseases with mixed patterns, i.e, restrictive and obstructive
	Obstructive sleep-disordered breathing
	Alveolar hypoventilation
	Chronic exposure to high altitudes
	Occupational pulmonary diseases
Category 4	Pulmonary hypertension due to chronic thromboembolism
Category 5 - Pulmonary hypertension with unclear multifactorial mechanisms	Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
	Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleimoyomatosis
	Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
	Others: tumoral obstruction, fibrosing mediastinitis, chronic renal insufficiency, segmental pulmonary hypertension

HIV: human immunodeficiency virus.

Parenteral prostaglandins are recommended in patients in NYHA FC IV or patients who show evidence of severe right ventricular involvement. Most experience is with intravenous epoprostenol. In patients with preserved ventricular function who are in NYHA FC I/II, inhaled prostaglandins, such as Ilosprost, may be indicated. Parenteral prostaglandins may be combined with oral phosphodiesterase inhibitors, with satisfactory results.[252]

Endothelin receptor blockers and soluble guanylate cyclase stimulators are contraindicated in pregnancy.[251,252] Intravenous prostaglandins may be considered during delivery, with invasive monitoring via CVC and arterial access.

It is worth remembering that a large number of maternal deaths occur during the postpartum period, with the following causes standing out: HF due to right ventricular failure, hypoxemia, and thromboembolism (pulmonary thrombosis *in situ*).[248] Therefore, anticoagulation is essential, with therapeutic doses of LMWH (1 mg/kg every 12 h) during the first trimester and after 36th week of gestation and, warfarin in a daily dose, INR target of 2, another other periods (Figura 6).

3.6.3.1. Key Points

- Diagnosis of PAH should be confirmed by right chamber catheterization.
- Pregnancy should be advised against in women with PAH;
- Categories of PH according to current classification have different prognoses and treatments;
- The proposal to interrupt pregnancy should be considered in patients with PH during the first trimester, except in patients in category 2;
- In pregnancy in maintained, the prenatal care and delivery should be at a tertiary hospital with specialized PH staff;
- Current pharmacological therapy has assisted in successful pregnancy in PH.

3.6.4. Aortic Diseases

Aortic diseases may be present in women of reproductive age, and they are considered to be important causes of complication and even death during gestation.[253] This is due to 3 physiological phenomena of pregnancy that have detrimental impacts of aortic diseases. These phenomena are hemodynamic (increased cardiac output), structural (progressive aortic root growth until the third trimester), and hormonal (vascular wall fragility). The following are the most frequent causes of aortic disease in pregnant women: bicuspid valve, Marfan syndrome, coarctation of the aorta, Ehlers-Danlos syndrome, Turner syndrome, and Loeys-Dietz syndrome.

3.6.4.1. Aortic Dissection and Rupture

Gestation increases a woman's susceptibility to dissection and rupture of the aorta. In the general population, the incidence of aortic dissection is 6 cases per 100,000 individuals yearly; nevertheless, during pregnancy, the occurrence increases 100-fold, to approximately 0.6%.For this reason, diagnosis of aortic dissection should be considered in all patients with chest pain during pregnancy. It occurs more frequently during the last trimester (50%) or the initial postpartum period (33%).[52]

Marfan syndrome is the most common conjunctive tissue disease, caused by a mutation in the FBN-1 gene, which codifies the inherited glycoprotein fibrillin in an autosomal dominant pattern.[254] Average increase in aortic diameter growth during gestation in patients with Marfan syndrome is 0.3 mm/month, while in the general population with Marfan syndrome, it is 0.38 mm/year.[254] This increased rate of aortic dilatation decreases after delivery, but it remains higher than the pre-gestational rate.[253]

Diagnosis includes history, physical examination, echo, and magnetic resonance of the aorta. Thoracic aortic angiography complements investigation when there is strong suspicion of dissection based on previous examinations.

One of the most important factors for determining the risk of dissection of the aorta is maximum diameter (< 40 mm, 1% risk of dissection; > 40 mm, 10% risk of dissection).[255] Pregnancy is generally contraindicated if the ascending aorta diameter is greater than 40 mm in patients with family history of dissection or sudden death, even though the exact dimension is still a question of debate.[254] There seems to be a low incidence of dissection if aorta diameter is lower than 4.5 cm; pregnancy, however, increases the late risk of aortic complications.[52,254,256]

One important consideration is body surface area, especially in small women. Aorta diameter index higher than 27 mm/m^2 is associated with a high risk of dissection, and prophylactic replacement of the aortic root should be considered.[52]

It is also necessary to evaluate associated cardiovascular problems, including the possibility of aortic regurgitation and mitral valve prolapse with associated regurgitation.

Beta-blockers have been shown to increase aortic distensibility and reduce pulse wave velocity and reducing the rate of complications such as regurgitation, dissection, and congestive HF. A 20% decrease in resting heart rate is considered to be the objective of treatment.[257]

Periodic echocardiographic monitoring is recommended every 6 to 8 weeks to monitor the size of the mother's aortic root; the interval depends on initial echocardiographic findings.[254]

The preferred route of delivery is cesarean in patients with aortic dilatation > 45 mm, and delivery should take place in a tertiary center where there is an experienced surgery team. In patients with diameters < 45 mm, with no previous events, delivery may be vaginal, with early analgesia and relief forceps.

Preconception counseling requires determination of the underlying disease, genetic evaluation, and aortic dilatation correction in accordance withdiameter thresholds (Table 26).

Table 26 – Aorta diameter thresholds and indication for intervention in patients considering pregnancy[257]

Underlying disease	Ascending aorta diameter
Marfan syndrome	45 mm
Loeys-Dietz syndrome	40 – 45 mm
Ehlers-Danlos syndrome type IV	Pregnancy contraindicated
Bicuspid valve	50 mm
Turner syndrome	27 mm/m^2

Ehlers-Danlos syndrome type IV occurs with severe vascular complications, with characteristics of autosomal dominant inheritance and 50% risk of transmission to offspring.

Maternal mortality is significant, and it is related to uterine rupture and dissection of the great arteries and veins. Pregnancy is, therefore, considered a high-risk situation, and it is not advised (WHO risk IV); in this manner, when contemplating pregnancy, these women should be advised in a shared decision-making process.[52]

In vascular Ehlers-Danlos syndrome, also a rare severe conjunctive tissue disease, characterized by fragile vascular tissue, vascular rupture has been related during pregnancy in up to 50% of cases, with mortality rates between 5% and 50%. Gestation, in these cases, is also associated with premature rupture of fetal membranes, spontaneous abortion, and prematurity.[52]

Turner syndrome[256] is the most common sexual chromosome abnormality in women, and it occurs in 1 of every 1,500 to 2,500 female live births. Chromosome constitution may be absence of an X chromosome (karyotype 45,X) or chromosome mosaicism (karyotype 45,X/46,XX), as well as other structural anomalies of chromosome X.[256] Turner syndrome is associated with increased risk of heart disease, aortic dilatation, hypertension, diabetes mellitus, and atherosclerotic disease events.[256]

Dissection of the aorta in patients with Turner syndrome is estimated to be 36 in 100,000 cases, but it is 6 times more common in younger age ranges than in the general population.[52] Risk factors include dilatation of the aorta, bicuspid aortic valve, and coarctation of the aorta.[52] Pregnancy should be avoided when aortic size index is > 25 mm/m^2. Furthermore, after aortic root surgery, patients continue to be at a risk of a type B dissection.

Although spontaneous pregnancy may occur in patients with Turner mosaic (0.5% to 10%), it is more common with assisted fertility. For this reason, cardiovascular evaluation is recommended before beginning fertility treatment. Furthermore, good blood pressure and diabetes control during pregnancy is mandatory for all patients with Turner syndrome.[52]

Loeys-Dietz syndrome[258] is an autosomal dominant condition. It was described for the first time in 2005, and it is associated with formation or dissection of an aneurysm in the aorta or in other arteries, generally at a young age.[258] It has been identified in individuals referred for investigation for Marfan syndrome[257] or vascular Ehlers-Danlos syndrome who did not present the classical characteristics of these conditions, but rather others characteristics, including general arterial tortuosity, hypertelorism, bifid/broad uvula, or cleft palate.[257]

The syndrome results in mutations in the genes that codify components of the transforming growth factor beta (TGF-beta) signaling pathway. Aortic pathology is particularly concerning in this condition, but other vascular abnormalities may also be present.[258]

Significant maternal morbimortality has been described in patients with Loeys-Dietz syndrome, but it is possible for pregnancy to be successful and free of complications.[258] Nonetheless, all patients with this condition should, at present, be treated as high-risk during pregnancy and the postpartum period, until reliable risk prediction tools become available.[258]

There are no studies on the benefits and risks of cesarean delivery in comparison with vaginal delivery in patients with hereditary aortic disease. Cesarean delivery is, nonetheless, recommended, according to the aortic dilatation thresholds shown in Table 26. Vaginal delivery may be considered in cases below these limits.

3.6.4.2. Key Points

Aortic diseases constitute an important cause of maternal death during the pregnancy-postpartum cycle;

Pregnancy increases women's susceptibility to aortic dissection and rupture;

Pregnancy planning includes diagnosis of the underlying disease, magnetic resonance of the aorta and base vessels, eventual corrective aortic surgery in accordance with limits for risk of dissection, and genetic counseling;

The occurrence of dissection of the aorta with a viable fetus (> 28 weeks of gestation) indicates emergency cesarean delivery; if, however, the fetus is not viable, the case should proceed to cardiac surgery and maintain the pregnancy;

Women with Ehlers-Danlos, Turner, or Loeys-Dietz syndrome, in addition to the high risk of dissection of the aorta, are exposed to complicated events, such as hypertension, diabetes, and other aneurysms, which, in conjunction, represent a significant increase in maternal death during pregnancy.

3.6.5. Chagas Disease

3.6.5.1. Prevalence

Global estimated prevalence of *T. cruzi* infection in pregnant women has varied from 1% to 40%, with approximately 1.8 million women of fertile age infected in Latin America.[259] In Brazil, the prevalence of infection in pregnant women is accepted to be 1.1%, with a vertical transmission rate of 1.7%.[259,260]

3.6.5.2. Diagnosis and Practice for Cases with T. cruzi Infection during Gestation

Serological evaluation for *T. cruzi* infection is recommended during prenatal care in pregnant women who reside in or come from endemic areas and in those who have received blood transfusions in these regions.[259,261] The most frequently used tests are based on higher sensitivity and specificity for detecting *T. cruzi* infection. They include enzyme-linked immunosorbent assay (ELISA); indirect hemagglutination (IHA), and indirect immunofluorescence (IF). Transmission may occur at any moment during pregnancy, but specific antiparasitic treatment for *T. cruzi* infection is contraindicated during gestation and breastfeeding, owing to teratogenicity in animals. Accidental exposure to benzonidazol does not indicate adverse effects in the newborn, and it is not a criterion for interrupting gestation.[259]

Elevated maternal parasitemia is associated with a greater risk of vertical transmission and miscarriage.[261] For this reason, during the acute phase of Chagas disease, pregnant women should be individually evaluated, and the decision to initiate antiparasitic treatment should be based on the risk-benefit ratio.

Evidence of *T. cruzi* infection does not justify indicating cesarean delivery, even though congenital *T. cruzi* infection may result in uterine growth restriction and prematurity.[259,261] It is worth emphasizing the importance of proceeding to recommended evaluations during prenatal care, including anti-HIV tests. Simultaneous infection with *T. cruzi* and HIV represents an increased risk of congenital transmission of *T. cruzi* owing to elevated parasitemia, which also implies higher perinatal morbimortality.[260,261] After delivery, women should be referred for clinical evaluation and specific treatment. Figure 7 shows indications for practice in Chagas disease during pregnancy.[259]

3.6.5.3. Chronic Chagas Heart Disease

Chagas heart disease, in its indeterminate form, does not present any additional risks to pregnancy, whereas forms with ventricular or arrhythmogenic dysfunction are associated with complications such as HF, thromboembolism, and complex arrhythmias. In these cases, pregnancy is considered high-risk, and it is advised against at times, depending on the degree of cardiac involvement, which may be established by echo with 24-Holter monitoring.

3.6.5.4. Vertical Transmission of Trypanosoma cruzi

Vertical transmission (from mother to child) of *T. cruzi* depends on the degree of parasitemia; transplacentally, it may occur at any stage (acute or chronic) of the disease, which requires treatment prior to gestation in infected women of fertile age. It is worth emphasizing that vertical transmission may recur during the reproductive period, and detection of vertical transmission in practice is complicated, given that most congenital cases are asymptomatic. Cases of congenital Chagas disease are considered acute, and it is compulsory to notify them within disease surveillance programs.[259,262,263]

During the acute phase of Chagas disease, there exists a possibility of transmission through breast milk, whereas, during the chronic phase, transmission occurs during lactation in cases of bleeding from fissures in the nipple rather than through milk itself.

3.6.5.5. Reactivation of Chagas Disease

During gestation, mechanisms and immunological alterations in the maternal organism may favor the reactivation of chronic Chagas disease in previously infected cases. Reactivation is defined by positivity on the following examinations, regardless of other signs and symptoms:

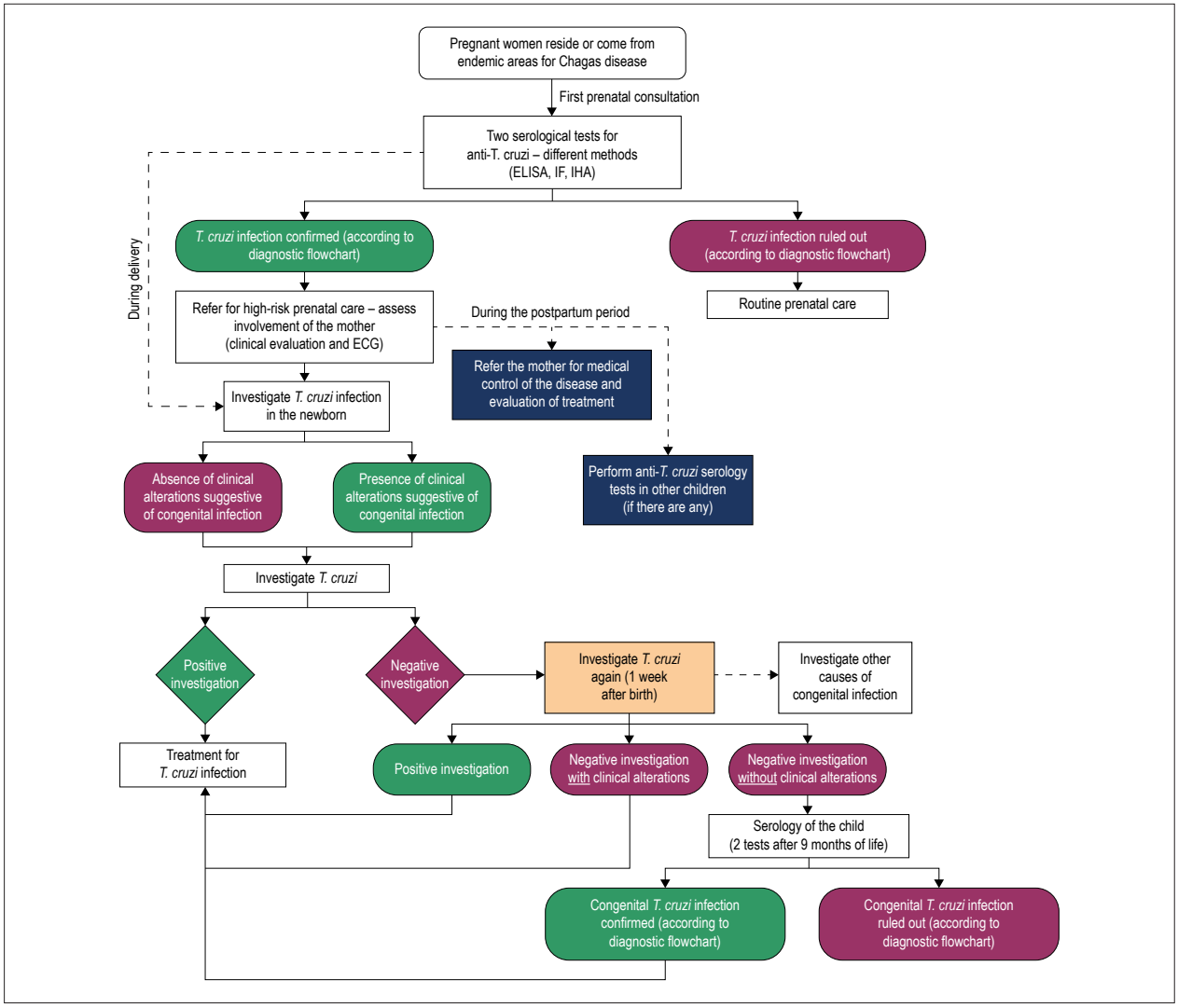

Figure 7 – *Flowchart for approaching Trypanosoma cruzi infection in the mother/child binomial. ELISA: Enzyme Linked Immunosorbent Assay; IF: indirect immunofluorescence; IHA indirect hemagglutination. Adapted from: Second Brazilian Consensus on Chagas Disease.*[259]

- Presence of the parasite in direct microscopic examination of blood or biological secretions, such as cerebrospinal fluid, pleura, pericardium, and ascitic fluid;
- Histopathological examination of tissue lesions (panniculitis, myocarditis, encephalitis, enteritis, colpitis) with parasite nests found in acute inflammatory infiltrates.

3.6.5.6. Breastfeeding

Suspending lactation is not recommended in women in the postpartum period with chronic Chagas disease, except in cases with breast fissure, in situations with elevated parasitemia, or in women in the acute phase of the disease.[259]

If a breastfeeding child is exposed to milk from an infected mother, either in the acute or chronic form, with nipple fissures, the child should be monitored for acquisition of *T. cruzi* infection during the exposure period. In some cases, it is possible to consider thermal treatment of breast milk before administration to the child.[259,262,263]

Lactation should be suspended in cases of *T. cruzi* and HIV coinfection, given that lactation, regardless of association with Chagas disease, is associated with a 7% to 22% additional risk of HIV transmission. Similarly, in cases of acute maternal HIV infection, natural breastfeeding increases the probability of vertical transmission of the virus to 29%. In Brazil, mothers have the right to receive infant milk formula until their children are at least 6 months old.[259,263]

3.6.5.7. Key Points

- Serological evaluation is recommended for all pregnant women who are positive for the disease;
- The risks to gestation depend on the clinical form of Chagas disease;
- Pregnancy may favor reactivation of the disease;
- Breastfeeding should not be advised against;
- Antiparasitic treatment is contraindicated during gestation and breastfeeding;
- Route of delivery is indicated by the obstetrician.

4. Hypertensive syndromes

4.1. Introduction

Hypertensive syndromes during gestation are considered to be a public health problem, with an expressive rate of maternal and fetal mortality, in both developed and developing countries. It is the most common medical complication, and it affects 5% to 10% of pregnancies worldwide.

Preeclampsia occurs in approximately 3% of all pregnancies in the United States, where it is responsible for 9% of maternal deaths.[264] Its incidence has shown a 25% increase over the past 2 decades. In recent years, an increase has been registered in the proportion of women with preeclampsia. In 2009, it was 2.2%; in 2013, it was 5.58%, and over the past 5 years, 22.5% suffered a severe general complication.[265]

Although research has evolved in the area of hypertensive syndromes during gestation, its etiology remains unknown. The methodological challenges to research related to preeclampsia are numerous; they include defining hypertension, level of severity, and physiopathology during pregnancy. These data probably interfere with research and outcomes, which justifies the following recommendations.

4.2. Recommendations for Measuring Arterial Pressure

- Blood pressure measurement devices in pregnant women must be accurate and validated for this special population. The cuff should be appropriately sized 1.5 times the circumference of the arm.
- Blood pressure should be measured with the patient sitting. The patient should rest for at least five minutes before measurement. Measurement may also take place in the left lateral decubitus position, while resting, and it should not differ from the measurement taken in the seated position;
- It is necessary to consider Korotkoff phase V to determine diastolic arterial pressure (DAP);[266]
- White coat hypertension and masked hypertension are considered to be relatively common presentations during pregnancy. They occur in at least 1/3 of pregnant women, to the extent that ABPM and home blood pressure monitoring (HBPM) are useful complementary examinations for making the clinical decisions which are fundamental to avoiding treatments which are unnecessary and potentially harmful to the fetus;[33,267]
- Pregnant women with SAP ≥ 140 mmHg and/or DAP ≥ 90 mmHg are considered hypertensive;
- Severity of hypertension during pregnancy is assessed based on the occurrence of target organ involvement, as well as arterial pressure level;[268]
- Severe hypertension is defined based on pressure levels ≥ 160/110 mmHg, which are associated with increased risk of stroke in pregnant women.[52,266,268]

4.3. Classification

The most widely used classification for hypertensive syndromes during gestation is the one adopted by the Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy,[269] which is also applied in the Brazilian Cardiology Society's Guidelines on Pregnancy in Women with Heart Disease (Figure 8).[270] In accordance with this classification, syndromes are classified in the following manner:

- Chronic, preexisting hypertension (due to any cause);
- Preeclampsia/eclampsia;
- Chronic hypertension with superimposed preeclampsia;
- Gestational hypertension.

Based on this position, classification into 4 categories will be maintained, emphasizing the importance of other presentations of arterial hypertension, such as the following:

- White coat hypertension;
- Masked hypertension;
- Transitory gestational hypertension occurs without the development of preeclampsia; arterial pressure normalizes within 12 weeks postpartum and it is resolved without treatment;[267,270]
- Postpartum hypertension generally arises between 2 weeks and 6 months after delivery. It is mild and labile, and it normalizes within the first year. It may be related to persistent gestational hypertension, preeclampsia, or chronic hypertension, or it may be secondary to other causes;[269]
- Unclassified prenatal hypertension is the term used when the first pressure measurement is recorded after week 20, and it is not clear if it is chronic or preexisting; diagnosis is only established during postpartum reevaluation between weeks 6 and 12.[52]

4.3.1. Chronic, Preexisting (Essential or Secondary) Hypertension

This occurs when arterial pressure is ≥ 140/90 mmHg (preexisting hypertension; in general, essential hypertension or hypertension diagnosed before week 20 of pregnancy). It is commonly diagnosed around the first trimester or right at the beginning of the second. It is associated with adverse maternal and fetal outcomes; there should, therefore, be more rigorous control of maternal arterial pressure (110 to 140/85 mmHg), monitoring fetal growth and repeatedly evaluating the development of preeclampsia and maternal complications.[267]

Hypertension may not be diagnosed in many women whose first prenatal consultations occur during the second trimester. Pregnant women may be considered normotensive during the initial phase of gestation, due to the physiological decrease in arterial pressure during the first trimester of pregnancy, in the same manner that an increase in arterial pressure may be diagnosed as gestational hypertension, because pressure levels were not verified before week 20 of gestation. Chronic hypertension usually persists until 42 days postpartum.[268]

Diagnosis of chronic hypertension can only be made correctly once arterial pressure has been reevaluated after 6 to 12 weeks postpartum.[271]

4.3.2. Preeclampsia/Eclampsia

This is a complex hypertensive syndrome, and it may deteriorate rapidly and without warning; classifying it as "mild"

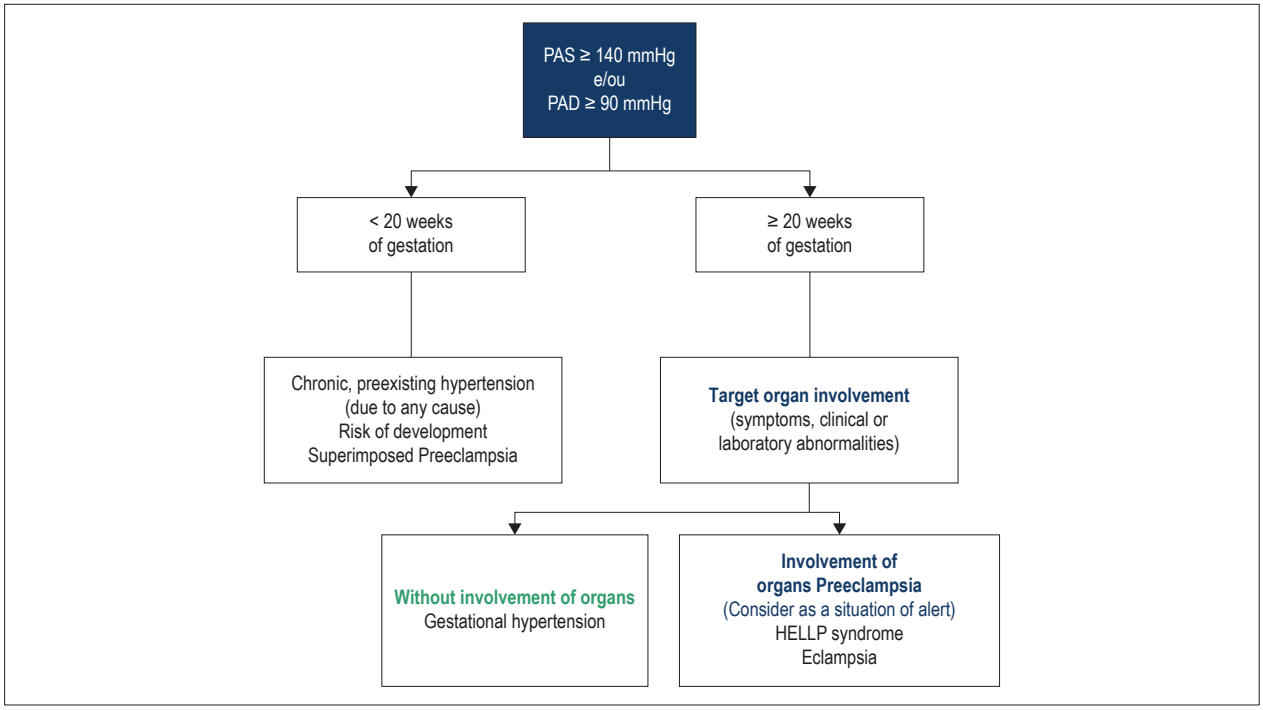

Figure 8 – *Classification of hypertensive syndromes. HELLP: hemolysis, elevated liver enzymes, and low platelet count; DAP: diastolic arterial pressure; SAP: systolic arterial pressure.*

or "severe" is not recommended. Diagnosis occurs with the appearance of hypertension, with onset from week 20 of gestation, with one or more of the following related conditions:

- Proteinuria (> 0.3 g/24 h) and/or maternal organic dysfunctions, such as evidence of maternal acute renal lesions (creatinine ≥ 1 mg/dL);
- Hepatic dysfunction (elevated hepatic transaminases, > 40 IU/L);
- With or without abdominal pain (upper quadrant or epigastric);
- Neurological complications (including eclampsia, altered mental state, blindness, stroke, clonus, intense headaches, persistent visual scotoma);
- Hemolysis or thrombocytopenia and/or uteroplacental dysfunction (restricted fetal growth, abnormal analysis of umbilical artery Doppler waveform or stillbirth).

The existence of proteinuria is not mandatory for diagnosis, and it may occur for the first time during the intrapartum period. In this manner, it is ideal to identify pregnant women with a risk of developing preeclampsia. Recommendations for screening, such as investigating proteinuria to this end, are fallible; the only consensual routine is to measure arterial pressure regularly during prenatal consultations.[272,273]

4.3.2.1 HELLP Syndrome (Hemolysis, Elevated Liver Enzymes, and Low Platelet Count)

This is a severe manifestation of preeclampsia, and it should not be considered as a separate entity.

4.3.3. Chronic (Preexisting) Hypertension with Superimposed Preeclampsia

This occurs in 25% of pregnant women with chronic hypertension. It is diagnosed when a pregnant woman with chronic essential hypertension develops maternal organic dysfunctions compatible with preeclampsia. As a routine increase in arterial pressure may occur after week 20 of gestation, elevations in arterial pressure alone do not qualify for diagnosis of superimposed preeclampsia, in the same manner that restricted fetal growth may be part of the clinical picture of chronic hypertension.

In cases of kidney disease with underlying proteinuria, an increase in proteinuria is also not a diagnostic parameter for superimposed preeclampsia; if, however, there is no preexisting proteinuria, its appearance within the context of elevated arterial pressure is sufficient for diagnosis.

4.3.4. Gestational Hypertension

Gestational hypertension is a recent hypertension that arises after week 20 of gestation, in the absence of proteinuria, without any biochemical or hematological abnormalities. It is generally not accompanied by IUGR, and outcomes are frequently positive; however, approximately one quarter of women with gestational hypertension (especially those who present before week 34) evolve to preeclampsia and present unfavorable outcomes. In general, it resolves itself within 6 weeks postpartum.[52]

4.3.4.1. Key Points

- Consider hypertensive pregnant women, when SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg;

- Define as severe hypertension when blood pressure levels ≥ 160 x ≥ 110 mmHg. These levels are associated with increased risk of stroke in pregnant women;
- Pre-existing Chronic Hypertension (Essential or Secondary) should have tighter control of maternal blood pressure (BP = 110 - 140/85 mmHg), monitoring fetal growth and repeatedly evaluating the development of preeclampsia and maternal complications;
- Preeclampsia/Eclampsia – complex hypertensive syndrome, may deteriorate rapidly and without warning. Not recommend classifying it as "mild" or "severe";
- Proteinuria is not mandatory for diagnosis and may occur for the first time during the intrapartum period or early postpartum.

4.4. Treatment of Gestational Hypertension Syndrome

4.4.1. Non-pharmacological Treatment[269]

Considering pregnant women with SAP ≥ 140 mmHg or DAP ≥ 90 mmHg hypertensive, the following recommendations are applied:

- Routinely, there is no indication for rest in pregnant women with gestational hypertension syndrome (GHS);[274]
- Physical exercise is recommended for at least 3 days per week, with an average of 50 min per session, including aerobic, strength, and flexibility training;
- Physical activity with moderate exercise may be continued in women who are already accustomed to practice;[112]
- Diet should be healthy, rich in nutrients, proteins, fibers, and cereals;
- Calcium supplementation, between 1.5 and 2.0 g daily, is necessary, especially in areas with low dietary calcium ingestion;
- Weight gain in pregnant women is based on pre-gestational body mass index (BMI):[131]
  - BMI of 25 kg/m² (normal): weight gain from 11.2 to 15.9 kg;
  - BMI of 25 to 29.9 kg/m² (overweight): weight gain from 6.8 to 11.2 kg;
  - BMI ≥ 30 kg/m² (obese): weight gain of 6.8 kg.

The following are not recommended:

- Any type of low-calorie diet, even in obese women, because low-calorie diets may lead to fetal growth retardation;
- Salt restriction during gestation with the intention of preventing GHS or low sodium (less than 100 mEq daily) diets in pregnant women with chronic arterial hypertension;
- Use of dietary supplements (magnesium; vitamins C, E, and D; fish or algae oil; or garlic) with the goal of preventing GHS.

4.4.2. When to Treat – Target Arterial Pressure

In international consensuses, there are points of divergence regarding the beginning of pharmacological treatment for GHS.[131,275-279] This notwithstanding, the prevailing recommendation is to begin oral anti-hypertensive drugs in GHS when SAP is 140 to 155 mmHg and DAP is 90 to 105 mmHg, measured during a consultation, or when arterial pressure is ≥ 135/85 mmHg at home. Specifically, in cases of chronic hypertension, gestational hypertension, or preeclampsia, anti-hypertensive therapy is recommended if SAP is ≥ 140 mmHg or DAP ≥ 90 mmHg.[273,280]

Treatment with anti-hypertensive drugs should maintain arterial pressure at 110 to 140/80 to 85 mmHg, and treatment should be reduced or ceased if DAP is ≤ 80 mmHg. An abrupt drop in maternal arterial pressure, by more than 25% of the initial value, increases the risk of hypoperfusion in maternal target organs and low blood flow to the fetus.

The primary objective of treating hypertension in GHS is to prevent stroke, progression of preexisting kidney disease, or other lesions in target organs, while preserving uteroplacental circulation. Pressure levels should be correlated to the gestational period in course, observing the physiological changes that occur with each gestational trimester,[281] such as the increased glomerular filtration rate, which interferes in bioavailability of drugs during gestation.[61,282]

In women with chronic hypertension, to date, there is not enough evidence to demonstrate that, by reaching or maintaining a specific (ideal) arterial pressure level or by using a specific anti-hypertensive drug, it is possible to decrease the risk of developing superimposed preeclampsia.[279-282]

The latest systematic review by Cochrane[283] concluded that data are insufficient to determine the benefits of anti-hypertensive medications for mild to moderate hypertension (SAP from 140 to 169 mmHg and DAP from 90 to 109 mmHg) during gestation; more research is, therefore, necessary. Treatment with anti-hypertensive drugs, however, decreases the risk of severe arterial hypertension, but not of preeclampsia, IUGR, premature placental detachment, or adverse neonatal outcomes.

The international multicenter randomized clinical trial Control of Hypertension in Pregnancy Study (CHIPS) with pregnant women who were non proteinuric and whose hypertension was "non severe" (arterial pressure = 140 to 159/90 to 109 mmHg), demonstrated that "less tight" pressure control, with DAP target of 100 mmHg *versus* "tight" control with DAP target of 85 mmHg showed a correlation with a higher incidence of severe hypertension (arterial pressure ≥ 160/110 mmHg), with preeclampsia, fetal loss, low birth weight, prematurity, and hospitalization in neonatal ICU.[284,285]

4.4.3. Oral Anti-hypertensive Drugs- Chronic Hypertension /Gestational Hypertension

All anti-hypertensive medications cross the placental barrier; for this reasons, the use of pharmacological therapy during pregnancy requires risk-benefit analysis with individualized treatment.[278,282]

In Brazil, the available oral medications that are usually used are methyldopa, beta-blockers (except atenolol), hydralazine, and CCB (nifedipine, amlodipine, and verapamil).[275] Initial anti-hypertensive therapy to pregnant women with gestational hypertension or chronic

hypertension should be with monotherapy, with first-line drugs,[67-276] such as methyldopa, CCB, long-acting oral nifedipine, and beta-blockers (except atenolol).

If ideal blood pressure levels are not achieved, the association with second-line oral medications: clonidine, hydralazine and thiazide diuretics should be considered.[271,274] The potential of diuretics to cause depletion of intravascular volume and therefore compromise placental uterine circulation, IUGR or oligohydramnios, is not supported in more recent randomized studies and in a systematic review of diuretics for the prevention of preeclampsia.[71,286-287]

1st line drugs should be considered:

- **Sympathetic nervous system inhibitors (centrally acting alpha-2-adrenergic receptor agonist):** decrease blood pressure by reducing peripheral vascular resistance. They can change the heart rate and output. A-Methyldopa is the best studied antihypertensive drug in pregnancy.[67,68] However, methyldopa has only a mild antihypertensive effect, with a slow onset of action (3 to 6 h) and with an average duration of 6 hours. to 8 hours. The most common dose-dependent maternal side effects are drowsiness and dry mouth. Dose independent agents include elevated liver enzymes in up to 5% of women and autoimmune hemolytic anemia.[68] The recommended starting dose is 250 mg, 2 or 3 times a day (maximum dose 3 g/day);
- **Calcium channel blockers (BCC):** oral nifedipine does not appear to be teratogenic.[64-66,81-83,288,289] Clinical trials demonstrate that blood flow in the umbilical artery is not affected. Maternal side effects with the use of BCC include tachycardia, palpitations, peripheral edema, headaches and facial flushing. Experience with nifedipine has been favorable.[276] Although not specifically licensed for pregnancy, it is recommended and its use together with labetalol and methyldopa. The maximum daily dose of nifedipine is 120 mg, divided into three or four doses or 30-60 mg once daily (prolonged release).[270-273] Administration by sublingual route is contraindicated because it determines an unpredictable hypotensive response, excessive autonomic activation and acute myocardial ischemia;
- The exposure to amlodipine in early pregnancy does not appear to be associated with an increased rate of fetal malformations compared to other antihypertensive agents[290,291] and the antihypertensive effect is slow (± 8 hours);
- **Beta-blockers:** none of the beta-blockers have been associated with teratogenicity[76-79] IUGR and low placental weight have been associated with the use of atenolol.[79,80,271] The exposure to any beta-blocker is associated with the risk of bradycardia and neonatal hypoglycemia, which can cause sedation, sleep disorders and depression in pregnant women. In the case of propranolol, there are reports of IUGR, bradycardia and neonatal hypoglycemia, especially with high doses (160 mg/day).[81] Labetalol is not marketed in Brazil.

Drugs of second line are:

- The following are second-line drugs:
  - Clonidine shows an exaggerated increase in arterial pressure (rebound effect) when treatment is discontinued abruptly. It has a greater hypotensive effect than methyldopa;
  - Hydralazine is predominantly used intravenously for treatment of severe hypertension in preeclampsia;
  - Diuretics: the use of diuretic therapy during pregnancy continues to be controversial, mainly due to theoretical concerns regarding reduced maternal plasma volume. Thiazide diuretics may be continued in pregnant women with chronic SAH, provided that they do not promote volume depletion. Chlorothiazide may increase the risk of congenital anomalies and neonatal complications.[276,286]

The following oral anti-hypertensive are contraindicated during gestation:[290]

- ACEI and ARB, which are associated with fetal acute kidney injury and oligohydramnios and which should be suspended before conception;[291]
- Atenolol (beta-blocker), which leads to IUGR and low placental weight;[292,293]
- Spironolactone, which has an antiandrogenic effect during fetal development;[287]
- Chlorothiazide, which may increase the risk of congenital anomalies and neonatal complications.

4.4.4 Anti-hypertensive Drugs for Severe Hypertension in Preeclampsia[275,276,278,279,298-300]

The maternal and fetal prognosis in severe hypertension is correlated **to i**nitial care provided to these pregnant women.[292] Severe hypertension in preeclampsia is when systolic arterial pressure ≥ 160 or diastolic arterial pressure ≥ 110 mmHg; or both during pregnancy, intrapartum or postpartum period.[277] It is an obstetric emergency, and it requires immediate anti-hypertensive treatment. The goal is not to normalize blood pressure, but to reach levels of 140-150 / 90-100 mmHg[277] or to reduce 15% to 25% of BP.[275]

Severe preclampsia grave is associated with reversible encephalopathy syndrome (PRES) characterized by headache, visual symptoms, impaired consciousness, epileptic crises, and, occasionally, focal neurological defects.[301]

Pregnant women with severe preeclampsia should be attended or transferred to tertiary healthcare centers. Prior to inter-hospital transfer, blood pressure (BP) must be stabilized and other measures initiated, such as magnesium sulfate for eclampsia prophylaxis.[293] It is recommended that magnesium sulfate should be used for the prevention and treatment of seizures in women with gestational hypertension and pre-eclampsia with severe characteristics or imminence of eclampsia. Maternal stabilization should occur before delivery, even in urgent circumstances.

Admission to the ICU should be considered, in accordance with the following criteria: pregnant women with severe preeclampsia (SAP ≥ 160 mmHg and DAP ≥ 110 mmHg), respiratory insufficiency requiring mechanical ventilatory assistance, eclampsia, HELLP syndrome, oliguria, acute pulmonary edema, and neurological complications, such as stroke or PRES.[294]

Endotracheal intubation is another risk in hypertensive emergencies. Induction of general anesthesia and intubation should never be performed without first taking measures to eliminate or minimize the hypertensive response to intubation. Maternal-fetal monitoring must be strict by the medical and nursing staff during treatment. After initial stabilization, the team should monitor BP closely and institute maintenance therapy as needed.

The American College of Obstetricians and Gynecologists[268,269,280] makes the following recommendations and conclusions:

- Treatment with first-line agents should be immediate or occur as soon as possible within 30 to 60 minutes after confirmed severe hypertension (blood pressure greater than 160/110 mmHg and persistent for 15 minutes) to reduce the risk of maternal stroke . The patient must be positioned in a sitting or semi-reclining position, with the back supported, they must not be repositioned to be reclined or to stand on their side to obtain low blood pressure, as it will provide a false reading of the pressure measurement;[292]
- Maternal and fetal monitoring by a doctor and nursing staff is recommended during the treatment of severe acute onset hypertension;
- After initial stabilization, the team should monitor blood pressure closely and institute maintenance therapy as needed;
- Intravenous labetalol and hydralazine (IV) are considered first-line drugs for the treatment of severe acute onset hypertension in pregnant women and women in the postpartum period;
- Immediate-release oral nifedipine can also be considered as first-line therapy, especially when IV access is not available;
- The use of labetalol IV, hydralazine IV or oral nifedipine of immediate release for the treatment of severe acute onset hypertension in pregnant or postpartum patients does not require cardiac monitoring;
- In the rare circumstances in which immediate release oral labetalol, hydralazine or nifedipine boluses fail to relieve acute onset, severe hypertension and are administered in appropriate successive doses, emergent consultation with an anesthetist, subspecialist in maternal-fetal medicine or subspecialist in intensive care to discuss second-line intervention is recommended;
- Magnesium sulfate is not recommended as an antihypertensive agent, but magnesium sulfate remains the drug of choice for the prophylaxis of seizures in women with severe acute onset hypertension during pregnancy and the postpartum period. The onset of magnesium should not be delayed in the setting of acute severe hypertension; it is recommended regardless of whether the patient has severe gestational hypertension, pre-eclampsia with severe features or eclampsia.

