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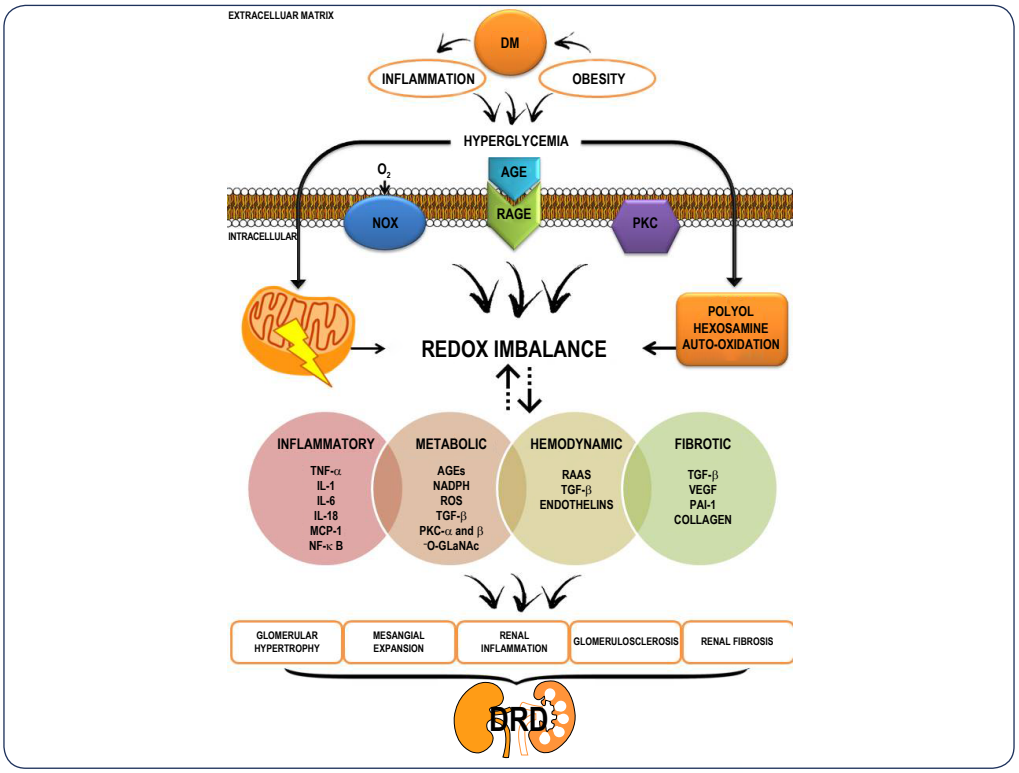

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JOURNAL OF BRAZILIAN SOCIETY OF CARDIOLOGY - Published since 1943

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Is There Any Cardiovascular Concern Regarding the Use of Aromatase Inhibitors in Breast Cancer?

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Breast cancer is the most frequent malignancy in women worldwide, and the second leading cause of cancer mortality.[1] Due to advances in prevention, early detection and treatment, breast cancer mortality has decreased by nearly 40% during the last four decades.[1] However, this optimistic scenario has been counterbalanced by an increasing risk from cardiovascular disease (CVD) in breast cancer survivors. Indeed, CVD is a leading cause of mortality in breast cancer survivors.[2-5] The mechanisms by which these patients are at increased cardiovascular risk are multiple ones, including the effects of cancer itself (inflammation, oxidative stress, prothrombotic status, autonomic dysfunction, etc.) or due to the side effects related to chemotherapy and radiotherapy (metabolic dysfunction, cardiotoxicity).[6] Some of these pathways may have prognostic significance: a previous investigation showed that autonomic modulation in breast cancer patients is an independent predictor of cardiovascular risk.[6]

In this issue of the *Arquivos Brasileiros de Cardiologia*, the study "Changes in Cardiac Autonomic Modulation in Women with Breast Cancer Using Aromatase Inhibitors and the Relation with Biochemical Variables"[7] was aimed to explore not breast cancer but the associations of one of its treatments (namely aromatase inhibitors, AI) with markers of autonomic dysfunction, as well as metabolic and inflammatory parameters in postmenopausal women. The rationale for exploring this specific therapy was based on a recent meta-analysis showing that prolonged AI use had a marginally effect of having a CVD event (odds ratio: 1.18, 95% CI = 1.00–1.40) as compared to placebo.[8]

In the current investigation,[7] the authors performed a cross-sectional analysis comparing two groups of participants: 1) women with breast cancer, treated with AIs and 2) postmenopausal women without breast cancer. For the evaluation of the autonomic modulation, heart rate was recorded beat-to-beat for 30 minutes and the series of RR intervals obtained were used to calculate rate variability indices (RVI): mean RR ms, SDNN (standard deviation of all normal RR intervals, expressed in milliseconds) ms, mean Heart Rate (HR), RMSSD (square root of the mean of the squared differences between adjacent normal RR interval) ms, NN50 (number of pairs of successive NNs that differ by more than 50 ms) count, p NN 50% (proportion of NN 50 divided by total number of NNs), RRtri (RR triangular), TINN (triangular interpolation of NN interval) ms, SD1ms, SD2 ms, LF (low frequency) ms^2, HF(high frequency) ms^2. LF; HF ms^2. Despite some criticism, all these parameters provide an indirect evaluation of autonomic function. In addition, the following metabolic and inflammatory parameters were analyzed: fasting glycemia, triglycerides. HDL-cholesterol and C-reactive protein (CRP). The study showed that lower values of HR variability indices were observed in breast cancer patients in relation to the control group. Besides, there was an inverse correlation between the indices SDNN, SD2 and HFms with triglycerides. No statistically significant correlations were found between HR variability indices and other biochemical variables.

While this study is timely, addressing the increasing awareness of the cardiovascular effects attributed to cancer and its treatments, there are significant limitations that deserve an appropriate discussion. This is a small cross-sectional study addressing autonomic and cardiovascular parameters in patients already on AI treatment. The lack of baseline measurements (before starting AI therapy) prevent any conclusion from being drawn on whether the main results were related to AIs, the breast cancer per se or some other residual factor. Regarding the latter, the authors did not evaluate the potential role of important confounding factors (such as hypertension or chronic use of medications) that could affect autonomic modulation or the cardiovascular biomarkers.

Having said that, this study raised more questions than answers, but certainly stimulates additional investigations testing the cardiovascular safety of this important chemotherapy class. In the past decade, AIs have been the recommended first-line adjuvant endocrine therapy in postmenopausal women with hormone receptor–positive breast cancer; they are associated with improved disease-free survival and overall survival.[9] Based on the increasing prevalence of breast cancer worldwide and the related burden of survivors, it is crucial to clarify the cardiovascular safety of the related drugs. The benefits of cancer treatment should be balanced with the presence and magnitude of severe side effects – including cardiovascular events – in the long-term follow-up.

Keywords

Aromatase Inhibitors; Breast Neoplasms; Cholesterol; Blood Glicose; Estrogen Replacement; cardiovascular Diseases/prevention & control.

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Unscheduled Emergency Visits after Cardiac Devices Implantation: Comparison between Cardioverter Defibrillators and Cardiac Resynchronization Therapy Devices in less than one year of Follow Up

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Abstract

Background: **The use of Cardiovascular Implantable Electronic Devices (CIED), such as the Implantable Cardioverter Defibrillator (ICD) and Cardiac Resynchronization Therapy (CRT), is increasing. The number of leads may vary according to the device. Lead placement in the left ventricle increases surgical time and may be associated with greater morbidity after hospital discharge, an event that is often confused with the underlying disease severity.**

Objective: **To evaluate the rate of unscheduled emergency hospitalizations and death after implantable device surgery stratified by the type of device.**

Methods: **Prospective cohort study of 199 patients submitted to cardiac device implantation. The groups were stratified according to the type of device: ICD group (n = 124) and CRT group (n = 75). Probability estimates were analyzed by the Kaplan-Meier method according to the outcome. A value of $p < 0.05$ was considered significant in the statistical analyses.**

Results: **Most of the sample comprised male patients (71.9%), with a mean age of 61.1 ± 14.2. Left ventricular ejection fraction was similar between the groups (CRT 37.4 ± 18.1 vs. ICD 39.1 ± 17.0, p = 0.532). The rate of unscheduled visits to the emergency unit related to the device was 4.8% in the ICD group and 10.6% in the CRT group (p = 0.20). The probability of device-related survival of the variable "death" was different between the groups (p = 0.008).**

Conclusions: **Patients after CRT implantation show a higher probability of mortality after surgery at a follow-up of less than 1 year. The rate of unscheduled hospital visits, related or not to the implant, does not differ between the groups. (Arq Bras Cardiol. 2019; 112(5):491-498)**

Keywords: **Defibrillators, Implantable; Cardiac-Gated Imaging Techniques; Cardiac Resynchronization Therapy Devices; Patient Readmission; Mortality.**

Introduction

In the cardiovascular disease scenario, patients with reduced left ventricular ejection fraction (LVEF) after acute myocardial infarction show an increased risk of sudden death related to cardiac arrhythmia. The use of Cardiovascular Implantable Electronic Devices (CIED), such as Implantable Cardioverter Defibrillators (ICDs), has shown to be beneficial in improving survival rates in this patient profile.[1] The Cardiac Resynchronization Therapy (CRT) also demonstrates benefits in reducing hospitalization rates, improving ventricular function, as well as decreasing mortality in the context of heart failure (HF).[2,3]

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During the CIED implantation, according to the clinical indication, it is necessary to use one, two or even three intracardiac leads. In CRT, the difficulty in cannulating the coronary sinus, or the lack of an adequate venous branch for this purpose, tends to increase the surgical procedure complexity, which may be associated with greater morbidity in the follow-up after hospital discharge – a situation often attributed or confused with the underlying disease severity. Regardless of the implantation route used for left ventricular estimation, we know there are lead dislodgement and dysfunction rates of approximately 5%[4] after the surgery, and the presence of a higher number of leads makes the probability of this type of event occurrence even higher. On the other hand, unscheduled emergency visits related to CIED occur, not necessarily because of the leads, in up to 12% of patients undergoing this type of therapy.[4,5] Local data that assess the rate of unscheduled hospital visits related to the implants are limited to the southeast region, and there is no recent literature disclosing data from the southern region of the country. The present study aims to contribute to this issue.

Methods

Study design

This was a prospective single-center cohort study developed in a high-complexity cardiology hospital located in southern Brazil.

Population

Patients aged 18 years or older submitted to ICD implantation or CRT from February 2014 to July 2015 were consecutively included. The cases of changes in generators without lead implantation were excluded.

Data collection

Data collection was performed from the moment immediately prior to the device implantation and, subsequently, at the time of visits to the emergency unit for medical care. The obtained data, recorded in the electronic medical record, were exported to an Excel database. The analyzed variables were clinical ones and related to the implant. The clinical variables were: (1) LVEF at the two-dimensional echocardiogram (Teicholtz or Simpson method, when indicated); (2) HF etiology, defined as valvular, ischemic or non-ischemic. In case of more than one etiology, we selected the one considered to be predominantly accountable for the condition; (3) patient functional class, classified according to the New York Heart Association classification. The variables related to the CIED implant were: (1) operative wound infections; (2) operative wound pain; (3) need to replace the leads; (4) upper limb venous thrombosis; and (5) device pocket hematoma.

Outcomes

The primary outcome was the occurrence of an unscheduled hospital visit related to the CIED implant. Visits resulting from HF worsening or progression were also considered for this analysis. The secondary outcome was all-cause mortality.

Ethical Considerations

This study was approved by the Research Ethics Committee of Instituto de Cardiologia – Fundação Universitária de Cardiologia do Rio Grande do Sul, under number 4983/14.

Data analysis

The Statistical Package for Social Sciences (SPSS), version 18.0, was used for the analyses based on the data stored in the Microsoft Excel spreadsheets. A two-tailed *p* value of less than 0.05 was considered significant in the statistical analyses. Continuous variables with parametric distribution were expressed as mean ± standard deviation, while nonparametric variables were shown as median and interquartile range. The comparisons were made with Student's *t*-test for independent samples in variables with central tendency distribution and with Mann-Whitney test in those considered to be asymmetric. Categorical variables were expressed as absolute (n) and relative (%) frequencies and compared with the chi-square test. Probability estimates were calculated by the Kaplan-Meier method using long-rank. It was not possible to perform the multivariate analysis using Cox Regression due to the absence of events occurring in the ICD group, which prevented the calculation of the hazard ratio (HR).

Results

During the study period, 1,174 surgeries were performed for device implantation. Of these, 224 were for ICD/CRT, 25 of which were exclusively for generator change, and were excluded from the evaluation. Figure 1 shows patient inclusion flowchart. The final analysis was performed with 199 patients. Table 1 shows the characteristics of the assessed population. There was a higher prevalence of male individuals in both groups. The mean age was similar, as well as the ejection fraction. The non-ischemic cardiomyopathy was the most prevalent etiology in both groups. Most implants were performed through the Brazilian Unified Public Health System (SUS). There was a statistically significant difference between the functional classes, with a higher percentage of patients in class III in both groups. Of all procedures, 57% were carried out for primary prevention of sudden death.

Outcomes

Regarding the outcomes, the rate of unscheduled visits to the emergency unit related to the device was 4.8% in the ICD group and 10.6% in the CRT group ($p = 0.20$). Operative wound pain was the most prevalent complication related to the device (Table 2).

Figure 2 shows the incidence of the primary outcome of emergency visits-free survival during a median follow-up of 285 days ($p = 0.214$). The incidence of unscheduled visits related to clinical conditions (not related to device implantation) did not differ between the groups, being 28.2% in the ICD group and 18.6% in the CRT group ($p = 0.17$), including readmissions due to HF, as shown in Table 3.

Figure 3 shows the survival curve in both groups. There were 4 deaths in the CRT group and none in the ICD group. None of the deaths were related to the procedure itself. The causes of death were: 1 hemorrhagic stroke, 1 sudden death at home, 1 death due to multiple organ failure as a complication of infective endocarditis (secondary to a dental abscess, diagnosed 194 days after the implant) and 1 due to refractory HF.

Discussion

Artificial cardiac stimulation has shown significant benefits since its initial implantation in 1958, crossing generations in continuous technical evolution and extending its range from the atrioventricular conduction disorders to dyssynchrony reduction. However, it still shows a significant percentage of complications, despite almost sixty years of use. Currently, the volume of procedures for CIED implantation shows increasing annual rates, due to the technological evolution of the method, the increase in the indications and the higher number of eligible patients.[6] At the same time, the greater longevity of the affected populations is a non-modifiable risk factor for long-term complications. Such a change in the scenario limits

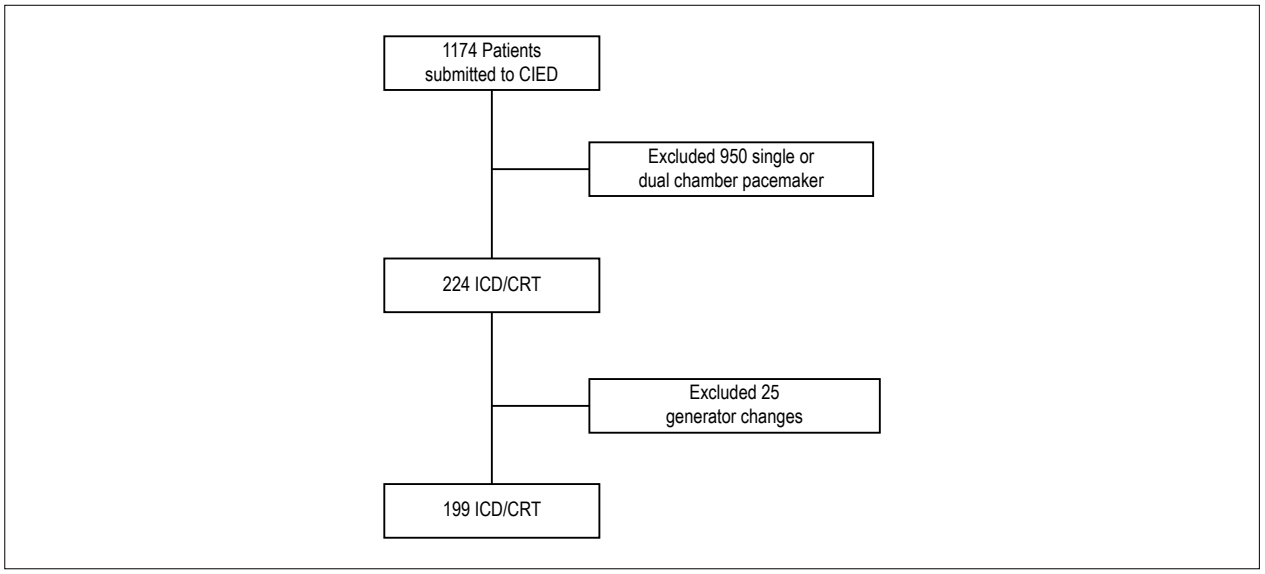

Figure 1 – *Inclusion flowchart of the study patients. CIED: cardiac implantable electronic device. ICD: implantable cardioverter-defibrillator. CRT: cardiac resynchronization therapy.*

Table 1 – Sample characteristics. Porto Alegre, RS

Variable	Total n = 199	ICD n = 124	CRT-P/D n = 75	p value
Age, years*	61.1 ± 14.2	61.1 ± 14.3	61.0 ± 14.2	0.963
Male gender †	143(71.9)	94(75.8)	49(65.3)	0.153
LVEF (%)*	38.4 ± 17.4	39.1 ± 17.0	37.4 ± 18.1	0.532
Etiology†				**0.043**
Non-ischemic cardiomyopathy	116(58.3)	66(53.2)	50(66.7)	
Ischemic cardiomyopathy	79(39.7)	56(45.2)	23(30.7)	
Valvular etiology	4(2)	2(1.6)	2(2.7)	
Type of health care†				**0.349**
SUS	134(67.3)	87(70.2)	47(62.7)	
Supplementary health care	65(32.7)	37(29.8)	28(37.3)	
Functional Class				
I	39(19.5)	32(25.8)	7(9.3)	0.007
II	24(12)	13(10.4)	11(14.6)	
III	72(36.1)	36(29)	36(48)	
IV	31(15.5)	21(16.9)	10(13.3)	

** Data shown as mean ± standard deviation; †Absolute and relative frequency; ICD: implantable cardioverter-defibrillator; CRT-P/D: cardiac resynchronization therapy; LVEF: left ventricular ejection fraction; SUS: Brazilian Unified Health System.*

the comparison of current data with the first era of stimulation, not only by the device evolution curve, the implant technique and population factor alterations, but also by the database of previous records – many of them comprising only complications demanding surgical intervention. Over the years, the variability of complication definitions has become more homogeneous, with a further description of conservative management adverse effects, with the inaccuracies in temporal definition of events having been overcome, now dichotomized as early or late within a time frame of 2 months.[6-8] The current series, many limited to the review of the last 20 years, indicate the first sixty days as the period with the highest incidence of complications, with rates that fluctuate around 10%, in their majority.[9,10]

This study brings current national data on morbidity and mortality after ICD/CRT implantation. Our hospital is a tertiary cardiology center that performs approximately 1,000 device implants per year. The total incidence of complications related to the devices was 7% in the studied period, similar to that of other studies on the subject.[11] Our sample had an incidence of cable dislocation, infections and mortality of 0.5%, 2.5% and 2%, respectively.

Table 2 – Outcomes of the study population. Device-related unscheduled emergency visit

Variable	Total n = 199	ICD n = 124	CRT-P/D n = 75	p value
Device-related unscheduled emergency visit*	14(7%)	6(4.8%)	8(10.6)	0.20
Device-related complications*				**0.45**
Surgical wound infection	5(2.5%)	2(1.6%)	3(4%)	
Surgical wound pain	6(3%)	2(1.6%)	4(5.3%)	
Lead change	1(0.5%)	0	1(1.3%)	
Upper limb venous thrombosis	1(0.5%)	1(0.8)	0	
Pocket hematoma	1(0.5%)	1(0.8)	0	
Inappropriate shocks	2(1%)	2(1.6%)	0	
Mortality				**0.008**
Related to device implantation	0			
Other causes	4(2%)	0	4(5.3%)	

** Data shown as absolute and relative frequency; ICD: implantable cardioverter-defibrillator; CRT-P/D: cardiac resynchronization therapy.*

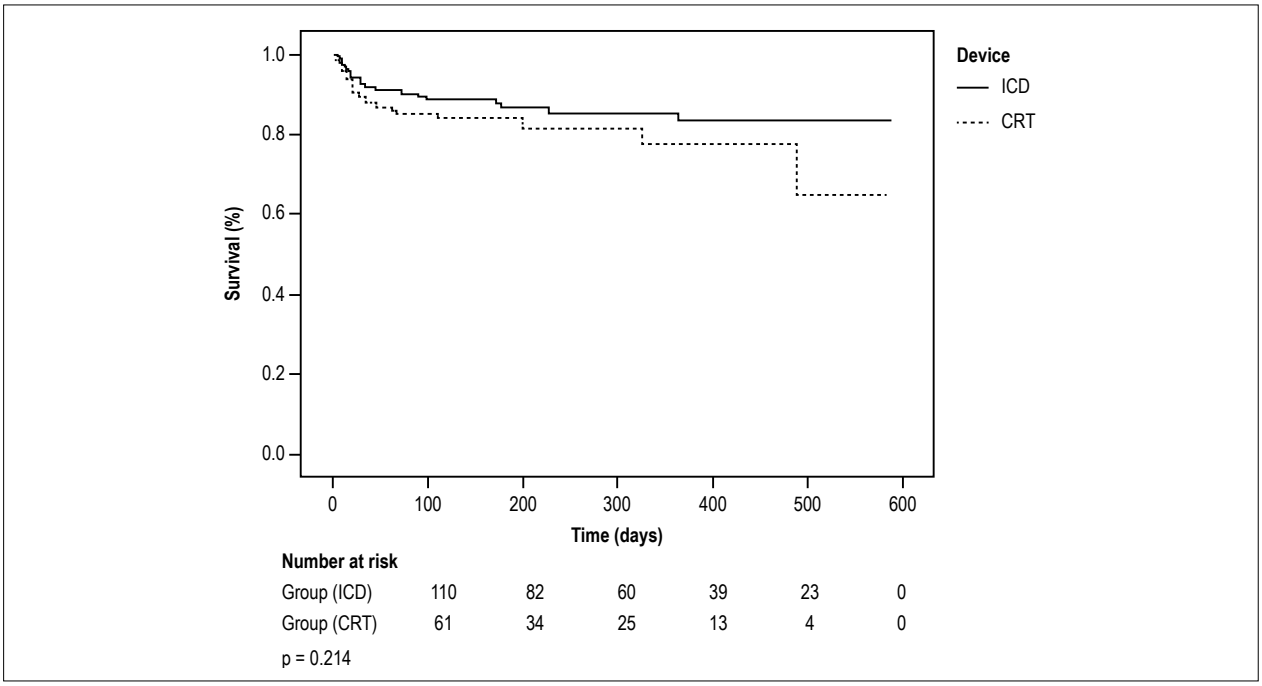

Figure 2 – *Kaplan-Meier estimate of survival probability according to device-related unscheduled emergency visits. Note: p = 0.214.*

Van Rees et al.,[6] in a systematic review of 18 clinical trials involving ICD/CRT implantation, found a mortality rate of 2.7% after ICD implantation (0.6% if considering only those without thoracotomy) and 0.7% after CRT. The incidence of lead dislodgement was 1.8% in the ICD group (without thoracotomy) and 5.9% in the CRT studies. Device pocket hematomas occurred in 2.4% of those with ICD and 2.2% with CRT; however, these percentages represented only cases that required surgical intervention. In our study, there was no difference between devices regarding the incidence of cable dislodgement, which is probably due to the low incidence of this complication in our sample. The incidence of CIED pocket hematoma found in our center was 0.8% in the ICD group and 0% in the CRT group.

When compared to other cohorts, we also found similar incidences of CIED-related complications. In a cohort of 1,929 patients, the incidence of surgical reintervention due to stimulation cable dislodgement, infection and mortality was, respectively, 4.4%, 1.5% and 3.2%.[9] Our cohort showed lower mortality and cable dislodgement rates, but 1% more incidence of bleeding. Among the patients with CRT, the incidence of cable dislodgement was 5%, compared to 1.3% in our cohort.

A retrospective record of 30,984 Medicare users submitted to device implantation found an incidence of major complications (cable dislodgement, cardiac tamponade, hemothorax and pneumothorax) of 4.26%, with no difference between CRT and ICD.[12] In the same analysis, ICD implantation showed a higher incidence of mechanical

Table 3 – Outcomes of the study population. Unscheduled emergency visit unrelated to the device

	Total n = 199	ICD n = 124	CRT-P/D n = 75	p value
Unscheduled emergency visit unrelated to the device	49(24.6%)	35(28.2%)	14(18.6%)	0.17
Stroke	1(0.5%)	-	1(1.3%)	0.79
Tiredness	1(0.5%)	1(0.8%)	-	0.43
Headache/vertigo	3(1.5%)	3(2.4%)	-	0.44
Glycemic disorders	1(0.5%)	-	1(1.3%)	0.79
LUL pain – non-anginal	2(1%)	2(1.6%)	-	0.70
Chest pain	13(6.5%)	9(7.2%)	4(5.3%)	0.81
Abdominal pain	1(0.5%)	1(0.8%)	-	0.43
Heart failure	18(9%)	13(10.4%)	5(6.6%)	0.51
Acute lower limb ischemia	2(1%)	2(1.6%)	-	0.70
Lower-limb myalgia	1(0.5%)	-	1(1.3%)	0.79
Nausea/vomiting	1(0.5%)	1(0.8%)	-	0.43
Pneumonia	2(1%)	1(0.8%)	1(1.3%)	0.71
Deep vein thrombosis	1(0.5%)	1(0.8%)	-	0.43
Pulmonary thromboembolism	1(0.5%)	-	1(1.3%)	0.79
Herpes zoster	1(0.5%)	1(0.8%)	-	0.43

** Data shown as absolute and relative frequency; ICD: implantable cardioverter-defibrillator; CRT-P/D: cardiac resynchronization therapy; LUL: left upper limb*

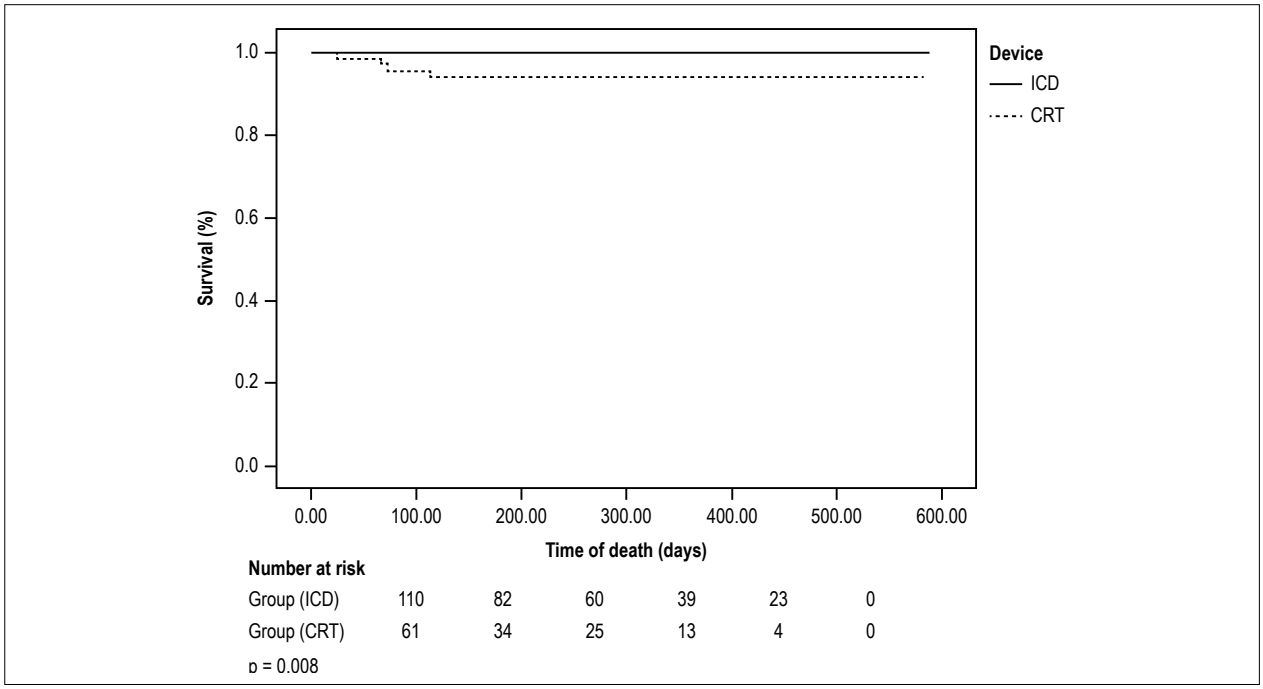

Figure 3 – *Kaplan-Meier estimate of device-related survival probability. Note: p = 0.008.*

complications and infections, whereas CRT implantation showed a higher incidence of hematoma and hemorrhage – findings that were opposite to those identified in our study.

In a prospective Dutch cohort of 1,517 patients,[4] early complications were 9.2% and tended to a decrease after the first 6 months of implantation; the main ones, in order of frequency, were related to the cable in 5.54% (3.34% of dislodgement), device pocket (4.75%, excluding infection), hematoma 2.9%, local trauma (2.77% – with pneumothorax being 2.24%) and pocket infection (0.64%). In the late period, cable complications remained the same and pocket-related complications decreased, especially regarding the infection

and local hematoma subcomponents. There was no evaluation of CRT and ICD implants, with the sample being restricted to the conventional pacemaker implant. Nevertheless, the rates of infection and cable dislodgement were higher than that recorded in the present study.

Infections

An analysis of the PEOPLE[13] study (prospective cohort) evaluated 6,314 CIED implants at 44 centers. After 1 year, there were 633 deaths (10.1%), 548 (8.9%) non-infectious complications and 42 infections (0.56% in patients submitted to the first CIED implantation). In the multivariate analysis, the factors related to a higher risk of infection were the occurrence of fever in the 24 hours prior to the implantation, use of a temporary pacemaker and the need for early reintervention. Our sample found an incidence of pacemaker pocket infection in 2.5% of cases. The higher incidence, albeit in accordance with the literature, may be due to the fact that we did not evaluate the *de novo* implants and did not collect data regarding the use of a temporary pacemaker prior to the procedure.

A Polish registry with 1,105 patients showed substantially lower infection rates when compared to the other recent studies: 0.1% at 2 months and 0.4% at the late follow-up of 2.4 years.[14] Although the antimicrobial prophylaxis is a well-established outcome factor of protection,[15,16] the registry differed from the others by the extended use of prophylaxis for a period of 5 days for surgical time >1h or immunosuppressive condition such as diabetes, chronic kidney disease, neoplasia or age >75 years. On the other hand, the percentages of device pocket hematoma were higher (6.1%), associated with platelet antiaggregation, triple therapy or, mainly, anticoagulation (present in 56% of patients). If, on the one hand, there is evidence that the occurrence of hematoma increases by 15-fold the risk of local infection,[13] prospective studies on the duration of anticoagulation do not show worse outcomes with their maintenance in the peri-implantation period: on the contrary, they show a decrease of events.[17,18] In a direct comparison between the two forms of stimulation, the ICD and CRT did not significantly differ, although absolute rates were higher in the ICD group.

In the present study, there was a difference between the groups regarding the proportions of ischemic etiology, which was higher in the ICD group, and in the functional class, characterized by higher class I proportions in the ICD group and class III in the CRT group. Among the non-device-related hospitalizations, the difference in functional class did not translate into a statistical discrepancy regarding the percentage of unscheduled visits, either in absolute numbers or the specific causal etiology (Table 3). Although there were no recorded deaths, the ICD group showed a higher proportion of important events, such as chest pain in the ischemic scenario, HF decompensation and acute limb ischemia. Compared to predictors of cardiac mortality models in resynchronization therapy,[19,20] only 25% of the recorded deaths had an ejection fraction < 25% (specifically 28, 20, 58 and 29%) and 75% used loop diuretics at doses of 80mg/day or more. Right ventricular contractile dysfunction, an important factor associated with mortality, was not specifically analyzed in the present study. Inappropriate shocks, an important source of emergency consultations, were recorded in only 2 patients (14.28% of device-related visits) – both with cardioverter defibrillators.

Compared with recent national data,[21] the present study displayed a large difference regarding pocket hematoma rates, showing a much lower percentage in our cohort, but a higher percentage of unplanned device-related readmissions (7% *vs*. 3.6%). It is important to emphasize that the current study did not account for the implantation of pacemakers without the ICD or CRT functions, situations that represented the majority of patients that were initially candidates for follow-up (Figure 1) and who, in fact, were included in a similar study,[21] hindering the direct comparison between the findings. Furthermore, it should be remembered that the two assessed populations showed very different percentages of patients in functional class I and II (84.8% *vs*. 31.5% in this study).

Limitations

Among the main limitations of the study is the small sample size when compared to the larger series, and the follow-up period duration, which may have been short for some outcomes and prevents the direct comparison with the larger cohorts in the literature; the analysis of the MIRACLE-ICD study subgroup,[19] for instance, suggests that left ventricular cable dislodgements becomes more frequent in the long term, so our follow-up may have underestimated the occurrence of this complication in the CRT group.

Also, we emphasize the fact that the data represent the practices and the results of a single cardiology center in the south of Brazil, with the limitations of unicentric studies on the extrapolation of results. Compared with recent local literature,[21] there are methodological differences regarding patient eligibility (mainly related to the type of device eligible for evaluation) and, consequently, considerable differences in baseline functional class and contractile function that limit the direct comparison between the studies regarding readmission predictors.

The difference between etiology and functional class between the groups is also a factor to be remembered. Although not statistically significant regarding the percentage of unscheduled visits to the emergency unit, regardless of whether or not it is associated with the procedure, the population's characteristics could lead to different results in the long-term follow-up, given the chronicity of the underlying diseases and their several forms of temporal evolution.

Conclusion

The results showed that patients submitted to CRT implantation, when compared to the ICD implantation cases, show a higher probability of mortality in the follow-up

period of less than 1 year. In contrast, the implant-related unscheduled hospital visit rate does not differ between the groups.

Acknowledgment

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Author contributions

Conception and design of the research, analysis and interpretation of the data and writing of the manuscript: Warpechowski Neto S, Ley LLG, Almeida ED, Saff MAL, Dutra LZ, Ley ALG, Sant`Anna RT, Lima GG, Kalil RAK, Leiria TLL; acquisition of data: Warpechowski Neto S, Ley LLG, Almeida ED, Saff MAL, Dutra LZ, Ley ALG, Lima GG, Kalil RAK; statistical analysis: Warpechowski Neto S, Ley LLG, Almeida ED, Dutra LZ, Ley ALG, Sant`Anna RT, Lima GG, Leiria TLL; obtaining funding: Kalil RAK, Leiria TLL; critical revision of the manuscript for intellectual content: Warpechowski Neto S, Ley LLG, Almeida ED, Saff MAL, Dutra LZ, Ley ALG, Sant`Anna RT, Lima GG, Kalil RAK, Leiria TLL.

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 Instituto de Cardiologia/Fundação Universitária de Cardiologia under the protocol number 5374/17. 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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Unscheduled Return Visits to the Emergency Department after Cardiac Electronic Devices Implantation

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Short Editorial related to the article: Unscheduled Emergency Visits after Cardiac Devices Implantation: Comparison between Cardioverter Defibrillators and Cardiac Resynchronization Therapy Devices in less than one year of Follow Up

In recent years, many initiatives have been made to improve the quality and efficiency of healthcare services leading to the creation and standardization of health quality indicators in order to improve the interaction between clinicians, researchers, and healthcare managers, enabling the generation of evidence-based strategies. In this context, the rate of hospital readmissions is one of the most important indicators to measure the quality of healthcare services.

The use of quality indicators to measure healthcare performance across different hospitals has been considered of great value for the improvement of healthcare routines, enhancing the expenditure rationalization of health services. In this scenario, the adoption of the International Consortium for Health Outcomes Measurement (ICHOM) as a strategy to measure outcomes across hospitals has increased worldwide and it is now gaining familiarity among Brazilian hospitals.

Specifically in heart failure patients, the quality indicators can be measured by hard outcomes such as mortality, hospital readmissions or unscheduled visits to the emergency department. However, other measures should also be taken into account, especially patient-reported outcomes as quality of life, functional capacity, as well as the adherence to the treatment in terms of medications, diet and physical rehabilitation. In this sense, discharge instruction regarding the prescribed medications, dietary restrictions, regular physical activities, weight monitoring and the importance of follow-up appointments play a significant role in the promotion of successful treatment. Another factor of great impact for the success of the treatment is the close contact between the healthcare providers and the patient, by telephone or text messages, in order to reinforce the main instructions and to detect early signs of clinical decompensation. From this perspective, knowing the rate of unscheduled visits may be a good start for evaluating our results.

Keywords

Pacemaker, Artificial/utilization; Intraoperative Complications/mortality; Defibrillators, Implantable; Heart Failure; Cardiac Pacing, Artificial.

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The study of Warpechowski Neto et al.[1] showed a high incidence of unplanned visits after defibrillators (ICD) or cardiac resynchronization therapy (CRT) devices implantation. Device-related complications were seen in 7% of readmitted patients. On the other hand, in 24.6% of the patients, the reason for an unscheduled visit was cardiac and non-cardiac clinical conditions.

A 12-month follow-up study of 713 patients undergoing cardiac implantable electronic devices (CIED) procedures, published by Silva et al.[2] in 2016 the Arquivos Brasileiros de Cardiologia, showed that the odds of new readmission in CRT patients was 1.6 times higher than in the general group of patients studied and that ICD implant increased this chance by 4.2 times. This study also showed that the mortality was 2.2 times higher in patients with left ventricular dysfunction and 2.3 times higher in those who used warfarin.[2]

In a prospective multicenter study conducted by the Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, which included 3,550 patients from 9 geographically distributed cardiology centers, the 12-month readmission rate was 23.8%, 24.0% and 38.3% and the mortality rate was 9.4%, 11.5% and 18.3%, respectively, for ICD, CRT-P and CRT-D initial implantation. Device-related complications, heart failure decompensation and non-cardiac causes were the reason for readmissions in 15.5%, 22.1% and 19.2% of patients and for death in 3.7%, 15.7% and 51.8%, respectively.[3]

Analysis of the United States Nationwide Readmissions Database, which included 70,223 patients submitted to CIED implantation, showed a 30-day hospital readmission rate of 12%. Besides identifying several readmission predictors, mostly related to patient's comorbidities, these 30-day readmissions resulted in an additional median cost of US $30,692 per patient, which reinforces the importance of establishing strategies to reduce in-hospital readmissions.[4]

Analysis of the above-mentioned information shows the great importance of monitoring outcomes in CIED patients after the hospital discharge. In this sense, the conduction of prospective registries for all CIED types and procedures will provide us with more accurate information about the clinical practice in a real-world scenario. Ultimately, this knowledge will be critical for physicians, hospitals, and healthcare payers to know the results of their activities, in order to improve patient outcomes, while reducing costs. As important as knowing our results is to establish strategies to minimize complications. And certainly, reducing the rate of unscheduled visits should be a clear goal to be pursued.

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Left Atrial Stiffness: A Predictor of Atrial Fibrillation Recurrence after Radiofrequency Catheter Ablation - A Systematic Review and Meta-Analysis

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Abstract

Background: Radiofrequency catheter ablation (RFCA) is a standard procedure for patients with atrial fibrillation (AF) not responsive to previous treatments, that has been increasingly considered as a first-line therapy. In this context, perioperative screening for risk factors has become important. A previous study showed that a high left atrial (LA) pressure is associated with AF recurrence after ablation, which may be secondary to a stiff left atrium.

Objective: To investigate, through a systematic review and meta-analysis, if LA stiffness could be a predictor of AF recurrence after RFCA, and to discuss its clinical use.

Methods: The meta-analysis followed the MOOSE recommendations. The search was performed in MEDLINE and Cochrane Central Register of Controlled Trials databases, until March 2018. Two authors performed screening, data extraction and quality assessment of the studies.

Results: All studies were graded with good quality. A funnel plot was constructed, which did not show any publication bias. Four prospective observational studies were included in the systematic review and 3 of them in the meta-analysis. Statistical significance was defined at p value < 0.05. LA stiffness was a strong independent predictor of AF recurrence after RFCA (HR = 3.55, 95% CI 1.75-4.73, p = 0.0002).

Conclusion: A non-invasive assessment of LA stiffness prior to ablation can be used as a potential screening factor to select or to closely follow patients with higher risks of AF recurrence and development of the stiff LA syndrome. (Arq Bras Cardiol. 2019; 112(5):501-508)

Keywords: Atrial Fibrillation; Catheter Ablation/methods; Heart Atria; Tachycardia, Paroxysmal; Metanalysis.

Introduction

Radiofrequency catheter ablation (RFCA) is a standard procedure for the treatment of atrial fibrillation (AF) in patients not responsive to previous treatments.[1] However, growing evidence has shown lower rates of AF recurrence and AF burden in patients with paroxysmal AF that were submitted to ablation as a first-line therapy option.[2] In addition to that, progression from paroxysmal AF to persistent AF appears to be delayed by early catheter ablation of AF.[2] Therefore, catheter ablation has been increasingly considered as a first-line therapy option, which makes it more important to use screening factors to closely follow patients with higher risk of AF recurrence and post-procedural complications.

Recently, the importance of studying left atrial (LA) stiffness has been growing exponentially, since it has been linked to the stiff left atrial syndrome (SLAS), a severe consequence of RFCA.[3] Moreover, a previous study[4] showed that an increase in LA pressure is associated with AF recurrence after ablation. Since a high LA pressure may be secondary to an increase in LA stiffness,[5] LA stiffness itself could be a predictor of AF recurrence after RFCA and, thereby promote a closer follow-up of patients at higher risk of AF recurrence and development of the SLAS. However, no systematic review or meta-analysis has been published to investigate this relationship, although these studies could provide the strongest and the highest quality of evidence.

Therefore, this systematic review and meta-analysis aims to investigate if LA stiffness itself could be a predictor of AF recurrence after RFCA and discusses the clinical usefulness of this new predictor.[6]

Methods

A systematic review was performed using the criteria established by the Meta-analysis of Observational studies in the Epidemiology Group (MOOSE).

Search strategy

Two investigators (ETOC, ETM) searched the MEDLINE and the Cochrane Central Register of Controlled Trials databases,

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until March 2018. We searched for a combination of English terms and Medical Subject Headings (MeSH) descriptors, consisting of seven keywords [("left atrial" OR "left atrium") AND ("stiff" OR "stiffness" OR "compliance") AND ("ablation" OR "pulmonary vein isolation")]. A manual search of references was also used to identify possible studies for inclusion. If necessary, an English translation of the retrieved articles would be obtained. Each title and abstract were independently analysed by the two investigators, who selected the articles which would be relevant to the review. After that, the full texts of the remaining articles were reviewed to select which would be included in the qualitative or quantitative analysis. In case of disagreement, the decision was made by discussion and consensus of the authors.

Inclusion criteria

We included observational studies (with prospective or retrospective nature) in humans, whose objective was to study the association between LA stiffness and recurrence of AF after the first RFCA.

For qualitative analysis, studies with the following characteristics were included: 1) The study evaluated AF recurrence after the first RFCA in human subjects; 2) Retrospective or prospective observational studies; 3) The mean follow-up period was longer than 6 months; 4) The study included more than 20 subjects.

For the quantitative analysis, we included studies that fulfilled all the previous criteria and reported hazard ratio (HR) and 95% confidence intervals (CI) of LA stiffness as predictors of AF recurrence.

Quality assessment

The risk of bias in the studies was evaluated using the National Heart, Lung and Blood Institute Quality Assessment Tool for Case Series Studies.[7] The evaluation was done independently by two raters (ETOC, LMSB), and in case of disagreement the decision was made by consensus of the raters. The following characteristics were assessed: 1) Was the study question or objective clearly stated?; 2) Was the study population clearly and fully described, including a case definition?; 3) Were the cases consecutive?; 4) Were the subjects comparable?; 5) Was the intervention clearly described?; 6) Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?; 7) Was the length of follow-up adequate?; 8) Were the statistical methods well-described?; 9) Were the results well-described?

After these characteristics were assessed, the authors gave the studies one of the quality ratings (good, fair or poor). Studies were rated as 'poor' if they met less than three criteria, 'fair' if they met three to five criteria, and 'good' if they met more than five criteria. All four articles selected met almost all the criteria and received a good quality rating by the two raters. The quality assessment of the four studies is reported in Table 1.

Data extraction

Data extraction was performed using a standard form by two investigators (ETOC, OMPS) and cross-verified by a third (ETM). Extracted data included: 1) First author's last name, publication year; 2) Characteristics of included studies: number of patients, region of the study, study design, ablation strategy, method of LA stiffness measurement, method of AF detection, length of follow-up period, length of blanking period and main findings; 4) Outcome results: HR and 95% CI of LA stiffness as a predictor of AF recurrence in multivariate analysis.

Statistical analysis

The association between AF recurrence and LA stiffness following RFCA was measured by HR with 95% CI. Adjusted HRs were used, since all the studies included in the quantitative analysis employed multivariate analysis by Cox proportional hazard model to adjust for potential confounders. Log of the HR was obtained by calculating their natural logarithms. Then, standard errors were determined from the logarithmic scale and corresponding 95% CIs. The inverse variance method was used to weigh studies for the combined overall statistics. Statistical significance was defined at p-values < 0.05. Heterogeneity between studies was assessed using the Cochran's Q test and I^2 statistics and then evaluated by I^2 values. I^2 values less than 30% were defined as low heterogeneity; less than 60% were considered moderate heterogeneity; and above 60% defined as high heterogeneity.[8] The random-effects model was chosen because of the different methods of LA stiffness measurements, what could lead to heterogeneity. Sensitivity analysis was done by leaving out studies and checking the consistency of the overall effect estimate. A meta-regression was not done because of the small number of studies included. The results are presented in a forest plot with 95% CI. Publication bias was verified by a funnel plot, although only 3 studies were included, which made the interpretation more difficult. All analyses were done using Review Manager 5.3 software.

Results

Study selection

Initially, a total of 62 studies were identified in the databases, 57 in PubMed and 5 in the Cochrane Central Register of Controlled Trials. In the duplicate analysis, we identified 2 duplicates, which were then excluded. After a careful reading of the titles and abstracts, 57 of 62 studies were excluded because they were not related to the present review. The full texts of the five studies were analysed, and 4 of them included in the qualitative analysis. The study excluded, by Marino et al.[9] analysed only 20 patients and the mean follow-up period was shorter than 6 months. For the quantitative analysis, one full-text article was excluded because it did not report HR and 95% CI of LA stiffness as predictors of AF recurrence.[10] Finally, four studies were included in the qualitative analysis and three in the quantitative analysis. The flow diagram of the study selection is depicted in Figure 1.

Characteristics of the included studies

Four studies were included in this review,[10-13] all of them prospective single centre case series studies (Table 1). The study of Machino-Ohtsuka et al.[11] included 155 patients, and in the

Table 1 – Characteristics of the included studies

Study, year	Region	Study design	Number of Patients	Ablation strategy	Measurement of LA stiffness	Method of AF detection	Follow-up, months	Blanking period, months	Findings	Quality
Machino Ohtsuka et al., 2011	Asia	Prospective case series, single centre	155	PVI	Ratio of the difference between the LA peak v-wave pressure and the LA x-wave pressure nadir of the global S-LAs [(LAP-v – LAP-x) / global S-LAs]	12-lead ECG, arrhythmia-related symptom, 24-hour Holter monitoring and portable ECG monitoring	Mean follow-up period of 33.8 ± 12.2 months (range, 14 to 54 months)	3	LA stiffness index was an independent predictor of recurrence of AF (HR: 2.88; 95% CI: 1.75 to 4.73, p < 0.001)	Good
Park et al., 2015*	Asia	Prospective case series, single centre	334	PVI	Direct measurement of LA pulse pressure (the difference between LAP peak and LAP nadir) and assumed a minimal change in LA volume based on the previous physiologic studies	ECG and 24- or 48-hour Holter monitoring	Mean follow-up period of 16.7 ± 11.8 months (range, 3 to 47 months)	NR	Low LA compliance was independently associated with two fold-higher risk of clinical AF recurrence (HR: 2.202; 95%CI: 1.077 to 4.503; p = 0.031)	Good
Kawasaki et al, 2016	Japan	Prospective, case series, single centre	109	PVI	LA stiffness was obtained by using ePCWP as ePCWP/LA strain obtained by STE	ECG and Holter recordings	At least 12 months	1	LA stiffness index was not a predictor of recurrence of AF (OR: 0.37, 95%, CI: 0.041 to 3.462, p = 0.39)	Good
Khurram et al., 2016†	North America	Prospective, case series, single centre	160	PVI	Ratio of change in LAP to the change in LA volume during passive filling of LA.	24-hour Holter monitoring or 30-day event monitoring	Mean follow-up period of 10.4 ± 7.6 months	3	LA stiffness index was an independent predictor of AF ablation outcome (HR: 8.22; 95% CI: 3.54 to 19.11; p < 0.001)	Good

*LA: Left atrial; LAP: Left atrial pressure; AF: atrial fibrillation; PVI: pulmonary vein isolation; NR: not reported; ECG: electrocardiogram; global S-LAs: average mean values for peak strain during ventricular systole (S-LAs) obtained from the 4- and 2-chamber views; ePCWP: estimated pulmonary capillary wedge pressure; STE: speckle tracking echocardiography. *The analysis included only the structured normal heart patient population. †Only the 160 patients included for outcome analysis are depicted in this table.*

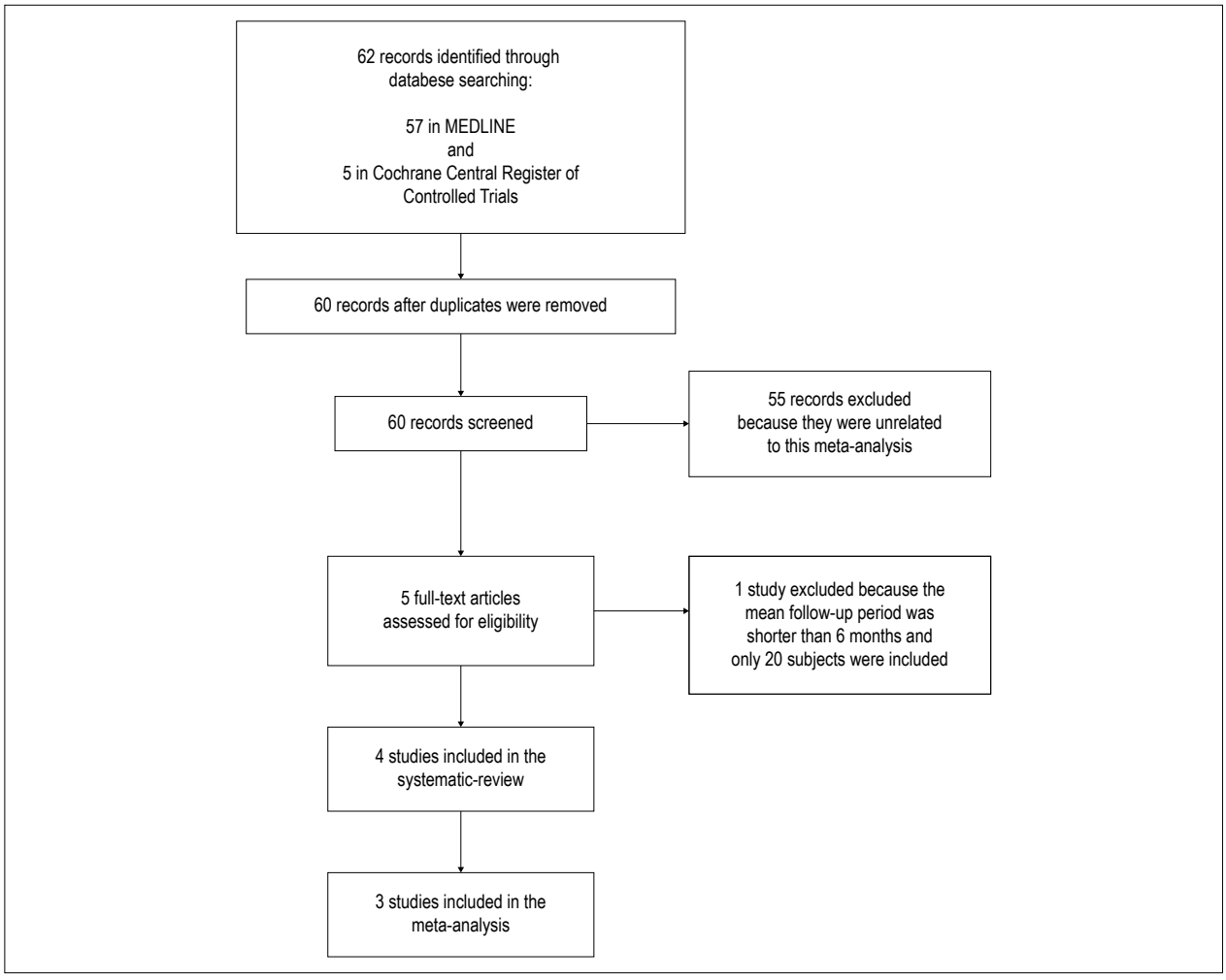

Figure 1 – *Flow diagram of the study selection.*

study by Khurram et al.,[13] 160 patients from the original study were included in the analysis of the outcomes, and hence included in the present review. The study of Park et al.[12] analysed 1,038 patients, however only 334 patients had a structurally normal heart and were included in the analyses. Although Kawasaki et al.[10] analysed 137 subjects, only 109 patients underwent first ablation, and were included in the present review. Overall, 758 and 649 patients were included in our qualitative and quantitative analysis, respectively. The mean follow-up period ranged from 10.4 to 33.8 months. Studies used different techniques to measure LA stiffness, which are depicted in Table 1. All studies performed pulmonary vein isolation as ablation strategy and Holter monitoring for diagnosing AF. Also, three[10-12] of four studies used electrocardiogram (ECG) to perform the diagnosis. Khurram et al.[13] did not perform an ECG, although they also used 30-day event monitoring. Blanking period for AF recurrence post-RFCA lasted three months in two studies,[11,13] one month in one study,[10] and was not mentioned in the study by Park et al.[12] Characteristics from all included studies are summarized in Table 1.