4.5. Practice for Hypertensive Emergency in Preeclampsia (PA ≥ 160/110 mmHg)

In the hypertensive emergency, the most effective drugs are nifedipine, hydralazine and labetalol. There may be subtle differences in your security profiles. The evidence is inadequate for other drugs. Medicines for intravenous use are hydralazine and intravenous labetalol (not available in Brazil). Oral nifedipine is now accepted as first-rate. A recent systematic review by Cochrane found no significant differences between these three drugs in the treatment of hypertensive crisis in terms of efficacy or safety between hydralazine and labetalol or between hydralazine and BCC.[277,295-297]

- **Nifedipine:** initial dose of 10-20 mg orally. The onset time of action of oral nifedipine is 5-10 minutes. The dose should be repeated in 20 minutes, if necessary (if blood pressure is> 155/105 mmHg). Maintaining 10-20 mg every 2-6 hours with the maximum daily dose is 120 mg. Repeat medication if blood pressure is> 155/105 mmHg and administer a maximum of three doses. After 20 min of the third dose and the persistence of arterial hypertension, administer a drug of second choice. It should be noted that the tablets should not be chewed and the formulations should not be used sublingually;
- **Hydralazine:** Initial dose of 5 mg intravenously (maximum dose of 45 mg) in bolus, slowly, over 1 to 2 min, repeat, if necessary, 5 mg every 20 minutes (note: The hydralazine ampoule contains 1 ml, in concentration of 20 mg / ml, dilute an ampoule (1 ml) in 19 ml of distilled water, thus obtaining a concentration of 1 mg / ml). The action starts within 10 to 30 minutes and lasts 2 to 4 hours. Parenteral hydralazine may increase the risk of maternal hypotension (systolic BP, 90 mmHg or less);[271]
- In the rare circumstances in which the bolus of labetalol (not available in Brazil), hydralazine or oral nifedipine (retard) administered in appropriate and successive doses does not control blood pressure levels, it is recommended to discuss intervention with drugs considered to be second line;[267]
- **Nitroglycerin** is considered a medication of choice for preeclampsia associated with acute pulmonary edema (intravenous infusion of 5 mg/min, gradually increasing every 3 to 5 min to a maximum dose of 100 mg/min);
- **Sodium nitroprusside** should be considered as a preferential option for controlling arterial pressure in exceptional situations, such as refractory hypertension of severe hypertension with risk of death. Prolonged treatment with sodium nitroprusside is associated with fetal risk sodium nitroprusside is associated with the fetal risk of intoxication by cyanide, a metabolic product of sodium nitroprusside;for this reason, it should be initiated at 0.25 μg/kg/min up to a maximum of 4 μg/kg/min, for no longer than 4 hours of continuous infusion.[275]

4.6. Prophylaxis of Seizure in Preeclampsia - Eclampsia and Magnesium Sulfate Therapy[293,275, 299-303]

Since the publication of the results of results of The Collaborative Eclâmpsia Trial – Maggie Trial,[302] o magnesium sulfate ($MgSO_4$) is the drug of choice when eclampsia is imminent, and it is the only drug that is effective against seizures in preeclampsia.[299] Randomized clinical trials have demonstrated that it is superior to hydantoin, diazepam, and placebo for preventing eclampsia and recurrence of seizuresn, in addition its low cost, easy to administer and does not cause sedation.[300-303] Therefore, the use of magnesium sulfate is highly recommended for cases of imminent eclampsia, HELLP syndrome (15% of these patients develop eclampsia) and pre -eclampsia with clinical and/or laboratory deterioration, including difficult-to-control hypertension.[303]

The initial dose, properly administered, does not pose a risk of intoxication. However, it is recommended to monitor the patellar reflex, respiratory rate and diuresis. If there is no patellar reflex, respiratory depression (respiratory rate < 16 rpm) and diuresis below 25 ml/h, it is recommended to stoped MgSO4 intravenous and measure serum levels.

The therapeutic concentration of the magnesium ion varies from 4 to 7 mEq/L (4.8 to 8.4 mg/dl). The patellar reflex is abolished with 8 to 10 mEq/L, the risk of respiratory arrest starting at 12 mEq/L and cardiac arrest of 25 mEq/L. Calcium gluconate (1 g intravenously – 10 ml at 10% – administered slowly) should be used in cases of signs of magnesium intoxication. In respiratory arrest, in addition to calcium gluconate, endotracheal intubation and mechanical ventilation should be performed. In patients with renal impairment (creatinine ≥ 1.2 mg/dl), the maintenance dose should be half the recommended dose. Magnesium sulfate infusion should be stopped only if diuresis is less than 25 ml. In view of values within normal limits, treatment should be maintained or restarted.[304]

The prevention of convulsive crises in preeclampsia is guided by the following recommendations:

- **Loading dose:** (MgSO4 50% – ampoule with 10ml – contains 5 g de magnésio) – 4 to 6 g of $MgSO_4$, intravenous, in a single dose (dilute 8 to 12 ml of 50% solution in 100 ml of 5% glucose solution and administer, with an infusion pump, for 30 minutes);
- **Maintenance dose:** 1 to 2 g per hour, intravenous (dilute 10 ml of MgSO4 50% (1 ampoule) in 490 ml of 0,9% of saline solution. The final concentration will be 1 g/100 ml. Infuse the solution intravenously at a rate of 100 ml per hour in a continuous infusion pump.

It is necessary to maintain the MgSO4 for 24 hours after delivery or the last seizure. In cases of recurrence of the seizure, an additional 2 g of magnesium sulfate is administered intravenously (bolus) and the dose of 2 g/h is used as maintenance. If two of these boluses do not control seizures, the drug of choice will be diphenylhydantoin in its classic regimen for treating seizures. In these cases, the investigation of brain complications, especially intracranial hemorrhages, is recommended.

After the first 24 hours of observation and evaluation, it is necessary to decide on conservative conduct or termination of pregnancy. Childbirth is the only intervention that leads to the resolution of pre-eclampsia and eclampsia. It is recommended that the expectant conduct is only until 37 weeks of gestation. After this gestational date or if the diagnosis of pre-eclampsia is performed at term, the resolution of the pregnancy should be indicated, thus reducing maternal risks, without altering the perinatal results.

4.6.1 Key Points

- In women with gestational hypertension, pre-existing hypertension overlapping with gestational hypertension or with damage or symptoms of hypertension and subclinical organs, initiation of drug treatment is recommended when SBP ≥ 140 mmHg or DBP ≥ 90 mmHg;
- A goal treatment for blood pressure in SHG should be 140/80 to 85 mmHg. DBP to ≤ 80 mmHg, antihypertensive drugs should be reduced or discontinued;
- Methyldopa, beta-blockers (except atenolol) and calcium channel blockers are recommended as the drugs of choice for the treatment of hypertension in pregnancy;
- ACE inhibitors, ARBs or direct renin inhibitors are not recommended during pregnancy;
- Diuretic therapy is usually avoided because plasma volume is reduced in women who develop preeclampsia;
- Considers SBP ≥ 170 mmHg or DBP ≥ 110 mmHg to be an emergency in a pregnant woman who should be admitted to hospital immediately for treatment; The consensus is to reduce BP to < 160/105 mmHg to avoid acute hypertensive complications in the mother; fetal heart rate monitoring;
- Magnesium sulphate should be used to prevent and treat seizures in women with gestational hypertension and preeclampsia with severe or imminent eclampsia;
- In a hypertensive emergency, the most effective drugs are nifedipine, hydralazine and labetalol (not available in Brazil);
- In preeclampsia associated with pulmonary edema, nitroglycerin administered as i.v. infusion is recommended;
- The delivery is a single intervention that leads to resolution of preeclampsia and eclampsia.

4.7. Prognosis and Prevention of Preeclampsia

Clinical prediction models based on risk factors have low sensitivity, and they generally do not include a large number of pregnant women who might develop preeclampsia during the course of gestation. The following biochemical markers stand out: placental growth factor (PlGF), which is proangiogenic and, when its levels are low between weeks 11 and 13, and soluble FMS-like tyrosine kinase 1 (sFlt-1), which is antiangiogenic and which, when its levels are high, may predict preeclampsia. As neither of them have sufficient sensitivity, the relationship between both factors (sFlt-1/PlGF) is currently being studied, with more promising results. There is, at the moment, however, no predictive laboratory test available in clinical practice.[304]

It is also possible to utilize Doppler ultrasound as an auxiliary tool. By evaluating pulsatility and resistance in uterine arteries, it may classify pregnant women by risk of developing

preeclampsia. Doppler ultrasound should be performed between weeks 20 and 22, although there is a good correlation between late preeclampsia (> 34 weeks) and IUGR. In contrast, Doppler ultrasound performed at the end of the first trimester has lower accuracy; nonetheless, in conjunction with clinical history and comorbidities, it may be useful for identifying pregnant women with higher risks and selecting those who will require prophylaxis for preeclampsia.[305]

Diverse substances have been tested to reduce the incidence of preeclampsia. Studies on diet, weight loss, physical activity, vitamins, antioxidants, nitrates, dipyridamole, heparins (LMWH and UFH), and antiplatelet agents have been conducted; of these, only calcium replacement and acetylsalicylic acid (ASA) have shown some benefit.

Calcium replacement (1.5 to 2.0 g daily) reduces the risk of preeclampsia effectively only in the subpopulation with calcium ingestion below 600 mg daily.[306]

Studies have shown the benefits of ASA in low doses (between 75 and 150 mg) for preeclampsia prevention,[307] and it has recently been included in the recommendations of important international guidelines.[278,308,269] Study[309] with 1,776 patients, using 150-mg doses of ASA *versus* placebo, starting between weeks 11 and 14, demonstrated that the total of preeclampsia events was significantly reduced in the ASA group compared to placebo group, reinforcing the protective effect of ASA in pregnant women with high risks.

The precise indication of ASA is for patients classified as high-risk for preeclampsia (Table 27), and it should be initiated between weeks 12 and 16.

4.7.1. Key Points

- Predicting preeclampsia in low-risk patients is difficult and depends on joint assessment of clinical history and Doppler US;
- Calcium replacement in patients with low intake reduces the risk of preeclampsia;
- The use of low dose AAS in moderate to high risk pregnant women reduces the risk of preeclampsia and should ideally be started between 12 and 16 weeks.

4.8. Arterial Hypertension during the Postpartum Period

Arterial hypertension during the postpartum period has been little studied, because there is still a belief that once the placenta has been removed the problem is solved. To a certain extent, placental delivery marks the moment when the stimulation of the production of inflammatory and vasoconstrictive substances ceases, leading to a gradual return in arterial pressure to pre-gestation levels; nevertheless, some of these inflammatory and vasoconstrictive alterations may remain in the maternal organism for a few days.

4.8.1. Recommendations

Hypertension normally improves within the first week (5 to 7 days); however, during this period, there continues to be a risk of related complications, especially in patients with preeclampsia, in addition to the possibility of preeclampsia itself manifesting only during the postpartum period. There is also a risk of eclampsia during this period, and 32% to 44% of convulsions may occur during the postpartum period.

Hypertension during the postpartum period may be aggravated or prolonged by situations such as volume overload (hydration) and use of pain medication, such as non-steroidal anti-inflammatory drugs (vasoconstriction and sodium retention), in addition to cases of stroke with reactive vasoconstriction and in patients with previously undiagnosed chronic hypertension.

In postpartum women with preeclampsia, a new elevation in arterial pressure may occur between 3 and 6 days postpartum, probably due to reabsorption of accumulated edema in the third space, which is a rather common syndrome of preeclampsia.[310]

The treatment objective is to decrease the risk of target organ injury due to hypertensive emergency (acute pulmonary edema, stroke, dissection of the aorta, acute kidney disease). Thus, postpartum women with mild to moderate hypertension (SAP < 160 mmHg and/or DAP < 110 mmHg), who are asymptomatic, may receive follow up without anti-hypertensive medication.

Table 27 – Recommendations for acetylsalicylic acid use in preeclampsia prophylaxis

Risk level	Risk factor	Recommendation
High	Preeclampsia with adverse fetal outcomes Multifetal gestation Chronic SAH Diabetes mellitus type 1 or 2 Kidney disease Autoimmune disease (lupus/APAS)	A low dose of ASA is recommended if the patient meets one or more of these criteria
Moderate	Nulliparity Obesity (BMI ≥ 30) Family history of preeclampsia (mother or sister) Age ≥ 35 years Poor previous obstetric history (SGA, prematurity, low birth weight, an interval of more than 10 years between gestations)	Consider using a low dose of ASA if the patient has more than one risk factor

APAS: antiphospholipid antibody syndrome; ASA: acetylsalicylic acid; BMI: body mass index; SAH: systemic arterial hypertension; SGA: small for gestational age.

Women may receive any anti-hypertensive medication during the postpartum period. The factor that limits use is breastfeeding; thus, preference should be given to anti-hypertensive medications which pass through breast milk in lower quantities.

In 2013, a review from the Cochrane Library[311] suggested that the use of furosemide might assist in more effective control and shorten hospitalization time in patients with preeclampsia. The review recommends that each service use its routine medication without giving preference to any class of anti-hypertensive drug. Diuretics should become part of the anti-hypertensive regime after the second day, when the reabsorption of peripheral edema begins. The consultation site https://toxnet.nlm.nih.gov, reviews publications and updates recommendations for use of medication while breastfeeding.[312]

The ACEI captopril and enalapril, which are contraindicated during gestation, are permitted during breastfeeding, as they pass through breast milk in very small quantities. Regarding ARB group II, there is not a sufficient number of studies for liberating the use of this class of medication. The most utilized CCB is nifedipine, which also passes through breast milk in small quantities. Amlodipine and other CCB, such as ARB, lack studies to liberate them without restrictions. Beta-blockers should be individualized on a case-by-base basis. Propranolol and metoprolol are compatible with breastfeeding, whereas atenolol should be avoided.

Diuretic drugs, such as hydrochlorothiazide and furosemide, may deplete intravascular space and decrease milk production; for this reason, they should be used in low doses. Spironolactone may be administered without restriction, and it may be used in patients with resistant hypertension (primary hyperaldosteronism).

Treatment of hypertensive peaks in postpartum women may be done conventionally. A study comparing captopril and clonidine for controlling hypertension (SAP ≥ 180 mmHg and DAP ≥ 110 mmHg) verified that there was no significant difference between the substances, only a tendency for clonidine to be better during the third day of the postpartum period. Both were considered effective and safe for treating postpartum women with hypertensive emergencies.[313]

We recommend hospital discharge after at least 24 hours in cases of SAP < 160 mmHg and DAP < 110 mmHg. After that they should receive close outpatient follow up, with brief reevaluation 1 to 2 weeks after discharge.[314]

4.8.2. Key Points

- Hypertension usually improves in the first five to seven days, but after this period there is still a risk of complications, including preeclampsia/eclampsia;
- Priority should be given to medications low-releasing for breastfeeding;
- Outpatient follow-up is important as most of these patients leave the hospital still on medication.

4.9. Hypertension During Gestation and Future Cardiovascular Risk

Preeclampsia is an established risk factor for coronary artery disease, chronic hypertension, peripheral vascular disease, and stroke. Possible mechanisms behind the increase in cardiovascular disease include endothelial, vascular, and metabolic dysfunctions found during preeclampsia, which have a common link to other traditional risk factors, such as dyslipidemia, obesity, diabetes mellitus, and kidney disease.

The CHAMPS Study,[315] conducted retrospectively with more than one million women with cardiovascular disease after their first gestation, showed an increase in the risk of myocardial revascularization and hospitalization due to cardiovascular disease, stroke, and peripheral arterial vascular disease; this risk was 2 times higher in patients who had had preeclampsia, gestational hypertension, placental rupture, or infarction.

Another large review[316] including more than 3 million women and nearly 200,000 pregnant women showed increased relative risks of 3.7 for chronic SAH, 2.16 for ischemic heart disease and 1.81 for stroke after 10.4 years, in women whose had preeclampsia.

In this manner, hypertension during gestation should be seen as a sex-related marker of future cardiovascular risk. Furthermore, although it is not one of the main factors used for calculating cardiovascular risk, it is necessary, as part of clinical routine, to include precautions when counseling women after delivery and to intensify control of other modifiable factors with the aim of decreasing their cardiovascular risks.[317]

4.9.1. Key Points

- Preeclampsia is a risk factor for coronary artery disease, chronic hypertension, peripheral vascular disease and stroke;
- Patients who have high blood pressure during pregnancy should intensify control of other modifiable factors to reduce future cardiovascular risk.

5. Treatment and Prevention of Cardiac Complications

5.1. Cardiac Arrhythmias

5.1.1. Epidemiology

Arrhythmias are very frequent complications during pregnancy, whether or not they are associated with structural or electrical heart disease. The first manifestation may occur during gestation, or an aggravation of preexisting arrhythmias may occur.[318]

The occurrence of arrhythmias during gestation requires investigation with special attention to definition or exclusion of structural or electric cardiac injury; this practice is fundamental to determining treatment and prognosis for the patient.[52,318]

A study in hospitalized pregnant women has shown that: 60% of arrhythmias correspond to sinus bradycardia or tachycardia; 19% to supraventricular or ventricular extrasystoles; 14% to supraventricular tachycardia (SVT); 5% to VT or VF; and 2% to other disorders.[319]

AF and paroxysmal supraventricular tachycardia (PSVT) are the most frequently diagnosed sustained SVT during gestation; bradyarrhythmias, conduction disorders, other atrial tachycardias, VT, and VF are relatively rare.[320]

The accepted risks of antiarrhythmic drugs affecting organogenesis and fetal development should be considered during pregnancy, given that most diagnosed arrhythmias do not require specific treatment. Nevertheless, recurring or persistent arrhythmias that cause important symptoms or hemodynamic repercussion should be treated in the same manner they would be for non-pregnant women.[321]

The risks inherent to ionizing radiation used to perform catheter ablation may by minimized with electromechanical mapping and, in some cases of device implantation (pacemaker, ICD, and resynchronizer), with the use of 2-dimensional echo.[322]

5.1.2. Clinical Presentation

Palpitations occur frequently during pregnancy. They may be related to arrhythmias, or they may be consequent to hemodynamic alterations during gestation. Diagnostic evaluation of palpitations in pregnant women does not differ from diagnosis in non-pregnant women, and it has been demonstrated that palpitations are associated with the presence of arrhythmias in only 10% of cases.[323]

Symptomatic sinus bradycardia is rare, and it is generally associated with gestational supine hypotensive syndrome, which is treated by placing pregnant patients in left lateral decubitus. Syncope linked to atrioventricular blocks is, similarly, infrequent, and congenital complete atrioventricular block, especially supra-hisian, with narrow QRS, presents favorable evolution during gestation. Sudden Cardiac Death (SCD), which is rare during gestation, presents a greater risk of occurring in women with VT associated with structural heart disease, and, during gestation and the postpartum period, in women with channelopathies (especially women with long-QT syndrome).[319,320]

5.1.3. Maternal-fetal Risks

Sustained cardiac rhythm disorders may lead to maternal hemodynamic impairment, the risk of thromboembolism, and SCD. They may also compromise fetal development, leading to low birth weight, premature delivery, fetal abnormalities, and other indications for cesarean delivery. For this reason, these disorders should be diagnosed and adequately treated.

The modified WHO classification for maternal risk considers isolated supraventricular and ventricular extrasystoles as class I (in which there is no detectable risk of increased maternal mortality, but there is a mild increase in maternal morbidity); supraventricular arrhythmias are in class II (in which there is a mild increase in maternal mortality and a moderate increase in maternal morbidity), and VT are included in class III (in which there is a significant increase in maternal mortality and morbidity).[324]

Current recommendations suggest that arrhythmias be classified during gestation, in accordance with potential hemodynamic impairment, as the following: low-risk of SCD (PSVT and AF with hemodynamic stability, idiopathic VT, low-risk long QT syndrome, and Wolff-Parkinson-White syndrome); medium-risk of SCD (unstable SVT, VT in patients with structural heart disease, Brugada syndrome, long QT syndrome, and moderate-risk catecholaminergic polymorphic VT); high-risk of SCD (unstable VT in patients with structural heart disease, *torsades de pointes* in patients with long QT syndrome, short QT syndrome, and high-risk catecholaminergic polymorphic VT).[52,320]

For the low-risk group, a cardiologist should participate in delivery planning, and delivery should be indicated by the obstetrician. In the medium-risk group, delivery continues to be indicated by the obstetrician; nevertheless, the multidisciplinary team that accompanies the pregnant patient should include an electrophysiologist, and, during delivery, the team should be prepared to use drugs such as adenosine and beta-blockers, as well as cardioverter-defibrillator (CD). In the high-risk group, there is an indication for cesarean delivery, during which it is necessary to be prepared to use CD and antiarrhythmic drugs, in addition to beta-blockers; patients in this group may require admission to the ICU during the postpartum period.[52]

5.1.4. Treatment

Treatment of arrhythmias in pregnant women is similar to that in non-pregnant women.[325] According to indication, the following methods may be used: electrical cardioversion, vagal maneuvers, antiarrhythmic drugs, device implantation (pacemaker, ICD, and cardiac resynchronizer), and catheter ablation (Table 28). Treatment of cardiac arrhythmias in the emergency room will be discussed in section 5.7.

Due to a lack of randomized clinical trials, the indication or contraindication of a given method is based on experimental data from animal studies, registries of side effects of medications used in clinical practice, and case reports or case series. This means that these treatments should only be used when there is maternal and fetal hemodynamic impairment as a result of arrhythmia and/or when there is a risk of maternal SCD during pregnancy and the postpartum period. Whenever possible, all treatments should be postponed to the second or third trimester (thus avoiding the organogenesis period); in the event that medications are used, it is necessary to utilize the lowest dose for the shortest time necessary.

Synchronized electrical cardioversion, which is indicated for reversion of unstable SVT (AF, atrial flutter, atrial tachycardias, PSVT), and unstable or stable VT in the presence of heart disease, is safe during all phases of gestation; it does not compromise fetal blood flow. The pads should be placed in the anterolateral position, with the lateral pad below the mother's left breast and fetal rhythm monitoring.[326]

During gestation, vagal maneuvers, such as the Valsalva maneuver, carotid sinus massage, immersing the face in 10ºC water, placing a wet towel on the face, may be used safely for acute reversion of PSVT (caused by nodal reentry or by an accessory route, the latter being characteristic

of Wolff-Parkinson-White syndrome).[52,325] The Valsalva maneuver is typically more effective than carotid sinus massage. Eyeball compression is potentially dangerous and should never be used.

When vagal maneuvers fail in the attempt at acute reversion of PSVT, adenosine (6 mg initially; maximum dose of 24 mg) is the drug of first choice for pregnant women, because there is no evidence of negative effects on the fetus, and the maternal effects (chest discomfort and flushing) have short duration.[52,325,327] Even though they are not first-choice drugs, beta-blockers (metoprolol, propranolol), verapamil, procainamide, and amiodarone may also be used in the attempt at reversion.

In acute management of other sustained supraventricular arrhythmias (AF, flutter, atrial tachycardia), beta-blockers, verapamil and digitalis drugs are indicated for controlling ventricular response, and other drugs, including flecainide, ibutilide, and propafenone, may be used for acute reversion to sinus rhythm.[52,325,327] For reversion to sinus rhythm in stable idiopathic VT, beta-blockers, sotalol, flecainide, procainamide, lidocaine are indicated. For SVT, overdrive ventricular pacing is an alternative that should be considered (Table 29).

Permanent treatment of SVT and VT should be the same as that applied to non-pregnant women, with the exception of restrictions to the use of amiodarone due to fetal implications (hypothyroidism, hyperthyroidism, growth retardation, and prematurity). It should also be considered that bradycardia, fetal hypoglycemia, and low birth weight might be associated with the chronic use of beta-blockers; nevertheless, this fact appears to be dose-dependent. Prescription of beta-blockers should contemplate the benefits, which should exceed the risks; the exception is atenolol, which has recognized teratogenic effects and should, therefore, be avoided during gestation. There are also reports of teratogenicity with the use of diltiazem. Sotalol should not be permanently used in pregnant women with Wolff-Parkinson-White syndrome to prevent episodes of PSVT (Tables 30 and 31).[52,325,327]

In general, catheter ablation and device implantation, whenever possible, should be performed outside of the gestational period, due to the risks inherent to these procedures, including the risk related to exposure to ionizing radiation. Catheter ablation during gestation has been indicated only for pregnant women who present recurring or persistent severe tachycardias with severe hemodynamic impairment and who do not respond to the usual treatments. There are case reports and small case series of patients with SVT who underwent catheter ablation with the use of mapping strategies that use increasingly smaller amounts of ionizing radiation, thus increasing maternal and fetal safety regarding the future risks of this exposure.[328] There are no reports of catheter ablation for VT to date.

Women with pacemakers and ICD show positive evolution during gestation; this notwithstanding, the complications inherent to underlying heart disease and devices appear to be present, leading to the need for specialized care.[329] In the event that they are absolutely indispensable, these devices may be implanted safely during gestation with or without minimal fluoroscopy.[330]

Devices (pacemakers and ICD) should be reprogrammed before cesarean delivery, due to functional interference caused by the electric scalpel. In the event of emergency cesarean delivery, a magnet is placed over the pacemaker generator pocket while the electric scalpel is in use, and the cautery plate is placed far away from the thoracic region. For vaginal delivery, reprogramming is not necessary.

For pregnant women with chronic AF or atrial flutter that are not associated with structural heart disease risk stratification should be performed for thromboembolic phenomena, by means of the CHA_2DS_2-VASc risk score,[331] including indication for anticoagulation when the score is ≥ 2. It is controversial whether the state of hypercoagulability increases the risk score for indication of anticoagulants during gestation. It is necessary to emphasize that new oral anticoagulants (dabigatran, rivaroxaban, apixaban, and edoxaban) should not be used in pregnant women.[332,333]

5.1.5. Key Points

- Initial practice for arrhythmias during pregnancy is to investigate structural cardiac injury;
- "New" arrhythmias, in the absence of structural cardiac injury, should be treated according to maternal symptoms or the complexity of the arrhythmia;
- A 24-hour Holter monitor examination is essential to therapeutic decision making;
- Device implantation (pacemaker, ICD) and radiofrequency ablation with electroanatomical mapping are safe during pregnancy, and they should be indicated when a case is refractory to pharmacological treatment;
- Devices such as pacemakers, ICD, and cardiac resynchronizers should be reprogrammed after cesarean delivery.

5.2. Thromboembolism

5.2.1. Epidemiology

Venous thromboembolic events are important causes of maternal mortality and they are potentially preventable.[131,334] They are the main direct cause of maternal death in developed countries and in Brazil; in 2013,[335] they were the sixth leading cause, behind severe hemorrhage, hypertension during gestation, infection, delivery complications, and abortion. Furthermore, they are a relevant cause of morbidity due to post-thrombotic syndrome. Late diagnosis, delayed or inadequate treatment, and inappropriate prophylaxis are responsible for approximately 3.5% of maternal deaths.[336]

Thromboembolism includes both deep vein thrombosis (DVT) and PTE; 75% to 80% of cases of pregnancy-associated thromboembolism are DVT, and 20% to 25% are PTE. The real incidence of the disease associated with gestation is unknown, but it appears to be between 7 and 25 cases per 10,000 pregnancies, and the clinical impression is that chances are increased 5- to 10-fold during this period. The risk appears to be greater during the third trimester, but it is elevated since the first. During the postpartum period, the risk reaches 20 times that of non-pregnant women, and it decreases gradually until

Table 28 – Practice for acute supraventricular tachycardia

Recommendation
Immediate electrical cardioversion as a first choice for SVT with maternal hemodynamic instability and AF in pregnant women with ventricular pre-excitation syndrome
Vagal maneuvers; in the event that they are inefficient, adenosine for acute reversion of PSVT
Endovenous beta-blockers (metoprolol, propranolol) for acute reversion of PSVT
Endovenous verapamil for acute reversion of PSVT when adenosine and beta-blockers are not effective, or when they are contraindicated
Endovenous procainamide for acute reversion of SVT
Flecainide or ibutilide for acute reversion of flutter and AF in pregnant women with structurally normal hearts
Amiodarone for acute reversion of potentially severe SVT when other therapies are not effective, or when they are contraindicated

AF: atrial fibrillation; PSVT: paroxysmal supraventricular tachycardia; SVT: supraventricular tachycardia.

Table 29 – Practice for chronic supraventricular tachycardia

Recommendation
Beta-blockers or verapamil to prevent PSVT in pregnant women without pre-excitation on ECG
Beta-blockers for controlling ventricular response in pregnant women with AF or atrial tachycardia
Flecainide or propafenone for preventing PSVT in patients with Wolff-Parkinson-White syndrome
Flecainide, propafenone, or sotalol syndrome for preventing PSVT, atrial tachycardia, and AF when there is no response to beta-blockers
Digoxin or verapamil for controlling heart rate in atrial tachycardia and AF when there is no response to beta-blockers
Catheter ablation with the use of electroanatomical mapping systems for SVT that are not well tolerated or refractory to treatment with antiarrhythmic drugs

ECG: electrocardiography; AF: atrial fibrillation; PSVT: paroxysmal supraventricular tachycardia; SVT: supraventricular tachycardia.

Table 30 – Practice for acute ventricular tachycardia

Recommendation
Immediate electrical cardioversion as a first choice for pregnant women with sustained VT, with or without hemodynamic instability
Beta-blockers, sotalol, flecainide, procainamide, or overdrive ventricular pacing for reversion of hemodynamically stable, idiopathic, monomorphic sustained VT

VT: ventricular tachycardia.

6 weeks postpartum. Nonetheless, recent studies have shown an increase in the risk of thromboembolism for up to 180 days postpartum in patients with some obstetric risk factors, including cesarean delivery and twin gestation.[131,334,335]

5.2.2. Risk Factors

The Table 32 lists preexisting, transitory, and obstetric risk factors associated with thromboembolism during gestation. It has been suggested that the presence of 2 or more of these factors further increases the risk of disease; prior history of thrombosis, however, is the most important individual risk factor. The recurrence of thrombosis during this period increases 3- to 4-fold, accounting for 15% to 25% of all cases of thromboembolism during gestation.[336,337]

5.2.3. Thrombophilia

Thrombophilia comprises a state of congenital or acquired hypercoagulability. This issue, when isolated, even in the context of pregnancy, does not necessarily result in the occurrence of thromboembolism;[338] the rarity of thromboembolism during pregnancy and the high incidence of hereditary thrombophilias do not justify systematic tracking of this disease.

Venous thrombosis is a polygenic disease with incomplete penetration, which makes genetic counseling uncertain. The risk of thromboembolism associated with different thrombophilias and its prevalence in the general population are shown in Table 33.

There is limited value to tracking thrombophilias in pregnant women with acute thromboembolism, because it does not modify clinical practice. For this reason, investigation of thrombophilia is recommended during gestation in the following situations,[339] with the following classes of evidence:

- Based on clinical risk (class IB);
- Family history (first-degree relatives) of thromboembolism without a detectable cause or occurring during hormonal exposure, or a minor risk factor, or still under the age of 50 should be investigated (class IIC);

Table 31 – Practice for chronic ventricular tachycardia

Recommendation
Beta-blockers in pregnant women with long QT syndrome and catecholaminergic polymorphic VT during gestation and the postpartum period, including those who are breastfeeding
ICD implantation should be performed before gestation; in the event that this is indicated during gestation, it should be performed using minimal radiation (guided by echocardiogram, for example) and, preferably, after the first trimester
Beta-blockers or verapamil for preventing episodes of idiopathic sustained VT
Sotalol or flecainide for preventing episodes of idiopathic sustained VT, if other substances are not effective
Catheter ablation, with the use of electroanatomical mapping systems, for sustained VT that are not well tolerated or refractory to treatment with antiarrhythmic drugs

ICD: implantable cardioverter-defibrillator; VT: ventricular tachycardia.

Table 32 – Risk factors for venous thromboembolism during gestation

Preexisting factors	Transitory factors	Obstetric factors
1. Prior thromboembolism	1. Gestation	**Prenatal:**
2. Thrombophilias	2. Hyperemesis gravidarum	1. Assisted reproduction
3. Family history of thromboembolism	3. Dehydration	2. Multiple pregnancy
4. Comorbidities: SLE, nephrotic syndrome, drepanocytosis, cancer, paraplegia	4. Ovarian hyperstimulation syndrome	3. Preeclampsia
5. Diabetes mellitus	5. Infection	**Delivery:**
6. Inflammatory diseases (especially intestinal)	7. Immobility	1. Prolonged labor
7. Over 35 years of age	8. More than 4 hours of travel	**Surgical:**
8. Obesity		2. Cesarean delivery, Postpartum sterilization
9. Tobacco use		3. Stillbirth
10. Lower limb varicose veins		4. Forceps
11. Parity ≥ 3		**Postpartum:**
12. History of stillbirth		1. Postpartum hemorrhage
13. Pre-term delivery		2. Blood transfusion

SLE: systemic lupus erythematosus.

- Thromboembolism with lower transitory risk factor, such as travel time (class IIC).

Investigation of thrombophilia is not recommended in the following situations:

- Prior thromboembolism without an apparent cause (class IB) and thromboembolism related to hormone use or during a previous gestation (class IIC) require indication of tromboprophylaxis;
- Personal history of the disease with a major transitory risk factor (fracture, surgery, prolonged immobility) (class IIB);
- Obstetric history of recurring fetal loss, placenta praevia, IUGR, and preeclampsia.

5.2.4. Diagnosis

Final diagnosis may be compromised by signs and symptoms which are inherent to normal pregnancy, such as edema, pain in lower limbs, chest pain, precordial palpitation, and dyspnea. Nevertheless, clinical evaluation is the essential basis for seeking conclusive diagnosis, because there is still not a single screening test that is sufficiently sensitive to define the situation. Furthermore, most studies that evaluate diagnostic imaging examinations for thromboembolism and flowcharts for diagnosis exclude pregnant women due to a concern for maternal-fetal safety.

5.2.4.1. Deep Vein Thrombosis

Diagnosis based on clinical picture (anamnesis and clinical examination) is concerning, because it determines whether or not the patients will require permanent anticoagulant therapy during gestation. This situation requires subsidiary examinations in order to conclude diagnosis, which should be expedited, given that sudden death is not uncommon in pregnant women with signs and symptoms compatible with this disease.

Structured risk scores for classifying pregnant women as low-, intermediate-, or high-risk for DVT, such as the Wells' score, have not been validated for use during gestation. The LEFT rule on the other hand has been proposed for specific prediction of the chance of DVT during pregnancy, and it appears to be promising. If none of its variables

Table 33 – Risk of venous thromboembolism associated with different thrombophilias

Factor	Prevalence in the general population (%)	Risk during pregnancy (%) (with no prior history)	Risk during pregnancy (%) (with prior history)	Percentage of all thromboembolisms
Factor V Leiden heterozygote	1 to 15	0.5 to 3.1	10	40
Factor V Leiden homozygote	< 1	2.2 to 14	17	2
G20210A heterozygote	2 to 5	0.4 to 2.6	> 10	17
G20210A homozygote	< 1	2.0 to 4.0	> 17	0.5
Factor V Leiden/G20210A heterozygote	0.01	4.0 to 8.2	> 20	1 to 3
Antithrombin deficiency	0.02	0.2 to 11.6	40	1
Protein C deficiency	0.2 to 0.4	0.1 to 1.7	4 to 17	14
Protein S deficiency	0.03 to 0.13	0.3 to 6.6	0 to 22	3

G20210A: mutation of the prothrombin gene.

are present, the negative predictive value appears to be 100% but this method still needs to be validated by larger prospective studies.[340,341]

- The variables considered by risk scores for DVT are the following:
- Presentation of thrombosis in the left leg;
- Difference of ≥ 2 cm in calf circumference (edema);
- Presentation during the first trimester of pregnancy.

Table 34 lists the complementary examinations used for diagnosing DVT, their sensitivity, specificity, advantages, and disadvantages.

5.2.4.2. D-dimer

D-dimer dosage is present in the classical algorithm for diagnosing thromboembolism; during pregnancy, however, this marker loses its accuracy for diagnosing PTE, given that it undergoes an increase of approximately 40% during all trimesters, the postpartum period, and complications such as preeclampsia and placenta abruption.[342] These uncertainties influence the disagreement regarding use of D-dimer in the algorithm for diagnosing thromboembolism during gestation.[336,340,343]

5.2.4.3. Venous Ultrasound

A practical approach to suspected DVT begins with the use of compression ultrasound in the affected limb. Analysis of vein compressibility on this examination presents a sensitivity of 96% and a specificity of 98% for diagnosis of DVT above the knee; this is slightly lower for those beneath the knee, although there is a substantial chance of diagnosis in these as well. Knowledge of the fact that DVT frequently presents in proximal veins, but that it may be isolated in iliac veins may limit the ability to exclude DVT with compression ultrasound alone in symptomatic pregnant women. Given that compression maneuvers may not be performed in iliac veins, iliac vein thrombi are diagnosed by direct visualization of intraluminal echogenic mass or absence of spontaneous venous flow on Doppler.

If ultrasound is positive, diagnosis is confirmed, and treatment is initiated immediately. In the event that it is negative and the patient continues to present symptoms, the examination should be repeated every 3 to 7 days, and treatment should be initiated if diagnosis is confirmed. Figure 9 shows 2 flowcharts for diagnosis of DVT during gestation: a venous compression ultrasound starting with the femoral veins and the use of D-dimer to evaluate the need for investigation of the iliac region; and complete venous ultrasound in the leg, including evaluation of the iliac vein.

5.2.4.4. Iliac Vein Magnetic Resonance

When the clinical picture of isolated iliac thrombosis arises (whole limb edema, with or without pain in the flanks, buttocks, or lumbar regions), ultrasound does not resolve the situation well, and magnetic resonance should be used. Magnetic resonance may be used to diagnose DVT involving iliac veins during pregnancy, but it depends on the examiner's expertise.[336,340,341]

5.2.4.5. Pulmonary Thromboembolism

Currently, approach to diagnosis of PTE during gestation is uncertain, and further studies are required. Approximately seven guidelines consider diagnosis of PTE during gestation, and the orientations regarding the use of rules for predicting risk, using D-dimer dosage, and choosing imaging methods diverge. Most of the guidelines do not include D-dimer dosage in the diagnostic algorithm for PTE. In relation to ultrasound, some guidelines initially use investigation for diagnosis of DVT; its positivity, however, is only 20% to 40% for PTE, and, if it is negative, diagnosis has to be confirmed by other imaging methods.

Examinations of choice for diagnosing PTE are pulmonary V/Q scintigraphy or CTPA; both tests, however, carry the risk of maternal and fetal exposure to radiation. Pulmonary V/Q scintigraphy exposes the fetus to a greater radiation dose than CTPA; thus, if chest X-ray is normal, only perfusion scintigraphy is considered, therefore reducing the radiation dose. V/Q scintigraphy also exposes the child to a greater risk of neoplasm, and CTPA exposes the mother to a higher radiation dose, leading to a small, yet significant increase in the risk of breast cancer (1 case in 280,000 *versus* less than 1 case in 1,000,000).