LA stiffness as a predictor of AF recurrence

Two[11,13] of the four included studies found that LA stiffness was the most important predictor for recurrence of AF post-ablation on a multivariate analysis, among several factors such as LA volume and persistent AF.

Khurram et al.[13] observed that LA stiffness index was an independent predictor of AF ablation outcome (HR: 8.22; 95% CI: 3.54 to 19.11; $p < 0.001$). Besides that, 25% of patients (40 of 160) had AF recurrence after AF ablation during a follow-up period of 10.4 ± 7.6 months. Patients with AF recurrence had a higher LA stiffness index than those without recurrence. These findings are also confirmed by the study by Machino-Ohtsuka et al.,[11] which also showed that the patients with recurrence (29%, 45 of 155) had a higher LA stiffness than those without recurrence during a follow-up period of 33.8 ± 12.2 months. In addition, the study also showed that a higher LA stiffness index was an independent predictor of recurrence of AF (HR 2.88; 95% CI 1.75 to 4.73, $p < 0.001$).

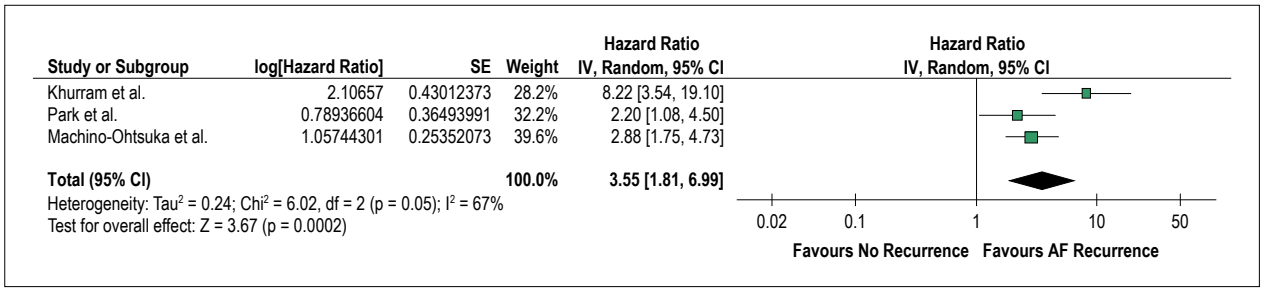

Figure 2 – *Forest plot showing left atrial stiffness as a predictor of atrial fibrillation recurrence after radiofrequency catheter ablation.*

Also, Park et al.[12] showed that in a follow-up period of 16.7 ± 11.8 months, a low LA compliance was associated with a two-fold increased risk of AF recurrence. Also, in the multivariate analysis, adjusting for several factors, LA stiffness was the second most important predictor for AF recurrence after RFCA (HR), only behind persistent AF.

Kawasaki et al.[10] showed that in patients submitted to the first or second ablation, the recurrence group had a significant higher LA stiffness than the group with a successful ablation. However, in the multivariate analysis, when analysing patients undergoing the first RFCA, LA stiffness index was not a significant predictor of AF recurrence (OR).

Meta-analysis

This meta-analysis showed that LA stiffness is associated with a higher AF recurrence after RFCA (HR = 3.55, 95% CI 1.75–4.73, p = 0.0002), as shown in Figure 2. The heterogeneity test showed that there were significant differences between studies (p = 0.05, I^2 = 67%). The sensitivity analysis, performed to find the origin of the heterogeneity, revealed that, after removing the study by Khurram et al.,[13] who used cardiac magnetic resonance to measure LA stiffness, there was no significant heterogeneity across the studies (p = 0.55, I^2 = 0%). However, the overall outcome remained the same (HR = 2.64, 95% CI 1.75–3.97, p < 0.00001). A funnel plot (Figure 3) was used to verify the existence of publication bias. There was no obvious asymmetry, suggesting that there was no publication bias.

Discussion

As mentioned before, catheter ablation has been increasingly considered as a first-line therapy, and therefore, the importance of screening factors has also increased. This systematic review shows that in two[11,13] of four included studies, the LA stiffness was the single most important predictor for recurrence of AF post-ablation on a multivariate analysis, among several factors such as LA volume and persistent AF. Moreover, this meta-analysis, including three studies, showed that LA stiffness is a strong predictor of AF recurrence after RFCA (HR = 3.55, 95% CI 1.75–4.73, p = 0.0002). Therefore, the use of LA stiffness in a preoperative routine may be useful for a close follow-up of patients with higher risk of developing the SLAS and AF recurrence.

AF and stiffness of the left atrium

Previous studies have shown, despite some limitations, that patients with paroxysmal AF have increased LA stiffness.[14,15] Also, structural remodelling caused by AF leads to LA fibrosis,[16] which may also be a mechanism of LA stiffening. Therefore, an increase in LA stiffness could be an important mechanism of AF genesis and propagation or a consequence of AF episodes.

Extensive Catheter Ablation

Previous studies have shown that completely circumferentially scarred pulmonary vein by RFCA was associated with less AF recurrence.[17,18] Also, the more scarring overlaps fibrosis, decreasing the amount of unablated fibrotic tissue, the better the arrhythmia free survival.[19] Thus, an extensive ablation appears to be the best option to reduce AF recurrence. However, in a previous study, LA scarring was associated with the development of the SLAS,[5] leading to poor clinical outcomes post-RFCA.

LA stiffness as a screening factor for catheter ablation

In 1988, Pilote et al.[20] described a condition in patients undergoing mitral valve surgery for LA scarring, characterised by loss of LA compliance, pulmonary hypertension, LA dysfunction and new-onset dyspnea, the so-called SLAS.[5] Subsequently, this syndrome was also reported by Gibson et al.[3] in patients undergoing RFCA, with a relatively rare occurrence (1.4%). Patients with a low-compliant left atrium before the ablation may be more susceptible to develop the SLAS, as RFCA is related to an increase in LA stiffness,[21] probably because the formation of multiple scars in the LA wall induced by the procedure.[22] Therefore, patients with low-compliant left atrium could benefit from a measure of LA stiffness derived from a non-invasive assessment prior to AF ablation, as part of the preoperative screening process, or even routine assessment. This could help to prevent AF recurrence and the SLAS, and to promote a close follow-up of these patients.

Marino et al.,[9] despite the study limitations, observed a linear relationship between left ventricular (LV) longitudinal strain and invasively measured LA stiffness (calculated during the ascending limb of the V-loop as the ΔLA pressure/ΔLA volume ratio). Since there is an association between the

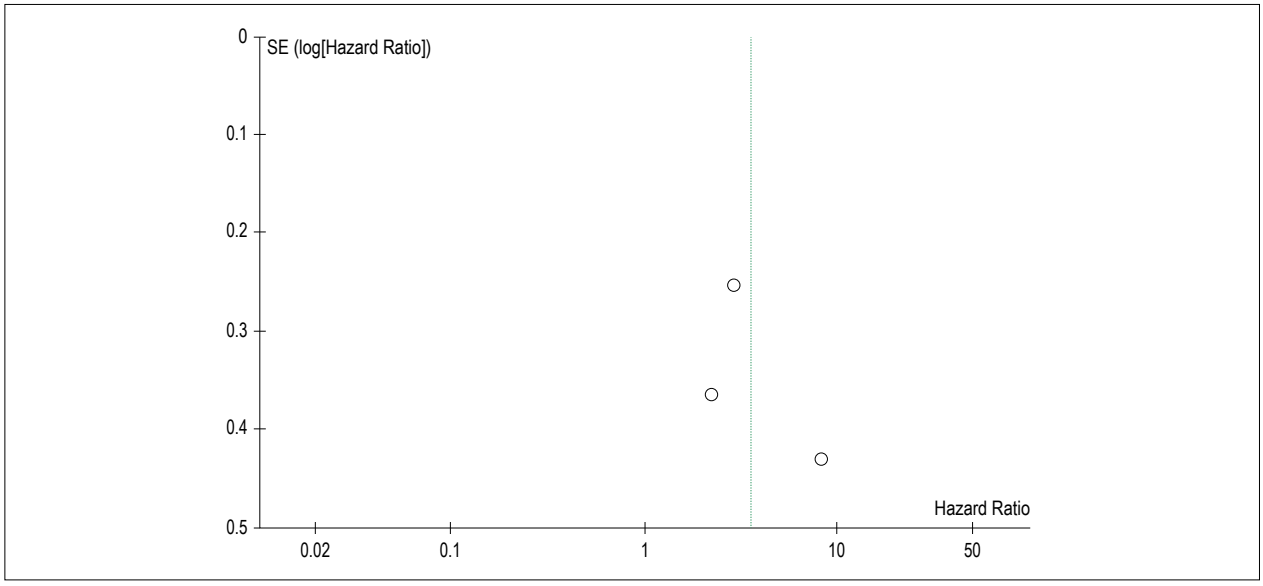

Figure 3 – *Funnel plot showing no publication.*

longitudinal deformation of the LA and the movement of the shared mitral annulus and the adjacent ventricle, information from LV longitudinal strain could be used to estimate LA stiffness.[9] With this non-invasive measurement by a simple ECG, LA stiffness could be a potential new screening factor in the preoperative routine.

Future studies

The present review shows a need for further studies to better understand the relation between LA stiffness and AF. First, an increase in the number of studies and in total sample could increase reliability of results. Also, a development of a standard non-invasive LA stiffness index would contribute for screening of patients which would not benefit from the ablation. Finally, further studies are also needed to investigate if LA stiffness is a real risk factor that could lead to AF development and propagation or if it is just a consequence of AF.

Limitations

The present review has some limitations. First, in the quantitative analysis only three observational studies were included. Also, the I^2 test showed a high heterogeneity ($p = 0.05$, $I^2 = 67\%$), although the overall outcome remained the same after excluding the study of Khurram et al.,[13] which caused heterogeneity. This heterogeneity might be related to several factors. First, the study of Khurram et al.[13] took place in North America, while the other two studies were performed in Asia. Second, although all methods used for the measurement of LA stiffness were different between studies, the study by Khurram et al.[13] was the most varied among all in this sense, because it used cardiac magnetic resonance, and did not use ECG for diagnosing AF. Also, the study by Khurram et al.[13] had the shorter mean follow-up period of all studies. In addition to these limitations, although adjusted HRs from multivariate analysis were used to reduce the effect of confounding variables, they cannot exclude them completely.

Conclusions

The present review shows that LA stiffness is a strong predictor of AF recurrence after RFCA (HR = 3.55, 95% CI 1.75–4.73, p = 0.0002). Therefore, a standard non-invasive LA stiffness measure, could be routinely used prior to AF ablation, tracking patients with higher chances of AF recurrence and development of the SLAS.

Author contributions

Conception and design of the research, acquisition of data, analysis and interpretation of the data, writing of the manuscript and critical revision of the manuscript for intellectual content: Correia ETO, Barbetta LMS, Silva OMP, Mesquita ET; statistical analysis: Correia ETO, Barbetta LMS.

Potential Conflict of Interest

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

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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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Left Atrial Stiffness, a Marker of Atrial Cardiomyopathy, and Atrial Fibrillation – Relationships and Predictors for Procedure Success after Catheter Ablation

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Short Editorial related to the article: Left Atrial Stiffness: A Predictor of Atrial Fibrillation Recurrence after Radiofrequency Catheter Ablation – A Systematic Review and Meta-Analysis

Over the past years, catheter ablation (CA) for atrial fibrillation (AF) has established itself as a well-recognized strategy in the management of patients with AF and an important option for rhythm control. Although CA is more effective than antiarrhythmic drug therapy, AF recurrences are common during the follow-up.[1]

Late recurrence, during the first 9 months after the blanking period, occurs in 25%–40% of cases and is predominantly linked to the recovery of electrical conduction between the pulmonary veins (PVs) and the left atrium (LA), irrespective of the type of AF. The incidence of very late recurrence (after more than 12 months postablation) has been shown to be higher than previously expected, with an annual recurrence rate estimated at 7.6%.[2] Bunch et al.[3] reported AF recurrence rates ranging from 52% (≤ 50 years + paroxysmal AF) to 75% (> 80 years + paroxysmal AF).[3] In a series of 509 consecutive patients undergoing paroxysmal AF ablation by Teunissen et al., after a single procedure, antiarrhythmic drugs free success rate was 41.3%[4]. The predominant mechanism of very late recurrence includes, in addition to the PV connection, the development of non-PV triggers, and development and maturation of substrate. The predictors appears to be the nonparoxysmal form of AF at baseline, organic heart disease, advanced age, and obesity.

AF is often associated with atrial structural remodeling and causes LA fibrosis/scarring and dilatation. Substrate progression is a multifactorial and time-dependent response of cardiac myocytes to varying "stressors", including electrical, mechanical, and metabolic stressors. Some components of the LA changes are reversible (adaptive), whereas others are permanent (maladaptive). Most risk factors affect AF by causing structural remodeling. Progression of atrial damage due to underlying heart disease is a major factor. Recent studies suggest that AF recurrence can be prevented by effectively managing risk factors such as sleep apnea, obesity, high blood pressure, hyperglycemia, and dyslipidemia, presumably by curtailing further damage and/or reversing existing abnormalities. Conversely, AF itself can cause progression of the substrate. In addition to complexion-channel remodeling that accelerates repolarization and alters conduction properties, rapid activation of atrial cardiomyocytes causes profibrotic changes in fibroblast function and promotes atria fibrosis.

Increased LA scar is associated with increases LA stiffness, which reflects a deteriorated reservoir function. Therefore, LA stiffness could be associated with LA histological changes and predicts sinus rhythm maintenance after treatment in AF patients.[5] Timely intervention for patients with these conditions may interrupt and perhaps reverse LA remodeling, with a consequent reduction in LA size and improved function.

The scar tissue formation after CA may also adversely impact the diastolic properties of the LA, especially after multiple ablation procedures, worsening the diastolic function or LA compliance. Stiff LA syndrome has been recognized as pulmonary hypertension and dyspnea that develops after CA, a potential complication of the procedure with a low prevalence.[6,7]

Thus, evaluation of the LA as cardiovascular biomarker, especially in AF, has become increasingly important.[8,9] LA remodeling is monitored in clinical practice using various noninvasive imaging modalities, but it has not been yet incorporated into clinical decision making. In this published issue, Correia et al.,[10] investigated, through a systematic review and meta-analysis, if LA stiffness could be a predictor of AF recurrence after CA, and to discuss its clinical use.[10] Only 4 prospective observational studies were included in the systematic review and 3 of them in the meta-analysis, with different methods, and most of all used LA pressure measured invasively during CA to estimate LA stiffness. They found that LA stiffness was a strong independent predictor of AF recurrence after CA (HR = 3.55, 95% CI 1.75-4.73, p = 0.0002), and concluded that a non-invasive assessment of LA stiffness prior to CA can be used as a potential screening factor to select or to closely follow patients with higher risks of AF recurrence and development of the stiff LA syndrome. The small number of studies, with heterogeneity and a short mean follow-up in 3 studies were limitations in this meta-analysis.

These findings add to our knowledge by clarifying the association between atrial remodeling and outcomes after AF ablation. Current guidelines recommendation is to perform CA as second-line treatment after failure or intolerance to at least one antiarrhythmic drug. As first-line treatment, the

Keywords

Atrial Fibrillation; Catheter Ablation; Atrial Function, Left; Atrial Remodeling; Recurrence; Treatment Outcome.

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indication recommendations are weaker and only limited to patients with paroxysmal AF. These recommendations usually lead physicians to treat patients with CA after a longer history period of clinical AF. The development of tools and methods to determine markers of atrial cardiomyopathy may allow to avoid the mismatch of the best time for CA, in accordance with more substrate and patient-oriented process of diagnosis and therapy of AF. Certainly, further studies will be required to support identification by noninvasive cardiac imaging of patients for whom CA should be considered early before there is significant LA functional remodeling with associated fibrosis.

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Stent versus Coronary Artery Bypass Surgery in Multi-Vessel and Left Main Coronary Artery Disease: A Meta-Analysis of Randomized Trials with Subgroups Evaluation

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Abstract

Background: Comparison between percutaneous coronary intervention (PCI) using stents and Coronary Artery Bypass Grafting (CABG) remains controversial.

Objective: To conduct a systematic review with meta-analysis of PCI using Stents versus CABG in randomized controlled trials.

Methods: Electronic databases were searched to identify randomized trials comparing PCI using Stents versus CABG for multi-vessel and unprotected left main coronary artery disease (LMCAD). 15 trials were found and their results were pooled. Differences between trials were considered significant if $p < 0.05$.

Results: In the pooled data (n = 12,781), 30 days mortality and stroke were lower with PCI (1% versus 1.7%, p = 0.01 and 0.6% versus 1.7% p < 0.0001); There was no difference in one and two year mortality (3.3% versus 3.7%, p = 0.25; 6.3% versus 6.0%, p = 0.5). Long term mortality favored CABG (10.6% versus 9.4%, p = 0.04), particularly in trials of DES era (10.1% versus 8.5%, p = 0.01). In diabetics (n = 3,274) long term mortality favored CABG (13.7% versus 10.3%; p < 0.0001). In six trials of LMCAD (n = 4,700) there was no difference in 30 day mortality (0.6%versus 1.1%, p = 0.15), one year mortality (3% versus 3.7%, p = 0.18), and long term mortality (8.1% versus 8.1%) between PCI and CABG; the incidence of stroke was lower with PCI (0.3% versus 1.5%; p < 0.001). Diabetes and a high SYNTAX score were the subgroups that influenced more adversely the results of PCI.

Conclusion: Compared with CABG, PCI using Stents showed lower 30 days mortality, higher late mortality and lower incidence of stroke. Diabetes and a high SYNTAX were the subgroups that influenced more adversely the results of PCI. (Arq Bras Cardiol. 2019; 112(5):511-523)

Keywords: Myocardial Revascularization/mortality; Percutaneous Coronary Intervention; Drug-Eluting Stents; Stents; Coronary Vessels; Randomized Controlled Trial; Meta-Analysis.

Introduction

Percutaneous coronary intervention (PCI) using stents and coronary artery bypass grafting (CABG) are well-accepted alternatives for treatment of coronary artery disease (CAD). A large number of randomized controlled trials (RCT) comparing the two procedures were published.[1-23] Most studies were underpowered to evaluate isolated endpoints like death, stroke and acute myocardial infarction (AMI). Several meta-analyses were subsequently carried out, pooling results in order to overcome this limitation.[24-31] The largest meta-analysis included a limited number of drug-eluting stent (DES) era trials and/or included also single vessel disease and balloon era trials. On the other side, modern meta-analysis included a lower number of trials (only of DES era) and evaluated specific group of patients.[28-32] The objective of this study was to perform a systematic review of RCT comparing stents (bare-metal and drug-eluting) versus CABG in multi-vessel and/or left main coronary disease (LMCAD) pooling data of mortality at different periods of time and using meta-regression analysis to evaluate sub-groups.

Methods

Search strategies

Randomized studies comparing PCI with Stents versus CABG in multivessel lesions and/or obstruction of left main CAD published between January 1990 and December 2017 were searched in the databases MEDLINE and Cochrane library and in bibliographic references published on the subject. The search terms used were: *"coronary stents" and "coronary artery bypass surgery" and "randomized controlled trial"*.

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Inclusion criteria

Clinical trials were included in the review if they were randomized, if had compared PCI with stents versus CABG, if included exclusively multi-vessel and/or LMCAD and if had a follow up of at least 1 year. We did not limit our search to DES trials because bare-metal stents (BMS) are still frequently used in many developing countries, had the peculiarity of evaluating patients with less complex coronary artery disease and there is no definitive evidence that BMS are inferior to DES in the outcome mortality. Figure 7 show a flow diagram of the search strategy in the databases. We identified a total of 15 RCT that satisfied the requirements: AWESOM[1], ERACI II,[2,3] MASS II,[4-6] SOS,[7,8] ARTS,[9,10] LE MANS,[11] SYNTAX,[12-14] CÁRDia,[15] Boldriot et al.,[16] PRECOMBAT,[17,18] Va-Cards,[19] FREEDOM,[20] BEST,[21] NOBLE[22] and EXCEL.[23] Three reviewers (PJNA, ATA and JLAF) assessed the quality of the studies using the Cochrane Collaboration's tool.

Data extraction

Two reviewers (JLAAF and PJNA) obtained the data from the studies, examining abstracts, results, tables, appendices and figures. A third author (BAAF) checked the results.

The main outcomes evaluated were all case-mortality, stroke, AMI and new revascularization. Mortality was divided into early mortality, mortality at one year and late mortality. Early mortality was defined as percentage of deaths that occurred in the first 30 days after the procedure, including deaths after randomization but before the procedure. Late mortality was defined as percentage of deaths reported in the last publication, after at least three years of follow-up. For the incidence of stroke, we considered the events occurring up to 1 year after the procedure. In twelve studies we obtained the results up to 30 days, in 2 studies [9,12] up to 1 year and in one [21] this observation was unavailable. For the incidence of myocardial infarct, we considered the reported up to one year of the procedure. AMI were reported in 13 trials.[2-5-15] We did not consider in the pooled data the results of NOBLE because it excluded perioperative myocardial infarct in the majority of the patients.

New revascularization was divided in any form of new revascularization (PCI or CABG) and new revascularization by alternative procedure (PCI for patients of the CABG group or CABG for the patients of the PCI group).

Data synthesis

The characteristics of patients from the eligible studies were obtained through a weighted average of published data. For pooling results of mortality and stroke, the numerator was the number of events and the denominator the total of patients. The total of patients was the number of patients effectively followed, including the deaths. Trials were divided into DES era trials and BMS era trials. Trials that used both types of stents[11,15] were classified as DES era trials. We evaluated separately the results of studies in the left main coronary artery and late mortality in the subgroup of patients with diabetes. We also performed analysis of combined major adverse cardiac and cerebrovascular events (MACCE) and assessed the variables age, gender, presence of diabetes, SYNTAX score, and compromised ejection fraction in subgroups based on data published in five trials. Combined MACCE comprised death, AMI, and new revascularization. In order to aggregate the outcomes of mortality and stroke, as well as those of MACCE (in subgroups), we considered whenever possible the absolute number of events and the number of patients followed up. Otherwise, percentages were transformed into absolute numbers.

Statistical analysis

We measured the relative risk and the risk difference after grouping the results of each outcome. In order to assess the statistical significance of the differences between the DES and the surgery groups, we performed a meta-analysis using the Mantel-Haenszel method, with a random-effect model. We calculated the heterogeneity of the studies using Cochran's Q test and the significance of the measure of the meta-analytic effect using the Z test. Finally, we performed a meta-regression analysis using diabetes, age, gender, ejection fraction, and syntax scores as factors. The differences between the results in the PCI and CABG groups were considered significant if $p<0.05$. The statistical analyses were performed using the program Review Manager (RevMan), version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and SPSS for Windows v 23, IBM Inc. In order to represent the heterogeneity of the studies, we constructed Forest plots. We used the risk difference to plot these graphs since this is a more stable index. The possibility of publication bias was assessed by visual inspection of funnel plots.

Results

Studies Characteristics

The studies (table 1) included a total of 12,781 patients (6,382 in the CABG group and 6,399 in the PCI group). All studies were, considered of quality A or B in terms of adequate randomization, adequate concealment and inexistence of selection bias, but not in terms of adequate making. In all studies, the PCI and CABG groups were similar, with the exception of VaCards where the PCI group had a higher incidence of the previous revascularization (in most of the cases a previous PCI) and showed a higher percentage of patients with ejection fraction < 55%. The mean age of the patients was 64 years; 74% were male; 42% were diabetics; 28% were smokers; 64% were hypertensive. Unstable angina was the clinical presentation in 34%; mean ejection fraction was 58%. With the exception of AWESOME, all studies tended to exclude patients with previous CABG. The mean SYNTAX score was 26. According to number of arteries affected 20% had two vessel disease, 43% had three-vessel disease and 37% had LMCAD (alone or associated with diseases of other arteries). In the CABG group, at least one arterial graft was used in 90% of the patients. In trials of the BMS era surgery was done almost always using on-pump technique; in trials of the era, the DES off-pump technique was used in 28% of the patients. Some characteristics of the studies deserve special mention:

ERACI II included more them 90% of patients with unstable angina. AWESOME included only patients with high surgical risk; MASS II included predominantly stable angina and had a clinical arm; LE MANS used drug-eluting and BMS, reserving the DESs for left main coronary arteries with a reference diameter < 3.8 mm; CARDia used initially BMS and only assessed patients with diabetes and multivessel disease; SYNTAX evaluated left main coronary artery obstruction and multivessel disease and used first-generation DESs (TAXUS); FREEDOM and VA CARDS exclusively assessed patients with diabetes and multivessel disease; BEST evaluated patients with multivessel disease and used only everolimus-eluting stents; the study by Boudriot et al. evaluated left main coronary artery obstruction and used only sirolimus-eluting stents; EXCEL evaluated left main coronary artery obstruction and used only everolimus-eluting stents; NOBLE evaluated left main coronary artery obstruction and used mostly a biolimus-eluting stent.

Outcomes

The results are summarized in Figures 1 to 6. Regarding 30-day mortality, the results favoured PCI (1% versus CABG 1.7%, p = 0.01), but the trials showed moderate overall heterogeneity (I^2 = 49%). The heterogeneity was particularly higher in BMS era trials (I^2 = 83%) and could be attributed to the significant inferior results of surgery in ERACI II and AWESOME. The incidence of stroke was lower with PCI (0.6% versus CABG 1.7%, p < 0.0001), with trials showing low heterogeneity (I^2 = 0). There was no difference in mortality up to one year (PCI 3.3% versus CABG 3.7%, p = 0.25) or up to two year (PCI 6.3% versus CABG 6.0%, p = 0.5). Long-term mortality showed a trend to superiority of CABG (10.6% versus 9.4%, p = 0.04), with trials showing moderate heterogeneity (I^2 = 25%). The differences were significant in trials of DES era (10.1% versus 8.5%, p = 0.01). After excluding FREEDOM (that included only diabetics) the overall difference in long-term mortality between PCI and CABG became not significant (10.2% versus 9.4%, p = 0.17). The incidence of myocardial infarct was lower with CABG (PCI 6.4 % versus CABG 5.3% at one year and PCI 8,8% versus CABG 6.7 % after 3 or more years), but the trials showed high heterogeneity.

In 6 studies of LMCAD (n = 4700), there was no difference in 30 days mortality (0.6% versus 1.1%, p = 0.15) between PCI and CABG, but the incidence of stroke was significantly lower after PCI (0.3% versus 1.1%, p = 0.007). There was no difference in one-year mortality (3% versus 3.7%, p = 0.18) or long-term mortality (8.1% versus 8.1%) between PCI and CABG.

Nine trials (n = 4394) reported long-term mortality in diabetics (AWESOME, ARTS, ERACII, MASS II, SOS, SYNTAX, CARDia, FREEDOM and BEST). After pooling of results, CABG was associated with significantly lower long-term mortality (13.7% versus 10.3% CABG, p < 0.0001); After excluding the diabetic patients of these nine trials the overall difference in long-term mortality between PCI and CABG was no longer significant (9.2% versus 9.2%).

The data regarding new revascularization are shown in figure 5. The superiority of surgery over PCI was consistent in all 15 trials. However, if we consider the risk of new revascularization by alternative procedure there was a trend to superiority of PCI in ARTS and in all studies of DES era.

Subgroups results

Five trials reported long-term results of major Adverse Composite Events (death, myocardial infarct and stroke) in subgroups. In three of them (SYNTAX, PRECOMBAT and BEST) the results were obtained through the collaborative meta-analysis of Lee et al.[24] (Figure 4). The pooled data showed that CABG, compared to PCI, was associated with a lower incidence of MACCE (18.4% vs 14.4%, p < 0.0001). The subgroups in which PCI had worse results, when compared with CABG, by meta-regression analysis were presence of diabetes (23% versus 17.5, p < 0.0001) and a high SYNTAX score (22.7 vs. 16.3%, p = 0.001). There was no difference between PCI and CABG in non-diabetics (14.1% versus 12.3%, p = 0.11), low SYNTAX score patients (14.1% vs. 13.3% scores, p = 0.4) and LMCAD patients (14.7% vs 14.1%, p = 0.5). Female sex and old age less significantly influenced the results. Left ventricular dysfunction did not influence the results. Figure 5 shows that the meta-Adjusted value of p for diabetes was 0.03 (adjusted for age or sex) and 0.09 (adjusted for SYNTAX score). The same figure shows that the meta-adjusted value of p for SYNTAX score was 0.03 (adjusted for diabetes).

Discussion

To our knowledge this meta-analysis is the most comprehensive and up to date overview of randomized trials that compared coronary stents (DES and BMS) versus CABG. It is also the only major meta-analysis of the stent era that evaluated mortality at different times (up to 30 days, up to one year and after three or more years of follow-up). Another peculiarity of the present meta-analysis was the statistical meta-regression analysis of sub-groups.

The superiority of PCI on 30 days mortality is in accord with the New York state Registry[33] and with the meta-analysis of Palmerini et al.[32] This superiority should be seen with caution considering the heterogeneity of the trials and cannot be extended to patients with high SYNTAX score, considering the mortality curve of the study of Cavalcante et al.[30] The significant difference, favoring PCI found in the incidence of stroke is a relevant finding. A recent study showed that, after death (relative weight 0.23), stroke is the most feared event for patients (relative weight 0.18), being considered more important them longevity (relative weight 0.17), myocardial infarct (relative weight 0.14) and risk of repeat revascularization (relative weight 0.11).[34]The lack of difference in intermediate mortality was an expected finding, having been reported in almost all trials.

The trend superiority of surgery in long-term mortality was shown in other meta-analysis[26,29,31] and is probably related to the higher percentage of diabetics in recent trials. Our results of long-term mortality (HR 1.13) were similar to the results of Smit el al.[26] (HR 1.11) and Lee et at.[29] (HR 1.18). They were much less unfavourable to PCI them the reported by Benedetto et al (HR 1.5).[31] The reason for this is that

Table 1 – Overview of clinical trials

Study	Origin	Period of recruitment	Number of Patients	Disease extension	Characteristics	Unstable angina (%)	Average ejection fraction (%)	Off pump surgery (%)	Diabetics (%)
AWESOME	North America (USA)	1995-2000	454	Two and three vessel disease	BMS. Previous CABG included	36	45	0	32
ARTS	International	1997-2000	1205	Two and three vessel disease	BMS. Majority two vessel disease	30	61	0	21
ERACI II	South America (Argentina)	1996-1998	450	Two and three vessel disease	BMS. Majority unstable angina	92	ND	0	17
SOS	Europe and Canada	1995-1999	988	Two and three vessel disease	BMS. Majority two vessel disease	33	ND	3	15
MASS II	South America (Brazil)	1995-2000	408	Two and three vessel disease	BMS. Clinical arm	36	65	0	30
LEMANS	Europe (Poland)	2001-2004	105	Left main coronary disease	BMS and DES DES if LM < 3.8	32	53	0	25
SYNTAX	Europe and USA	2005-2007	1800	Left main and three vessel disease	DES (Taxus)	28	ND	15	35
CARDia	Europe (United Kingdom)	2002-2007	510	Two and three vessel disease	BMS and DES. Only diabetics.	22	59	31	100
Boudriot et al	Europe (Germany)	2003-2009	201	Left main coronary disease	DES (Sirolimus)	ND	ND	46	30
PRECOMBAT	Asia (Korea)	2003-2009	600	Left main coronary disease	DES (Everolimus)	45	60	64	42
FREEDOM	International	2005-2010	1900	Two and three vessel disease	DES. Only diabetes	30	65	19	100
Va-Cards	North America (USA)	2006-2010	198	Two and three vessel disease	DES. Only diabetics	ND	ND	ND	100
BEST	Asia (Korea)	2008-2013	880	Two and three vessel disease	DES. (Everolimus)	42	59	64	45
EXCEL	International	2010-2014	1905	Left main coronary disease	DES. (Everolimus)	37	57	29	25
NOBLE	Europe	2008-2015	982	Left main coronary disease	DES (Biolimus)	18	60	16	18

AWESOME: Angina with extremely severe outcomes; ERACI II: Argentine randomized study: coronary angioplasty with stenting versus coronary bypass surgery in patients with multivessel disease; MASS II: Medicine, Angioplasty, or Surgery Study; ARTS: Arterial Revascularization Therapies Study; SOS: Stent or Surgery trial. SYNTAX: Synergy between PCI with Taxus and Cardiac Surgery; CARDia: Coronary artery revascularization in diabetic; Le Mans: Left main stenting; FREEDOM: Future Revascularization Evaluation in Patients with Diabetes Mellitus; Va-Cards: Coronary Artery Revascularization in Diabetes in VA Hospitals; BEST: Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease; PRECOMBAT: Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease; EXCEL: Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; NOBLE: Nordic-Baltic-British Left Main Revascularization Study. Boldriot et al: J Am Coll Cardiol. 2011; 57: 538-545. DES: drug-eluting stent; BMS: bare-metal stent.

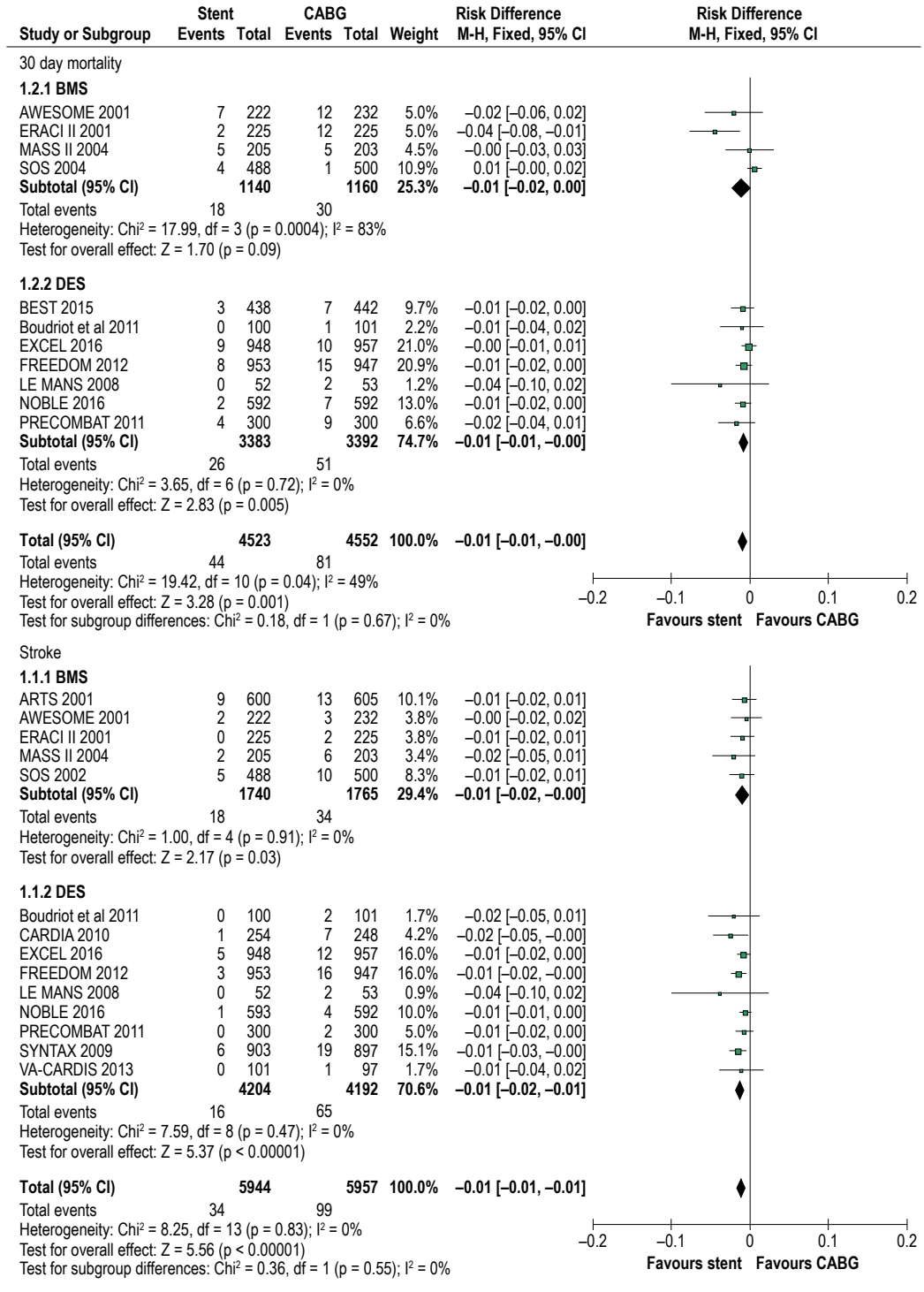

Figure1 – *Stent versus CABG: 30 days mortality (top) and stroke (bottom). The size of each box is proportional to the number of patients of the trial. The bars represent 95% confidence interval. The diamond represents the syntheses of results. DES: trials of the drug-eluting stent era. BMS: trials of the bare-metal stent trials era. CABG: coronary artery bypass grafting. ARTS: Arterial Revascularization Therapies Study; AWESOME: Angina with extremely severe outcomes; ERACI II: Argentine randomized study: coronary angioplasty with stenting versus coronary bypass surgery in patients with multi-vessel disease; MASS II: Medicine, Angioplasty, or Surgery Study; SOS: Stent or Surgery trial; BEST: Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multi-vessel Coronary Artery; Boldriot, trial of Boldriot et al: J Am Coll Cardiol. 2011; 57: 538-545. CARDia: Coronary artery revascularization in diabetic; LE MANS: Left main coronary artery stenting; EXCEL: Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; FREEDOM: Future Revascularization Evaluation in Patients with Diabetes Mellitus NOBLE, Nordic-Baltic-British Left Main Revascularization Study; PRECOMBAT: Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease; SYNTAX: Synergy between PCI with Taxus and Cardiac Surgery; Va-Cards: Coronary Artery Revascularization in Diabetes in VA Hospitals.*

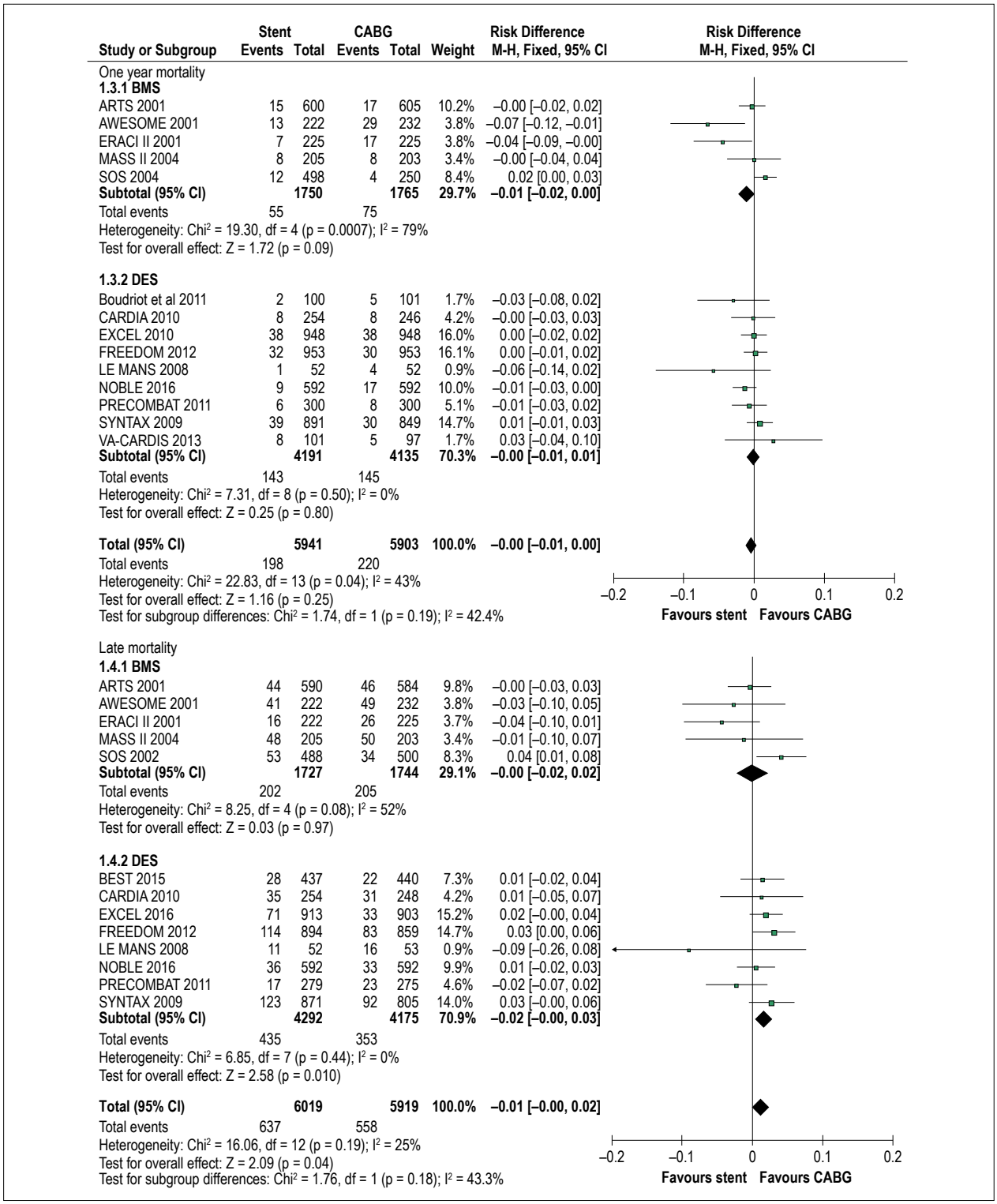

Figure 2 – *STENT versus CABG: One-year mortality (top) and late mortality (bottom). The size of each box is proportional to the number of patients of the trial. The bars represent 95% confidence interval. The diamond represents the syntheses of results. DES: trials of the drug-eluting stent era; BMS: trials of the bare-metal stent trials era; CABG: coronary artery bypass grafting; ARTS: Arterial Revascularization Therapies Study; AWESOME: Angina with extremely severe outcomes; ERACI II: Argentine randomized study: coronary angioplasty with stenting versus coronary bypass surgery in patients with multi-vessel disease; MASS II: Medicine, Angioplasty, or Surgery Study; SOS: Stent or Surgery trial; BEST: Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multi-vessel Coronary Artery; Boldriot, trial of Boldriot et al: J Am Coll Cardiol. 2011; 57: 538-545. CARDia: Coronary artery revascularization in diabetic; LE MANS: Left main coronary artery stenting; EXCEL: Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; FREEDOM: Future Revascularization Evaluation in Patients with Diabetes Mellitus; NOBLE: Nordic-Baltic-British Left Main Revascularization Study; PRECOMBAT: Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease; SYNTAX: Synergy between PCI with Taxus and Cardiac Surgery; Va-Cards: Coronary Artery Revascularization in Diabetes in VA Hospitals.*

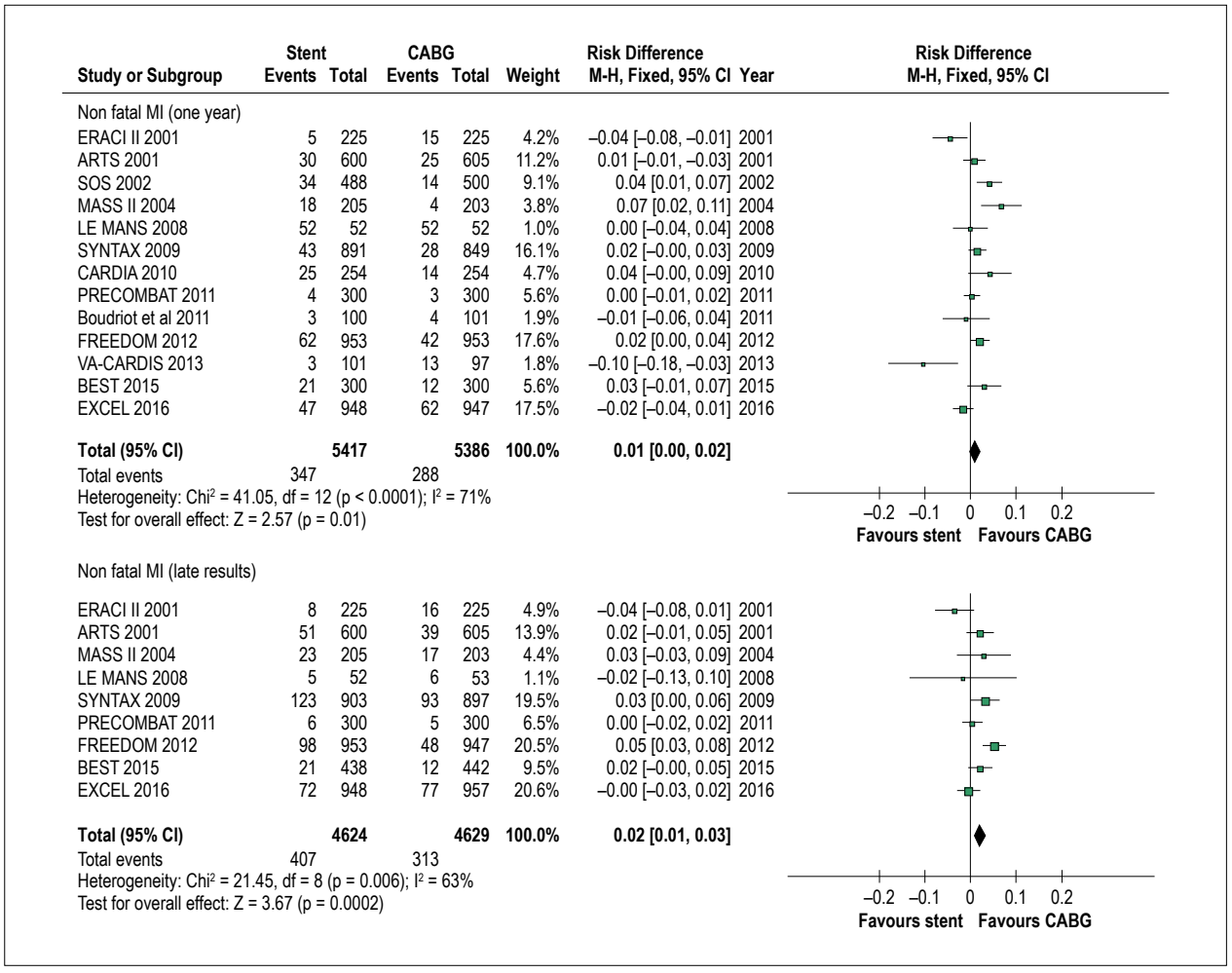

Figure 3 – *Stent versus CABG: Acute myocardial infarct at one year (top) and after three or more years (bottom). The size of each box is proportional to the number of patients of the trial. The bars represent 95% confidence interval. The diamond represents the syntheses of results. DES: trials of the drug-eluting stent era; BMS: trials of the bare-metal stent trials era; CABG: coronary artery bypass grafting; ARTS: Arterial Revascularization Therapies Study; AWESOME: Angina with extremely severe outcomes; ERACI II: Argentine randomized study: coronary angioplasty with stenting versus coronary bypass surgery in patients with multi-vessel disease; MASS II: Medicine, Angioplasty, or Surgery Study; SOS: Stent or Surgery trial; BEST: Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multi-vessel Coronary Artery; Boldriot, trial of Boldriot et al: J Am Coll Cardiol. 2011; 57: 538-545. CARDia: Coronary artery revascularization in diabetic; LE MANS: Left main coronary artery stenting; EXCEL: Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; FREEDOM: Future Revascularization Evaluation in Patients with Diabetes Mellitus; NOBLE: Nordic-Baltic-British Left Main Revascularization Study; PRECOMBAT: Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease; SYNTAX: Synergy between PCI with Taxus and Cardiac Surgery; Va-Cards: Coronary Artery Revascularization in Diabetes in VA Hospitals.*

Benedetto et al excluded LMCAD (that presented similar results of mortality with the two methods of revascularization) and BMS trials (that involved patients with less complex CAD), did not include AWESOME and included two years results of VaCards. Another reason for the significant worse comparative results of PCI-stent in the meta-analysis of Benedetto et al. was that diabetics represented 66% of their population. Recently a pooled analysis of an individual database from 11 trials was published by Head et al.[35] and their overall results are similar to ours. Small differences can be explained by the fact that they included late results of VACards and did not include AWESOME, CARDia, Boldriot and LEMANS.