Table 34 – Examinations used for diagnosing deep vein thrombosis

Examinations	Accuracy	Advantages	Disadvantages
Physical Examination	Se - 25% to 35% Sp - 30% to 50%	Harmless, may suggest other diagnoses	None
D-dimer dosage	Se - 100% Sp - 60%	Excellent negative predictive value**	Must be associated with ultrasound
Compression ultrasound/duplex scan	Se - 96% for proximal veins Sp - 98%	Low cost Easily repeated	None
MR angiography	Se - 91.5%* Sp - 94.8%*	Pelvic and iliac vein thrombosis	Cost
Venous CT angiography	Se - 95.5%* Sp - 95.2%*	It may be performed in conjunction with pulmonary CT angiography	Cost Use of contrast Radiation

*CT: computed tomography; MR: magnetic resonance; Se: sensitivity; Sp: specificity. * Data from meta-analysis of largely heterogeneous studies. ** Not validated for gestation.*

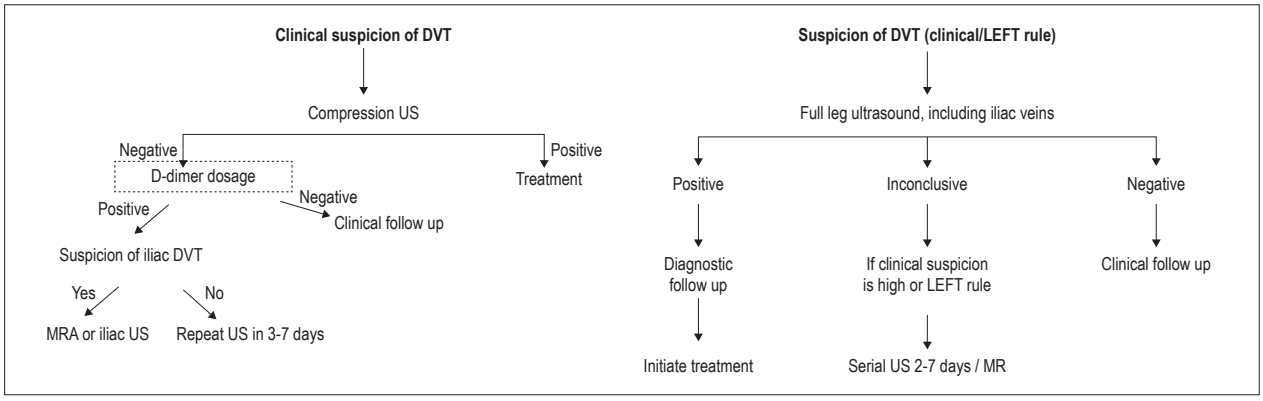

Figure 9 – *Flowchart used for investigating deep vein thrombosis during gestation. DVT: deep vein thrombosis; MR: magnetic resonance; MRA: magnetic resonance angiography; US: ultrasound.*

Table 35 – Estimated absorbed radiation of procedures used to diagnose pulmonary thromboembolism

Test	Estimated fetal radiation (mSv)	Estimated maternal breast radiation (mSv)
Chest X-ray	< 0.01	0.01
Pulmonary perfusion scintigraphy with technetium 99m:		
Low dose (40 MBq)	0.11 to 0.20	0.28 to 0.50
High dose (200 MBq)	0.20 to 0.60	1.20
Pulmonary ventilation scintigraphy	0.10 to 0.30	< 0.01
Pulmonary angiotomography	0.24 to 0.66	10 to 70

mSv: millisievert.

The choice between V/Q and CTPA is divergent. Most recommendations indicate V/Q scintigraphy as a first choice, especially perfusion, in the presence of normal chest X-ray. Others, however, recommend using CTPA with low doses for diagnosing PTE, even though they produce a higher proportion of inconclusive results during gestation. Approximately 80% of scintigraphy examinations are diagnostic, i.e., 70% are normal, and 5% to 10% are high probability. Table 35 shows absorbed radiation doses of diagnostic tests for PTE during pregnancy.[131,340]

Pregnancy-Adapted YEARS Algorithm[334] was applied for the diagnosis of PTE in a population of pregnant women and showed that in the absence of factors such as deep venous thrombosis, hemoptysis, PTE as the most likely diagnosis and, D-dimer not exceeding 1000 ng/ml, the diagnosis of PTE it can be ruled out and, consequently, chest angiotomography could be avoided in 32 to 65% of patients.[334]

5.2.4.6. Differential Diagnosis

Differential diagnosis of PTE is wide-ranging, given that pulmonary embolism has clinical manifestations similar to those of pneumonia, HF, and AMI. For this reason, it is wise to exclude the presence of coexisting pulmonary embolism with pneumonia manifestations. From the peripheral point of view,

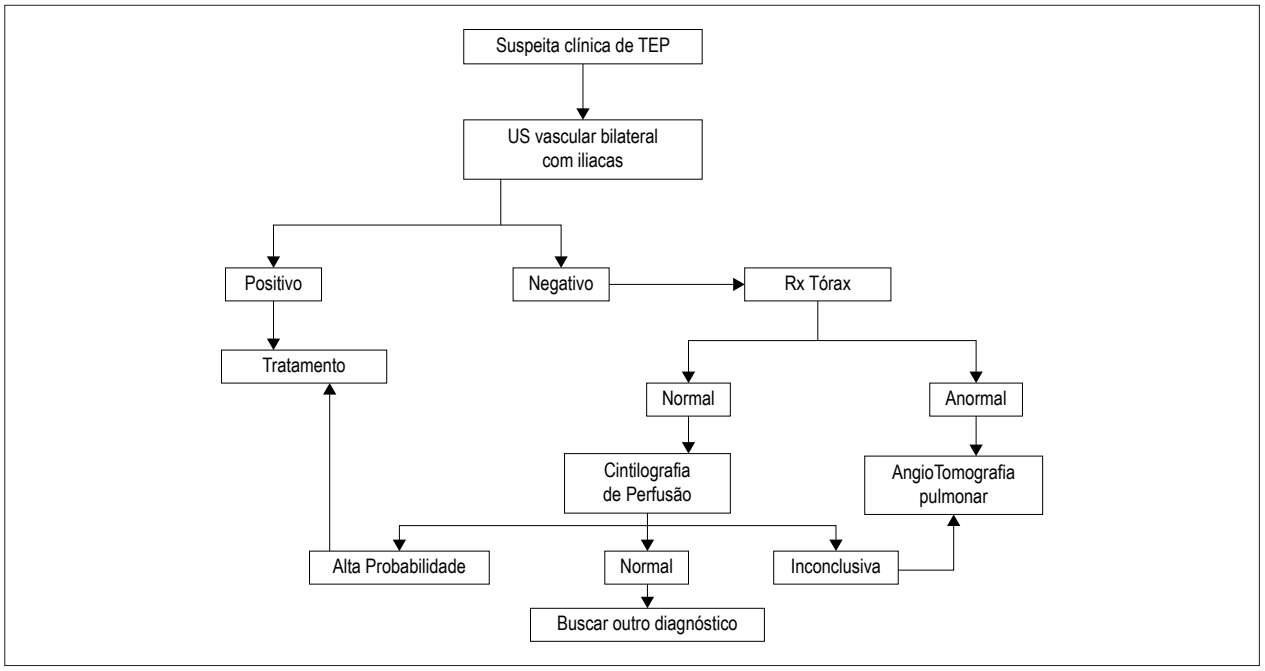

Figure 10 – *Flowchart for diagnostic investigation of pulmonary thromboembolism during gestation. PTE: pulmonary thromboembolism; US: ultrasound.*

DVT in lower limbs should be differentiated from osteomuscular diseases, such as tendinitis, muscular distension, popliteal cyst, popliteal aneurysm, hematoma, cellulitis, lymphangitis, and post-thrombotic syndrome (Figure 10).

5.2.5. Treatment

5.2.5.1. General Approach

Faced with strong clinical suspicion of thromboembolism, full permanent anticoagulation should be initiated before confirmation of diagnosis, unless it is contraindicated. Heparin is the preferred anticoagulant, whereas "new" oral anticoagulants, such as dabigatran, rivaroxaban, and apixaban, have not been approved for use during gestation and lactation. In cases of allergy or thrombocytopenia induced by heparin, fondaparinux may be indicated, and it seems to be safe during the second and third trimesters of pregnancy.

5.2.5.2. Heparin Use

LMWH and UFH are the options for treating PTE during gestation. LMWH is easy to use, and it seems to be safer and more efficacious than UFH, with data extrapolated from studies that did not include gestation. Intravenous UFH is indicated in patients with increased risk of bleeding or persistent hypotension during PTE. Prolonged heparin use, i.e., for more than 7 weeks, is associated with the risk of osteoporosis, hemorrhage, allergic reactions, skin necrosis, and thrombocytopenia, which are less frequent with the use of LMWH. Suspension is indicated when platelet count drops below 150,000 or the equivalent of 50% of the initial count. In this case, although it is controversial, substitution with fondaparinux may be indicated.

Anticoagulation should be continued throughout the pregnancy and at least during the first 6 weeks postpartum. Platelet count should be performed daily to investigate thrombocytopenia during the first 3 days of treatment and weekly thereafter.

5.2.5.2.1. Recommended Doses

- Subcutaneous LMWH: dalteparin 200 units/kg daily or 100 units/kg every 12 hours, or enoxaparin 1 mg/kg every 12 hours. The heparin dose should be controlled by anti-Xa factor in the therapeutic range between 0.6 and 1.0 IU/ml, when it is applied every 12 hours, and in the range of 1 to 2 IU/ml, when it is applied in a daily dose;
- Intravenous UFH: UFH bolus of 80 units/kg followed by an infusion of 18 units/kg/h, adjusted every 6 hours to maintain APTT between 1.5 and 2.5 times baseline. Stabilization of the therapeutic range allows for daily APTT control;
- Subcutaneous UFH: It is reasonable to initiate with 17,500 IU every 12 hours, adjusted every 6 hours to maintain APTT between 1.5 and 2.5 times control. Stabilization of the therapeutic range allows for daily APTT control.

5.2.5.2.2. Labor and Delivery

Delivery planning in patients under anticoagulation requires the involvement of a multidisciplinary team, as risks of bleeding and thrombosis should be weighed during the stages of labour, delivery and postpartum period. In cases of spontaneous labor, heparin should be suspended immediately; in planned induced or cesarean delivery, LMWH should be suspended 24 hours in advance; this practice makes neuraxial anesthesia possible. In cases when it is judged risky to suspend heparin for 24 hours, it should be substituted by intravenous UFH, which should be interrupted 4 to 6 hours before delivery. Neuraxial anesthesia may be performed when

APTT returns to normal. In the event of planned preterm delivery (triplet gestation, premature rupture of membranes, significant cervical dilatation, preeclampsia, or IUGR), LMWH or subcutaneous UFH should be discontinued at week 36 and substituted with intravenous UFH.

In the occurrence of delivery in patients under full anticoagulation, more bleeding is predicted during the intrapartum and postpartum periods; in addition to this, the risk of spinal hematoma contraindicates neuraxial anesthesia. Accordingly, oxytocin use is suggested during the third stage of labor.[342]

5.2.5.2.3. The Postpartum Period

Heparin should be reinitiated 12 hours after cesarean delivery or 6 hours after vaginal delivery, once it has been verified that there is no significant bleeding. Warfarin, when it is indicated, should be initiated on the second day postpartum, in conjunction with heparin, until INR is between 2 and 3 IU. It is indispensable for patients to be on heparin when an oral anticoagulant is initiated, because the oral anticoagulant can stimulate coagulation and may cause vascular purpura during the first days. Oral anticoagulant use does not contraindicate lactation.

5.2.5.2.4. Duration of Anticoagulation

Duration of anticoagulant treatment should be individualized. According to studies in the general population, total duration should be from 3 to 6 months in patients with only transitory risk factors. Anticoagulation should be extended for at least 6 weeks postpartum; patients with persistent risk factors, however, may require more prolonged duration of anticoagulation.[131,342]

5.2.5.3. Inferior Vena Cava Filters

Temporary removable inferior vena cava filters may be used during gestation with indications similar to non-pregnant patients. This means that they are contraindicated in cases of conventional anticoagulation, such as the following: hemorrhagic stroke, active bleeding and recent surgery; thromboembolism in spite of full anticoagulation; need to interrupt anticoagulation; or when pulmonary circulation is significantly impaired. The use of vena cava filters is limited, because it is associated with risks of insertion and removal, such as filter migration in more than 20% of cases, filter fracture in more than 5%, perforation of the inferior vena cava in 5%, and mortality in 0.12% to 0.3%.[131]

5.2.5.4. Thrombolysis

Thrombolysis is reserved for patients with massive PTE and associated hypotension. Maternal mortality is estimated at 1%, fetal loss at 6%, and maternal hemorrhage at 8%. Intravenous UFH should be initiated immediately after thrombolysis, and LMWH should only be initiated once the clinical picture has stabilized.

5.2.6. Prophylaxis

Proposed prophylaxis regimes (Table 36) against thromboembolic phenomena during gestation in diverse clinical situations are the following:[131,336,338,342]

- Prophylactic UFH: 5,000 units of subcutaneous UFH, every 12 hours;
- Intermediate dose of UFH: 10,000 units of subcutaneous UFH, every 12 hours;
- Adjusted UFH: subcutaneous UFH, every 12 hours with APTT adjusted to 1.5 to 2.5 times baseline;
- Prophylactic LMWH: dalteparin (5,000 units subcutaneous daily), enoxaparin (40 mg or 0.5 mg/kg subcutaneous), or tinzaparin (4,500 units subcutaneous);
- Intermediate dose of LMWH: dalteparin (5,000 units subcutaneous, every 12 hours) or enoxaparin (40 mg subcutaneous, every 12 hours);
- Adjusted dose of LMWH: dalteparin (200 U/kg or 100 U/kg every 12 hours) or enoxaparin (1 mg/kg every 12 hours) in doses adjusted to 0.6 to 1.2 anti-Xa factor;
- Postpartum: Initiate with intravenous UFH or subcutaneous LMWH + warfarin until INR reaches 2.0. Subsequently, maintain warfarin for 4 to 6 weeks with INR between 2.0 and 3.0.

5.2.7. Key Points

- Thromboembolism is an important cause of morbimortality during gestation;
- Gestation and other related factors may increase the risk of the disease;
- Diagnosis of thromboembolism should be confirmed in order to justify treatment of the disease, which is prolonged, requires prophylactics measures, and has future therapeutic implications;
- When thromboembolism is suspected during gestation, venous ultrasound should be the first complementary examination solicited;
- While normal D-dimer dosage appears to have a negative predictive value, it has not been validated during gestation;
- Pulmonary V/Q scintigraphy or CTPA are examinations of choice for diagnosing PTE during gestation;
- Treatment of DVT or low-risk PTE during gestation is based on the use of LMWH or UFH;
- Treatment should be maintained throughout the entire gestation and at least for 6 weeks postpartum;
- Thromboembolic prophylaxis should be used in pregnant women with past history of thromboembolism. It should also be considered in the presence of other risk factors;
- Investigation of thrombophilia should be individualized;
- The absence of factors such as deep vein thrombosis, hemoptysis, PTE as the most likely diagnosis and, D-dimer not exceeding 1000 ng/ml, makes the diagnosis of PTE unlikely.

5.3. Therapy and Prevention

5.3.1. Heart Failure

HF stands out as the main cause of complications associated with maternal mortality in women with heart disease.

Table 36 – Proposed prophylaxis regimes

Clinical history	Practice during pregnancy	Practice during postpartum
History of thromboembolism with transitory RF unrelated to estrogen use or the current pregnancy*	Observation	Anticoagulant prophylaxis with a prophylactic or intermediate dose of UFH/LMWH for 6 weeks
History of idiopathic thromboembolism	Prophylactic or intermediate dose of UFH/LMWH	Anticoagulant prophylaxis with a prophylactic or intermediate dose of UFH/LMWH for 6 weeks
Patients with high risk** thrombophilias with history of thromboembolism	Prophylactic or intermediate dose of UFH/LMWH	Prophylactic or intermediate dose of UFH/LMWH for 6 weeks
Patients with lower risk of thrombophilia, without prior thromboembolism or family history of the disease	Observation or prophylactic dose of UFH/LMWH	Prophylactic or intermediate dose of UFH/LMWH for 6 weeks
High-risk patients, without previous thromboembolism and positive family history	Prophylactic or intermediate dose	Prophylactic or intermediate dose of UFH/LMWH for 6 weeks
Pregnant women with previous thromboembolism	Elastic socks	Elastic socks
Pregnant women with ovarian hyperstimulation syndrome	Prophylactic dose of LMWH during the first trimester	

** The British Society for Haematology recommends prenatal prophylaxis in this situation. ** High-risk thrombophilias: antithrombin deficiency, positive antiphospholipid antibody, homozygous for factor V Leiden, or mutation G20210A (prothrombin gene), double heterozygosis (factor V Leiden or mutation G20210A). LMWH: low molecular weight heparin; RF: risk factor; UFH: unfractionated heparin.*

It has a prevalence of 0.04% in the general population of pregnant women and 12.5% among women with heart disease. It is important to emphasize that approximately 60% of cases of HF occur during the postpartum period.[344] Although they are asymptomatic, 0.85% of women in Brazil may eventually present ventricular dysfunction during the postpartum period.[345] The most frequent situations that should be considered in diagnosis of HF during the pregnancy-postpartum cycle are shown in Table 37.[346] HF associated with PPCM has been discussed in section 3.3.7.

Diagnosis of HF during gestation is difficult, because adaptive physiological changes during pregnancy cause signs/symptoms, which should be considered when they are exacerbated. In this manner, interface in interpretation of physiological symptoms of pregnancy *versus* those of HF, as shown in Table 38, requires the application of specific knowledge in order to make the most appropriate decision regarding eventual therapeutic intervention.

From initial evaluation to clinical follow up, the physician should pay attention to personal and family history of heart disease, gestational age at the time when FC progressed from I/II to III/IV, and identification of factors such as cardiac arrhythmias, anemia, and infections (Figure 11).

Pregnancy is generally poorly tolerated in women with LVEF < 40% and FC III/IV (NYHA), both of which are considered predictive factors of mortality,[347] and pregnancy should be advised against. In cases with LVEF < 20%, pregnancy should be contraindicated, and, during the first trimester, interruption should be considered.

The routine for pregnant women with suspicion of HF should include basic subsidiary examinations, namely, the following: laboratory tests (blood count, serum electrolytes, renal function, fasting blood glucose, glycosylated hemoglobin, lipid profile, thyroid function and liver function); 12-lead ECG to identify arrhythmias, cardiac chamber overload, and conduction disorders; chest X-ray to detect pulmonary congestion; and 2-dimensional transthoracic Doppler echo with Doppler flow analysis, which is the preferred diagnostic imaging test, not only due to its wide availability, but also to the fact that it does not require ionizing radiation. Echo identifies structural cardiac alterations, including myocardial, valve, and pericardial abnormalities, in addition to evaluating hemodynamic aspects.[345]

Table 37 – Heart failure during pregnancy

Obstetric causes
Preeclampsia
Peripartum cardiomyopathy
Amniotic fluid embolism
Non-obstetric causes
Cardiomyopathy
Pulmonary embolism + right ventricular dysfunction
Obstructive valve disease (mitral and aortic stenoses)
Valve prostheses (calcification or thrombosis)
Cardiomyopathies due to cardiotoxicity (drug use)

Adapted from: John Antony and Karen Sliwa.[346]

Studies have confirmed the value of BNP as a marker for HF during gestation as well.[348] Values above 100 pg/ml contribute to sustaining clinical diagnosis of HF, and they facilitate the implementation of appropriate therapeutic measures. It may be useful to incorporate serum levels of BNP into clinical practice, especially when assessing cardiac events during pregnancy.

Evaluation of prognosis of HF during pregnancy is similar to conventional evaluation; the following invasive examinations, however, should be postponed until after pregnancy: transesophageal echo, CMR, myocardial perfusion spect, PET scan, coronary angiotomography, and cardiopulmonary test.

HF prevention during gestation requires multidisciplinary counseling with the obstetrician, and it should observe the

Table 38 – Signs and symptoms of pregnancy

Signs/symptoms	Normal pregnancy	Complicated pregnancy
Dizziness, palpitation	Common	Exercise syncope
Dyspnea	Common (75%), mild, and non-progressive	Progressive or NYHA FC IV
Orthopnea	Common, especially at the end of gestation	–
Decreased exercise tolerance	Mild and non-progressive	NYHA FC IV
Chest pain	Common, non-progressive, generally skeletal-muscular	Typical angina or important chest pain during gestation or in the postpartum period
Pulse	Increased volume or frequency	Decreased or ascending volume
Peripheral edema	Common, mild	Important or progressive
Apical heart sound	Hyperdynamic, slightly lateralized	Third sound with splitting
Heart rate	Common, sinus tachycardia	AF, persistent SVT, symptomatic ventricular arrhythmias
Neck veins	Slightly distended	Progressively distended with dominant 'v' wave

AF: Atrial Fibrillation; FC: Functional Class; NYHA: New York Heart Association; SVT: Supraventricular Tachycardia.

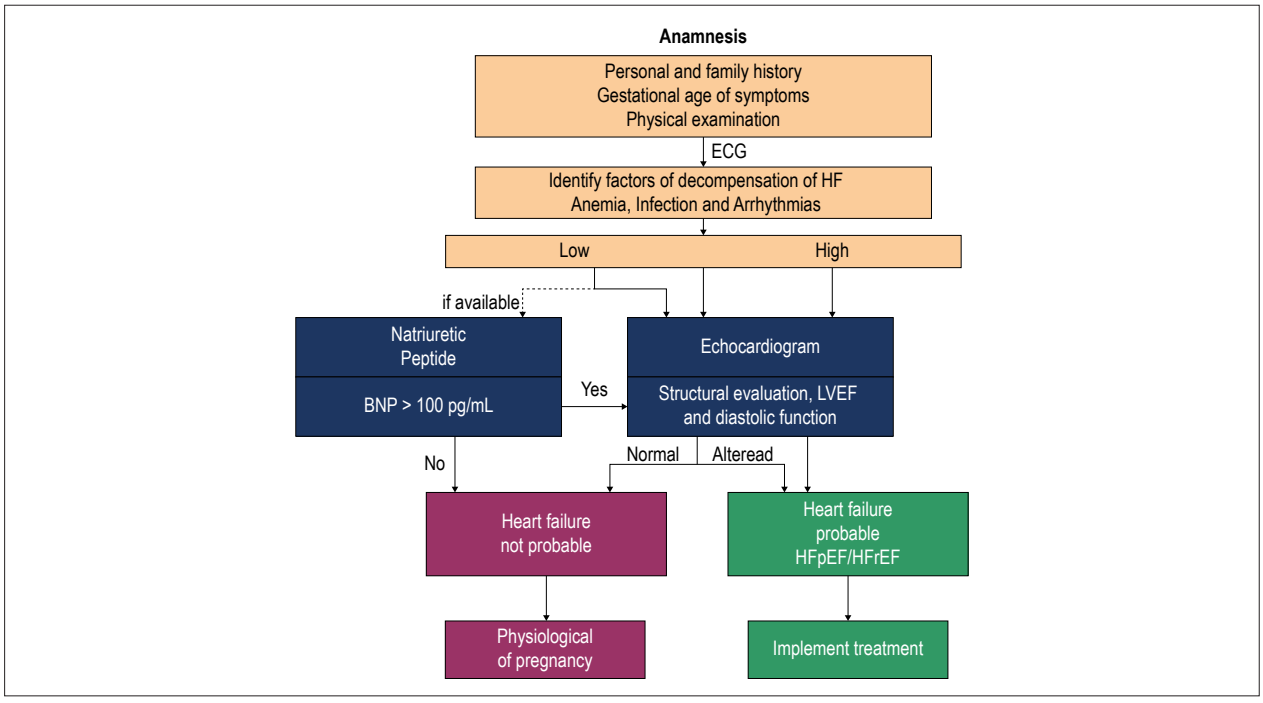

Figure 11 – *Algorithm for diagnosis of heart failure. BNP: natriuretic peptide; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction. Adapted from Rohde et al., 2018.*[345]

following recommendations: (1) weekly or biweekly medical consultation; (2) body weight control; (3) insisting on avoiding activities that require great effort; (4) moderate salt intake restriction; (5) eventual removal from professional activities that require great effort; (6) maintaining non-teratogenic medications and (7) hospitalizing patients who continue in NYHA FC III with optimized medication.[349]

Obstetric evaluation concomitant to cardiologic care is important to establishment of gestational age. In this manner, fetal viability and growth conditions and the placental flow situation are factors that support therapy and reflect the maternal hemodynamic condition.

Pharmacological treatment of HF with reduced ejection fraction (HFrEF) differs from treatment for the general population of women with heart disease regarding the class of drugs used, daily dose, and therapeutic goals,[52] given that teratogenic drugs should be substituted during preconception.

Beta-blockers, especially beta-1-cardioselective ones (metoprolol, bisoprolol, and carvedilol), are considered first-line drugs, because they are beneficial with respect to mortality due to HF and CSD, and they improve symptoms and reduce rates of re-hospitalization due to HF.[345] For these reasons, the use of these beta-blockers should be maintained during gestation in cases with HFrEF.

The literature is lacking in data on target doses for reaching therapeutic goals during gestation, which should not be the same as those considered for the general population of women with heart disease. This is because reduced heart rate and decreased arterial pressure resulting from high doses, which are usually factors applied to the population of patients with HF, can impair uteroplacental circulation.

It is generally prudent for doses of drugs used during pregnancy to be fractionated; they should initially be low and gradually increase, with caution, seeking the highest dose tolerated by the mother and the fetus. The following are thus recommended: an initial dose of bisoprolol of 1.25 mg daily, carvedilol of 3.125 mg 2 times daily, and metoprolol succinate of 12.5 mg 2 times daily, in accordance with the recommendations for the population of patients with HF.[345]

Vitality (biophysical profile and cardiotocography) and fetal maturity should be assessed more frequently when compared to the population of healthy pregnant women. During the neonatal period, supervision should last from 24 to 48 hours after birth, considering the most frequent symptoms and signs, such as respiratory depression, bradycardia, hyperbilirubinemia, and hypoglycemia. For this reason, when a patient is close to delivery, a prudent measure is to reduce the beta-blocker progressively, seeking the lowest dose with maternal efficacy.[344]

The occurrence of pulmonary congestion requires the use of loop diuretics, preferably furosemide and thiazide diuretics, in the attempt to optimize preload. In the event that there is no congestion, they should be avoided, due to the risk of causing reduced uteroplacental flow.[346] Attention should be paid to the deleterious effects of the permanent use of diuretics, such as worsened placental flow, increased uric acid (early marker of preeclampsia), appearance of maternal-fetal electrolytic disorders, and IUGR.

Hydralazine may be used to treat symptoms of HF, with or without nitrates, as an alternative treatment in the event that SAP is > 110 mmHg, especially in cases with associated arterial hypertension, severe left ventricular dysfunction, and/or evidence of congestion.[52,345] Nevertheless, during pregnancy, the association between hydralazine and nitrates has been related to low maternal tolerance due to the usual arterial hypotension.

Digoxin may be used when volume overload persists, notwithstanding therapy with vasodilators and diuretics. When it is necessary in patients with HFrEF, digitalis plays an important role in controlling maternal heart rate, especially in the presence of AF.[345]

Anticoagulation in HF during pregnancy is controversial. LMWH or UFH may be considered in patients in the most common situations, such as dilated cardiomyopathy with LVEF < 35%, prolonged hospitalization and history of thromboembolic events. It is worthwhile to consider that the postpartum period adds a higher risk of thromboembolism; for this reason, anticoagulation is indicated during this phase of the pregnancy-postpartum cycle.

Regarding arrhythmias in HF, AF if the most common, and it may be treated with beta-blockers; if necessary, digoxin is added to control heart rate. Regarding frequent ventricular arrhythmias or sustained ventricular tachyarrhythmia, treatment includes the use of amiodarone and, when risks are higher, ICD are indicated.

When hemodynamic instability and cardiogenic shock occur, the patient should initially be transferred to the ICU, if possible, with MCS.[346] Urgent cesarean delivery should be considered, with MCS immediately available; in the event of elective delivery, however, it is at the obstetrician's discretion whether the route of delivery is vaginal or cesarean, considering maternal parity, existing comorbidities, and the severity of cardiac injury.

During the postpartum period, it is necessary to avoid volume overload as a result of infusion of fluids during the intrapartum and postpartum periods. The use of oxytocin in low doses should be considered, in spite of its vasoactive properties, and ergometrine should be avoided due to its peripheral vasoconstrictive effect.

5.3.2. Key Points

- The physiological symptoms and signs of pregnancy may delay diagnosis of HF;
- BNP (≤ 100 pg/ml) is a marker of HF that is also valid during pregnancy;
- Serial BNP during gestation assists in HF diagnosis and therapy;
- Beta-blockers are considered first-line drugs, and they should be maintained during gestation in cases of HFrEF;
- During family planning, pregnancy should be advised against in women with chronic HF who present LVEF < 40% and contraindicated in those in FC III/IV with LVEF < 20%.

5.4. Therapy and Prevention

5.4.1. Infective endocarditis

IE is rare during pregnancy; it occurs in 0.006% of the general population. However in patient with valve disease or congenital heart disease, this percentage reaches 1.2%.[270,350] Patients with valve prostheses and complex cyanotic heart disease, as well as those who use illicit drugs, constitute a higher-risk group.

IE is a severe disease with maternal mortality close to 33%, consequent HF, and thromboembolic phenomena.[350,351] During pregnancy, special attention should be paid to fever without an apparent cause and new precordial heart murmur, given that it appearance is very common during normal pregnancy.

The approach to IE requires multidisciplinary care in a tertiary cardiology center, with decisions supported by a heart team that is qualified to offer the resources available for diagnosis, treatment, and follow up, according to conventional recommendations.[350]

Prophylaxis for IE during pregnancy follows the same recommendations that apply non-pregnant patients.[350,351] Given that the oral cavity is the entryway for the most frequent etiological agents, basic orientations for preventing IE include

promotion of oral health, advice on hygiene, and periodic dental consultation for surveillance of gingivitis, which favors periodontal disease.

Antibiotic prophylaxis for dental treatment is controversial; nonetheless, when it is indicated, 2 g of oral amoxacillin or 600 mg of oral clindamycin are used for patients who are allergic to penicillin, 1 hour before dental intervention.

Antibiotic prophylaxis for IE at the moment of vaginal or cesarean delivery is also controversial,[350] and the lack of evidence regarding disease prevention with antibiotic use at the moment of delivery renders their indication fragile. Nevertheless, it is necessary to consider that the occurrence of IE during the postpartum period is severe, given that, during this period, complications that elevate bacteremia (manual extraction of the placenta, curettage, or placental retention)[352] are not predictable, and postpartum infection in Brazil is one of the leading obstetric causes of maternal death. For this reason, the decision to use antibiotic prophylaxis for IE at the moment of delivery should be at the discretion of the team caring for the parturient patient, with individualization of each case.

Although it is still controversial, clinical situations at a high risk of IE that may require routine antibiotic prophylaxis are shown in Table 39,[350] and recommendations regarding means of application are shown in Table 40.

Clinical diagnosis of IE reviews history of fever; chills; decline in general condition; embolic, peripheral, or central phenomena; vascular or immunological phenomenon; glomerulonephritis; and new murmur. Regarding complementary examinations, transthoracic Doppler echo should be performed whenever clinical suspicion exists; transesophageal echo is indicated when transthoracic echo is negative for IE and in cases of prosthetic valve. Blood cultures should be collected prior to the introduction of antibiotics. A minimum of 3 samples should be taken at 30-minute intervals, by means of sterile peripheral venipuncture, regardless of fever peak. Treatment should be initiated following blood culture collection, and it should be based on epidemiology, clinical history, and blood culture and antibiogram results, in accordance with conventional guidelines.[350,351]

It is worth remembering that the most common etiological agent of IE in Brazil is *Streptococcus viridans* in the oral cavity. The choice of antibiotic, intravenous administration, and duration of antibiotic therapy are the same as in non-pregnant patients, considering the possible toxic effects of antibiotics on the fetus.[52,350,351,353]

There are, accordingly, 3 groups of antibiotics classified regarding risks to gestation: (1) the safest, which include ampicillin, penicillin, amoxacillin, oxacillin, erythromycin, daptomycin, and cephalosporins; (2) those which present intermediate risk and should thus be monitored, such as vancomycin, imipenem, rifampicin, and teicoplanin; and (3) those that are contraindicated, namely, aminoglycosides, quinolones, and tetracycline.[354]

Surgical treatment in cases of IE follows conventional indications, such as failure of etiological treatment, refractory HF, repeat embolic phenomena, periprosthetic complications, abscess, or prosthetic dehiscence. It is recommended that delivery take place before cardiac surgery in cases where the fetus is viable.[351,353]

5.4.2. Rheumatic Disease

Rheumatic fever (RF) is an autoimmune disease which occurs following infection of the oropharynx by Lancefield Group A beta-hemolytic *Streptococcus*.[355] The first rheumatic outbreak affects children in early childhood, and it contributes to an important number of women with valve disease in reproductive age and, therefore, during pregnancy.

Acute RF is rare during pregnancy, but its diagnosis should be considered in pregnant adolescents without previous prophylaxis or those who present a clinical picture of severe HF that does not correspond to the degree of valve involvement.

Diagnosis is guided by the Jones criteria and complementary examinations.[355] Both major (carditis, Sydenham's chorea, migratory arthritis, erythema marginatum, and subcutaneous nodules) and minor (fever and arthralgia) criteria are valid during gestation; however, acute phase reagents, such as alpha acid-glycoprotein, C-reactive protein, and protein electrophoresis, may be influenced by pregnancy. For this reason, diagnosis is strongly based on the patient's clinical presentation and history.

Accordingly, it is worth considering that Sydenham's chorea is a common cause of chorea in patients who have prior history, and there should be differential diagnosis with chorea gravidarum, which may be associated with morbidities other than RF. Both manifestations of chorea are linked to high obstetric risks, such as fetal loss, and they require differential treatment.[355]

Table 39 – High-risk heart diseases for infectious endocarditis[350]

Prosthetic valves	
Transcatheter valve prostheses	
Prosthetic material used for valvuloplasty, such as rings for annuloplasty and artificial chord	
Prior infectious endocarditis	
Congenital heart disease	**Unoperated cyanotic**
	Complex heart disease with residual lesion (shunts, valve regurgitation in the graft location, valve tubes)

Table 40 – Antibiotics and doses used one hour before delivery

Antibiotic	Doses
Ampicillin	2.0 g IV or IM
Associated with gentamicin	1.5 mg/kg O, IV, or IM
Patients allergic to penicillin/ampicillin/amoxacillin	
Vancomycin	1.0 g IV for 1 h
Associated with gentamicin	1.5 mg/kg IV or IM

IM: intramuscular; IV: intravenous; O: oral.

The same applies to the distinction between HF consequent to rheumatic carditis and chronic heart valve disease; both increase the risk of maternal death, and they have very different forms of treatment.[356]

Treatment of rheumatic outbreak, which is rare during pregnancy, should be the same as in the general population. Hospitalization is indicated in all cases of suspected carditis, incapacitating arthritis, or severe chorea, and home rest should last for a minimum of 4 weeks and, eventually, until delivery.[357]

Secondary prophylaxis for RF should be maintained during gestation in accordance with the following recommendations: penicillin G benzathine 1,200,000 IU intramuscular every 21 days or phenoxymethylpenicillin 250 mg orally 2 times daily. In patients who are allergic to penicillin, erythromycin 250 mg orally 2 times daily or clindamycin 600 mg daily are recommended.[357] The use of sulfadiazine is contraindicated during pregnancy.

Duration of prophylaxis does not depend on occurrence during pregnancy, and it is related to the following factors: RF without prior carditis (for 21 years or 5 years after the latest outbreak, applying whichever covers the longer period); RF with prior carditis, mild residual heart valve disease, or resolved valve lesion (for 25 years or 10 years after the latest outbreak, applying whichever covers the longer period); moderate to severe residual valve lesion (for 40 years or lifelong); after valve surgery (for 40 years or lifelong). Patients with risk of repeat pharyngitis, such as those who work in daycare centers or nursing homes, should use secondary prophylaxis for the rest of their lives.[353,358]

5.4.3. Key Points

- Antibiotic prophylaxis for IE at the moment of delivery should be performed in patients at a high risk for IE;
- Prophylaxis for RF should be maintained during pregnancy.

5.5. Cardiovascular Surgery During Pregnancy

Worldwide experience in cardiac surgery during pregnancy has shown controversial results. Studies are characterized by retrospective nature and heterogeneity of procedures, associated with difficulties to standardization of surgical techniques, which render difficult the judicious analysis of prognostic variables and their reflexes in practice during pregnancy.[359,360]

It is accepted that the risk of maternal death due to cardiac surgery is not greatly modified by pregnancy.[359] For emergency surgery, however, the risk of maternal mortality increases.[361] The maternal mortality rate verified of 7.5% to 13.3% is relatively high, in comparison with that of cardiac surgery in the population of young women of fertile age, which encompasses the age range of pregnancy.[359,361,362,363]

Another important aspect for indication of cardiac surgery is gestational age. This is because, the earlier complications appear in patients with severe lesions, the greater the tendency to indicate early surgery, because there is a very high tendency for hemodynamic deterioration to progress during pregnancy, leading to an increase in emergency surgery and maternal death. This logic justifies the notion that the best period to plan cardiac surgery is during the second trimester of gestation, given that the fetus is still not viable, and the physiological and mechanical modifications pregnancy are still not very significant; furthermore, it provides the mother with a reasonable postoperative recovery period. One of the highest risk variables associated with worse maternal-fetal outcomes is emergency.[362,363]

Surgery during pregnancy requires specific precautions; the following stand out: choice of anesthetic drug, continuous maternal-fetal monitoring, and adequate control of anticoagulation. The obstetric team should initiate both maternal and fetal monitoring simultaneously, by means of cardiotocography, in order to control uterine dynamics and fetal heartbeat. Induction of anesthesia should be cautious to avoid periods of hypoxia and hypotension, and drugs without teratogenic effects should be chosen.[52]

Cardiovascular surgery techniques during pregnancy do not differ from those for non-pregnant patients; the surgical team's experience, however, is fundamental in order to reduce duration of surgery, especially of CPB, in addition to specific precautions which are shown in Table 41.

Typically, a drop in fetal heart rate occurs during initial installation of CPB, which returns to normal by completion.[359] This is mainly due to the change to continuous flow, embolic effect of microbubbles, initial hypotension, hemodilution, stacking of red cells, and alterations in peripheral vascular resistance. This "acute dysfunction" of the placenta as a result of impaired uteroplacental flow is the cause of the high incidence of fetal loss, prematurity, neonatal death, and malformations.[361,364]

It has been recommended to indicate delivery before cardiac surgery if the fetus is viable. Nevertheless, it is worth highlighting that corticoid use for fetal pulmonary maturation is very risky for pregnant women with unstable, severe hemodynamic conditions, which are very frequent in this situation. This is because corticoid use in recommended doses (2 doses of betamethasone, 12 mg intramuscular, 12 hours before delivery), associated with delivery, whether cesarean or vaginal, may lead to aggravation of HF, cardiogenic shock, and maternal death.

Table 41 – Precautions for cardiac surgery with cardiopulmonary bypass during pregnancy

Control of hemodilution, which should not be below 25% hematocrit level
Use of flow 30% to 40% above usual flow, maintaining mean arterial pressure above 60 mmHg
Use of mild hypothermia or normothermia, in order to avoid fetal arrhythmias in cooling and warming and to decrease uterine contractions
Use of added glucose in the perfusate, in order to avoid fetal bradycardia and improve fetal energy conditions
Adequate control of acid-base balance, avoiding acidosis

Prevention of premature labor with the use of natural progesterone suppositories (50 mg, every 12 hours during the intra- and postoperative) is preferable, given that indometacin may lead to closure of the arterial canal, especially after 26th week of gestation.[365]

Cardiac surgery, even though it constitutes a high risk for pregnancy, should be indicated for clinical conditions without other therapeutic options for maternal survival. Surgical procedures in emergency situations are significantly correlated with maternal complications during the postoperative period; for this reason, the moment of surgical indication has direct implications on maternal-fetal results.[361,366]

5.5.1. Key Points

- Cardiac surgery during pregnancy should be indicated in clinical conditions without other therapeutic options for maternal survival;
- Emergency surgery is significantly correlated with maternal complications during the postoperative period;
- Cardiac surgery during pregnancy requires differentiated precautions and a hospital protocol.

5.6. Percutaneous Cardiac Intervention

5.6.1. General Principles

The use of percutaneous interventions during gestation has gradually increased, driven by their greater availability and by the risks imposed during surgery with CPB. In general, these interventions are considered during gestation for severe symptomatic heart diseases whose treatment cannot be postponed because they pose risks to the mother's life.[52]

The goal of percutaneous intervention during gestation is to save the mother's life and protect the fetus from the potential risks of radiation. Accordingly, proposing that intervention be performed at the beginning of the second trimester takes the following into consideration: (1) organogenesis is almost complete; (2) fetal thyroid function is not active; (3) uterine volume is moderately increased (greater distance between the fetus and the maternal thorax); 4) facility of using barrier devices for protection.[52]

An alternative method to protect the fetus is by using echo (transthoracic, esophageal, or 3-dimensional) as a substitute to fluoroscopy. This makes it possible to place the catheters and to measure valve orifice diameters and aortic coronary outflow position; it also serves as a guide for balloon catheter valvuloplasty procedures and prosthetic valve insertion, including valve-in-valve procedures, and it assists coronary stent release.

Fluoroscopy should follow the criteria that include; (1) low radiation doses, (2) abdominal shielding, (3) distancing direct radiation from the abdominal region. Procedure duration should be as short as possible, because the risk of radiation to the fetus must always be taken into consideration. Nevertheless, this concern should not impede the use of essential diagnostic procedures, making use of the best available method for the given clinical situation.[52]

5.6.2. Percutaneous Valve Interventions

5.6.2.1. Balloon Catheter Valvuloplasty in Mitral Stenosis

BCV in mitral stenosis should preferably be performed during the second trimester of gestation, and it should be indicated for women with significant mitral stenosis in NYHA FC III/IV, who do not respond satisfactorily to conventional clinical treatment.[52] The results of BCV, when its indications are followed, have been shown to be superior to those of conventional surgery, with lower mortality and better clinical condition in approximately 80% of cases.[367]

The criteria for indicating mitral BCV include the following:

- Absence of: (1) severe mitral regurgitation; (2) concomitant valve or coronary lesion requiring correction; (3) left atrial thrombus proven by transesophageal echo;
- Compatible anatomical condition of the mitral valve, namely: (1) certain flexibility; (2) non-excessive calcification; (3) commissural fusion; (4) approachable subvalvular portion;
- Wilkins echocardiographic score equal to or less than 8, allowing for better immediate and long-term result.[368]

Expanding to include patients with Wilkins score up to 10 as a result of pregnancy is controversial, because the potential for complications such as acute mitral insufficiency can be fatal. In very special situations, mitral BCV with an index above 8 requires previous discussion with a heart team and availability of resources in the event that emergency surgery is necessary.[369]

5.6.2.2. Aortic Stenosis

Patients who present severe aortic stenosis with manifestations of HF, limiting angina, and syncope during pregnancy are indicated for valve intervention, and balloon aortic valvuloplasty (BAV) may be performed by an experienced operator.[370] In adolescents, it has good immediate and long-term results; in patients in higher age ranges, however, results are worse. BAV may thus serve as a "bridge"[371] to temporary improvement in clinical condition, making it possible to reach gestational age for safe delivery in favorable hemodynamic conditions. It is worthwhile to remember that, when the procedure is performed, conventional rescue surgery should be available in the event of emergency. It is, furthermore, essential that, after gestation, these patients receive follow up with clinical examinations and periodic echo to determine the eventual need for definitive heart valve disease correction.

5.6.2.3. Congenital Pulmonary Valve Stenosis

Severe, symptomatic pulmonary valve stenosis (PVS) with manifestations of HF, arrhythmias, or syncope is uncommon during pregnancy. In this situation, BCV has been indicated with immediate success.[372]

5.6.2.4. Percutaneous Implantation of Prosthetic Valve

In recent years, we have witnessed the development of transcatheter aortic valve implantation (TAVI). It has the great

advantage of avoiding cardiac surgery with CPB, but it requires intensive use of ionizing radiation by means of aortic valve tomography for preliminary study of the structures involved (aortic ring, prosthesis diameter, coronary height, and the thoracic and peripheral arterial system), as well as radioscopy during the procedure, to assist in catheter placement and visualization of prosthesis expansion. Conventional TAVI is thus, not approved, during gestation, due to the high fetal radiation burden.

This notwithstanding, arterial ultrasound for evaluation of the arterial system (iliac, aorta, and coronary height), in conjunction with 3-dimensional echo (evaluation of the valve ring) was successful in the first reported case of TAVI during gestation,[373] which used short periods of radioscopy to place the prosthesis. The fact that pregnant women are younger, with healthy arterial vascular beds, facilitates navigation with catheters; nevertheless, there should exist a degree of valve calcification to allow for prosthesis placement, and this is not always found in this group of patients.

5.6.2.5. Valve-in-Valve Procedure for Bioprosthetic Valve Dysfunction

BPV dysfunction is very common in young women, and it sometimes requires valve replacement during gestation. In this scenario, valve-in-valve type procedures are promising in order to avoid surgery with CPB. Prostheses are introduced by means of catheters, using the following routes: femoral artery or other arterial accesses to the aorta, femoral vein followed by transseptal puncture and left atrial access, and left ventricular apical (transapical) incision. A case report[374] during pregnancy has described transapical implantation of 2 prostheses, mitral and aortic, with the aid of transesophageal echo and restricted use of fluoroscopy, which made it possible to reach vaginal delivery with positive maternal-fetal results.

5.6.2.6. Coronary Angioplasty

Primary percutaneous coronary intervention is the treatment of choice for acute coronary syndrome during gestation, while thrombolysis is less utilized. Coronary angioplasty with conventional stents has been considered safe in cases of obstructive arterial disease due to atherosclerotic disease.

While the safety of drug-eluting stents is still not known, the need for dual antiplatelet therapy for a prolonged period of time with this type of stent constitutes a serious restriction to their use during gestation, owing to the hemorrhagic risks. Furthermore, clopidogrel should be interrupted 7 days before delivery, which adds a risk of stent thrombosis.

In spontaneous coronary dissection, the indication for angioplasty should consider the technical difficulties and the vascular fragility peculiar to this situation, which increases the risk of extension of coronary damage, in addition to the fact that its success is considered suboptimal.[375] For this reason, most cases of coronary dissection benefit from conservative treatment.[376,377] In situations where coronary angioplasty is indicated, the option to use the latest generation of drug-eluting stents, which require dual antiplatelet therapy for a shorter time (3 months) may be a safer option.

The dilemma of this decision is that obstetric risk (maternal hemorrhage) and cardiac risk (stent thrombosis) must be judged on a case-by-case basis by an interdisciplinary team, because, to date, there are no studies on these circumstances that support decision making.

5.6.3. Key Points

- Percutaneous intervention during pregnancy should be indicated in cases of complications refractory to conventional clinical treatment or in conditions of imminent risk of maternal life;
- Percutaneous intervention should always be performed after discussion with the Heart Team in Tertiary Cardiology Services.

5.7. Cardiovascular Emergencies

5.7.1. Acute Heart Failure

Circulatory overload during the pregnancy and postpartum period in patients with structural heart disease, even if it is asymptomatic, may be responsible for acute heart failure (AHF),[378] treating it during gestation can lead to improvement of symptoms and prevention of maternal death. The orientation of attendance follows the recommendations for patients with HF in the emergency room[345] (Figure 12), but it is necessary to consider the risks of medication use regarding the mother, the fetus, labor, and lactation, as well as necessary adjustments according to gestational age.

It is worth mentioning that in addition to the symptoms of CHF, the identification of systemic and/or pulmonary congestion and low output, supported by subsidiary exams, define the determining cause in most cases.[345,378,379]

Laboratory examinations should be part of the investigation of AHF during pregnancy, and they include the following: electrolyte dosage, BNP,[348,380] renal function, markers of myocardial necrosis, thyroid profile, blood count, and other infectious parameters.

Interaction with the obstetric team is mandatory to determine both gestational age and parameters of fetal vitality and viability. Eventual indication of therapeutic delivery and the route of delivery should be part of the algorithm for attending cases with AHF during pregnancy.

Acute dyspnea during pregnancy should include the following differential diagnoses: AMI, pulmonary congestion in preexisting heart disease, PPCM, PTE, and myocarditis.[222] Orientation for differential diagnosis may be summarized by the following points:

- AMI: dyspnea and angina pain; over 35 years of age; history of tobacco use and use of contraceptives with estrogen components; elevated serum troponin levels; echo with alterations in segmental motility. Definitive diagnosis is made by coronary cineangiography;
- Preexisting heart disease: Dyspnea is more frequent during the second and third trimesters. Serum levels of BNP may be elevated, and echo shows structural cardiac injury. In Brazil, acute pulmonary edema is common as the first manifestation of mitral stenosis, from the second trimester of gestation on;

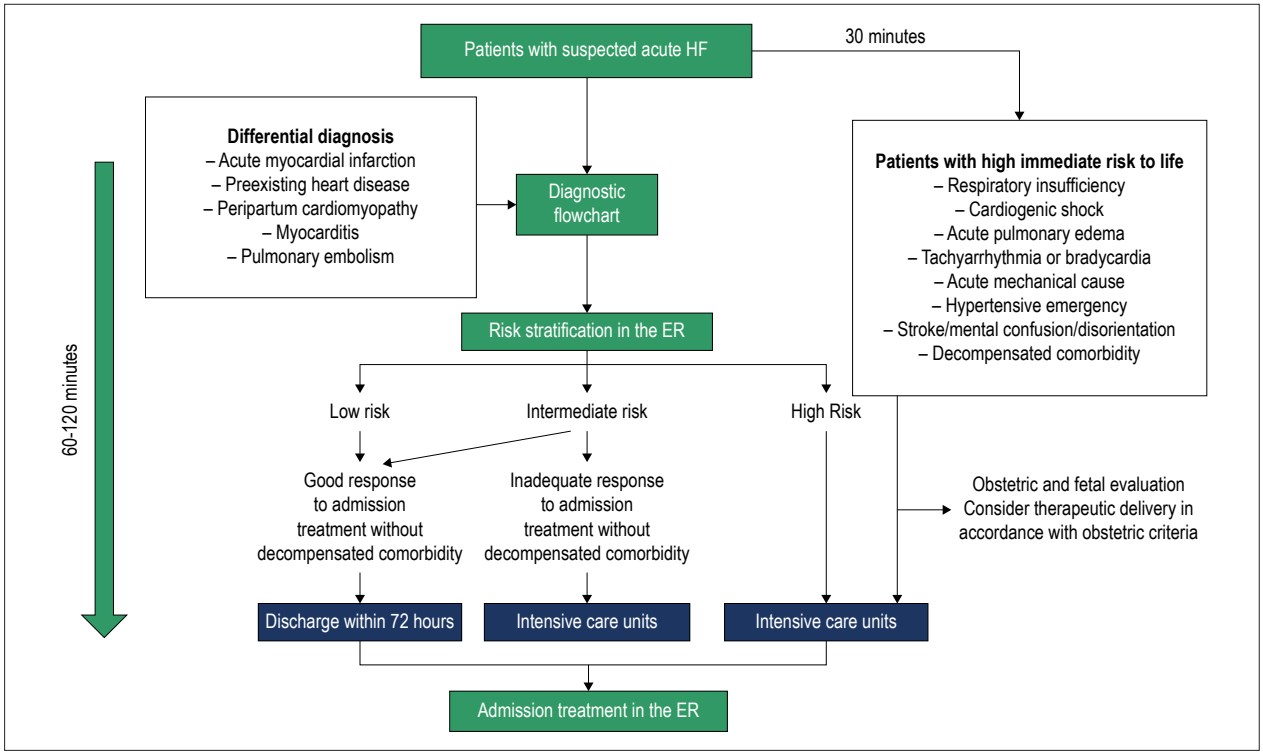

Figure 12 – *Algorithm for diagnosis when there is clinical suspicion of acute heart failure. ER: emergency room. Adapted from Rohde et al., 2018.*[345]

- PPCM: dyspnea during the last month of gestation or, more frequently, after delivery, with significant elevation in levels of BNP and new systolic dysfunction in the left and right ventricles. CMR is important to determine diagnosis;[222]
- Thromboembolism: Dyspnea is associated with pleuritic chest pain. Levels of troponin and BNP are elevated, and right ventricular dysfunction and PH are signs of greater severity of this event. It is worth emphasizing that sensitivity and negative predictive value of D-dimer are limited when there is suspicion of PVS during pregnancy;[381]
- Myocarditis: Dyspnea is associated with unspecific symptoms related to viral infection. Troponin may be elevated (myocardial inflammatory processes increase cellular release), and echo may demonstrate segmental akinesis or diffuse hypokinesis. CMR with identification of myocardial edema or mesocardial fibrosis reinforce diagnosis.[382,383]

During clinical evaluation, it is fundamental to determine hemodynamic profile. In patients classified as profile B (wet and warm), volume adjustment with diuretics and vasodilators, in the absence of hypotension and shock, should be considered sparingly, keeping the formal contraindication to the use of ACEI and ARB in mind and giving preference to the use of nitrates and hydralazine, in combined therapy, whenever possible.

Loop diuretics are safe. Furosemide is the most commonly used, at an initial dose of 20 to 40 mg, with the possibility of optimization, depending on previous chronic use, diuretic response, and improvement of dyspnea and hypoxemia.[384] Fetal risks are consequent to reduced placental flow due to volume adjustment beyond what is necessary.

In more severe patients or cases of acute pulmonary edema, without hypotension or shock, nitroglycerin or sodium nitroprusside is used in continuous infusion, preferably guided by invasive arterial monitoring. Doses and infusion rates are described in Table 42. Continuous fetal monitoring should also be performed, seeing that the abrupt reduction in maternal arterial pressure may compromise fetal vitality.

Non-invasive ventilation (NIV) support with positive pressure is indicated for all patients with peripheral arterial saturation < 90% and respiratory distress or discomfort who do not improve with oxygen therapy.[369] It is also indicated for patients with acute pulmonary edema, given that, in non-pregnant women, it is known to have benefits for reducing the need for invasive mechanical ventilation support.[348]

In patients with symptomatic hypotension, signs of low cardiac output with organic dysfunction, or cardiogenic shock, there is a need for inotropic agents and, in some cases, association with vasoconstrictors, similarly to non-pregnant patients. Dobutamine is the most widely used inotropic agent, because it promotes a dose-dependent increase in cardiac output, even though its arrhythmogenic effect is limiting, and it presents lower efficacy in cases of chronic beta-blocker use. Milrinone, in addition to increasing cardiac output, is able to reduce peripheral and pulmonary resistance. It is, therefore, indicated in patients with congenital heart disease and PH.[344] Levosimendan presents a positive inotropic effect, due to its vasodilatory action, however, it should be used with greater caution in pregnant women. Table 43 shows drugs and their recommended doses for treatment of AHF during pregnancy. In patients with AHF due to PPCM, as discussed in section 3.3.7, levosimendan is preferable, keeping the biomolecular

Table 42 – Recommendations for intravenous vasodilators in acute heart failure

Vasodilator	Posology	Adjustments
Nitroglycerin	Initial: 10 to 20 mcg/min Maximum: 200 mcg/min	Every 15 min Increase: 10 to 20 mcg/min
Sodium nitroprusside	Initial: 0.3 mcg/kg/min Maximum: 5 mcg/kg/min	Every 15 min Increase: 0.3 to 0.5 mcg/kg/min

Table 43 – Posology of inotropic and vasoconstrictor drugs

Inotropic	Posology	Maximum dose
Dobutamine	2.5 mcg/kg/min Evaluate adjustment every 15 min Hemodynamic effect in up to 2 h	10 to 20 mcg/kg/min
Milrinone	Initial: 0.375 mcg/kg/min Adjustment every 4 h	0.75 mcg/kg/min 0.5 mcg/kg/min*
Levosimendan	0.1 mcg/kg/min Adjustment of 0.05 mcg/kg/min every 4 h Infusion for 24 h	0.15 mcg/kg/min
Norepinephrine	Initial: 0.1 to 0.2 mcg/kg/min Adjustment every 15 min	1 mcg/kg/min

** Dose for patients with renal insufficiency.*

effects inherent to catecholamines in mind. A recent study has demonstrated a beneficial effect of levosimendan (at a dose of 0.1 mcg/kg/min) in relation to improvements in ventricular function and systemic congestion in pregnant women with AHF due to PPCM.[385]

Norepinephrine is indicated in the occurrence of significant arterial hypotension or cardiogenic shock, because, in addition to its vasoconstrictor effect that modulates vasoplegia and redistributes blood flow, it also has an effect on cardiac output. In refractory patients, who do not respond to pharmacological measures, success has been described with the use of temporary mechanical circulatory assist devices, such as intra-aortic balloon (IAB) and extracorporeal membrane oxygenation (ECMO).[386]

5.7.2. Arrhythmia

The main consideration in practice for poorly tolerated arrhythmias with hemodynamic impact is to prioritize the mother's life. Nonetheless, treatment should also be weighed in relation to the side effects of antiarrhythmic drugs on maternal cardiac output and uteroplacental flow, oxytocic effects, and proarrhythmogenic effects on the fetus.

For these reasons, antiarrhythmic medication, maintenance, discontinuation, or dose optimization should be individualized depending on the type of arrhythmia, gestational period, maternal structural disease, and risk of sudden death.[387]

Nodal reentry tachycardia is the most common SVT, followed by atrioventricular tachycardia. Its occurrence is more frequently observed during pregnancy; its treatment in the emergency room, however, does not present modifications in relation to non-pregnant women. In stable patients, the vagal maneuver is the first choice, followed by the use of adenosine, which does not pass the placental barrier, in a bolus (6 mg, followed by 12 mg if it persists). Regarding CCB, verapamil is a good, safe option. In patients with signs of pre-excitation on resting ECG, there is a formal contraindication to the use of beta-blockers. In patients with hemodynamic instability, synchronized electrical cardioversion is indicated.[388] There are no contraindications to cardioversion, and, other than choosing the most appropriate form of sedation, there are no additional precautions.[74] Indication for catheter ablation may be considered during pregnancy, using electromechanical mapping in refractory cases.

AF, atrial flutter, and atrial tachycardia are uncommon during gestation in patients without structural cardiac injury. In situations of accelerated ventricular response, there is a risk of hemodynamic degeneration in both the mother and the fetus. In all patients, it is necessary to rule out association with infection, anemia, and thyrotoxicosis.[389] In order to control AF frequency in patients with high ventricular response, lanatoside-C, verapamil, or metoprolol are used. Under hemodynamic instability that might be attributable to tachycardia, synchronized electrical cardioversion is indicated. Patients with AF and heart valve disease have a precise indicated for anticoagulation. In cases that are more clinically stable, when opting for rhythm control, electrical cardioversion is preferable to chemical cardioversion, considering the teratogenic effect of amiodarone and the scarcity of evidence in relation to the safety of high doses of propafenone. In cases where time since onset of arrhythmia exceeds 48 hours, it is necessary to perform transesophageal echo.[390]

For patients with flutter, cardioversion is preferable, given its high reversibility rate, observing less than 48 hours of onset or after performance of transesophageal echo to rule out the presence of intracavitary thrombi.

The occurrence of VT during gestation is rare, but it may occur in high-risk patients, especially those with structural disease and ventricular dysfunction. Electrical cardioversion is indicated when the maternal clinical picture is unstable. In patients without hemodynamic instability, lidocaine is safe,

and it has the best reversibility rate. The use of amiodarone should be excluded to isolated situations, when cases are refractory and ventricular arrhythmia recurs following electrical cardioversion, and it is necessary to be aware of its dose-dependent effects on the fetus.[391] ICD implantation in indicated patients is approved during pregnancy when it ensures better prognosis during delivery and the postpartum period.[392]

5.7.3. Acute Myocardial Infarction

AMI, which is uncommon during pregnancy, is potentially fatal. Over the past decades, its incidence has been found to increase, notwithstanding reduced maternal mortality due to the issue during gestation.[224]

In general, practice for treating AMI during gestation follows the same recommendations as the general population, including revascularization with stent angioplasty or surgical revascularization.[393] Multiprofessional care includes obstetric evaluation and continuous monitoring of the fetus, with evaluation of fetal vitality and cardiotocography.

Clinical treatment of AMI during pregnancy considers the following:[394]

- Oxygen therapy: nasal O_2 catheter, 2 to 3 L/min;
- Pain control: Morphine sulfate is considered to be safe and effective, but it may lead to respiratory depression in the fetus if administered near delivery;
- Nitrates: Attention should be paid to the risk of maternal hypotension and consequent low uteroplacental flow;
- Beta-blockers: metoprolol, carvedilol, or propranolol. Fetal monitoring with cardiotocography is recommended to control uterine dynamics and fetal heartbeat;
- Aspirin: low doses (< 150 mg);
- Clopidogrel may be used, but it should be suspended 7 days before delivery;
- Heparins: UFH and LMWH are used according to indications. Fondaparinux should only be used when heparins are contraindicated.

Indicated treatment of AMI with ST-segment elevation is coronary reperfusion, as early as possible,[389,395] by means of either thrombolytic[396] drugs or, preferably, primary coronary angioplasty with stents. Thrombolytics should be restricted to cases where the hemodynamic room is not available in a timely manner. Restrictions to its use are due to the risk of placental hemorrhage. If percutaneous angioplasty is indicated, there is still controversy regarding the preference of conventional stents to drug-eluting stents.[52]

Risk stratification of patients with acute coronary syndrome without ST segment elevation is indicated, in the same manner as in non-pregnant patients, considering age, vital signs, risk factors, recent or recurrent symptoms, and electrocardiographic and laboratory findings. In low-risk pregnant patients without signs of HF, refractory pain, or electric instability, conservative clinical treatment is indicated. In contrast, in high-risk pregnant patients, invasive stratification during the first 24 to 48 hours following the onset of the acute condition should be prioritized in order to proceed to myocardial revascularization.[396]

Spontaneous coronary artery dissection is a frequent cause of AMI in women, it should, therefore, be the first hypothesis when faced with an acute ischemic event during gestation. Treatment should follow conventional recommended measures.[397]

5.7.4. Acute Aortic Syndrome

Most acute aortic syndromes occur in women with diseases predating gestation, but they may also affect patients who were previously healthy. It is estimated that the incidence of dissection of the aorta in the population is from 2.4 to 2.9 out of 100,000 patients yearly, and there appears to exist a strong correlation with pregnancy in women under 40 years of age.[398]

Chest pain in women with aortic disease requires investigation with angiotomography of the aorta, in order to rule out suspicion of acute dissection of the aorta. In pregnant patients with type A dissection, with involvement of the ascending aorta, there is an indication for emergency cardiac surgery, in addition to pressure and heart rate control. The procedure should take place in conjunction with a multiprofessional team in a tertiary cardiology center, and cesarean delivery is indicated when the fetus is viable, followed by correction of the dissection. In situations where the fetus is not viable, cardiovascular surgery is performed, prioritizing the mother's life (contemplating that fetal mortality is from 20% to 30%).[399]

In women with uncomplicated type B dissection of the aorta, without involvement of the ascending aorta, initial conservative treatment is indicated, maintaining adequate arterial pressure and heart rate control. In the event that there are signs of complication, such as persistent pain, uncontrolled arterial hypertension, progression of dissection, ischemia in a target organ or symptoms of aortic rupture, percutaneous treatment should be considered, even though it has been little described during gestation.[400] Route of delivery should be cesarean once fetal viability has been ensured.

5.7.5. Prosthetic Valve Thrombosis

The incidence of thrombosis in mechanical prostheses during pregnancy varies according to the anticoagulation regime utilized. Diagnosis should be considered in previously asymptomatic pregnant women who present dyspnea, chest pain, and symptoms of hypotension. Transesophageal echo is the gold standard examination for definition.[401]

Treatment of valve thrombosis during pregnancy or the postpartum period should be the same as that proposed for non-pregnant patients, taking their clinical condition, thrombus size and localization of the affected prosthesis into consideration.[96]

Thrombolytic use should be considered in critical patients who would present great risks of death if they underwent surgery, in places where a surgical team is not available, and in the event of thrombosis in the tricuspid or pulmonary valve. The following thrombolytic doses are recommended: streptokinase, 1,500,000 IU for 60 minutes without UFH; or alteplase (rT-PA), 10 mg in a bolus + 90 mg for 90 min with UFH.[151,402] In partially successful cases, i.e., cases that persist with residual thrombi, patients should be referred for surgery 24 hours after thrombolytic infusion has been discontinued.

A protocol with low-dose thrombolytic therapy in slow infusion (rT-PA 25 mg, intravenous infusion for 6 hours, repeated after 24 hours and, if necessary, up to 6 times, reaching a maximum dose of 150 mg, without bolus or concomitant use of heparin) has recently been proposed for pregnant women with prosthesis thrombosis. The results have shown that thrombolysis was efficacious, with no maternal deaths, and fetal mortality rate was around 20%, which is better than the routinely used strategies.[403] With the enhancement of surgical techniques, however, it is not possible to infer that thrombolysis is superior to surgery during pregnancy.

The issue with surgery is due to high perioperative mortality (between 5% and 18%), which is closely associated with NHYA FC, which is the main predictor variable. Patients in NHYA FC I/III present 4% to 7% mortality, whereas those in FC IV present 17.5% to 31.3%. In contrast, surgery presents a higher rate of success than thrombolysis (81% *versus* 70.9%).[399] In this scenario, it should be considered in urgent or emergency cases, depending on the patient's clinical condition. Surgical procedures are associated with maternal and fetal risks, when performed during pregnancy.

In patients with non-obstructive thrombi, who are stable from the hemodynamic point of view and who have no signs of decompensated HF, parenteral anticoagulation at therapeutic doses, with heparin according to APTT and echocardiographic imaging control, is the option. In cases that fail to respond to treatment, thrombolysis or conventional surgery should be indicated.[151,402]

5.7.6. Cardiorespiratory Arrest

Cardiorespiratory arrest (CRA) in pregnant women is one of the most dramatic and challenging situations in the emergency room. Although the steps for cardiopulmonary resuscitation (CPR) in pregnant women are very similar to those related to the conventional protocol stipulated by advanced cardiac life support (ACLS), there are different details that require due attention, which are summarized in Figure 13.[404]

It is worthwhile to remember that many episodes of CRA are preceded by signs of hemodynamic instability. For this reason, teams providing care should receive training regarding not only prompt recognition and evaluation of these findings, but also complete performance of CPR in a synchronous manner.[405]

The mechanical effects of the pregnant uterus can aggravate desaturation and hypotension in aortocaval compression, favoring cardiorespiratory collapse.In the attempt to reduce aortocaval compression by the gravid uterus, manual left uterine displacement should be performed throughout attendance and during care following CRA.[406]

When indicated, defibrillation should be performed promptly, without delay or questioning. It is known that it does no harm to the fetus; it is completely safe, and the energy doses established by current protocols should be maintained.[407]

In the same manner as the indications for defibrillation regarding energy doses, medications and their doses should be the same as those defined by protocols used in adults in general.[405,407,408]

Attention should be paid to venous access above the diaphragm, thus minimizing the effects of aortocaval compression caused by the gravid uterus, which would make it difficult to recirculate the medication.[409]

For pregnant women, in addition to considering the classic causes of CRA established by the ACLS protocol, which makes use of a mnemonic device with letters *A* to *H*, there are other diverse conditions which may favor cardiorespiratory collapse, and which may be corrected[409] (Table 44).

As soon as CRA is identified in a pregnant patient, the performance of perimortem cesarean delivery should promptly be considered if the patient's uterus is above her umbilicus.[410] This measure is characterized by performing cesarean delivery and birth of the fetus after maternal CRA, in most cases during the period of CPR. A review of the last decade has shown that perimortem cesarean delivery is related to maternal survival in 31.7% of cases, and it has no harmful effects on the mother.[411]

One of the purposes of performing this type of delivery is to facilitate CPR, because it possible to release aortocaval compression by the gravid uterus completely, seeing that lateralizing it to the left is not sufficient. The other purpose is to deliver the child, reducing the risk of anoxia during the period of CRA, thus minimizing definitive neurological sequelae.[412]

The decision to perform urgent cesarean delivery should be made within the first 4 minutes after CRA. Delivery should be in the same place as attendance for CPR, given that patient transfer may lead to delays that increase risks to the fetus and compromise resuscitation maneuvers.[409] It is worth highlighting that the entire CPR protocol should be maintained during performance of the procedure. In situations where the maternal clinical picture is considered irreversible, perimortem cesarean delivery should be performed immediately.

5.7.7. Key Points

- In emergency cases, practice should prioritize the mother's life. It is not justified to omit any treatment that is essential to the mother on account of concerns regarding potentially harmful effects to the fetus;
- Practice for cardiac emergencies during pregnancy should follow conventional protocols, such as ACLS.
- Cesarean section is considered "perimortem" in pregnant women with uterine height above the umbilical scar, in order to improve the maternal-fetal prognosis.

6. Family Planning

6.1. Pregnancy Counseling and Maternal Risk Stratification

Preconception counseling is essential for women of reproductive age with heart disease, with emphasis on maternal and fetal risks related to gestation and information regarding the safety and efficacy of contraception. The criteria of functional evaluation for approving or contraindicating pregnancy include anamnesis, clinical examination, and subsidiary examinations, such as ECG, chest X-ray, transthoracic or transesophageal echo, CMR, ergospirometry

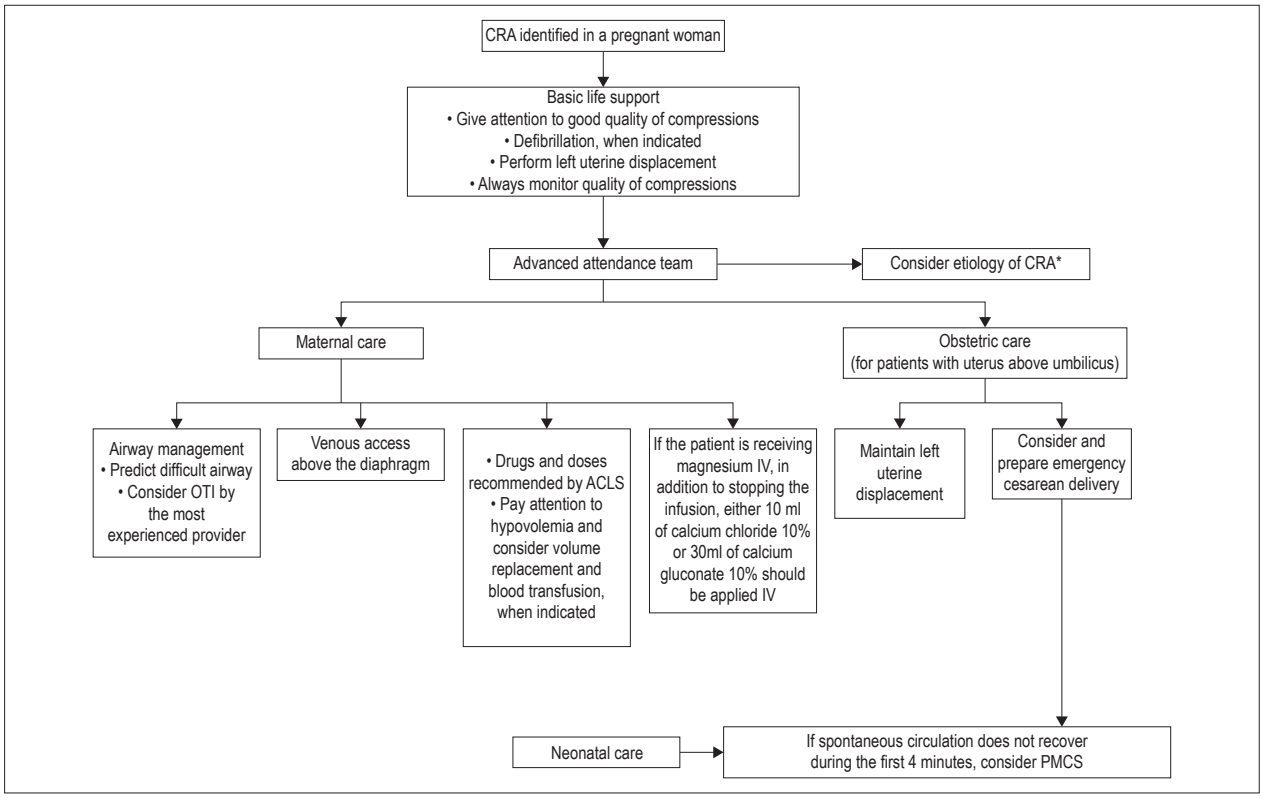

Figure 13 – *Flowchart for guiding intra-hospital care for cardiorespiratory arrest in pregnant women. ACLS: advanced cardiology life support; CRA: cardiorespiratory arrest; IV: intravenous; OTI: orotracheal intubation; PMCS: postmortem cesarean section. * Causes are shown in Table 44.*

test, and other more specific tests. Invasive intervention for eventual treatment of cardiac lesions, if indicated, should be performed before gestation.

Once a diagnosis of heart disease (anatomical, functional, and syndromic) has been determined, the risk of pregnancy is weighed together with the couple or relatives.[270] Identification of risk predictors for pregnancy contributes to determining maternal prognosis and decision making, such as approving or advising against conception.

The prospective multicenter study known as CARPREG[190] considered a study population composed 75% of women with congenital heart disease and 25% of women with acquired heart disease, verifying cardiovascular complications in 13%, including 3 cases of maternal death. The predictors of maternal mortality proposed by this study are shown in Table 45.

Subsequently, the ZAHARA study[413,414] defined independent predictors of mortality for women with congenital heart disease, generating a very specific risk estimate. The event rate in the 1,300 women studied was 7.6%, and the most frequent complications were arrhythmia (4.7%) and HF (1.6%) (Table 46).

The classification for the WHO which divides heart diseases by increasing level of severity: (1) risk I includes low-risk heart diseases (accepted as equal to that of the general population); (2) risk II denotes a slight risk of mortality and moderate risk of morbidity; (3) risk III, there is a significant risk of mortality or severe morbidity, (4) risk IV denotes a high risk of mortality that contraindicates pregnancy (Table 47).[415]

Comparison between the 3 studies,[324] considering the CARPREG, ZARAHA, and WHO scores, revalidated the WHO classification as the most accepted and reliable for predicting risks of heart disease to pregnancy (Tabela 47).

Patients included in the IV-WHO risk should be advised against pregnacy.[324] The Registry of Pregnancy and Cardiac Disease (ROPAC) validated the modified WHO classification,[416] which includes an intermediate category (risk II/III-WHO) which means moderate risk of morbidity and mortality. This study also showed differences between developed and emerging countries regarding the characteristics of heart diseases and the complication rates that can lead to distortions in the interpretation of the risk score. The ESC[52] Guidelines suggest using the modified WHO classification to establishment maternal risk.

This Brazilian Statement understand that WHO classification is the most accepted, and it should be applied to risk stratification of heart diseases for pregnancy. It is worth considering that complicating factors that are expected throughout the natural history of heart diseases, such as complex arrhythmias, prior HF, thromboembolism, or IE, aggravate maternal risk. The resources for care and the availability of a multidisciplinary team should also be considered and individualized during pregnancy counseling.

The ESC Guidelines[52] added aortic diseases associated with the following to WHO risk IV category: Turner syndrome (aortic size index of 25 mm/m^2); tetralogy of Fallot (aorta diameter > 50 mm), Ehlers-Danlos vascular syndrome; and Fontan circulation with complications.

Table 44 – Main causes of cardiorespiratory arrest in pregnant women and maternal mortality

Letter	Causes	Etiology
A	Accident/trauma Anesthetic complications	High neuraxial block Hypotension Bronchoaspiration Respiratory depression Respiratory airway obstruction Trauma Suicide
B	Bleeding	Coagulopathy Uterine atony Placenta accreta Placenta praevia Uterine rupture Premature placental abruption Transfusion reaction Retained products of conception
C	Cardiovascular causes	Acute infarction Dissection of the aorta Cardiomyopathy Arrhythmias Valve disease Congenital heart disease
D	Drugs	Oxytocin Magnesium Illicit drugs Opioids Insulin
E	Embolic causes	Amniotic fluid embolism Pulmonary embolism Cerebrovascular event
F	Fever	Infection Sepsis
G	General	H's (hypovolemia, hypoxia, hypoglycemia, hypokalemia, hyperkalemia, hypothermia) T's (tension pneumothorax, cardiac tamponade, toxicity, infarction, and pulmonary thromboembolism)
H	Hypertension	Preeclampsia Eclampsia HELLP syndrome Intraparenchymal bleeding

HELLP: hemolysis, elevated liver enzymes, and low platelet count.

6.1.1. Key Points

- Family planning is essential for women with heart disease, regarding both risk stratification for pregnancy and contraceptive choice;
- Risk predictors should be defined before pregnancy;
- The risk classification elaborated by the WHO is currently the most accepted;
- Resources for attendance and availability of a specialized multidisciplinary team should be considered during pregnancy counseling.

6.2. Contraception in Patients with Cardiovascular Disease

6.2.1. Different Contraceptive Methods

Contraception is the use of methods and techniques with the aim of impeding sexual relations from resulting in pregnancy. It is a family planning resource for constituting desired and consciously planned reproduction. There are currently numerous known contraceptive strategies, which may be grouped into the following categories: behavior-based methods, barrier methods, intrauterine devices (IUD), hormonal methods, and surgical methods.

Hormonal methods include combined (containing estrogen and progestin) and progestin-only methods. The former include combined pills, vaginal rings, patches, and monthly ingestions. Progestin-only methods include progestin-only pills, quarterly injections, etonogestrel subdermal implant, and levonorgestrel-releasing IUD.

Understanding that different means of contraception present different mechanisms of action, adverse event profiles, beneficial non-contraceptive effects, which vary according to any given clinical context, is the basis for selecting the most appropriate contraceptive method; it is also indispensable to evaluate patients' wishes and expectations, in addition to their beliefs regarding the method, in order to optimize adherence.

Table 45 – Predictors of maternal events and risk score from the CARPREG study

1. Previous cardiac event (HF, transitory ischemic attack, pulmonary stroke prior to gestation, or arrhythmia)
2. NYHA FC > II or cyanosis
3. Left heart obstruction (mitral area < 2 cm^2, aortic valve area < 1.5 cm^2, or peak left ventricular outflow gradient > 30 mmHg on echo)
4. Reduced systolic ventricular function (< 40%)
CARPREG risk score (each predictor is worth 1 point)
• 0 points – 5% risk
• 1 point – 27% risk
• More than 1 point – 75% risk

FC: functional class; HF: heart failure; NYHA: New York Heart Association.

Table 46 – Predictors of maternal risk from the ZAHARA study

History of arrhythmia before gestation – **1.5 points**
HF with NYHA FC > II – **0.75 points**
Left heart obstruction (aortic valve stenosis with peak gradient > 50 mmHg or valve area < 1 cm^2) – **2.5 points**
Mechanical prosthetic valve – **4.25 points**
Moderate to severe systemic atrioventricular valve regurgitation (possibly due to ventricular dysfunction) – **0.75 points**
Moderate to severe subpulmonary atrioventricular valve regurgitation (possibly due to ventricular dysfunction) – **0.75 points**
Cardiovascular medication use before gestation – **1.5 points**
Repaired or unrepaired cyanotic heart disease – **1 point**
ZAHARA risk score:
0 to 0.5 – 2.9% risk
0.51 to 1.5 – 7.5% risk
1.51 to 2.5 – 17.5% risk
2.51 to 3.5 – 43.1% risk
> 3.5 – 70% risk

FC: functional class; HF: heart failure; NYHA: New York Heart Association.

In order to choose a contraceptive method, should be considerer 1) safety supported on the into medical eligibility criteria of available methods 2) clinical condition of patiente; 3) effectiveness, determined by the number of failures (i.e. pregnancies) that occur in every 100 women utilizing the method for 12 months, which is known as the Pearl index[417] (Figure 14).

Patients with severe diseases that contraindicate pregnancy or patients who wish to postpone or avoid pregnancy should receive adequate counseling regarding contraception.[418] Furthermore, patients with contraindications to gestation have higher surgical risks; for this reason, permanent methods (laparotomic, laparoscopic, or hysteroscopic tubal ligation) are not any more recommended than any other highly efficacious methods.

In recent years, special attention has been given to long-acting reversible contraception (LARC) methods. These methods have greater adherence because they do not depend on the user remembering them; furthermore, they have greater contraceptive efficacy, with a lower number of failures, and they do not contain estrogen. This category includes both types of IUD (copper and levonorgestrel) and etonogestrel subdermal implant.[419,420]

6.2.2. Medical Eligibility Criteria

The WHO has analyzed the safety of different contraceptive methods, taking each clinical condition and their relevant characteristics into consideration, including the following: whether the method worsens a preexisting condition or adds additional health risks; and whether the condition renders the contraceptive method less effective.[421] Safety should always be weighed when comparing the risk of an unplanned pregnancy. It is fundamental to remember that refusing patients access to all contraceptive methods due to concerns related to diseases they have increases the risk of decompensating these diseases should pregnancy occur.

Table 48 shows a summary of the categories of medical eligibility criteria for contraceptive choice.