LMCAD was, for a long time, an indication type III for PCI, but this concept began to change after four trials showed similar results in mortality.[11,12,16,17] However, AHA/ACC guidelines have accepted PCI only as class IIA or IIB indication for LMCAD and yet, only for patients at high surgical risk. In the present study, we found results similar in mortality, while the incidence of stroke was lower, favouring PCI. Our findings are similar to the collaborative study of Head et al and to the meta-analysis of Palmerini et al.[32] This study provided also mortality results in subgroups, showing that in patients with low SYNTAX SCORE there was a trend to higher long-term mortality with CABG (HR, 0.68, CI 0.43-1.08; p = 0.09); intermediate SYNTAX score patients had similar

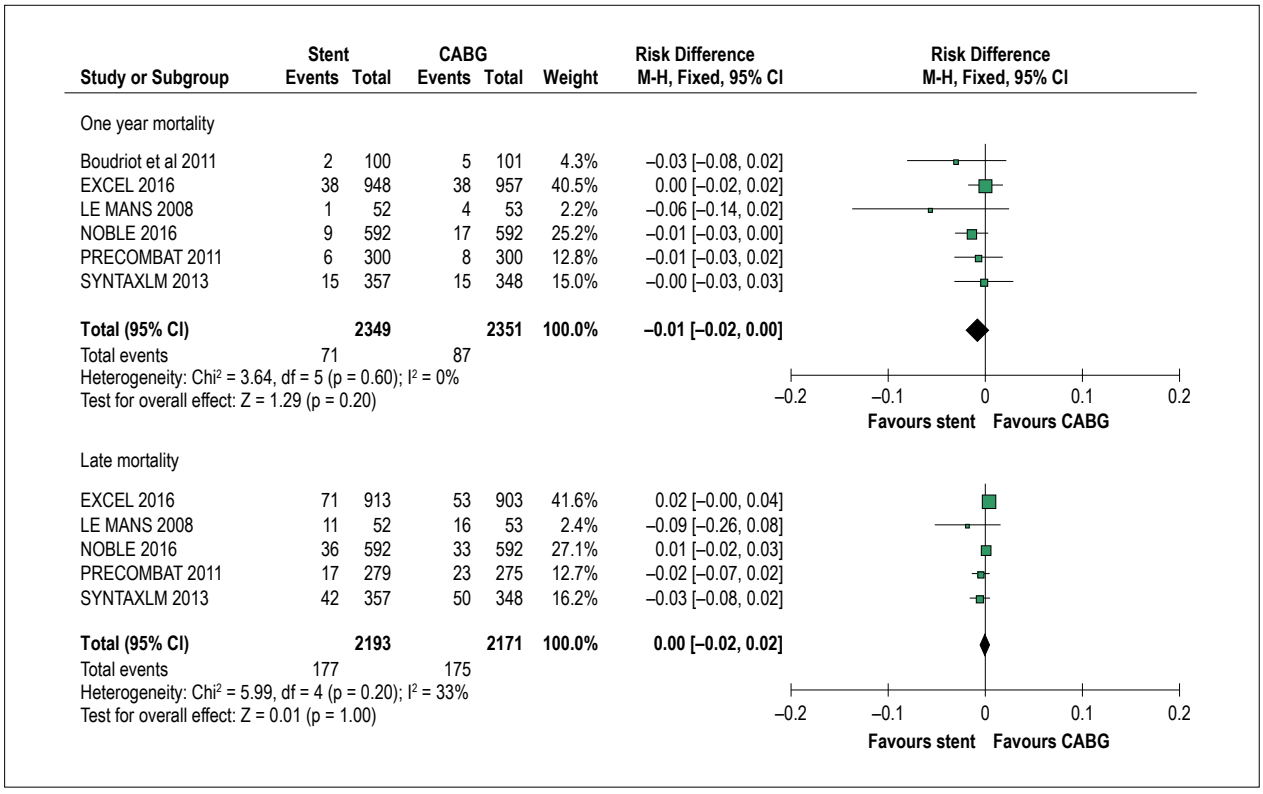

Figure 4 – *Stent versus CABG in left main coronary artery disease: one-year mortality (top) and long-term mortality (bottom). The size of each box is proportional to the number of patients of the trial. The bars represent 95% confidence interval. The diamond represents the syntheses of results. ULMCAD: unprotected left main coronary artery disease. CABG: coronary artery bypass graft. LE MANS: Left Main coronary artery stenting study; SYNTAX LEMANS: subgroup of ULMCAD of SYNTAX (Synergy between PCI with Taxus and Surgery); PRECOMBAT: Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease; EXCEL: Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; NOBLE: Nordic-Baltic-British Left Main Revascularization Study. Boldriot: Boldriot et al: J Am Coll Cardiol. 2011; 57: 538-545.*

results (HR 1.16, CI 0.51-264, p = 0.49). Considering this, we believe that PCI indications for LMCAD in AHA/ACC guidelines may be modified in near future.

Diabetic patients are a present challenge for PCI. A more diffuse atherosclerotic disease is a possible explanation for the worse comparative results of PCI in this population. Our results suggest that there is still a superiority of surgery over PCI in long-term mortality, even in the DES era. There is a hypothesis that the greater mortality of PCI compared to CABG in diabetic patients may be attributed to the presence of more complex lesions in diabetic patients and, not to the metabolic disturbance. The fact that in the subgroup analysis of MACCE results (Figure 5) the meta-Adjusted value was 0.09 (adjusted for SYNTAX score) supports this hypothesis.

This review was not aimed to compare the results of BMS and DES for several reasons: in BMS trials patients had less complex angiographic lesions (average of 2.3 stents per patient in ARTS and SOS trials versus 3.8 stents per patient in SYNTAX, FREEDOM, BEST, PRECOMBAT and CARDia trials) and had a small percentage of diabetic patients. Otherwise, medical adjunctive treatment and results of surgery for patients with failed PCI also evolved. But the good comparative results of PCI in BMS era trials suggest that for patients with less complex lesions, or patients with unstable angina (ERACI II trial) or high surgical risk (AWESOME trial) initial PCI is a good alternative to CABG.

In terms of major adverse composite events, the analysis of subgroups showed that diabetes and a high SYNTAX score were the most important factors to influence adversely the results of PCI. Presence of left ventricular dysfunction did not influence the results, but the number of patients with this finding was small. A high SYNTAX score was an independent risk factor for adverse outcomes, even when adjusted for diabetes, but diabetes was not an independent risk factor for adverse outcomes when adjusted for SYNTAX score.

In the present review despite the clear superiority of CABG in the outcome of new revascularization, it is possible to notice the progressive improvement of PCI results. This was particularly striking when we consider the outcome "new revascularization by alternative procedures", in which there was a tendency to superiority of PCI in the DES era.

The evidence presented here should be used to inform patients, helping them in choosing the more adequate form of revascularization in multi-vessel and LMCAD. Some patients may prefer having PCI to avoid the higher morbidity and short-term mortality of surgery. Other patients may put greater emphasis on the superiority of surgery regarding long-term mortality. However, PCI using second generation DES may still be considered as an alternative to CABG,

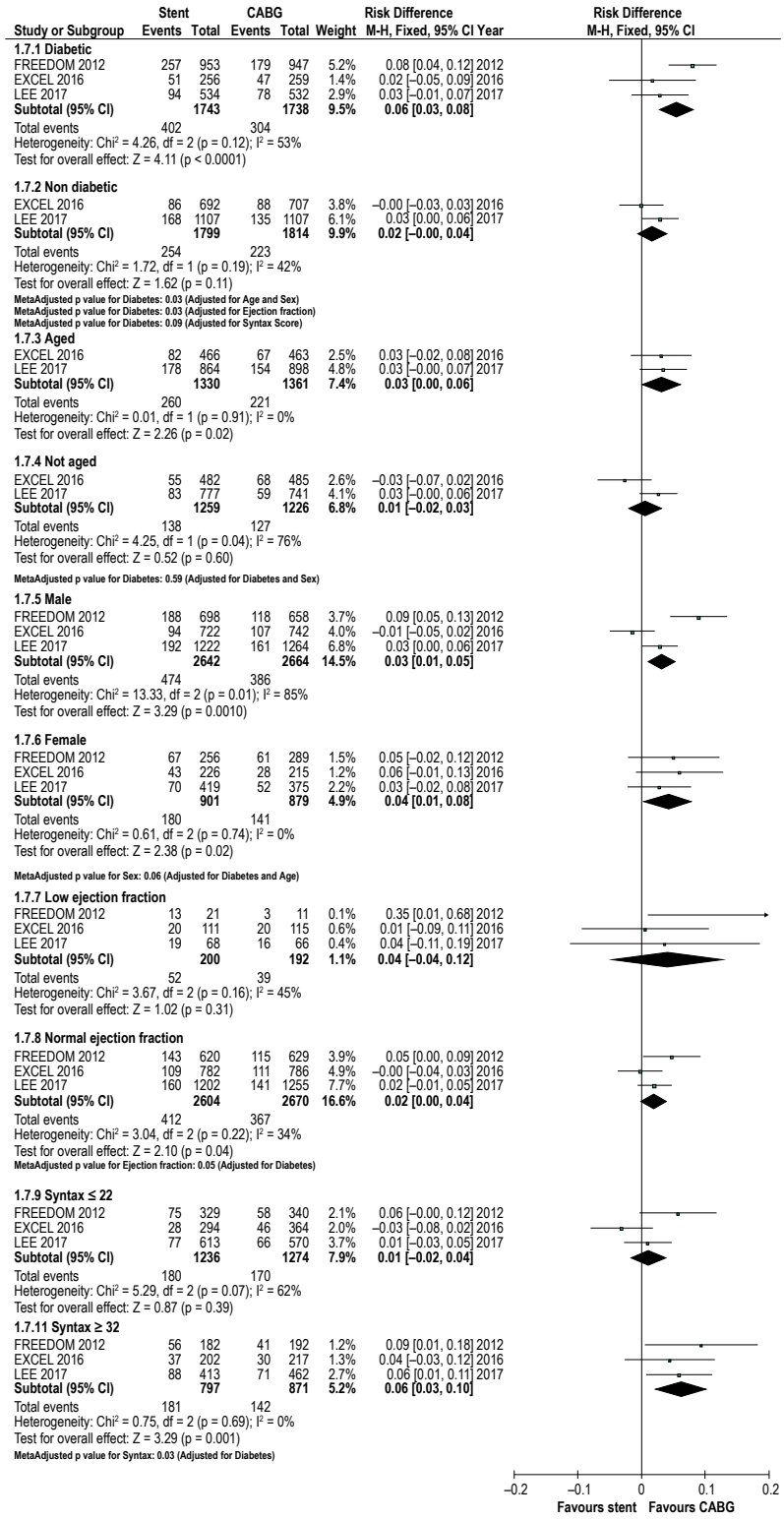

Figure 5 – *Stent versus CABG: risk difference of long-term major composite adverse outcomes (MACCE) in subgroups. The size of each box is proportional to the number of patients of the subgroups. The bars represent 95% confidence interval. The diamond represents the syntheses of results. CABG: coronary artery bypass grafting. LEE = Lee et al, J Am Coll Cardiol Intv 2016; 9:2481–9 (Meta-analysis of individual patient data of SYNTAX, PRECOMBAT and BEST); EXCEL: Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; FREEDOM, Future Revascularization Evaluation in Patients with Diabetes Mellitus. Low ejection Fraction was defined as < 50% in EXCEL and as < 40% in FREEDOM and LEE.*

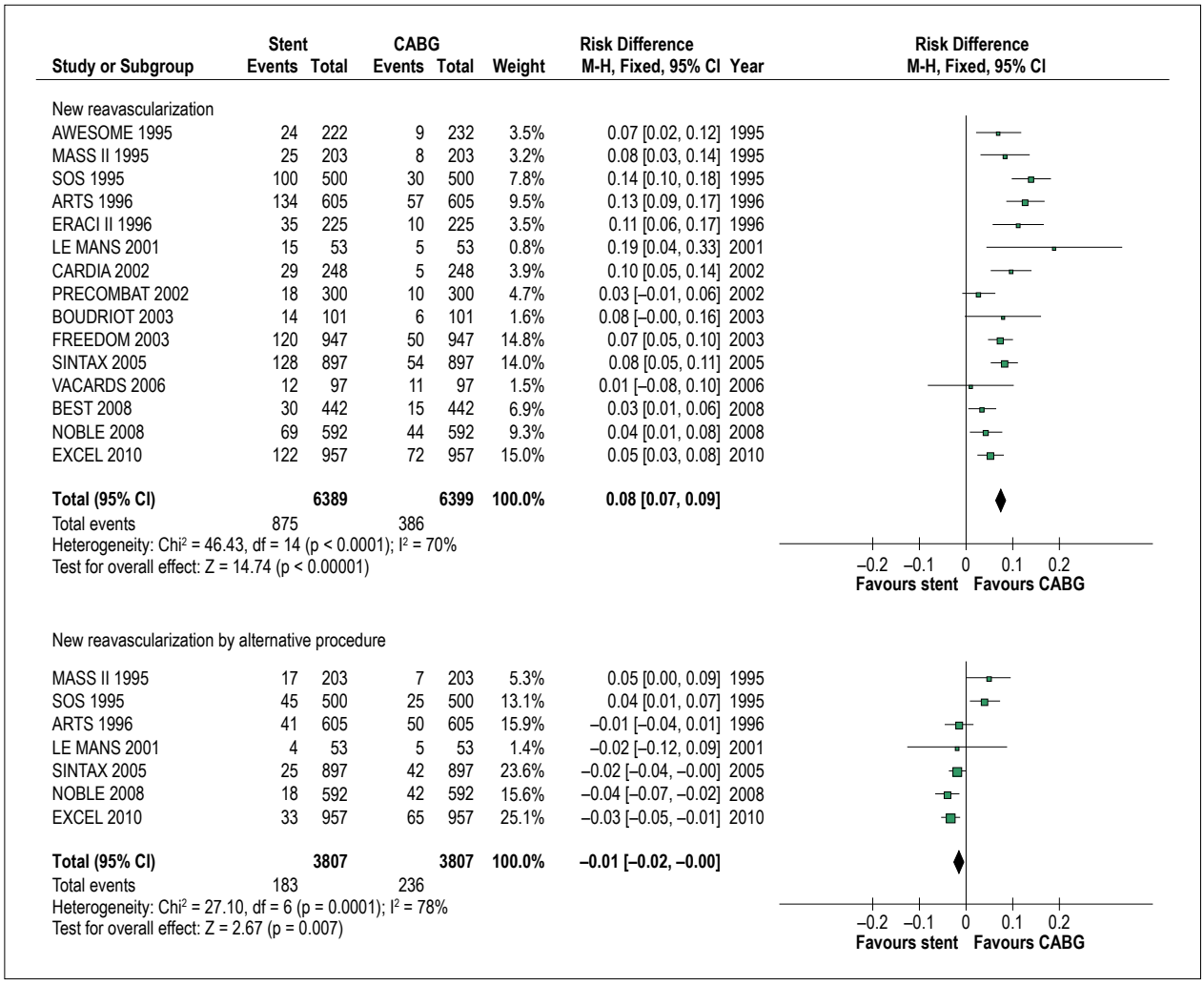

Figure 6 – *Stent versus CABG: new revascularization (top) and new revascularization by alternative procedure (bottom). The size of each box is proportional to the number of patients of the trial. The bars represent 95% confidence interval. The diamond represents the syntheses of results. DES: trials of the drug-eluting stent era; BMS: trials of the bare-metal stent trials era; CABG: coronary artery bypass grafting; ARTS: Arterial Revascularization Therapies Study; AWESOME: Angina with extremely severe outcomes; ERACI II: Argentine randomized study: coronary angioplasty with stenting versus coronary bypass surgery in patients with multi-vessel disease; MASS II: Medicine, Angioplasty, or Surgery Study; SOS: Stent or Surgery trial; BEST: Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multi-vessel Coronary Artery; Boldriot, trial of Boldriot et al: J Am Coll Cardiol. 2011; 57: 538-545. CARDia: Coronary artery revascularization in diabetic; LE MANS: Left main coronary artery stenting; EXCEL: Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; FREEDOM: Future Revascularization Evaluation in Patients with Diabetes Mellitus; NOBLE: Nordic-Baltic-British Left Main Revascularization Study; PRECOMBAT: Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease; SYNTAX: Synergy between PCI with Taxus and Cardiac Surgery; Va-Cards: Coronary Artery Revascularization in Diabetes in VA Hospitals.*

having similar mortality results, for patients with LMCAD of low or intermediate complexity (SYNTAX score < 33). This may also be the case for multi-vessel disease patients with lesions of low complexity (SYNTAX score < 23). For all other patients, particularly if diabetics, surgery remains the best form of revascularization. There is the possibility that second-generation DES and a more functional strategy, using free fractional reserve and avoiding unnecessary revascularizations will improve the comparative results of PCI in the future. The one year results of the SYNTAX II[36] study suggests that this will be true, but long-term follow-up is waited and a randomized trial with contemporary CABG is warranted.

The present study presents important limitations. It is a meta-analysis of published data and not a collaborative meta-analysis with access to individual data of patients. The inclusion of BMS era trials can also be criticized. It should also be noted that 30 days mortality and late mortality showed moderate heterogeneity, reducing the robustness of our results. Otherwise, our findings apply only to patients for whom revascularization may be performed using either method, without high surgical risk, no history of prior surgical revascularization, normal or near-normal ejection fraction and with the procedures carried out in institutions of excellence.

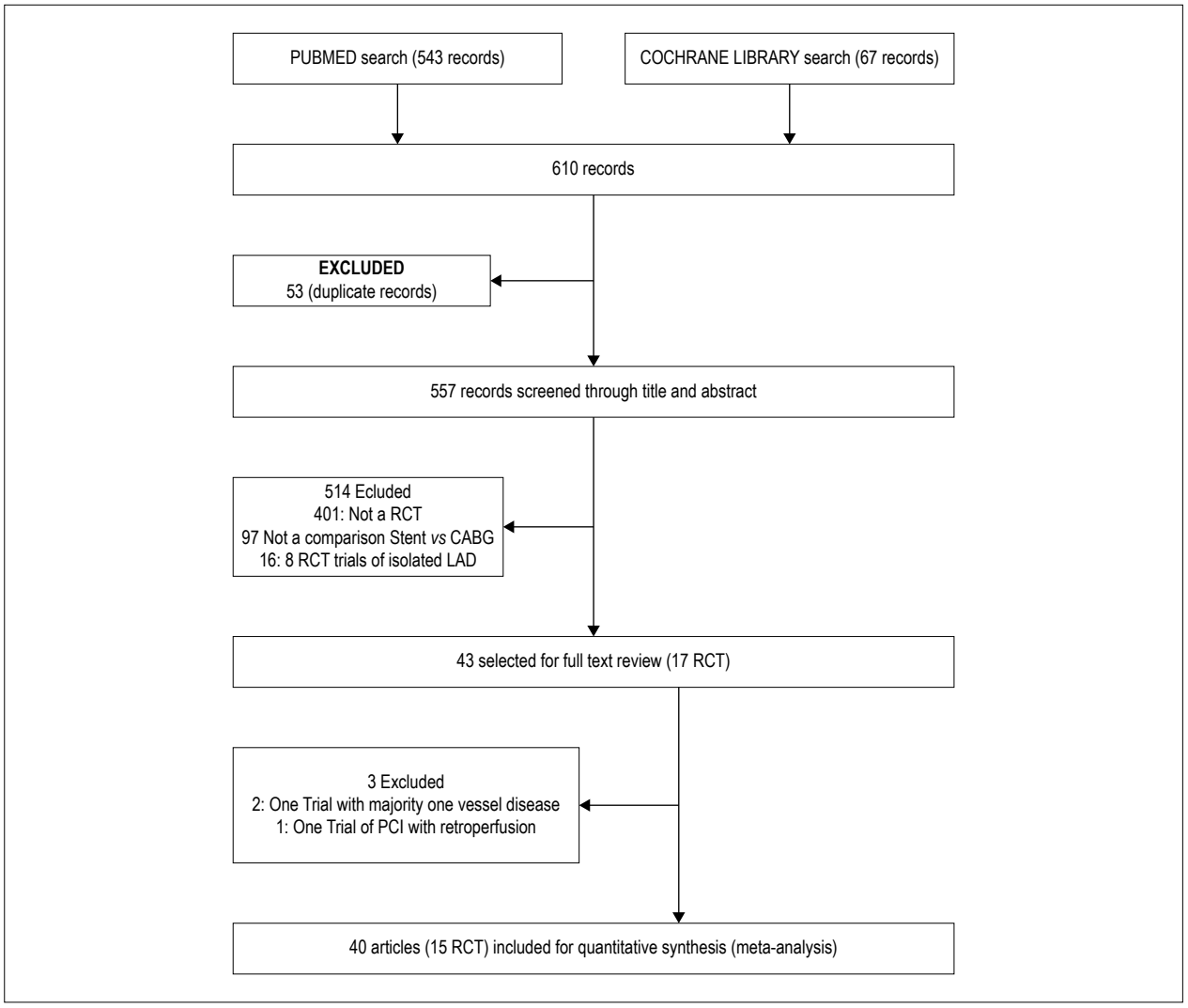

Figure 7 – *Study Flow Diagram. RCT: randomized controlled trial; CABG: coronary artery bypass grafting; LAD: left anterior descending; PCI: percutaneous coronary intervention.*

Conclusion

PCI using stents when compared to CABG was associated with a trend to lower mortality at 30 days, similar one-year mortality, lower incidence of stroke up to one-year, and a trend to higher long-term mortality. There was no long-term mortality difference in non-diabetics and in LMCAD patients. In terms of composite adverse outcomes, the SYNTAX score and diabetes were the most important factors to consider when choosing between the two methods of revascularization.

Author contributions

Conception and design of the research and critical revision of the manuscript for intellectual content: Andrade PJN; acquisition of data: Andrade PJN, Falcão JLAA, Falcão BAA; analysis and interpretation of the data and writing of the manuscript: Andrade PJN, Falcão JLAA, Falcão BAA, Rocha HAL; statistical analysis: Rocha HAL.

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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Evidence based decision making between PCI and CABG

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Short Editorial related to the article: Stent versus Coronary Artery Bypass Surgery in Multi-Vessel and Left Main Coronary Artery Disease: A Meta- Analysis of Randomized Trials with Subgroups Evaluation

For the last five decades, coronary artery bypass grafting (CABG) surgery has been recommended for patients with unprotected left main (ULM) and multivessel coronary artery disease (MVD).[1] In these populations, CABG reduces mortality compared to medical management.[2] In patients with MVD, several randomized clinical trials established the superiority of CABG over percutaneous coronary interventions (PCI) in terms of hard clinical endpoints.[3,4] In the ULM subgroup of the SYNTAX I trial, comparable outcomes between PCI and CABG were observed at five years.[5] This finding triggered the design and execution of the EXCEL and NOBLE trials that confirmed equipoise in major adverse cardiovascular and cerebral events between PCI and CABG in patients with ULM coronary artery disease (CAD).[6,7]

The accumulation of evidence has allowed to better understand which patients may benefit from a determined revascularization strategy.[8] In the current issue of the Journal, Negreiros de Andrade et al.[9] present a study-level meta-analysis comparing clinical outcomes after PCI and CABG in patients with ULMCAD and MVD. The authors should be commended for the stratified analysis aiming at providing practical information for the cardiovascular community. Based on the current state of evidence we can state that 1) in patients with ULMCAD, PCI can be considered an alternative to CABG in patients with low anatomical complexity, and 2) patients with MVD have better clinical outcomes when treated with CABG. When these two populations were combined, the present meta-analysis showed an early (<30 days) benefit of PCI in terms of mortality and stroke, and long-term advantage of CABG in death and myocardial infarction.

Heart team's interaction is the mainstay of the clinical decision-making process. Key clinical factors such as age, sex, the presence of diabetes mellitus, chronic obstructive pulmonary disease (COPD) and left ventricular ejection fraction should be accounted for in the selection between PCI and CABG. In addition, anatomical consideration based on the presence of isolated ULMCAD and/or MVD must also influence the treatment decision.[8] The SYNTAX score II was developed to aid the heart team in the decision-making process considering the interaction of between clinical variables and anatomical complexity. The score incorporates the clinical variables with the anatomical SYNTAX score providing a treatment recommendation (i.e. PCI or CABG) based on predicted 4-year mortality.[10] Mortality estimation based on individual patient profiles enhances heart team discussion, patient's information and shared decision making. Furthermore, the SYNTAX II score has been validated in contemporary clinical trials; in the EXCEL trial patients randomized to PCI in whom the SYNTAX score II recommended CABG had higher all-cause mortality at 3-year follow-up.[11] Moreover, in the SYNTAX II study, patients with MVD selected based on a mortality risk equipoise between PCI and CABG had similar outcomes compared to a matched population undergoing CABG.[12,13] A practical recommendation, supported by the findings of this meta-analysis are that: females, young patients, diabetics, low-ejection fraction and MVD with high anatomical complexity (e.g. high anatomical SYNTAX score) have better prognosis when treated with CABG, whereas in old patients, with COPD or ULMCAD with low anatomical complexity PCI is an acceptable alternative. Long term data (i.e. 10 years) from the original SYNTAX and FREEDOM have become available and showed a persistent advantage of CABG over PCI in patients with MVD.[3] Long term clinical follow-up of patients with ULMCAD included in EXCEL and NOBLE are awaited to further define the best treatment strategy.

Further refinement in the evaluation of patients with ULM and MVD can be achieved using coronary physiology indexes. Systematic use of fractional flow reserve has been shown to reduce the number of lesions that appear to be angiographically significant, reclassify a significant proportion of patients to lower SYNTAX score tertiles and improve clinical outcomes compared to angiographic-guided PCI and optimal medical therapy.[14-16] A Comparison of Fractional Flow Reserve-Guided Percutaneous Coronary Intervention and Coronary Artery Bypass Graft Surgery in Patients With Multivessel Coronary Artery Disease (FAME 3) will further provide answers on the best revascularization strategy tailoring treatment decision based on coronary physiology. In the near future, virtual tool predicting functional improvement after PCI or CABG will further refine patients' selection potentially improving clinical outcomes in stable CAD.

Keywords

Myocardial Revascularization/mortality; Percutaneous Coronary Intervention; Drug-Eluting Stents; Stents; Coronary Vessels; Randomized Controlled Trials; Clinical Decision Making

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Analysis of the Appropriate Use Criteria for Coronary Angiography in Two Cardiology Services of Southern Brazil

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Abstract

Background: Despite its great relevance, there are no studies in our country evaluating the application of the 2012 guidelines for the appropriate use of cardiac diagnostic catheterization.

Objective: To analyze the adequacy of coronary angiography performed in two hospitals in the southern region of Brazil.

Methods: This is a multicenter cross-sectional study, which analyzed indications, results and proposals for the treatment of 737 coronary angiograms performed in a tertiary hospital with multiple specialties (Hospital A) and a tertiary cardiology hospital (Hospital B). Elective or emergency coronary angiographies were included, except for cases of acute myocardial infarction with ST segment elevation. The level of statistical significance adopted was 5% ($p < 0.05$).

Results: Of the 737 coronary angiograms, 63.9% were performed in male patients. The mean age was 61.6 years. The indication was acute coronary syndrome in 57.1%, and investigation of coronary artery disease in 42.9% of the cases. Regarding appropriation, 80.6% were classified as appropriate, 15.1% occasionally appropriate, and 4.3% rarely appropriate. The proposed treatment was clinical for 62.7%, percutaneous coronary intervention for 24.6%, and myocardial revascularization surgery for 12.7% of the cases. Of the coronary angiographies classified as rarely appropriate, 56.2% were related to non-performance of previous functional tests, and 21.9% showed severe coronary lesions. However, regardless of the outcome of coronary angiography, all patients in this group were indicated for clinical treatment.

Conclusion: We observed a low number of rarely appropriate coronary angiograms in our sample. The guideline recommendation in these cases was adequate, and no patient required revascularization treatment. Most of these cases are due to non-performance of functional tests. (Arq Bras Cardiol. 2019; 112(5):526-531)

Keywords: Coronary Angiography; Coronary Artery Disease/diagnostic imaging; Acute Coronary Syndrome; Percutaneous Coronary Intervention; Multicenter Study; Epidemiology.

Introduction

The management of coronary artery disease (CAD), the leading cause of mortality in the developed world, is based on the use of diagnostic and therapeutic procedures. Six decades after the first selective coronary angiography performed by Dr. Sones under improbable circumstances,[1] coronary angiography remains the gold standard for diagnosis of CAD,[2] although noninvasive methods have progressively gained some space.[3]

Advances in medical technology were followed by rising costs, motivating research on cost-effectiveness issues. The identification of the exaggerated use of medical procedures has led to questions about when they will actually be needed.[4] In 2011 a significant drop in the rate of inappropriate angioplasties in the American state of New York was observed after the government announced that the payment would be connected to appropriation. That is, the financial question influenced the selection of patients for angioplasty. Analyzes of appropriate use should follow the progression of ways of financing.[5]

In an effort to present criteria for rational use of cardiology services, the American College of Cardiology Foundation, and 11 other medical entities have issued the 2012 guideline for appropriate use of diagnostic cardiac catheterization. This recommendation has the potential to impact clinical decisions, the quality of health care, and health policies through the efficient use of resources.[6]

In Brazil, this issue was previously studied with the 1999 guideline. An analysis of 145 coronary angiograms in patients with suspected stable ischemic disease was published in 2005. It was also observed that 34.5% of the indications were appropriate, and 65.5% uncertain, or inappropriate.[7] Also, based on the 1999 guideline, an Italian group studied the indications of 460 coronariographies, with no inappropriate angiography in its sample.[8] Based on the perspectives of the 2012 guideline, the indications of

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coronary angiography in New York,[9] and in a large Canadian cohort of patients suspected of having a stable CAD, were evaluated.[10] The results in the literature are discordant regarding the validation of the guideline, generating concern about its reliability to guide decision-making.[10]

The objective of this study is to analyze the appropriation of coronary angiographies performed in two hospitals in the southern region of Brazil in accordance with the 2012 guidelines.

Methods

This is an observational, cross-sectional, multicenter study. The two centers together perform more than 1,700 procedures per year; one of them is a tertiary hospital with multiple specialties (Hospital A) and the other a tertiary cardiology hospital (Hospital B). All the elective or emergency coronary angiograms were included in the period from May to October 2016. Catheterizations performed in cases of acute myocardial infarction with ST segment elevation were excluded. The information was entered into a database at the time of the procedure. The work was approved by the Research Ethics Committees of the institutions involved.

All indications were classified as appropriate, occasionally appropriate, or rarely appropriate, according to current terminology,[11] and following the 2012 guidelines for appropriate use of diagnostic cardiac catheterization. In this guideline, indications are divided into three broad groups: 1. Evaluation of CAD; 2. Evaluation due to conditions other than CAD (valvar, pericardial or cardiomyopathy diseases); 3. Right heart catheterization. The guideline covers 102 possible indications, which were classified by a score that combines evidence-based medicine and practical experience of the members of a technical panel. Each indication received an average score of 1 to 9, being classified as appropriate when between 7 and 9, occasionally appropriate when between 4 and 6, and rarely appropriate when between 1 and 3.[6]

The analysis also included age, sex, clinical status, coronary angiographic findings regarding the presence of obstructive disease, and the treatment proposal.

The clinical picture was simply characterized as an acute coronary syndrome (ACS) or as a stable condition, which included all patients who did not fit the first group. ACS was characterized by presenting with typical chest pain at rest or in progress, associated or not with the electrocardiographic alteration suggestive of ischemia (ST segment depression and/or T wave alteration), and may or may not be associated with changes in myocardial necrosis markers.[12]

In order to check if the recommendation of the guideline adequately predicts the angiographic result and therapeutic perspective, the coronary angiography result was classified according to the extent of the severe CAD, and the treatment proposal for each case was documented.

A reduction of greater than or equal to 50% in the diameter of the left coronary artery trunk (LCT), and greater than or equal to 70% for the other vessels, was considered severe, either by visual angiographic evaluation or by quantitative angiography, with the projection in which the lesion was more severe being chosen.[11,13]

Patients with severe LCT lesions were classified regardless of the presence of other severe lesions.

The treatment proposal was defined by the hemodynamicist in charge, after coronary angiography, and may be clinical treatment, coronary angioplasty or myocardial revascularization surgery, according to available clinical data and the anatomical result found in the examination.

Data analysis was performed in order to also allow the comparison between two services with different profiles, with Hospital A being a general hospital and Hospital B a reference center for high complexity in cardiology in the state, with a large flow of coronary patients in its emergency service. The two services are provided exclusively by the Unified Health System (SUS).

Statistical Analysis

For data analysis, the IBM SPSS Statistics 23 software (IBM Corp. Released 2015, IBM SPSS Statistics for Windows, Version 23.0, Armonk, NY: IBM Corp.) was used. The results were expressed in numbers and (absolute and relative) proportion, for categorical variables, and in measures of central trend (mean) and dispersion (standard deviation) for continuous variables. The chi-square test was used to study possible associations between categorical variables. For the comparison between continuous variables, the unpaired Student t test was used. The Kolmogorov-Smirnov test was applied to evaluate the sample normality assumption. The level of statistical significance adopted was 5%, considering a 95% confidence interval.

Results

Of the 737 coronary angiograms analyzed, 76.8% were performed at Hospital B, 63.9% in male patients. The mean age was 61.6 years. The indication for coronary angiography was due to ACS in 57.1%, and CAD investigation in 42.9% of the cases. Regarding appropriation, 80.6% of the coronary angiograms were classified as appropriate, 15.1% occasionally appropriate, and 4.3% rarely appropriate. We observed that 41.2% of coronary angiograms did not show severe CAD, 27.4% severe single-vessel CAD, 17.2% two-vessel CAD, 11.3% three-vessel CAD, and 2.8% severe LCT lesion. The proposed treatment was clinical for 62.7% of the patients, percutaneous coronary intervention for 24.6%, and myocardial revascularization surgery for 12.7% of the cases.

There was no statistically significant difference in the prevalence of male and female patients between the two institutions (Table 1). The mean age was 59.1 years in Hospital A, and 62.3 years in Hospital B ($p < 0.05$).

All patients with ACS have appropriate indication for coronary angiography. In this group of patients there was no statistically significant difference regarding the distribution by gender, coronary angiography result and treatment (Table 2).

Among the stable patients, there was a lower proportion of patients with appropriate indications in Hospital A compared to Hospital B and a higher proportion of occasionally appropriate ones. Among the stable patients, no difference was observed regarding the distribution by gender, outcome and treatment. There was a higher incidence of indication

Table 1 – Distribution of patients between the two institutions according to gender, clinical presentation, classification of appropriate use, coronary angiography result and treatment

		Source				
		Hospital A		Hospital B		
		Score n = 171	%	Score n = 566	%	
Gender	Female	70	40.9%	196	34.6%	p = 0.132
	Male	101	59.1%	370	65.4%	
Clinic	ACS	46	26.9%	375	66.3%	p < 0.001
	Stable	125	73.1%	191	33.7%	
Evaluation of appropriation	Rarely Appropriate	10	5.8%	22	3.9%	p = 0.084
	Occasionally Appropriate	61	35.7%	50	8.8%	p < 0.001
	Appropriate	100	58.5%	494	87.3%	p < 0.001
Result	Normal	90	52.6%	214	37.8%	p = 0.008
	Single-vessel	38	22.2%	164	29.0%	p = 0.078
	Two-vessel	27	15.8%	100	17.7%	p = 0.568
	Three-vessel	12	7.0%	71	12.5%	p = 0.045
	LCT	4	2.3%	17	3.0%	p = 0.647
Treatment	Clinical	122	71.3%	340	60.1%	p < 0.001
	Angioplasty	31	18.1%	150	26.5%	p = 0.025
	Surgical	18	10.5%	76	13.4%	p = 0.318

*ACS: acute coronary syndrome; LCT: left coronary artery trunk. * Statistical significance analyzes performed using the chi-square test.*

Table 2 – Distribution of patients with ACS within the two institutions according to gender, result of coronary angiography and treatment

		Source				
		Hospital A		Hospital B		
		Score n = 46	%	Score n = 375	%	
Gender	Female	19	41.3%	124	33.1%	p = 0.266
	Male	27	58.7%	251	66.9%	
Result	Normal	10	21.7%	96	25.6%	p = 0.569
	Single-vessel	12	26.1%	126	33.6%	p = 0.305
	Two-vessel	15	32.6%	81	21.6%	p = 0.093
	Three-vessel	6	13.0%	57	15.2%	p = 0.698
	LCT	3	6.5%	15	4.0%	p = 0.424
Treatment	Clinical	20	43.5%	188	50.1%	p = 0.394
	Angioplasty	19	41.3%	130	34.7%	p = 0.374
	Surgical	7	15.2%	57	15.2%	p = 0.997

*ACS: acute coronary syndrome; LCT: left coronary artery trunk. * Statistical significance analyzes performed using the chi-square test.*

for preoperative cardiac surgery exams at Hospital B when compared to Hospital A, and a predominance of CAD investigation at Hospital A (Table 3).

Of the 737 patients, 32 (4.3%) had their coronary angiography classified as rarely appropriate. Of these, 18 cases (56.2%) were related to non-performance of previous functional tests; six (18.8%) were asymptomatic patients or those with stable symptoms who underwent prior revascularization; six (18.8%) were stable asymptomatic non-cardiac surgery patients with functional capacity ≥ 4 METS; one (3.1%) had known CAD receiving clinical treatment, and with low-risk findings in noninvasive tests, or stable symptoms, and one (3.1%) with mild or moderate aortic valve stenosis of native or prosthetic valve, and asymptomatic regarding valve disease.

Among those classified as rarely appropriate, seven cases (21.9%) had severe coronary lesions but, regardless of the result of the coronary angiography, all patients in this group

Table 3 – Distribution of patients being investigated for CAD within the two institutions according to gender, assessment of appropriation, reason for indication, result of coronary angiogram and treatment

		Source				
		Hospital A		Hospital B		
		Score n = 125	%	Score n = 191	%	
Gender	Female	51	40.8%	72	37.7%	p = 0.580
	Male	74	59.2%	119	62.3%	
Evaluation of Appropriation	Appropriate	54	43.2%	119	62.3%	p <0.001
	Occasionally Appropriate	61	48.8%	50	26.2%	p <0.001
	Rarely Appropriate	10	8%	22	11.5%	p = 0.317
Reason for Indication	Diagnosis of CAD	97	77.6%	114	59.7%	p <0.001
	Reassessment of CAD	14	11.2%	33	17.3%	p = 0.146
	Pre-Op. of Cardiac Surgery	6	4.8%	40	20.9%	p <0.001
	Pre-Op. of Non-Cardiac Surgery	8	6.4%	4	2.1%	p = 0.049
Result	Normal	80	64%	118	61.8%	p = 0.690
	Single-vessel	26	20.8%	38	19.9%	p = 0.844
	Two-vessel	12	9.6%	19	9.9%	p = 0.919
	Three-vessel	6	4.8%	14	7.3%	p = 0.366
	LCT	1	0.8%	2	1%	p = 0.824
Treatment	Clinical	102	81.6%	152	79.6%	p = 0.658
	Angioplasty	12	9.6%	20	10.5%	p = 0.801
	Surgical	11	8.8%	19	9.9%	p = 0.733

*CAD: coronary artery disease; LCT: left coronary artery trunk. * Statistical significance analyzes performed using the chi-square test.*

were indicated for clinical treatment. Of the seven patients, in four (57.1%) lesions were observed in vessels of fine caliber (< 2 mm); in two (28.6%), there were distal lesions in vessels of fine caliber, and one (14.3%) underwent coronary angiography due to moderate aortic valve stenosis, being asymptomatic from the cardiological point of view.

In 13.5% of those classified as occasionally appropriate, and in 43.8% of the appropriate, the option was either percutaneous or surgical revascularization.

Discussion

The balance between cost and effectiveness is necessary because funding sources are pressed by increased demand, technology, and consequently, resources. The rational use of these resources is part of the physician's social responsibility.[4] Even so, many cardiologists believe that angioplasty is beneficial for patients with stable CAD, and the approach continues to be the search for ischemia. It is not surprising that a substantial minority of cardiologists believe that angioplasty and coronary stenting prevent myocardial infarction. These beliefs are seen in practice with poor application of resources: it is estimated that up to half of elective angioplasties may be inappropriate.[14] This reality also applies to diagnostic methods, such as coronary angiography.[7,9]

Historically there is great international variability in the proper use of diagnostic cardiac catheterization. This issue was studied in more than ten countries between 1987 and 2006, with appropriate use rates between 34.5%[7] and 91%,[15] with most studies showing rates of appropriation above 72%.[16]

Differently from other large multicenter retrospective studies analyzing the 2012 guideline for appropriate use of diagnostic cardiac catheterization,[9,10] the present study validates the guideline when we relate the adequacy of coronary angiography and the treatment. Another relevant aspect is the possibility of analyzing the characteristics of two institutions with different profiles (general tertiary hospital and tertiary cardiology hospital) within the same micro-region. In addition, although the 2012 guideline still uses the classification of appropriate, uncertain and inappropriate, we chose to use the most current classification of appropriate, occasionally appropriate and rarely appropriate, used in the most recent guidelines.[11]

We included the cases of ACS in our analysis, which were not included in other studies, because it is the subgroup of patients that accounts for the main difference between the centers studied, and due to the relevance of documenting these institutional characteristics. The cases of ACS do not qualitatively stratify coronary angiography indications, since, in these cases, all of them are classified as appropriate. We observed the expected predominance of these cases in the cardiology hospital (Hospital B), and higher prevalence of stable patients in the general hospital (Hospital A) (Table 1). To analyze the quality of the indications for coronary angiography, the analysis of the subgroup of patients in the CAD investigation was performed.

The results of analysis of a large retrospective cohort with 48,336 patients with suspected stable CAD in the region of Ontario, Canada, were published in 2015.[10] In the Canadian study, rates of 58.2% of appropriate cases, 31% of occasionally appropriate ones, and 10,8% of rarely appropriate cases were observed, which are similar to those found in our sample of patients being investigated for CAD, with 54.7% classified as appropriate, 35.1% occasionally appropriate, and 10.2% rarely appropriate.

Despite the apparent balance in the proportion of indications, while 18.9% of the patients classified as rarely appropriate in the Canadian study underwent revascularization procedures, 100% of the patients so classified in our study were referred for clinical treatment despite the presence of severe coronary lesions. This can be explained by the presence of distal lesions in thin or minor vessels that make clinical treatment the best option in this context. This information validates the application of the guideline in our population, since patients with an indication of rarely appropriate for coronary angiography would not have an indication of treatment of revascularization as a complement to the optimal drug therapy.

Another large retrospective study in the state of New York analyzed the indications of 8,986 coronary angiographies, and found that 24.9% of their cases were classified as rarely appropriate,[9] a number that is considerably larger than the 10.8% and 10.2% in the Canadian study and in our sample, respectively. To explain why about a quarter of cases were classified as rarely appropriate, it was argued that at the time of coronary angiography, the 2012 guideline for the appropriate use of diagnostic cardiac catheterization had not yet been published. However, the situation is similar to that of the Canadian cohort, which had its coronary angiograms performed between 2008 and 2011, and presented more modest proportions of rarely appropriate coronary angiograms. A significant portion of the rarely appropriate coronary angiographies enters this classification due to non-performance of previous functional tests,[16,17] a situation that is responsible for 56.2% of these cases in our sample. The performance of functional tests would provide the reclassification of these cases, improving the use of coronary angiography.[6,17,18]

When we observed the differences between the two institutions involved in the present study, a higher proportion of coronary angiographies with appropriate indication at Hospital B, and a higher proportion of occasionally appropriate at Hospital A (Table 3) were evident in the subgroup of patients being investigated for CAD. The highest proportion of preoperative cardiac surgery tests performed at Hospital B, an indication classified as appropriate by the guideline,[6] explains part of this difference. The performance of cardiac surgeries in Hospital B, an institution dedicated to cardiology, appears as the main factor for the difference of appropriation between the two institutions.

The limitations of our study are the reduced size of its sample, which precludes a detailed analysis of each indication of the guideline; and failure to follow patients for prognostic evaluation related to outcome and treatment. In addition, more than 50% of our sample are cases of ACS, in which invasive stratification is appropriate according to the guideline, limiting the analysis of the quality of the indication in this scenario. The results represent the reality of the patients treated in two public hospitals located in the southern region of Brazil. Further studies are necessary to evaluate the indications of coronary angiography in other contexts and regions of the country.

Conclusion

We conclude that our sample has appropriation indices similar to those in the literature, with a small rate of rarely appropriate procedures. The guideline recommendation in rarely appropriate cases was adequate in our study, with no patients in this group requiring revascularization treatment. Most of these cases are due to non-performance of previous functional tests.

The difference between the two hospitals, a general and a cardiology hospital, was inherent in the population served, with similar adjusted appropriate use rates.

Author contributions

Conception and design of the research: Luciano LSC, da Silva RL; Acquisition of data: Luciano LSC, da Silva RL, Waldrich L, Panata L, Preve JC, Fattah T, Giuliano LC, Thiago LEKS; Analysis and interpretation of the data: Luciano LSC, da Silva RL, Londero Filho OM; Statistical analysis: Luciano LSC, da Silva RL, Trombetta AP;Writing of the manuscript: Luciano LSC, da Silva RL; Critical revision of the manuscript for intellectual content: Luciano LSC, da Silva RL, Londero Filho OM, Trombetta AP, Preve JC, Giuliano LC, Thiago LEKS.

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 Instituto de Cardiologia de Santa Catarina under the protocol number CAAE 83732218.8.0000.0113. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. As it was not an experimental study, the informed consent was dispensed by the Ethics Committee.

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Appropriate Use Criteria for Coronary Angiography at Two Hospitals in Southern Brazil: "Doing the Right Things And Doing Things Right"

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Short Editorial related to the article: Analysis of the Appropriate Use Criteria for Coronary Angiography in Two Cardiology Services of Southern Brazil

Cardiovascular disease and particularly coronary artery disease (CAD) remain a global health issue,[1] notwithstanding major advances in cardiovascular care that have resulted in a reduction in CAD mortality over the last decades.[2] Indeed, the most recent trends point towards a bottoming out of CAD mortality rates and, for certain subgroups, rates might even be increasing.[3] The reasons for these alarming trends relate to the prevalence of risk factors, health care system failures in dealing with chronic diseases, unequal access to technology, decreasing levels of investment in cardiovascular research, and persistent heterogeneity in the quality of care.[4]

In contrast, cardiovascular health care costs continue to follow a linear upward trend.[5] As a consequence, the delivery of high-value cardiovascular care has been reduced.[6] In the long run, cardiovascular research and innovation should stimulate the development of novel drugs and therapies. In the short term, for struggling health care systems facing escalating costs, avoiding inappropriate tests and ineffective therapies is part of a value-based healthcare agenda.[7,8] The fundamental concept of moving from volume to value may mitigate conflicting expectations among payers, providers, patients and physicians, who should share a common objective of reducing unwarranted health costs while improving outcomes.[9]

However, it is time for this agenda to be transformed from discussion into action. Taking the lead in this transformation over the last decade, physicians representing the North American medical societies have come together to provide evidence-based recommendations and expert opinions for a range of diagnostic and therapeutic procedures. These evolving recommendations, namely Appropriate Use Criteria (AUC), aim to assist physicians in providing high-value cardiovascular care.

In this issue of Arquivos Brasileiros de Cardiologia, Luciano et al.[10] present results on the use of AUC for diagnostic catheterization (DC) in Brazil.[10] From May to October 2016, data were obtained for DC performed at two tertiary hospitals (a general hospital vs. a cardiology hospital). The authors collected data that allowed appropriateness scores to be assigned for each DC, namely, "appropriate" (7 to 9), "occasionally appropriate" (4 to 6) or "rarely appropriate" (1 to 3). Of note, according to the original AUC, the same scoring system was used, but the descriptive terms used were "appropriate", "uncertain" and "inappropriate", respectively.[11] Additionally, the authors compared each of the three AUC categories between hospitals and with the presence of CAD. The presence of obstructive CAD was defined as angiographic obstruction of more than 50% in the left main coronary artery or 70% elsewhere.

The sample included 737 DC in patients with a mean age of 62 years. Taken together, 80.6% of the exams were deemed appropriate according to AUC criteria, and 15.1% occasionally appropriate (uncertain), while 4.3% were rarely appropriate (inappropriate). Among similar studies, the rates of appropriate, uncertain and inappropriate use of diagnostic catheterization were 52.8%, 31% and 10.8% in Ontario, and 35%, 40% and 25% in New York, respectively.[12,13] Notably, in the Brazilian study, the rate of inappropriate use in stable patients only (~10.1%) was similar to that in the Ontario cohort (10.8%) and roughly two-fold lower than in the US study. Interestingly, both Canada and Brazil have public universal health systems, which differ from that in the United States, where the health system is predominately financed by private funds.[9]

The second finding that deserves careful attention is the lack of severe obstructive CAD in 41.2% of DC. Although this frequency is lower than that in the Canadian cohort (54.5%), it stills represents an important source of cardiovascular expenditure that can be improved through a comprehensive and specialized assessment (pre-test probability). Indeed, the frequency of normal DC findings was significantly lower at the specialized cardiology hospital than at the general hospital (37.8% vs. 52.6%; $p = 0.008$), despite a three-times higher volume at the former. Moreover, among patients under CAD investigation, the rates of appropriate DC were significantly higher at the cardiology hospital compared with the general hospital (87.3% vs. 58.5%; $p < 0.01$). Therefore, these results constitute indirect evidence of higher quality performance in high-volume and specialized centers of cardiovascular care.

There are a number of caveats relating to the study. First, the sample size was relatively small. Second, the AUC categorization was made by the same non-blinded physician who performed the DC and participated in the final decision on whether to proceed with intervention. Third, neither baseline risk factors nor stress test findings were reported, particularly for the general hospital that had a higher proportion of CAD investigation (stable patients)

Keywords

Coronary Artery Disease/diagnostic imaging; Coronary Angiography; Síndrome Coronariana Aguda; Percutaneous Coronary Intervention/methods; Epidemiology.

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compared with cardiology hospital (73% vs. 34%) Fourth, there was a lack of functional and intravascular invasive imaging assessments. Finally, the sample included only patients from the public health system and clinical outcomes were not presented.

A further interesting finding of Luciano et al.[10] relates to the reasons behind the rarely appropriate (inappropriate) category of DC and the decision-making upstream. The higher the frequency of inappropriate DC, the more likely the frequency of further inappropriate interventions, a phenomenon called the "diagnostic-therapeutic cascade".[14] The danger of this cascade was averted in the two Brazilian hospitals, however, where ALL patients rated as receiving an inappropriate DC, 21.9% of whom had severe obstructive CAD, remained under clinical treatment, which was carried out according to the best evidence available. We commend the authors and physicians for "doing the right things AND doing things right", thus benefiting patients and the health care system.

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Thermoregulation in Hypertensive Rats during Exercise: Effects of Physical Training

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Abstract

Background: **Spontaneously hypertensive rats (SHR) show deficit in thermal balance during physical exercise.**

Objective: **To assess the effects of low-intensity physical exercise training on thermal balance of hypertensive rats undergoing an acute exercise protocol.**

Methods: **Sixteen-week-old male Wistar rats and SHR were allocated into four groups: control Wistar rats (C-WIS), trained Wistar (T-WIS), control SHR (C-SHR) and trained SHR (T-SHR). Treadmill exercise training was performed for 12 weeks. Blood pressure, resting heart rate and total exercise time was measured before and after the physical exercise program. After the exercise program, a temperature sensor was implanted in the abdominal cavity, and the animals subjected to an acute exercise protocol, during which core temperature, tail skin temperature and oxygen consumption until fatigue were continuously recorded. Mechanical efficiency (ME), work, heat dissipation threshold and sensitivity were calculated. Statistical significance was set at 5%.**

Results: **Physical training and hypertension had no effect on thermal balance during physical exercise. Compared with C-WIS, the T-WIS group showed higher heat production, which was counterbalanced by higher heat dissipation. Hypertensive rats showed lower ME than normotensive rats, which was not reversed by the physical training.**

Conclusion: **Low-intensity physical training did not affect thermal balance in SHR subjected to acute exercise. (Arq Bras Cardiol. 2019; 112(5):534-542)**

Keywords: **Rats; Hypertension; Exercise/physiology; Physical Exertion; Body Temperature Changes; Fatigue.**

Introduction

During exercise, elevation of core temperature (Tcore) results from an imbalance between heat production and dissipation, since heat production increases exponentially before the mechanisms of heat dissipation are activated.[1,2] Hyperthermia may be a sign that individuals will reach fatigue and interrupt exercise, and hence an adequate control of the Tcore is critical for maintenance of physical performance.[3]

Arterial hypertension is a public health problem in the world and considered one of the main risk factors for cardiovascular diseases.[4] Among the experimental models used in studies on the pathophysiology of arterial hypertension, the spontaneously hypertensive rats (SHR) is the most commonly used. Similar to humans, SHR develop progressive left ventricular hypertension in response to blood pressure elevation and to increased peripheral vascular resistance.[5,6]

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In recent studies of our group, we observed that untrained SHR showed disturbances in the regulation of body temperature during acute physical exercise. During exercise, hypertensive animals showed lower heat dissipation and higher heat production, leading to marked increase in Tcore compared with normotensive animals.[7,8] This was associated with lower mechanical efficiency (ME) in hypertensive animals.[7]

Several benefits of aerobic physical training have been demonstrated in hypertensive individuals, including reduction of blood pressure, improvement of cardiac function, and reduction in total peripheral resistance.[9,10] However, the effects of low-intensity, aerobic physical training on thermal balance in hypertensive animals have not been investigated.

Thus, the present study aimed to evaluate the effects of low-intensity physical training on thermal balance of hypertensive rats subjected to an acute physical exercise protocol. We tested the hypothesis that low-intensity exercise could promote positive adaptations and reversal of the effects on the thermal balance in SHRs.

Methods

Experimental animals

Sixteen-week-old normotensive Wistar rats and SHR were randomly stratified into four groups: control Wistar rats (C-WIS,

n = 8), trained Wistar (T-WIS, n = 8), control SHR (C-SHR, n = 8) and trained SHR (T-SHR, n =8). Sample size was determined based on sample size calculation.[11] The animals were housed in group cages in a temperature-controlled room under a 12-h light-dark cycle, and had free access to water and food. Systolic blood pressure (SBP), diastolic blood pressure (DPB) and mean blood pressure (MBP) were measured using tail plethysmography (LE5001; Panlab, Spain). Resting heart rate (RHR) was measured through the sensor placed on the tail, connected to a computer system (PowerLab 4/30; LabChart/ADInstruments, USA) before the first and 48 hours after the last session of physical training. All exercise protocols were approved by the Ethics Committee of Universidade Federal de Viçosa (Protocol # 76/2014) and conducted according to the Helsinki declaration.

Physical training protocol

Prior to the beginning of exercise training, rats were adapted to a motorized treadmill (Insight Instruments, Brazil), five minutes/day at 5 m/min for five days. In addition, all animals underwent an incremental exercise test (starting at 5 m/min, increasing by 3 m/min every 3 minutes until fatigue) at the beginning of the study, at week 4 and at week 8 of training to determine total exercise time (TET) and maximum running speed (MRS). The exercise program was performed five days a week, 60 minutes/day, at 50-60% MRS for 12 weeks, in a temperature-controlled room (approximately 22ºC). Both intensity and duration of exercise were gradually increased as proposed by Lavorato et al.[12] Animals of the control group were handled in the same manner as the hypertensive group and underwent the same treadmill exercise program two days a week, 5 minutes/day at 5 m/minute.[12]

Experimental protocol following the physical training

Familiarization with the experimental protocol

The animals were familiarized with the treadmill (Panlab, Harvard Apparatus, Spain) – five minutes per day, 5 degrees of inclination for three consecutive days, at 11 m/min, 13 m/min and 15 m/min). A thermocouple was taped to the tail of the rat and the electrical stimulation delivered at 0.4 – 0.6 mA.[7] This protected the animals from having their legs wrapped around the thermocouple wire and reduced their exposure to electrical stimulation during the running test.[13]

Temperature sensor implantation

Immediately prior to the surgery, the animals received a prophylactic dose of antibiotic (enrofloxacin 10 mg. kg-1, intramuscular) and analgesics (tramadol, 4 mg.kg^{-1}, subcutaneously). Anesthesia was induced with 1.5% isoflurane (BioChimico, Brazil) and 100% oxygen (White-Martins, Brazil) at constant flow of 1L/min. Following preparation of the incision site, a temperature sensor (G2 E-Mitter, Mini-Mitter, USA) was implanted in the abdominal cavity.[14] After this procedure, the animals were housed in individual boxes and received two additional doses of tramadol in regular intervals of 8 hours.

Acute physical exercise protocol

After 48 hours of recovery from the surgery, each animal underwent to two exercise sessions at constant speed (60% of MRS), 5º slope and electrical stimulation (0.4-0.6 mA) until fatigue. Treadmill speed was 16.0 ± 0.4 m/min; 23.0 ± 0.7 m/min; 16.2 ± 0.5 m/min; 19.6 ± 0.8 m/min for C-WIS, T-WIS, C-SHR and T-SHR, respectively. Fatigue was defined as the point when the animals were unable to keep pace with the treadmill. The animals received electrical stimulation up to ten seconds.[15] The experimental conditions were randomized and balanced. All exercise sessions were carried out from 7 to 12 o'clock, with 48-hour interval between the sessions.

During each session, Tcore, skin temperature (T_{skin}) and VO_2 were recorded every minute. Measurements of the Tcore were made by telemetry (ER-4000 energizer/receptor, Mini-Mitter Respironics, USA). T_{skin} was measured using a thermometer (THR-140, Instrutherm Instruments, Brazil) connected to a thermocouple (S-09K, Instrutherm Instruments, Brazil) using an impermeable adhesive tape at approximately 20 mm from the lateral base of the tail.[16] VO_2 (ml.Kg$^{-0.75}$.min^{-1}) was measured by an open-circuit indirect calorimetry system (Panlab, Harvard Apparatus, Spain). The temperature was maintained at 25ºC throughout the exercise session.

Calculations

Work (W) = body mass (Kg)·force of gravity (9.8 m/s^2) ·TET (min)·treadmill speed (m.min^{-1})·cos θ (treadmill slope).[17] ME = (W/energy cost)·100.[7]

The threshold for cutaneous heat loss was defined as the mean Tcore registered at the time when T_{skin} significantly increased from the lowest measure registered during exercise.[8]

Heat loss sensitivity was calculated from the regression slope of Tcore and T_{skin} during the first four minutes after the threshold was achieved.[8] Heat accumulation (HA) = (ΔTcore)·body mass (g)·h, where ΔTcore corresponded to variation of Tcore (T_{final}-$T_{initial}$), and h corresponds to specific heat of body tissues (0.826 cal.g^{-1}.ºC^{-1}).[18] HA was normalized by 100 g of body mass. The HA/W ratio (cal.j^{-1}) was considered an index of thermal efficiency.

Statistical analysis

Data normality was tested using the Shapiro-Wilk test. Normally distributed variables were expressed as mean ± SD. Tcore, T_{skin} and VO_2 were compared using the two-way ANOVA followed by post-hoc analysis with t-test (LSD, Least Significant Difference) or the Scott Knott test, as appropriate. TET, E, ME, SBP, diastolic blood pressure (DBP), MBP and RHR were analyzed by two-way ANOVA followed by Tukey's post-hoc test. Paired t-test was used to assess the effects of low-intensity exercise on body mass, SBP, DBP, MBP and RHR. The level of significance was set at 5%. All statistical analyses were performed using the Sisvar software, version 5.6 (Brazil).

Results

The effects of physical training on body mass, SBP, DBP, MBP, RHR and TET are described in Table 1. Body mass

Table 1 – General characteristics of the animals studied; data expressed as mean ± standard deviation

Variable	C-WIS (n = 8)	T-WIS (n = 8)	C-SHR (n = 8)	T-SHR (n = 8)
Initial BM (g)	390.0 ± 16.9	356.6 ± 23.7 #	258.6 ± 14.7 +	271.3 ± 13.5 +
Final BM (g)	462.6 ± 15.8 *	421.0 ± 35.9 *#	326.5 ± 20.9 *+	309.1 ± 24.6 *+
Initial SBP (mmHg)	132.2 ± 9.8	123.7 ± 7.6	172.5 ± 14.9 +	189.7 ± 9.6 #+
Final SBP (mmHg)	129.6 ± 7.6	127.8 ± 8.7	190.0 ± 8.4 *+	167.3 ± 16.6 *#+
Initial DBP (mmHg)	84.0 ± 13.2	90.0 ± 13.2	135.5 ± 18.1 +	143.3 ± 17.8 +
Final DBP (mmHg)	90.3 ± 7.9	98.5 ± 14.1	144.5 ± 18.6 +	117.3 ± 28.0 *#+
Initial MBP (mmHg)	100.3 ± 10.7	100.8 ± 10.7	147.6 ± 16.1 +	157.7 ± 14.9 #+
Final MBP (mmHg)	104.0 ± 7.3	107.2 ± 13.2	158.6 ± 12.1 +	133.1 ± 22.6 *#+
Initial RHR (bpm)	338.7 ± 19.5	340.2 ± 12.1	374.2 ± 11.0 +	370.1 ± 12.4 +
Final RHR (bpm)	337.5 ± 10.7	311.7 ± 12.1 *#	374.2 ± 16.4 +	365.7 ± 18.6 +
TET (min)	21.9 ± 1.9	34.8 ± 4.2 #	23.4 ± 2.5	28.4 ± 3.6 #+

*C-WIS: control Wistar; T-WIS: trained Wistar, C-SHR: control SHR, T-SHR: trained SHR. BM: body mass; SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: mean blood pressure; RHR: resting heart rate; TET: total exercise time at week 8 of the incremental test. * p < 0.05: initial vs. final. # p < 0.05: trained vs. controls within same lineage; + p < 0.05: WIS vs. SHR at the same training level*

increased in all groups after 12 weeks of training. Lower body mass and higher SBP, DBP, MBP and RHR were observed in SHRs compared with Wistar rats. After the exercise program, RHR was significantly lower in Wistar rats, which was not observed in SHRs. Besides, the low-intensity physical training significantly reduced SBP (12%), DBP (18%) and MBP (12%) in T-SHR, whereas the SBP increased in C-SHR after 12 weeks. The exercise training increased physical performance in both Wistar and SHR groups. Also, T-SHR showed lower physical capacity compared with T-WIS.

The effects of acute exercise (at 60% of RMS) on Tcore, VO_2 and T_{skin} are described in Figure 1. Hypertension and physical training had no effect on Tcore during moderate exercise (Figure 1A). The T-WIS group showed higher VO_2 (from 6 minutes to 16 minutes, and at the point of fatigue; Figure 1B) and T_{skin} (from 14 minutes to 18 minutes, and at the point of fatigue; Figure 1 C) compared with the WIS-C. The C-SHR group showed higher T_{skin} than the C-WIS (from 13 minutes to 17 minutes; Figure 1C). Low-intensity training had no effect on T_{skin} or VO_2 in SHR during moderate exercise. In addition, a lower T_{skin} was found in the T-SHR group at the point of fatigue compared with the T-WIS (Figure 1C).

Figure 2 shows the threshold and sensitivity of heat dissipation during acute exercise. These parameters did not change with hypertension or low-intensity physical training.

In addition, neither hypertension nor physical training affected W during acute exercise (Figure 3A). Hypertensive animals showed lower ME compared with normotensive animals, both in control and trained groups (Figure 3B). Also, physical training had no effect on ME in both Wistar and SHR (Figure 3B).

Results of HA and HA/W ratio are illustrated in Figure 4. The T-WIS group showed higher HA than the C-WIS (Figure 4A), and the T-SHR had lower HA compared with T-WIS (Figure 4A). However, when HA was corrected for W, no difference was found in the effects of SAH and physical training (Figure 4B).

Discussion

The present study aimed to evaluate the effects of low-intensity physical training on thermal balance in hypertensive rats subjected to an acute exercise program. We tested the hypothesis that low-intensity training could promote positive adaptations and ultimately reversal of the changes in the thermal balance of SHRs. For this purpose, we evaluated Tcore, heat production and heat dissipation in response to exercise. Altogether, our results showed that low-intensity physical training did not cause significant changes in the variables related to thermal balance, and thus, our hypothesis was rejected.

Thermal balance results from the relationship between heat production and dissipation,[18] resulting in the Tcore regulation within satisfactory limits. During acute physical exercise, heat production occurs before heat dissipation, and consequently Tcore increases more rapidly than dissipation.[19] This dynamics was observed in the present study (Figure 1) for the thermal balance variables in all experimental groups, *i.e.*, for heat production (VO_2), heat dissipation (T_{skin}) and resulting outcome (Tcore). Throughout the exercise session, the Tcore threshold for heat dissipation is achieved and the thermoeffector response of heat dissipation occurs, measured by vasodilation in the tail skin. These adaptations allow achievement of thermal balance and regulation of Tcore within adequate limits,[20] which was also observed in our study. An important adjustment, commonly reported in the literature, that confirms this pattern of response is the absence of vasodilation, and even occurrence of vasoconstriction, in the animals' tails in the beginning of exercise[19] (Figure 1C).

Although recent studies of our group have shown that untrained SHR show disturbances in the regulation of body temperature during acute exercise, findings of the present study do not confirm the hypothesis that these thermal balance changes could be reversed by low-intensity aerobic physical training. In these previous studies, untrained SHR showed higher Tcore during constant-intensity acute exercise (60%

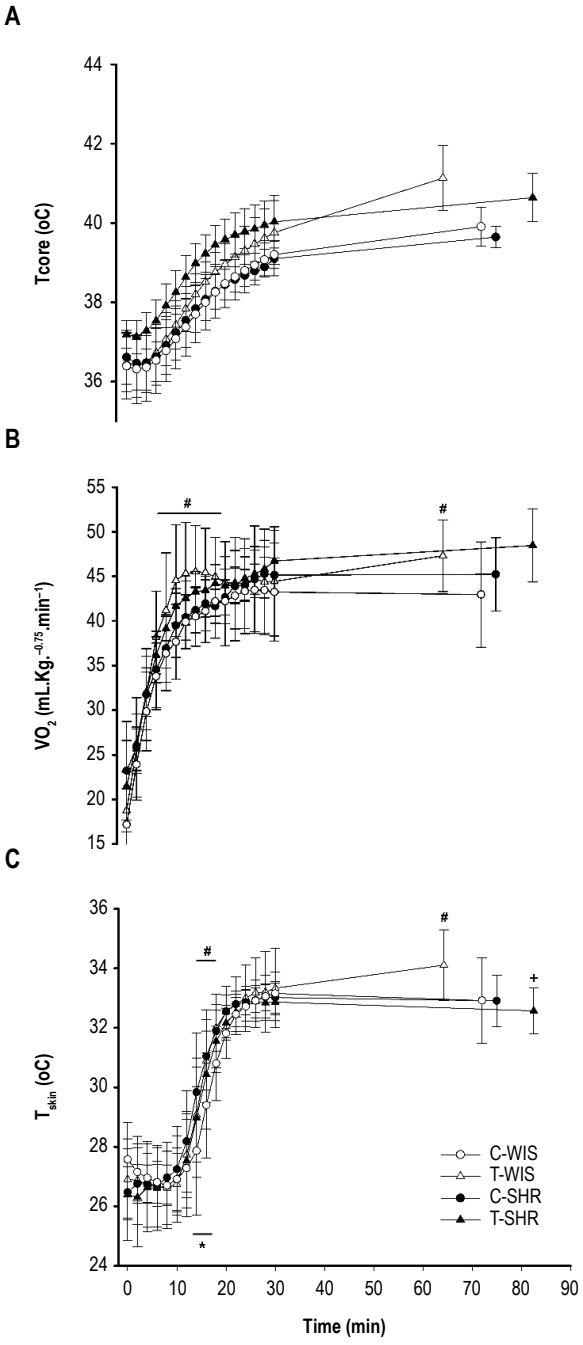

Figure 1 – *Core temperature (Tcore, A), oxygen consumption (VO_2, B) and tail skin temperature (T_{skin}, C) during acute exercise, until fatigue. Control Wistar (C-WIS), trained Wistar (T-WIS), control SHR (C-SHR), trained SHR (T-SHR). Data expressed as mean ± SD; * p < 0.05: C-SHR vs. C-WIS; # p < 0.05: T-WIS vs. C-WIS; + p < 0.05: T-SHR vs. T-WIS.*

MRS) associated with higher heat production and dissipation.[7,8] It is worth pointing out that the age of the animals and the absolute running speed during the acute exercise protocol were different among these studies, which could explain this difference. Future studies should test other exercise intensities and duration, since the effects of training are known to be dependent on these variables.[21]

In the present study, the intensity of acute physical exercise (60% of MRS) was established according to the American College of Sports Medicine recommendations.[22] It is of note that, during the acute exercise session, although the animals were subjected to the same relative exercise intensity, the absolute speed was higher in trained animals. Gant et al.[23] analyzed the relationship between Tcore and relative exercise

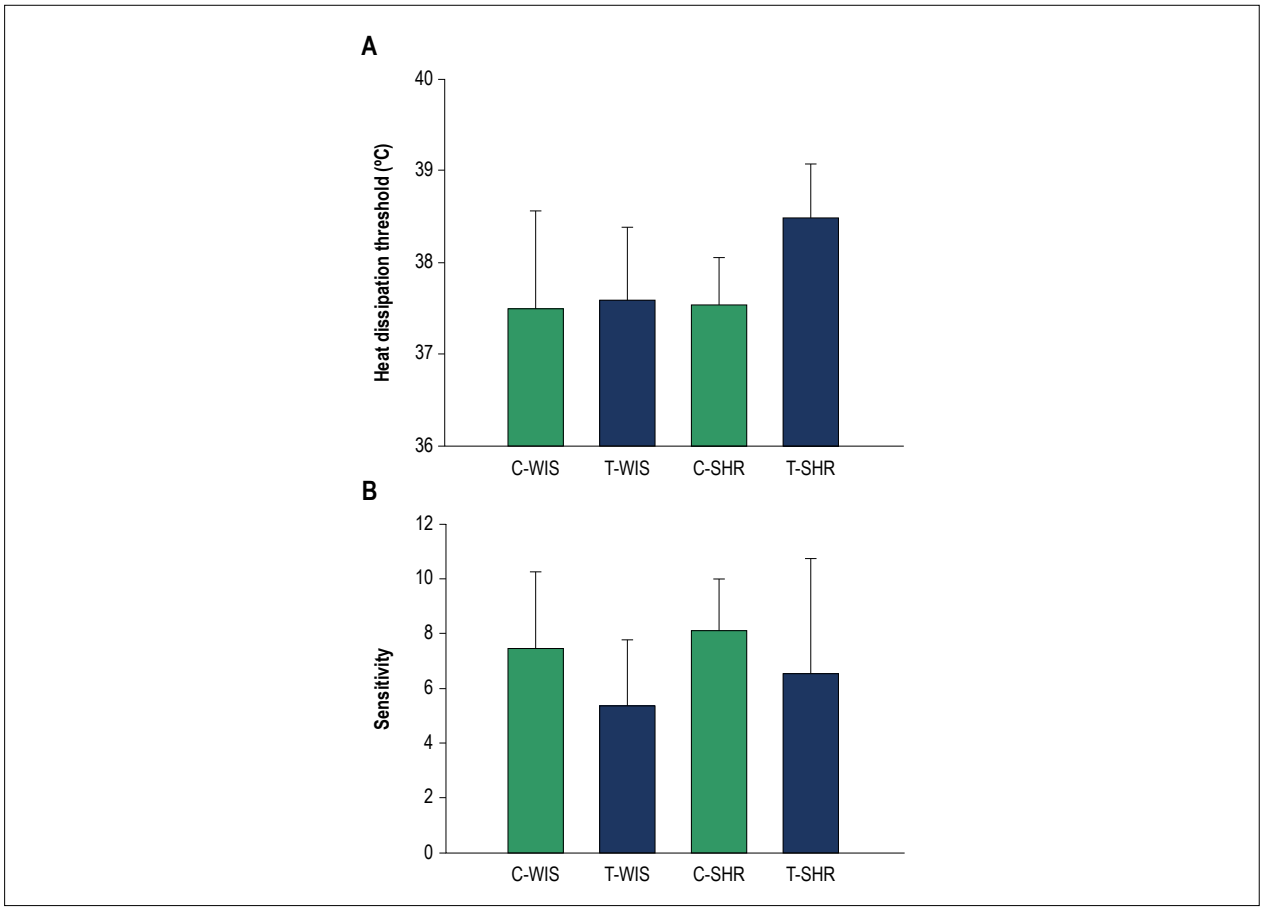

Figure 2 – *Heat dissipation threshold (ºC) (A) and sensitivity (B) during the acute physical exercise protocol. Data expressed as mean ± SD. C-WIS: control Wistar, T-WIS: trained Wistar, C-SHR: control SHR, T-SHR: trained SHR.*

intensity. Although the authors did not observe differences in Tcore between groups of animals with different VO_{2max} throughout one hour of exercise at 60% of VO_{2max}, when subjected to exercise at similar absolute intensity, these groups showed different Tcore between them. These data suggest that the magnitude of hyperthermia may be associated with the absolute exercise load, regardless of the training status. In the present study, the T-WIS group showed greater heat production compared with the C-WIS group. This may be due to the higher intensity of exercise, which was counterbalanced by higher heat dissipation, resulting in comparable Tcore values in relation to the C-WIS group.

Low-intensity physical exercise increased physical capacity in SHR and reduced blood pressure, without promoting resting bradycardia. The mechanisms responsible for the reduction of blood pressure levels in hypertensive rats following aerobic physical training include structural, vascular and neurohumoral adaptations, such as reduction in sympathetic vasomotor activity,[24,25] lower vascular reactivity,[26] reduction in peripheral vascular resistance,[27,28] reduction of oxidative stress,[29] and changes in the endothelium-derived relaxing and contractile factors.[30]

Hypertensive animals showed lower ME compared with normotensive animals, as previously described.[7] This could be explained, at least in part, by the higher proportion of type IIA fibers to type I fibers in the soleus muscle, as type I fibers are inherently more efficient than type IIA fibers.[31] The physiological mechanisms responsible for the change of the muscle fiber profile may be associated with microcirculation rarefaction that precedes microvascular apoptosis, which would result in reduction of type I muscle fibers and augmented muscle anaerobiosis.[31] However, the lower ME did not compromised work performance in the SHR group during acute physical exercise. Low-intensity exercise did not increase ME, neither in normotensive nor in hypertensive rats.

The present study has some limitations. It is possible that the difference in body mass between hypertensive and normotensive animals may have influenced the changes in Tcore induced by exercise, since the energy cost of running and heat dissipation from the skin depend on body mass.[32] Nevertheless, this limitation is somewhat expected when both normotensive animals and SHR are studied, especially when they are matched by age.[7,8,10] On the other hand, Drummond et

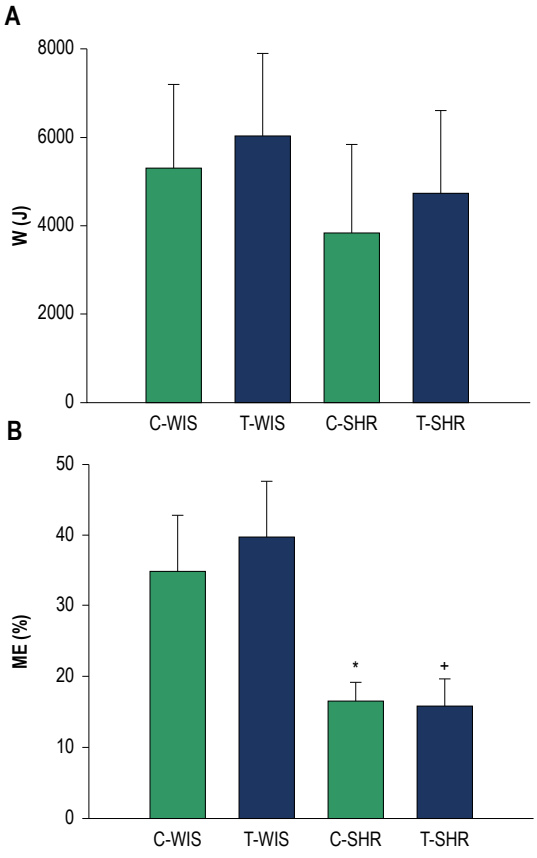

Figure 3 – *Work (W, A) and mechanical efficiency (ME, B) during the acute physical exercise protocol. Data expressed as mean ± SD; * p < 0.05: C-SHR vs. C-WIS; + p < 0.05: T-SHR vs. T-WIS. C-WIS: control Wistar, T-WIS: trained Wistar, C-SHR: control SHR, T-SHR: trained SHR.*

al.[8] demonstrated that differences in the thermoregulation between normotensive animals and SHR during acute exercise were not dependent on variations of body mass. These differences could also affect the ability of the animals to be trained, since they could be associated with differences in body composition, and consequently in differences in physical capacity. Finally, we cannot affirm that the results would have been the same if physical training had been started before a SBP higher than 150 mmHg was achieved by the SHR, or if animals of different ages were studied.

Conclusion

Low-intensity physical training did not affect thermal balance in hypertensive rats subjected to an acute exercise protocol.

Author contributions

Conception and design of the research: Gomes LHLS, Natali AJ, Prímola-Gomes TN; Acquisition of data: Gomes LHLS, Rezende LMT, Prímola-Gomes TN; Analysis and interpretation of the data and critical revision of the manuscript for intellectual content: Gomes LHLS, Drummond LR, Campos HO, Rezende LMT, Carneiro-Júnior MA, Oliveira A, Natali AJ, Prímola-Gomes TN; Statistical analysis: Gomes LHLS, Drummond LR, Campos HO, Rezende LMT, Oliveira A, Prímola-Gomes TN; Obtaining financing: Prímola-Gomes TN; Writing of the manuscript: Gomes LHLS, Drummond LR, Campos HO, Carneiro-Júnior MA, Prímola-Gomes TN.

Potential Conflict of Interest

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

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade Federal de Viçosa under the protocol number 76/2014. 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.

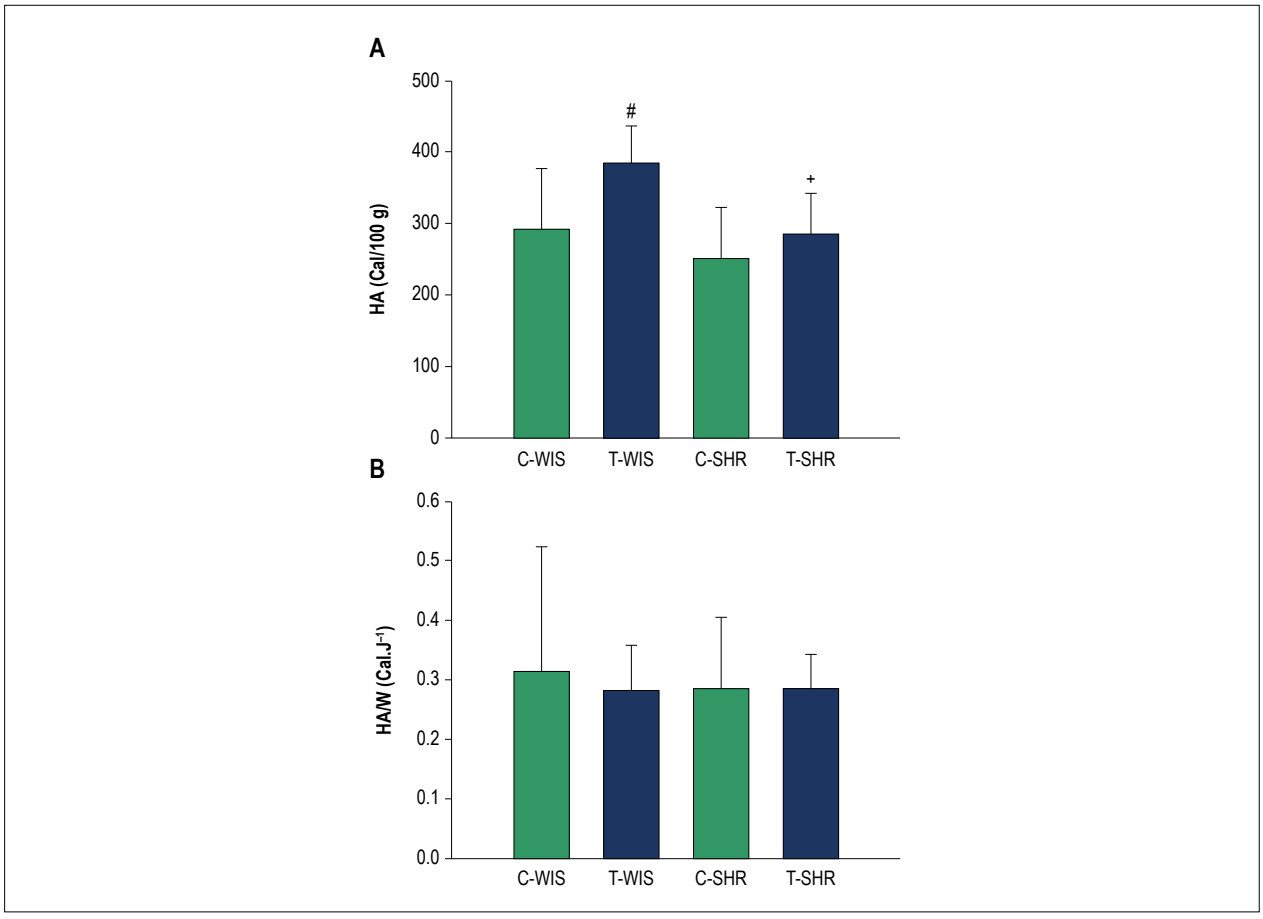

Figure 4 – *Heat accumulation (HA, A) and heat accumulation/work ratio (HA/W, B). Data expressed as mean ± SD; # p < 0.05: T-WIS vs. C-WIS. + p < 0.05: T-SHR vs. T-WIS, C-WIS: control Wistar, T-WIS: trained Wistar, C-SHR: control SHR, T-SHR: trained SHR.*

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Control of Body Temperature during Physical Exercise

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Short Editorial related to the article: Thermoregulation in Hypertensive Rats during Exercise: Effects of Physical Training

Physical exercise is currently recommended for health promotion and as a non-pharmacological treatment of cardiovascular diseases. Regular exercise results in improved body composition and physical capacity, as well as decreased insulin resistance and arterial hypertension, leading to ameliorated quality of life.[1]

During exercise, heat is a by-product of metabolism, which leads to increased body temperature. However, the human body needs to maintain a stable temperature, around 37ºC, using neural and cardiovascular mechanisms. The temperature-regulating center is found in the anterior hypothalamus. It receives information on the ambient temperature, through the skin thermoreceptors, and on the internal temperature, through the hypothalamic thermoreceptors. Thus, the hypothalamus promotes appropriate responses of heat generation or dissipation, which involve arteriovenous redistribution of blood.[2] Therefore, individuals with cardiovascular comorbidities such as type II diabetes, hypercholesterolemia and arterial hypertension may present impairment of thermoregulation mechanisms.[3]

In order to study and evaluate hypertension, Spontaneously Hypertensive Rats (SHR) are commonly used as a model, since they resemble the condition found in humans.[4,5] Therefore, the Gomes et al.[6] used SHR rats to evaluate the effects of low-intensity physical exercise training on thermal balance.

After 12 weeks of exercise protocol, the Gomes et al.[6] showed a reduction in blood pressure in trained SHR. In addition, trained SHR presented lower skin temperature than trained Wistar. This show an impaired heat dissipation in SHR. However, physical exercise did not influence the promotion of positive adaptations on thermoregulation.[6]

In humans, heat dissipation responses involve increased sweating, as the main mechanism, and cutaneous active vasodilation.[2] Thermoregulatory responses in rats are different. Cutaneous vasodilation of the tail is the main mechanism of heat dissipation in this species, accounting for 40% of heat loss during exercise.[7] This mechanism can be activated by central cholinergic stimulation via modulation of arterial baroreceptors by increasing the blood flow of the rat´s tail.[8,9] Additionally, vasodilation of the skin of the feet, the evaporation of saliva spread onto the body surface, the evaporation of water from the respiratory tract and even voluntary urination associated with urine spreading activity may also contribute to the total heat dissipation.[10]

Considering the relationship between the cardiovascular system and the regulation of body temperature, hypertension can affect the mechanisms of heat dissipation. In SHR rats, for example, decreased baroreceptor sensitivity, sympathetic hyperactivity, which leads to increased peripheral resistance, and endothelial dysfunction may impair cutaneous vasodilation of the tail and, consequently, heat dissipation.[7,9]

In fact, the Gomes et al.[6] found lower skin temperature in trained SHR than in trained Wistar. This shows a lower heat dissipation in hypertensive animals during exercise. However, the author did not observe alterations in the internal temperature, heat dissipation threshold, sensitivity and cumulative heat normalized by the work. One possible explanation is that other mechanisms of heat dissipation, besides cutaneous vasodilation of the tail, may have been used by these animals.

Keywords

Exercise; Rats; Rats, Inbred SHR/physiology; Body Temperature Regulation.

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Resistance Exercise Modulates Oxidative Stress Parameters and TNF-α Content in the Heart of Mice with Diet-Induced Obesity

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Abstract

Background: **Obesity can be characterized by low-grade chronic inflammation and is associated with an excess production of reactive oxygen species, factors that contribute to coronary heart disease and other cardiomyopathies.**

Objective: **To verify the effects of resistance exercise training on oxidative stress and inflammatory parameters on mice with obesity induced by a high-fat diet (HFD).**

Methods: **24 Swiss mice were divided into 4 groups: standard diet (SD), SD + resistance exercise (SD + RE), diet-induced obesity (DIO), DIO + RE. The animals were fed SD or HFD for 26 weeks and performed resistance exercises in the last 8 weeks of the study. The insulin tolerance test (ITT) and body weight monitoring were performed to assess the clinical parameters. Oxidative stress and inflammation parameters were evaluated in the cardiac tissue. Data were expressed by mean and standard deviation ($p < 0.05$).**

Results: **The DIO group had a significant increase in reactive oxygen species levels and lipid peroxidation with reduction after exercise. Superoxide dismutase and the glutathione system showed no significant changes in DIO animals, with an increase in SD + RE. Only catalase activity decreased with both diet and exercise influence. There was an increase in tumor necrosis factor-alpha (TNF-α) in the DIO group, characterizing a possible inflammatory condition, with a decrease when exposed to resistance training (DIO+RE).**

Conclusion: **The DIO resulted in a redox imbalance in cardiac tissue, but the RE was able to modulate these parameters, as well as to control the increase in TNF-α levels. (Arq Bras Cardiol. 2019; 112(5):545-552)**

Keywords: **Exercise; Oxidative Stress; Obesity; Diet, High-Fat; Mice.**

Introduction

The World Health Organization (WHO)[1] defines obesity as an abnormal or excessive accumulation of fat that brings health risks. The WHO brings data from the Global Health Observatory showing a worldwide prevalence of obesity of 39% in men and women over 18 years of age (2016 updated data). In this scenario, obesity is also a risk factor for lifestyle-related diseases, such as cardiovascular disease and type 2 diabetes mellitus.[2] It can be characterized by low-grade chronic inflammation and is associated with increased levels of proinflammatory cytokines, as well as an excess production of reactive oxygen species.[3,4]

Studies have shown that hyperglycemia and alterations in glucose uptake in diabetes may lead to oxidative stress with consequent mitochondrial dysfunction, as well as to an inflammatory process with the presence of elevated proinflammatory cytokines, such as TNF-α. Both cases may be triggering factors for coronary heart disease and other cardiomyopathies[5] (see review by Adeghate and Singh). Gamez-Mendez et al.,[6] also showed that 8 weeks of high-fat diet (HFD) led to an increase in oxidative stress, resulting in an imbalance of vasoactive substances and consequent endothelial dysfunction of the coronary arteries in obese rats.

Studies point to physical exercise as an important ally in reducing the risks related to obesity due to its ability to reestablish the balance between pro-anti-inflammatory cytokines and regulate the cell redox state.[7,8] According to Boardman et al.,[9] physical exercise is not only an important therapeutic approach in obesity, but it is also crucial for cardiac function improvement and ischemic injury prevention in obese and/or diabetic animals.

Although the literature indicates that exercise is important to prevent or complement the treatment of obesity,[10] one should consider the characteristics of the performed exercise, such as: intensity, duration, frequency and type.

Based on the aforementioned facts, this study aimed to identify whether resistance exercise (RE) modifies the oxidative stress and inflammation parameters caused by an HFD in an experimental model of obesity.

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Methods

Animals

Male Swiss mice (40 days), obtained at the *vivarium* of Universidade do Extremo Sul Catarinense – UNESC (Criciúma/SC – Brazil), with an average weight of 35.45 g (± 1.29) were studied. The animals were kept at a 12/12h light/dark cycle at 22°C in collective boxes (6 animals per box) and randomly divided into four groups (n = 6): standard diet (SD); diet-induced obesity (DIO); SD + RE; DIO + RE. The random selection procedure was carried out by arbitrarily or randomly allocating the animals to the respective groups, without prior performance evaluation or using any other indicator that allowed the groups to be divided.

Diet

The animals were fed *ad libitium* for 26 weeks with low-fat SD (SD: 27%, 23% and 50% of calories from proteins, fats and carbohydrates, respectively – 3.3kcal/g) or HFD (HFD: 15%, 59% and 26% of calories from proteins, fats and carbohydrates, respectively – 5.3kcal/g). The SD was purchased from the *Puro Trato Nutrição Animal* (Puro Lab 22PB) Santo Augusto/RS – Brazil, and the HFD from PragSoluções Biociência, Jaú/SP – Brazil.

Exercise

The exercise adaptation protocol was started in the 17th week of the diet and the RE protocol in the 18th. The resistance training was performed in a 1-m ladder apparatus with 2cm steps and 85º-slope.[11] The animals were familiarized with the climbing exercise on the steps for 5 consecutive days without load. The training protocol, adapted from Scheffer et al.,[12,13] started 3 days after the last adaptation training, and was performed with a 48-h interval between sessions, for 8 weeks, totaling 28 training sessions. The exercise was performed with intensity progression by adding a weight to the animal's tail (load increase of 20% to 75% of body weight), and volume progression (5-10 series per session) (Table 1), with a 2-min interval between sessions in the rest area (closed box at the top of the steps measuring 20x20x20 cm). Each series was performed until the animals completed 5 repetitions/climbings (without interval), or could not climb the stairs even after encouragement (manual stimulation at the base of the tail).

Table 1 – Resistance training protocol

Weeks	Load	Series	Interval between series
1st	20%	5	1 (2min)
2nd	20%	7	1 (2min)
3rd	50%	5	1 (2min)
4th	50%	7	1 (2min)
5th	50%	10	1 (2min)
6th	50%	10	1 (2min)
7th	75%	7	1 (2min)
8th	75%	10	1 (2min)

Source: Study data. Adapted from Scheffer et al.[12]

Body weight and insulin tolerance test (ITT)

Individual body weight was measured at the start of the study and at weeks 3, 6, 10, 14, 18, 22 and 26. After 17 weeks on the diet, an ITT was performed to confirm insulin resistance. After 6 hours of fasting,[14] all animals received a dose of 2 U/kg of insulin. Blood glucose was measured with a glycometer using a drop of blood collected from a small incision at the tip of the animal's tail. The same protocol was performed at the end of the experiment, 48 hours after the last exercise session.

Euthanasia

24 h after the last insulin tolerance test, euthanasia by decapitation was performed and the left ventricle of the heart was surgically extracted, immediately frozen in liquid nitrogen, and stored at -80°C for biochemical analysis.

Biochemical analyses

For the biochemical assays described below and ELISA test, all samples were homogenized in 50 mM phosphate-buffered saline (PBS), with the addition of 10uM aprotinin. The homogenate was centrifuged for 10 min at 4°C and the supernatant was stored at -80°C. Protein levels were determined in all samples using the Bradford method.[15]

Oxidation of dichlorodihydrofluorescein (DCFH)

Reactive species levels were measured based on oxidation of the 2',7'-dichlorodihydrofluorescein diacetate (DCFH-DA) probe in a fluorescent 2',7'-dichlorodihydrofluorescein (DCF) compound as previously described.[16] An aliquot of the lysate was incubated with 80 mM DCFH-DA at 37ºC for 15 minutes. The production of reactive species was quantified using a standard DCF curve and data were expressed as nM DCF/mg protein.

Antioxidant enzyme activity

The superoxide dismutase (SOD) activity was estimated by inhibiting the auto oxidation of adrenaline and read spectrophotometrically at 480 nm according to the method described by McCord and Fridovich.[17] Catalase (CAT) activity was established based on the rate of hydrogen peroxide (H_2O_2) decomposition, generated by the enzyme present in the sample using a 10 mM H_2O_2 solution in potassium phosphate buffer with pH of 7.0. The maximum rate of H_2O_2 decomposition was measured at 240 nm.[18] Values were expressed as units of SOD or CAT per mg of protein.

Total glutathione (GSH) levels

GSH levels were measured using the Hissin method.[19] Samples were incubated in 0.6% sulfosalicylic acid followed by a reaction of the GSH present in the sample with 2-nitrobenzoic acid (5,5'-Dithiobis) (DTNB) producing an oxidized glutathione–TNB adduct (GS–TNB). The resulting

color from the reaction between the DTNB and thiols compared to the standard curve for GSH was kinetically established at 412 nm for 10 min. Values were expressed as nmol/min/mg protein.

Lipoperoxidation

The concentrations of malondialdehyde (MDA) in the samples were determined by high-performance liquid chromatography (HPLC) (Agilent Technologies 1200 Series; Santa Clara, CA, USA),according to Grotto et al. (2007)[20] using a derivative of thiobarbituric acid (TBA). A standard curve was created using MDA tetrabutylammonium salt at concentrations ranging from 0.5 to 5 μmol/L. The MDA was determined at 532 nm and the results were expressed as umol/L of MDA/milligram protein.

Inflammatory Parameter

The concentration of tumor necrosis factor-alpha (TNF-α) was assessed by enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's recommendations (ThermoFisher Scientific, cat.KMC3011). The results were expressed in pg/mg of protein.

Statistical analysis

Initially, the data were assessed using Grubbs test to verify possible outliers followed by the Shapiro-Wilk normality test, and in both of them the data met the assumptions for the use of parametric tests. Then, the Two-way ANOVA test was performed, followed by the Bonferroni post-hoc test when necessary. For analysis of the ITT data (table 2), the one-way variance test (one-way ANOVA) of repeated measures was performed, followed by post-hoc Tukey test when necessary. The level of significance was set at $p < 0.05$. The Graph Pad Prism software, version 5, was used as the statistical package. All data were expressed as mean and standard deviation, except for figure 1A, expressed as mean and standard error of mean.

Results

Body weight and insulin resistance

The RE had a beneficial effect, preventing the DIO + RE group from continuing to gain weight even with the HFD consumption, not characterizing weight loss, but rather weight maintenance, even without food intake control (Figure 1A-C).

The pre-exercise ITT showed that the DIO animals had insulin resistance ($p > 0.05$) (Table 2). The results demonstrated that HFD can lead to a loss of glucose uptake even with an external insulin stimulus (2U/kg body weight). The RE ($p < 0.05$), even with HFD intake, was able to delay the progression of the disease, maintaining a better glucose decay rate when compared to the sedentary DIO group ($p < 0.01$). There was no significant difference between pre- and post-exercise in any group (Figure 1D).

DCFH oxidation

DCFH oxidation levels were measured as indicators of the reactive species production, especially hydrogen peroxide, and the results showed that in untrained animals, DIO caused an increase in DCF levels ($p < 0.001$) in comparison to animals with SD. HFD-fed animals submitted to resistance training (DIO + RE) showed a significant decrease in DCF levels compared to the DIO group ($p < 0.01$) (Figure 2A).

Lipoperoxidation

As shown in Figure 2B, MDA levels suggest an increase in lipoperoxidation in DIO animals ($p < 0.05$), with reversion of the condition ($p < 0.05$) with resistance training (DIO + RE).

SOD Activity

The results observed in Figure 2C show that DIO did not alter SOD activity, but resistance training was able to increase its activity in the SD + RE group ($p < 0.05$), an increase not observed when exercise was performed in the obese group.

Table 2 – Insulin tolerance test (ITT) – blood glucose curve

		Time of collection (Glucose mg/dL and variation in relation to time 0 min)						
		0 min	5 min	10 min	15 min	20 min	25 min	30 min
Pre-exercise	SD	154.3	139.2 (-15.0)	98.7 (-55.5)	77.5 (-76.8)	65.2 (-89.0)	56.7 (-97.5)	43.2 (-111.0)
	SD + RE	129.3	134.7 (+5.5)	57.7 (-71.5)	54.7 (-74.5)	46.7 (-82.5)	35.3 (-94.0)	25.5 (-103.8)
	DIO	191.0†	186.0 (-5.0)	125.5 (-65.5)	118.0 (-73.0)	106.5 (-84.5)†	101.3 (-89.8)†	99.0 (-92.0)†
	DIO + RE	163.8*†	164.5 (+0.8)	128.0 (-35.8)†	115.2 (-48.5)†	107.3 (-56.5)†	100.8 (-63.0)†	99.5 (-64.3)†
Post-exercise	SD	129.0	97.5 (-31.5)	71.0 (-58.0)	54.5 (-74.5)	59.0 (-70.0)	37.5 (-91.5)	27.0 (-102.0)
	SD + RE	122.3	102.0 (-20.3)	66.2 (-56.0)	53.5 (-68.8)	42.0 (-80.3)*	23.0 (-99.3)	15.8 (-106.5)
	DIO	150.8†‡	120.7 (-30.0)‡	110.5 (-40.3)†	105.5 (-45.3)†	97.0 (-53.8)†	94.0 (-56.8)†	92.0 (-58.8)†
	DIO + RE	127.8*‡	133.5 (+5.8)	93.7 (-34.0)	68.0 (-59.8)‡	64.3 (-63.5)*‡	58.5 (-69.3)*†‡	46.5 (-81.3)*†‡

*Source: study data. Pre-adaptation/exercise (week 17) and post-exercise (week 26). Blood glucose was measured after 6 hours of fasting (data from the table) at times 0 min (baseline), followed by an intraperitoneal insulin injection (2 U/kg) and measurements at times 5-30 min. *p < 0.05 versus respective untrained; †p < 0.05 versus respective standard diet; ‡p < 0.05 versus respective pre-exercise. SD: standard diet; RE: resistance exercise; DIO: diet-induced obesity.*

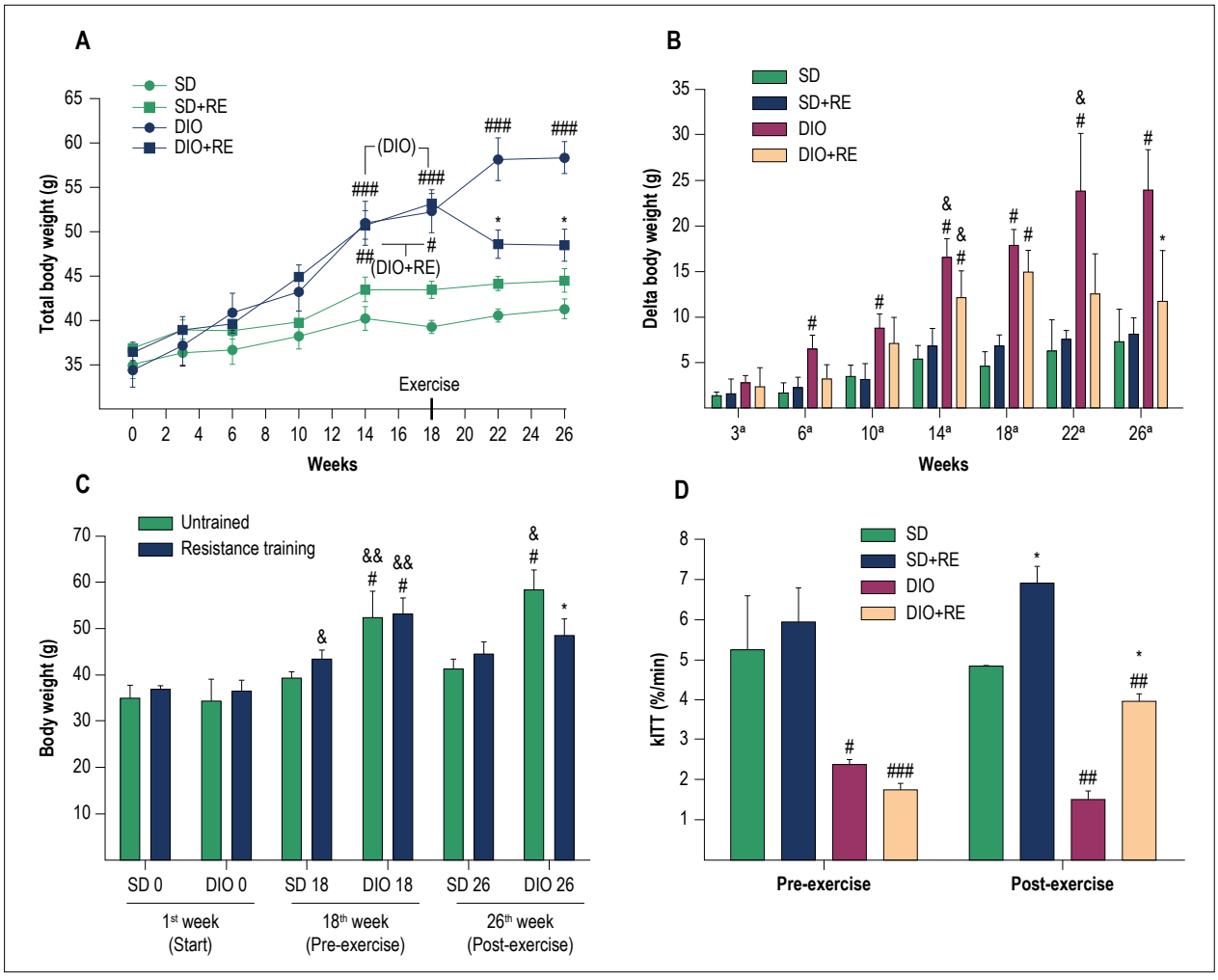

Figure 1 – *A – Total body weight during the study; B - Delta (body weight variation in relation to the start of the study); C - weight comparison between the 1st week (start), 18th week (pre-exercise) and 26th week (post-exercise); D - Glucose decay rate in the insulin tolerance test (kITT). Figure A, B and D - *p < 0.05 vs. respective untrained of the same period, #p < 0.05, ##p < 0.01 and ###p < 0,001 vs. respective SD of the same period; &p < 0.05 vs. same group of the previous week. Figure C - *p < 0.001 vs. respective untrained of the same period; #p < 0.01 and ##p < 0.001 vs. respective SD of the same period; &p < 0.05, &&p < 0.001 vs. same group of the previous week.*

CAT Activity

The results observed in Figure 2D show a reduction in CAT activity in trained animals (SD + RE, $p < 0.001$ and SD, DIO + RE, $p < 0.01$ *vs*. untrained animals). On the other hand, the HFD animals also showed a decrease in CAT ($p < 0.05$), but only when compared to the SD animals.

GSH

Total glutathione levels were not significantly altered in both the interventions used in the present study (diet and exercise) (Figure 2E).

Inflammatory Parameter

The levels of TNF-α were used as an inflammatory indicator in cardiac tissue and the results observed in figure 2F showed an increase in TNF-α content in DIO animals ($p < 0.05$), which was significantly reduced ($p < 0.05$) after the intervention with resistance physical exercise (DIO + RE).

Discussion

Studies have shown that the consumption of a diet rich in fat, concomitant with a sedentary lifestyle, can trigger several health problems[21,22] with a significant impact on the cardiovascular system. Therefore, experimental studies have been used to study the cellular effects of a high fat diet.[6,23,24] The results of body weight and ITT showed that the adopted experimental model was effective in increasing weight and causing insulin resistance. Increased body weight has been associated to inflammatory changes and oxidative stress, and both these alterations to insulin resistance in skeletal muscle,[25,26] but recent studies have also shown that cardiac cells are also susceptible to weight gain, by elevating inflammatory mediators and oxidative stress.[6,23,24,27,28] In this context, previous studies suggested an important role of physical exercise, specifically aerobic or endurance, on the biochemical and molecular changes occurring in the myocardium as the result of a diet rich in fat.[3,7] However, these effects depend on the characteristics of the exercise, such as duration, frequency, intensity and type.