Table 47 – Modified WHO classification

Risk I
• Pulmonary stenosis, PDA, and mild to moderate uncomplicated mitral valve prolapse
• IAC, IVC, PDA, and uncomplicated, successfully repaired pulmonary vein drainage anomalies
• Isolated atrial or ventricular extrasystoles
Risk II (uncomplicated):
• Unoperated uncomplicated IAC and IVC
• Repaired tetralogy of Fallot
• Most arrhythmias
Risk II-III (individualized evaluation)
• Mild left ventricular impairment
• Hypertrophic cardiomyopathy
• Native or tissue valvular heart disease (not considered WHO risk I or IV)
• Marfan syndrome without aortic dilatation
• Bicuspid aortic valve with aorta diameter < 45 mm
• Repaired coarctation of the aorta
Risk III
• Mechanical prosthetic valve
• Systemic right ventricle
• Fontan circulation
• Cyanotic heart disease (unrepaired)
• Complex congenital heart diseases
• Marfan syndrome with aorta diameters between 40 and 45 mm
• Bicuspid aortic valve with aorta diameters between 45 and 50 mm
Risk IV (pregnancy contraindicated):
• Pulmonary arterial hypertension of any etiology
• Severe systemic right ventricular dysfunction (LVEF < 30%, NYHA FC III/IV)
• Peripartum cardiomyopathy with ventricular dysfunction
• Severe mitral stenosis, severe symptomatic aortic stenosis
• Marfan syndrome with dilated aorta > 45 mm
• Aortic dilatation associated with bicuspid valve > 50 mm
• Turner syndrome with aortic index > 25 mm/m^2
• Tetralogy of Fallot with aorta > 50 mm
• Ehlers-Danlos syndrome
• Fontan procedure with any complication
• Severe coarctation of the aorta

FC: functional class; IAC: interatrial communication; IVC: interventricular communication, LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; PDA: patent ductus arteriosus.

Accompanying women of fertile with heart disease requires decisions on the application of family planning methods and, therefore, contraception counseling. A pioneering study on the efficacy and safety of contraceptives that included low-dose combined oral contraceptives, quarterly injection of progestin, and IUD in women with heart disease showed good tolerance and safety for patients who followed the eligibility criteria.[422]

6.2.3. Contraception in Adverse Conditions

6.2.3.1. Hypertension

In patients with hypertension, the use of combined contraceptive methods may worsen blood pressure control. Ethinylestradiol increases the hepatic synthesis of angiotensinogen, which leads to an increase in angiotensin II and aldosterone, with higher systolic volume and greater cardiac output, as well as increased peripheral vascular resistance, thus resulting in greater arterial pressure. In susceptible patients, this increase may be considerable, causing clinical decompensation.[423] For this reason, patients with hypertension, even if it is controlled, should not use combined methods; there is, however, no contraindication to the use of progestin-only methods in patients with controlled hypertension, and, in patients with uncontrolled hypertension, only quarterly injections should be avoided. Table 49 shows the medical eligibility criteria for different types of contraception in relation to patients with SAH.

6.2.3.2. Diabetes Melittus

Patients with diabetes are at a greater risk of cardiovascular events than healthy women, and they are more exposed to unfavorable outcomes during pregnancy.[424] For this reason, contraception in patients with diabetes should be guided by the best available evidence.[425] Table 50 summarizes the eligibility criteria for different contraceptive methods in patients with diabetes.

There is a theoretical concern that, due to its glucocorticoid effect, quarterly depot injections of medroxyprogesterone acetate may worsen glycemic control, and, in patients with vasculopathy, they may increase the risk of thromboembolic and cardiovascular events; for this reason, it is classified as category 3.

6.2.3.3. Heart Valve Disease

Complicated heart valve diseases are included in the WHO list of conditions that expose women to greater health risks due to undesired pregnancy.[415,426] Nevertheless, several studies have shown expressively low rates of use of contraceptive methods in women with heart disease.[422,427] To comprehend the criteria summarized in Table 51, heart valve diseases are divided into complicated and uncomplicated. Those that are accompanied by PH, risk of AF, and history of subacute bacterial endocarditis are considered complicated. Table 51 shows the medical eligibility criteria for different types of contraception in relation to patients with heart valve disease.

Currently, the indication for antibiotic prophylaxis during IUD insertion is controversial, and the available evidence does not seem to justify making it mandatory. Deciding whether or not to use it is at the attending physician's discretion, considering associated risks and benefits. It is, however, indispensable to remember that the best way to avoid pelvic infection is by performing adequate antisepsis.

6.2.3.4. Previous Cardiovascular Events

Women with ischemic coronary disease or stroke may safely initiate progestin-only contraceptive methods, with the exception of the quarterly injection. However, if events

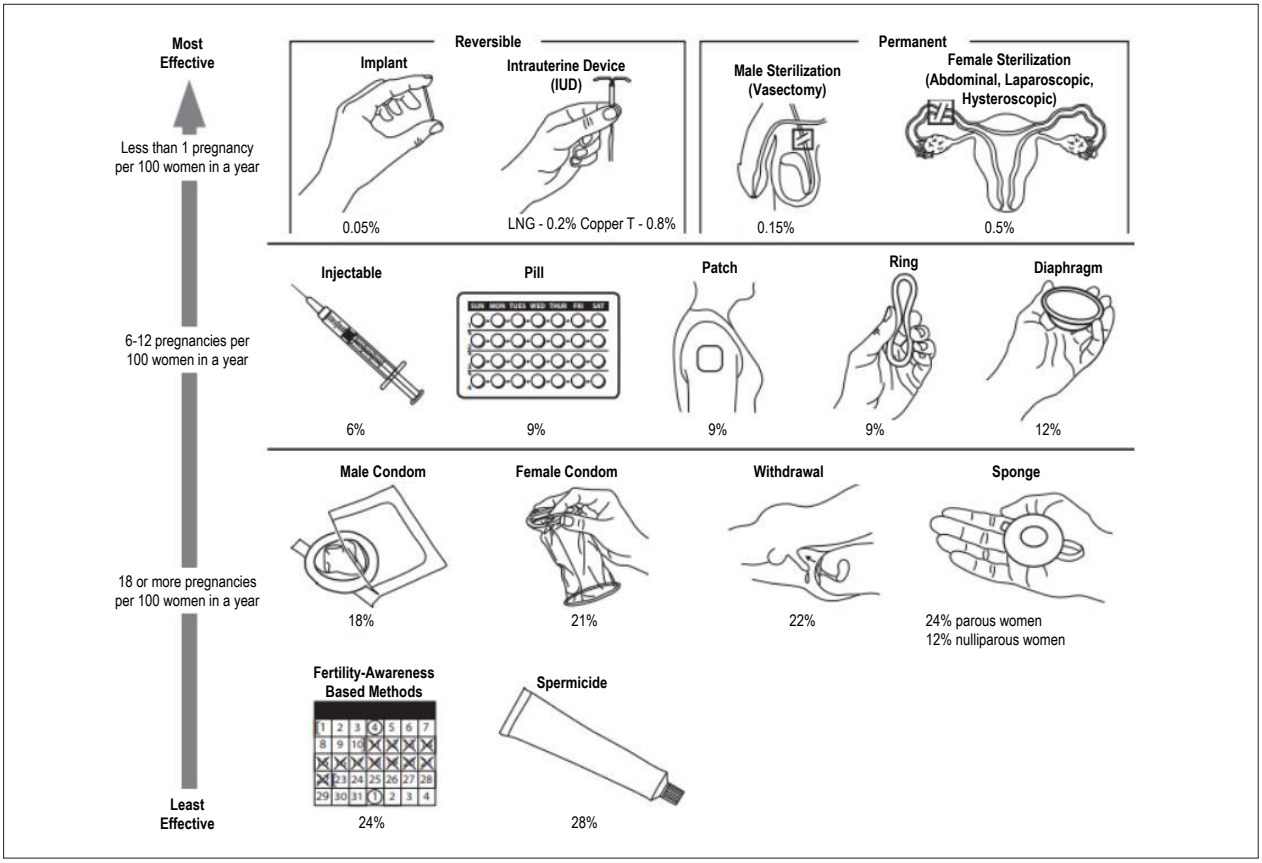

Figure 14 – *Pearl indexes of the main contraceptive methods. Adapted from Curtis et al.*[417]

Table 48 – Categories of medical eligibility criteria for contraceptive choice.

Condition for which there is no restriction regarding use of the contraceptive method
Condition where the advantages of using the method generally outweigh theoretical or proven risks
Condition where the theoretical or proven risks outweigh the advantages of using the method
Condition that represents an unacceptable health risk if the contraceptive method were used

Adapted from the World Health Organization, 2015.[421]

occurred after hormonal contraceptive use, it should be changed to a non-hormonal method. In this clinical context, combined methods, also should be avoided.[428,429] Table 52 shows the medical eligibility criteria of different contraceptive methods in relation to patients with previous cardiovascular events.

6.2.3.5. Obesity

In the absence of other clinical conditions, obese patients do not have contraindications to the use of any method. Furthermore, even if it is necessary to investigate metabolic syndrome and screen for other cardiovascular conditions due to obesity, the results of complementary examinations should not delay the introduction of contraceptive methods.[430]

With respect to quarterly injections (150-mg doses of intramuscular depot medroxyprogesterone acetate), there is a Brazilian study showing significantly higher weight gain in women using quarterly injections, in comparison with copper IUD.[431] For this reason, quarterly injections are not typically the first choice; there is, however, no formal contraindication, and the method may be used.

Specifically in obese women, there is a theoretical concern that methods may be less efficacious. Even if this is the case, their efficacy continues to be high; for this reason, they should not be contraindicated.

6.2.3.6. Congenital Heart Disease

Contraception counseling in patients with congenital heart disease begins at menarche, with advice regarding the risks of gestation and choice of contraception method. Congenital heart diseases are not explicitly listed in the WHO's eligibility criteria, and they should be understood within

Table 49 – Medical eligibility criteria for different types of contraception in relation to patients with systemic arterial hypertension

	Combined hormonal contraception				Progestin-only contraception			Intrauterine device	
	Oral	Patch	Vaginal ring	Monthly injection	Oral	Quarterly injection	Subdermal implant	Copper	Levonorgestrel
History of SAH where blood pressure is not known	3	3	3	3	2	2	2	1	2
Controlled SAH	3	3	3	3	1	2	1	1	1
SAH with elevated blood pressure – SAP 140 to 159 mmHg and/or DAP 90 to 99 mmHg – SAP ≥ 160 mmHg and/or DAP ≥ 100 mmHg	3	3	3	3	1	2	1	1	1
	4	4	4	4	2	3	2	1	2
Target organ disease	4	4	4	4	2	3	2	1	2

DAP: diastolic arterial pressure; SAH: systemic arterial hypertension; SAP: systemic arterial pressure. Adapted from the World Health Organization, 2015.[421]

Table 50 – Medical eligibility criteria for different types of contraception in relation to patients with diabetes

	Combined hormonal contraception			Progestin-only contraception			Intrauterine device	
Oral	Patch	Vaginal ring	Monthly injection	Oral	Quarterly injection	Subdermal implant	Copper	Levonorgestrel
Without vascular lesion	2	2	2	2	2	2	1	2
2								
Nephropathy, neuropathy, or retinopathy	3 / 4	3 / 4	3 / 4	2	3	2	1	2
3/4								
Other vascular disease	3 / 4	3 / 4	3 / 4	2	3	2	1	2
3/4								
or > 20 years' disease duration								

Adapted from the World Health Organization. Medical Eligibility Criteria for Contraceptive Use. 5th ed. Geneva: World Health Organization; 2015.[421]

Table 51 – Medical eligibility criteria for different types of contraception in relation to patients with heart valve disease

	Combined hormonal contraception				Progestin-only contraception			Intrauterine device	
	Oral	Patch	Vaginal ring	Monthly injection	Oral	Quarterly injection	Subdermal implant	Copper	Levonorgestrel
Uncomplicated	2	2	2	2	1	1	1	1	1
Complicated	4	4	4	4	1	1	1	2	2

Adapted from the World Health Organization. Medical Eligibility Criteria for Contraceptive Use. 5th ed. Geneva: World Health Organization, 2015.[421]

the physiopathology of each group of heart disease and the risk of unplanned pregnancy (Table 53). Complex congenital heart diseases present diverse structural lesions which complicate risk stratification of contraceptive use.[415,427] In any event, cyanotic heart diseases, diseases with PAH, Eisenmenger syndrome, and diseases with an elevated risk of thromboembolism have an absolute contraindication to the use of combined methods. For these groups of patients in WHO classes III and IV, the use of progestin-only methods is recommended, and monthly injections are recommended in cases with low risks of tromboembolism.[432-434] Due to pain issues, when patients have more delicate heart conditions that occur with the risk of arrhythmias, the IUD should be inserted in a hospital environment, with the possibility of prompt relief provided by an anesthesiologist with experience in women with heart disease, due to the risk of vagal reaction following IUD insertion.

6.2.3.7. Pulmonary Hypertension

As the literature is very limited, eligibility criteria for patients with PAH are not included. For this reason, contraception should be effective, tolerable, and non-harmful, because all patients with PAH should be advised against becoming pregnant. For this reason, barrier methods or "fertility-awareness" based methods are not recommended, because they have very elevated failure rates. Among reversible hormonal contraceptives, estrogen-containing compounds are not recommended due to the risk of PTE, leaving progestin-only methods, which may be injectable, oral, or via subcutaneous implantation, which is the most indicated.[419,420]

Table 52 – Medical eligibility criteria for different types of contraception in relation to patients with previous cardiovascular events

	Combined hormonal contraception				Progestin-only contraception			Intrauterine device	
	Oral	Patch	Vaginal ring	Monthly injection	Oral	Quarterly injection	Subdermal implant	Copper	Levonorgestrel
Ischemic heart disease	4	4	4	4	I: 2, C: 3	3	I: 2, C: 3	1	I: 2, C: 3
Stroke	4	4	4	4	I: 2, C: 3	3	I: 2, C: 3	1	2

I: initiation; C: continuation. Adapted from the World Health Organization, 2015.[421]

Table 53 – Recommendations for contraceptive use in patients with congenital heart disease

	OC	Progestin-only pill	Implant	Depo-Provera	IUD	Barrier
1. Surgically corrected defects:						
Without residual lesions: IAC/IVC/PDA	1	1	1	1	1	
Shunt and/or residual obstruction	3	1	1	1	3	1
Prosthetic valve, tubes, patches	2	1	1	1	2	1
Pulmonary and/or systemic hypertension	4	2	2	2	3	1
2. Uncorrected, residual, or postoperative defects:						
Small IVC	2	1	1	1	4	1
Mild to moderate shunt (IAC, IVC, PDA)	4	1	1	1	4	2
Residual pulmonary or systemic hypertension (CoA)	2	1	1	1	4	3
Complex cyanotic defects	4	1	1	1	4	1
3. Complicated defects due to:						
Cyanosis	4	1	1	1	-	1
Ventricular dysfunction	3	1	1	1	-	1
Atrial fibrillation/flutter	4	2	2	2-	4	2
Eisenmenger syndrome	4	2	2	2	4	4

CoA: Coarctation of the aorta; IAC: interatrial communication; IUD: intrauterine devices; IVC: interventricular communication; OC: oral contraceptives; PDA: patent ductus arteriosus.

Copper-T IUD pose a risk of metrorrhagia, while long-acting reversible contraceptive (LARC) methods with levonorgestrel may be recommended when the patient does not present structural cardiac injury.

Unplanned pregnancy is very frequent in women with heart disease, especially due inadequate contraception counseling. In fact, myths about the eventual risks and lack of knowledge about the efficacy and application of eligibility criteria are factors which favor maternal mortality. Faced with this reality, contraception counseling regarding preferences, contraindications, and efficacy of methods should be initiated during the immediate postpartum period, even before hospital discharge.[435]

6.2.4. Contraception and Adolescence

Age alone does not represent a contraindication to different methods of contraception; nevertheless, during adolescence, doubts may arise regarding strategies for presenting and prescribing contraceptives. Indication of methods should be based on eligibility criteria and, when attending adolescents, it is necessary to consider ethical and legal aspects, which are not always known.

Article 226 of the Brazilian Constitution guarantees the right to family planning free of coercion, and the Child and Adolescent Statute (Law Number 8069, July 13, 1990) clearly addresses important issues in providing care to adolescents who require contraceptive methods, based on privacy and confidentiality rights.

Adolescent patients have the right to privacy, i.e., to be attended alone, in a private consultation space. Confidentiality is defined as an agreement between physicians and patients, meaning that information discussed during and after consultation may not be disclosed to adolescents' parents or guardians without their express consent.[420]

Confidentiality is supported by rules of medical bioethics, through moral principles of autonomy (article 103 of the Code of Medical Ethics). In this manner, adolescents have the right to sexual education, access to information about contraception, confidentiality and secrecy regarding their sexual activity, and the prescription of contraceptive methods; there are no ethical infractions when medical professionals proceed in this manner.

Contraceptive counseling involving short-lasting methods such as pills is generally applied without problems following these precepts. On the other hand, in relation to long-lasting methods (intrauterine methods and implants), as they require medical procedure for insertion, doubts may arise. The Brazilian Federation of Gynecological and Obstetric Associations (FEBRASGO, acronym in Portuguese) suggests that, for these methods, the consent of adolescents and their legal guardians should be considered, reinforcing contraceptive counseling.[436]

With respect to adolescents with heart disease, contraception should be safe and effective; there is, however, a great barrier to the knowledge of different options and their access, often due to the high initial costs. During contraception counseling for adolescents with WHO risks III/IV for pregnancy, it is necessary to present all available methods with low Pearl indexes, good tolerance, and acceptance for continuity of the method, such as IUD and implants. Nevertheless, the most popular forms of contraception in adolescents continue to be condoms and withdrawal, which represent a high rate of unplanned pregnancy and high risk.

Lack of knowledge, inadequate counseling, social-cultural taboos, legal restrictions, and moralistic attitudes regarding sexuality during adolescence are common, even in patients who choose or wish to use a contraceptive method. Although long-acting methods (IUD and implant) are prioritized by medical entities,[419] difficulties in access and acceptance by adolescents demonstrate that traditional methods, such as combined oral contraceptives and condoms, should receive focus during counseling, with the aim of improving rates of continuity and, in final analysis, reducing the possibility of high-risk pregnancies and maternal mortality due to heart disease.

6.2.4.1. Key Points

- There are numerous contraceptive methods (behavior-based, barrier, IUD, hormonal, and surgical) that may be prescribed to women with heart disease;
- Choice of contraceptive methods should consider patients individually, including their wishes and tolerance, as well as the eligibility criteria proposed by the WHO;
- Ethical and legal aspects should be considered regarding contraception in adolescents.

6.3. Ethical Considerations

The advances in medicine transformed Michel Peter's proverb, *"Women with heart disease, don't get married, and, if you do, don't get pregnant,"* outdated. That was the case two centuries ago for preserving the lives of young women with heart disease. We are currently living in a new era, in which the risk of pregnancy is generally lower, with resources to cope with most complications that may eventually occur.

Heart disease and pregnancy should be a comprehensive topic based on medical ethics, integrating several moments during which the multidisciplinary interface is stablished in the care of pregnant women and her child. Physicians should apply scientific rigor, based on validated clinical recommendations, clarify the benefits and possible risks and respect the patient's right to participate freely and actively in the decision-making process, obtaining consent informed for all decisions.

From moments before conception there have been situations related to maternal and fetal safety. Heart evaluation may reveal different degrees of risk due to pathological, clinical and therapeutic situations. Decision-making results in possible conflicts in the doctor-patient relationship, which require the application of bioethics fundamentals. Prudence must prevail. Therapeutic measures should consider the informed consent of the patient, which is based on their right to answer yes or no.

Furthermore, qualification of multidisciplinary teams is fundamental to family planning in young women with heart disease, based on maternal risk stratification, regarding the article 226 of the Brazilian Constitution, which states the following: "Based on the principles of human dignity and responsible parenthood, family planning is a free choice of the couple, it being within the competence of the State to provide educational and scientific resources **for the exercise of this right, any coercion by official or private agencies being forbidden" (our emphasis added). This norm refers to other items: a) dignity of the human person (Article 1, III) and b) right to liberty (Article 5, Heading)."

During pregnancy, the doctor-patient relationship requires total reception by the doctor and adherence by the patient, obviously with adequate availability of institutional resources and the health system.

Interdisciplinary team is desirable at all times of pregnancy and postpartum period; however, it expands its value in the approximation of childbirth, when it is essential the professional competence of the care team. The decision of moment and type of delivery, the search for technological and infrastructure support in general are well assisted by the application on bioethics fundaments.

The puerperium has specific peculiarities and the mother with heart disease demands a higher level of care than usual, while the newborn already has a life of her own, with her particular demands. Thus, there are conflicts, such as non-consent for a medical instruction, it is up to the doctor – or the Service – to make a critical reassessment, based on bioethics at the Bedside for the specific case. The agreement made with the patient must be strictly adhered to by the doctor.

Erratum

In the Statement "Brazilian Cardiology Society Statement for Management of Pregnancy and Family Planning in Women with Heart Disease – 2020", with DOI number: https://doi.org/10.36660/abc.20200406, published in the periodical Arquivos Brasileiros de Cardiologia, 114(5): 849-942, on page 851, in the conflict of interests of Dr. Fernando Souza Nani, in the item " Spoke at events or activities sponsored by industry related to this statement", consider the company CSL Behring to be correct instead of Boehringer.

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Brazilian Cardiovascular Rehabilitation Guideline – 2020

Development: *Department of Exercise Testing, Sports Exercise, Nuclear Cardiology, and Cardiovascular Rehabilitation of the Brazilian Society of Cardiology (SBC)*

Norms and Guidelines Council: *Brivaldo Markman Filho, Antonio Carlos Sobral Sousa, Aurora Felice Castro Issa, Bruno Ramos Nascimento, Harry Correa Filho, Marcelo Luiz Campos Vieira*

Norms and Guidelines Coordinator: *Brivaldo Markman Filho*

Guideline Coordinators: *Tales de Carvalho e Mauricio Milani*

Guideline Authors: *Tales de Carvalho,[1,2] Mauricio Milani,[3] Almir Sergio Ferraz,[4] Anderson Donelli da Silveira,[5,6,7] Artur Haddad Herdy,[1,8,9] Carlos Alberto Cordeiro Hossri,[4,10] Christina Grüne Souza e Silva,[11] Claudio Gil Soares de Araújo,[11] Eneas Antonio Rocco,[12] José Antonio Caldas Teixeira,[13] Luciana Oliveira Cascaes Dourado,[14] Luciana Diniz Nagem Janot de Matos,[15] Luiz Gustavo Marin Emed,[16] Luiz Eduardo Fonteles Ritt,[17,18] Marconi Gomes da Silva,[19] Mauro Augusto dos Santos,[20,21] Miguel Morita Fernandes da Silva,[22] Odilon Gariglio Alvarenga de Freitas,[23] Pablo Marino Corrêa Nascimento,[13,21] Ricardo Stein,[5,6,7] Romeu Sergio Meneghelo,[4,15] Salvador Manoel Serra[24]*

Clínica de Prevenção e Reabilitação Cardiosport,[1] Florianópolis, SC – Brazil
Universidade do Estado de Santa Catarina (Udesc),[2] Florianópolis, SC – Brazil
Fitcordis Medicina do Exercício,[3] Brasília, DF – Brazil
Instituto Dante Pazzanese de Cardiologia,[4] São Paulo, SP – Brazil
Programa de Pós-Graduação em Cardiologia e Ciências Cardiovasculares da Universidade Federal do Rio Grande do Sul (UFRGS),[5] Porto Alegre, RS – Brazil
Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul (HCPA/UFRGS),[6] Porto Alegre, RS – Brazil
Vitta Centro de Bem Estar Físico,[7] Porto Alegre, RS – Brazil
Instituto de Cardiologia de Santa Catarina,[8] Florianópolis, SC – Brazil
Unisul: Universidade do Sul de Santa Catarina (UNISUL),[9] Florianópolis, SC – Brazil
Hospital do Coração (Hcor),[10] São Paulo, SP – Brazil
Clínica de Medicina do Exercício, Clinimex,[11] Rio de Janeiro, RJ – Brazil
Hospital Samaritano Paulista,[12] São Paulo, SP – Brazil
Universidade Federal Fluminense (UFF),[13] Rio de Janeiro, RJ – Brazil
Instituto do Coração (Incor) do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP),[14] Rio de Janeiro, RJ – Brazil
Hospital Israelita Albert Einstein,[15] São Paulo, SP – Brazil
Hospital Cardiológico Costantini,[16] Curitiba, PR – Brazil
Hospital Cárdio Pulmonar,[17] Salvador, BA – Brazil
Escola Bahiana de Medicina e Saúde Pública,[18] Salvador, BA – Brazil
SPORTIF – Clínica do Exercício do Esporte,[19] Belo Horizonte, MG – Brazil
ACE Cardiologia do Exercício,[20] Rio de Janeiro, RJ – Brazil
Instituto Nacional de Cardiologia,[21] Rio de Janeiro, RJ – Brazil
Universidade Federal do Paraná,[22] Curitiba, PR – Brazil
Minascor Centro Médico,[23] Belo Horizonte, MG – Brazil
Instituto Estadual de Cardiologia Aloysio de Castro (IECAC),[24] Rio de Janeiro, RJ – Brazil

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Nota: These guidelines are for information purposes and should not replace the clinical judgment of a physician, who must ultimately determine the appropriate treatment for each patient.

Correspondence:
Sociedade Brasileira de Cardiologia – Av. Marechal Câmara, 360/330 – Centro – Rio de Janeiro – Postal Code: 20020-907.
E-mail: diretrizes@cardiol.br

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Almir Sergio Ferraz	Novartis, Amgen, Sanofi	No	No	No	No	Boehringer	No
Anderson Donelli da Silveira	No	No	No	No	No	No	No
Artur Haddad Herdy	No	No	No	No	No	No	No
Carlos Alberto Cordeiro Hossri	No	No	No	No	No	No	No
Christina Grüne Souza e Silva	No	No	No	No	No	No	No
Claudio Gil Soares de Araújo	No	No	No	No	Inbramed	No	No
Eneas Antonio Rocco	No	No	No	No	No	No	No
José Antonio Caldas Teixeira	No	No	No	No	No	No	No
Luciana Diniz Nagem Janot de Matos	No	No	No	No	No	No	No
Luciana Oliveira Cascaes Dourado	No	No	No	No	No	No	No
Luiz Gustavo Marin Emed	No	No	No	No	No	No	No
Luiz Eduardo Fonteles Ritt	No	No	No	No	No	No	No
Marconi Gomes da Silva	No	No	No	No	No	No	No
Mauricio Milani	No	No	No	No	No	No	No
Mauro Augusto dos Santos	No	No	No	No	No	No	No
Miguel Morita Fernandes da Silva	No	No	No	No	Novartis	No	No
Odilon Gariglio Alvarenga de Freitas	No	No	No	No	No	No	No
Pablo Marino Corrêa Nascimento	No	No	No	No	No	No	No
Ricardo Stein	No	No	No	No	No	No	No
Romeu Sergio Meneghelo	No	No	No	No	No	No	No
Salvador Manoel Serra	No	No	No	No	No	No	No
Tales de Carvalho	No	No	No	No	No	No	No

Lista de Abreviaturas de Acrônimos

1RM – One repetition maximum test
ABI – Ankle-brachial index
AMI – Acute myocardial infarction
ARVC – Arrhythmogenic right ventricular cardiomyopathy
AV – Atrioventricular
BP – Blood pressure
CABG – Coronary artery bypass graft
CAD – Coronary artery disease
CI – Confidence interval
CKD – Chronic kidney disease
CPET – Cardiopulmonary exercise test
CVD – Cardiovascular disease
CVR – Cardiovascular rehabilitation
DBP – Diastolic blood pressure
ECG – Electrocardiogram
HBCR – Home-based cardiovascular rehabilitation
HCM – Hypertrophic cardiomyopathy
HF – Heart failure
HIIT – High-intensity interval training
HR – Heart rate
HTN – Hypertension
HTx – Heart transplantation
ICD – Implantable cardioverter–defibrillator
IMT – Inspiratory muscle training
LVEDD – Left ventricular end-diastolic diameter
LVEF – Left ventricular ejection fraction
LVESD – Left ventricular end-systolic diameter
LYS – Life-year saved
MET – Metabolic equivalent
MICT – Moderate-intensity continuous training
MRI – Magnetic resonance imaging
NCM – Noncompaction cardiomyopathy
NMES Neuromuscular electrical stimulation
NYHA – New York Heart Association
PAOD – Peripheral arterial occlusive disease
PASP – Pulmonary artery systolic pressure
PCI – Percutaneous coronary intervention
pmp – Per million population
SBP – Systolic blood pressure
SCD – Sudden cardiac death
TMET – Treadmill exercise test
VO_2 – Oxygen consumption

Content

1. Introduction

It is common sense—and has been scientifically proven – that physical activity helps to preserve and restore the health of both body and mind. The favorable effects of cardiovascular rehabilitation (CVR), with an emphasis on physical exercise, include significant reductions in cardiovascular and overall morbidity and mortality,[1] reductions in hospitalization rate,[1,2] and significant gains in quality of life,[1,2] as consistently documented in the literature, including in meta-analyses of randomized clinical trials. These effects justify the consensual, emphatic recommendation of CVR by major medical societies worldwide.[3-6]

Sedentary behavior, which is highly prevalent in Brazil and elsewhere, is strongly associated with cardiovascular disease (CVD) and early mortality.[7,8] Conversely, higher levels of physical activity are positively associated with better quality of life and longer life expectancy.[9-13] In addition, there is a strong, inverse association of the various components of physical fitness with all-cause mortality and with occurrence of adverse cardiovascular events: the lower the level of physical fitness, the higher the mortality rate.[14-21]

Therefore, the main objective of CVR, with an emphasis on physical exercise, is to improve the various components of physical fitness, both aerobic and non-aerobic (muscle strength/endurance, flexibility, balance). This requires a combination of different exercise modalities and types of training. In this view, beyond rehabilitation, CVR aims to provide the highest achievable level of physical fitness – in order to reduce the risk of further cardiovascular events – and to promote all of the other benefits derived from regular physical exercise.[14-21]

However, despite its documented benefits and excellent cost-effectiveness,[22,23] CVR is underutilized worldwide. In Brazil, considering the size of the country and the diversity of its population, several barriers limit access to RCV,[24,25] such as a scarcity of structured services, limited urban mobility, and high rates of violence in cities.[26,27] Within this context, so-called home-based cardiovascular rehabilitation (HBCR) programs,

in which most sessions take place in the patient's home under indirect supervision, can supplement or serve as an alternative to traditional programs in which training sessions are always carried out under direct supervision.

As in previous documents on this topic published by the Brazilian Society of Cardiology,[6,28-31] this guideline will exclusively address interventions based on physical exercise. The strength (or grade) of recommendation will always be proportional to the level of evidence available, as explained below.

1.1. Strengths (Grades) of Recommendation

- **Grade I**: there is conclusive evidence, or, failing that, a consensus that the procedure is safe and useful/effective;
- **Grade II**: there is conflicting evidence and/or divergent opinions on the safety and utility/effectiveness of the procedure:
  - **Grade IIA**: weight of the evidence/opinion is in favor of the procedure. Most experts approve;
  - **Grade IIB**: safety and utility/effectiveness are less well established, with no predominance of opinions in favor.
- **Grade III**: there is evidence and/or expert consensus that the procedure is not useful/effective and, in some cases, can even be harmful.

1.2. Levels of Evidence

- **Level A**: data obtained from multiple, large, concordant randomized studies and/or robust meta-analyses of randomized clinical studies;
- **Level B**: data obtained from a less robust meta-analysis, based on a single randomized trial or on non-randomized (observational) studies;
- **Level C**: data obtained from consensus expert opinions.

2. Structure of a Cardiovascular Rehabilitation Program

2.1. Staffing and Individual Responsibilities

The makeup of CVR teams must be adjusted to its objectives, target audience, and availability of human and material resources, taking into account regional characteristics, the modality of rehabilitation (direct or indirect supervision), and the site or setting (hospital, outpatient clinic, etc.). A multidisciplinary CVR team is usually composed of physicians, physical educators, physical therapists, and nurses, but may also include other professionals, such as dietitians, psychologists, and social workers.[31,32]

2.1.1. Primary Physician

CVR is an integral part of the optimized clinical treatment of patients with stable CVD. Thus, it is essential that the CVR team and the patient's primary physician work in an integrated manner. When referring a patient for rehabilitation, primary clinicians must be aware of its indications and potential benefits and should carry out the necessary pre-exercise evaluation. As this integration will involve frequent progress reports, potential needs for adjustment of drug therapy, awareness of complications and intercurrent events, etc., it is very important that mechanisms be established to facilitate communication between the patient's primary physician and the CVR team.[31]

2.1.2. Lead Physician of Cardiovascular Rehabilitation Program

The lead physician coordinates all medical activities. In Brazil, this role usually falls to the general coordinator of the CVR program. He or she must have in-depth subject knowledge of CVR and be trained to act in cardiovascular emergencies.[6,32-34]

Some of the main activities of this position include:

a) Perform pre-exercise evaluation, including cardiopulmonary exercise testing as needed, to provide inputs for the initial prescription of CVR training sessions.[31]

b) Train the CVR team to identify high-risk situations and provide appropriate care in emergencies.

c) Establish restrictions and set limits for the exercise prescription.

d) Lead and interact with other team members, to optimize the quality and safety of exercise prescription.

e) Schedule follow-up evaluations, always in coordination with the patient's primary physician.

2.1.3. Other Health Care Workers

Like physicians, the other members of the team, when carrying out their respective duties, must follow the program's rules and guidelines as well as the formal recommendations of their respective professional associations.[31]

2.1.4. Physical Therapists and Physical Educators

Physical therapists and physical educators are directly involved in the prescription and supervision of physical exercise, within the targets and limits defined by the physician as a result of the pre-exercise evaluation and follow-ups. They must have specific knowledge of CVD and exercise physiology and training in basic life support, including the use of an automated external defibrillator. Such training must be periodically refreshed to ensure continued competence. In addition to their direct role during CVR sessions, these professionals can provide patient guidance and contribute to other lifestyle measures aimed at adopting healthy habits.

2.1.5. Nurses

In a CVR program, nurses and other nursing professionals can assist in clinical evaluation and obtain and provide information on the patient's medical status, including through contact with family members. Nurses can also be in charge of blood glucose measurements and blood pressure (BP) checks before and/or during exercise sessions. In case of complications or intercurrent events, nurses can provide direct care, assist the physician and administer medications. Nurses must, of course, also be trained in basic life support, including the use of an automated external defibrillator.

2.2. Physical Infrastructure of a Rehabilitation Service

2.2.1. General Aspects

A CVR program can be run out of various types of facilities, depending on its objectives and on the available resources. Most often, CVR programs are carried out indoors, in air-conditioned environments, although exercise sessions can be held in outdoor venues such as running tracks, courts, gymnasiums, parks, or public recreation spaces.[29]

Indoor venues should be adequately sized and appointed, with dimensions and characteristics varying according to local resources and service capacity. The space should be large enough for patients to exercise in, ideally with a ceiling height not less than 2.5 meters. It should also be properly lit, well ventilated, and climate-controlled so as to maintain a temperature of 22–25°C and a relative humidity of 40–65% during sessions. The exercise area per se, not considering changing rooms, restrooms, and the reception area or waiting room, varies greatly – from 20 m^2 to a several hundred square meters. Proper changing rooms and restrooms are essential. To minimize the risk of accidental falls, slip-resistant flooring is mandatory.[29]

2.2.2. Fitness and Exercise Equipment

2.2.2.1. Aerobic Exercise

The most commonly used aerobic exercise equipment are treadmills and stationary bicycles (cycle ergometers), but upper-body ergometers, rowing machines, cross-country ski machines, and elliptical trainers can be used, among countless others.[29]

Treadmills must be electric, with a nominal capacity of at least 100 kg body weight, front and side supports for the hands, and a safety key. They must also allow individualized adjustments of speed and slope over a wide range. Cycle ergometers can be mechanical or electromagnetically braked. There are specific models for the upper body, and even some models which allow all four limbs to be exercised simultaneously. Conventional (lower body) models may be upright or recumbent. Ideally, the cycle ergometer should provide a readout of cadence or speed and, most importantly, power (in watts). Some cycle ergometers allow the user to program the intensity directly in watts, so that the resistance of the pedals increases when the cadence decreases and vice versa.

Rowing machines, ski machines, and elliptical trainers can be particularly useful for patients with a lower degree of functional limitation or who have had previous experience with such equipment. These devices provide the advantage of allowing simultaneous exercise of the upper and lower limbs.

2.2.2.2. Strength Training

Several types of equipment can be used for strength training. Bodyweight exercises, which require no equipment at all, are often sufficient in the most debilitated patients. One representative and functional example is rising from a seated position, which requires only a chair or bench.

Ropes or straps, firmly attached to the ceiling or high on a wall, can also be used to facilitate a wide range and variety of bodyweight exercises. Free weights, dumbbells, or ankle weights are often adopted in CVR programs, as they allow patients to execute a wide range of movements and provide appropriate stimulation of different muscle groups. Specific devices consisting of weights connected to cables and pulleys, known as cable machines or stack machines, can also be used. Other useful equipment includes workout bars, weighted exercise balls (also known as medicine balls), stability balls (also known as Swiss balls), and elastic bands or tubes (also known as exercise bands or resistance bands) with varying degrees of resistance.[29]

During all exercises, attention must be paid to proper posture and execution of the prescribed movements, so as to prevent musculoskeletal injuries. Attention when handling exercise equipment is also important to prevent accidents and potential injury.

2.2.2.3. Other Exercise Modalities

With a view to overall health, considering heart disease and associated conditions, patients may benefit from or even require other types of exercise, such as isometric handgrip training, inspiratory muscle training, and exercises designed to improve balance and flexibility.

2.2.3. Monitoring

Several modalities are available for patient monitoring, including heart monitors, mobile applications for monitoring heart rate (HR), glucometers, pulse oximeters, and conventional devices such as sphygmomanometers and stethoscopes. Depending on the clinical complexity and the risk of unfavorable cardiovascular events, continuous electrocardiographic monitoring (at rest or during exercise) may be convenient. This can be achieved by conventional ECG (connected directly to the patient) or by telemetry systems. Rapid access to monitoring equipment is of fundamental importance for proper detection and subsequent management of potential cardiovascular events.

2.2.4. Safety

Although serious cardiovascular events – such as cardiac arrest, which, in most adults, results from ventricular fibrillation or pulseless ventricular tachycardia – are extremely uncommon during CVR, it is essential that all programs have a plan in place to respond appropriately to these events if they do occur. Therefore, a defibrillator (whether manual or automated) is mandatory safety equipment. Other basic and advanced life support supplies must also be available, such as laryngoscopes, orotracheal tubes of various sizes, masks, a bag-valve-mask manual resuscitator, and supplemental oxygen.

For more detailed guidance on techniques, equipment, and recommended drugs, readers are advised to check subject-specific guidelines.[35,36]

3. Phases of Cardiovascular Rehabilitation and Risk Stratification

Traditionally, CVR is divided into time-bound phases, with phase 1 occurring in hospital and phases 2 to 4 in the outpatient setting. In the early days of CVR, phase 1 was intended for recovery after acute myocardial infarction (AMI) or coronary artery bypass surgery (CABG). Subsequently, in the context of what is now known as cardiopulmonary and metabolic rehabilitation, phase 1 was expanded to include hospitalized patients who underwent percutaneous coronary intervention (PCI), valve replacement or repair surgery, procedures for congenital heart disease, and heart transplantation (HTx), in addition to those with heart failure (HF), coronary artery disease (CAD), diabetes, hypertension, and chronic lung and kidney disease (once clinically stable). Therefore, CVR should begin immediately once the patient is considered clinically stable as a result of clinical and/or interventional treatment.[31]

In phase 1 of CVR, the aim is for the patient to be discharged from the hospital in the best possible physical and psychological condition and with guidance to pursue a healthy lifestyle, especially with regard to physical exercise. A combination of low-intensity physical exercise, techniques for stress control, and education on risk factors and heart disease is recommended. The team must be composed of at least one physician, one physical therapist, and one nurse. All should be trained specifically in CVR, but full-time dedication to the rehabilitation program is not required; team members are free to perform other duties in the hospital.[31]

Upon discharge from hospital, patients must be referred to the outpatient phases of CVR. Phase 2 begins immediately after hospital discharge and lasts, on average, 3 months. Phase 3 usually lasts 3 to 6 months, and phase 4 is quite prolonged. In all phases, the goal is to obtain progressive benefits from RCV or at least maintain any gains obtained.

A strict division of CVR into time-bound phases may fail to take into account that some very symptomatic, debilitated patients with severe heart disease will remain in long-term "phase 2" rehabilitation, as they continue to require direct supervision of physical exercise, while other low-risk patients may be fit for phase 3 or even phase 4 programs straight away, and are thus candidates for home-based CVR (in which most sessions take place under indirect, remote supervision).[31]

Therefore, stratification of clinical risk is recommended to enable a more rational use of CVR programs, with individualized targeting of phases and modalities. In this context, high-risk patients, those with less physical capacity, and those most symptomatic should participate in supervised sessions indefinitely, while those at lower risk, with greater physical capacity and fewer or less severe symptoms can engage in a wider range of more intense exercises without direct supervision (Figure 1).

Stratification of clinical risk as high, intermediate, or low is based on existing recommendations,[4,28,37] while the cut-off points for this classification are based on expert opinion (level C evidence), and can thus be modified according to the experience of the CVR team and the discretion and judgment of the clinician in response to the pre-exercise evaluation and subsequent evaluations (Table 1).