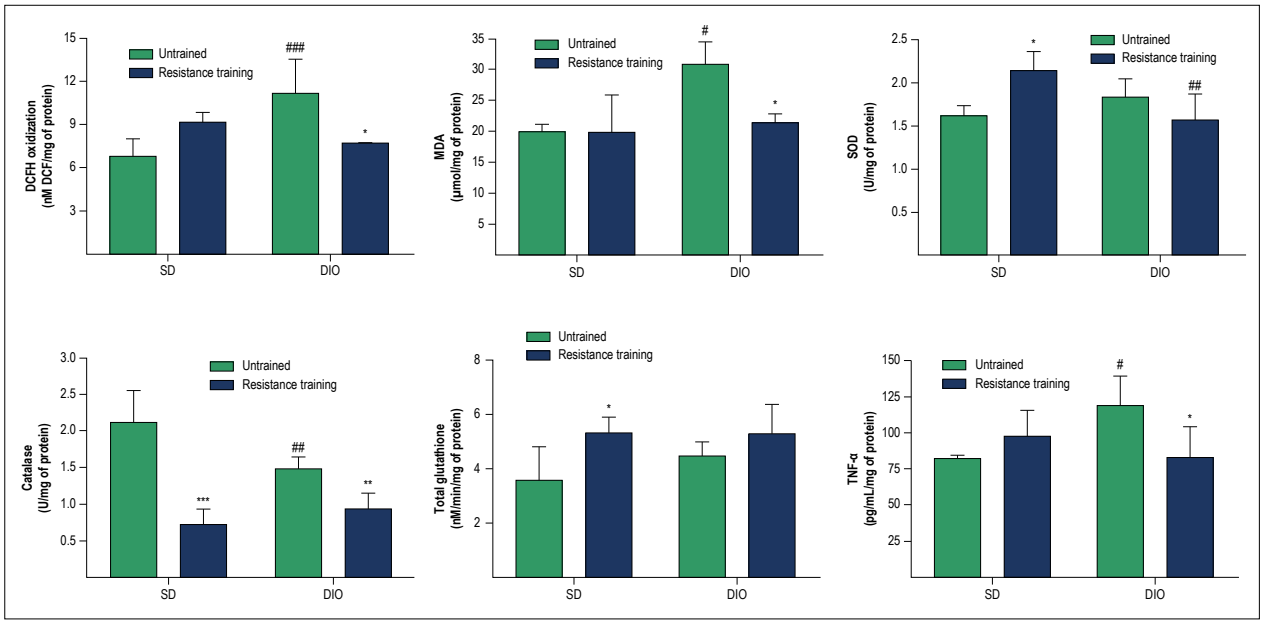

Figure 2 – *Redox balance and inflammatory parameters in cardiac tissue of animals fed standard or high-fat diet and subsequently submitted to resistance training. A - DCFH oxidation; B - MDA content; C - SOD enzyme activity; D - CAT enzyme activity; E - Total glutathione content (reduced and oxidized); F - levels of TNF-α. *p < 0.05, **p < 0.01 and ***p < 0.001 vs. respective untrained; #p < 0.05, ##p < 0.01 and ###p < 0.001 vs. respective SD.*

The initial results of our study show that DIO animals have elevated levels of DCF, an indirect indicator of hydrogen peroxide production.[29] These data were also observed by a recent study published in 2017 by Zeng et al.[23] The authors showed high myocardial susceptibility to oxidative stress, with a significant increase in DCFH oxidation, both *in vitro* and *in vivo*, mediated by a high-fat diet. These increased DCF values, observed in DIO animals, were significantly reduced after resistance training, which suggests an important role of this type of training in the regulation of cell oxidant levels. Such effect may be associated to the fact that resistance training has a modulatory role on endogenous antioxidant enzymes. This observation is based on previous studies of our group in other experimental models of inflammation, which show the important role of resistance training on the enzymatic antioxidant system in different tissues.[30,31]

SOD and CAT are two enzymes that act synergistically in the formation (via superoxide radical dismutation) and catalysis of hydrogen peroxide, respectively. DIO animals showed no changes in SOD activity, suggesting that an increased production of DCF may be associated with other stimuli independent from SOD. One of the factors responsible for it is that, although the oxidation of DCFH to DCF is widely used as an indicator of hydrogen peroxide production, studies have observed that DCFH can also be oxidized by other reactive species, on a smaller scale, such as hydroxyl, peroxyl, nitric oxide and peroxide nitrite.[29] It is also noteworthy that the formation of hydrogen peroxide is not totally dependent on SOD activity. On a smaller scale, auto-oxidation events of biomolecules also contribute to the formation of hydrogen peroxide.[32] These conditions would limit SOD activity, which may justify the results found.

Catalases constitute a group of enzymes that catalyze the decomposition of hydrogen peroxide into water and oxygen. Our results show a reduction in the activity of this enzyme after resistance training in the group exposed to SD. As observed, SOD activity was increased in this same group, thus generating higher levels of hydrogen peroxide. However, the decrease in enzyme activity suggests a lower hydrogen peroxide catalysis, but it is worth noting that hydrogen peroxide can be catalyzed under these conditions by other cell detoxification systems, such as glutathione and peroxins,[33] which could justify our results since the glutathione system showed an increase in this group (SD + RE). Furthermore, we observed reduced levels of CAT after resistance training in the DIO + RE group and, therefore, considering that the diet significantly increases the production of cell oxidants such as hydrogen peroxide, a reduced CAT activity could have an impact on the possible oxidative damages in the myocardium, if hydrogen peroxide were not catalyzed by other aforementioned systems (not investigated in the present study, although they deserve attention in future studies).

Aiming to observe the effects of RE on oxidative damage in the myocardium induced by the DIO model, we evaluated the levels of MDA, a byproduct of lipoperoxidation, and observed that DIO animals showed greater lipid damage in relation to the SD group and that the RE was able to reverse these effects. These effects of the DIO model on lipoperoxidation levels were also observed in a study with BL6/C57 mice performed by Muthulakshmi and Saravanan (2013).[34] Positive RE results are possibly associated with the exercise capacity to promote the modulation of antioxidant systems, in addition to the activity of primary antioxidant enzymes such as SOD and CAT. One of the mechanisms

that can be mediated by RE is the Nuclear Factor Erythroid 2 (NRF2) translocation to the nucleus and expression of several antioxidant enzymes such as NADH: quinone oxidoreductase 1 (NQO1) and Heme Oxygenase-1 (HO1). which help to detoxify the biological system and contribute to the reduction of oxidative stress.[35] Merry and Ristow (2016)[36] suggest that exercise may stimulate NRF2 translocation to functionally regulate mitochondrial biogenesis of skeletal muscle and the expression of antioxidants defense genes. Although these results are obtained from aerobic training and in skeletal muscle, it is believed that such effects may also occur via resistance training, as resistance training activates the Adenosine Monophosphate-Activated Protein Kinase (AMPK)[37], which enhances the phosphorylation of NRF2 in the cell and increases the level of phosphorylated NRF2 in the nucleus.[38]

The increased production of oxidants in the myocardium can be mediated by a possible inflammatory response induced by obesity/HFD with the secretion of different mediators. In this context, TNF-α is a mediator sensitive to the HFD model that shows a wide range of pro-inflammatory actions. Our results showed a significant increase in TNF-α levels in DIO animals with a consequent reduction after resistance training. Increased levels of TNF-α in the myocardium induced by a HFD have also been observed in previous studies.[3,28] The effects of exercise may be related to the fact that aerobic and resistance exercises promote increased secretion of anti-inflammatory cytokines and regulate TNF-α levels.[30,31] During the exercise, the muscles release myosins, which are involved in tissue growth, repair and anti-inflammatory responses.[39] IL-6 is the primary myosin released in response to exercise and increases IL-10 and decreases TNF-α levels.[40] IL-10 reduces cardiac dysfunction by decreasing cardiac fibrosis.[39] In this scenario, HFD-induced obesity decreases IL-10 protein levels, but physical training significantly increases the IL-10 levels in cardiac tissues.[3]

According to data from previous studies, the control of TNF-α secretion in the myocardium by RE is considered an important factor in the cardioprotection mechanisms related to oxidative stress.

Conclusion

Our results showed an important effect of RE on the control/stabilization of body weight even without food intake control. It was also demonstrated that there is a redox alteration in the cardiac tissue with an obesity model, but it does not seem to be mediated mainly by the classic antioxidant production and control of hydrogen peroxide, but rather by other reactive species. However, RE was able to reverse lipid damage and the production of reactive species, even with the consumption of a HFD, as well as positively modulate one of the main cytokines responsible for the activation of the inflammatory process.

Therefore, RE can be a great ally in the health process regarding the therapeutic approach to obesity. Some limitations found in these studies were the data related to the quantification of serum insulin to better confirm insulin resistance, and the evaluation of other molecules that can alter the cell redox balance. These tests were not performed for technical reasons.

Finally, other studies should be performed aiming to better explain how RE promotes these effects, particularly in the regulation of reactive species such as hydroxyl, peroxyl, nitric oxide and peroxide nitrite, as well as other inflammatory and anti-inflammatory parameters in cardiac tissue.

Author contributions

Conception and design of the research: Ceddia RB, Pinho RA; Acquisition of data: Brescianini SMS, Fernandes BB, Fidelis GSP, da Silva PRL, Nesi RT; Analysis and interpretation of the data: Effting PS, Brescianini SMS, Silveira PCL, Nesi RT, Pinho RA; Statistical analysis: Effting PS, Silveira PCL, Pinho RA; Obtaining financing: Pinho RA; Writing of the manuscript: Effting PS, Pinho RA; Critical revision of the manuscript for intellectual content: Ceddia RB, Pinho RA.

Potential Conflict of Interest

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

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Study Association

This article is part of the thesis of Doctoral submitted by Pauline Souza Effting, from Universidade do Extremo Sul Catarinense.

Ethics approval and consent to participate

This study was approved by the Ethics Committee on Animal Experiments of the Universidade do Extremo Sul Catarinense under the protocol number 067/2014-2.

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Cardioprotective Effects of Resistance Training on Obesity

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Short Editorial related to the article: Resistance Exercise Modulates Oxidative Stress Parameters and TNF-α Content in the Heart of Mice with Diet-Induced Obesity

Obesity is characterized as a complex metabolic disorder and is associated with several complications such as cardiovascular diseases, diabetes, renal dysfunction, liver dysfunction and cancer, resulting in impairment of quality of life.[1]

The pathogenesis of obesity has a multifactorial origin and the oxidative stress may play an important role. Studies on animals and cell culture have reported how oxidative stress can contribute to the development of obesity, causing increased preadipocytes proliferation, adipocyte differentiation, and size of mature adipocytes, resulting in increased production of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α).[2,3]

Experimental model of high fat diet-induced obesity aims to reproduce the characteristics observed in human, such as the development of cardiovascular abnormalities.[4,5] The study of Effting et al.[6] evaluated the effects of resistance training on parameters of oxidative stress and inflammation in mice with high fat diet-induced obesity.

Currently, regular physical exercise has been recommended for the treatment of obesity. Exercise practicing results in numerous health benefits, such as improvement in body composition, physical capacity, insulin resistance, endothelial function, arterial hypertension, antioxidant status and quality of life.[7,8]

Data presented by the authors of the article "Resistance Exercise Modulates Oxidative Stress Parameters and TNF-α Content in the Heart of Mice with Diet-Induced Obesity" showed important cardioprotective effects of resistance training, which resulted in decreased levels of lipid peroxidation and reactive oxygen species, modulation of antioxidant enzymes activity and a decrease in myocardial TNF-α concentration of obese mice[6]. Similarly, Alves et al.[9] observed that eight weeks of resistance exercise was associated with an improvement on inflammatory profile in the heart of rats with myocardial infarction.

The effects of resistance exercise on oxidative stress have been investigated mainly in skeletal muscle.[10-12] There are few studies evaluating the effects of resistance exercise on the redox status of the cardiac muscle in the literature. Therefore, Effting et al.[6] presented relevant data supporting resistance exercise as a therapeutic approach to obesity, being able to prevent or mitigate metabolic changes and improve the quality of life.

Keywords

Obesity/complications; Cardiovascular Diseases/mortality; Diabetes Mellitus; Hypertension; Mice; Diet, High-fat; Exercise; Quality of Life.

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Changes in Cardiac Autonomic Modulation in Women with Breast Cancer Using Aromatase Inhibitors and the Relation with Biochemical Variables

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Abstract

Background: **The use of autonomic modulation as a predictor of cardiovascular risk in women with breast cancer is important.**

Objective: **To evaluate the cardiac autonomic modulation of postmenopausal women using aromatase inhibitors for breast cancer treatment, as well as its relation with the following biochemical variables.**

Methods: **Postmenopausal women who did not have breast cancer (n = 33) and postmenopausal women with breast cancer (n = 15). For evaluation of the autonomic modulation the heart rate was recorded beat-to-beat for 30 minutes and the series of RR intervals obtained were used to calculate the following heart rate variability indices: Mean RR ms, SDNN (standard deviation of all normal RR intervals, expressed in milliseconds) ms, Mean HR, RMSSD (square root of the mean of the squared differences between adjacent normal RR interval) ms, NN50 (number of pairs of successive NNs that differ by more than 50 ms) count, pNN50% (proportion of NN50 divided by total number of NNs), RRtri (RR triangular), TINN (triangular interpolation of NN interval) ms, SD1 ms, SD2 ms, LF ms², HF ms², LH/HF ms². The values of biochemical variables (fasting glycemia, triglycerides, HDL-cholesterol, and C-reactive protein) were analyzed by blood sample.**

Results: **Lower values of heart rate variability indices were observed in postmenopausal women with breast cancer in relation to postmenopausal women who did not have breast cancer: Mean RR (p = 0.03); SDNN (p = 0.03); RMSSD (p = 0.03); NN50 count (p = 0.03); pNN50 % (p = 0.03); RRtri (p = 0.02); SD1 (p = 0.01); SD2 (p = 0.02); LF ms² (p = 0.01); HF ms² (p = 0.03).There was an inversely proportional correlation between the indices SDNN, SD2, and HFms² with triglycerides (SDNN p = 0.04; SD2 p = 0.04; HF ms² p = 0.04). No statistically significant correlations were found between heart rate variability indices and others variables. Statistical significance was set at 5% for all analyses.**

Conclusion: **Women with breast cancer present reduced autonomic modulation and in these women of heart rate variability indices are inversely correlated with triglyceride values. (Arq Bras Cardiol. 2019; 112(5):555-563)**

Keywords: **Aromatase Inhibitors; Breast Neoplasms; Cholesterol; Blood Glucose; Cardiovascular Dieases/prevention and control; Estrogen Replacement Therapy/adverse effects.**

Introduction

Breast cancer is the second most common type of neoplasm in the world and the most common among women. Annually, in both developing and developed countries, about 22% of new cases arise[1] and, according to the World Health Organization,[2] in 2011 more than 508,000 deaths occurred worldwide due to this disease.

Chemotherapy, radiation therapy, and hormone therapy can be used as treatment for breast cancer. These treatments are indispensable and promote positive impacts on the cure for cancer, recurrence, and metastasis; however, the side effects can cause numerous discomforts, compromising other aspects related to women's health.[3]

Among the side effects precipitated by the various treatments for breast cancer, those related to hormone therapy, more specifically to the use of aromatase inhibitors (AI), deserve attention. These substances block the enzyme aromatase, responsible for the conversion of androgens to estrogens in postmenopausal women.[3–5]

Estrogen is associated with a better lipid profile and an increase in the synthesis of vasodilatory enzymes,[6,7] so its reduction in women with breast cancer promoted by the use of AI, associated with its lower production in the menopausal period, may be related to a worse lipid profile and, consequently, a higher risk of cardiovascular diseases (CVD).[6,7]

In this context, the evaluation of women with breast cancer who are in the menopause becomes fundamental so that CVD

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can be avoided and/or prevented. Autonomic modulation analysis can be used for this purpose since the autonomic nervous system (ANS) is one of the components involved in the etiology and consequences of cardiovascular disorders caused by the treatment of breast cancer.[8,9]

The use of autonomic modulation as a predictor of cardiovascular risk in women with breast cancer was evidenced by Lakoski et al.,[9] who identified autonomic dysfunctions in these women characterized by increased sympathetic modulation and decreased parasympathetic modulation, suggesting a higher risk of CVD in women with breast cancer.

As can be observed, the risk of CVD in women with menopausal breast cancer may be related to a reduction in autonomic modulation and worsening of the lipid profile, which can be precipitated by both menopause and the use of AI.[10,11]

These women are also more prone to weight gain after chemotherapy and, consequently, to suffer changes in visceral adiposity, leading to changes in lipid profile and insulin resistance.[3] In addition, elevated levels of inflammation have been observed in cancer patients,[12] a condition also responsible for lower survival in these patients.[12,13]

However, the correlation between autonomic modulation and these factors has not been explored. Therefore, investigating the autonomic modulation of women with breast cancer in menopause who use AI and the relationship with cardiovascular biochemical variables could improve the targeting of future treatments and quality of life of women with breast cancer.

In this context, this study aimed to evaluate the cardiac autonomic modulation of postmenopausal women using AI to treat breast cancer, as well as its relationship with the following cardiovascular biochemical variables: fasting glycemia, triglycerides, HDL cholesterol, and C-reactive protein (CRP).

Methods

This is a cross-sectional study, carried out from March 2015 to July 2016, in a city in the southeastern region of Brazil. A total of 348 women, who were treated for breast cancer and registered in the records of the Oncology Pharmacy of the city's Regional Hospital, were analyzed. The medical records of these patients were analyzed and only women who were using AI were invited to participate in the study, totalling 124 women. Postmenopausal women without breast cancer were invited and recruited through radio, television, and local newspapers, totalling 189 women.

The inclusion criteria of the study were: aged between 50 and 80 years; being in the menopause, defined by the self report of absence of the menstrual cycle in the previous 12 months; signing the informed consent form to participate in the study, and not having participated in supervised physical exercise for at least six months immediately prior to the study. Specifically for women with breast cancer, in addition to all the criteria mentioned above, they were required to present stages I to IIIa of breast cancer,[14] certified by doctors through the medical records.

The study was approved by the Institution's Ethics and Research Committee (Protocol No. 6727715.1.0000.5402/2015) and registered in the ClinicalTrials.gov Platform with the identifier NCT02804308.

Experimental draw

The experimental design of the present study included two groups of women with different characteristics: one with and one without breast cancer. According to the inclusion criteria specific to this study, the convenience sampling consisted of 48 postmenopausal women, who were distributed as follows: 33 without breast cancer and 14 survivors of breast cancer under treatment with AI. The selection of the participants in this study can be better visualized in figure 1.

On the first day, all the women participating in the study answered questionnaires related to sociodemographic information (with questions related to age, education level, marital status, occupation, children, and self-reported diseases - cardiac, respiratory, metabolic, musculoskeletal). After answering the questionnaires, the volunteers underwent an evaluation of body composition using DEXA equipment - Dual Energy X-ray Absorptiometry, brand Lunar DPX-NT. Subsequently, the volunteers received a referral to the clinical analysis laboratory for blood sample collections, heart rate variability (HRV) assessments were scheduled, and the guidelines provided.

For HRV analysis, the heart rate was recorded beat-to-beat in the morning (8 am to 11 am) in a quiet environment with a temperature between 21ºC and 24ºC and relative air humidity of 40-60% and the series of RR intervals obtained were used for the calculation of HRV indices.

Body composition

Body composition was measured using DEXA Dual Energy X-ray Absorptiometry, brand Lunar DPX-NT, General Electric Healthcare, Little Chalfont, Buckinghamshire, UK, software version 4.7. The following outcome variables were collected: percentage of body fat (%), lean mass (kg), fat mass (kg), and total bone mineral density (g/cm^2).

Analysis of HRV

For the analysis of HRV, initially, the volunteers were instructed not to consume alcoholic beverages and/or ANS stimulants such as coffee, tea, soda, and chocolate, and not to perform any type of intense physical exercise during the 24 hours preceding the evaluation.

The Polar S810i heart rate monitor (Polar, Finland), previously validated equipment for recording heart rate and its use for calculation of HRV[15] indices, was used to record heart rate. The equipment pick-up strap was positioned on the distal third of the sternum and the heart rate receiver on the volunteer's wrist. During the uptake, the volunteers were instructed to remain silent, awake, at rest, and breathing spontaneously for 30 minutes in the supine position.

For the analysis of the HRV indices, 1000 RR intervals were obtained from the most stable section of the trace, which was subjected to digital filtering in the proprietary software of the cardio-frequency meter, Polar Pro Trainer 5 version 5.41.002, complemented by manual filtering for elimination

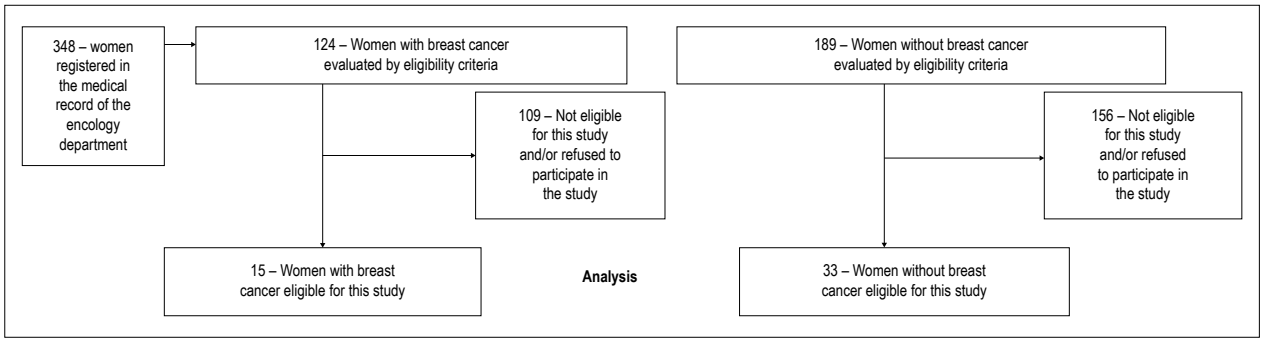

Figure 1 – *Study design: recruitment and analysis.*

of premature ectopic beats and artefacts and only series of RR intervals that presented more than 95% of sinus beats were included in the study. Calculations of the HRV indices were performed using Kubios HRV Analysis software version 2.0 (Kuopio University, Finland).[16]

The following indices were analyzed in the time domain: Mean RR, which represents the mean RR intervals; Mean HR, which corresponds to mean heart rate; SDNN, which represents the standard deviation of all normal RR intervals; RMSSD, which corresponds to the square root of the sum of the square of the differences between the RR intervals in the record, divided by the number of RR intervals in a given time minus one RR interval; and finally the NN50 (number of pairs of successive NNs that differ by more than 50 ms) and pNN50 (proportion of NN50 divided by total number of NNs), where the NN50 is the counter of the number of times that successive NN intervals present a duration difference greater than 50ms, and the pNN50 is the ratio obtained by the NN50 / n ratio.[17,18]

In the frequency domain, low frequency (LF: 0.04 - 0.15 Hz) and high frequency (HF: 0.15 - 0.40 Hz) spectral components were analyzed in ms^2 as well as the ratio between the components (LF/HF). The spectral analysis was calculated using the Fast Fourier Transform algorithm.[18]

In addition, the RRtri (RR triangular), TINN (triangular interpolation of NN interval), and Poincaré plot were also calculated, which was quantitatively and qualitatively analyzed. The RRtri and TINN were calculated by constructing a density histogram of normal RR intervals, which contains the length of the RR intervals on the x-axis and the frequency with which they occurred on the y-axis.[18] The union of the points of the columns of the histogram forms a figure similar to a triangle from which these indices are extracted.[18]

The Poincaré plot is the two-dimensional graphical representation of the correlation between consecutive RR intervals, where each interval is plotted against the next interval. For quantitative analysis of the plot, the SD1 (standard deviation of instantaneous beat-to-beat variability) and SD2 indices (long-term standard deviation of continuous RR intervals) were calculated.[18]

The qualitative analysis of the plot was carried out through the analysis of the figures formed by its attractor, which demonstrates the degree of complexity of the RR intervals. The following patterns were considered: I) Figure showing an increase in the dispersion of RR intervals, characteristic of a normal plot; II) Figure with small global dispersion, with no increase in the dispersion of RR intervals in the long term, characteristic of a plot with lower variability.[19]

Blood samples

Blood collection was performed in a private laboratory and for the biochemical analyzes the volunteers respected a 12-hour fast. The collection was performed in a vacuum tube with separator gel without anticoagulant; after collection, the blood was centrifuged for 10 minutes at 3000 rpm to separate the serum from the other blood components, which was used for the analyzes.

For the determination of glycemia, triglycerides, and the HDL-cholesterol fraction, a colourimetric enzyme kit was used in an Autohumalyzer A517 device[17] (HUMAN et al., 2004). CRP was measured using an enzyme ELISA kit: Immulite 2000 analyzer (Siemens Healthcare Diagnostics).[20]

Statistical analysis

The descriptive data for characterization of the sample are expressed as percentage, mean, standard deviation. In order to compare the anthropometric variables, age, and the HRV indices between the groups, the normality of the data was initially tested using the Shapiro-Wilk test. If the normal distribution was accepted, the Student's t-test for unpaired data was applied, while for non-normal distributions the Mann-Whitney test was applied. The continuous variables that did not present normal distribution were described through median and interquartile range and those that presented normal distribution were described through mean and standard deviation.

The correlation between the HRV indices and the independent variables CRP, fasting glycemia, triglycerides, and HDL-cholesterol was verified by linear regression in unadjusted and adjusted models, considering the age of the volunteers.

For both analyzes, statistically, significant differences were considered when the "p" value was lower than 0.05. The program used for statistical analysis was the "Statistical Package for Social Sciences" version 15.0 (SPSS Inc., Chicago, Illinois, United States of America).

Results

Table 1 presents the sociodemographic and clinical characteristics of the postmenopausal women without breast cancer and breast cancer survivors who participated in the study. There were no significant differences between groups ($p > 0.05$). The losses of the sample composition can be visualized in Figure 1.

Approximately 70.8% of women who survived breast cancer and 25% of the non-cancer group attended high school. Regarding marital status, 70.8% of women who survived and 60.1% without the disease are married. Of the women analyzed, 41.7% of the survivors of the disease and 55.6% of those without the disease worked from the home, while, 62.4% and 72.8%, respectively, reported having up to two diseases. Regarding the body composition variables analyzed (total body mass, BMI, total lean and fat mass, trunk fat mass, bone mineral density, and bone mineral content), there were no statistically significant differences between the groups.

In women with breast cancer, it was observed that 52% had undergone mastectomy surgery and 67% received treatment with chemotherapy. Most women have diagnosed in breast cancer stage I and the mean time of AI use was 19.3 months.

The Mean RR, SDNN, RMSSD, NN50, pNN50, RRtri, SD1, and SD2 indices demonstrated statistically significant reductions (Table 2) ($p \leq 0.05$) in the breast cancer group when compared to the group without the disease. The Mean HR index (1/me), which represents the heart rate (HR), was lower in the group without the disease. For the TINN index, no significant differences were found between groups ($p = 0.216$).

In the qualitative analysis of the Poincaré plot, there was a lower dispersion of the RR intervals in the cancer group compared to the non-disease group (Figure 2).

The indices in the frequency domain of HRV are presented in table 3. For the VLF (ms^2), LF (ms^2), and HF (ms^2) indices, statistically significant reductions ($p \leq 0.05$) were found in the breast cancer group when compared to the group without the disease, whereas the LF/HF ratio did not present significant differences between the groups ($p = 0.747$).

Table 1 – Sociodemographic and clinical characteristics of postmenopausal women without breast cancer and breast cancer survivors who participated in the study

Variables	Group with Breast Cancer (n = 14)	Group without Breast Cancer (n = 27)	p value
Age[a]	62.17 ± 5.79	60.03 ± 7.57	0.23
Education			
Illiterate[b]	8.3%	12.4%	
First level completed[b]	16.7%	37.6%	0.63
Second level Completed[b]	70.8%	25%	
Superior[b]	4.2%	25%	
Marital status			
Single[b]	4.2%	11.1%	
Married[b]	70.8%	61.1%	0.49
Divorced[b]	16.7%	5.6%	
Widow[b]	8.3%	22.2%	
Occupation			
From home[b]	41.7%	55.6%	
Work[b]	41.7%	5.6%	0.25
Retired[b]	16.6%	38.8%	
Self-Reported diseases			
Up to 2 diseases[b]	62.4%	72.8%	0.49
More than 2 diseases[b]	16.6%	27.8%	
Total body mass (kg)[a]	70.62 ± 12.29	69.67 ± 12.99	0.61
BMI[a]	30.71 ± 6.03	30.19 ± 4.57	0.59
Total lean mass (kg)[a]	34.94 ± 4.39	35.53 ± 4.76	0.19
Total fat mass (kg)[a]	33.38 ± 9.53	31.83 ± 9.54	0.36
Fat mass of thoracic (kg)[a]	18.17 ± 4.84	16.70 ± 4.75	0.24
BMD[a]	1.11 ± 0.11	1.17 ± 0.12	0.09
BMC[a]	2.12 ± 0.32	2.31 ± 0.32	0.11

Student t test[a]: Mean ± standard deviation; Qui Square test[b]: categorical variables, percentage. BMI: body mass index; BMD: bone mineral density; BMC: bone mineral content.

Table 2 – Linear indices in time domain of heart rate variability in each group

	Group with breast cancer (n = 14)	Group without breast cancer (n = 27)	p value
Mean RR ms[a]	707.76 ± 89.86	867.80 ± 128.87	0.047
SDNN ms[a]	17.92 ± 5.05	35.20 ± 14.94	0,042
Mean HR 1/mim[a]	85.89 ± 10.49	70.77 ± 10.75	0,050
RMSSD ms[b]	11.30 ± 8.40	18.40 ± 16.00	0.010
NN50 count[b]	0.00 ± 4.00	15.00 ± 90.50	0.022
pNN50 %[b]	0.00 ± 0,40	1.50 ± 9.05	0.022
RRtri[a]	5.76 ± 1.58	9.93 ± 4.01	0.015
TINN ms[a]	86.00 ± 22.19	138.40 ± 79.38	0.243
SD1 ms[b]	8.00 ± 5.75	13.00 ± 11.35	0.009
SD2 ms[a]	23.90 ± 6.51	46.91 ± 19.95	0.022

Student t testa: Mean ± standard deviation; Mann Whitney testb: Median ± interquartile range; SDNN: standard deviation of all normal RR intervals; HR: heart rate; RMSSD: square root of the mean of the squared differences between adjacent normal RR interval; NN50: number of pairs of successive NNs that differ by more than 50 ms; pNN50: proportion of NN50 divided by total number of NNs; RRtri: RR triangular; TINN: triangular interpolation of NN interval; SD1: instantaneous variability of beat-to-beat variability, SD2: long-term standard deviation of continuous RR intervals index; ms: milliseconds.

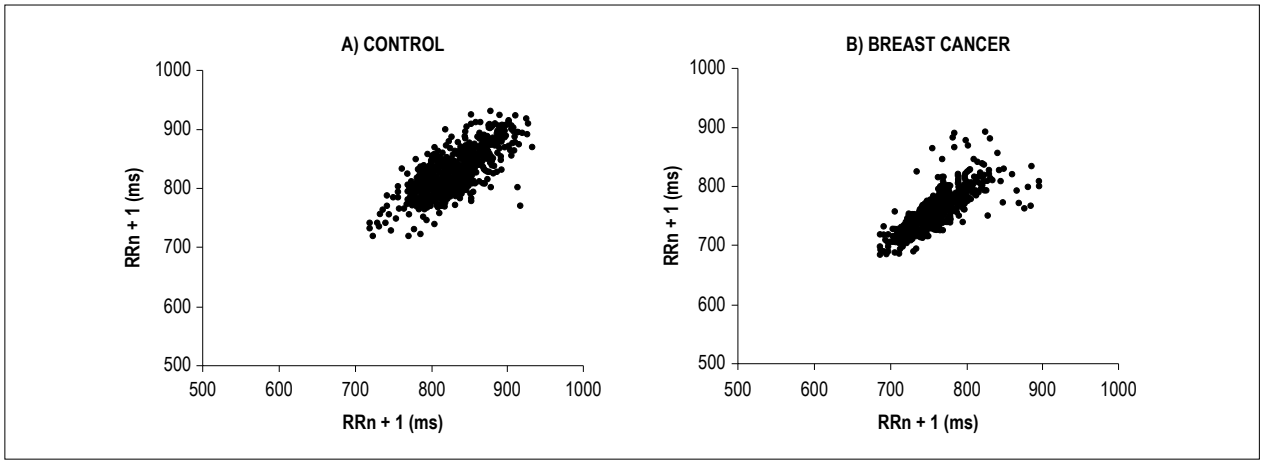

Figure 2 – *Qualitative analysis of the Poincare plot. SD1 (standard deviation of instantaneous variability), SD2 (standard deviation of the continuous RR intervals). Control: SD1 = 18 ms; SD2 = 45 ms / Breast Cancer: SD1 = 10.9 ms; SD2 = 32.6 ms.*

Table 4 shows the correlation of HRV indices with the inflammatory marker PCR and table 5 presents the variables blood glucose, triglycerides, and high-density lipoprotein with and without age adjustments in women with breast cancer.

There were no statistically significant correlations between the indices and the inflammatory marker, even when adjusted for age ($p > 0.05$), or between the Mean RR, Mean HR, RMSSD, NN50, pNN50, RR tri, TINN, VLF ms², LF ms², LF/HF, and SD1 for the variables blood glucose, triglycerides, and high density lipoprotein ($p > 0.05$).

When adjusted for age the RR tri, HF ms², and SD2 indices presented inversely proportional correlations with the triglycerides [HF - β95% CI = -0.53, p = 0.045; SD2 - β95% CI = -0.13, p = 0.044]; RRtri - β 95% CI = -0.02, p = 0.046].

Discussion

The main findings of this study demonstrate that women who are survivors of breast cancer who use AI present reductions in HRV compared to women without cancer and that these HRV indices correlate with the lipid profile.

In the present study, a statistically significant reduction in the SDNN and RR tri indices, as well as the RMSSD, SD1, NN50, and HF indices, can be observed in women with breast cancer using AI when compared to the non-cancer group, suggesting a reduction in global and vagal modulation, respectively. Moreover, the visual analysis of the Poincaré plot demonstrates a lower dispersion of the RR intervals in the cancer group, indicating that these women present HRV reduction.

Table 3 – Linear indices in frequency domain of heart rate variability in each group

	Group with breast cancer (n = 14)	Group without breast cancer (n = 27)	p value
LF ms$^{2\,b}$	67.00 ± 46.50	203.00 ± 257.50	0.009
HF ms$^{2\,b}$	70.00 ± 61.50	136.00 ± 264.00	0.008
LF/HF ms$^{2\,b}$	0.47 ± 0.99	0.71 ± 0.66	0.564

Mann Whitney testb: Median ± interquartile range; ms^2: milliseconds; LF: low frequency; HF: high frequency; VLF: very low frequency.

Table 4 – Correlation of heart rate variability indices with the inflammatory marker PCR with and without adjustments for age in woman with breast cancer

	PCR			
	Without adjustment		Adjusted (age)	
	β95% CI	p	β95% CI	p
Mean RR ms	-8.53 (-20.65; 3.58)	0.149	-6.36 (-20.21; 7.48)	0.330
SDNN ms	-0.92 (-1.98; 0.13)	0.082	-0.92 (-2.17; 0.32)	0.129
Mean HR 1/min	0.81 (-0.34; 1.96)	0.150	0.62 (-0.70; 1.94)	0.322
RMSSD ms	-0.50 (-1.03; 0.02)	0.059	-0.52 (-1.15; 0.09)	0.089
NN50 count	-0.68 (-2.25; 0.88)	0.360	-0.86 (-2.69; 0.95)	0.315
pNN50 %	-0.06 (-0.22; 0.08)	0.360	-0.08 (-0.26; 0.09)	0.315
VLF ms^2	0.00 (-0.00; 0.00)	0.588	0.00 (-0.00; 0.00)	0.685
LF ms^2	-12.40 (-34.90; 10.10)	0.251	-14.94 (-41.16; 11.27)	0.233
HF ms^2	-4.59 (-10.64; 1.45)	0.123	-6.00 (-12.76; 0.76)	0.076
LF/HF ms^2	0.00 (-0.07; 0.07)	0.972	0.01 (-0.09; 0.06)	0.699
RR tri	-0.22 (-0.45; -0.00)	0.053	-0.23 (-0.50; 0.04)	0.087
TINN ms	-3.07 (-8.00; 1.85)	0.198	-4.28 (-9.76; 1.19)	0.112
SD1 ms	-0.36 (-0.74; 0.01)	0.056	-0.37 (-0.81; 0.07)	0.092
SD2 ms	-1.26 (-2.74; 0.21)	0.086	-1.27 (-3.15; 0.47)	0.136

PCR: C reactive protein; SDNN: standard deviation of all normal RR intervals, expressed in milliseconds; HR: heart rate; RMSSD: square root of the mean of the squared differences between adjacent normal RR intervals; NN50: number of pairs of successive NNs that differ by more than 50 ms; pNN50: proportion of NN50 divided by total number of NNs; TINN: triangular interpolation of NN interval; VLF: very low frequency; LF: low frequency; HF: high frequency; RR tri: RR triangular; SD1: instantaneous variability of beat-to-beat variability; SD2: long-term standard deviation of continuous RR intervals index; ms: milliseconds.

Reduction in global variability and parasympathetic modulation was also observed by Caro-Morán et al.[8] in women with breast cancer undergoing chemotherapy, radiotherapy, and hormone therapy after 1 year of treatment. The authors observed reduced values of SDNN, RMSSD, and HF ms^2 in the cancer group in relation to the group without the disease. In these women, no significant differences were found in the LF ms^2 and LF/HF indices, although higher values were found in the cancer group.

It is important to note that higher parasympathetic modulation has been reported as an important factor related to a better prognosis for these patients, as observed by Giese-Davis et al.,[21] who reported that high baseline HF values were associated with higher survival and lower cardiovascular risk. Greater parasympathetic modulation is generally associated with lower cardiovascular risk,[22] so the reduced parasympathetic modulation found in the present study, observed through lower values of the RMSSD, pNN50, SD1, and HF ms^2 indices in the cancer group, may indicate higher cardiovascular risk and a worse prognosis in this population.

High HRV is associated with higher levels of parasympathetic modulation and longer survival in patients with myocardial infarction and those under palliative care.[21] Regarding cancer, alterations in autonomic modulation influence the development and prognosis of the disease.

In a study carried out with an animal model it was shown that stimulation of the nervous system with the release of catecholamines can activate beta-adrenergic receptors in tumour cells, leading to more aggressive growth and dissemination of malignant cells, whereas in humans the use of beta- has been shown to be beneficial in reducing the risk of recurrence in patients with breast cancer.[23] Regarding parasympathetic modulation, Erin et al.[24] demonstrated that vagal blockade promotes the increase of metastases in mice.

Table 5 – Correlation of heart rate variability indices with the metabolic variables blood glucose, triglycerides, and high-density lipoprotein with and without adjustments for age in women with breast cancer

	Blood Glucose				Triglycerides				HDL			
	Without adjustment		Adjusted (Age)		Without adjustment		Adjusted (Age)		Without adjustment		Adjusted (Age)	
	β95% CI	p	β95% CI	p	β 95% CI	p	β95% CI	p	β95% CI	p	β95% CI	p
Mean RR ms	-0.08 (-2.96; 2.79)	0.950	-0.23 (-3.08; 2.61)	0.86	-0.76 (-1.81; 0.29)	0.141	-0.75 (-1.78; 0.27)	0.135	-2.68 (-10.25; 4.88)	0.454	-0.52 (-9.52; 8.47)	0,900
SDNN ms	-0.06 (-0.34; 0.21)	0.609	-0.07 (-0.36; 0.22)	0.60	-0.09 (-0.19; -0.00)	0.045	-0.09 (-0.19; 0.00)	0.055	0.03 (-0.733; 0.79)	0.930	0.13 (-0.81; 1.07)	0,766
Mean HR ms	-0.00 (-0.28; 0.26)	0.943	-0.00 (-2.26; 0.27)	0.97	0.06 (-0.03; 0.16)	0.194	-0.81 (-2.18; 0.54)	0.189	0.26 (-0.44; 0.98)	0.431	0.07 (-0.78; 0.92)	0,856
RMSSD ms	-0.03 (-0.18; 0.10)	0.584	-0.03 (-0.19; 0.11)	0.58	-0.04 (-0.09; 0.01)	0.107	-0.04 (-0.09; 0.01)	0.123	0.01 (-0.38; 0.40)	0.958	0.04(-0.43; 0.53)	0,828
NN50 count	-0.05 (-0.40; 0.29)	0.738	-0.05 (-0.42; 0.32)	0.76	-0.05 (-0.18; 0.08)	0.448	-0.18 (-0.19; 0.09)	0.466	0.08 (-0.86; 1.04)	0.844	-0.06 (-1.12; 1.24)	0,913
pNN50 %	-0.00 (-0.04; 0.03)	0.738	-0.00 (-0.04; 0.03)	0.76	-0.00 (-0.01; 0.00)	0.448	-0.18 (-0.20; 0.01)	0.466	0.00 (-0.08; 0.10)	0.844	0.00 (-0.11; 0.12)	0,913
RR tri	-0.01 (-0.08; 0.04)	0.563	-0.01 (-0.08; 0.05)	0.563	-0.02 (-0.04; -0.00)	0.037	-0.02 (-0.04; -0.00)	0.046	0.02 (-0.12; 0.20)	0.769	0.04 (-0.17; 0.27)	0,634
TINN ms	-0.29 (-1.48; 0.89)	0.599	-0.26 (-1.51; 0.97)	0.646	-0.18 (-0.65; 0.28)	0.397	-0.19 (-0.67; 0.29)	0.405	1.62 (-1.45; 4.70)	0.273	1.57 (-2.25; 5.39)	0,955
VLF ms^2	-1.7E-005 (0.00; 0.00)	0.882	-2.0E-00 (-0.00; 0.00)	0.868	-5.5E-005 (0.00; 0.00)	0.218	-5.5E-005 (0.00; 0.00)	0.239	0.00 (-0.00; 0.00)	0.577	0.00 (-0.00; 0.00)	0,642
LF ms^2	-1.21 (-6.41; 3.97)	0.619	-1.20 (-6.70; 4.29)	0.639	-1.48 (-3.37; 0.41)	0.114	-1.48 (-3.48; 0.51)	0.131	0.95 (-13.16; 15.07)	0.885	-0.81 (-16.72; 18.35)	0,920
HF ms^2	-0.62 (-2.11; 0.86)	0.381	-0.59 (-2.16; 0.96)	0.419	-0.53 (-1.05; -0.01)	0.045	-0.53 (-1.07; 0.00)	0.051	0.36 (-3.76; 4.49)	0.850	-0.14 (-5.23; 4.95)	0,951
LF/HF ms^2	-0.00 (-0.02; 0.00)	0.291	-0.00 (-0.02; 0.00)	0.334	-0.00 (-0.00; 0.01)	0.390	0.00 (-0.01; 0.01)	0.482	0.00 (-0.03; 0.05)	0.674	-0.00 (-0.05; 0.04)	0,945
SD1 ms	-0.28 (-0.13; 0.07)	0.568	0.10 (-0.48; 0.70)	0.561	-0.03 (-0.06; 0.00)	0.095	-0.03 (-0.07; 0.00)	0.110	0.00 (-0.28; 0.28)	0.991	0.03 (-0.31; 0.38)	0,830
SD2 ms	-0.09 (-0.48; 0.29)	0.604	-0.10 (-0.51; 0.30)	0.596	-0.13 (-0.27; -0.00)	0.044	-0.13 (-0.27; 0.00)	0.053	0.05 (-1.01; 1.11)	0.918	0.19 (-1.11; 1.50)	0,749

PCR: C reactive protein; SDNN: standard deviation of all normal RR intervals, expressed in milliseconds; HR: heart rate; RMSSD: square root of the mean of the squared differences between adjacent normal RR intervals; NN50: number of pairs of successive NNs that differ by more than 50 ms; pNN50: proportion of NN50 divided by total number of NNs; TINN: triangular interpolation of NN interval; VLF: very low frequency; LF: low frequency; HF: high frequency; RR tr: RR triangular; SD1: instantaneous variability of beat-to-beat variability; SD2: long-term standard deviation of continuous RR intervals index; ms: milliseconds.

Estrogen is indicated as the main cardioprotective factor for women and its reduction in menopause is related to the increase in sympathetic activity; a circumstance that may be aggravated in women with breast cancer due to treatment of the disease with AI.[19] In this context, the present study presents important results regarding the clinical framework of these patients.

Regarding the correlation between HRV indices and cardiovascular biochemical variables, no correlation was observed with CRP, fasting glycemia, or HDL-Cholesterol. CRP has been highlighted, since elevated levels of this protein are associated with an increased risk of peripheral arterial disease, myocardial infarction, stroke, and sudden death,[25] and high levels of CRP are predictive of poor prognosis for cancer patients, regardless of lifestyle, menopausal status, and the presence of CVD.[12]

Although no statistically significant negative correlations were observed between HRV and CRP levels, indices reflecting overall variability and parasympathetic modulation presented marginal statistical values in relation to the correlation with CRP levels of the cancer group (SDNN – β95% CI = 0.92, p = 0.082; SD2 – β95% CI = 1.26, p = 0.136; RMSSD – β 95% CI = -0.50, = 0.089; SD1 – β95% CI = 0.36, p = 0.092).

Regarding the correlation between HRV and the triglyceride indices, we observed an inversely proportional correlation of triglycerides with the $HFms^2$ index β95% CI = -0.53; p = 0.045) and, although not significant, the SD1 index presented similar behavior (β95% CI = -0.03; p = 0.095). In addition, the indices that reflect global variability, SDNN and SD2, also presented inversely proportional correlations with the triglycerides (SDNN – β95% CI = -0.09; p = 0.045; SD2 – β95% CI = - 0.13; p = 0.044), suggesting that changes in autonomic modulation in women with breast cancer, characterized by a reduction in HRV, may be associated with a worse lipid profile. Studies show that ANS imbalance is associated with hormonal and metabolic alterations since this system plays a fundamental role in metabolic control.[26]

The study presents some methodological points to be raised. In the analyzes, we did not take into account associated heart diseases or the use of medications which could alter cardiac activity. In addition, the sample size considered for correlation analyzes may not have been sufficient for correlations between CRP, blood glucose, HDL-Cholesterol and HRV to be considered statistically significant.

Despite this, the study presents an important clinical implication regarding alterations in the autonomic modulation of women with breast cancer who use AI and the inversely proportional relationship between HRV and triglyceride values in this population, suggesting a higher risk of CVD and a worse prognosis for these women. This information reinforces the need to use preventive strategies that are safe and effective in the clinical approach of these patients.

Conclusion

Based on our findings, women with breast cancer who use AI present reductions in HRV compared to women without cancer and in these women HRV indices are inversely correlated with triglyceride values.

Author contributions

Conception and design of the research: Paulo TRS, Viezel J, Freitas Jr. IF; acquisition of data: Paulo TRS, Viezel J; analysis and interpretation of the data: Gonzaga, LA, Vanzella LM; statistical analysis: Gonzaga, LA, Vanzella LM, Vanderlei LCM; writing of the manuscript: Gonzaga, LA, Paulo TRS, Vanzella LM; critical revision of the manuscript for intellectual content: Freitas Jr. IF, Vanderlei LCM.

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 Faculdade de Ciências e Tecnologia - UNESP under the protocol number 672.7715.1.00005402/2015. 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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Disparities In The Use Of Drug-eluting Stents For Diabetic Patients With ST-elevation Acute Myocardial Infarction Assisted In the Public versus Private Network - VICTIM Register

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Abstract

Background: **Primary angioplasty (PA) with placement of either bare metal or drug-eluting stents (DES) represents the main strategy in the treatment of ST-elevation myocardial infarction (STEMI). Diabetic patients, however, represent a special population in STEMI, with high rates of restenosis and unfavorable clinical outcomes, and with the use of DES, level of evidence A and indication class II, being indicated to reduce these damages.**

Objectives: **To evaluate the DES rate of use in patients with STEMI and in the subgroup of diabetics assisted in the public versus private health network in Sergipe.**

Methods: **This is a population-based, cross-sectional study with a quantitative approach using the data from the VICTIM Register. These were collected in the only four hospitals with capacity to perform PA in Sergipe, from December 2014 to March 2017.**

Results: **A total of 707 patients diagnosed with STEMI were evaluated, of which 589 were attended at SUS and 118 at the private network. The use of DES in PA was lower in SUS compared to the private network in both the total sample (10.5% vs 82.4%, p<0.001) and in subgroup diabetic patients (8.7% vs 90.6%, p < 0.001), respectively. In all hypotheses tested, the level of significance was 5% (p < 0.05).**

Conclusions: **The study reveals a disparity in the use of DES during the performance of PA between the public and private network, both in the total sample and the subgroup for diabetics, with lower rates for SUS users, demonstrating the challenges that need to be overcome in order to achieve quality improvements of the services provided. (Arq Bras Cardiol. 2019; 112(5):564-570)**

Keywords: **ST Elevation Myocardial Infarction; Drug-Eluting; Diabetes Mellitus; Case-Control Studies; Angioplasty; Hospitals,Private; Hospitals, Public.**

Introduction

The early use of coronary reperfusion therapies is one of the main factors associated with the longer survival of patients with acute ST-segment elevation myocardial infarction (STEMI). In this context, primary angioplasty (PA) is the preferred option for this purpose, if started up to 90 minutes after confirmation of the diagnosis of infarction.[1,2] Coronary stent implantation is considered the device of choice for the completion of angioplasty because its use reduces the rates of acute vessel occlusion, and the need for late surgical revascularization when compared to the procedure performed with balloon alone.[3]

However, diabetic patients diagnosed with STEMI represent a special population because of the greater difficulty of percutaneous treatment.[4] This group shows high rates of restenosis and is associated with unfavorable clinical outcomes, even with the use of bare metal stents.[1,5] Thus, the Brazilian Society of Hemodynamics and Interventional Cardiology (SBHCI) recommends the preferential use of the

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drug-eluting stent in diabetics, with evidence level A and indication class II, since these devices release substances that inhibit intimal hyperplasia of the treated vessel, further reducing the chances of restenosis.[1,3]

A major obstacle faced with the use of drug-eluting stents (DES) is the high cost of the device when compared to the bare metal one, in addition to the expenses with prolonged double antiplatelet therapy, which further increases its treatment cost.[1,6] However, the cost-effectiveness ratio is attractive for the incorporation of this technology when it comes to diabetic patients, since they reflect a lower budget impact by avoiding late complications and the need for future reinterventions. Thus, this device was released for use in the Brazilian Unified Health System (SUS) for the patients above mentioned in 2014, according to ordinance no. 29 of the Ministry of Health.[7]

Therefore, this study aims to evaluate the rate of DES in patients with STEMI, and in the subgroup of diabetic patients assisted in the public versus private healthcare network in Sergipe.

Methods

The present analysis used data from the VICTIM Register (VIa Crucis for the Treatment of Myocardial Infarction), a study that aims to analyze and compare the access of STEMI patients to hospitals with capacity to perform angioplasty in the public and private networks of the state of Sergipe.

This is a cross-sectional study, with a quantitative approach, developed from December 2014 to March 2017. Data collection was performed in the only four hospitals in the state of Sergipe with capacity to perform AP, all located in the capital city Aracaju. Among these, only one offers service through SUS, and does not have "open door" care, which requires that the patient be referenced from another health institution to be admitted to that hospital. The other three hospitals offer private service, either through health plans or private payment.

To collect data, a study-specific tool, CRF (Case Report Form), was used; data includes information on socio-demographic conditions, onset of symptoms and clinical presentation, hospitalization data, angiographic procedure, patients' progression during hospitalization and up to 30 days after AMI. To be filled, the interview with the patient (or with the relative, when the patient had no clinical conditions) was used as source, besides the analysis of the medical record.

Patients older than 18 years, with a history consistent with AMI, electrocardiographic confirmation of the STEMI according to the defining criteria of the V Guideline of the Brazilian Society of Cardiology on the treatment of STEMI,[1] and who signed the Free Informed Consent Term (FIC) were included. Those unable to sign had their participation authorized by a person responsible for them; the illiterate patients gave permission by fingerprint.

The following patients were excluded: those who died before the interview; who did not characterize the Via Crucis, that is, those who were hospitalized for other causes when they had STEMI; those who refused to participate in the survey; those whose acute STEMI event was characterized as reinfarction (occurring within 28 days of the incident infarction); those who had a change of diagnosis - that is, they entered the tertiary hospitals with an initial diagnosis of STEM, but after having undergone exams, another finding was observed; and those attended through a health plan in a philanthropic hospital.

This research was submitted to the Research Ethics Committee of Universidade Federal de Sergipe (UFS) and approved with CAAE no. 23392313.4.0000.5546.

Statistical analysis

All STEMI patients, representing all the cases treated in the State, were included in the sample, since all the centers with a hemodynamic service were included in the study. To evaluate the association for categorical variables presented in absolute numbers and percentage, Pearson chi-square test was used. Continuous variables were presented by mean and standard deviation and the unpaired Student t-test was used to evaluate the means differences, and its adherence to the normal distribution was tested using Kolmogorov-Smirnov test ($p>0.05$). In all hypotheses tested, the level of significance was 5% ($p<0.05$). The SPSS for Windows Version 17 software was used for statistical analysis.

Results

Sociodemographic profile

A total of 707 patients were analyzed, of which 83% were attended by the public service and 17% by the private network. In both services, most patients were male (67.1% vs 71.2%, $p = 0.382$), with a mean age of 61.2 ± 12.2 years vs. 62.3 ± 12.2 years ($p = 0.332$), respectively. Ethnicity was a variable collected based on the self-declaration of the patients involved. In this context, a statistically significant difference was observed when the two services are compared, with 68.7% of the SUS patients declaring being non-whites, while 60% of the patients in the private network declared themselves to be white ($p < 0.01$) (Table 1).

Other expressive data regarding the differences between the patients attended by SUS and the private network are related to social class and educational level. Regarding social class, it can be observed that in the public service 61.2% of the patients had family income consistent with class E (gross family income of up to two minimum wages), while in the private network 33% of the patients were class C (gross family income from 4 to 10 minimum wages) ($p < 0.001$). Regarding the level of education, 57% of public service patients studied until elementary school, while 30.5% of the patients attended by the private network studied until higher education level ($p < 0.001$). It is worth mentioning that about 27% of the public service patients never studied (Table 1).

Cardiovascular risk factors

The cardiovascular risk evaluated for patients from SUS and from the private network admitted to the study were: systemic arterial hypertension, diabetes mellitus, dyslipidemia and smoking. In both services, hypertension was shown to be the most prevalent factor (39.2% vs 71.2%, $p = 0.033$), followed by dyslipidemia (33.6% vs 55.9%, $p < 0.001$). Diabetes mellitus

Table 1 – Sociodemographic profile of STEMI patients attended at Sergipe State Hospitals with capacity to perform primary angioplasty (SUS x Private care)

Demography	SUS (n = 589)	Private network (n = 118)	p value
Age, years (mean ± SD)	61.2 ± 12.2	62.3 ± 12.2	0.332
Gender, n (%)			
Male	395 (67.1)	84 (71.2)	0.382
Female	194 (32.9)	34 (28.8)	
Ethnicity, n (%)			
White	179 (31.3)	69 (60.0)	< 0.001
Non-white	393 (68.7)	46 (40.0)	
Social class, n (%)			
A*	2 (0.4)	11 (9.8)	< 0.001
B†	8 (1.5)	30 (26.8)	
C ‡	39 (7.1)	37 (33.0)	
D §	163 (29.8)	24 (21.4)	
E //	334 (61.2)	10 (9.0)	
Level of Education			
Never studied	161 (27.3)	6 (5.1)	< 0.001
Elementary School	335 (57.0)	29 (24.5)	
High School	78 (13.2)	31 (26.3)	
Higher Education	12 (2.0)	36 (30.5)	
Postgraduate studies	3 (0.5)	16 (13.6)	
Marital status, n (%)			
Single	91 (15.5)	4 (3.4)	< 0.001
Married	298 (50.6)	84 (71.2)	
Lives with a partner	92 (15.6)	4 (3.4)	
Divorced	39 (6.6)	9 (7.6)	
Widower	69 (11.7)	17 (14.4)	

A: Above 20 minimum wages (*); B: 10 to 20 minimum wages (†); C: 4 to 10 minimum wages (‡); D: 2 to 4 minimum wages (§); E: Up to 2 minimum wages (//).

was third in prevalence in the private service (35.6%, $p < 0.001$), while in the public service it was fourth (33.8%, $p < 0.001$). Smoking was a factor of great disparity between the two care networks (34% vs 9.3%; $p < 0.001$). Most patients presented the association of 2 risk factors in both services (35.1% vs 40.7%, $p = 0.534$) (Table 2).

When the characteristics related to the pathological history of both groups were evaluated, a prevalence of factors related to the patients attended by the private service was observed, with them being a previous history of AMI (7.1% vs 16.1%, $p = 0.002$), and previous angioplasty (4.9% vs 10.2%; $p = 0.026$), and prior coronary artery bypass grafting (0.8% vs 5.1%, $p < 0.001$). The prevalence of family history of previous coronary artery disease (29.4% vs 44.1%, $p = 0.002$) and peripheral vascular disease (5.3% vs 15.3%; $p < 0.001$) (Table 2) are also observed for the patients of the private service.

Coronary reperfusion

During STEMI, there was a significant disparity between the results obtained by all patients attended at SUS and all those who sought private care regarding the use of PA. For the former, the reperfusion rate was 45.3% while for the latter it was 79.7% ($p < 0.001$). In both services, the use of conventional and pharmacological stents was analyzed, and in this aspect an important discrepancy was also observed, since there was a predominance of the use of bare metal stents in SUS (89.5%, $p < 0.001$), and DES in the private network (82.4%, $p < 0.001$) (Table 3).

Coronary reperfusion in diabetic patients

In view of the recommendation of guidelines[1,3] for the use of DES in diabetics, with level of evidence A and indication class II, these patients were grouped in a special subgroup to assess if the recommendations for stent placement are being followed during coronary angioplasty. A total of 199 diabetic patients were seen in the public service; of these, 47.7% had access to PA and, in most interventions (91.3%), bare metal stents were used, while only 8.7% used DES ($p < 0.001$). In the private service, 42 diabetics were attended; of these, 78.6% had access to primary PCI, with placement of drug-eluting

Table 2 – Pathological background of STEMI patients attended at Sergipe State Hospitals with capacity to undergo primary angioplasty (SUS x Private care)

Pathological background	SUS (n = 589)	Private network (n = 118)	p value
Cardiovascular risk factors, n (%)			
Hypertension	358 (39.2)	84 (71.2)	0.033
Diabetes	199 (33.8)	42 (35.6)	0.705
Dyslipidemia	214 (36.3)	66 (55.9)	< 0.001
Smoking	200 (34.0)	11 (9.3)	< 0.001
Number of risk factors, n (%)			
0	75 (12.7)	14 (11.9)	0.534
1	191 (32.5)	31 (26.2)	
2	207 (35.1)	48 (40.7)	
≥ 3	116 (19.7)	25 (21.2)	
Previous coronary disease, n (%)			
AMI	42 (7.1)	19 (16.1)	0.002
Angina pectoris	94 (84.0)	22 (18.6)	0.472
Previous Angioplasty	29 (4.9)	12 (10.2)	0.026
Revascularization			
Previous	5 (0.8)	6 (5.1)	0.001
Family history of early CAD, n (%)	173 (29.4)	52 (44.1)	0.002
Stroke previous, n (%)	41 (7.0)	7 (5.9)	0.685
Peripheral vascular disease, n (%)	31 (5.3)	18 (15.3)	< 0.001

AMI: acute myocardial infarction; CAD: coronary artery disease.

Table 3 – Percutaneous coronary angioplasty and use of stents in STEMI patients attended in tertiary Hospitals in the State of Sergipe (SUS x Private network)

Coronary angioplasty	SUS (n = 589)	Private network (n = 118)	p value
Door-to-balloon time, min	121.2 ± 107.1	129.8 ± 90.2	0.48
Primary Angioplasty, n (%)	267 (45.3)	94 (79.7)	< 0.001
Type of stent used, n (%)			
Bare metal	229 (89.5)	16 (17.6)	< 0.001
Drug-eluting	27 (10.5)	75 (82.4)	
Non-Primary Angioplasty, n (%)	193 (32.8)	21 (17.8)	0.001
Type of stent used, n (%)			
Bare metal	166 (90.7)	3 (14.3)	< 0.001
Drug-eluting	17 (9.3)	18 (85.7)	

stent in 90.6% of this subgroup of patients (p < 0.001) (Table 4). The mean and standard deviation of the port-balloon time of diabetics seen at SUS versus the private system were 114 (± 91) and 133 (± 67), respectively (p = 0.26).

Discussion

A disparity between the public and private services regarding the performance of PA and the use of DES for patients with STEMI, especially for diabetics, is observed. It is also worth noting a remarkable overuse of bare metal stents with higher utility rates for the public service, which is in disagreement with the guidelines recommendations.[1,3]

The value found for performing PA at the Unified Health System (SUS) was below the expected average in relation to procedures performed in the North-Northeast (52.5%), according to a study by Nicolau et al. in 2012.[8] Primary PCI with the use of stents is considered the gold standard in the treatment of STEMI,[1,2] and these findings reflect the underuse of this therapy at SUS, which may directly contribute to these patients' prognosis.

Table 4 – Percutaneous coronary angioplasty and use of stents in diabetic STEMI patients attended in tertiary Hospitals in the State of Sergipe (SUS x Private network)

Coronary angioplasty In diabetic patients	SUS (n = 199)	Private network (n = 42)	p value
Primary Angioplasty, n (%)	95 (47.7)	33 (78.6)	< 0.001
Type of stent used, n (%)			
Bare metal	84 (91.3)	3 (9.4)	< 0.001
Drug-eluting	8 (8.7)	29 (90.6)	
Non-Primary Angioplasty, n (%)	63 (31.7)	10 (23.8)	0.314
Type of stent used, n (%)			
Bare metal	52 (88.1)	0 (0)	< 0.001
Drug-eluting	7 (11.9)	10 (100)	

Although the proportion of patients undergoing PA is higher in the private network (79.7%, $p < 0.001$), this result may still be suboptimal, since Sergipe is small in size, which should facilitate access to Primary Care. Therefore, there is a need to improve the quality of the service provided, with the training of multiprofessional teams for the rapid and adequate diagnosis of AMI both in the intra- and prehospital settings, so that access to reperfusion therapies for myocardial infarction is optimized.

It is also observed that 82.4% of the patients seen at the private network received DES in the PA, while in the public network only 10.5% ($p < 0.001$) received them. This result in Sergipe at SUS is below the rate of use of DES in the public network throughout Brazil (14%) between the years 2004 and 2005, when these devices were not yet released for use in SUS, according to data of the CENIC Registry.[9] The indication for use of DES follows specific criteria determined by the SBHCI, such as stenosis in the single remaining vessel, intra-stent restenosis, and diabetics with stenosis that can be treated with PA.[3] The wide low use of DES in the public network, however, is justified by possible additional expenses inherent to the procedure. These devices have a much higher cost compared to bare metal ones, and require sustained dual antiplatelet therapy, which further increases their effective cost.[10]

On the other hand, the large use of these stents at the private network (in approximately 80% of the total analyzed) may suggest the lack of an adequate protocol of use instructions, extrapolating the classic and evidence-based indications. The high financial cost that this therapy entails is expressive; thus, the cost-effectiveness of DES is potentially questionable in such situations.[11,12]

An American study conducted in 2007 by Beohar et al.[12] showed that the use of DES in patients without formal indications that were not tested by clinical trials was related to more severe outcomes when compared to those patients who had a standard indication. Another more recent American study, conducted in 2017,[13] argues that the superiority of DES should not automatically translate into the end of the use of bare metal stents, since the latter still have a potential advantage in specific situations because of the short-term need for antiplatelet aggregation. Patients who will undergo another surgical procedure, either cardiac or not, or those who have high risk of bleeding strongly benefit from the use of metal prostheses. Therefore, DES should not be indiscriminately and randomly used.[13]

Regarding the use of DES for diabetic patients, the results also revealed a disparity when the public and private networks were compared. During PA, the DES use rate in diabetics was 8.7% vs. 90.6%, $p < 0.001$. It is worth mentioning that diabetes mellitus is one of the most common clinical conditions with increasing incidence. They represent a special group of patients facing coronary angioplasty, with large international randomized studies demonstrating high rates of late reintervention and restenosis during the use of conventional prostheses.[14-16] Because in such cases the cost-effectiveness ratio makes the use of the technology economically viable, with less impact on the budget, it is known that DES are allowed for use at SUS in these situations.[9] However, the data found in the present study also reveal a much lower use of this technology in the public service.

These findings point to the fact that even after the creation of national legislation, recommendations for drug-eluting stent use have not been followed in Sergipe. In this scenario, diabetics receiving bare metal stents would not have the benefit of reducing morbidity and mortality when compared with the use of DES, as demonstrated in international studies, such as DIABETES, SCORPIUS and ISARDESIRE.[17-19]

Thus, failure to follow the current recommendations triggers a warning signal for the need to monitor the adequate implementation of public health policies in Sergipe, as well as recommend the adoption of a system of governance in the use of stents according to criteria adopted by the guidelines in force.

The present study has some limitations. First, it is an observational study, in the form of a record. Therefore, there is a possibility that other aspects, other than those found in the analysis, may have influenced the choice of the stent, including logistic phenomena, such as occasional lack of a given material. Secondly, the low level of education, especially in the SUS group, impaired self-information regarding personal medical history, with a tendency to underestimate risk factors and comorbidities. Third, late follow-up of patients was not performed. As a consequence, it was not possible to evaluate whether the disparity in the indication resulted in a significant impact on the restenosis rate.

Conclusion

The study reveals a disparity in the use of DES during coronary angioplasty among patients attended at SUS and at the private network, either in the total sample or in the subgroup of diabetic patients, since lower rates of DES use were observed at SUS in both populations. This fact shows failure to follow an adequate protocol in the use of DES and their classic indications, which increases treatment cost-effectiveness. In addition, the diabetics in the public network have been mostly receiving bare metal stents, even after legislation has been in place to regulate the use of DES in this special subgroup of patients. Therefore, it is necessary to monitor the proper implementation of health policies, and to reassess therapeutic strategies and their real cost-effectiveness.

Author contributions

Conception and design of the research: Oliveira JC, Oliveira JC, Barreto-Filho JAS; Acquisition of data: Oliveira JC, Oliveira LCS, Oliveira JC, Lima TCRM, Arcelino LAM, Silva ISBS, Barreto-Filho JAS; Analysis and interpretation of the data: Oliveira JC, Oliveira LCS, Barreto IDC, Almeida-Santos MA, Sousa ACS, Barreto-Filho JAS; Statistical analysis: Oliveira JC, Barreto IDC, Barreto-Filho JAS; Obtaining financing: Oliveira JC, Barreto-Filho JAS; Writing of the manuscript: Oliveira JC, Lima TCRM, Arcelino LAM, Silva ISBS, Sousa ACS, Barreto-Filho JAS; Critical revision of the manuscript for intellectual content: Oliveira JC, Oliveira LCS, Oliveira JC, Almeida-Santos MA, Lima TCRM, Barreto-Filho JAS.

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade Federal de Sergipe under the protocol number 483.749. 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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Brazil: Two Realities for the Treatment of One Disease

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Short Editorial to the article: Disparities In The Use Of Drug-eluting Stents For Diabetic Patients With ST-elevation Acute Myocardial Infarction Assisted In the Public versus Private Network - VICTIM Register

Current drug-eluting stents (DES) are safer and more effective (lower restenosis rates) than bare-metal stents (BMS),[1,2] and are able to reduce short- and long-term cardiovascular outcomes.[3,4] In patients with ST segment elevation acute myocardial infarction (STEMI), the randomized study EXAMINATION[5] evaluated 1,498 patients with STEMI, who were allocated for the treatment of percutaneous coronary intervention (PCI) with new-generation DES containing everolimus or BMS. After a 5-year follow-up, there was a relative reduction of combined outcomes and mortality of 20% and 30%, respectively, in favor of DES. Finally, despite the higher initial cost in the index procedure, DESs present better cost-effectiveness compared to BMS on long-term.[6] In this context, in 2018, the most current Guideline for coronary artery bypass grafting of the European Society of Cardiology considers recommendation Class I the use of DES in any and all clinical settings, including STEMI.[7]

Cardiovascular disease is the leading cause of death worldwide and diabetes mellitus is one of the most important risk factors for coronary atherosclerotic disease (CAD).[8] Diabetic patients present 2 to 3-fold higher mortality after acute coronary syndrome compared to non-diabetics.[9] Besides, as these patients present expressive endothelial dysfunction, high inflammatory response to vascular injury, diffuse CAD and coronary arteries of smaller caliber, they develop higher rates of in-stent restenosis.[10,11] In view of that, using DES is even more imperative in patients with diabetes, and presents 87% less risk of in-stent restenosis and 77% less risk of revascularization of the target lesion compared to BMS.[12]

In this study VICTIM Oliveira et al.,[13] analyzing the incorporation of DES in public and private institutions in the State of Sergipe (between 2014 and 2017; after the approval of its use in Brazil's public health system [SUS] at the amount of BRL 2,034.50), found that only 8.7% of diabetic patients with STEMI were treated with DES in the public system, while 90.6% received DES in the private healthcare system. These figures make evident the worrying reality of the Brazilian public health system regarding the treatment of STEMI, especially in a vulnerable population such as diabetics. Moreover, despite the official approval (Ordinance No. 29 issued by the Ministry of Health) of such advanced technology, in Brazil's public healthcare system, its use in non-diabetics and diabetics is important and significantly lower than that of the private healthcare system. In this study, there was no statistical difference for the number of risk factors per patient between the groups, with most of them presenting ≥ 2 cardiovascular risk factors. Noted that the main determinants to receive this globally recommended and proven superior therapy were: family income and education level and, consequently, being able to afford private healthcare. In the United States, in 2003 (one year after DES started being used), 32.7% of diabetic patients undergoing PCI received DES and, in 2011, this number was in excess of 75%.[14]

According to the Brazilian National Health Agency (ANS), in 2019, only 24.3% of Brazilians have private health insurance and, because of that, less than one quarter of the population has access to the treatment recommended by international and Brazilian guidelines.[15] On the other hand, the vast majority of the population of diabetics only have BMS available. In the international scientific community, unlike the Brazilian reality, the debate about the use of BMS versus DES is now outdated. Also, progress of a new generation of DES such as those of ultrathin struts with bioabsorbable and non-polymeric polymers is discussed.

Thus, as demonstrated in the VICTIM registry, Brazil – a developing country – could be divided into two major nations regarding the treatment of STEMI by PCI: one, the public healthcare system, with most of the population exposed to non-contemporary treatment and unequivocally inferior clinical outcomes; another, the private health system with a population with better socioeconomic conditions and access to the best technologies, similar to those of developed countries. By addressing the deficiencies found in Brazil's public healthcare system in the treatment of a significant portion of the population, this study is expected to stimulate reflections and changes in health promotion and the provision of new treatments to the impoverished population.

Keywords

Coronary Artery Disease; Cardiovascular Diseases/mortality; ST Elevation Myocardial Infarction; Myocardial Revascularization; Diabetes Mellitus; Percutaneous Coronary Intervention; Drug-Eluting Stents.

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Continuous Intravenous Inotropes in Ward Units: Expanding Therapy Outside Intensive Care using a Safety-Oriented Protocol

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Abstract

Selected clinically stable patients with heart failure (HF) who require prolonged intravenous inotropic therapy may benefit from its continuity out of the intensive care unit (ICU). We aimed to report on the initial experience and safety of a structured protocol for inotropic therapy in non-intensive care units in 28 consecutive patients hospitalized with HF that were discharged from ICU. The utilization of low to moderate inotropic doses oriented by a safety-focused process of care may reconfigure their role as a transition therapy while awaiting definitive advanced therapies and enable early ICU discharge.

Introduction

In advanced heart failure (HF), patients with low output syndrome may benefit from intravenous inotropes to provide symptomatic relief and hemodynamic support with different purposes – stabilization of the acute setting, bridge to more definitive surgical therapies for advanced disease and palliation. Among patients admitted with decompensated HF, around 12 to 14% receive inotropes.[1] However, the safety of inotrope use remains a concerning issue.[2]

In the acute setting, continuous inotropic infusions are usually initiated in intensive care units (ICU), where doses may be titrated with careful monitoring of pro-arrhythmogenic and vasodilatory effects until the patient is stabilized. Some patients may require longer periods of inotropic support, and, depending on their clinical status, may benefit from the continuity of inotropic therapy in a less intensive care setting. Our aim is to report the initial experience of a structured protocol for intravenous inotropic therapy in non-intensive care units, focusing on safety processes and end-points.

Methods

We retrospectively reviewed all consecutive patients hospitalized with HF that were discharged from ICU on an intravenous inotropic infusion in our tertiary, academic hospital from July, 2015 to December, 2017. The strategy to promote discharge to the ward on inotropic therapy was supported by an institutional protocol, which is summarized in the Table 1. Briefly, stabilized HF patients receiving a low to moderate dose of continuous intravenous inotrope (dobutamine or milrinone) for different indications in the ICU were considered for transition of care to a ward unit equipped with cardiac telemetry, except if inotrope was intended for palliation, in which case telemetry was not used. Adverse events - defined as readmission to ICU due to worsening HF, atrial arrhythmia, ventricular arrhythmia requiring inotropic dose reduction, and infection related to central intravenous access - that occurred while the patient was receiving inotropic infusion in the ward were recorded. In-hospital outcomes (death, heart transplant, left ventricular assist device - LVAD - implant or weaned off inotropes), 30-day hospital readmissions, readmission for transplant and all-cause mortality up to a censoring date on December 31st, 2017 were recorded.

Statistical analysis

Categorical variables are presented as absolute numbers and percentages, and quantitative variables as mean ± standard deviation or median and interquartile range, as appropriate. A Kaplan-Meier curve was plotted for survival free from heart transplant or LVAD implant during follow-up, and cumulative incidence curves were calculated for all-cause mortality and heart transplant or LVAD using competing risk analysis with the R Software, version 3.4.4 (R Project for Statistical Computing, Vienna, Austria).[3]

Results

We reviewed 28 patients with HF that were discharged from the ICU to the ward on intravenous inotropes after the protocol was created. Table 2 describes both patient and clinical care data during the inotropic support period. Figure 1A depicts in-hospital outcomes of patients according to intention for inotropic support.

The cohort was followed for a median of 154 days. Among those in whom inotropes were discontinued and that had hospital discharge free of heart transplant or LVAD implant (n = 8), two were readmitted for HF within 30 days. Competing outcomes for mortality during the follow-up period are demonstrated in Figure 1B.

During the period on inotropic support in the ward, nine patients returned to ICU due to worsening HF - two of those for worsening pre-existing atrial fibrillation or atrial flutter. No episodes of new atrial fibrillation or atrial flutter were observed. Six patients developed recurrent non-sustained

Keywords

Cardiotonic Agents; Dobutamine; Heart Failure/physiopathology; Inotropes; Milrinone.

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Table 1 – Standard operating procedures for administration of continuous inotrope infusion in ward units

Eligibility
Patients that are clinically stable for more than 24 hours on a stable dose of one continuous intravenous inotrope and able to be discharged from the ICU.
Central venous catheter (preferentially PICC).
Safety procedures
Discharge to a continuous cardiac telemetry ward (except if intended for palliation).
Medical prescription including both inotropic dose (mcg/kg/min) and rate of infusion (mL/min).
Maximal recommended doses for inotropes in the ward: dobutamine = 5 mcg/kg/min; milrinone = 0.5 mcg/kg/min.
Fixed or gradually reduced the dose of inotrope, as clinically appropriate.
No dose increments in the ward (patient preferentially transferred back to ICU for dose augmentation).
Rigorous electrolyte targets (potassium 4.0-4.5 mmol/L; magnesium ≥ 2.0 mmol/L) and bicarbonate monitoring.
Systematic nursing evaluation of the patient and the administered drug according to the ward routines.
Daily patient assessment by the medical team.
Considerations
Exclusive intravenous access line for inotrope infusion.

ICU: intensive care unit; PICC: peripherally inserted central catheter.

Table 2 – Characteristics of study patients and data pertaining the inotropic support

Characteristic	n = 28
Baseline Characteristics	
Age, years	54 ± 16
Male sex	20 (71.5)
Ischemic etiology of HF	16 (57)
Left ventricular ejection fraction, %	23 ± 7.5
History of atrial fibrillation	13 (46)
Implantable cardioverter defibrillator	13 (46)
Chronic kidney disease (GFR < 30 mL/min/1.73 m^2)	7 (25)
Inotrope infusion	
Intravenous inotrope	
Milrinone	24 (86)
Dobutamine	4 (14)
Inotrope dose	
Milrinone, mcg/Kg/min	0.25 (0.2 - 0.34)
Dobutamine, mcg/Kg/min	5.7 (4.37 - 6.55)
Total duration of inotropic therapy, days	23.5 (13.75 - 45.5)
Duration of inotropic therapy at ward, days	10.5 (6.75 - 25)
Venous access for drug infusion	
Central venous catheter	4 (14)
Peripherally inserted central catheter	22 (79)
Peripheral venous access	2 (7)
Systolic blood pressure, mmHg*	93 ± 14
Diastolic blood pressure, mmHg*	59 ± 10

*Data expressed as number (percentage), mean ± standard deviation or median (interquartile range). * Blood pressures values at the initiation of inotropic therapy. Data from one patient not available. HF: heart failure; GFR: glomerular filtration rate.*

ventricular arrhythmia, and inotropic dose was reduced; of those, four were hypokalemic (≤ 3.5 mmol/L) when arrhythmias were observed. One patient had a central venous catheter exit-site infection, and one had a peripherally inserted central catheter-related bloodstream infection. Seven events of protocol violation were identified: use of peripheral venous access for drug infusion (n = 2); and, increments in inotropic dose in the ward (n = 5). None of them incurred in clinical adverse events.

Discussion

In the present report, we described our initial experience with a safety-focused protocol for the use of continuous intravenous inotropes in hospitalized patients with advanced HF outside the ICU. We demonstrated that a subset of clinically stable patients on inotropes may benefit from transition to a less intensive care setting following careful standard operating procedures, without a significant burden of adverse events. These safety measures are aligned with our institutional program for quality improvement.

Current guidelines indicate that inotropes can be used in specific clinical settings, especially cardiogenic shock or bridge therapy in patients with refractory HF awaiting heart transplant or LVAD. Also, those not candidates for definitive therapies could be considered for long-term inotrope as palliation.[4] The use of intravenous inotropic agents remains controversial, as many reports have associated its utilization with unfavourable outcomes. A deleterious effect of its use on long-term mortality among patients discharged alive, however, has not been suggested by a recent European registry report.[1]

In this study, we describe a selected population of patients with advanced HF that has not been well-documented in most studies evaluating inotropes – mostly clinically stable hospitalized patients intended for inotropic wean or bridge to definite therapies. Concerning safety outcomes, most of the arrhythmogenic events occurred in the context of electrolyte

Figure 1A

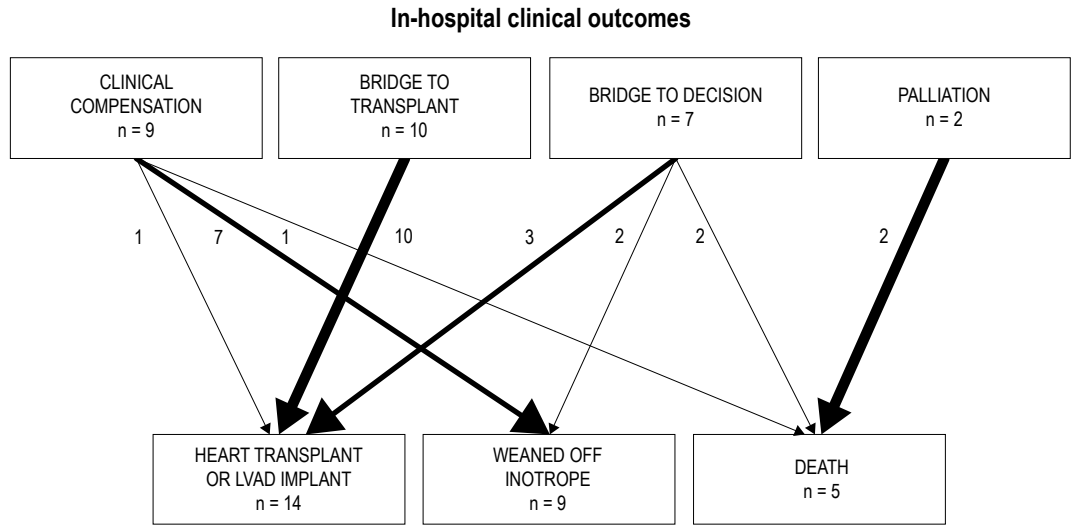
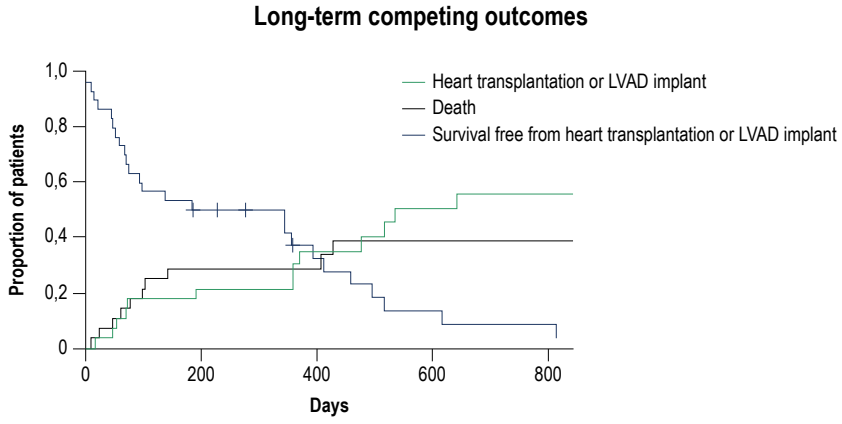


Figure 1B



LVAD: left ventricular assist device.

disturbances, which can be potentially avoided with careful monitoring. Considering the growing HF severity and the inotrope potential as a bridge therapy in hospitalized patients, a contemporary approach to their utilization has been to focus on the safety profile of its use while maintaining the traditional goals of therapy (the 'until' therapy), as described by Stevenson.[5] Avoidance of traditional high doses of inotropes, the administration under careful monitoring conditions and strict electrolyte correction strategies may allow broader use of these agents.

Conclusions

A contemporary, safety-focused approach to the use of low to moderate doses of intravenous inotropic agents in less resource-intensive settings may be feasible, potentially reconfiguring the use of these agents in different scenarios, ranging from bridge therapy to end-of-life palliation.

Author contributions

Conception and design of the research: Hastenteufel LCT, Clausell N, Domingues FB, Caballero LG, da Silva ERR, Goldraich LA; Acquisition of data: Hastenteufel LCT, Domingues FB, Caballero LG, da Silva ERR; Analysis and interpretation of the data and Statistical analysis: Hastenteufel LCT, Neyeloff JL, Goldraich LA; Writing of the manuscript: Hastenteufel LCT, Clausell N, Goldraich LA; Critical revision of the manuscript for intellectual content: Clausell N, Goldraich LA.

Potential Conflict of Interest

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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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Review Article

Kidney Disease in Diabetes Mellitus: Cross-Linking between Hyperglycemia, Redox Imbalance and Inflammation

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Abstract

Chronic hyperglycemia is the key point of macro- and microvascular complications associated with diabetes mellitus. Excess glucose is responsible for inducing redox imbalance and both systemic and intrarenal inflammation, playing a critical role in the pathogenesis of diabetic kidney disease, which is currently the leading cause of dialysis in the world. The pathogenesis of the disease is complex, multifactorial and not fully elucidated; many factors and mechanisms are involved in the development, progression and clinical outcomes of the disease. Despite the disparate mechanisms involved in renal damage related to diabetes mellitus, the metabolic mechanisms involving oxidative/inflammatory pathways are widely accepted. The is clear evidence that a chronic hyperglycemic state triggers oxidative stress and inflammation mediated by altered metabolic pathways in a self-perpetuating cycle, promoting progression of cell injury and of end-stage renal disease. The present study presents an update on metabolic pathways that involve redox imbalance and inflammation induced by chronic exposure to hyperglycemia in the pathogenesis of diabetic kidney disease.

Introduction

Diabetic kidney disease (DKD) is a devastating outcome of diabetes mellitus (DM), responsible for high morbidity and overall mortality. It is clinically characterized by persistent renal dysfunction for a period equal to or longer than three months, marked by urinary excretion of albumin >30 mg/24 h or an albumin/creatinine ratio (ACR) ≥ 30 mg/g or glomerular filtration rate (GFR) < 60 mL/min/1.73 m after a hyperfiltration phase, in addition to structural abnormalities (e.g. diabetic glomerulosclerosis) in individuals with previous diagnosis of DM.[1,2]

It is estimated that approximately 425 million people have DM in the world, with a projected increase by 48% to the yar of 2045. Approximately 12.5 million people are diagnosed with DM in Brazil, which occupies the third position in number of individuals with DM in the world in 2017.[3] Nearly 90% of DM patients develop microvascular and macrovascular complications; DKD is considered one of the most severe clinical outcomes, affecting 20-40% of the patients, most of them type 2 DM patients.[1] DKD is currently the main cause of dialysis in developed countries, the second main cause in Brazil.[4-6]

DKD is a progressive and irreversible condition, whose pathogenesis has been associated with functional and structural changes of renal cells in response to metabolic stress induced by excessive glucose inflow, by means of activation of specific metabolic pathways linked to redox imbalance and inflammation.[7]

Although many classical mechanisms involved in the development and progression of DKD have been described, new molecular and epigenetic pathways have been suggested to be responsible for the early kidney functional loss and DKD-related complications.[8]

In this review we discuss current knowledge of metabolic pathways involving redox imbalance and inflammation induced by chronic exposure to hyperglycemia in the pathogenesis of DKD, aiming to propose new paradigms.

Pathophysiology of DKD induced by hyperglycemia: new paradigms

DKD is a chronic metabolic disease in which hyperglycemia causes dysfunction of renal and vascular cells. The pathophysiology of DKD and the consequent end-stage renal disease requiring dialysis is caused by a chronic hyperglycemic state that leads to activation and changes of metabolic pathways and hemodynamic dysfunction. Some of these changes occur in an integrated way, leading to several other changes. Although diabetic hyperglycemia is an important but not crucial factor for the development of glomerular lesions in DKD, we will describe metabolic changes induced by intermittent and chronic exposure to hyperglycemia. The following topics will be discussed: glucose auto-oxidation, polyol and hexamine pathways, formation of advanced glycation end-products (AGEs), synthesis of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX), protein kinase C (PKC) activation, and abnormal activity of angiotensin II (Ang II).[9,10]

Glucose uptake by diabetic kidney cells

Hyperglycemia is the main clinical manifestation of DM, the main driving force for the development of chronic complications of the disease, including DKD. It is caused by two main mechanisms: the first involves dysfunction and apoptosis of pancreatic beta cells caused by an autoimmune abnormality (type 1 DM), and the second results from an

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Diabetes Mellitus/complications; Kidney, Diseases; Oxidation-Reduction; Inflammation; Oxidative Stress; Renal Dialysis.

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overstimulation of insulin synthesis and secretion in the presence of insulin resistance (IR), mostly associated with overweight/obesity, which characterizes type 2 DM.[11]

In the context of obesity, which is common in patients at risk of type 2 DM, IR results from increased levels of free fatty acids (FFAs), and the FFA by-products pro-inflammatory cytokines and diacylglycerols (DAG), that inhibit phosphorylation of the insulin receptor substrate 1 (IRS-1) in phosphorylation domains (serine/threonine), preventing the propagation of signals to the translocation of the glucose transporter-4 (GLUT4) translocation to the plasma membrane. This affects the interaction between insulin and its receptor, leading to decreased glucose uptake by insulin-dependent cells, and ultimately hyperglycemia and hyperinsulinemia.[12,13]

In additional, in obese diabetic individuals, excessive accumulation of fat causes stress of adipocytes by hyperplasia and hypertrophy, leading to hypoxia and subclinical inflammation, increased macrophage infiltration and release of pro-inflammatory cytokines – tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6) and interleukin-1 (IL-1) – which, in turn, aggravates IR.[12,14] TNF-α stimulates the secretion of other cytokines and chemokines and directly activates the transcription factor-kappa B (NF-kappa B), thereby leading to maintenance of chronic hyperglycemia, by affecting glucose uptake and promoting IR.[15]

In attempt to reestablish homeostasis, glucose uptake occurs in cells not dependent on GLUT4, and hence, non-insulin-dependent, such as renal cells, that have GLUT 1 and GLU2 as glucose transporters. These glucose carriers do not regulate glucose entry into cells, leading to glucotoxicity. In this situation, there is elevated expression of these transporters, leading to increased entry of glucose into renal cells, as occurs with the high-affinity glucose transporter GLUT 2, stimulated by hyperglycemia, and the sodium-glucose co-transporter (SGLT) 1 and SGLT 2, responsible for tubular reabsorption.[16,17] Thus, in DM patients, glucose reabsorption in the proximal tubule is increased, contributing to hyperglycemia and, consequently, hyperfiltration.[18]

Generation of reactive oxygen and nitrogen species (RONS) induced by hyperglycemia

Glucotoxicity is caused by an inability of the cells to compensate for the increased glucose uptake in case of IR/hyperglycemia, as in DM. Increased stimulation of glucose oxidation pathways in non-insulin-dependent cells leads to the activation of alternative pathways, increased production of RONS and oxidative stress (OS) in hyperglycemic state.[19]

Glucose auto-oxidation

In glycemic homeostasis and in the absence of oxygen, glycolysis is the primary energy source in the cells. By-products of these reactions are coenzymes responsible for the uptake of high energy electrons, released during oxidation-reduction (redox) reactions, that participate in additional energy pathways.[20] The synthesis of substrates by glycolysis activates two other energy pathways: the tricarboxylic acid cycle (or the Krebs cycle) and the electron transport chain (ETC) (or the oxidative phosphorylation) in the mitochondria through protein complexes.[20-22]

In DM, the hyperglycemic state promotes the overactivation of the three main energy pathways previously described. The increased stimulation of glycolysis and Krebs cycle result in elevated production of reduced flavin adenine dinucleotide (FADH2) and reduced nicotinamide adenine dinucleotide (NADH), fed into the ETC.[23]

The ETC is a source of reactive oxygen species (ROS), especially in renal cells, which have a large number of mitochondria.[24] In diabetic kidney cells, highly stimulated, hyperpolarized mitochondria with high redox potential, produce increased levels of adenosine triphosphate (ATP) and superoxide anion ($O_2^{-\bullet}$) through the complexes I and II. O2-• originates both radical and non-radical RONS, including hydrogen peroxide (H2O2), the hydroxyl radical (•OH) and the $ONOO^-$, which may be involved in the genesis of the lesions (Figure 1).[25,26]

In the kidney of diabetic or diabetic/obese individuals, mitochondrial energy, altered by hyperglycemia and hyperlipidemia, causes mitochondrial dysfunction and excess ROS, which are harmful to mitochondrial DNA (mtDNA) by inhibiting the mammalian target of rapamycin complex 1 (mTORC1) and the AMP-activated protein kinase (AMPK). These changes alter the activation of the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), and thereby affect mitochondrial biogenesis, by increasing mitochondrial fission and the synthesis of defective mitochondria. This can lead to impairment of the ECT functions, with reduced synthesis of ATP, leading to renal cell lesion and apoptosis.[27]

In addition, increased glycolysis causes hyperactivation of polyol and hexosamine metabolic pathways, and increases the synthesis of AGEs and activation of PKC. This also result in decreased ATP levels, contributing to mitochondrial dysfunction and fragmentation.[28]

Polyol pathway

One of the consequences of the increased glucose uptake by the cells is the increment in the NADPH-dependent conversion of glucose into sorbitol by aldose reductase. Sorbitol is then converted to fructose, by nicotinamide adenine dinucleotide (NAD).[29,30] NADPH is an important cofactor for regeneration of the antioxidant glutathione (GSH). Therefore, in light of increased aldose reductase activity, the low availability of NADPH affects the antioxidant defense, resulting in redox imbalance.[31]

The increase in O2•- inhibits the activity of glyceraldehyde 3-phosphate dehydrogenase (GAPDH), which, in turn, inhibits glycolysis and activates alternative pathways. The increase in the NADH/NAD ratio increases the production of DAG, which activates PKC. Fructose, an end-product of the pathway, has been recently related to kidney injury markers.[20]

Protein kinase C (PKC)

Both hyperglycemia and increased stimulation of glycolysis by-products increase the synthesis of glyceraldehyde-3-phosphate and its conversion into dihydroxyacetone, and thereby promote the synthesis of DAG, a PKC-activating factor (Figure 2).[31]

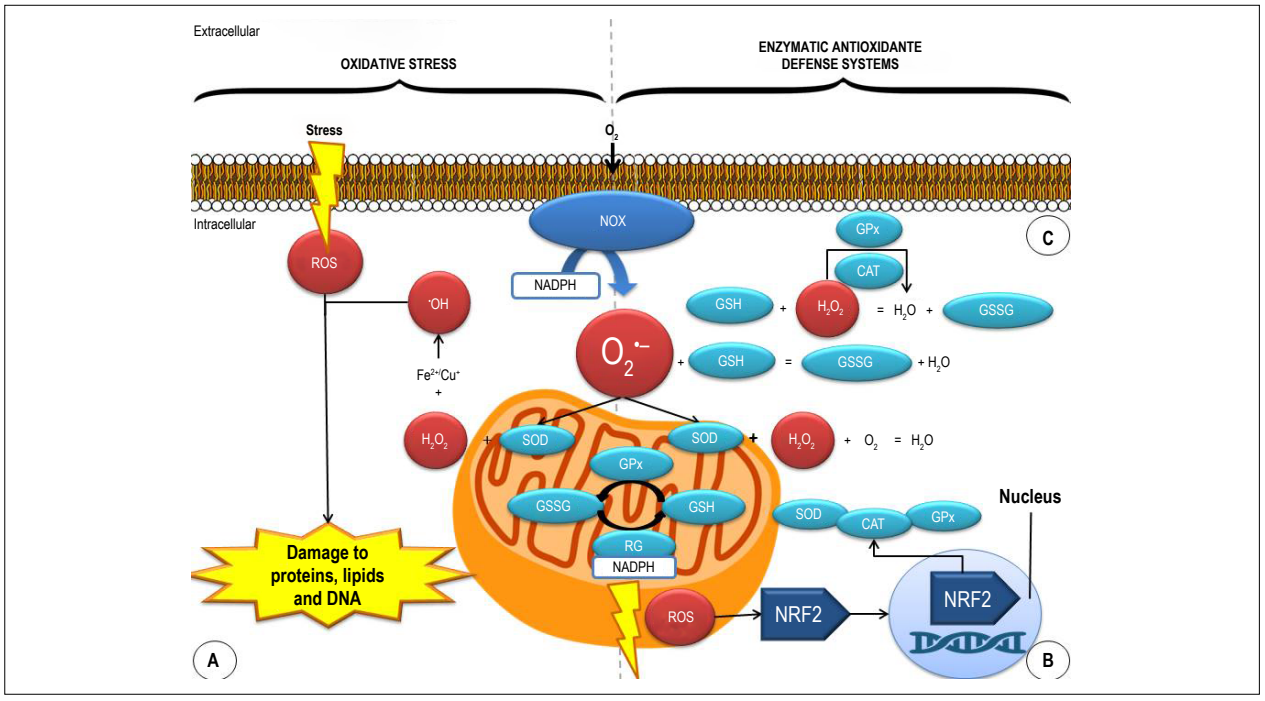

Figure 1 – *Oxidative stress and enzymatic antioxidant defense system in diabetic renal cells. CAT: catalase; ROS: reactive oxygen species; GPx: glutathione peroxidase; GSH: glutathione; GSSG: oxidized glutathione; RG: reduced glutathione; H_2O_2: hydrogen peroxide; NRF2: nuclear erythroid 2-related factor 2; O_2: molecular oxygen; NOX: NADPH oxidase; $O_2^{\bullet-}$: superoxide anion radical; ·OH: hydroxyl radical; SOD: superoxide dismutase. Adapted from Bhargava.*[28]

In renal cells, increased PKC stimulates several mechanisms involved in the development of kidney injury. The induction and activation of endothelial nitric oxide synthase (eNOS) by PKC increases the availability of nitric oxide (NO) in diabetic kidney in the first stages of DKD.[32] Increased NO contributes to elevation of prostaglandin E1 levels, Ang II activity, and activation of the vascular endothelial growth factor (VEGF), resulting in increased permeability, endothelial dysfunction, glomerular hyperfiltration and albuminuria.[33,34]

In prolonged diabetes, persistent hyperglycemia reduces the levels of tetrahydrobiopterin (BH4), an eNOS cofactor, with proportional reduction in NO synthesis in vascular endothelium, leading to vasoconstriction and glomerular and systemic hypertension.[34]

Hyperglycemia-related endothelial damage is caused by a nitroso-redox imbalance, by increased RONs (resulting from the interaction between O2•- and NO, which leads to increased ONOO- and decreased vascular NO), leading to endothelial dysfunction and DKD progression.[35]

Increased expression of PKC leads to activation of the transforming growth factor-beta (TGF-β) and the plasminogen activator inhibitor-1 (PAI-1), resulting in increased deposition of fibronectin, collagen types I and IV and extracellular matrix deposition, and consequently, renal hypertrophy, glomerulosclerosis and renal fibrosis.[30]

Hexosamines

The hyperfunction of this pathway, stimulated by hyperglycemia, promotes the conversion of fructose 6-phosphate, and the synthesis of uridine diphosphate N-acetylglucosamine (UDP-GlcNAc) as end product, which is *O*-glycosylated into N-acetylglucosamine (*O*-GlcNAc) by the *O*-GlcNAc transferase.[29,30]

The excess of *O*-GlcNAc is responsible for stimulating and modifying cell protein. In DKD, changes in genetic expression increase TNF-α transcription, thereby inducing renal damage via OS, and overproduction of extracellular matrix proteins.[20,29,36]

Advanced glycation end products (AGEs)

AGEs are uremic toxins and their involvement in the development of renal damage may be partially explained by increased endogenous synthesis resulting from hyperglycemia, diet and insufficient clearance of these products due to reduced GFR.[37]

AGEs are formed through non-enzymatic amino-carbonyl reactions, or Maillard reaction between the carbonyl group of glucose, fructose, galactose and ribose, or intermediates of glucose metabolism (glucose-6-phosphate, fructose-6-phosphate, ribose-5-phosphate, deoxyribose-5-phosphate and glyceraldehyde), with an amine group and other molecules, to form a reversible Schiff base, and subsequently, Amadori products, which are initial products of the Maillard reaction.[13] Synthesis of the Amadori products is accelerated in hyperglycemic conditions, and these compounds are highly reactive with amine groups and metal ions through glycoxidation of biological molecules, forming glyoxal (GO), methylglyoxal (MGO), and malondialdehyde (MDA).[38,39]

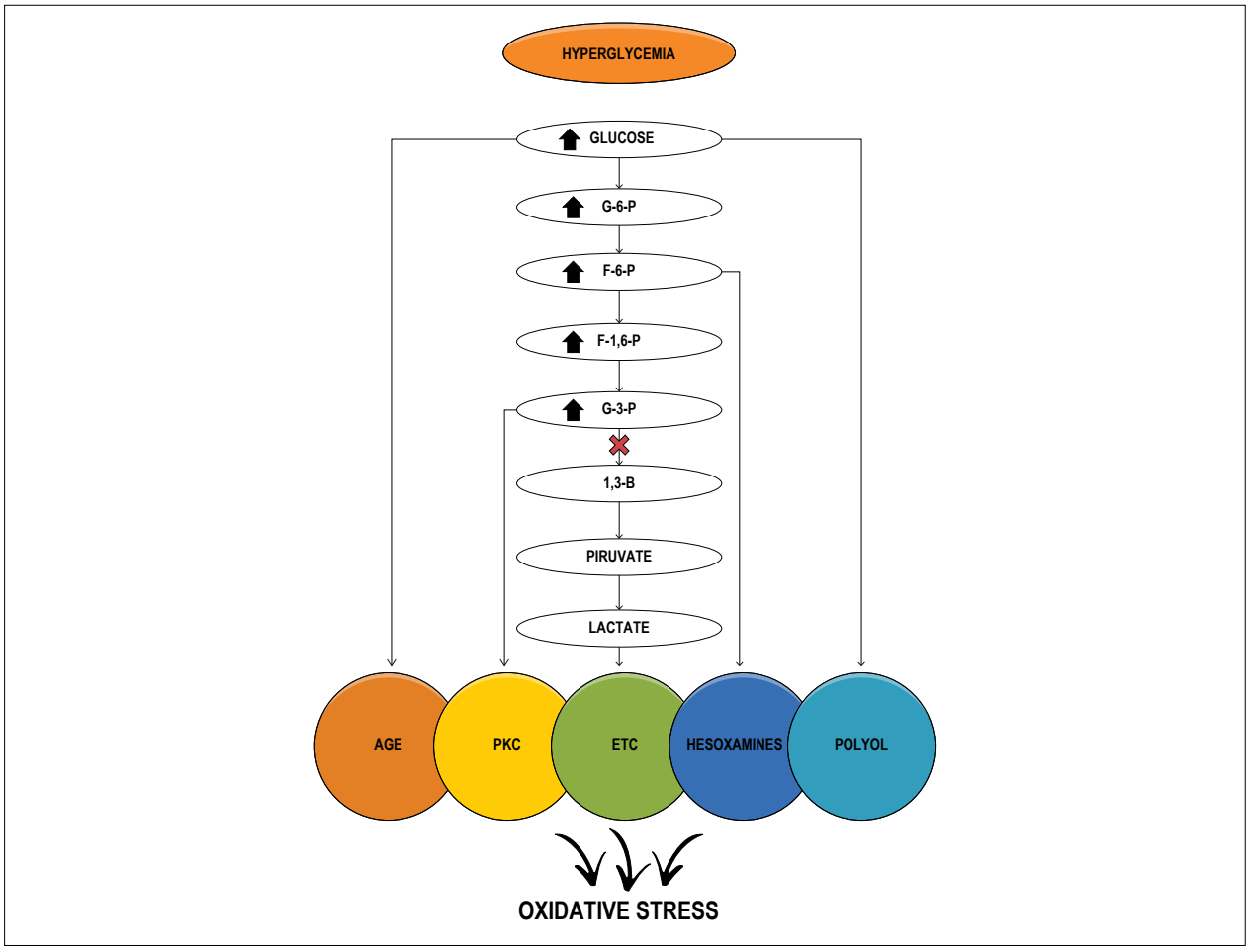

Figure 2 – *Schematic representation of the pathways preceding glycolysis and induction of oxidative stress. ETC: electron transport chain; 1,3-BPG: bisphosphoglycerate; G6P: glucose 6-phosphate; G3P: glyceraldehyde-3-phosphate; GAPDH: glyceraldehyde-3-phosphate dehydrogenase; F6P: fructose-6-phosphate; F-1,6-P: fructose-1,6-phosphate; PKC: protein kinase C; AGE; advanced glycation end-products*

After AGEs' metabolism and removal from the tissues, the low molecular weight, soluble peptides and the second generation AGEs need to be excreted in the urine. Second generation AGEs can be highly reactive products, but their effects are limited by renal excretion. However, in renal failure, AGEs excretion is impaired, contributing to the increased levels in serum and tissues.[38]

Such increase in the endogenous pool of AGEs causes direct damage to the cells by interaction of extracellular proteins with cellular components (proteins, carbohydrates, lipids and nucleotides), affecting cellular structure and functions. These modified proteins have decreased enzymatic hydrolysis, resulting in excessive accumulation of extracellular matrix proteins, glomerulosclerosis, and consequently, renal fibrosis.[34]

In addition to direct extra- and intracellular damage, AGEs interact with their transmembrane receptor – the receptor for advanced glycation end products (RAGE), which are expressed in many types of renal and inflammatory cells.[40] Following the substrate/receptor interaction, a cascade of reactions inside the cell is initiated. These reactions regulate the transcription of proteins, adhesion molecules and proinflammatory cytokines, such as IL-1, IL-6 e TNF-α, mediated by the activation of macrophages via NF-κB, exacerbating subclinical tissue inflammation associated with DM in DKD.[41,42]

The AGEs/RAGEs interaction is associated with increased production of RONs; it contributes to the OS by direct activation of NOX (by mitochondrial activation through the RAGEs in renal cells and infiltrated immune cells). Also, AGs reduces the expression of eNOS and increases the expression of inducible NOS (iNOS), triggering OS by increased $ONOO^-$ production and reducing NO availability. Consequently endothelial dysfunction occurs by synthesis of vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), monocyte chemotactic protein-1 (MCP-1) and TGF-β.[38,39]

NADPH-oxidases

The NOX family of NADPH oxidases is an important source of ROS in DM. There are seven different NOX isoforms: NOX1, NOX2, NOX3, NOX4 (formerly known as "renox" due to its high expression in renal tissue), NOX5 and the

dual oxidases 1 and 2 (DUOX1 and DUOX2, respectively).[9] NADPH oxidases are transmembrane proteins responsible for transferring electrons from cytosolic NADPH to the O_2, which is reduced to $O_2^{\bullet}$, thereby perpetuating the oxidative stress state in renal cells.[9,25]