3.1. High Clinical Risk

The duration of CVR can vary according to the patient's clinical picture and progress of physical training. The initial classification, maintenance, and reclassification of risk profile must be based on the pre-exercise evaluation and on subsequent revaluations, carried out by the physician and other CVR team members. This evalution may vary according to the logistics, infrastructure and experience of each CVR service, but must at least consist of a clinical history, physical examination, resting electrocardiogram (ECG), and cardiopulmonary exercise test (CPET) or treadmill exercise test (TMET).

High-risk patients will often need immediate or short-term medical attention during CVR (hospital readmission, intervention, or adjustment of drug therapy). Therefore, they require closer monitoring by the team, which must be able to identify signs and symptoms of high-risk events and act immediately if such an event arises, providing basic and advanced life support, including with use of a manual or automated external defibrillator as necessary. It is preferable that this equipment be present in the room at all times. The medical team must be readily available on site to attend to the patient in the event of any serious complications.

It should be noted that the best way to prevent cardiovascular events during a rehabilitation program, and especially after events and interventions, is to conduct systematic pre-exercise evaluation and revaluations.

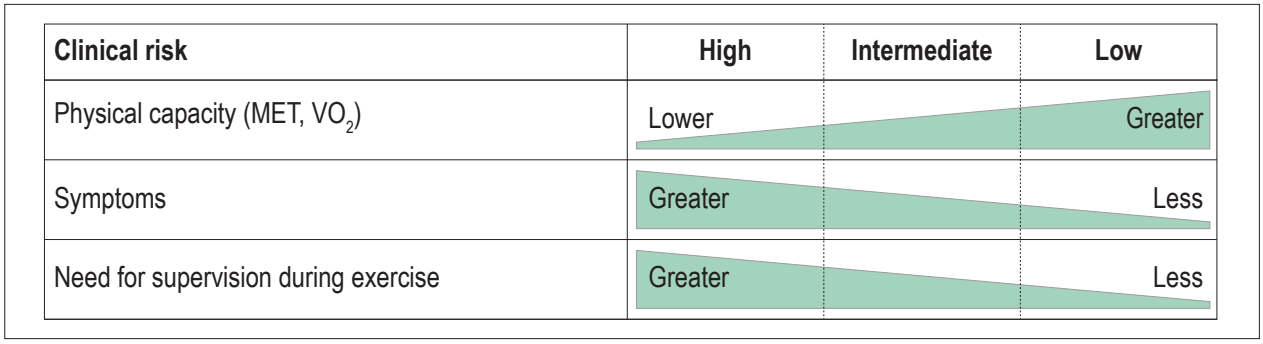

Figure 1 – *General characteristics of patients undergoing outpatient cardiovascular rehabilitation stratified by clinical risk. MET: metabolic equivalent; VO_2: oxygen consumption*

Table 1 – Clinical risk stratification of patients undergoing outpatient cardiovascular rehabilitation

Risk	High	Intermediate	Low
Features			
Cardiovascular event, cardiovascular intervention, or clinical decompensation	Less than 8 to 12 weeks	12 weeks or longer	6 months or longer
Physical functioning	TMET: < 5 MET CPET: Weber C/D or VO_2 peak < 60% of predicted	TMET: 5–7 MET CPET: Weber B or VO_2 peak 60–85% of predicted	TMET: > 7 MET CPET: Weber A or VO_2 peak > 85% of predicted
Signs and symptoms of myocardial ischemia (ischemic threshold)	At low loads TMET: at < 6 MET CPET: at < 15 $ml.kg^{-1}.min^{-1}$	TMET: at > 6 MET CPET: at > 15 $ml.kg^{-1}.min^{-1}$	Absent
Symptoms	HF: NYHA III and IV Angina: CCS III and IV	HF: NYHA I and II Angina: CCS I and II	Absent
Other clinical features:	Dialytic CKD; oxygen desaturation on exertion; complex ventricular arrhythmia.	At clinician's discretion and judgment during pre-exercise evaluation	At clinician's discretion and judgment during pre-exercise evaluation

CCS: Canadian Cardiovascular Society; CKD: chronic kidney disease; CPET: cardiopulmonary exercise test; HF: heart failure; MET: metabolic equivalent; NYHA: New York Heart Association functional class; TMET: treadmill exercise test; VO_2: oxygen consumption.

The exercise program must be individualized in terms of intensity, duration, frequency, training modality, and progression, according to the functional testing performed at the start of the program and subsequently. Proper measurement of HR and BP at rest and during exercise are mandatory; measurement of oxygen saturation, capillary blood glucose, and electrocardiographic monitoring should also be available.

The rehabilitation program should also include an educational program aimed at lifestyle modification, with an emphasis on dietary re-education and strategies for smoking cessation, if necessary. It is essential that patients acquire knowledge about their illness and learn to self-monitor, both while exercising and in terms of red-flag signs and symptoms which may signal unstable or high-risk clinical situations.

The clinical characteristics of patients who would initially be classified as high clinical risk (presence of at least one such feature) are:

- Hospitalization due to recent (< 8–12 weeks) cardiovascular events: AMI or unstable angina; surgical or percutaneous revascularization; complex arrhythmias; cardiac arrest; acute decompensated HF.
- Chronic heart disease with or without recent cardiovascular events and/or interventions but with significant functional changes on physical exertion, i.e.:
  - Low functional capacity on TMET (< 5 MET) or CPET (Weber C/D classification or VO_2 peak < 60% of predicted for age and sex).
  - Signs and symptoms of myocardial ischemia at low loads (< 6 MET or at a VO_2 of < 15 $ml.kg^{-1}.min^{-1}$).
  - Exacerbated symptoms (HF with NYHA functional class III or IV, or angina with CCS functional class III and IV).
- Other clinical characteristics of patients at increased risk during physical exercise include dialytic chronic kidney disease (CKD), oxygen desaturation on exertion, and complex ventricular arrhythmias at rest or exertion.

Considering that high-risk patients often need frequent readjustment of drug therapy and reassessment and occasionally need advanced intervention (revascularization or other procedures), constant communication between the CVR team and the patient's primary physician(s) is essential. It is also important to note that some patients who experience intercurrent events during exercise or unfavorable findings on follow-up evaluations may remain in the high-risk classification (i.e., requiring direct supervision of physical exercise) indefinitely.

3.2. Intermediate Clinical Risk

Patients may have completed previous stages of CVR and been reclassified; may be classified directly into this category despite no previous engagement in exercise; or may have been referred from other exercise programs. The duration of CVR under this classification can also be variable, depending on the clinical status and progress achieved with physical training as demonstrated in follow-up evaluations.

Exercises should be supervised by a physical therapist or physical educator, and the service should (ideally) rely on the coordination of a physician with experience in CVR. Devices for measurement of HR and BP at rest and during exercise are recommended; measurement of oxygen saturation, capillary blood glucose, and electrocardiographic monitoring should also be available as necessary.

If there is no on-site physician, one must be readily on call. Basic life support material must be available on site and all team members must be trained in cardiopulmonary resuscitation, including use of an automated external defibrillator, which must also be present on site.

It is essential that pre-exercise evaluation be carried out by the CVR team, with appropriate risk stratification. Regular medical follow-up and revaluations as necessary must be carried out to ensure the safety of the exercise regimen.

The clinical characteristics of patients who would initially be classified as intermediate risk (presence of at least one such feature) are:

- Longer than 12 weeks since the latest cardiovascular event or intervention and currently stable clinical condition.
- Chronic heart disease with some loss of function on exertion:
  - Moderate functional capacity on TMET (5–7 MET) or CPET (Weber B classification or VO_2peak 60–85% of predicted for age and sex).
  - Signs and symptoms of myocardial ischemia at loads > 6 MET or at a VO_2 > 15 $ml.kg^{-1}.min^{-1}$.
  - Mild to moderate symptoms (HF with NYHA functional class I or II, or angina with CCS functional class I and II).
- Any other clinical features judged by the physician responsible for pre-exercise evalution to pose intermediate cardiovascular risk on exertion.

The main objective of CVR in patients with this risk profile remains the improvement of physical fitness, both aerobic and non-aerobic (muscle strength, flexibility, balance, body composition), as well as superior disease control. The need to promote wellness and improved quality of life, in addition to other procedures that contribute to reducing the risk of clinical complications, such as strategies for smoking cessation, dietary reeducation, and weight control, should all be considered. An emphasis on maintaining and adhering to prescribed drug therapy is also essential to preventing the progression or instability of CVD. Acquisition of knowledge about the disease itself, allowing for better self-management, increases the accuracy in identifying signs and symptoms of disease progression or red flags of unstable clinical situations, which may require interruption of the exercise program and medical revaluation.

Patients in this category, after an initial period of guidance and knowledge acquisition about physical exercise and self-monitoring, may be able to adapt to home-based CVR, in which physical exercise is performed under the indirect supervision of team members. Such supervision, as well as adjustments to the exercise prescription or patient education to clarify any questions, should take place during periodic face-to-face or remote follow-up sessions.

3.3. Low Clinical Risk

Patients may have completed previous stages of CVR and been reclassified; may be classified directly into this category despite no previous engagement in CVR; or may have been referred from other physical exercise programs. Training for these patients is a long-term endeavor, aimed at maintaining overall health and achieving the greatest possible gains in physical fitness, with the objective of reaching the highest attainable standard of health.

Depending on availability and individual preferences, exercises can be carried out under direct (face-to-face) or remote supervision. However, given their lower clinical risk and reduced need for supervision, patients at this stage are a perfect fit for home-based rehabilitation models, so that the CVR team can devote on-site resources to patients at higher clinical risk.

Patients must nevertheless undergo periodic reevaluation by their primary physician and by the CVR team, including CPET or TMET. In principle, the time between follow-up revaluations should not exceed 12 months. The purpose of follow-up is to readjust the exercise prescription and identify any deterioration of the underlying disease or red flags for clinical decompensation or cardiovascular events, thus allowing preemptive adjustment of drug therapy and/or surgical or percutaneous intervention as needed.

Patients receiving home-based programs should be periodically reevaluated and receive guidance on exercise. These occasions are advised to serve as opportunities for participation in supervised exercise sessions, especially for less-experienced patients, as well as for readjustment of the exercise prescription as needed and to answer any questions. Periodic remote assessment by the CVR team (through virtual and/or telephone contact), at least once every 6 months, is recommended to encourage continued adherence to the physical exercise program.

The clinical characteristics of stage 4 patients are (all of the following must be present):

- Longer than 6 months since the latest cardiovascular event or intervention and currently stable clinical condition.
- Chronic heart disease with little or no loss of function on exertion.
- Patients in this classification usually exhibit the following:
  - Good functional capacity on TMET (> 7 MET) or CPET (Weber A classification or VO_2peak > 85% of predicted for age and sex).
  - No signs or symptoms of myocardial ischemia and no unusual symptoms on physical exertion.

4. Cost-Effectiveness of Cardiovascular Rehabilitation

According to the World Health Organization, between 2000 and 2016, the rise in global health expenditures outpaced the global economy, reaching USD 7.5 trillion in 2016.[38] In 2010 alone, USD 863 billion were spent worldwide on CVD, a figure estimated to reach USD 1.04 trillion by 2030.[39]

In Brazil, where nearly 50% of health expenditures are borne by the government,[40] the situation is no different. CVD accounts for the largest share of expenditure on inpatient care within the Brazilian Unified Health System, and is the leading reason for disability benefits.[41-45] It is estimated that, in 2015, public expenses on inpatient and outpatient care of CVD exceeded R$ 5 billion, while the cost of temporary sick leave or disability exceeded R$ 380 million.[40]

Therefore, the economic impact of CVD, coupled with the need for rational use of financial resources, requires the large-scale implementation of low-cost models to ensure the feasibility of caring for a greater number of patients. CVR is a strategy that, in patients with stable CAD, is more cost-effective than procedures used much more widely, such as percutaneous coronary intervention.[46,47] In addition, its use on a larger scale would reduce health care expenditures due to a decrease in new cardiovascular events,

hospital readmissions, and interventional treatment.[48,49] Therefore, wider dissemination of CVR should be considered a priority public health strategy.

Assessment of cost-effectiveness, which is done through a combined analysis of clinical consequences (effectiveness) and health-system expenditures, is essential in evaluating the relevance of large-scale implementation of a given treatment.[50-52] According to Georgiou et al.,[53] measures that require investments of less than USD 20,000 per life-year saved (LYS) are considered to have excellent cost-effectiveness, whereas those that require investments of USD 20,000–40,000/LYS are acceptable and those requiring investments of USD > 40,000/LYS are unacceptable.

According to 1985–2004 data, CVR can be considered an intervention with an excellent cost-effectiveness ratio, as its addition to conventional treatment resulted in an increase in expenditures from USD 2,193 to USD 28,193 per LYS. In 2005, Papadakis et al.[23] published the first systematic review of studies on the cost-effectiveness of CVR as a secondary prevention strategy in patients with CAD and HF. In a 2018 evaluation of studies published after 2001,[54] the cost-effectiveness ratio was very similar to that described by Papadakis; the addition of CVR to conventional treatment resulted in an increase in expenditure of USD 2,555 to USD 23,598 per LYS.

It is worth mentioning that, although more than 75% of CVD deaths occur in low- and middle-income countries,[55] there is a lack of data on the cost-effectiveness of CVR in these settings.[56] Most of the information available comes from high-income nations, such as the United States, Canada, and European countries, which hinders extrapolation of results to the Brazilian reality. However, those few studies which are available from lower-income nations show a similar trend. In Brazil, the addition of rehabilitation to conventional treatment of patients with HF resulted in an increase in expenditures of USD 21,169 per LYS.[57]

Despite the clear clinical and economic benefits of CVR, the percentage of eligible patients who effectively receive this type of care is far short of desired levels. According to international data, only around 30% of patients attend a CVR program; in Brazil, this number is estimated to be well below 15%.[26,58,59] In fact, most Brazilian states – including most capitals and large cities – lack even a single cardiac rehabilitation service.

As a result, the use of home-based models has grown. Initially, concerns about the safety of physical exercise meant that HBCR was intended only for low-risk patients. However, with growing evidence of noninferiority in terms of safety and similar clinical benefits in relation to the conventional strategy,[60-62] in addition to advances in technology that now allow remote monitoring, the use of HBCR has been expanded to patients with a higher risk profile.

Recent studies show that HBCR has effectiveness similar to traditional CVR, as demonstrated by Ades et al.,[60] who compared the effects of a 3-month program of either model in low- and moderate-risk CAD patients after an acute coronary event. Although the group of patients who attended the traditional program performed a higher volume of exercise, there was no difference in increase in functional capacity or quality of life between the two groups. Jolly et al.[62] compared cardiovascular risk outcomes between patients undergoing traditional and home-based rehabilitation for longer periods, with 6, 12, and 24 months of follow-up, and also observed no differences.

A recent systematic review by Anderson et al. of studies enrolling patients with a history of AMI, CABG, or HF[61] also found no significant differences between conventional and home-based rehabilitation across a series of outcomes (death, cardiac events, functional capacity, quality of life, and modifiable risk factors) in the short term (3 to 12 months) or long term (up to 24 months).

Thus, HBCR programs should be considered as a strategy to facilitate access, adherence, and wider use of rehabilitation. Despite the aforementioned evidence of noninferiority in outcomes, comparatively few studies have demonstrated that the cost of HBCR is comparable to that of traditional CVR programs.[61,63,64] This major research gap precludes comparison of the two models in terms of cost-effectiveness.[65-67]

Given the facts, it is unsustainable that countries of all income levels – and, most worryingly, lower-incomes – continue to provide high-cost therapeutic interventions massively, without stricter indications and criteria, while they continue to neglect the highly effective, economically viable, and readily applicable intervention that is CVR. There is an urgent need for public health policies to expand the availability of, participation in, and adherence of eligible patients to both traditional and home-based CVR programs.

Finally, considering the relevance of CVR given its broad clinical benefit and excellent cost-effectiveness, strategies must be implemented to change medical culture and stances toward it and facilitate the dissemination of structured rehabilitation programs. In this context, it is particularly relevant that specialty cardiology services offer CVR to their patients both during hospitalization and after discharge. The availability of a CVR service should be considered as a mandatory prerequisite for a medical institution to be recognized or accredited as having excellence in cardiology.

5. Home-Based Cardiovascular Rehabilitation

There are several barriers to patient access and adherence to conventional CVR,[24-27,68] which, compounded by the scarcity of referral to CVR programs and the limited availability of services, lead to very low levels of actual participation in supervised exercise programs. In this context, programs of indirectly supervised exercise carried out in the home, known as home-based cardiovascular rehabilitation (HBCR), are an attractive alternative or supplement to conventional, on-site CVR. Given its inherently greater availability, HBCR should be considered the main modality of CVR intervention when it comes to public health strategies, aiming at mass engagement of the CVD population in rehabilitation programs.

A Cochrane review[61] of 23 studies including 2,890 patients with heart disease (post-AMI, post-CABG, angina or HF) compared the effects of conventional CVR and HBCR. No differences were found in mortality, physical capacity, or quality of life. Therefore, the decision to participate in conventional (on-site) or home-based programs depends on the availability of services and patients' individual preference.

HBCR is understood as the practice of physical exercise without face-to-face supervision, but with guidance and follow-up from the CVR team. It is thus also known as semi-supervised rehabilitation, or rehabilitation under indirect or remote supervision. The indications and objectives of HBCR are the same as those of conventional CVR; the same care is required regarding pre-exercise evaluation and exercise prescription. Most sessions are held under indirect supervision, but participation in some on-site classes, especially at the start of the program, is of fundamental importance to ensure that patients understand the exercise prescription, consolidate guidance and clarity doubts. Exercise can be done at home, in parks, on public roads, gyms, sports centers, and health clubs, among others, with patients self-monitoring and following the guidance received.

Therefore, in order to achieve HBCR as a viable population strategy, it is first necessary to expand the availability and capacity of conventional CVR programs, in order to enable initial evaluation, guidance, exercise prescription, and follow-up of home sessions (with periodic reassessment for any adjustments). Thus, the home strategy must be aligned with that of conventional CVR. The two modalities may be used in parallel, including patients with different risk profiles, or in sequence, with the same patient engaging in conventional or home-based CVR depending on clinical status.

Just as in conventional CVR, the first step of HBCR is referral by the primary physician, followed by evaluation by the rehabilitation physician and other team members, ideally including a stress test (CPET or TMET) or other physical fitness tests. After the pre-exercise evaluation, patients defined as high risk can be prioritized for conventional, face-to-face CVR. Those at lower risk, who are capable of self-monitoring and according to individual preference, can be routed to the HBCR component of the program. After receiving instruction on the prescribed exercises, patients perform the sessions on their own. The exercises may be documented in printouts or spreadsheets, with the aid of resources such as cardiac monitors, pedometers, or fitness trackers. Smartphone apps can mediate this exchange of information between patients and the health care team.

In some cases, a combined CVR program – with both on-site and home-based sessions – may be an option for moderate-risk patients who are still learning to self-monitor or find it difficult to attend face-to-face sessions due to social issues or reduced mobility. The proportion of on-site versus home-based sessions will vary according to the patient's clinical characteristics and the logistics and infrastructure of the CVR service.

The overall focus is always to make patients more physically active; a reduction in sedentary behavior and its harmful consequences is the imperative. It is essential that all available resources – whether alone or in combination, whether informal physical activity, home rehabilitation, or conventional CVR – be deployed toward this goal.

6. Integration of Cardiovascular Rehabilitation into Optimized Clinical Care of Cardiovascular Diseases

CVR must be integrated with full clinical treatment of CVD, which consists of a synergistic combination of structured lifestyle changes and optimized drug therapy. For instance, in patients with stable coronary disease – even those with moderate and severe ischemia – interventional treatments have not been shown to be superior in reducing major outcomes (cardiovascular mortality, all-cause mortality, AMI, HF).[69,70]

To increase the efficacy and safety of CVR, it is important that drug therapy of CVD be properly optimized. The aim is to increase exercise tolerance and thus facilitate engagement in physical exercise while reducing the risk of further events.[3,5,71-73] In this context, it may be necessary to adjust current drugs or prescribe additional agents prior to the start of the physical exercise program. Once CVR has been initiated and adequate adherence has been achieved, some patients may require dose reduction or even discontinuation of some drugs due to adaptations to physical training, e.g., patients who develop hypotension, marked bradycardia, or symptomatic hypoglycemia.[74,75]

6.1. General Guidance for Increasing Physical Activity and Engagement in Physical Exercise

There is an association between sedentary lifestyle (e.g., screen time), and higher all-cause and cardiovascular mortality.[76] Therefore, for health promotion and CVD prevention, medical guidelines have recommended the practice of moderate-intensity physical activity for at least 150 minutes per week or high-intensity for at least 75 minutes per week (grade 1B recommendation).[77-83] Engagement in more than 300 minutes/week of moderate- to high-intensity exercise can confer additional benefit, as has already been demonstrated in patients with CAD.[84]

According to the results of individual evaluation, the exercise prescription may vary in terms of type (aerobic, endurance, flexibility), modality (walking, running, cycling, dancing, etc.) and duration; weekly frequency and intensity should also be considered (Tables 2 and 3).

Sedentary patients should start exercising at the lower limit of the exercise prescription and progress gradually over the following weeks. Progression should initially be based on the duration of each session and, later, on exercise intensity. Physically active patients can perform exercises at a more intense level from the outset, aiming at a minimum duration of 75 minutes divided into two or more weekly sessions.

Resistance training of localized muscle groups (whether strength or endurance training) has proven quite beneficial for overall health and for the cardiovascular and musculoskeletal systems, and is particularly important – in fact, essential – in patients with sarcopenia and/or osteopenia. Resistance training should be performed at least twice a week, favoring the large muscle groups of the upper limbs, lower limbs, and core. Exercise can be done against the individual's own body weight or using implements such as free weights, ankle weights, bands, or weight machines. The load (or weight) for each exercise or movement must be individually adjusted, and particular attention should be paid to proper posture and technique.

Several protocols for resistance training are available, with variations in parameters such as the number of exercises per session (e.g., 6 to 15), the number of sets per exercise (usually 1 to 3), and the number of repetitions

Table 2 – Classifications of physical exercise

Classification		Features
By predominant metabolic pathway	Alactic anaerobic	High intensity, very short duration
	Lactic anaerobic	High intensity, short duration
	Aerobic	Low or medium intensity, prolonged duration
By pace	Fixed, constant, or continuous	No change of pace over time
	Variable, intermittent, or interval	Pace changes over time
By relative intensity*	Low or light	Easy to breathe, barely short of breath (Borg < 4)
	Medium or moderate	Breathing faster and labored, but still controlled. Can speak a sentence (Borg 4–7)
	High or heavy	Breathing very rapid and labored; short or out of breath. Barely able to speak (Borg > 7)
By muscle mechanics	Static	There is no movement; mechanical work is zero
	Dynamic	Involves movement; mechanical work is positive or negative

**A Borg scale of 0 to 10 was considered.*

Table 3 – Methods for prescription of moderate-intensity aerobic exercise

Method	Description
Rating of perceived exertion (Borg)	Exercises yielding a rating of perceived exertion of 2–4 on the 0–10 Borg scale or 10–13 on the 6–20 Borg scale
Speech test	Exercise intensity maintained so that breathing is labored but still controlled, and the patient is still able to speak a complete sentence without pause
Percent peak HR	Exercise intensity titrated to an HR target of 70–85% of peak HR* Target HR = peak HR x desired percentage
HR reserve (Karvonen)	Exercise intensity titrated to an HR target of 50–85% of reserve HR (peak HR – resting HR). Target HR = resting HR + (peak HR – resting HR) x desired percentage
Cardiopulmonary exercise test thresholds	Exercise intensity titrated to remain between ventilatory threshold 1 (anaerobic threshold) and ventilatory threshold 2 (respiratory compensation point)

**Peak HR preferably measured during a maximal exercise stress test, as interindividual variability can cause errors in the prediction of HR by age, especially in patients who are on medications with negative chronotropic effect. HR: heart rate.*

per set (6 to 20). The intensity of resistance training can be adjusted according to the relative intensity of the maximum force, and can be expressed as a function of the maximum load that can be borne during a single repetition (one repetition maximum test or 1RM). Light intensity would be up to 30% of 1RM; medium intensity, between 30 and 60–70% of 1RM; and high intensity, above 60–70% of 1RM. Resistance exercises may also be prescribed subjectively, on the basis of perceived exertion alone (see Table 2).

A practical approach is the variable repetition method, which aims to perform a range of repetitions (e.g., 10 to 15 repetitions). If the patient is unable to perform the movement correctly for the minimum number of repetitions prescribed, the applied load is too high. On the other hand, if the patient reaches the maximum prescribed number of repetitions easily, the load is insufficient. Thus, the load will be adjusted so that training takes place within the proposed range of repetitions. This method can be applied to a wide range of localized exercises and can be altered as the patient progresses; the repetition ranges can also be modified depending on the desired objective (strength, hypertrophy, or endurance).

Flexibility exercises can also provide musculoskeletal benefits, improve health-related quality of life, and prevent falls in the elderly. By facilitating and increasing the efficiency of joint movement, they reduce oxygen demand during motion, thus enhancing cardiovascular performance. The aim of these exercises is to reach the maximum range of motion (point of mild discomfort) and remain static for 10 to 30 seconds.

Depending on the age group, clinical condition, and objectives of the exercise program for a given patient, other types of exercise can be included in the prescription, such as motor coordination and balance exercises. The countless benefits of more playful, social-based forms of exercise, such as dance and other modalities, should also be considered.[85,86]

Assessment of aerobic and non-aerobic physical fitness enables a more individualized exercise prescription, with the objective of achieving the best outcomes while minimizing hazard to the patient through proper risk stratification and a thorough search for possible abnormalities. In general, the initial evaluation is based on a thorough history, physical examination, and ECG. More detailed assessments should be individualized to include CPET or TMET, anthropometric measurements, and evaluation of muscle strength/endurance and flexibility. The initial evaluation allows quantification of the patient's functional deficit in relation to the desired level of function, as well as goal setting. Even those patients with poor baseline physical fitness can benefit

from adequate adherence to a supervised exercise program.[87] Such adherence can also provide clinical and functional inputs that enable adequate counseling as to whether and how patients can resume sexual activity, based on the KiTOMI model, which was proposed by Brazilian authors in 2016.[88] In addition, periodic reevaluation is essential to encourage commitment and measure the progress and benefits obtained.

Finally, it is important to establish a systematic follow-up revaluation scheme which, in addition to encouraging patient commitment, will allow measurement of the progress and benefits obtained and yield reports to support treatment adjustments. Therefore, these reports should always be sent to the patient's primary physician, who is obviously an integral part of full clinical treatment.

6.2. Hypertension

Hypertension (HTN) remains one of the leading risk factors for the development of CAD, HF, CKD, and ischemic or hemorrhagic stroke, representing a huge social and economic challenge to global public health.[89] Worldwide, the number of patients with HTN rose from 594 million in 1975 to 1.13 billion in 2015, with growth largely credited to underdeveloped and developing countries.[90] Considering that most cases of HTN are lifestyle-related, with sedentary behaviors as a prominent cause, the importance of physical exercise is clear, alongside other behavioral measures and drug therapy as indicated.[72]

6.2.1. Therapeutic Benefits of Physical Exercise

HTN has a complex, multifactorial pathophysiology involving structural and physiological modifications, particularly to the vasculature (increased arterial stiffness, increased arteriole wall-to-lumen ratio, capillary rarefaction), kidneys (increased plasma renin and water and sodium resorption, decreased glomerular filtration), and nervous system (increased sympathetic and chemoreceptor activity, decreased parasympathetic activity and baroreflex sensitivity).[91] The regular practice of physical exercise has a therapeutic effect on the physiological restructuring of these systems, reducing oxidative stress and inflammation, correcting baroreflex dysfunction, increasing vagal tone, decreasing sympathetic activity, reversing hypertrophic arteriolar remodeling in exercised tissues, and reducing peripheral vascular resistance, with a consequent decrease in BP levels similar, or even superior, to that provided by drug therapy.[92,93]

In vascular tissue, HTN is characterized by disorganization of smooth muscle cells, increased collagen deposition, and a decreased elastin/collagen ratio, in addition to the formation of abnormal elastic fiber and internal elastic lamina with a smaller fenestrated area.[94] All of these structural changes in the vessel wall, which occur in both arteries and arterioles, increase the overall stiffness of the vasculature, with a consequent increase in pulse wave velocity, pulse pressure – the difference between systolic BP (SBP) and diastolic BP (DBP) – and hydrostatic pressure in the capillaries. These structural imbalances are compounded by endothelial dysfunction, with an increase in vasoconstrictive compounds, inflammatory mediators, and oxidizing agents, to the detriment of synthesis of vasodilating and antioxidant compounds.[95,96]

Physical exercise, by increasing the tangential stress derived from the friction of blood flow on the endothelial surface of the vessel wall (commonly described by the term shear stress) positively stimulates the endothelial tissue, increasing production of antioxidant enzymes and vasodilating agents, in addition to decreasing the action of free radicals, pro-inflammatory cytokines, adhesion molecules, and vasoconstricting agents, thus restoring the balance of endothelial function.[97,98] Experimental studies[94] in spontaneously hypertensive rats have demonstrated reorganization of all vascular structures of the aorta after implementation of a period of aerobic exercise. Aerobic training promotes vascular adaptations in the conductance arteries (with decreased arterial stiffness and improved endothelial function), arterioles (by decreasing the vessel wall-to-lumen ratio), and capillaries, stimulating angiogenesis.[99,100]

Thus, physical exercise has multifactorial effects on HTN, and is considered a key intervention to mitigate the burden of the disease and its comorbidities.[101] The antihypertensive effect of exercise is comparable to that of medication,[102] and both can be additive, occasionally requiring adjustments of drug dosage.

The greatest evidence of benefit in BP reductions among hypertensive patients is for aerobic physical exercise, as corroborated in a meta-analysis by Cornelissen et al. which showed an average SBP reduction of 8.3 mmHg and DBP reduction of 5.2 mmHg as a result of aerobic exercise.

The goal of resistance training (which also has an antihypertensive effect[103]) is to preserve or increase muscle mass, strength, and endurance, factors that decrease the relative intensity needed to perform the activities of daily living, with consequent damping of the blood pressure response to exertion. Furthermore, resistance training may also promote improvement in baroreflex sensitivity.[104]

In addition to aerobic and dynamic resistance exercises, some studies have focused on isometric (static resistance) exercises and shown significant effects in reducing BP levels.[105-107] A meta-analysis found that isometric handgrip training, performed for 12 minutes three to five times a week, reduced SBP and DBP by 5.2 and 3.9 mmHg respectively.[108] However, studies on the safety and effectiveness of isometric modalities in the long term are still lacking.

6.2.2. Indications for Physical Exercise in Hypertension

Higher levels of physical activity have been associated with a decrease in the risk of developing HTN. With the advent of electronic activity trackers and ambulatory BP monitoring, it has become increasingly feasible to conduct studies that correlate physical activity with BP.[109] Physical fitness, measured objectively through graded stress tests, attenuates the increase in BP with age and prevents the development of HTN. In a cohort of 20-to-90-year-old men who were followed for 3 to 28 years, greater physical fitness decreased the rate of BP increase over time and delayed the onset of HTN.[110] Epidemiological studies have revealed that both level of physical activity and cardiorespiratory fitness are inversely associated with hypertension.[111,112]

Large randomized controlled trials and meta-analyses have confirmed that regular exercise can reduce BP levels.[102,112] In addition, the continuous practice of physical activities can be beneficial for both the prevention and the treatment of hypertension, further reducing cardiovascular morbidity and mortality. Demonstrating this, active individuals have up to a 30% lower risk of developing hypertension than sedentary ones,[111] and increasing daily physical activity significantly reduces BP.[113]

Physical inactivity is one of the greatest public health issues of modern society,[114] as it is the most prevalent of the cardiovascular risk factors and one of the leading factors contributing to mortality worldwide.[115] Survival is lower among people who spend most of their time sitting than in those who spend little time in this position.[116] Television viewing time is directly associated with high BP levels and cardiovascular morbidity and mortality;[117] therefore, to reduce time spent in the seated position, standing for at least 5 minutes for every 30 minutes spent sitting is recommended as a valid preventive measure. Physical exercise is indicated for all patients with HTN (Table 4).[72,73,118]

In addition to exercise, the treatment of HTN requires other lifestyle changes, such as proper diet, weight control, and cessation of risk factors such as smoking and excessive alcohol intake.

In addition to the direct effect of exercise on HTN, another important component of CVR concerns the management of drug therapy, which can be optimized in the rehabilitation environment through disease education, advice on the need for treatment, and information on adverse effects and on the importance of adherence.[119]

6.2.3. Pre-Exercise Evaluation

Obviously, it is up to the patient's primary physician to establish the diagnosis of HTN, search for other cardiovascular risk factors, and screen for target organ damage and other comorbidities in order to define the treatment strategy, which can be pharmacological and/or composed of one or more behavioral changes.[72]

A CPET or TMET should be performed during pre-exercise evaluation, especially if there is suspicion of heart disease, target organ damage, or presence of three or more risk factors.[72] When CPET or TMET is used to support exercise prescription, it should ideally be performed with the patient on all of their usual medications, especially those with negative chronotropic effect, in order to mimic the actual conditions encountered during physical training. This will allow use of peak HR (TMET) or ventilatory thresholds (CPET) to determine the target training zone.

6.2.4. Special Considerations for the Prescription and Follow-Up of Physical Exercise Programs

The exercise recommendation for hypertensive patients, is similar to that proposed for the general population: at least 150 minutes per week (five 30-minute sessions) of moderate-to-intense aerobic activity. In addition, two to three resistance training sessions per week are advisable. For greater benefit, absent any contraindications, patients may gradually increase their engagement towards a goal of 300 min/week of moderate aerobic exercise or 150 min/week of intense aerobic exercise.

During training, it is important that BP be assessed at rest and in exertion. Patients with a resting BP higher than 160/100 mmHg or with target organ damage (left ventricular hypertrophy, retinopathy, nephropathy, etc.) are advised to optimize antihypertensive therapy for better BP control before starting or resuming exercise,[37] or to reduce training intensity until better BP control is achieved. In supervised CVR programs, these recommendations are flexible and can be adjusted individually at the discretion of the rehabilitation physician and according to the BP response observed during the stress test and exercise sessions. During exercise, it is recommended that BP remain below 220/105 mmHg. If BP exceeds this level, the session should be halted or the load reduced, and adjustment of drug therapy should be considered.[37]

BP must be measured after each exercise session, and is commonly found to be lower than before the start of activities. In hypertensive patients, the acute antihypertensive effect of a single session tends to be greater with more intense levels of aerobic exercise.[120] This acute effect of physical training can cause symptomatic hypotension once the session ends, which usually improves with rest and hydration. Patients on alpha blockers, beta blockers, calcium channel blockers, and vasodilators may be at increased risk of post-exercise hypotension, and thus require special attention during the cooldown period. If post-exercise hypotension becomes recurrent, which usually results from an add-on antihypertensive effect of training, the need for dose adjustments or even discontinuation of medications must be considered.

There is little data regarding the effect of exercise in patients with resistant hypertension, which is characterized by BP above target despite the use of three or more antihypertensive medications. In these patients, who require closer monitoring, a randomized, single-center clinical trial showed that exercising in warm water (30 to 32ºC) resulted in a pronounced reduction in BP (36/12 mmHg) after 3 months.[121] Although such effects need to be reproduced in further studies, exercise in warm water appears to be appropriate for patients with resistant hypertension.

Table 4 – Indications for physical exercise in hypertension

Indication	Recommendation	Level of evidence
Aerobic exercise to prevent development of hypertension [110-112]	I	A
Aerobic exercise in the treatment of hypertension [93,102,103,112]	I	A
Dynamic muscle endurance training in the treatment of hypertension [103,112]	I	B
Isometric training in the treatment of hypertension [105-108]	IIa	B

6.3. Stable Coronary Artery Disease after an Acute Event or Revascularization

Cardiovascular disease (CVD), led by coronary artery disease (CAD), is responsible for the majority of deaths in the adult population worldwide.[122-124] The underlying mechanisms of stable CAD include atherosclerotic obstruction of the epicardial vessels, microvascular disease, and coronary spasm, either alone or in combination.[5] Clinically, the most common manifestation of stable CAD is angina pectoris, which is characterized by reversible episodes of chest pain due to myocardial ischemia, resulting from the imbalance between myocardial oxygen supply and consumption, usually triggered by physical exertion or emotional stress, which resolve with rest or the administration of fast-acting nitrates.[5]

Stable CAD has a good prognosis, with annual mortality estimated at 1.5% and a nonfatal infarction incidence of 1.4%.[125] Nonetheless, full clinical treatment is essential, including optimization of drug therapy and regular physical exercise, in addition to other behavioral changes to address smoking, diet, and body composition. Elective revascularization (whether surgical or interventional) may also be indicated in patients with stable CAD, depending on their symptoms and cardiovascular risk.[5] However, it is worth noting that, in stable patients, even those with angina, exclusively clinical treatment has not been shown to be inferior to treatment with the addition of an interventional approach.[70,126,127]

Development of an acute coronary syndrome, with AMI or unstable angina, is associated with increased cardiovascular risk and may require adjustment of drug therapy plus urgent surgical or percutaneous revascularization.[128-131]

6.3.1. Therapeutic Benefits of Physical Exercise

The short- and long-term beneficial effects of regular physical exercise in patients with stable CAD have been demonstrated in the scientific literature. During the first 8 to 12 weeks of CVR, there is a marked increase in ischemic threshold,[132-136] improvement of cardiorespiratory functional capacity,[132,134,136] and improvement in myocardial perfusion imaging.[137-140] These benefits persist as long as regular physical exercise is maintained,[103,141-144,] which contributes to improvement in quality of life[1,146] and reduction of hospitalization and mortality from cardiovascular causes.[1,144,146-148]

In patients with stable CAD, different mechanisms explain the increase in ischemic threshold, which gradually allows physical activity at higher loads. Reduction of the double product at submaximal loads is associated, among other mechanisms, with an improvement in cardiac autonomic modulation.[144] Myocardial perfusion increases due to an improved endothelium-dependent vasodilator response[149-151] and increased recruitment of collateral vessels during exercise,[134,144,152] which is reflected in the reduction of ST segment depression during exercise.[35,132,137] It is also notable that the combination of physical training and a low-fat diet can influence the progression of atherosclerotic plaque.[152,153]

CVR is an adjunctive therapy that is also effective after acute coronary events and surgical or percutaneous revascularization. A systematic review and meta-analysis[1] of 63 studies involving 14,486 patients aged 47–71 years revealed that CVR reduced cardiovascular mortality by 26% and overall hospitalization rates by 18%, with additional improvement in quality of life. In this population, CVR should be encouraged whenever possible.

The improvement in cardiorespiratory fitness is one of the factors responsible for reduction of all-cause mortality after CVR. In a cohort of 5,641 CVR patients in Canada, every 1 MET increase in cardiorespiratory capacity was found to decrease all-cause mortality by 25%.[154] Other similar studies reported reductions in cardiac or all-cause mortality on the order of 8–34% for each MET of improvement in cardiorespiratory fitness.[155,156]

In addition, CVR provides an add-on effect to reduce cardiovascular events after coronary angioplasty, as demonstrated in the ETICA trial (Exercise Training Intervention After Coronary Angioplasty). A 26% increase in VO_2peak, 27% improvement in quality of life, and 20% reduction in cardiac events, including fewer AMIs and fewer hospitalizations, were observed in patients who underwent CVR after angioplasty when compared to those who remained sedentary.[157]

6.3.2. When Is Rehabilitation Indicated?

CVR is indicated in all cases of CAD (Table 5). It is considered useful and effective both when it consists exclusively of physical exercise and when educational content, management of risk factors, and psychological counseling are added.[146]

Despite increasingly early interventional treatments and decreased length of hospital stay after acute coronary syndromes, it is not uncommon for patients to begin rehabilitation only after outpatient follow-up with their primary physician, which may mean 15 days or longer after the event. Early initiation of CVR is possible, and can have a direct, positive influence on adherence and on the degree of clinical benefit achieved after the acute event.