NOX-derived ROS regulate physiological processes in the kidneys. However, they are upregulated in hyperglycemic renal cells, and abnormally activated by AGEs, PKC, TGFβ and Ang II, resulting in $O_2^{\bullet-}$ overproduction and accumulation. $O_2^{\bullet-}$ acts as an important mediator of redox imbalance and damage to different kidney cell components.[9,43]

Angiotensin II

Chronic hyperglycemia in DM induces increased synthesis of Ang II and its receptors by glomerular and mesangial cells, and podocytes. It increases the expression of renin and angiotensinogen in mesangial cells, elevating intrarenal angiotensin levels. This mechanism is exacerbated by ROS accumulation in adipose tissue, where Ang II is produced.[34,44]

Elevations of Ang II contribute to abnormal activation of the renin-angiotensin-aldosterone system (RAAS), aggravating mechanical damages induced by systemic and intraglomerular hypertension in the kidney. Additional effects of Ang II include direct mediation in RON production, early hyperplasia and late hypertrophy of renal cells, by stimulation of TGF-β, IL-6 and MCP-1, and activation and upregulation of NF-κB.[45]

Hemodynamic changes in diabetic kidney damage

Early DKD is marked by changes in renal hemodynamics caused by hyperglycemia.[46] The initial hemodynamic events are characterized by glomerular hyperperfusion, hypertension and hyperfiltration, and responsible for functional and structural changes in the glomeruli, resulting in albuminuria, increase followed by decrease of GFR, glomerular hypertrophy, mesangial expansion, podocyte injury, glomerulosclerosis and renal fibrosis, and natural history DKD.[47,48]

Hypertension commonly precedes DKD, especially in DM2. However, persistent metabolic disturbances cause sustained hypertension, and dysregulation of pressure levels, inducing and/or aggravating diabetic kidney injury.[45] The mechanism of hypertension in DKD is complex, multifactorial, and involves altered sodium regulation, such as renal tubular reabsorption of sodium, abnormal activation of the RAAS and of sympathetic nervous system (SNS), endothelial cell dysfunction, and increased OS. These processes mediate vasoconstriction and increase extracellular volume with consequent increase in blood pressure.[49,50]

Among hemodynamic factors that contribute to hypertension and renal hyperfiltration, RAAS has been the most widely accepted for the development of DKD, and its blockade has shown to delay the progression of the disease.[51] Mechanical stress on vascular wall induced by hypertension, hyperglycemia, inflammation and ROS considerably increase Ang II production in renal cells and contribute to RAAS hyperactivation.[45,51] This in turn, contributes to systemic and renal vascular vasoconstriction, and renal reabsorption of sodium via interaction with Ang II receptor type 1 (AT1) and aldosterone release, leading to elevations in blood pressure, intraglomerular pressure and renal damage.[52]

The effects of Ang II on redox imbalance (additional effects of Ang II on inflammation and redox imbalance, and important factors in the pathophysiology of DKD are described above) via production of $O2^{\bullet-}$ by local NOXs induce endothelial dysfunction (due to an imbalance between vasoconstrictor and vasodilator factors).[53] In response to increased ROS, there is a reduction in the synthesis of NO, a potent vasodilator that interacts with the substrate BH4, reducing eNOS activity. Besides, there is a direct effect of the $O2^{\bullet-}$ on reducing NO and $ONOO^-$, and reducing NO availability, leading to sustained vasoconstriction.[50]

The actions of Ang II, in addition to endothelial dysfunction, vasoconstriction and vascular resistance, induced by the OS, result in elevations in the pressure of afferent arterioles, which, in turn, cause an increase in systemic blood pressure, glomerular hyperperfusion and hyperfiltration, and proteinuria, leading to progressive DKD.[50]

In addition, sodium-hydrogen exchangers (NHEs) play an important role on renal and systemic hemodynamics in DKD. NHEs are expressed in different types of renal cells and regulate sodium (Na^+) and hydrogen (H^+) transport, essential for different cell functions, including maintenance of intracellular pH, fluid volume and cell survival.[54] In the kidneys, particularly in tubular cells and macula densa cells, NHE isoforms 1, 2 and 3 (NHE1, NHE2 and NHE3, respectively) play an important role in the pathogenesis of DKD, by inducing intraglomerular hypertension and mesangial proliferation, and by promoting of inhibiting programmed cell death (apoptotic factors), contributing to renal fibrosis.[55]

In macula densa cells, the NHE2 receptors are involved in the regulation of renin and salt sensors. The suggested mechanism is that cell shrinkage (induced by hypertonicity), together with Ang II, is the renin-release signal, leading to the overexpression of the RAAS and increase in intraglomerular pressure. This would activate the signaling pathway that results in increased expression of the NHE receptors in renal cells (promoting a vicious circle).[56] Also, salt excess, induced by NHE in the macula densa, causes an increase in intracellular pH and cell depolarization, leading to activation of ROS synthesis by the NOX enzymes.[57]

NHEs are targets of many drug therapies, including inhibitors of the RAAS and of SGLTs, which are involved in NHE blockade in the kidneys, contributing to reduction of intraglomerular pressure, and of proliferative and fibrotic processes.[56]

Blockade of the RAAS and Ang II with angiotensin-converting enzyme inhibitors and Ang II receptor blockers (either combined or alone), have shown to be effective in reducing proteinuria and delaying the progression of DKD by their hemodynamic/anti-hypertensive, anti-inflammatory and antifibrotic effects, and hence could be used to improve the prognosis of DKD patients.[58]

Redox imbalance in DKD

OS is the first stage of DKD and activates pathological pathways in practically all types of renal cells, including endothelial, mesangial, epithelial, tubular cells and podocytes.[19] OS results from an imbalance in which the increase in RONs overwhelms the lower efficient (enzymatic and non-enzymatic) antioxidant system, leading to the redox imbalance between pro- and antioxidants.[59,60]

The generation of RONs occurs in many types of cells in the kidneys and infiltrating cells, such as immune cells, neutrophils and macrophages. A substantial increase in glucose auto-oxidation, combined with greater ETC activation and mitochondrial stress, is accompanied by increased RON production, accounting for nearly 80% of all reactive species.[25,61] In addition to these pathways, other enzymatic systems, such as uncoupled eNOS and NOXs, and non-enzymatic systems, such as Ang II, are involved in ROS generation in the kidney of diabetic patients and obese diabetic patients.[62]

The overproduction of RON induced by hyperglycemia reduces the expression of antioxidant enzymes, including the superoxide dismutase (SOD) (particularly the manganese SOD subtype that acts in the mitochondria), thioredoxin reductase, and catalase (CAT), and decreases regeneration of reduced glutathione (GSH) by activation of the polyol pathway. In addition, spontaneous reduction of non-enzymatic antioxidants occurs in consequence of increased ROS in response to increased demand.[63] The SOD is considered the main physiological defense against ROS, as it initiates the enzymatic antioxidant defense by reacting with $O2^{\cdot\bullet}$ to form H_2O_2, which will be degraded by CAT and GPx (Figure 1).[21,59]

In low concentrations, RONs modulate transcription factors of antioxidant enzymes, essential for OS attenuation. Among these transcription factors, there is the nuclear erythroid 2-related factor 2 (NRF2), which translocate to the nucleus to activate the transcription of genes responsible for codifying antioxidant enzymes like SOD, CAT and GPx, thereby suppressing the NF-kB activity. However, in ROS overproduction, as found in DM, these defenses are not effective in blocking or preventing the establishment of the redox imbalance.[64]

In diabetic kidney, RONs decreases the expression of sirtuins (SIRT), enzymes responsible or modulating the regeneration of antioxidants via acetylation of the ETC, essential for the stimulation of mitochondrial SOD and induction of transcription factors, (such as the PGC1-α), attenuating mitochondrial stress and NRF2 activation.[62] Also, the O-GlcNAc, product of hexosamines, attenuates the SIRT activity, contributing to exacerbation of this process in DM.[63] In the kidney of diabetic rats, reduced expression of PGC-1α, a regulator of oxidative metabolism and mitochondrial biogenesis, has been associated with higher production of RONs by aggravating mitochondrial dysfunction and fragmentation.[65]

A gradual decrease in the antioxidant defenses in chronic kidney disease has been described *in vivo*, opening a new field of treatment.[66] Recent studies have shown the efficacy of high antioxidant intake as an adjuvant in the treatment of DKD, by helping in both enzymatic and non-enzymatic antioxidant defense against harmful compounds.[67]

In a recent meta-analysis, Bolignano et al.[68] evaluated 14 studies (4,345 participants) for the effects of antioxidant supplementation (including vitamin C, vitamin E and zinc, either combined or alone) on DKD disease progression and markers of renal function. The authors concluded that the antioxidant therapy significantly decreased albuminuria, but apparently had no tangible effect on renal function in patients with diabetic kidney disease. Stronger evidence of benefits was found for vitamin E at doses varying from 480 mg to 1,200 mg/day.

Experimental studies on vitamin and mineral supplementation, such as vitamin D, vitamin E and zinc, have shown favorable results in reducing renal failure, inflammation and OS.[67-70] Besides, phenolic compounds and flavonoids have shown beneficial effects as therapeutic agents in the treatment of DKD in cells and animals.[71]

Immunological disorders in DKD: the role of inflammation

DKD has been associated with systemic and intrarenal inflammation. Persistent metabolic and hemodynamic stimuli in diabetic kidney result in cell lesion that releases molecules known DAMPs – danger-associated molecular pattern – including PGAs, ROS, FFAs. These compounds interact with pattern recognition receptors, including Toll-like receptors 2 and 4 and RAGE, positively regulated by hyperglycemia. In the presence of DAMPs/receptors interaction, the intrarenal innate immune response is activated.[5]

The myeloid lineage of innate immune cells causes renal inflammation in diabetic conditions, with involvement of several immune cells in the pathogenesis and severity of renal damage. However, pro-inflammatory factors released in diabetic renal tissue include not only infiltrating inflammatory cells, but also cytokines and chemokines found in non-immune cells, such as in parenchymal cells (podocytes, and endothelial, epithelial, mesangial and tubular cells), exacerbating the inflammatory process that leads to progressive damages in DKD (Chart 1).[19]

In addition, the binding of DAMPs with their receptors has been associated with activation of molecular and transcription factors that promote activation of NF-κB, facilitating the expression of many pro-inflammatory genes (cytokines, chemokines, adhesion molecules, immune receptors and growth factors). Consequently, NF-κB has been considered a master regulator of immune responses and inflammation in DKD.[26,72]

The main proinflammatory cytokines are IL-1, IL-6, IL18 and TNF-α; all of them have autocrine, paracrine and juxtacrine mechanisms with pleiotropic effects that regulate the expression of cytokines, interleukins, TNF-α, interferons, growth factors, adhesion molecules and nuclear transcription factors, promoting the increase and perpetuation of inflammation and OS in diabetic kidney (Chart 1).[73,74]

Intracellular metabolic changes with increased AGEs and ROS lead to increased release of MCP-1, which promotes the activation of monocytes and macrophages. These, in turn, are associated with increased expression of adhesion molecules and synthesis of pro-inflammatory cytokines, leading to hyperfiltration and glomerular lesions, typical of DKD.[75,76]

Due to its close relationship with obesity, kidney damage of patients with type 2 DM is associated with early activation of the immune system, which is related to chronic, low-grade systemic inflammation induced by adipose tissue.[44,50]

Chart 1 – Inflammatory cytokines and their effects on renal function in diabetes mellitus

Cytokines	Stimulated by	Specialized producing cells	Exerts positive effects on	Effects on DKD	Target cells in the kidneys	Ref.
IL-1α, IL-1β	Inflammasome IL-18 and NF-κB	Macrophages, Granulocytes* Tubular epithelial Endothelial, Mesangial† Fibroblasts‡	↑ ICAM-1, ↑ VCAM-1, ↑ Prostaglandin E2	↑ Intraglomerular hemodynamic abnormality, ↑ Synthesis of hyaluronic acid, ↑ Proliferation of mesangial cells and fibroblasts, ↑ECM accumulation	Epithelial, Mesangial, Tubular	[77, 83]
IL-6	Hyperglycemia, AGEs, TNF-α, LPS, IL-1, IL-4	T lymphocytes, Macrophages, Neutrophils* Endothelial, Podocytes, Mesangial, Tubular epithelial† Fibroblasts‡	↑ MCP-1, ↑ expression of Ang II receptors, ↑ ROS	↑ Recruitment of monocytes, ↑ Differentiation of macrophages, ↑ Synthesis of fibronectin, ↑ Synthesis and accumulation of ECM, ↑ Mesangial cell proliferation, ↑ Endothelial dysfunction ↑ Tubulointerstitial fibrosis	Mesangial, Podocytes, Endothelial, Tubular epithelial	[84, 85]
IL-18	NF-κB, Inflammasome, Caspase-1	T lymphocytes and Macrophages* Epithelial, Tubular†	↑ IFN-γ, ↑ IL-1, IL-6, TNF-α, iNOS, ICAM-1, TGF-β, MCP-1	↑ Apoptosis of endothelial cells, ↑ infiltration off macrophages and neutrophils	Endothelial, Tubular epithelial	[30, 86, 87]
TNF-α	NF-κB	Dendritic, Monocytes, Macrophages, T lymphocytes* Mesangial, Endothelial, Tubular†	↑ Immune response ↑ NF-κB	↑ Inflammatory cells, cell infiltration ↑ Citotoxicity, apoptosis, ↑ Endothelial permeability, ↓ Capillary wall barrier function, ↑ PKC, ↑NOX, ↑ ROS; ↑ ECM	Mesangial, Podocytes, Endothelial, Glomerular; Tubular epithelial	[19, 78, 83]

**Infiltrating immune cells; †Renal cells; ‡Other cell types. Ang II: angiotensin 2; ROS: reactive oxygen species; TNF-α: tumor necrosis factors alfa; NF-κB: nuclear factor-kappa B; IFN-γ: interferon gamma; IL-1: interleukin 1; IL-1α: interleukin 1 alpha; IL-1β: interleukin 1 beta; IL-6: interleukin 6; IL-18: interleukin 18; IL-4: interleukin 4; LPS: lipopolysaccharide; ICAM-1: intercellular adhesion molecule 1; VCAM-1: vascular cell adhesion molecule; ECM: extracellular matrix; NOX: NADPH oxidase; AGE: advanced glycation end-products; MCP-1: monocyte chemoattractant protein; PKC: protein kinase C; iNOS: nitric oxide synthase; TGF-β: transforming growth factor-beta*

Redox imbalance and inflammation in DKD: a vicious circle

Several hemodynamic and metabolic pathways are involved in the pathogenesis of DKD. In a common pathway, the interrelation between redox imbalance and inflammation induced by hyperglycemia occurs by mechanisms that involves cellular and molecular processes in a cascade of bioenergetic changes, promoting changes in extracellular, cellular and mitochondrial morphology, genetic expression modulation, induction of lesions, tissue hypertrophy, and renal fibrosis and necrosis (Figure 3).[74]

Inflammation is mediated by the upregulation of NF-κB expression by OS, AGEs and TNF-α, which controls the immune response by stimulating genetic expression of pro-inflammatory cytokines, adhesion molecules, NOS, cell proliferation and progression of the inflammatory cycle and OS.[77,78] ROS and the AGE-RAGE interaction, stimulated by DM-related hyperglycemia, act as mediators of the multiprotein complex inflammasome Nlrp, which regulates the cleavage of pro-inflammatory cytokines from the mature, active forms into innate immune cells, renal endothelial cells, glomerular cells and podocytes.[79]

The upregulation of pro-inflammatory cytokines (IL-1, IL-6, IL-18, IFN-γ), mediated by AGE/RAGE, TNF-α and NF-κB, causes an increase in RONs and transcription factors (Chart 1), which lead to local and systemic inflammation, glomerular and tubular lesions, and ultimately, albuminuria.[80] Among the cytokines, TNF-α is known to cause direct cytotoxicity and apoptosis of renal cells.[17] A recent meta-analysis showed a statistically significant increase in serum concentrations of TNF-α in type 2 DM patients, especially in those with DKD, suggesting that increased inflammatory load in DKD contributes to disease progression.[81]

The expression of profibrotic transcription factors, such as the TGF-β and connective tissue growth factor, triggers the recruitment of extracellular matrix-producing cells, accelerating renal sclerotic and fibrotic processes.[9] TGF-β plays pleiotropic effects, promoting hyperplasia and hypertrophy of renal cells. In the extracellular matrix, TGF-β is found in a latent form, bound to proteins, requiring cleavage to release of its free, active form. This activation is performed by mediators produced under hyperglycemic condition, including AGEs, ROS, DAG, PKC, Ang II, among others. Once activated, TGF-β binds to its cell receptor, and regulates the transcription of target genes, including collagen types I, III and IV, fibronectin, plasminogen, and PAI-I, with net effect of protein synthesis and expansion of the extracellular matrix, glomerulosclerosis and renal fibrosis. It also activates NF-κB, contributing to the production of proinflammatory cytokines, exacerbating local inflammation.[34,74,82]

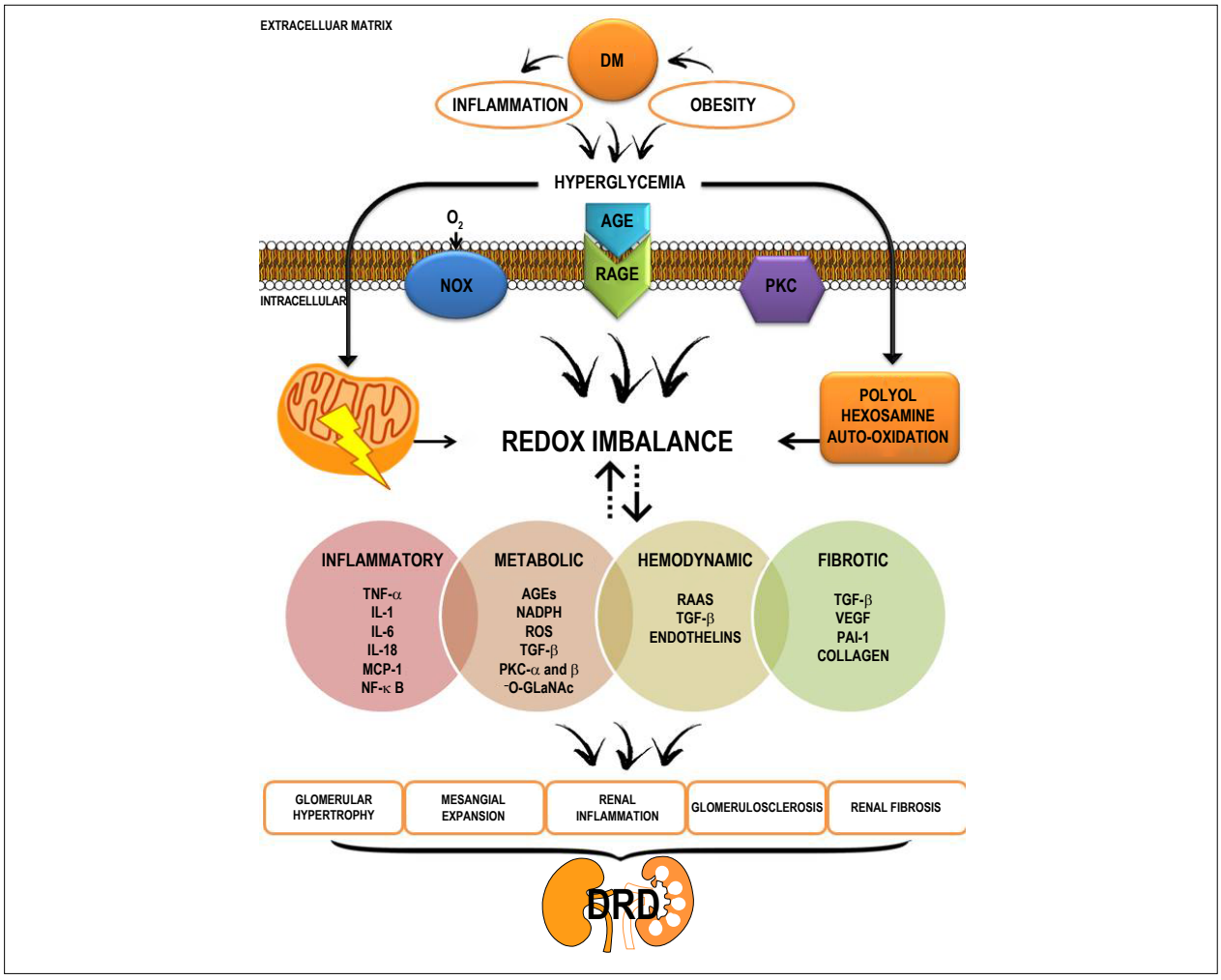

Figure 3 – *Mediators of kidney injury induced by chronic hyperglycemia via redox imbalance and inflammation in the pathogenesis of diabetic kidney disease. ROS: reactive oxygen species; ERK: extracellular signal-related kinases; TNF- α: tumor necrosis factor alpha; NF-κB: nuclear factor-kappa B; VEGF: the vascular endothelial growth factor; IL-1: interleukin 1; IL-6: interleukin 6; IL-18: interleukin 18; ECM: extracellular matrix; NOX: NADPH oxidase; -O-GLaNAc: O-glycosylated into N-acetylglucosamine; PAI-1: plasminogen activator inhibitor-1; AGE: advanced glycation end-products; PKC: protein kinase C; MCP-1: monocyte chemotactic protein-1; RPGA: receptor for advanced glycation end products; RAAS: renin-angiotensin aldosterone system; TGF-β: transforming growth factor-beta.*

Conclusion

Recently, there has been increasing evidence that redox imbalance and inflammation in response to intermittent or chronic exposure to hyperglycemia play an important role in initiation and perpetuation of DM complications, including DKD. They are now considered the main contributors to the development of DKD and end-stage kidney disease. New pathological pathways, associated with renal dysfunction in DM and that particularly exacerbate metabolic pathways, have been identified, such as the association between DKD and obesity. Therefore, metabolic, inflammatory and oxidative interference of DM and other risk factors for DKD should be continuously investigated and updated not only to improve the understanding of the mechanisms, but also to determine new therapeutic targets.

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Author contributions

Conception and design of the research: Santos JCF, Amorim RG, Vasconcelos S; Writing of the manuscript and Critical revision of the manuscript for intellectual content: Santos JCF, Amorim RG, Guedes GS, Vasconcelos S.

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Resident Macrophages Orchestrating Heart Rate

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Introduction

The electrical conduction system of the heart is essential for maintaining normal heart rhythm and function. This is due to the presence of specialized cells that generate electrical impulses that propagate throughout the heart tissue, quickly and efficiently. This electrical impulse starts at the sinoatrial node (SAN) and propagates sequentially to atrioventricular node (AVN), subsequently being transmitted to the ventricles via specialized conduction pathways. The electrical signals are conducted from cell to cell through a cardiomyocyte permeability control system formed by proteins called connexins, and connexin-43 is the type found in the heart and is associated with the formation of so-called gap junctions. By providing the single electrical connection between the atria and the ventricles, AVN plays an essential role in the dynamics of cardiac contraction. Clinically, when the PR interval is observed in the electrocardiographic recordings, we can correlate the electrical impulse conduction time from its generation in the SAN to the delay in the AVN region, which is called "decremental conduction".[1] When prolongation of the PR interval or an AV block occurs, which delays excessively or even eliminates the conduction of the electrical impulse from the atria to the ventricles, will result in hemodynamic deterioration, syncope and death, in case the patient is not submitted to the brand heart.[2]

Over the years, several studies have described the macrophages as cells of phagocytic functions that would exclusively act in the immune system protecting the organism against pathogens. However, more recently this paradigm was mainly questioned about the origin of macrophages. Several studies have provided evidence that a subpopulation of macrophages, which originated from embryonic development and do not come from the bloodstream, reside and proliferate in virtually all body tissues and apparently act specifically on each organ. For example, resident macrophages of adipose tissue contribute to the regulation of thermogenesis,[3] iron recycling in the spleen and liver,[4] and participate in the process of synaptic maturation in the healthy brain.[5] Such non-canonical activities emphasize the functional diversity of macrophages and their ability to perform specific tasks in the various tissues, in addition to host defence.[6] In cardiac tissue, macrophages are intrinsic components of the myocardium in normal functioning, where they appear as spindle cells intercalated between cardiomyocytes, fibroblasts and endothelial cells.[7]

Keywords

Macrophages; Heart Conduction System; Heart Rate; Myocites, cardiac; Fibroblasts; Connexins; Arrhythmias, Cardiac.

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Macrophages and the heartbeat

Cardiac function depends on the appropriate moment of contraction in several distinct regions, as well as the heart rate.[8] Hulsmans et al.[9] observed that mice that had their macrophage fauna weakened, had bradycardia and irregular beats. It is known that connexin-43 is predominant in ventricles of humans and that its reduction promotes bradycardia and AV block,[8] thus, in observing specialized cells in non-muscular electrical conduction, they found that macrophages are electrically coupled to cardiomyocytes and that these resident macrophages facilitate electrical conduction through the AV node.

Such conducting cells interleave with macrophages expressing connexin-43 forming additional gap junctions between cardiomyocytes (Figure 1). The investigators observed that the animals that had a reduction of resident macrophages, besides having bradycardia, had AV blockade of 2nd and 3rd degrees (Figure 2),[9] whose cause in humans is still unknown.[10] Another intriguing point is that cardiac macrophages have a resting membrane potential of -35 mV on average and depolarize in synchrony with cardiomyocytes. This makes the membrane potential at the rest of the cardiomyocytes more positive and according to the results obtained by computational simulation, accelerate both depolarization and repolarization phases.[9] The cardioprotective role of cardiac resident macrophages can go beyond the modulation of the electrophysiological properties of the coupled cardiomyocytes. The perivascular localization of cardiac macrophages makes them uniquely positioned to interpret systemic signals in the bloodstream.[10]

Macrophages and cardiovascular diseases

Monnerat et al.[11] demonstrated that inflammation caused by type I diabetes causes resident macrophages to secrete interleukin 1β (IL-1β), acting in a paracrine manner, increasing oxidative stress in the surrounding cells and destabilizing the electrical activity of cardiomyocytes provoking lethal ventricular arrhythmias. Moreover, atherosclerotic lesions are currently understood as inducers of important inflammatory processes, which comprise components of the innate and acquired immune systems. Clinical data showed that increased leukocyte count, interleukin-6 (IL-6), tumour necrosis factor (TNF) and IL-1β were at risk of more severe cardiovascular events.

In fact, IL-6 is locally regulated during the coronary occlusion process in patients with acute myocardial infarction with ST-segment elevation.[12-14]

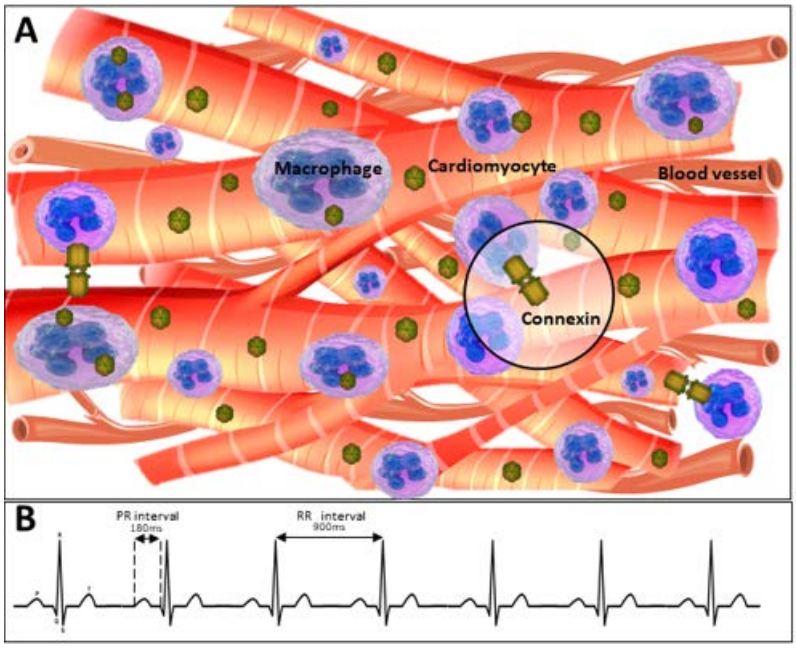

Figure 1 – *The normal condition of macrophage-cardiomyocyte couplings. Communications between cardiomyocytes and macrophages through connexin-43 (A) promoting normal cardiac rhythm (B).*

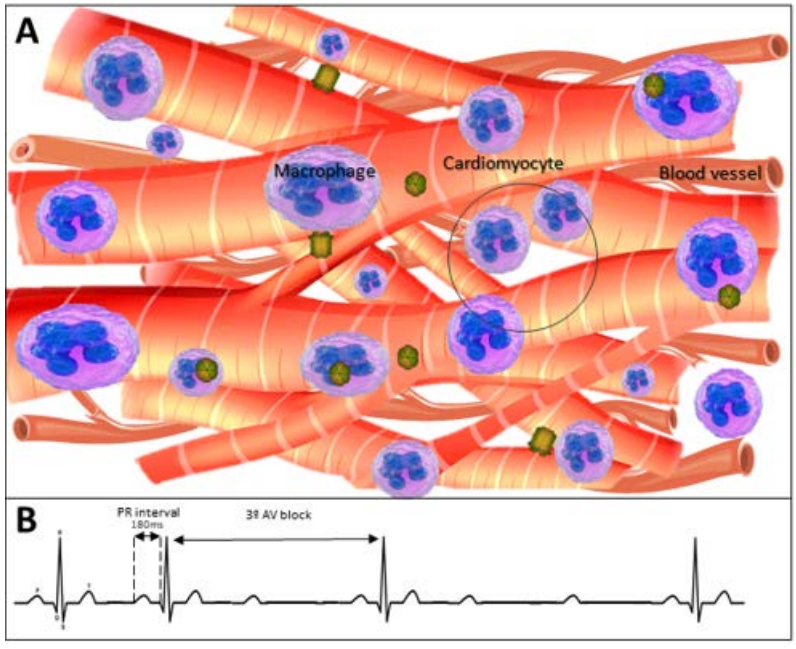

Figure 2 – *Reduction in the expression of connexins. The coupling between macrophages and cardiomyocytes is decreased due to the reduction of connexin-43 (A) expression promoting electrical conduction pathologies (atrioventricular block of 3º degree - B).*

Thus, a possible bias is one in which macrophages contribute to the arrhythmic complications of infectious, atherosclerotic and septicemic diseases, in which their inflammatory responses may interfere with their role in modulating electrical conduction of the cardiomyocyte.[11,12,15] Research has shown that sepsis is associated with an increased risk of acute and fatal coronary disease, but its cause is still a matter of debate, and acute coronary disease prevention may be an important consideration in post-sepsis medical care.[16,17]

Despite significant advances in prevention and treatment, cardiovascular diseases (CVD) continue to be the most common cause of death in the world. In fact, severe heart failure is more prevalent than cancer.[18] Several studies have demonstrated that pathological cardiac hypertrophy and fibrosis in heart failure are accompanied by a systemic inflammatory response, infiltration and activation of cells of the immune system.[19] In view of this, immunotherapies for cardiovascular diseases are on the rise.

The first cardiovascular immunotherapy was developed for the treatment of hypercholesterolemia and its positive results paved the way for the clinical evaluation of anti-inflammatory immunotherapy directed to interleukin 1β. CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study) has shown that subcutaneous injections of canakinumab (ACZ885), a human monoclonal antibody that selectively neutralizes IL-1β, significantly reduced levels of systemic inflammatory biomarkers in patients after acute myocardial infarction, reducing risk cardiovascular disease in patients with previous heart attack and inflammatory atherosclerosis.[20] Another study using CANTOS reinforces this idea and provides strong evidence that the modulation of the IL-6-induced signaling pathway induced by IL-1α is associated with reduced rates of cardiovascular changes and mortality.[13]

It is clear that further studies should be performed to address the actual involvement of resident macrophages in heart diseases. If alterations in macrophages' function are linked to these clinical conditions, immunotherapy with macrophage reprogramming *in situ* could be a reliable form of therapeutic strategy that could be applied to ensure normal cardiac rhythm in patients with signs of arrhythmia.[20,21] However, what we know so far is that resident macrophages act as "masters", orchestrating the heart rate.

Author contributions

Conception and design of the research and Critical revision of the manuscript for intellectual content: Souza DS, Barreto TO, Cruz JS; Writing of the manuscript: Souza DS, Barreto TO, Santana MNS, Menezes-Filho JER, Cruz JS, Vasconcelos CML.

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Study Association

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Case 3/2019 – Type IIB Tricuspid Atresia, in Natural Evolution, at 21 Years of Age

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Clinical data

Patient remained asymptomatic from birth until 16 years of age, when he started to show progressive fatigue at exertion, with the use of anti-congestive medication such as furosemide, enalapril, spironolactone, and carvedilol, in addition to warfarin. The diagnosis of heart disease characterized by heart murmur was attained in the first month of life.

Physical examination: good overall status, eupneic, acyanotic, normal pulses in the 4 limbs. Weight: 63 kg, Height: 171 cm, right upper limb blood pressure: 130/90 mmHg, HR: 63 bpm, Sat O_2: 89%.

Precordium: apex beat was palpable at the 6th left intercostal space in the anterior axillary line and diffuse, with systolic impulses in the left sternal border. Hyperphonetic heart sounds, with irregular splitting of the second heart sound. Moderate intensity ejection systolic murmur at the left upper sternal border with systolic thrill and holosystolic murmur ++/4 at the lower sternal border and at the tip with diastolic murmur ++/4. The liver was palpable 4 cm from the costal border and lungs were clear.

Complementary examinations

Electrocardiogram: Sinus rhythm and signs of left-chamber overload, with a narrow QRS of 0.87 ms (AQRS = +110°), a positive T wave in V1 (AT = +10°), and an enlarged P wave in II, III and in F (AP = + 60°) (Figure 1).

Chest x-ray: Significantly increased cardiac area on account of the right arch with double contour and left ventricular arch (CTI = 0.69). Increased pulmonary vascular network and bulging middle arch (Figure 1).

Echocardiogram: Absence of atrioventricular connection on the right, with ventricular-arterial discordance and extensive septal defects, both interatrial (34 mm) and interventricular (22 mm), and posterior deviation of the infundibular septum with pulmonary subvalvular stenosis. Pulmonary trunk dilatation was observed, and the mitral valve showed double dysfunction. The left ventricle (LV) was dilated, with an ejection fraction of 54%. Maximum pressure gradient LV-PT = 58 to 77 mmHg. (Figure 2).

Keywords

Heart Defects, Congenital; Tricuspid Atresia; Pulmonary Valve Stenosis; Clinical Evolution/methods.

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Magnetic Resonance Image (MRI): Same findings observed in the echocardiogram.

Cardiac catheterization: RV = LV: 110 mmHg; PT: 48 mmHg; PVR: 1.3 UW and SVR: 35.9 UW and Qp/Qs: 5.3/ L.

Laboratory findings: Hg: 19.3, Hct: 59%, uric acid: 9.5.

Clinical Diagnosis: Type II B tricuspid atresia with extensive septal defects and moderate infundibulum-pulmonary valve stenosis, mitral insuficiency, maintaining pulmonary hyperflow and high arterial saturation, undergoing natural evolution until adulthood.

Clinical Reasoning: There were clinical elements leading to a diagnosis of cyanogenic congenital heart disease with marked clinical repercussion, with pulmonary hyperflow. Tricuspid atresia or double LV inflow tract with mild to moderate pulmonary stenosis due to limitation of pulmonary flow, in the presence of auscultation characteristic of associated pulmonary stenosis. The electrocardiogram emphasized LV overload, compatible with the above diagnoses. Echocardiogram and MRI highlighted the diagnostic elements of the defect.

Differential Diagnosis: Other cyanogenic heart diseases with pulmonary hyperflow should be recalled with the same pathophysiological picture. Among them, left atrioventricular valve atresia in the presence of a well-developed LV and any other heart disease accompanied by right ventricular hypoplasia.

Clinical Conduct: Taking into account the harmonized pulmonary and systemic flows over time, with no signs of hypoxemia and / or heart failure and in the presence of good physical tolerance, the clinical expectant management was considered.

Comments: It is known that the different types of tricuspid atresia, whether with pulmonary flow limitation or not, has an unfavorable evolution, with signs of hypoxia or heart failure as early as in the first days of life, which progressively worsens over the first months, until the end of the first year of life. Therefore, the need for surgical intervention in this period. It can be affirmed that cases with tricuspid atresia and a mild repercussion who remain asymptomatic until adulthood are rarely identified.[1] In this circumstance, they may not require early surgical intervention. Thus, it is important to emphasize that these patients require a stringent and thorough evaluation, in order to be able to determine the most correct conduct for the infant, whether expectant or surgical intervention. This decision becomes even more difficult in adulthood, since heart failure that is observed at a later period, with myocardial dilatation and hypertrophy, and even with cardiac function preservation, is a parameter for an indefinite conduct, given the greater surgical risks in this age group. We did not find reports in the literature that were similar to the case described herein.

Clinicoradiological Correlation

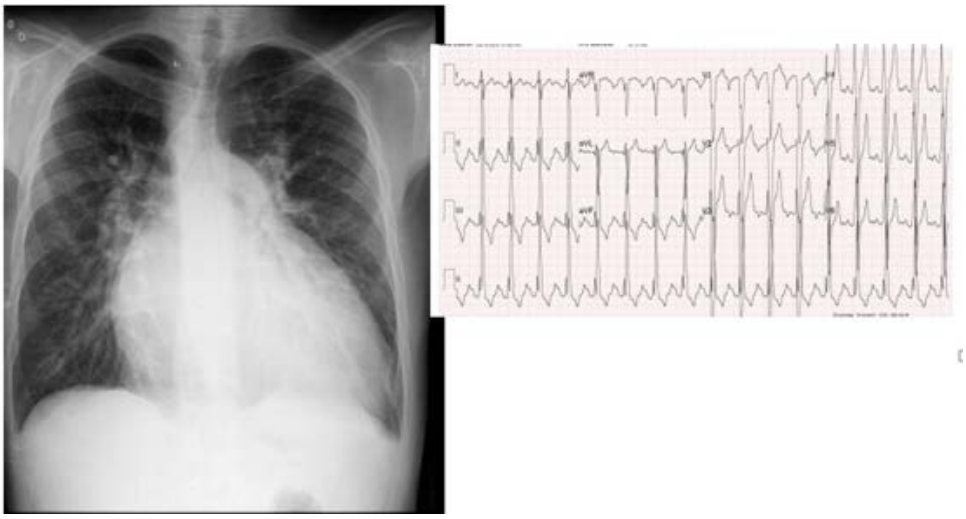

Figure 1 – *Chest x-ray highlights the marked increase of the cardiac area (CTI = 0.69) with increased pulmonary vascular network in the hila. Electrocardiogram shows left-chamber overload.*

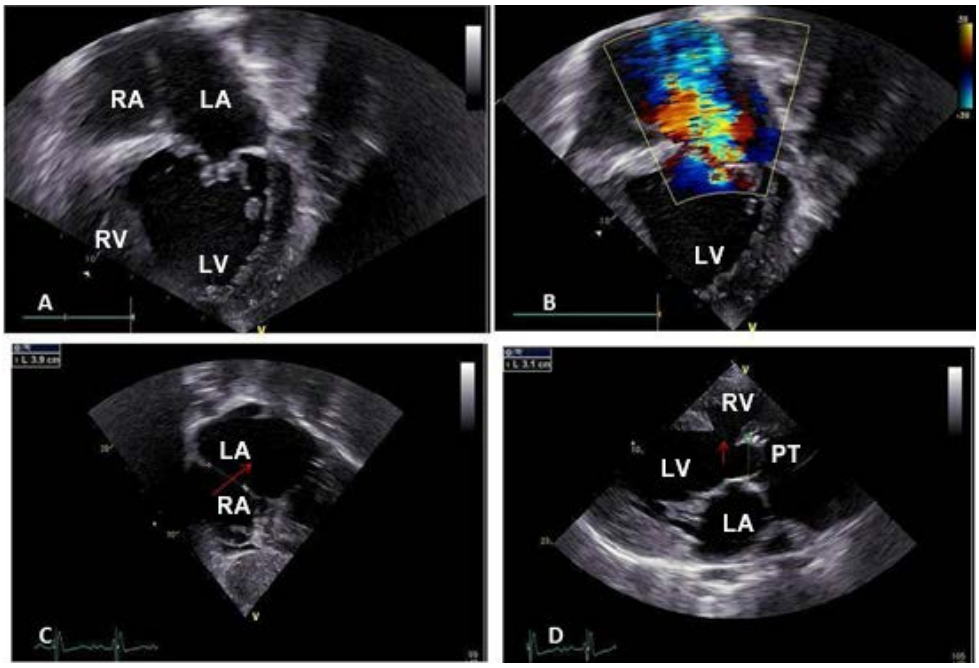

Figure 2 – *Echocardiogram highlights the marked increase in left heart cavities with right atrioventricular valve atresia and very hypoplastic right ventricle in subcostal view in A; marked mitral regurgitation in B; the large interatrial septal defect (arrow) in subcostal view in C; and the long-axis view image in D showing the interventricular septal defect (arrow) and the pulmonary valve-LV connection, characterizing type IIB tricuspid atresia. RA: right atrium; LA: left atrium; PT: pulmonary trunk; RV: right ventricle; LV: left ventricle.*

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Report of a Family with Craniofrontonasal Syndrome and Wolff-Parkinson-White Syndrome: Is it a New Finding?

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Introduction

Craniofrontonasal syndrome (CFNS; OMIM# 304110) is one of the craniofacial conditions that fall into the group called Craniofacial Dysostosis syndromes. Alternative names are Craniofrontonasal Dysplasia and Craniofrontonasal Dysostosis. CFNS is a rare X-linked disorder caused by mutations in the ephrin-B1 gene (EFNB1).[1] CFNS predominantly affects the head, face and limbs and characterized by coronal craniosynostosis, frontal bossing, severe hypertelorism, craniofacial asymmetry, down slant palpebral fissure, broad nasal root, bifid nasal tip, grooved fingernails, curly wiry hair, and abnormalities of the thoracic skeleton.[1] Phenotypic expression varies greatly amongst affected individuals. Paradoxical to other X-linked conditions, CFNS generally affects females more frequently and more severely than males.[1,2] Cellular or metabolic interference due to X inactivation explains this situation. There is no accurate measurement of its birth frequency and the incidence values that were reported ranged from 1:100,000 to 1:120,000. CFNS is not diagnosed in males unless they are a member of a family known to have the condition or the father of a daughter with the condition. In females, physical characteristics play a supportive role in establishing the diagnosis but the diagnosis CFNS is determined by the presence of a mutation in the EFNB1 gene.

Wolff-Parkinson-White (WPW) syndrome is a pre-excitation syndrome which is a common cause of supraventricular tachycardia with prevalence in Western countries of 1.5 to 3.1 per 1000 persons.[3] It is maintained by accessory pathway or pathways secondary to a developmental cardiac defect in atrioventricular electrical insulation.[3] Among patients with the WPW syndrome, 3.4% have first degree-relatives with a pre-excitation syndrome.[4] A familial form of WPW has infrequently been reported and is usually inherited as an autosomal dominant trait.[5-7]

There are very few cases describing association of CFNS with heart defects. We identified a CFNS family with WPW syndrome.

Keywords

Wolff-Parkinson White Syndrome; Craniofacial Abnormalities; Comparative Studies; Craniofacial Dysostose; Tachycardia, Supraventricular.

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Case Report

A 16 years old inbred girl was referred to the cardiology clinic because of paroxysmal palpitation. Her parents are consanguineous. The 12-lead electrocardiogram (ECG) showed short PR interval and Delta waves, and widened QRS complexes (Figure 1). The patient was considered as type-A WPW syndrome. Transthoracic echocardiography was normal. Patient, her sister and father have molecularly confirmed CFNS and both have heterozygous missense mutation (c.451G > A; Gly151Ser) in exon 3 of EFNB1 gene. She has undergone surgery for frontonasal dysplasia. Father was also had WPW syndrome and he had a successful catheter ablation for left lateral accessory pathway. The patient was refereed to electrophysiology department for electrophysiological study and transcatheter ablation of the accessory pathway.

Discussion

The EFNB1 gene, which maps to Xq13.1, encodes a member of the ephrin family of transmembrane ligands for ephrin tyrosine-kinase receptor.[2] This ephrin receptor is responsible for the cell migration, regulation of embryonic tissue-border formation, and is important for skeletal and craniofacial development.[8] In mice, the orthologous EFNB1 gene is expressed in the frontonasal neural crest and demarcates the position of the future coronal suture. As the ephrin receptor and its EFNB1 ligand are both bound to the (trans)membrane of the cell it's cascade is activated through cell-cell interactions.[8] These cell-cell interactions are disturbed due to the presence of cells with the mutant EFNB1 gene, as a result causing incomplete tissue-border formation.[1]

WPW syndrome is characterized with the existence of anomalous bundles of conducting tissue that bypassed all or part of the normal atrioventricular (AV) conduction system. This tissue directly connects the atria and ventricles, thereby allowing electrical activity to bypass the AV node. Tissue in the accessory pathways, which are congenital in origin and result from failure of resorption of the myocardial syncytium at the annulus fibrosis of the AV valves during fetal development, typically conducts electrical impulses more quickly than the AV node, resulting in the shorter PR interval seen on the ECG. The familial occurrence of the WPW syndrome is well documented, is typically inherited in an autosomal dominant pattern, and is sometimes associated with familial cardiomyopathy. Mutations in the genes encoding the gamma-2 regulatory subunit of adenosine monophosphate-activated protein kinase (PRKAG2) and lysosome-associated membrane protein 2 (LAMP2) have been associated with left ventricular hypertrophy in association with WPW syndrome.[4] Studies of two families

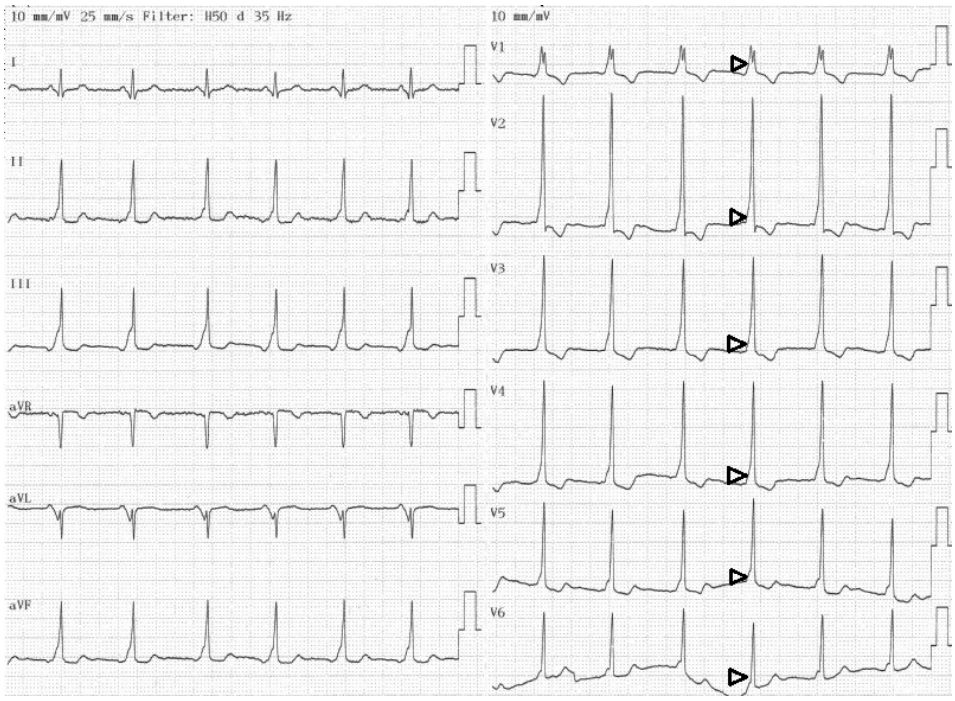

Figure 1 – *The 12-lead ECG of the patient showing Type A Wolff-Parkinson-White pattern: PR interval < 120 ms, positive delta waves (black arrowheads) in all precordial leads (V1-V6) with R/S > 1 in V1.*

with affected subjects who had ventricular pre-excitation with conduction abnormalities and cardiac hypertrophy, mapped the PRKAG2 gene responsible for WPW to chromosome 7q34-q36.[6] A missense mutation, Arg531Gly, was identified in affected individuals who had ventricular pre-excitation and conduction system disease with childhood onset and absence of cardiac hypertrophy.[7]

There are very few cases describing association of CFNS with heart defects such as atrial septal defect.[9,10] To date, there are no reported cases of CFNS with WPW syndrome, suggesting that this novel finding can be part of this condition. Approximately 100 different mutations have been reported in CFNS and Gly151Ser mutation in EFNB1 gene may cause familial WPW syndrome in this CFNS family.

Conclusion

To our knowledge, this is the first report of a family with WPW syndrome and CFNS. Genetic analyses are needed to explain this association between CFNS and WPW syndrome. Clinicians must be aware in patients with CFNS syndrome in terms of the presence of ventricular pre-excitation.

Author contributions

Conception and design of the research and analysis and interpretation of the data: Kilit C; writing of the manuscript and critical revision of the manuscript for intellectual contente: Kilit C, Kilit TP.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

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Comment on Myocardial Perfusion Study in Obese Patients without Known Cardiac Ischemia

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"All human knowledge is fallible and therefore uncertain. It follows that we must distinguish sharply between truth and certainty... This is the task of scientific activity. Hence, we can say: our aim as scientists is objective truth; more truth, more interesting truth, more intelligible truth. We cannot reasonably aim at certainty."

Karl Popper

We congratulate Dippe et al.[1] for their work that addressed the role of myocardial scintigraphy in the diagnosis of myocardial ischemia in obese patients.[1] Despite limitations, body mass index (BMI) has been the most used anthropometric tool for assessing nutritional status in adults.[2] Epidemiologic studies have identified high BMI as a risk factor for an expanding set of chronic diseases, including cardiovascular disease and diabetes mellitus. The Global Burden of Disease (GBD) Obesity Collaborators found that excess body weight accounted for about 4 million deaths in 2015. Nearly 70% of these deaths were due to cardiovascular disease, and more than 60% of them occurred among obese persons (BMI ≥ 30 Kg/m^2).[3] The use of a database of consecutive patients provides a sample of obese patients from the real-world scenario and portrays the current clinical practice in which the cardiologist faces major diagnostic challenges in obese patients. All diagnostic methods have significant challenges in obese patients such as the limitation of the acoustic window in the echocardiogram, higher incidence of photon attenuation on computed tomography and myocardial scintigraphy and bore size limitations to cardiac resonance imaging. Radiation-sparing techniques are more difficult to use in heavier patients.[4] The finding that clinical data such as the presence of diabetes mellitus, older age and typical symptoms of angina highlights the need of careful clinical evaluation in order to adequate request ischemic screening tests in patients with suspected coronary artery disease, especially in the obese. Another important finding of their study was the absence of association between obesity alone, especially in the group with BMI greater than 40, with the presence of ischemia. A technical aspect that was not clear in the article and whether the authors used the prone acquisition when there was doubt about the presence of breast attenuation and also the technique used to quantify the visual or automatic ischemia.

In an editorial about this article, Hueb[5] points out the multiple mechanisms involved in the pathophysiology of myocardial ischemia, including the microvascular mechanisms that determine ischemia in patients with epicardial coronary arteries without obstruction. Functional methods are important in the identification of microvascular ischemic abnormalities, which have diagnostic and prognostic value, especially in diabetic patients and in patients with multiple risk factors. Functional imaging is superior to anatomic imaging in patients with microvascular disease because of their focus on different levels of the ischemic cascade including wall motion abnormalities (echocardiography and stress cardiac magnetic resonance), relative perfusion abnormalities (stress cardiac magnetic resonance and single-photon emission computed tomography), and changes in physiological absolute regional myocardial perfusion (PET).[6] The creation of the patient-centered imaging culture that prioritizes patient safety and effectiveness requires the understanding of the better diagnostic techniques for every clinical need.[7]

Karl Popper stated that science is composed of transient truths. The role of scientists is to prove the falsifiability of their findings and others in the search of a more intelligible true. In the absence of contrary evidence, current evidence points that invasive treatment in patients with myocardial ischemia area greater than 10% is associated with better prognosis in comparison with medical management alone. The results of the ISCHEMIA study to be published in the near future should provide additional new scientific evidence regarding whether an invasive management strategy improves clinical outcomes when added to optimal medical therapy in patients moderate or severe ischemia.[8]

Keywords

Coronary Artery Disease; Myocardial Perfusion Imaging; Obesity/mortality; Myocardial Ischemia; Diabetes Mellitus.