One of the greatest concerns of early CVR refers to the effect of physical training on the ventricular remodeling process. While some authors report negative effects,[163] others report neutral[139] or even positive effects[158,164] on this process. A systematic review and meta-analysis[159] carried out to answer this question found that the changes observed in ventricular function, ventricular diameter, and functional capacity were directly related to the timing of CVR initiation. The greatest benefits in ventricular remodeling and functional capacity were obtained when programs were started in the acute phase (6 hours to 7 days) after the event, declining when initiated 7–28 days after the event and even further after 29 days, at which time the positive effect on ventricular remodeling was progressively lost. It is important to note that there was no difference in events between the initial training phases and that the sample studied was primarily composed of young men, which highlights the need for further studies, especially in other populations (such as older adults and women). For every 1-week delay in initiation of CVR after an AMI, an additional 1 month of training may be necessary to achieve similar benefits in end-systolic volume and left ventricular ejection fraction (LVEF).[160]

Table 5 – Indications for cardiovascular rehabilitation in coronary artery disease

Indication	Recommendation	Level of evidence
CVR to reduce myocardial ischemia[132-140,158]	I	A
CVR to increase physical capacity[132,134,140]	I	A
CVR to reduce mortality[1,154,155]	I	A
CVR after coronary events or revascularization[140,157]	I	A
Early CVR (1 week after an acute event)[159,160]	IIa	A
CVR in patients with refractory angina[161,162]	IIb	C

CVR: cardiovascular rehabilitation.

Although widely endorsed by the medical literature for their beneficial effects and cost-effectiveness, CVR programs are only attended by a minority of eligible patients. Multiple barriers can explain this, such as a lack of programs, difficulty in accessing existing services, few referrals, and poor urban mobility; women, the elderly, and ethnic minorities are most affected.[165-168] Therefore, political, social, and structural changes – as well as a shift in medical culture – are needed to change this scenario.

6.3.3. Pre-Exercise Evaluation and Exercise Prescription

Both in patients with stable CAD and after a coronary event and/or revascularization, risk stratification for CVR is essential and should be based on a targeted clinical evaluation focused on detailed knowledge of the patient's CVD and treatment history, whether clinical or interventional. Presence of symptoms, ventricular function, functional capacity, arrhythmias, and the possibility of residual ischemia all aid in stratification and should queried during the initial assessment. Ideally, this evaluation should be carried out by a CVR team member (rehabilitation physician).

The profile of a patient referred to CVR can vary widely, from individuals receiving elective treatment to patients with a complicated acute coronary syndrome and history of prolonged hospitalization. A broader assessment, including nutritional, psychological and musculoskeletal issues, should be part of the clinical history and examination, as these factors can directly impact the CVR process. In patients who have undergone percutaneous or surgical revascularization, examination of the arterial puncture site (especially of femoral access sites) or surgical wound (especially regarding sternal stability and wound infection) should always be performed. Any abnormalities or complex medical needs identified during the pre-exercise evaluation must be relayed to the CVR team members who will be involved in the patient's exercise sessions.

During pre-exercise evaluation for CVR, the purpose of functional tests is to gain better insight into functional capacity, identification of residual ischemia and stress-induced arrhythmias. Myocardial ischemia on exertion is identified by detection of symptoms such as angina pectoris and/or by ECG changes. The ischemic threshold can be identified during TMET by the onset of these clinical and/or ECG changes and expressed as the load and/or HR at which ischemia initiate. This information is essential to guide the exercise prescription.

When used for exercise prescription purposes, TMET should be performed on all of the patient's usual medications, especially those that may affect HR. This is important to reproduce the conditions that will be present during training sessions. If patients on beta blockers have their dose adjusted during rehabilitation, ideally a new TMET would be performed for adjustment of the exercise prescription. If this is impossible, a subjective (perceived exertion) test may assist in adjusting the prescription until a new test can be performed.

In some cases, patients entering CVR may have clinical limitations precluding a maximal exercise test. In these patients, the initial exercise prescription can be guided by a submaximal test, and a maximal test performed once there has been sufficient clinical improvement and/or optimization of drug therapy. Considering the possibility of serious error due to marked individual variation in chronotropic response, formulas that consider age as a parameter to define peak HR should never be used. The error is even greater in patients who are on beta blockers.

When rehabilitation is initiated without functional testing, the prescription may be based on the Borg scale of perceived exertion (a score of 11–15 on the 6–20 scale) and on arbitrary limitation of HR during training, i.e., the use of a resting HR + 20 bpm for patients who have had an acute coronary syndrome or resting HR + 30 bpm for those who have undergone elective surgical or interventional revascularization.[131] The target exercise intensity can also be determined by subjective assessment of breathing; moderate-intensity activity leaves the patient only slightly short of breath, but still able to speak complete sentences without interruption (see Table 3).

When a TMET is performed, the intensity of the prescribed exercise should lie between 40 and 80% of HR reserve (Karvonen formula: [Peak HR – resting HR] x percent intensity + resting HR). In such cases, the initial exercise prescription usually targets the lower limit of HR, progressing from there according to the patient's clinical course and improvement in functional capacity. Most patients will be prescribed an exercise intensity between 50 and 70% of their HR reserve. Those that are more functionally limited or have significant ventricular dysfunction may be prescribed at lower intensities (40–60%), while those who were previously active and still retain better functional capacity may be prescribed at a higher and wider range (50–80%). Percentages of peak HR can also be used, with moderate-intensity exercise corresponding to 70–85% of HR peak (see Table 3).

CPET, by allowing analysis of the oxygen pulse response, provides increased sensitivity and specificity for the diagnosis of myocardial ischemia.[169] When there is an occurrence of an early plateau of oxygen pulse or, particularly, a drop during exertion, the exercise prescription should be limited to loads below that alterations. Thus, CPET is considered the gold-standard assessment method to support exercise prescription and should be used whenever it is available.[169-171] In patients who complete a CPET, the prescribed exercise intensity should lie between the ventilatory thresholds and increase progressively from there.

Regarding the volume of exercise, at least 150 minutes/week are recommended, distributed across 3 to 5 sessions. Depending on tolerance, adaptations to training, and individual preferences, as well as consideration of clinical status, this volume may be increased to 300 minutes or more per week.

For resistance training, the gold-standard method to determine the optimal intensity is 1RM testing. However, in practice, many rehabilitation programs do not perform this test due to time constraints or clinical limitations, such as in patients who have undergone CABG and may thus be limited not only by sternotomy but also by saphenectomy. In such cases, subjective perceived exertion is a practical and useful alternative.

In patients who have undergone sternotomy, upper body exercise should be limited to low intensity and performed with restricted loads for 5 to 8 weeks. Exercises involving the full range of motion of the arms may be allowed after this period if there is no sternal instability, although recent and ongoing studies are evaluating the safety of earlier exercise after CABG.[172,173]

Patients should always be instructed on how to correctly perform movement and breathing, avoiding the Valsalva maneuver. The interval between series can range between 45 s and 1 min, depending on the load applied and the patient's tolerance.

6.3.4. Special Considerations for the Prescription and Follow-Up of Physical Exercise Programs

6.3.4.1. Refractory Angina

Refractory angina is defined as disabling angina of over 3 months' duration, despite optimized clinical treatment, with documentation of myocardial ischemia in a patient who is not considered eligible for percutaneous and/or surgical coronary intervention.[174,175] Such patients are generally not referred to CVR programs due to fear of adverse events during physical training, although rehabilitation has already been considered a feasible and safe possibility for these patients.[175]

The objective of therapeutic interventions in this setting is to improve quality of life and facilitate performance of the activities of daily living.[176-178] A single controlled study has evaluated CVR in patients with refractory angina. The study randomized 42 subjects to a CVR exercise program or usual care for 8 weeks. Patients in the CVR group were prescribed training to a target HR between 60 and 75% of HR reserve (for those with preserved ventricular function) or between 40 and 60% of HR reserve (when LVEF was <40%). Patients in the rehabilitation group increased their total distance on the shuttle walk test by 50 m, with no change in severity or frequency of angina. There were no adverse events in either group.[161]

An ongoing Brazilian randomized trial[162] will evaluate the safety and efficacy of a 12-week supervised exercise program in patients with refractory angina, carried out in a hospital environment with continuous ECG monitoring. Exercise prescription is individualized, on the basis of CPET findings and the ischemia and/or angina threshold. To date, 42 patients have been included, and no exercise-emergent cardiovascular events or hospitalizations related have been documented. Serum levels of high-sensitivity troponin T, a known predictor of worse prognosis,[179] did not change in 32 patients who completed a 40-minute acute aerobic exercise session (at the ischemia threshold) at the time of study enrollment (*unpublished data*).

In patients with refractory angina and a low ischemic threshold, administration of rapid-acting nitrates before the start of each physical training session can help prolong the duration of training and even allow exercise at higher intensities.[180]

6.3.4.2. Exercise Training with Myocardial Ischemia

Traditionally, there is a recommendation that physical exercises in patients with CAD be performed below the clinical and electrocardiographic ischemic threshold; however, this can be difficult to control. Previous studies have shown that physical exercise, even when prescribed according to literature recommendations, can trigger scintigraphic perfusion defects which are not demonstrable on ECG and do not trigger angina,[181,182] because changes in contractility and perfusion defects precede clinical and electrocardiographic ischemic changes.[183,184]

The functional significance of ischemic defects visible only on myocardial perfusion imaging is still unclear, but some studies of training above the ischemic threshold have been carried out. In one study of a single 20-minute training session conducted above the ischemic threshold, no evidence of acute myocardial damage was identified.[185] Other authors demonstrated in a small series of patients with CAD that, after 6 weeks of training, repetitive ischemic stimuli did not result in significant damage, myocardial dysfunction, or arrhythmias.[186,187]

Therefore, there is evidence to suggest that interval training, a modality that has proven to be safe and effective in improving physical fitness, endothelial function, and left ventricular function with results superior to those obtained with moderate-intensity continuous training (MICT), may be feasible in patients with stable CAD.[187,188] Additionally, there is evidence of the superiority of combined aerobic and resistance training as opposed to aerobic training alone in patients with CAD.[189]

6.3.4.3. Drug Adjustments in Response to Physical Exercise

Patients with stable CAD usually rely on medications for symptom relief, reduction of ischemia, improvement of endothelial function, stabilization of atherosclerotic plaque, control of risk factors, and maintenance of adequate hemodynamics. For example, high SBP and/or HR levels (increased double product) lead to clinical deterioration. On the other hand, systolic hypotension and bradycardia produce reduced cardiac output, which can cause abnormalities due to a drop in coronary flow.

In CVR programs, particular attention should be paid to improving the angina threshold before training begins, which allows greater tolerance to the progression of exercise intensity and, thus, facilitates achievement of the desired beneficial effects. Therefore, the optimization of drug therapy is essential for a safe and effective CVR.

Patients engaging in RCV can present a number of physiological adaptations to exercise, including modulation of the autonomic nervous system and reduced HR at baseline and on exertion. Together, these adaptations improve endothelial function and BP reduction, reduce afterload, and improve the diastolic function of the heart.[190] These adaptations can reduce the need for antianginal and antihypertensive agents. It is the role of the rehabilitation physician to discuss adjustments of drug therapy with the patient's primary physician as necessary.

6.4. Heart Failure

Chronic HF is a complex, multisystem syndrome that features dyspnea and progressive exercise intolerance are its core symptoms. Despite recent advances in drug therapy, which have reduced once very high morbidity and mortality rates, symptoms tend to persist, compromising patient quality of life. There is consistent evidence that reduced levels of physical activity in HF trigger a vicious circle that contributes to increasing symptoms and exercise intolerance, secondary to a reduction in functional capacity, producing negative psychological effects,[191] impairment of vasoreactivity, peripheral endothelial dysfunction,[192] and chronic inflammation.[193] In this context, physical exercise has been established as a safe therapeutic strategy that mitigates the effects of progressive physical deconditioning due to the natural course of the disease.[194]

Small randomized studies, systematic reviews, and meta-analyzes have consistently demonstrated that regular physical training is safe, increases exercise tolerance, improves quality of life, and reduces hospitalizations in HF.[195-197] A single large, multicenter randomized trial, HF-ACTION,[198] revealed a modest but nonsignificant reduction in primary outcomes (all-cause mortality and all-cause hospitalization), as well as major benefits in quality of life and a reduction in the rate of HF hospitalization. As a weakness of the study, poor adherence to exercise probably impaired the effectiveness of the intervention, a hypothesis that was confirmed later in another study, which demonstrated that adherence is a determining factor for obtaining medium-term benefits.[199]

In a systematic review[2] on physical training in patients with HF, which analyzed 33 randomized studies including 4,740 patients (with a predominance of reduced ejection fraction), there was a trend toward reductions in all-cause mortality in the physical exercise group at 1 year of follow-up. Compared to controls, the physical training group had a lower rate of HF hospitalization and improved quality of life. Regarding benefits in women with HF, the available studies suggest that a positive impact equivalent to that seen in men.[200]

For patients with advanced symptoms (NYHA class IV), data are still insufficient to indicate specific exercise programs. A single Brazilian randomized trial tested a daily exercise program on a cycle ergometer combined with noninvasive ventilation. The study evaluated patients hospitalized for acute decompensated HF, and found functional benefits and reduced length of stay.[201] Nevertheless, additional studies are needed to confirm these initial results before a stronger recommendation can be issued.

In HF with preserved LVEF, there is recent evidence from small randomized studies and a systematic review showing benefits in VO_2peak (measured by CPET),[202,203] quality of life,[203,204] and diastolic function (as assessed by echocardiography).[205,206]

In light of this evidence, exercise-based CVR is recommended in HF (Table 6) regardless of whether LVEF is preserved or reduced. Public policies must be adopted to ensure that a greater number of eligible patients benefit from treatment in structured CVR programs.[207]

Physical exercise alone should not be prescribed for patients with clinically unstable HF, with a clinical picture suggestive of acute myocarditis, or in the presence of acute systemic infection (Class IIIC).

6.4.1. Pre-Exercise Evaluation and Exercise Prescription

Internationally, CVR programs are implemented in a wide range of formats, using different exercise modalities alone or in combination. The exercises can include aerobic training (moderate- and/or high-intensity), localized resistance training, and respiratory muscle training (Figure 2).

Before starting the training program, it is essential that the patient be clinically stable and on optimized drug therapy; ideally, a functional assessment should be performed, preferably with CPET or a TMET. If the aforementioned functional tests are unavailable, the 6-minute walk test can serve as a parameter for monitoring functional gains.[208] Functional tests should be performed while the patient is on his or her prescribed medications, to mimic the conditions of actual training.

The recommended aerobic training can be MICT, which corresponds to the HR zone delimited by the ventilatory thresholds of CPET, or, in the case of a TMET, to the zone located between 60 and 80% of peak HR or 50 and 70% of reserve HR. Patients with more severe disease and greater functional limitations may start at the lower end of the prescription. Intensity can progress up to the upper limit as training advances.

Recently, the use of high-intensity aerobic exercises performed in an interval mode – known as high-intensity interval training, or HIIT – has become popular. In this modality, more intense periods of exercise alternate with periods of passive or active recovery, which allows a greater total duration of high-intensity exercise and, consequently, can increase stimuli for central and peripheral physiological adaptations.

In HF patients with reduced LVEF, Wisløff et al.[209] demonstrated that HIIT was superior to MICT in promoting improvement in functional capacity and in different cardiovascular parameters. Subsequently, other clinical trials were carried out and meta-analyzed. The superiority of HIIT over MICT in terms of effects on functional capacity was confirmed in a meta-analysis.[210] The largest multicenter study

Table 6 – Indications for cardiovascular rehabilitation in heart failure

Indication	Recommendation	Level of evidence
Regular aerobic exercise in patients with HF to increase functional capacity, reduce symptoms, and improve quality of life[2,195-199,205]	I	A
Regular aerobic exercise in patients with reduced LVEF to decrease HF hospitalization[2,198]	I	A
Aerobic exercise in patients with preserved LVEF to increase functional capacity and improve diastolic function[203,205,206]	IIa	B
Low-intensity aerobic exercises with noninvasive ventilation during the hospital phase of HF[201]	IIb	B/C

HF: heart failure; LVEF: left ventricular ejection fraction.

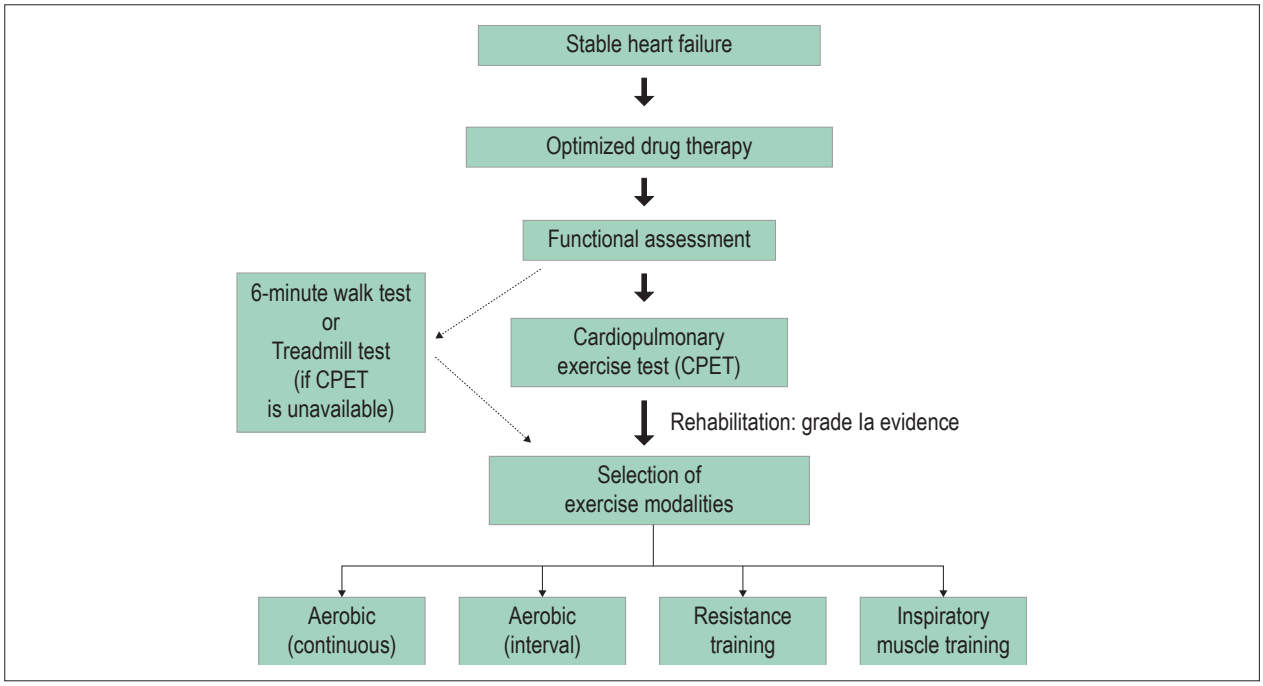

Figure 2 – *Flow diagram of cardiovascular rehabilitation in patients with heart failure.*

published to date, Smartex-HF,[211] compared MICT versus HIIT. The authors found similar benefit, with no superiority of one modality over the other in any respect. Therefore, the choice of protocol will depend on team experience, clinical conditions, physical capacity, and patient preferences.

In addition, HIIT protocols can vary widely; several have been described.[212] One consists of 4 min of high-intensity exercise (90 to 95% of maximum HR) alternating with 3 min of low-intensity exercise (70% of maximum HR).[209] Protocols with much shorter durations of high-intensity load (30 or 90s) have already been described, and the tolerance to different HIIT protocols may vary according to patient preference and physical capacity.[213] Therefore, the use of this modality will depend on the patient's clinical picture and choices, as well as on the experience and preferences of the CVR team.

The addition of localized muscle resistance exercises to aerobic training has been suggested as a means of obtaining additional benefit.[214] These exercised can be prescribed as percentages of maximum voluntary contraction or according to subjective perceived exertion. The recommended loads and repetitions may vary according to the patient's functional limitations and must be individualized, progressing as rehabilitation itself progresses.

The addition of breathing exercises has been recommended for patients with respiratory muscle weakness.[215] In a meta-analysis by Smart et al.[216] which evaluated 11 studies including 287 participants with HF, 148 of whom underwent inspiratory muscle training (IMT) compared with 139 sedentary controls, significant gains in VO_2peak, distance walked in the 6-minute test, quality of life, PImax, and VE/VCO_2 slope were observed. Thus, IMT provided gains in cardiorespiratory fitness and quality of life of a similar magnitude to those obtained with conventional training, and should be considered a valid alternative for severely deconditioned and debilitated HF patients, perhaps as a bridge to conventional physical exercise.

6.4.2. Final Considerations on Heart Failure

Given the variety of benefits observed, it is essential that patients with HF perform physical exercises regularly. Ideally, this should be done in the context of a CVR program, with an individualized prescription combining moderate- and/or high-intensity aerobic training, localized muscle resistance exercises, and respiratory muscle training, depending on the patient's clinical condition and functional limitations, and according to patient preferences and staff experience. In addition, there are valid alternatives even for very debilitated and severely deconditioned patients.[214,217]

6.5. Heart Transplantation

Heart transplantation (HTx) is the treatment of choice for patients with refractory HF, whose symptoms remain severe despite use of the entire pharmacotherapeutic arsenal and surgical procedures as indicated.

In recent years, there have been significant advances in HTx, with the emergence of new surgical techniques and the development of more efficient immunosuppressants. In Brazil, there has been substantial growth in the number of procedures, which had been stagnant since 2015, with a rate of 1.7 transplants per million population (pmp). In 2019, the rate grew 17.6%, reaching 2 transplants pmp, very close to the target set for the year (2.1 pmp). In 2018, 357 procedures were performed, and by March 2019, 104 hearts had been transplanted in Brazil.[218]

HTx aims to improve quality of life, as well as survival, in this population.[219,220] Recipients are able to return to work and lead normal lives with minimal or no symptoms.[221] The survival rate is estimated at 90% at 1 year and around 70% at 5 years.[222]

Although HTx significantly improves patients' functional capacity, VO_2peak is still reduced when compared to that of healthy, age-matched individuals.[223,224] Among other factors, this can be explained by: 1) in the immediate post-transplant period, the allograft is devoid of sympathetic and parasympathetic innervation (autonomic denervation), causing an increase in resting HR, attenuating its natural elevation in response to exercise, and impairing recovery after exertion[224,225]; 2) patients often exhibit skeletal muscle dysfunction (sometimes to the point of cachexia), in which immunosuppressive therapy and pre-transplant HF play prominent roles[226]; and 3) impairment of vascular and diastolic function.[227] During the acute phase of exercise, the increase in cardiac output of HTx recipients depends fundamentally on the Frank–Starling mechanism, i.e., on increase in venous return, inotropy, chronotropy, and reduction in afterload.[228,229] In addition, there is an increase in the concentrations of circulating catecholamines,[227] which decrease slowly after the end of exercise, explaining the slow recovery of HR in these patients.[230]

Immunosuppression may predispose HTx recipients to a higher risk of other complications,[231] and these patients may develop HTN, diabetes mellitus, and CAD.[232] Conversely, physical exercise is known to be an excellent therapy for management of these chronic diseases[93,233] and is effective in optimizing autonomic control.[230,234]

Physical training after HTx contributes to an increase in VO_2peak and improvements in hemodynamic control, muscle strength, and bone mineral density,[233-236] thus improving prognosis.[19] Although there are countless possibilities for training prescription, the recommended method remains aerobic exercise, which can be performed continuously or, in specific cases, at intervals and at different intensities,[170] combined with resistance training whenever possible.[6]

6.5.1. Benefits of Physical Exercise

In a pioneering study by Richard et al.,[237] the investigators found that, 46 months after HTx, patients who underwent aerobic training had a functional capacity and chronotropic function similar to those of healthy individuals. Previous studies had already demonstrated the safety of physical training in this population.[234,238-240]

A Cochrane meta-analysis of nine randomized clinical trials, including 284 patients, compared the effect of physical training to usual care in the post-HTx setting.[234] An average increase in VO_2peak of 2.5 $ml.kg^{-1}.min^{-1}$ was observed in those who received training versus those allocated to usual care. Rosenbaum et al.[241] assessed the relationship between early participation in a CVR program after HTx and found that the number of sessions performed in the first 90 days was directly associated with better 10-year survival.

Haykowsky et al.[242] described significant improvements in VO_2peak of HTx recipients, with an average increase of 3.1 $ml.kg^{-1}.min^{-1}$ after 12 weeks of combined training (resistance and aerobic). Kobashigawa et al.[243] studied 27 patients after HTx who received a combination of aerobic, resistance, and flexibility training for 6 months versus a control group. The duration and intensity of the aerobic exercise sessions had a goal of at least 30 minutes of continuous, moderate exercise on a cycle ergometer. The intervention group showed an average increase of 4.4 $ml^{-1}.kg^{-1}.min$ in VO_2peak, versus 1.9 $ml.kg^{-1}.min^{-1}$ in the control group. These data provide valuable information on the importance of both types of training for this population.

Regarding high-intensity training in patients after HTx, the number of studies is still small, but the results obtained have been encouraging. In a crossover study, Dall et al.[244] found a greater effect of HIIT compared to MICT on VO_2peak, with an additional gain of 2.3 $ml.kg^{-1}.min^{-1}$ and superior improvement in quality of life. One meta-analysis[233] included three randomized controlled trials that compared HIIT (intense blocks: 80 to 100% of VO_2peak or 85 to 95% of peak HR) to usual care. Post-HTx patients randomized to HIIT showed an increase in VO_2peak of 4.45 $ml.kg^{-1}.min^{-1}$ after the intervention period, which ranged from 8 to 12 weeks of three to five weekly sessions.

Nytrøen et al.[224] evaluated the effects of a HIIT program compared to a control group in 43 HTx recipients. The authors evaluated the progression of allograft vasculopathy, assessed by intravascular ultrasound, and found less progression of atheromatous plaque in the HIIT group. However, additional studies are still needed to elucidate these benefits.[245]

Some well-known common adverse effects of the use of glucocorticoids after HTx are muscle atrophy and weakness. In 1998, Braith et al.[235] were the first to study the effect of resistance training on glucocorticoid-induced myopathy in HTx recipients. One group received training and was compared with a control group. After 6 months, although both groups had increased muscle strength in the quadriceps and lumbar extensors, the increase was up to six times greater in the training group.

Resistance training also appears to have a major therapeutic effect on bone metabolism. After HTx, patients commonly experience significant bone loss at femur head and mineral total bone loss. In one study, patients were enrolled for resistance training 2 months after HTx, and training was shown to be able to restore bone mineral density to pre-transplant levels.[236]

6.5.2. Pre-Exercise Evaluation and Unique Features

HTx recipients must undergo a thorough history, physical examination, 12-lead resting ECG, color Doppler echocardiogram, and other tests at the discretion of the CVR team. Ideally, a functional stress test should be performed, preferably CPET, which is the gold-standard method for assessing functional capacity in this patient population. The stress test must be performed by a trained physician; it evaluate the cardiopulmonary and metabolic responses to increasing exercise and yields several variables that have an impact on the clinical examination and the exercise prescription.[246] The physical therapist and/or physical educator will prescribe, administer, supervise, and guide exercise, following the safety limits recommended by the physician on the basis of the pre-exercise evaluation.[6,247]

The impossibility of performing CPET should not be considered an impediment to exercises; if CPET is not available, a TMET is suggested.[170] When even this is unavailable or otherwise impossible, the 6-minute walk test can assist in clinical assessment, in addition to providing a parameter for comparing functional capacity during training.[248,249]

6.5.3. Exercise Prescription

Aerobic exercise is most recommended, with supplemental resistance training, starting on the 6th week after HTx. Different training methodologies have been studied in isolation and have proven effective in promoting cardiovascular health in individuals undergoing CVR.[6,170] In patients who have undergone HTx, most studies evaluated the effect of MICT.

Depending on the patient's clinical condition, the intensity of aerobic exercise may be gradually increased from moderate to high over the course of training, in order to optimize adaptation and obtain greater benefit, as exercise intensity is directly associated with the magnitude of cardiovascular adaptations.[250] In this sense, programs that include interval training (even HIIT) have demonstrated good outcomes.[233] However, an optimized and safe exercise prescription requires proper individualization of each component of the training session.[170]

The determination of target training zones is advised as a means of optimizing the exercise prescription.[170] However, as recent HTx recipients will exhibit a compromised chronotropic response,[251] prescriptions based on percent of peak HR or threshold HR will not be useful during the first training sessions, although they may be used once there has been improvement in autonomic response.[224] Continuous assessment of the HR response to exercise and during recovery is thus extremely important. When CPET is available, the prescription of aerobic exercise can be based on the ventilatory thresholds or on established percentages of VO_2peak. Another simple and feasible strategy is assessment of subjective perceived exertion using the Borg scale.[4,170,252] The multidisciplinary team must be firmly committed to educating the patient regarding the various levels of perceived exertion and the symptoms of which they should be aware.[4,6]

In addition to the evaluation and prescription of aerobic exercises, resistance exercises are essential. The methods traditionally used for pre-exercise assessment and exercise prescription are 1RM load tests. However, the use of these protocols after HTx – especially after a recent procedure – may be inappropriate, and clinical investigations on the safety of these tests in this specific patient population are still lacking. An alternative evaluation method is the 30-second sit-to-stand test.[253] This test has been validated in active older adults and proved to be reasonably reliable in providing information about lower limb strength, and is now widely used in rehabilitation centers and scientific research on a wide range of clinical conditions.[254-256]

Resistance exercises may also be prescribed subjectively, on the basis of perceived exertion alone. The variable repetition method may be used, whereby the aim of the user is not a set number but a range of repetitions (e.g., 10 to 15 repetitions). If the patient is unable to perform at the lower end of the range, the applied load is too high; if the patient can execute the maximum number of repetitions with ease, the load is too light. Thus, the load can be adjusted so that training takes place within the proposed range of repetitions.

During training, particular attention should be paid to any complications or intercurrent events, such as infections related to the transplant procedure. A. survey found that 36% of HTx recipients are hospitalized within the first year after transplantation, and 61% at 4 years.[257,258] This clearly demonstrates the importance of patient supervision throughout training, should any intercurrent event arise that warrants discontinuation of the exercise session. In view of the foregoing, some authors suggest that patients should not perform physical exercise when receiving pulse steroid therapy and on the days of myocardial biopsies.[170]

6.5.4. Home-Based Cardiovascular Rehabilitation

Previous studies have shown that HBCR programs are safe and effective,[1] and are recommended as an alternative to traditional CVR in low-risk patients.[71]

Wu et al.[259] conducted a prospective, randomized study to evaluate the effect of a home exercise program for 2 months in 37 patients after HTx. The control group maintained their usual lifestyle throughout the study period. Individuals in the intervention group performed an exercise program at least three times a week which included a 5-min warm-up, upper limb and lower limb strength training, 15 to 20 min of aerobic exercise at an intensity of 60 to 70% of VO_2peak, and a 5-min cooldown period. To ensure proper exercise performance at home, an initial period of direct supervision was enforced. At the end of the 2-month period, patients had improved muscle strength and endurance, fatigue index, and quality of life (physical domain). CPET revealed an increase in workload, but with no change in VO_2peak, probably due to the short follow-up period or the less-intense methodology used to guide the training prescription.

Another study,[260] with an equivalent aerobic training protocol but a longer duration (five times a week for 6 months), documented improvements in VO_2peak, workload, and BP in individuals after HTx. In addition, there were signs of cardiac sympathetic reinnervation and restoration of arterial sensitivity to autonomic modulation, with no changes in the control group.

Even beyond 5 years after HTx, HBCR can still improve functional capacity, as demonstrated by a study in which 21 patients were instructed to follow a home-based physical training program consisting of cycle ergometer exercises for 1 year. Nine patients served as controls. To ensure adequate control, patients received a smart card programmed for a 6-min warm-up and 20 min at a constant workload, with load adjustment according to the exercise prescription and HR monitoring. At the end of 12 months, there was a modest improvement in VO_2peak.[261]

Karapolat et al. [262] compared the effects of home-based and hospital-based exercise programs on exercise capacity and chronotropic variables in 28 patients after HTx and observed significant improvements in VO_2peak and HR reserve only in the traditional CVR group. However, new studies, with the inclusion of a larger number of patients, are necessary to better elucidate this superiority of the hospital-based program observed in this study.

6.5.5. Recommendations

Based on the evidence reviewed above, physical training has an unequivocal beneficial effect after HTx, is safe and feasible, and can be performed in the hospital or home environment (Table 7). However, although both strategies are effective in promoting an increase in functional capacity, the magnitude of the effect is greater when training is performed in supervised environments.

CVR should be started 6 to 8 weeks after the HTx, with referral at hospital discharge. In selected cases and after careful evaluation by the CVR team, rehabilitation may begin earlier. As in any post-sternotomy situation, special care must be taken not to prescribe exercises that might overload the chest muscles and lead to sternal traction, especially in the first 90 days after transplant.

The ideal prescription will include exercises that promote different components of physical fitness, always maintaining an emphasis on specific recommendations for each condition. After HTx, just as in other indications for CVR, aerobic exercise should be the main component of training sessions, supplemented by resistance and flexibility training within an individualized, periodically reassessed program. Sessions should always start with a warm-up period and end with a controlled cooldown period. This strategy aims not only to warm up the skeletal muscles but also to provide an adequate time for adjustments of HR and BP to exercise, as the exertion response in these patients is affected by denervation of the heart, especially in the early stages of the training program after transplant.

Aerobic exercise may consist of walking or cycling, whether indoors (using treadmills and/or cycle ergometers) or outdoors. A weekly frequency of three to five sessions, each lasting 20 to 40 minutes, is recommended. The frequency and duration of these sessions will be adjusted according to the patient's preexisting condition and should progress over time with training. Control of exercise intensity is essential; given the larger evidence base, MICT (between the first and second ventilatory thresholds) is recommended, with a perceived exertion no greater than 11 to 13 on the modified Borg Scale. In selected cases, interval training can be adopted to add variety and, potentially, to enhance functional gain.

Resistance training is essential, especially in the early phase after transplantation. Many HTx recipients had longstanding HF, endured prolonged hospitalizations, and have been exposed to massive surgical stress. In this regard, a resistance exercise program can be particularly useful. At the start of training, activities performed against body weight alone are considered sufficient for these patients. Over time, elastic bands, dumbbells, ankle weights, and weight machines can be added to the training program. Greater than usual care is needed during upper body exercises, considering that corticosteroid therapy may make for slower healing of the thoracotomy scar.

Further information and examples of training protocols for these patients are available elsewhere.[263-265]

6.6. Cardiomyopathies

This section will address hypertrophic cardiomyopathy (HCM), myocarditis, and other cardiomyopathies. The indications for CVR in this setting are listed in Table 8.

6.6.1. Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a disease characterized by left ventricular hypertrophy, usually without dilatation of the ventricular chambers, in the absence of another cardiac or systemic disease capable of explaining the magnitude of hypertrophy observed.[271] It is the most common hereditary

Table 7 – Indications for cardiovascular rehabilitation in heart transplant recipients

Indication	Recommendation	Level of evidence
CVR consisting of moderate aerobic exercise is recommended for patients after HTx[234,239,241,243]	I	A
CVR consisting of high-intensity aerobic exercise is recommended for patients after HTx[233,238,244]	IIa	B
CVR consisting of resistance training is recommended for patients after HTx[235,236]	I	B

CVR: cardiovascular rehabilitation, Htx: heart transplant (HTx).

Table 8 – Indications for physical exercise in cardiomyopathy

Indication	Recommendation	Level of evidence
Moderate aerobic exercise is recommended for selected patients with HCM[266,267]	IIa	B
Vigorous or competitive physical exercise in patients with HCM[268,269]	III	C
Moderate aerobic exercise for selected patients 3 to 6 months after acute myocarditis	IIb	C
Light to moderate aerobic exercise for selected patients with ARVC[270]	IIb	B
Vigorous or competitive physical exercise in patients with ARVC[268,269]	III	C

HCM: hypertrophic cardiomyopathy; ARVC: arrhythmogenic right ventricular cardiomyopathy.

heart disease in the general population, caused by a range of mutations in genes which encode the cardiac sarcomere proteins.[268] HCM has a characteristically heterogeneous clinical expression, with unique pathophysiological changes and a variable natural history. Up to 10% of cases are caused by other genetic disorders, including hereditary metabolic and neuromuscular disorders, chromosomal abnormalities, and genetic syndromes.[272] Some patients have other disorders that can mimic HCM, such as amyloidosis.[273]

The population-wide prevalence is estimated at around 0.2% or 1 in 500.[268] However, this estimate appears to differ in clinical practice, which allows us to infer that a portion of the affected individuals are asymptomatic. Various patterns of asymmetric hypertrophy of the left ventricle are commonly seen in HCM, and there may be different phenotypes in first-degree relatives. Typically, one or more regions of the left ventricle exhibit increased wall thickness when compared to others; transitions and variations in thickness may occur in adjacent or noncontiguous areas. However, although asymmetric septal hypertrophy is the most common finding, there is no "classic" HCM pattern, and virtually all possible patterns of left ventricular hypertrophy can occur. Hypertrophy may even be absent in genetically affected individuals, in what is known as a negative phenotype.

Several multicenter retrospective and observational cohort studies, conducted in different populations, have elucidated the natural history and clinical course of HCM. Recent studies have reported an annual mortality of around 1%, much lower than in older surveys.[274] Notably, only a small subgroup of patients with HCM experience significant complications and premature death; these complications can occur due to obstruction of the left ventricular outflow tract, HF with diastolic and/or systolic dysfunction and sudden cardiac death (SCD), or cardiac arrhythmias (atrial fibrillation and ventricular tachycardia or fibrillation).[275] In HCM, SCD can occur at any age, although it is most common in adolescents and young adults; therefore, identification of individuals at the highest risk is an essential component of the pre-exercise evaluation, especially in patients who may want to engage in competitive sports.[276]

In many cases, SCD can be the first manifestation of the disease; indeed, it occurs most commonly in those without warning symptoms and who had not been diagnosed prior to the event. Nevertheless, most patients with HCM have a normal or near-normal life expectancy, with mortality usually attributable to other causes, some even of non-cardiovascular etiology.[277-279] Therefore, encouraging a healthy lifestyle for HCM patients is essential to reducing the overall risk of morbidity.

6.6.1.1. Therapeutic Benefits of Physical Exercise

In the general population, cardiorespiratory fitness is a determinant of the risk of cardiovascular and all-cause mortality.[19] In patients with obstructive and minimally symptomatic HCM, an association of mortality with aerobic fitness has also been observed.[280,281] Patients with a VO_2peak below 18 ml.kg^{-1}.min^{-1} on CPET had higher mortality and were more symptomatic compared to those who achieved values equal to or greater than this threshold. A VO_2peak below 60% of predicted was associated with worse 4-year survival (as low as 60%).[280]

Myocardial fibrosis and myofibrillar derangement may underlie the increased risk of SCD in HCM, as these structural changes act as a substrate for fatal arrhythmias.[271] Evidence does suggest that high-intensity physical training could accelerate these changes, but this is still a controversial topic. However, it is well established that the increase in myocardial fibrosis is associated with a lower VO_2peak in this population.[282]

Therefore, assessing aerobic fitness – preferably through CPET – is essential in patients with HCM.[281] When there is a reduction in VO_2peak, physical exercise can help increase functional capacity.

To date, only one randomized controlled trial has examined the effect of physical training on patients with HCM (RESET-HCM). This study, which included 136 patients, demonstrated an increase in VO_2peak after 16 weeks of a moderate-training intervention (+1.35 ml.kg^{-1}.min^{-1} or < 0.5 MET).[266] Another prospective, non-randomized study included 20 patients with HCM and found a significant increase in treadmill test duration, as well as in estimated functional capacity (+2.5 MET).[267] In this study, patients completed a CVR program which consisted of 60-minute sessions of moderate to vigorous exercise, performed on a treadmill or cycle ergometer, twice a week. The intensity of exercise progressed from 50 to 85% of HR reserve, which resulted in a gradual increase in conditioning and may have minimized the risk of adverse events, such as exercise-induced arrhythmias. Serious adverse events, such as death, aborted SCD, implantable cardioverter-defibrillator (ICD) activation, or sustained ventricular tachycardia, did not occur in any of these studies.[266,267]

6.6.1.2. When Is Physical Exercise Indicated?

The intensity of exercise which patients with HCM can be cleared to do still represents a major challenge. If, on the one hand, intense physical exercise can be harmful, with an increased risk of potentially fatal arrhythmias, on the other hand, excessive restrictions on physical activity lead to deconditioning and can have negative effects on health and quality of life; they may even increase cardiovascular risk, given the well-established association between physical fitness and mortality.[280,281]

In its official position statement on management of HCM, the American Heart Association discourages patients with the disease from engaging in competitive sports of moderate to vigorous intensity (see Table 8). This limitation is meant to minimize sudden changes in BP and increases in cardiac output in order to protect patients from the negative effects of exercise on a pathologically hypertrophic heart.[283]

Exercise-triggered arrhythmias (in the short term) and adverse myocardial remodeling (in the long term) are the most fearsome side effects of exercise in HCM. The fear of SCD during sport extends to non-competitive athletic activities, although there is a clear lack of evidence about the safety of exercise in this patient profile. However, it should be emphasized that this risk of exercise is theoretical, and that recommendations to limit physical activity have been advocated with caution, based solely on the opinion of experts, and are not supported by more robust evidence.[284]

Thus, patients with HCM receive little guidance regarding the best dose or amount of physical activity to maintain general health and well-being; instead, greater focus is placed on restrictions on physical activities. As a result, more than 50% of patients with HCM do not achieve the minimum recommended physical activity target due to the belief that they are unable to exercise and/or that physical activity can worsen their disease.

Therefore, a balanced approach seems to be most appropriate, and extremes should be avoided (neither vigorous competitive exercise nor physical inactivity), as both could increase cardiovascular risk.

New evidence suggests a positive effect of moderate physical exercise in selected patients with HCM, with individualized risk assessment and exercise prescription. It is noteworthy that the evidence suggests benefits of MICT, while other modalities need further studies.

However, the presence of any of the following could be considered major contraindications to the practice of exercise: history of aborted SCD in the absence of an ICD; history of syncope on exertion; exercise-induced ventricular tachycardia; increased exercise pressure gradient (greater than 50 mmHg); and abnormal BP response to exertion.

6.6.1.3. Pre-Exercise Evaluation

Clearance to begin exercising must be based on the pre-exercise evaluation, including a thorough history, physical examination, and 12-lead ECG.

A large proportion of individuals with HCM are asymptomatic or oligosymptomatic; clinical suspicion is raised only by changes on resting ECG, which is abnormal in up to 95% of patients with the disease.[285] Electrocardiographic changes may precede structurally detectable disease for some years, which makes ECG extremely important in this scenario.[269] Only a minority of patients with HCM present with a normal ECG – usually those without any other phenotypic manifestations (positive genotype/negative phenotype).

Echocardiography remains the most widely used modality for diagnosis of HCM. Magnetic resonance imaging (MRI) is usually reserved for cases in which echocardiography is in conclusive, or to assess more localized hypertrophy (e.g., apical forms). In young athletes, distinguishing physiological hypertrophy ("athlete's heart") from the pathological hypertrophy of HCM is a challenge. This is because, most athletes with HCM exhibit an asymmetric pattern of left ventricular hypertrophy, as do sedentary individuals with the condition. In contrast, those with physiological left ventricular hypertrophy show a more homogeneous, symmetrical distribution of wall thickness, with only minor differences between contiguous segments and a symmetrical pattern of left ventricular hypertrophy.[286]

Exercise testing is always recommended in these patients prior to the start of CVR, whether to assess functional capacity or to detect abnormal BP responses and signs of increased dynamic obstruction of the outflow tract with exertion. For better detection of outlet tract obstruction during exercise, a combination of imaging (echocardiography) with stress testing is the gold standard and should be encouraged whenever possible. Patients with no obstruction at rest can present significant gradients on exertion, and thus be reclassified in relation to prognosis.[287]

When available, CPET is advised instead of TMET, as it allows direct measurement of VO_2peak, a parameter with documented prognostic value.[280,281] In addition, determining ventilatory thresholds contributes to a more individualized exercise prescription.

6.6.1.4. Special Considerations for the Prescription and Follow-Up of Physical Exercise Programs

Some particularities of exercise in patients with HCM should be noted:

- So-called "explosive" activities (e.g., basketball, football, tennis), with the potential for rapid acceleration and deceleration, should be avoided.
- Activities with steady, constant energy consumption (e.g., light jogging or swimming) are preferred.
- Exercise in adverse environmental conditions, including extreme heat or cold, should be avoided, as there is an increased risk of exacerbating exercise-induced physiological changes.
- Training programs that aim competitivity, or achievement of higher levels of fitness and excellence, should be avoided, as they usually motivate patients to strive beyond safe limits.
- Intense static (isometric) exercises, such as weight lifting, should be avoided, as there is an increased risk of left ventricular outflow tract obstruction due to the intense Valsalva maneuver involved.

- Resistance training with low loads and a greater number of repetitions is considered safe for patients with CVD, although there is no solid evidence for patients with HCM.

Some notes on drug therapy are warranted. Beta blockers and calcium channel blockers may be indicated in the treatment of HCM. As these medications attenuate the HR response to exercise, patients may experience a very reduced chronotropic response to exertion, which can cause increased exercise intolerance, suggesting a need for dosage adjustment. Excess diuretic use can be harmful because it increases the gradient of the outflow tract. Therefore, these agents should be used with caution. Like diuretics, exercise-induced dehydration can raise the outflow tract gradient; therefore, adequate hydration during training is of paramount importance.

6.6.2. Myocarditis

The pathogenesis of myocarditis consists of three phases: acute myocardial injury, usually of viral etiology; host immune response; and recovery, or transition to fibrosis and dilated cardiomyopathy. Clinically, there is no clear distinction between these phases. The initial insult can cause acute myocardial damage, with impairment of contractility mediated by cytokines produced by the local inflammatory process. This acute inflammation may progress, in the late phase, to extensive fibrosis, which can cause ventricular dilatation and dysfunction.

Acute myocarditis should be suspected when the following criteria are present:[283]

- A clinical syndrome of acute HF, angina-type chest pain, or myopericarditis of less than 3 months' duration
- Unexplained rise in serum troponin
- ECG changes suggestive of myocardial ischemia
- Global or regional wall motion abnormalities and/or pericardial effusion on echocardiography
- Characteristic changes in tissue signal on T2- or T1-weighted MRI, as well as late gadolinium enhancement.

The participation of myocarditis patients in CVR programs after resolution of the acute phase has been the subject of very little study. There is no published research on the safety and effectiveness of this intervention. However, reports of CVR in this patient population have demonstrated benefits in quality of life and physical fitness, especially when there is functional impairment, even after improvement of the acute condition and optimization of drug therapy.[288-290]

Before starting any exercise practice, patients with a history of myocarditis should undergo echocardiography, 24-hour Holter monitoring, and an exercise test no less than 3 to 6 months after the acute phase has resolved.[269,283] After this evaluation, selected cases may initiate moderate CVR, aiming at the general benefits obtained by patients with HF.

In sports, it is reasonable for athletes to return to their normal training routine only if they achieve: return of systolic function to normal values; markers of myocardial necrosis and inflammation within normal range; and absence of clinically significant arrhythmias on both Holter monitoring and an exercise test. It is noteworthy that the clinical significance of persistent late gadolinium enhancement on MRI in post-myocarditis patients whose clinical symptoms have resolved remains unknown. Thus, it seems reasonable that those with small areas of enhancement and without significant arrhythmias on Holter monitoring and exercise testing can return to sports, provided that clinical monitoring is continued.[269]

In chronic cases, in which ventricular dysfunction persists throughout the follow-up period, the patient should follow the general recommendations for CVR as described for chronic HF (see Table 6).

6.6.3. Other Cardiomyopathies

6.6.3.1. Arrhythmogenic Right Ventricular Cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited disease that is associated with SCD in young adults and athletes. Pathologically, myocytes are lost and replaced with fibroadipose tissue, especially in the myocardium of the right ventricle, although isolated left ventricular or biventricular involvement may also occur.[291]

There is evidence, in an experimental animal model, that exercise increases penetrance and risk of arrhythmias in patients with traditional ARVC mutations.[292] In individuals with positive genotypes, an increased risk of arrhythmias with exercise has also been confirmed. Ventricular tachyarrhythmias and SCD events in this condition usually occur during exertion, including sports and endurance exercise, with an increased risk of tachycardia, ventricular fibrillation, and HF.[293]

It has been shown that individuals with ARVC who are involved in competitive sports experience a higher incidence of ventricular tachyarrhythmias and SCD, in addition to earlier symptom onset, compared with those who participated only in light physical activity and those who were sedentary.[270] The reduction in exercise intensity was associated with a substantial decrease in the risk of ventricular tachyarrhythmias or death, especially in patients without a detected desmosomal mutation and with an ICD for primary prevention.[294] Therefore, the scientific evidence suggests that participation in sports and intense exercise are associated with early onset of symptoms and an increased risk of ventricular arrhythmias and major events in patients with ARVC. Therefore, these patients must be disqualified from participation in sport.[269, 276]

Regarding participation in CVR programs, there is no scientific data to indicate or suggest any benefits of physical exercise for patients with ARVC. On the other hand, keeping them sedentary, which contributes to low physical fitness, may also be inappropriate, as there is a general association of low physical fitness with mortality.[14,21]

In a small observational study of patients with ARVC, there was no difference in mortality rate between inactive individuals and those who performed only recreational physical activities.[270] Thus, it can be assumed that participation in a supervised CVR program, restricted to exercise of light to moderate intensity, could not be harmful. Depending on other individual clinical characteristics, such as the presence of cardiovascular risk factors, physical exercises could be prescribed to control these conditions.

Therefore, the inclusion of a patient with ARVC in CVR programs should only be carried out after a thorough pre-exercise evaluation and rigorous evaluation of the risk-benefit balance of physical exercises. Options should be discussed with the patient, exposing the absence of proven benefits versus the potential risks of physical inactivity and low physical fitness. It is then up to the patient to choose according to their own personal preferences.

In the context of CVR, extrapolating findings from athletes, a restriction on higher training intensities is also suggested. Patients with ARVC could thus perform supervised physical exercises of light to moderate intensity.

6.6.3.2. Noncompaction Cardiomyopathy

Noncompaction cardiomyopathy (NCM) is a heart disease that occurs due to embryonic interruption of myocardial compaction. It is characterized by segmental thickening of the left ventricular walls, consisting of two layers: a compacted epicardial one and an endocardial one with marked trabeculation and deep intratrabecular recesses, where spaces are filled by blood flow.[295,296]

Its incidence and prevalence are uncertain, ranging from 0.02 to 0.05% according to some echocardiographic records.[297] Clinically, it can be asymptomatic or present with symptoms of HF, ventricular and/or atrial arrhythmias, pre-excitation, thromboembolic events, or SCD. There are no universally accepted criteria for morphological diagnosis; however, a ratio between noncompacted/compacted myocardium greater than 2.1:1 at the end of systole on echocardiography or 2.3:1 at the end of systole on MRI has become the most widely accepted proposed criterion.[298]

It is not yet established how physical training can influence NCM, nor is the frequency of development of noncompaction morphology in the population known.[299,300] In recent studies, athletes have shown a high prevalence of increased ventricular trabeculation when compared to a control group (18.3 *versus* 7%). It is believed that the increase in ventricular trabeculation or the presence of isolated echocardiographic criteria for cardiomyopathy is probably of little significance, and may be part of the spectrum of athlete's heart.[300,301] Therefore, not all athletes with isolated ventricular compaction are diagnosed with NCM. Therefore, functional parameters (such as ejection fraction) must also be considered to guide management.[301]

To date, there is no evidence from studies of CVR or training in NCM. Therefore, patients with left ventricular dysfunction should follow the same exercise recommendations as those with chronic HF (see Table 6).

6.7. Valvular Heart Disease

Patients with valvular heart disease represent a very heterogeneous group with major variability in terms of age, etiology, affected valves, and severity of involvement, whether due to stenosis, regurgitation/insufficiency, or mixed lesions. However, most valvular heart diseases share a common feature in their clinical manifestations induced by exertion, which include chest pain, dyspnea, and/or functional limitations. The severity of these symptoms in patients with severe valvular heart disease can be used as one of several criteria to indicate surgical or percutaneous intervention. In addition, the identification of reduced aerobic fitness, as documented by CPET or TMET, is also a criteria used to define whether interventions are indicated.[302-304]

One major issue in the clinical follow-up of patients with valvular heart disease is the prolonged natural history of these conditions. The onset and progression of symptoms and functional limitations is often slow, which may lead patients to spontaneously reduce their engagement in physical activity due to symptoms on exertion. This sedentary lifestyle can contribute to further reductions in aerobic physical fitness and worsen symptoms.

Thus, doubts may arise regarding the clinical management and need for interventions when the patient undergoes a CPET or TMET, namely: are limitations in physical fitness identified on exercise testing a result of progressive valvular heart disease, a sedentary lifestyle, or both? In this context, the regular practice of physical exercise and the consequent maintenance or even improvement of physical fitness are important to elucidate these questions in the follow-up of patients with valvular heart disease.

Participation of these patients in CVR programs has been the subject of a single cost-effectiveness study.[305] However, increases in the functional capacity of individuals referred for CVR have been demonstrated consistently,[306,307] which justifies referral to exercise-programs (level of evidence C).

Rehabilitation in the setting of valvular heart disease can be subdivided into two phases: pre- and post-intervention (surgical or percutaneous).

6.7.1. Pre-Intervention Phase

Patients with moderate to severe valvular heart disease in the pre-intervention phase are rarely enrolled in CVR programs. Training is carried out mainly in asymptomatic cases, in whom there is still no indication for valve repair or correction.

CVR can be useful to keep the patient physically active while waiting for future intervention; after all, a sedentary lifestyle can deteriorate functional capacity and, thus, increase the risk of postoperative complications, especially when the intervention is performed in older adults with multiple comorbidities and established frailty.[308-310]

In addition, monitoring during supervised CVR sessions can be useful to observe changes in symptoms and physical fitness, which can indicate progression of valvular heart disease and suggest the need for medical reevaluation.

6.7.2. Post-Intervention Phase

Post-intervention patients are more common in CVR programs, as structured and supervised exercise is a useful means of observing the hemodynamic behavior of a patient's new (or newly repaired) valve. Information on a patient's response to physical exercise can help their primary physician adjust drug therapy and/or review valve function. In addition, supervised exercise provides a greater measure of safety for the patient to return to his or her activities of daily living, leisure, and sports.

Although there is no consensually defined time limit for referral to CVR in the setting of valvular heart disease, the earlier the patient starts exercise, the less function he or she will lose from inactivity.[305-307,310] The exchange of information between the patient's primary physician and the rehabilitation physician is the best strategy for defining the optimal timing of referral, and the pre-exercise evaluation has a fundamental role in consolidating this shared decision.

6.7.3. Pre-Exercise Evaluation

The pre-exercise evaluation should always consist of a thorough history, physical examination, and evaluation of laboratory tests and imaging. The clinical history must include: length of hospital stay; complications related to the procedure, such as pleural or pericardial effusion, mediastinitis, and infections; type and size of prosthetic valve; surgical technique; and whether CABG was performed concomitantly, in addition to other clinical information that may be relevant regarding other comorbidities.

On physical examination, cardiac and pulmonary auscultation are particularly important. In addition, attention should be paid to the surgical scar, which should be examined for signs of inflammation and infection, sternal instability, and pain or discomfort on palpation. If concomitant revascularization was performed, the saphenectomy and/or radial artery donor site must be examined. If valve repair or replacement was performed percutaneously, the access site should be checked for signs of peripheral vascular complications.

It is important that the clinician look for signs of anemia on physical examination and laboratory tests, because this is a common complication and can have a negative impact on functional capacity.[311] Laboratory evaluation of coagulation is relevant in patients who received a mechanical valve and were started on anticoagulants. Achieving the correct level of anticoagulation is important in preventing complications.

A resting ECG should be obtained to check for any arrhythmias and disturbances in rhythm or conduction. The most commonly used imaging modality in the evaluation of valvular heart disease is Doppler echocardiography, which allows assessment of ventricular function and cavity dimensions, measurement of transvalvular pressure gradients, estimation of pulmonary artery systolic pressure, and measurement of blood flow, which provides a good overview of valve function and cardiac function at rest. Echocardiography should always be performed before the start of a CVR program, to assess the risk of exercise-related complications.[312]

It is important to evaluate functional capacity by CPET or TMET.[313-316] These tests, especially CPET, provide extremely useful information regarding aerobic fitness and the hemodynamic repercussions of valvular heart disease, which may be underestimated by assessments performed at rest. In addition, treadmill tests identify parameters that are used to guide exercise prescription and restrictions. When TMET and CPET are unavailable, the use of functional tests, such as the 6-minute walk test and the step test, should be considered.[317-320]

It is important to emphasize that CPET and TMET pose greater risk in patients with stenotic lesions; therefore, they should only be carried out by experienced physicians and in a safe setting with the necessary infrastructure to respond in case of emergency.[321]

Functional tests are indicated not only in pre-exercise evaluation, but also to elucidate any doubts regarding the symptoms of patients in the pre-intervention phase of valvular heart disease. The combination of functional tests with echocardiography helps assess the response of the transvalvular pressure gradient and pulmonary artery systolic pressure to exertion, especially when there is a discrepancy between echocardiogram findings at rest and clinical signs and symptoms.[304,322,323]

Another relevant issue is the evaluation of elderly patients, who are frequently affected by valvular heart disease and have a high prevalence of risk factors and comorbidities.[324] Due to their high surgical risk, such patients are now considered candidates for percutaneous repair or replacement of the aortic[325] and mitral valves.[326] In this scenario, CVR can be considered before the intervention, with the aim of decreasing complication rates, length of hospital stay, and mortality and morbidity associated with the frailty syndrome.[327] After the intervention, CVR then provides an opportunity for monitoring and optimization of the outcomes of the procedure in all its aspects.[328-331]

The use of frailty syndrome assessment instruments is still a controversial subject in the literature; there is no consensus regarding the best protocol to assess CVR outcomes. The assessment should include objective tests and instruments to address risk in several domains: mobility, muscle mass and strength, independence in activities of daily living, cognitive function, nutrition, anxiety, and depression.[304,308,332]

6.7.4. Special Considerations for the Prescription and Follow-Up of Physical Exercise Programs

This section will only address guidelines and recommendations for exercise in patients with moderate or severe valvular heart disease, as there are no restrictions to exercise in patients with mild involvement. Participation in competitive sports should follow the recommendations of the specific literature on the subject.[276,333,334] Scientific evidence is scarce as to the impact of regular exercise on the progression of valvular heart disease and its complications; therefore, recommendations are based on expert opinion alone (level of evidence C).

Acutely, exercise causes an increase in adrenergic tone and in the hemodynamic load imposed on the cardiovascular system, which raises concerns regarding the potential for deleterious cardiovascular effects in patients with valvular heart disease, including progression of aortic disease, functional deterioration, pulmonary hypertension, cardiac remodeling, myocardial ischemia, and arrhythmias.

Patients with valvular heart disease who will start a CVR program must undergo a stress test to guide exercise prescription. Table 9 summarizes recommendations for asymptomatic patients, who have not undergone any intervention, with moderate or severe valvular heart disease. In general, training will consist of a combination of aerobic and resistance exercise. When there are no restrictions, the recommendations for exercise prescription will be the same as those for individuals without heart disease.

Table 9 – Physical exercise in asymptomatic individuals with valvular heart disease

Valvular heart disease	Aerobic exercise	Resistance exercise
Aortic insufficiency	**Moderate or severe** (normal ventricular function; LVESD < 50 mm in men or < 40 mm in women; good functional capacity) **No restrictions**	**Moderate or severe** **Avoid high intensity**
Aortic stenosis	**Moderate or severe** (normal ventricular function; good functional capacity; absence of myocardial ischemia, complex ventricular arrhythmias, or plateau response/fall in SBP) **Avoid high intensity**	**Moderate** Avoid high intensity **Severe** Limited to low intensity (enough to maintain activities of daily living)
Mitral insufficiency	**Moderate or severe** (normal ventricular function; LVEDD < 60 mm; PASP < 30 mmHg) **No restrictions**	**Moderate or severe** Avoid high intensity
Mitral stenosis	**Moderate or severe** (good functional capacity) **Avoid high intensity**	**Moderate or severe** (good functional capacity) **Avoid high intensity**

LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; SBP: systolic blood pressure; PASP: pulmonary artery systolic pressure.

For symptomatic patients in whom surgical correction is not indicated or who do not have the characteristics described in Table 9, the intensity of exercise should be limited by the occurrence of abnormalities observed during the CPET or TMET, as it is assumed that repeated insults at this intensity could increase the risk of exercise and induce potential deleterious effects in the long term. The exercise prescription should be limited to an intensity of exertion corresponding to 10 bpm below the HR at which the abnormality occurred during the CPET or TMET. Relative loads and subjective perceived exertion can be used to guide exercise prescription when HR is not a good indicator, such as in patients with atrial fibrillation or an artificial pacemaker (Table 10).

In patients who have undergone surgical correction of valvular heart disease, the exercise prescription will depend on the underlying disease, the outcome of the procedure, the presence of residual lesions, ventricular function, and the response to the exercise test (TMET or CPET). Therefore, each case must be assessed individually, and the limits of exercise prescription defined by the pre-exercise assessment and the results of physical examination and any other tests performed.

6.8. Patients with Artificial Pacemakers or Implantable Cardioverter-Defibrillators

This section describes particulars involving implantable devices: artificial pacemakers and implantable cardioverter-defibrillators (ICD). Artificial pacemakers are indicated in the management of electrical abnormalities, which may be isolated – sick sinus syndrome, advanced atrioventricular (AV) block – or associated with structural heart diseases. ICDs are indicated for the primary or secondary prevention of SCD in patients with severe electrical and/or structural heart disease. Depending on the underlying heart condition, the recommendations on CVR described elsewhere in this guideline apply.

One of the main concerns of physical exercise in patients with an artificial pacemaker or ICD is the risk of device-related complications, especially in high-impact activities. In patients with ICDs, there is the added fear of inadvertent activation, which can cause behavioral changes, such as reduced physical activity and participation in moderate-intensity exercise.[335,336] Health care providers also share these fears,[337] which may limit their exercise prescribing practices. However, studies have shown that physical exercise is safe and is not associated with an increased risk of shocks or other adverse events.[338-342] In addition, ICD-related complications have not been observed even in competitive athletes.[343,344]

Nevertheless, before clearing a patient for exercise, the clinician must be aware of the reasons for device placement and become familiar the device's programming parameters and settings, ideally during the pre-exercise evaluation.

6.8.1. Therapeutic Benefits of Physical Exercise

A meta-analysis[342] of 14 studies enrolling 2,681 patients with ICDs showed a beneficial effect of physical exercise on functional capacity in this population, with an average increase in VO_2 of 2.4 $ml.kg^{-1}.min^{-1}$. In another meta-analysis, which included five randomized trials and one nonrandomized study in patients with HF and ICDs,[341] a similar improvement in physical capacity was observed, with an increase in VO_2peak of 1.98 $ml.kg^{-1}.min^{-1}$ in relation to the control group.

As for the concern of inadvertent ICD activation during physical training, one meta-analysis found no significant differences. The rate of exercise-associated shocks ranged from 0 to 20% across studies, with an average of 2.2%, similar to the rate of shocks during an exercise-free follow-up period.[342] Thus, despite widespread fear of this phenomenon, physical training was not associated with increased ICD activation and proved safe.

Table 10 – Abnormalities observed on cardiopulmonary exercise test or treadmill exercise test that should limit exercise intensity in patients with valvular heart disease

Exercise-induced changes	Description
Signs and symptoms	Onset of angina, angina equivalent, or other signs and symptoms indicative of exercise intolerance
Blood pressure	Plateau response or decline in SBP; or, SBP >220 mmHg; or, DBP >115 mmHg
ST segment	Onset of ST segment depression (horizontal or descending) >1 mm
Ventricular function	Evidence of decreased ventricular function on exertion or onset of moderate to major left ventricular wall motion abnormalities
Pulse O_2 (CPET only)	Evidence of early plateau or decline on effort despite increased load
Arrhythmia	Grade 2 or 3 AV block, atrial fibrillation, supraventricular tachycardia, complex ventricular arrhythmias

CPET: cardiopulmonary exercise test; SBP: systolic blood pressure; DBP: diastolic blood pressure, AV: atrioventricular.

Table 11 – Indications for physical exercise and other treatments in patients with implantable cardioverter–defibrillators

Indication	Recommendation	Level of evidence
Physical exercise to increase physical capacity in stable patients with an ICD[341,342]	I	A
Physical exercise for potential reduction of the incidence of ICD activation (shocks)[341]	IIa	B
Use of neuromuscular electrical stimulation in patients with implantable devices with bipolar sensors, when performed on muscles far from the implant site[349]	IIb	B

ICD: implantable cardioverter–defibrillator. If any structural heart disease is present, the corresponding recommendations should be taken into account.

Another meta-analysis actually reported a lower likelihood of shocks during follow-up in patients participating in CVR compared to controls, corroborating the previous result of an observational study, which reported a higher incidence of ICD activation in patients who did not participate in CVR programs.[341,345]

One possible explanation or the lower incidence of arrhythmias and shocks in patients undergoing CVR would be the improvement of physical capacity, as it has been previously documented that greater physical fitness is associated with a lower incidence of arrhythmia.[16,17,346] In addition, exercise could reduce myocardial arrhythmogenicity due to remodeling and reduction of sympathetic excitability.[347]

In a nationwide study with 10 years of follow-up which included 150 patients with ICDs in a CVR program, all of which completed a CPET or TMET to support exercise prescription, there were only three shock events and all were appropriate.[348] This provides additional evidence of the safety of stress testing and CVR in this population.

6.8.2. When Is Cardiovascular Rehabilitation Indicated?

Physical exercise can and should be indicated as long as the patient's clinical condition is stable and clinical treatment is optimized. In addition to the potential beneficial effects on underlying heart disease, CVR increases physical fitness and can help reduce the incidence of arrhythmias and, consequently, of ICD activation (Table 11).

6.8.3. Pre-Exercise Evaluation

In patients with implantable devices, the clinician must become familiar with the reason for implant placement, the patient's ventricular function, whether any arrhythmias are present and, particularly, the device settings and parameters. For patients with an artificial pacemaker, this means understanding the programming mode, the set HR limits, and the type and response of the activity sensor. In patients with an ICD, essential information includes the HR threshold which has been set to trigger shock or burst therapies.

In addition to the standard clinical examination, pre-exercise evaluation is of paramount importance in these patients. Ideally, a CPET or TMET should be performed to determine functional capacity and analyze the behavior of the device during exertion. However, the impossibility of performing CPET or TMET should not prevent the practice of physical exercise. In these cases, monitoring during sessions may reveal a need for device reprogramming, usually of maximum HR and sensor response settings.

During CVR sessions, continuous ECG monitoring can be achieved with the use of telemetry systems. HR control devices, such as regular cardiac monitors, can also be used for monitoring CVR sessions.[350] However, due to changes in the ECG tracing caused by artificial pacing, automated HR measurement both by ECG telemetry systems and by cardiac monitors may be erroneous. The team should be aware of this potential for error and measure HR manually as needed.

6.8.4. Special Considerations for the Prescription and Follow-Up of Physical Exercise Programs

When prescribing and defining intensity limits for aerobic physical training, one should be aware of ICD programming and limit the intensity accordingly to 10–20 bpm below the HR set to trigger therapy (shock or burst). This is especially

important in young individuals who experience elevated HR during training. In older patients with HF who are on high-dose beta blockers, the peak HR observed during CPET or TMET is usually below the threshold that triggers ICD therapy.

Patients with an artificial pacemaker may have different chronotropic responses observed on CPET or TMET, which will impact the prescription of aerobic exercise. In addition, the individual's own pace, type of pacemaker, and presence of a rate sensor will influence the HR response to exertion and, consequently, the exercise prescription.[351]

The four possible types of artificial pacemaker response to exertion are as follows:

1) **Normal or depressed sinus-node chronotropic response. Pacemaker inhibited (not triggered).** The chronotropic response to stress is mediated by sinus rhythm and may be normal or depressed (due to sinus node dysfunction and/or drug effect). Ventricular conduction occurs via the own pathway, and the pacemaker is not triggered on exertion. In some cases, it can be triggered at rest and during initial loads, with atrial and/or ventricular pacing. However, during exertion, the pacemaker is inhibited, with a predominance of sinus responses and ventricular conduction via the own pathway. In this type of response to exertion, the intensity of exercise prescription should be based on the usual concerns and is entirely unaffected by the presence of an artificial pacemaker.

2) **Normal or depressed sinus-node chronotropic response. Pacemaker triggered (activity-initiated ventricular pacing).** The chronotropic response to exertion is mediated by the sinus rhythm. Sinus activity is sensed by the pacemaker and triggers synchronized ventricular pacing according to preset paced atrioventricular intervals. In this case, if the maximum pacemaker response limit has been set appropriately for the patient's sinus response, the exercise prescription may be HR-based, as the ventricle will be paired with sinus activity. However, if the maximum pacemaker response limit is set lower than the patient's sinus response, dyssynchrony of ventricular pacing and sinus activity will occur at moderate to high exercise intensity. The pacemaker will then block some sinus stimuli by mimicking AV-node Wenckebach activity, a phenomenon known as "electronic Wenckebach",[352] in order to keep the ventricular HR within the programmed limit; a plateau in the chronotropic response to exertion will ensue. In this scenario, the loss of synchrony between sinus rhythm and ventricular rate will interfere with the utility of HR to guide exercise intensity. The exercise prescription should instead be based on relative loads and/or subjective perceived exertion.

   When the electronic Wenckebach phenomenon occurs, extreme care is required to detect it during CPET or TMET. It is essential to obtain precise information on the atrial rate at which the pacemaker will initiate 2:1 block, because as this rate is reached, ventricular pacing will occur at a 2:1 ratio, with the potential for a sudden fall in HR on exertion and an abrupt, symptomatic reduction in cardiac output. Therefore, unless the programmed Wenckebach interval and the 2:1 block rate are quite far apart, the HR which triggers electronic Wenckebach may be used as the upper limit for CPET or TMET, as well as for the exercise prescription.

   In such cases, pacemaker reprogramming to better match the patient's sinus response should be considered and discussed with the primary physician. Another option, depending on the clinical picture, is the optimization of drug therapy with negative chronotropic agents (such as beta blockers). A reduced sinus response may prevent the aforementioned event.

3) **Fixed, pacemaker-mediated chronotropic response (no rate responsive pacing).** Some patients may have no sinus activity at all, as in atrial fibrillation. In these cases, individuals with complete AV block will be completely dependent on ventricular pacing. If the pacemaker has no rate responsive pacing, or if the sensor is disabled, there will be no chronotropic response to exertion; the pacemaker will be set to a fixed HR. This type of pacemaker and programming is now exceedingly rare. Nevertheless, in such patients, the HR is useless to guide exercise prescription, which should instead be based on relative loads and/or subjective perceived exertion.

4) **Pacemaker-mediated chronotropic response (rate responsive pacing).** In patients with atrial fibrillation and AV block, as previously described, but whose artificial pacemaker has an active sensor with rate responsive pacing, there will be dependence on ventricular pacing, but activation of the sensor by exertion will lead to a pacemaker-mediated chronotropic response. In patients with sinus rhythm, but with a large chronotropic deficit due to sinus node dysfunction and/or drug effects, a chronotropic response to exertion may also occur, mediated by the pacemaker sensor, with atrial pacing followed or not by ventricular pacing.

   The speed and magnitude of the rate sensor's response to exertion are programmable, with the possibility of adjusting the sensor activation threshold, the rate of increase in HR to exertion and the rate of reduction during recovery, and the maximal HR limit for the sensor. TCPE or TMET can be used to verify the adequacy of the response and identifying potential needs for pacemaker reprogramming, which should be discussed with the patient's primary physician.

   In such cases, as the chronotropic response will be artificially mediated by the device, HR-based prescription of exercise intensity may be inaccurate. Therefore, the use of relative loads and/or perceived exertion is preferred.

   Pacemakers with accelerometer sensors and axial motion detection, which are the most common, have a sensitive response to walking or running on a treadmill. However, as there is no vertical movement on a cycle ergometer, the sensor is activated very little or not at all. As a result, there is inferior chronotropic response during ciclo ergometer exercise, which may vary according to the individual response of the patient.

6.8.5. Resistance Training

Resistance training is an important component of CVR for several heart diseases. However, after implantation of a pacemaker of ICD, some care is required until healing is complete, to prevent vascular injury, displacement of the device, and electrode fracture. For instance, caution is recommended when performing weight training and any exercise which involves raising the arms during the first 6 weeks after the implant procedure. In addition, repetitive and intense movements of the limb ipsilateral to the device should be avoided.

However, such guidelines are geared more at patients involved in sports, and are unlikely to be relevant to the exercises carried out in CVR programs. A study of early, supervised shoulder mobilization immediately after artificial pacemaker implantation did not observe any device complications.[353]

6.8.6. Neuromuscular Electrical Stimulation

The use of neuromuscular electrical stimulation (NMES) in patients with HF has become widespread, especially for those unable to exercise due to disease severity. NMES can improve aerobic capacity, muscle strength, and cross-sectional area of the quadriceps muscles, and is an effective passive exercise modality in this population.[354-356] However, the use of electronic devices in these patients (ICDs, artificial pacemakers, resynchronization devices) is also increasing, which raises concerns of the possibility of electromagnetic interference.

A systematic review[349] demonstrated that NMES of the quadriceps muscles appears to be safe and feasible in patients with HF and a bipolar sensing ICD. However, the review itself notes that the number of studies and patients included is too small to allow more comprehensive conclusions, and concludes that NMES can be used provided the following conditions are met:

1) If individual hazards (pacemaker dependence, acute HF, unstable angina, ventricular arrhythmia in the last 3 months) have been excluded before starting NMES.
2) If NMES is performed only on the quadriceps and gluteal muscles.
3) If treatment is regularly supervised by a doctor, and the device is analysed after every NMES session.

Therefore, at the present time, although NMES seems safe to use in patients with bipolar-sensing implantable devices when performed on muscles far from the implant, there is still a need for studies with a larger number of patients to confirm that use is safe and feasible without the need for repeated, detailed device evaluation after sessions.

6.9. Peripheral Arterial Occlusive Disease

Stroke has been correctly viewed and addressed as a serious disease with massive impact on public health. However, peripheral artery disease, which is also highly prevalent worldwide and carries high morbidity and mortality rates, affecting more than 40 million individuals in Europe alone, have not been properly addressed, hindering prevention, diagnosis, and effective treatment.[357,358] In this context, peripheral arterial occlusive disease (PAOD) of the lower limbs is particularly concerning, as, at its most severe stage (critical ischemia), it is associated with a high risk of cardiovascular events, lower limb amputation, and death. With the growth of risk factors such as age, diabetes, and smoking, critical ischemia of the lower limbs has become more prevalent, and currently affects about 2 million individuals in the United States alone.[359]

The presence of PAOD is suspected when there is pain in the lower limbs on exertion, with no apparent musculoskeletal etiology, and the ankle-brachial index (ABI) is <0.90 at rest.[360,361] The ABI has been recommended as a diagnostic resource prior to use of imaging.[362] Functional tests during exertion effort may be necessary to establish the diagnosis, especially when the ABI is greater than 0.91, as well as for functional classification and exercise prescription in CVR.

Gait can be assessed by means of field tests, which allow the diagnosis of intermittent claudication and determination of the distance walked until onset of symptoms (initial claudication) and until development of total loss of function (absolute claudication).

A TMET with measurement of the ABI at rest and after exercise has also been proposed as a diagnostic test. The presence of PAOD is suggested by a greater than 20% reduction in post-exercise ABI as compared to resting values, or a decrease in post-exercise BP greater than 30 mmHg as compared to the resting state.[363] Another study reported lower cut-off scores, with PAOD being suggested when there is a greater than 18.5% reduction in ABI and a greater than 15 mmHg decrease in BP after exercise.[364]

Considering the overall cardiovascular risk of these patients, optimized clinical treatment should always be instituted. In addition, smoking cessation and drug therapy with statins and antiplatelet agents must be considered, as well as adequate blood glucose and BP control. Regarding the use of cilostazol, there is no consensus among the guidelines of different medical societies.[362,363]

In symptomatic patients, exercise has the potential to influence morbidity and mortality, reducing symptoms, improving quality of life, and increasing the maximum walking distance (Table 12).[365] Physical activities performed under direct supervision have been shown to be more effective than unsupervised exercise.[366] In 14 clinical trials (1,002 participants), with an intervention duration from 6 weeks to 12 months, pain-free walking increased about 180 meters more in training under direct supervision when compared to training under indirect supervision. Physical training is safe; in most studies, the sole exercise was walking to claudication, at least three times a week, for at least 3 months.[367]

In patients with PAOD, training under direct supervision is also superior in terms of cost-effectiveness,[368] although indirect supervision (HBCR) is a good alternative, with positive effects on quality of life and significantly greater improvement in walking tolerance as compared to a simple recommendation to walk.[369,370]

When walking is not feasible, other activities, such as cycling, resistance training, and use of an upper body

Table 12 – Treatment of peripheral arterial occlusive disease of the lower limbs

Indication	Recommendation	Level of evidence
Supervised physical exercise to improve function and quality of life and reduce symptoms of claudication[365,369,375,376]	I	A
Home-based physical exercise or other training modalities to improve functional status[366,370,371]	IIa	A
In symptomatic patients, a supervised physical exercise program should be discussed as a treatment option before revascularization[375,376]	I	B

ergometers, have also proven effective.[371] It is also worth noting that physical exercise is contraindicated in patients with critical ischemia, but should be considered as soon as possible after successful interventional treatment.[371-373]

A systematic review of 12 clinical trials including a total of 1,548 patients compared patients who received drug therapy with physical training, endovascular intervention, and open surgery for treatment of claudication. All modalities increased walking distance, reduced symptoms, and improved quality of life.[374] Endovascular intervention and open surgery have proven effective in relieving symptoms, increasing walking distance, and improving quality of life, and are indicated when severe symptoms that negatively influence daily life persist despite full clinical treatment (physical exercise and optimized drug therapy).

In a randomized clinical trial of 111 patients with aortoiliac disease, the increase in exercise time on a graded treadmill test was greater in the supervised exercise group than in the stent revascularization group.[375] However, after 18 months of follow-up, the functional and quality of life benefits were equivalent in the exercise and revascularization groups, and, in both cases, were superior to those in the group that received medication alone.[376]

Several clinical trials have compared the efficacy and effectiveness of supervised physical exercise, angioplasty, and optimized medical care, using a multitude of different designs. Most trials consisted of two treatment arms. The aforementioned systematic reviews suggested that supervised physical exercise may be superior to optimized medical care or angioplasty. However, these meta-analyses included head-to-head comparisons between two specific treatment arms (e.g., angioplasty versus supervised physical training) or used an approach that did not allow inclusion and direct comparison of all available treatments for intermittent claudication.[377]

For these reasons, a recent meta-analysis sought to establish comparisons between all available treatments in order to elucidate the best management of patients with symptomatic PAOD. The sample included 2,983 participants with intermittent claudication (mean age, 68 years), 54.5% of whom were male. The comparisons were optimized medical care (n = 688), supervised physical training (n = 1,189), angioplasty (n = 511), and angioplasty plus supervised physical training (n = 395). The mean follow-up period was 12 months. Compared with optimized medical care alone, angioplasty and supervised physical training outperformed all other therapeutic strategies, with a 290 m gain in maximum walking distance (95% CI: 180 to 390 m; $p < 0.001$), corresponding to a proportional gain of 141% (95% CI: 86.85 to 188.3%; $p < 0.001$), with an average follow-up period of 12 months.[378]

Supervised physical training alone and angioplasty plus supervised physical training again surpassed the other treatment modalities, with an additional gain of 110 m in maximum walking distance (95% CI: 16 to 200 m; $p < 0.001$), or a proportional gain of 66% (95% CI: 9.66 to 121%; $p < 0.001$). Supervised physical training alone yielded a 180-m gain in maximum walking distance (95% CI: 130 to 230 m), corresponding to a proportional gain of 87% (95% CI: 63 to 111%); this was higher than with angioplasty alone, but lower than with supervised physical training plus angioplasty, in terms of maximum walking distance.[378]

These review studies have important implications for clinical practice. This is because all patients with intermittent claudication should receive optimized clinical treatment, in view of the evidence that shows a reduction in future cardiovascular events and an improvement in limb-related outcomes. [379,380] In this context, supervised physical training and angioplasty are essential to improve walking distance and quality of life. This recent meta-analysis cited above strongly suggests that supervised physical training associated with angioplasty should be part of first-line treatment, always in the context of optimized drug therapy. The offer of angioplasty without optimized physical training should be avoided whenever possible.[378] However, DAOP treatment centers often offer angioplasty primarily due to the lack of centers focused on supervised physical training. Furthermore, it cannot be neglected that supervised physical training faces resistance on the part of patients themselves, who are often little adherent to treatment, which partly justifies the majority preference in favor of percutaneous treatment.[381]

However, recent studies have demonstrated the benefits of combining treatment modalities for symptomatic PAOD, which may increase the likelihood that CVR will become increasingly widespread and accessible.[378,382]

Thus, in addition to optimized medical care, angioplasty combined with supervised physical training seems to be the ideal strategy for initial treatment of patients with intermittent claudication, both to improve maximum walking distance and to improve quality of life. However, the data from these latest reviews cannot confirm whether supervised physical training should be followed by angioplasty or vice versa.

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