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Reply

Regarding our manuscript,[1] we would like to make some comments about the letter sent to the editor by Universidade Federal Fluminense (UFF) and about the short editorial written by Dr. Whady Rueb.[2]

Although body mass index (BMI) correlates with the percentage of body fat in most individuals, the limitations of this index is widely known.[3-5] On the other hand, major cohort, prospective and observational studies, such as the Framingham study[6] and the Nurse's Health Study,[7] used BMI as a diagnostic parameter for obesity, demonstrating a nearly linear relationship between BMI and coronary artery disease (CAD) from a value equal to or greater than 25 kg/m^2.

The World Health Organization (WHO) uses BMI for the diagnosis and classification of obesity.[8] In our study,[1] which evaluated 5,526 obese patients undergoing myocardial perfusion scintigraphy, one of the largest samples ever published in the world literature, 29.7% of the individuals had BMI equal to or greater than 35 kg/m^2.

Regarding the questioning of the UFF colleagues, we pointed out that the limitations of the manuscript include that our patients were not submitted to attenuation correction techniques routinely.

Before we make any specific comments on the short editorial, we would like to emphasize our deep admiration for Dr. Whady Hueb, a Brazilian scientist of great importance for the world cardiology, who we highly appreciate and respect. We would also like to emphasize, with no reservations, his contribution to the international literature with the MASS study,[9] quoted and admired all over the world. Today, among other things, the MASS study allows us to work together on the ISCHEMIA study,[10] on which both Dr. Whady Hueb's and our group worked hard for a successful completion.

Regarding the minieditorial on our study, we would first like to make some comments about the tests recommended and the perfusional abnormality rate we found.

Note that our registry in Curitiba, which is certainly one of the largest nuclear cardiology registries in the world, includes patients referred to our diagnostic center, about whom we have no control over which are the tests to be recommended, as this is the responsibility of the referring clinician. (I do not understand this)

Besides that, we cannot infer that the tests have been inappropriately recommended based on 77% of normal scintigraphies. We are sure that this data should not be used as a criticism of our study, since in many clinical situations this is exactly the information sought by the clinician requesting a provocative ischemia test, that is, the absence of ischemia can avoid unnecessary anatomical evaluations, such as cineangiocorography, for example.

It is true that many of these patients with suspected CAD could have their disease ruled out by coronary angiography. Unfortunately, this practice is still limited in our country, because of the restrictions imposed by health insurance plans or unavailability in the public health system (SUS). We believe that this would be an excellent way to "rule out" CAD, avoiding additional tests, including myocardial perfusion scintigraphy itself.

Although our perfusion abnormality rate (23%) was considered low by Dr. Whady Hueb, it is nearly three times greater than that found in reference laboratories in the United States, as found by the Cedars Sinai Hospital registry, which revealed about 8.7% of perfusion abnormalities.[11] Similarly, the randomized study PROMISE[12] found a perfusion abnormality rate close to 10% in symptomatic patients.

In our sample, 31% of the patients were known diabetics, and this certainly differentiates our group from other studies, and helps us understand our high abnormality rate.

Another excerpt of the short editorial reads: *based on this data, by applying a "creative statistics", they found a 245% risk increase for typical angina*.

Note that nowhere in the manuscript we mentioned that a perfusional abnormality would increase the risk of typical angina. We have published that the patients who reported typical angina before the test, compared to asymptomatic patients (reference) had 245% higher chances of having

Letter to the Editor

abnormal myocardial perfusion (odds ratio of 2.45 [1.82-3.31], see page 125 of the manuscript, table 4).[1] There is no "creative statistics" at all. This conclusion was reached after multivariate logistic regression analysis. It is pure statistics.

Finally, we would like to thank UFF for the letter sent to the editor of Arquivos Brasileiros de Cardiologia and to Dr. Whady Hueb for his short editorial. The productive discussion and scientific production certainly help to add further value to our admired Brazilian cardiology.

Tufi Dippe Junior

João Vicente Vítola

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Brazilian Fetal Cardiology Guidelines – 2019

Direction: Department of Congenital Heart Disease and Pediatric Cardiology (DCC-CP) and the Brazilian Cardiology Society (SBC)

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

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If the last three years the author/developer of the Guidelines:

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Content

1. Introduction

Over the years, Fetal Cardiology have been incorporated into the daily practice of Pediatric Cardiology. What was once restricted to a few fetal heart researchers, has slowly been incorporated into health institutions that deal with congenital heart diseases (CHD). Fetal echocardiography has generated extensive knowledge of the natural and modified history of heart diseases in utero, and normal fetal heart physiology and anatomy. The benefits of fetal diagnosis have become unquestionable over the years. Pioneers in the area succeeded in demystifying the fetal heart examination and proving the importance of screening for cardiac abnormalities during obstetric examinations. Prenatal detection rates have increased, and interest in fetal echocardiography is, thus, no longer merely a diagnostic tool; it has gone on to become a tool of the utmost importance in assisting medical and, progressively, interventional treatment of specific anomalies that occur in fetal life.

A vast body of literature currently supports the practice of Fetal Cardiology. In addition to diagnosis, anatomical and functional particularities may be identified in utero, with implications on the delivery planning and pre and postnatal management. Prenatal diagnosis has certainly led to increase the number of babies with complex heart diseases in Pediatric Cardiology hospital beds. Prior to this, children with complex heart diseases did not survive the immediate neonatal period and died in neonatal intensive care units without being diagnosed. Nowadays, these children require increasingly careful and specific management involving Pediatric Cardiology and thus modifying the practice of Neonatal Cardiology.

Despite the vast literature pertinent to Fetal Cardiology, due to the restricted number of cases, there is a lack of studies with large populations and randomization processes, being the information based on observational studies and description of small samples or cases reports. However, the accumulated knowledge is already enough to develop scientific statements or guidelines.

In April 2014, the American Heart Association (AHA) published the first scientific statement for Fetal

Cardiology, encompassing all the practical aspects involved in this area, including screening, diagnosis, medical or interventional therapy, counseling, delivery planning, and neonatal treatment. Considering this extremely thorough and highly useful document, we have accepted the challenge of bringing together professionals dedicated to Fetal Cardiology from different regions of Brazil in order to jointly establish guidelines which are adapted to our reality and which also take into consideration knowledge created in Brazil. We believe that the information brought together in this document will be of great use to professionals who face the challenge of dealing with possible abnormalities that affect the fetal heart in their daily practice.

2. Screening and Diagnosis of Fetal Heart Disease

2.1. Introduction

One of the main aims of prenatal diagnosis is the detection of severe CHD, whose diagnoses, in most cases, depend on delivery planning in a specialized referral center.[1-3] Although fetal echocardiography, which is traditionally designated for high-risk pregnancies, is quite accurate, the majority of newborns affected by heart diseases in most parts of the world, continue to be born without having been diagnosed. This occur because many cases of CHD affect low-risk groups and are not detected by screening prenatal ultrasound.[4,5]

The concept of prenatal screening for CHD was first suggested in 1985, with the recommendation of incorporating the four-chamber view into routine obstetric ultrasound.[6] For more than 25 years, countries such as France, the United Kingdom and Spain have recommended examination of the fetal heart during the routine obstetric ultrasound. Nonetheless, after many years of investment in educational training programs, regional variation in detection rates of prenatal heart diseases continue to be high. The classic study by Garne et al.,[7] conducted in 20 European centers showed that the global detection rate of fetal heart diseases was rather low (25%), France being the country with the best performance (48%), followed by Spain (45%), Germany (40%), and the United Kingdom (35%). Many studies have shown that detection rates of prenatal heart diseases significantly improve with the expansion of scanning planes for cardiac analysis, but they remain well below 50% and continue to lag behind in relation to prenatal detection of other forms of congenital malformation.[8,9]

Faced with this situation, some have argued that fetal echocardiography should be indicated for all pregnancies, given that, in experienced hands, it is able to detect nearly 100% of all cardiac anomalies in fetal life and is considered the gold standard for fetal cardiac diagnosis.[10-13]

Although it is almost intuitive that prenatal detection of heart diseases would improve perinatal results, it has not been easy to prove this observation scientifically, owing to the difficulty of comparing groups with pre- and postnatal diagnoses, which present rather peculiar and discrepant characteristics. The group with prenatal diagnosis often presents with fetal death or early neonatal death before surgery, as it pertains to the much more severe spectrum of fetal cardiac abnormalities, due to the inability of obstetric ultrasound to screen simpler heart diseases, thus resulting in higher global mortality. On the other hand, the group with postnatal diagnosis, that survives the fetal and early neonatal periods until the baby arrives in a tertiary center, has already demonstrated some constitutional advantages for survival.[2]

A study conducted in France comparing perinatal outcome between babies with transposition of the great arteries, with and without prenatal diagnosis, showed, for the first time, that prenatal diagnosis significantly decreased pre- and postoperative mortality.[14] Other studies have suggested better results for hypoplastic left heart syndrome (HLHS) and coarctation of the aorta when they are diagnosed during fetal life.[15,16]

Efforts and resources should be directed to teaching and training for prenatal screening of CHD by obstetric ultrasound to achieve a better and more uniform pattern of detection, since performing fetal echocardiography in all pregnancies is unrealistic and has yet to be adopted as a health policy in developed countries.[11,13,17]

Table 2.1 shows the main risk factors for fetal heart diseases, divided into absolute risk of ≥ 2% and < 2%.

2.2. Fetal Heart Screening During Morphological Ultrasound

Considering all these characteristics, we propose a very simple methodology for evaluating the fetal heart, which has been applied in various countries throughout the world. The main advantage of this systematized heart evaluation is that it eliminates the need for complex views and images, avoiding more difficult maneuvers, which is time-consuming and discourage the examiner who neglects this important part of the morphological exam.

With this technique, the fetal heart is evaluated on transverse plane images of the baby only, with no need to rotate the transducer. It starts from the fetal abdomen, from the infradiaphragmatic region to the

Tabela 2.1 – Clinical conditions that increase the risk of fetal heart disease and are formal indications to perform fetal echocardiogram

Absolute risk ≥ 2%		GOR/LOE
Pregestational maternal diabetes mellitus		I/A
Maternal diabetes mellitus diagnosed during the first trimester		I/A
Poorly controlled maternal phenylketonuria,		I/A
Maternal anti-RO and anti-LA (SSA/SSB) antibodies		IIa/B
Maternal medication exposures	ACE	IIa/B
	Retinoic acids	I/B
	Nonsteroidal anti-inflammatory medications during the third trimester	I/A
Maternal rubella during the first semester		I/C
Maternal infection, with fetal myocarditis suspected		I/C
Use of assisted reproduction technology		IIa/A
CHD in first-degree relative (mother, father, or sibling)		I/B
Mendelian inheritance associated with CHD in first- or second-degree relative		I/C
Suspected CHD on obstetric ultrasound		I/B
Suspected noncardiac abnormality on obstetric ultrasound		I/B
Abnormal fetal karyotype		I/C
Fetal bradycardia, tachycardia, or irregular cardiac rhythm		I/C
Increased nuchal translucency > 95% (≥ 3 mm)		IIa/A
Monochorionic twins		I/A
Fetal hydrops or pleural effusion		I/B
Absolute risk between 1 and 2%		
Maternal medication exposures	Anticonvulsants	IIb/A
	Lithium	IIb/B
	Vitamin A	IIb/B
	Selected serotonin reuptake inhibitor (only paroxetine)	IIb/A
	Nonsteroidal anti-inflammatory drugs during the first and second trimesters	IIb/B
CHD in second-degree relatives		IIb/B
Fetal abnormality of umbilical cord or placenta		IIb/C
Intra-abdominal fetal venous anomaly		IIb/C
Absolute risk ≤ 1%		
Gestational maternal diabetes mellitus with HbA1c < 6%		III/B
Maternal medication exposures	Selected serotonin reuptake inhibitor (excepting paroxetine)	III/A
	Vitamin K antagonists (warfarin)	III/B
Maternal infection other than rubella with seroconversion only		III/C
Isolated CHD in a distant relative (not first- or second-degree)		III/B

ACE: angiotensin-converting enzyme; CHD: congenital heart disease; GOR: grade of recommendation; HbA1c: hemoglobin A1c; LOE: level of evidence. Source: Adapted from Donofrio et al.[17]

upper mediastinum, obtaining 6 planes, as shown in Figure 2.1.

2.2.1. Step 1 – 1st Level: Evaluation of the Abdomen to Identify the Abdominal Aorta and the Inferior Vena Cava

This is a transverse view of the fetal abdomen, in the subdiaphragmatic region, and helps to determine the abdominal situs. Before starting, it is necessary to identify the right and left sides of the fetus, according to the fetal presentation; the stomach should be on the fetal left side and the liver on the right. Furthermore, the descending aorta should be seen posterior and to the left, close to the spine, and the inferior vena cava anterior and to the right, within the hepatic parenchyma.

2.2.2. Step 2 – 2nd Level: Four Chamber View

This view is obtained with a transverse scan of the fetal thorax, immediately above the diaphragm. The heart should occupy one third of the thorax, the greater part being in the left hemithorax, with the apex turned to the left. The interventricular septum should be at an angle of approximately 45th with the midline.

The first step for fetal cardiac analysis is the identification of the spine. Opposite to the spine is the anterior wall of the thorax, or sternum. Below is the right ventricle, which is characterized by the moderator band and the tricuspid valve, located a few millimeters displaced to the apex. Returning to the spine, the descending aorta is seen anteriorly as a circle in the mediastinum and, in front of it, is the left atrium. The left atrium is close to the descending aorta and can be identified by the characteristic movement of the foramen ovale flap. Other intracardiac structures, such as the right atrium and the left ventricle, may then be analyzed. They should have dimensions similar to those of the contralateral chambers. The atrioventricular valves should be analyzed in relation to their movement and size of their valve annulus.

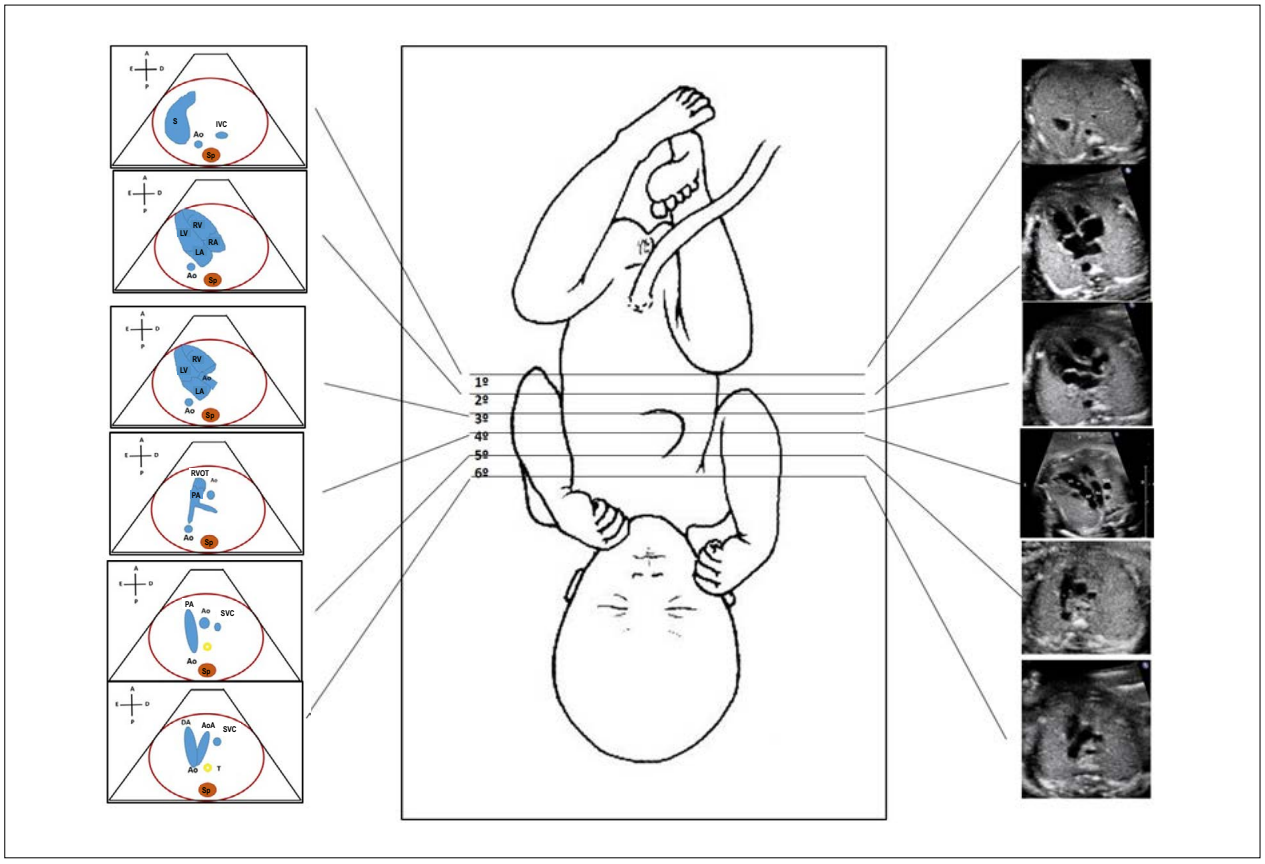

Figure 2.1 – *Standardization of fetal heart screening, scanning the fetal vessels and heart from the infradiaphragmatic region towards the cranium. There are 6 levels, being the first exactly below the diaphragm, which allows the identification of the descending aorta and inferior vena cava; second, the four-chamber view; third, left ventricular outflow tract; fourth, right ventricular outflow tract; fifth, three vessel view, and, sixth, three vessel and trachea view.*
Ao: Aorta; AoA: aortic arch; Asc: ascending; DA: ductus arteriosus; IVC: inferior vena cava; LA: left atrium; LV: left ventricle; PA: pulmonary artery; RA: right atrium; RV: right ventricle; RVOT: right ventricular outflow tract; S: stomach; Sp: spine; SVC: superior vena cava; T: trachea.

In summary, the analysis of the four-chamber view should include the following reference points:

- Spine.
- Descending aorta in a transverse plane.
- Left atrium close to the descending aorta and with the foramen ovale flap moving.
- Right ventricle with the apex "filled in" by a piece of muscle called the moderator band.
- Two atria of similar size.
- Two ventricles of similar size, thickness and contractility (the right ventricle may be slightly larger).
- The interatrial and interventricular septum join the atrioventricular valves in the middle of the heart, suggesting the image of a cross, the "crux cordis."
- The interventricular septum should be intact and make an angle of approximately 45º with the midline of the body.
- Two atrioventricular valves with equal opening orifices. The insertion of the septal leaflet of the tricuspid valve is closer to the cardiac apex, resulting in a minimal difference in the level of implantation of the anterior leaflet of the mitral valve. Sometimes, this difference is quite subtle, resulting in great difficulties in excluding the diagnosis of atrioventricular septal defect and single AV valve junction.
- The interatrial septum may be seen with the foramen ovale and its flap, tilting with the LA.
- The pulmonary veins drainage in the left atrium should be identified in two-dimensional view and confirmed by colored Doppler or power Doppler.

Failure to obtain a normal four chamber view during the obstetric ultrasound scan is an absolute indication for fetal echocardiogram. Because the four-chamber view does not include the examination of the right and left ventricular outflows, important diseases such as transposition of the great arteries, tetralogy of Fallot (TOF), common truncus arteriosus, among others may be missed. Tables 2.2 and 2.3 show the different heart diseases commonly associated with normal and abnormal four chamber views, respectively.

Table 2.2 – Heart diseases commonly associated with a normal four-chamber view

Tetralogy of Fallot
Transposition of the great arteries
Common truncus arteriosus
Anomalies of the aortic arch
Mild aortic and pulmonary valve stenosis
Perimembranous ventricular septal defect

Table 2.3 – Heart diseases commonly associated with an abnormal four-chamber view

Mitral and/or aortic atresia
Tricuspid and/or pulmonary atresia
Ebstein's anomaly/tricuspid valve dysplasia
Atrioventricular septal defects
Large ventricular septal defects
Single ventricles
Severe aortic and pulmonary valve stenosis
Coarctation of the aorta
Total anomalous pulmonary venous return
Cardiomyopathies
Cardiac tumors

2.2.3. Step 3 – 3rd Level: Left Ventricular Outflow Tract

Starting from the four-chamber views, the left and right outflow tracts and respective arteries can be seen swiping the transducer toward the fetal head. The left ventricular outflow tract is the first identified in the middle of the heart and it directs toward the fetal right shoulder. In this view it is possible to observe the membranous continuity of the septum with the aorta, which rules out a possible overriding aorta or great artery commonly seen in tetralogy of Fallot, truncus arteriosus, and other complex anomalies.

2.2.4. Step 4 – 4th Level: Right Ventricular Outflow Tract

Swiping slightly the transducer up, the right ventricular outflow tract is reached. It is the most anterior structure of the heart and is exactly below the fetal sternum. It crosses aorta from right towards the left. The great arteries are symmetric at the beginning of gestation, but during the second and the third trimesters the pulmonary trunk is slightly larger than the aorta.

2.2.5. Step 5 – 5th Level: Three Vessels View

This is a special view that allows to analyze the spatial relationship of the pulmonary artery, the aorta and the superior vena cava (SVC). In this view the vessels are seen immediately after their ventricular origins. Important information should be obtained from the

vessels: number – that should be three; position – SVC on the right, aorta on the middle and pulmonary artery on the left; size – SVC slightly smaller than aorta that should be slightly smaller than the pulmonary artery and finally, alignment – the SVC is more posterior, aorta is in the center and pulmonary artery is anterior.[19] In this plane, the right and left bronchi are observed.

2.2.6. Step 6 – 6th Level: Three Vessel and Trachea View

Immediately above this plane, i.e., tilting the transducer a bit further in the cephalic direction, a view of two large arches connecting with the descending thoracic aorta is obtained. The one on the left is the ductus arteriosus that originates from the pulmonary artery and the other on the right is the aortic arch, both connecting with the descending aorta. This view makes a figure that suggests the letter V. The trachea appears as an anechoic structure surrounded by a hyperechoic line which corresponds to cartilage, being situated in front of the spine, slightly to the right.

In this view, the aortic arch turns toward the left, which is defined exactly by its relation to the trachea. If the trachea is to the right of the aortic arch, the arch is turned toward the left and vice versa. It is worth highlighting that, the use of color flow mapping should be used during all screening steps and levels, and it is of particular importance during this final view. Both arches should present flow in the same direction, always directed from the heart toward the descending thoracic aorta (Figure 2.2).

2.3. Screening for Congenital Heart Disease During the First Trimester

Because CHD are the most common severe congenital defects and the least diagnosed by routine obstetric ultrasound, the challenge over recent years has been early screening methods for fetal heart disease, considering the fact that the majority of babies affected by heart disease are born to mothers who do not present the classic indications for fetal echocardiography.

Older studies have shown a sensibility of up to 40% in the detection of CHD in fetuses with increased nuchal translucency (NT), between weeks 11 and 14 of gestation (above the 99th percentile). Focusing on fetuses with increased NT and normal karyotype, they demonstrated an incidence of heart disease 5 to 7 times greater in this group.[20-22]

The most recent literature shows a sensibility of about 13.5% for the detection of cardiac abnormalities, being NT ≥ 3.5 mm considered an indication for fetal echocardiography.[23-25]

Doppler flow analysis of the fetal cardiovascular system is also applied to screen CHD that may or not be associated with chromosome diseases. Several studies have argued that abnormal flow of the ductus venosus, i.e., the appearance of the reverse wave during atrial contraction ("a" wave) in fetuses with NT ≥ 3.5 mm increases the probability of CHD three-fold, whereas a normal flow pattern decreases the risk of heart disease by half.[21] The presence of tricuspid regurgitation during the first trimester of pregnancy is highly associated

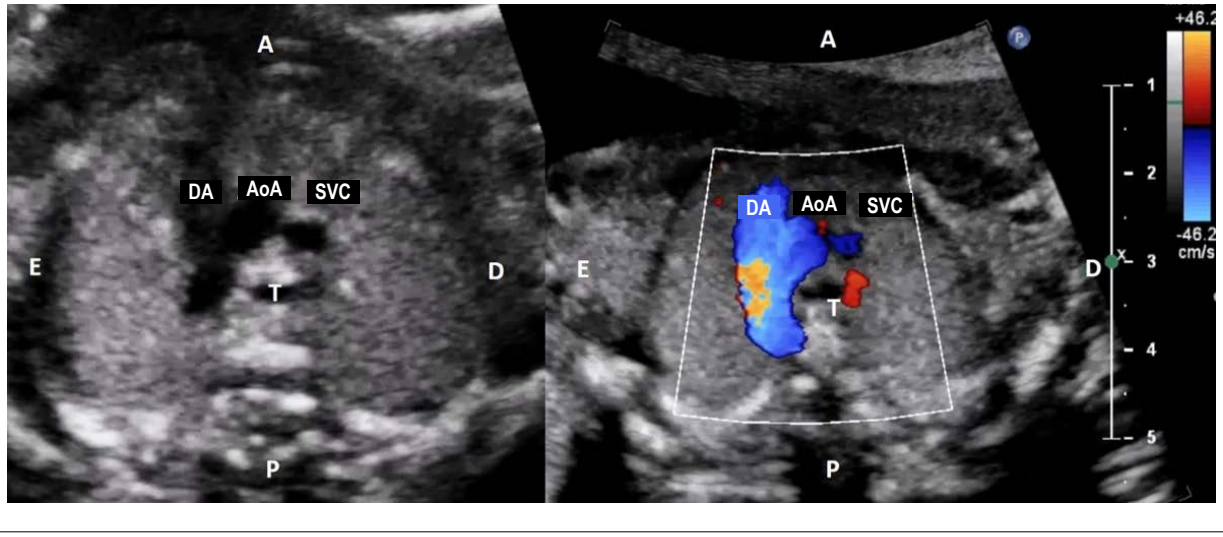

Figure 2.2 – *Aorta and pulmonary artery appear elongated, going toward the descending aorta. Both converge to the aorta forming an image similar to a V letter. The trachea is to the right of the aortic arch, demonstrating that the latter descends to the left. During color flow mapping, both arches are observed to have flow in the same direction, i.e., from the heart toward the descending thoracic aorta.*
AoA: aortic arch; DA: ductal arch; SVC: superior vena cava; T: trachea.

with trisomy. When present in chromosomally normal fetuses, the risk of heart disease is observed to increase eight-fold. The etiology of tricuspid regurgitation in the first semester is uncertain; it is known only that it disappears concomitantly with the normalization of nuchal thickness.[24]

2.4. Fetal Echocardiography

Before beginning the examination, it is very important to obtain information regarding gestational age, previous obstetric history, possible maternal disease or use of medications that may increase the risk for CHD, and the formal indication for the study. This will provide the cardiologist with the possible risks for cardiac anomalies.

The ultrasound system may be specific for echocardiography or ultrasonography, provided with a preset for fetal heart/echocardiography. Convex (ultrasonography) or phased array (echocardiography) transducers allow to obtain good quality images, with the observation that the majority of convex transducers do not provide continuous Doppler, which may be useful in cases of valvular stenosis or regurgitation.

Volumetric transducers may allow better two-dimensional imaging in obese pregnant women and first trimester examination, but they are not essential in daily practice, being considered sophisticated technology not available in the majority of fetal scanning laboratories.

After 18 weeks gestation, all cardiac structures may be securely analyzed by the fetal echocardiogram except in cases of poor acoustic windows like obesity, polyhydramnios, oligohydramnios and others. The best images, however, are obtained between weeks 24 and 28, when the heart is larger in size, the fetus continues moving well, and the bones do not constitute a significant ultrasound barrier. It is worth highlighting that early evaluation of the heart may be performed either by transvaginal or transabdominal ultrasound (after week 14); this is usually indicated in pregnancies with high risks of fetal heart disease, especially when screening at the first trimester is indicative of cardiac anomaly.[24]

It is essential that the fetal cardiologist has a basic understanding of ultrasonography concepts, particularly regarding fetal status and position. Before beginning the evaluation of the heart, the position of the fetus must be determined, identifying right and left sides. The main marker of the fetal left side is the stomach. In the event of situs inversus or situs ambiguous, the stomach may be displaced, and should not be used as a marker of the fetal left side.

The best image of the heart is obtained from the abdomen, sliding the transducer slightly toward the thorax. Although it is also possible to obtain images from the front or the back of the baby, the images obtained from the back may be of inferior quality, especially during the last trimester, when the ossification of the ribs and the spine represents an important barrier to ultrasound passage. In this situation, to improve image quality, one may request patient to lie in left or right lateral decubitus position.

Polyhydramnios is a condition that may pose great difficulties to perform the examination, since the fetus may be too far from the transducer and move constantly. Perform measurements and place the Doppler sample volume in place to obtain the usual traces may be really challenging. In situation like this, the fetus may be brought closer to the transducer, if the patient lies or her knees and elbows. Maternal obesity also poses difficulties to the technical quality of the study and it is often needed a low-frequency transducer, sometimes such as those used for adult echocardiography with more vigorous compression to the maternal abdomen.

Once the fetal heart has been identified, only small movements of the transducer are necessary to analyze all the cardiac structures. Considering that the fetal heart is relatively far from the transducer, small movements mean big changes in angle. Fetal echocardiography is considered complete when the heart has been examined from all possible views and planes, including the projections obtained in a conventional postnatal echocardiogram.

Differently from the recommendations for obstetric screening for cardiac malformations, fetal echocardiography must include transverse and longitudinal views of the fetus, what guarantees different sights of the same structure.[18] The following images should also be included to the 6 transverse levels: long axis of the aortic and ductal arches (Figures 2.3 and 2.4), bicaval view (Figure 2.5), and short axis of ventricles and great vessels (Figures 2.6 and 2.7).

2.5. Imaging Techniques Used on Fetal Echocardiography

Experienced imaging professionals, such as ultrasound specialists, radiologists, or echocardiographers may evaluate the fetal heart with high diagnostic accuracy. However, knowledge of the anatomical, physiological and possible therapeutic algorithms are essential to obtain the most accurate information and counsel the family. To avoid missing information, the international medical societies of echocardiography and ultrasound have established the obligatory contents of a complete fetal echocardiogram.

Based on the AHA guidelines published in 2014, mandatory elements (Class of Recommendation I), elements whose inclusion is reasonable (Class of

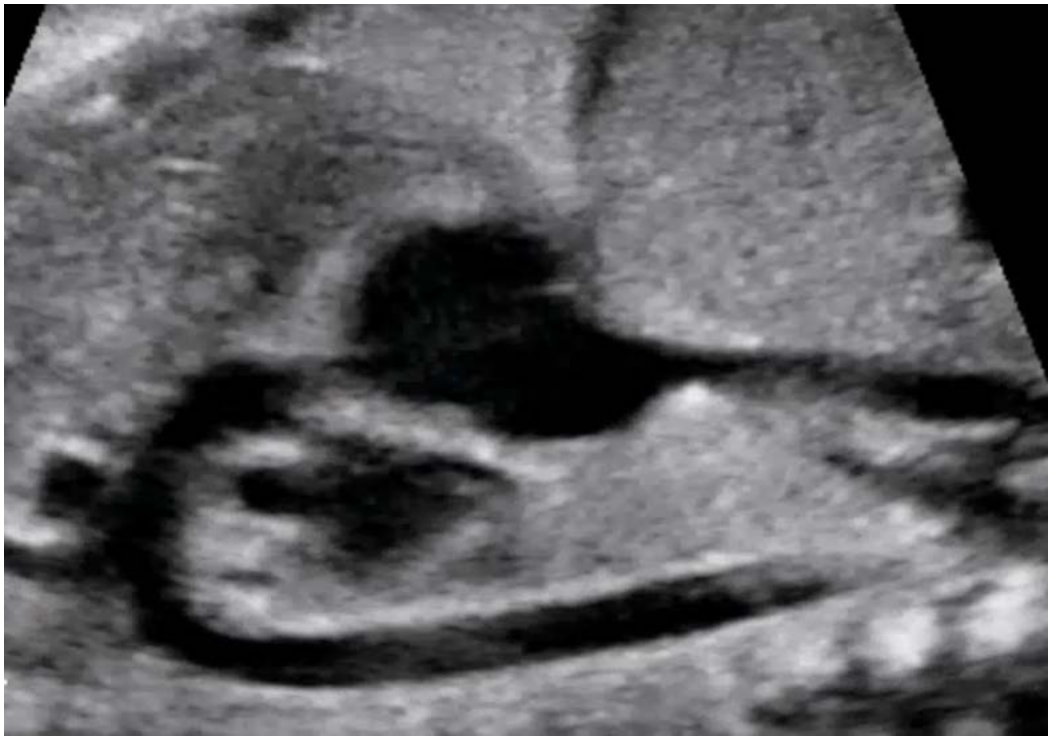

Figure 2.3 – *Long axis view of the aortic arch. The shape of the aortic arch is similar to a cane.*

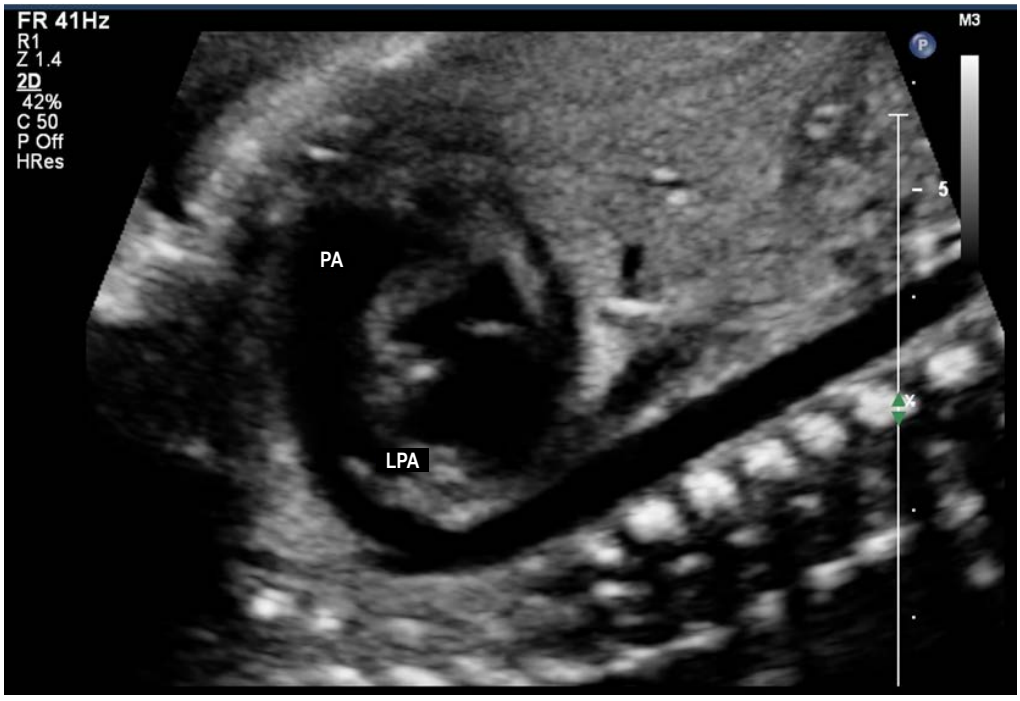

Figure 2.4 – *Longitudinal plane slightly anterior and to the left of the fetus, showing the long axis view of the ductal arch. The ductal arch has a different angle than the aortic and looks like a golf club.*
LPA: left pulmonary artery; PA: pulmonary artery.

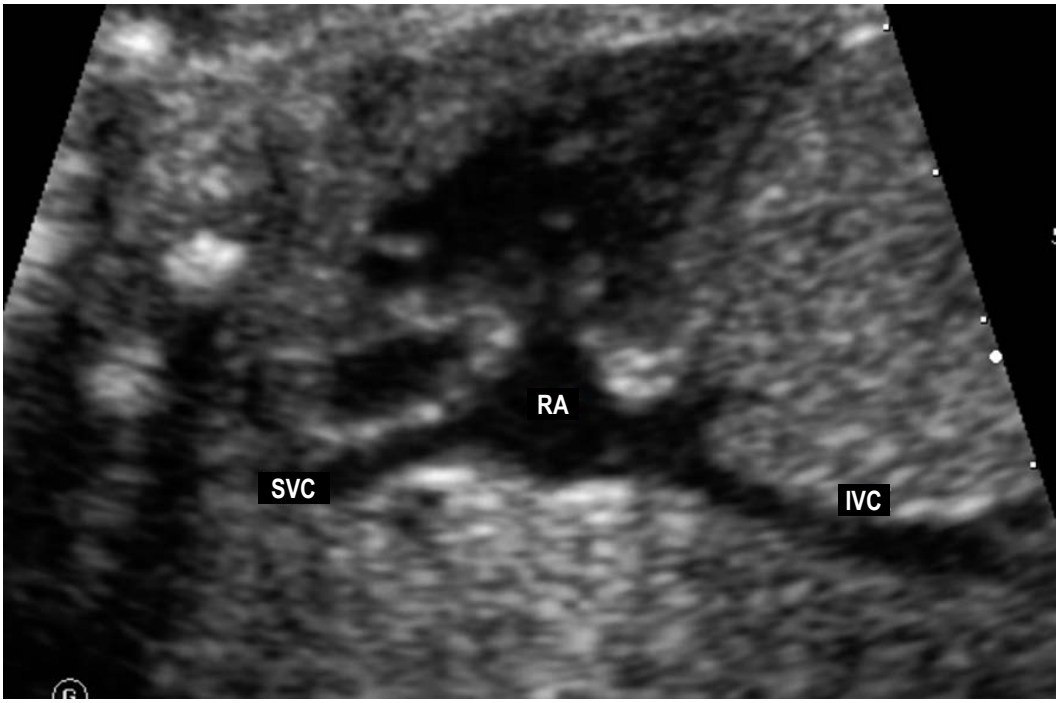

Figure 2.5 – *Longitudinal fetal plane tilting posteriorly, showing the bicaval view.*
IVC: inferior vena cava; RA: right atrium; SVC: superior vena cava.

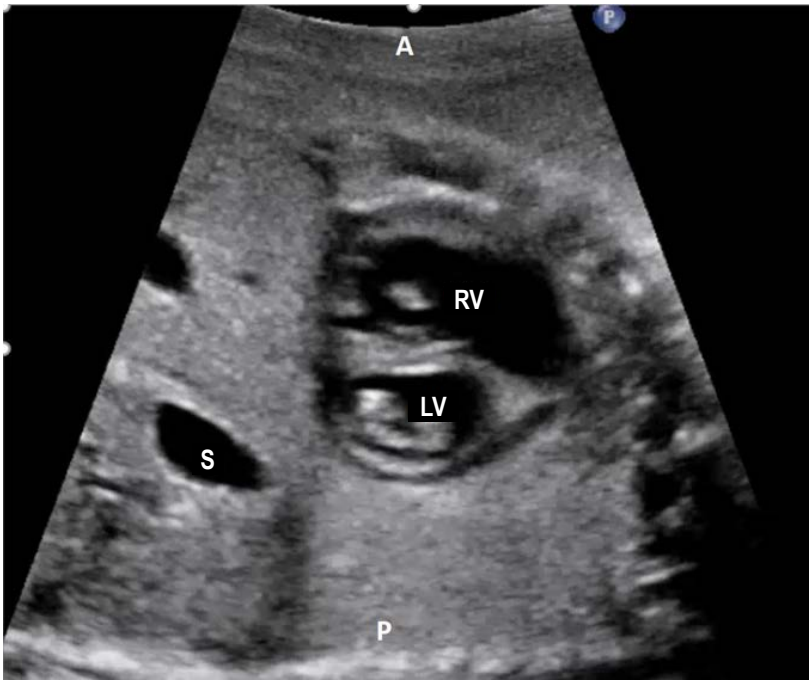

Figure 2.6 – *Short-axis of the ventricles. In this plane it is possible to analyze the position of the papillary muscles of the right and left ventricles. It is also of great utility in detecting subtler forms of atrioventricular septal defect when it is presented with two valvular orifices.*
A: anterior; P: posterior; LV: left ventricle; RV: right ventricle; S: stomach.

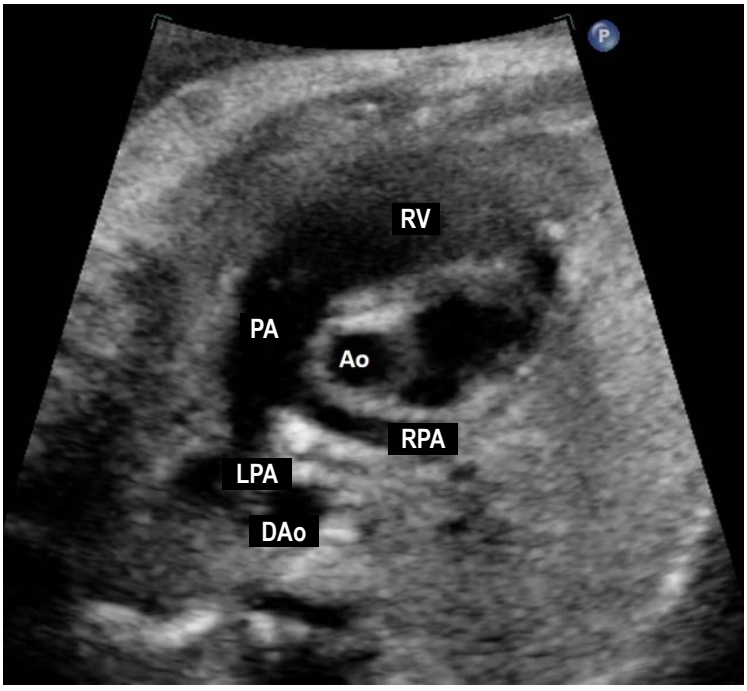

Figure 2.7 – *Short axis view of the great vessels. This plane shows the relationship between the great arteries, with the aorta being in the center of the heart and posteriorly and the right ventricular outflow tract surrounding the aorta anteriorly. This is an excellent plane for identifying perimembranous ventricular septal defects and pulmonary obstructions due to the anterior deviation of the infundibular septum observed in the tetralogy of Fallot.*
Ao: aorta; DAo: descending aorta; LPA: left pulmonary artery; PA: pulmonary artery; RPA: right pulmonary artery; RV: right ventricle.

Recommendation IIa) or may be reasonable (Class of Recommendation IIb) were distinguished (Table 2.4).[17]

3. Stratification of Centers that Work with Fetal Cardiology and their Potential Therapeutic Facilities

Congenital heart diseases are the most frequently malformations related to morbimortality in infancy, especially during the prenatal period.[26] Its incidence has been estimated as 6 to12 cases per 1,000 live births. During fetal life, it may be up to 5 times higher, being the difference justified by fetal losses.[27-29] Approximately 50% of cases have early hemodynamic consequences, requiring catheter or surgical interventions during the first year of life.[17] Extracardiac malformations may be observed in up to 50%, further increasing pre- and postoperative morbimortality.[30] It is worth highlighting that, in developed countries, treatment for CHD compared to other congenital anomalies, have the highest hospital costs.[31]

Over the past years, first-trimester ultrasounds and, widespread use of fetal echocardiography have contributed to increase the rates of fetal diagnosis of CHD and consequently, improve perinatal outcome.

However, fetal echocardiography has not become universally available in Brazil yet, with the majority of professionals trained in Fetal Cardiology being concentrated in the South and Southeast Regions and a more restricted number in the North, Northeast, and Central-West Regions. In the states located in these latter regions, the availability of this tool is mainly restricted to the capital cities and is of low availability in Brazil's public healthcare system (*Sistema Único de Saúde*, SUS).[32-34]

There is a decreasing tendency of Brazil's infant mortality rates over the last years, with a 77% decline over 22 years, from 62 deaths per 1,000 live births in 1990 to 14 per 1,000 in 2012.[35] Deaths during the first year of life represent 90% of mortality in the 0-4 age group, with 68% occurring between 0 and 28 days. Congenital cardiac anomalies have been identified as responsible for a significant part of these rates, especially during the neonatal period.[35] It is estimated that there are approximately 25,700 new cases of CHD per year in Brazil, which are distributed

Table 2.4 – Fetal echocardiogram mandatory, optional, and recommended elements

	Essential, mandatory elements (Class I)
Two-dimensional echocardiographic anatomy	Cardiovisceral situs
	Cardiac position
	Pericardial effusion
	Systemic and pulmonary venous connections
	Atrial morphology
	Atrial septal morphology
	Atrioventricular connection
	Ventricular morphology, size, and comparative analysis of the ventricular sizes
	Ventricular-arterial connection
	Atrioventricular valves morphology, size, and comparative analysis of the valvular sizes
	Semilunar valves morphology, size, comparative analysis of the valvular sizes
	Ventricular septal morphology
	Great arteries anatomy, size, and comparative analysis of the great arteries sizes
	Three vessels and three vessels and trachea views
	Aortic arch morphology
	Ductal arch morphology
	Proximal pulmonary arteries
Color doppler	Superior and inferior vena cavae
	Foramen ovale
	Atrioventricular valves/ventricular inflows
	Interventricular septum
	Semilunar valves/ventricular outflows
	Ductus venosus
	Pulmonary veins
	Great arteries
	Left and right pulmonary arteries
	Aortic and ductal arches
Pulsed-wave doppler	Atrioventricular valves/ventricular inflows
	Semilunar valves/ventricular outflows
	Ductus venosus
	Umbilical vein
	Umbilical artery
	Pulmonary veins
	Great arteries
	Ductal arch
Heart rate and rhythm assessment	

Optional elements (classes IIa and IIb)	
Cardiac and general biometry	Cardiothoracic ratio
	Atrial dimensions
	Ventricular dimension
	Atrioventricular valve diameters
	Semilunar valve diameters
	Ascending aortic and main pulmonary artery diameters
	Aortic and ductal arch diameters
	Branch pulmonary artery diameters
	Fetal biometry
Color doppler	Umbilical vein and arteries
Pulsed-wave doppler	Superior and inferior vena cavae
	Right and left pulmonary arteries
	Middle cerebral artery
Other doppler modalities	Continuous-wave doppler
	Tissue doppler
Additional cardiac function indexes	Ventricular shortening fraction
	Myocardial performance index
	Calculation of cardiac output

regionally as follows: 2,758 cases in the North Region; 7,570 in the Northeast; 10,112 in the Southeast; 3,329 in the South, and 1,987 in the Central West.[36] In 2010, the Live Births Information System (*Sistema de Informação sobre Nascidos Vivos*, SINASC) of the Ministry of Health, had 1,377 cases of live births with CHD notified. This represents only 5.3% of the estimated number.[36]

There are currently approximately 40 services accredited by the Ministry of Health to perform pediatric cardiac surgery, with a rather heterogeneous distribution, concentrated mainly in the South and Southeast Regions (62%). In accordance with 2002 data from the Brazilian Unified Health System's Department of Informatics (*Departamento de Informática do Sistema Único de Saúde*, DATASUS), the deficit in cardiac surgery for CHD in the North and Northeast Regions was 93.5% and 77.4%, respectively.[32,33] As the implantation of Fetal Cardiology is directly related to pediatric cardiac surgery services, the current situation in Brazil, with respect to fetal diagnosis, continues to be considerably heterogeneous.[34]

According to their potential therapeutic facilities, Fetal Cardiology centers were stratified on three specific levels:

- **Level 1:** Centers that can diagnose structural and functional fetal cardiac anomalies, make the follow-up of the affected fetuses and, stablishe the delivery planning according to the fetal heart disease.
- **Level 2:** Centers where, in addition to the fetal diagnoses of structural and functional fetal cardiac anomalies, have a multidisciplinary team with obstetricians, pediatric cardiologists, interventional cardiologists, and pediatric cardiac surgeons, and can provide the postnatal therapy.
- **Level 3:** Centers where, in addition to diagnosis and follow-up of the affected fetuses, have a multidisciplinary team with obstetricians, pediatric cardiologists, interventional cardiologists, and pediatric cardiac surgeons and provide invasive intrauterine interventions.

Currently, in Brazil, the majority of Pediatric Cardiology centers are considered levels 1 or 2. Intrauterine interventions are restricted to a very small number of fetuses with very specific pathologies and

particularities that benefit from fetal therapy. For this reason, the existence of more than 1 or 2 centers with these characteristics in Brazil is not justified.

It is clear that Brazil needs more Pediatric and Fetal Cardiology centers as well as increase the number of cardiac surgeries and percutaneous interventions. Nevertheless, due to various political and environmental issues, these changes will only occur in medium to long term.

Aiming to maximize referrals of fetuses with CHD to the existing centers, it is mandatory that all professionals involved in the screening of CHD know how to refer the patient to the appropriate care centers.[37,38] When fetuses with CHD are identified in places where there is no appropriate care, the doctor should promptly look for help to refer the patient to a specialized center according to the regulatory flow of the state. If the state has no specific hospital do refer the patient, the local health system should ask for outside treatment (tratamento for a de domicílio -TFD) which will look for the closest specialized center to take care of the mother and the fetus. This process is nowadays regulated by CNRAC (central nacional de regulação da alta complexidade) since directive instructions of the Ministry of Health to organize the health care for high-risk pregnancies were published. It is emphasized here that the high-risk pregnancies are "those in which the life or health of the mother, the fetus, or the newborn has higher chances of being affected when compared to the general population."[39]

When fetal cardiologist is dealing with a case of fetal heart disease, he or she needs to define whether there is any need of prenatal intervention or whether the treatment has to be started immediately after birth and if the patient needs to be referred to center levels 2 or 3 available in our country, reminding that not all the centers considered level 2 can treat all types of neonatal anomalies. It is known that HLHS and its variations, for example, have an extremely high fetal incidence, whereas few centers in our country have satisfactory operative results for this anomaly.

The Figure 3.1 is a flowchart that standardizes the specific care according to the fetal heart disease.

4. Classification of Fetal Heart Disease

With the development of fetal medicine as a medical subspecialty and with the recent advances in the ultrasound imaging, the detection of fetuses with congenital malformations has become increasingly frequent, making earlier treatment possible with significant reduction of fetal and neonatal mortality.[40] With prenatal diagnosis, diseases with potential risk to have hemodynamic compromise in utero and/or in the neonatal period can be followed up and have the specific pre and postnatal care planned. Taking into account the characteristics of the fetal circulation, it is particularly important to recognize the behavior of the different heart diseases in utero and after birth, identifying those that will require any kind of treatment (use of medications or invasive procedures) or anticipation of the childbirth.[41]

Fetal cardiac disease may be classified as structural or functional. The majority of the structural heart diseases do not have hemodynamic compromise in utero due to the fetal circulation physiology. Clinical manifestations will occur after birth, when the physiological intracardiac shunts close. Cardiomyopathies, conditions like high output fistulas, significant abnormalities of the cardiac rhythm and restricted foramen ovale, ductal constriction or absent ductus venosus may also occur in utero and compromise the fetal hemodynamic requiring prenatal treatment.

It is important to highlight the importance of a multidisciplinary team involved in the care of fetuses affected by heart diseases, since genetic syndromes or severe extracardiac malformations may be associated and significantly increase postnatal mortality.

For these reasons, fetal heart diseases were classified into 3 groups according to possible clinical presentation and in utero hemodynamic manifestations and were separated in groups A - structural and B - functional (Table 4.1).

4.1. Group I – Heart Diseases without Fetal Hemodynamic Compromise

4.1.1. Structural

This group includes simple or complex cardiac defects that do not usually present progression or hemodynamic decompensation during the fetal period and, thus, do not require treatment during pregnancy and do not change obstetric management. The main example of this group are diseases with left-to-right shunt, including atrial, ventricular and atrioventricular septal defects, and aortic to pulmonary window; heart diseases with mild obstruction of right or left outflow tracts, such as pulmonary valve stenosis, aortic stenosis, and localized coarctation of the aorta; and complex CHD such as TOF with mild pulmonary flow obstruction, corrected transposition of great arteries, double outlet right ventricle, and univentricular hearts without obstructions or with mild obstructions to systemic and pulmonary outflow tract flows.

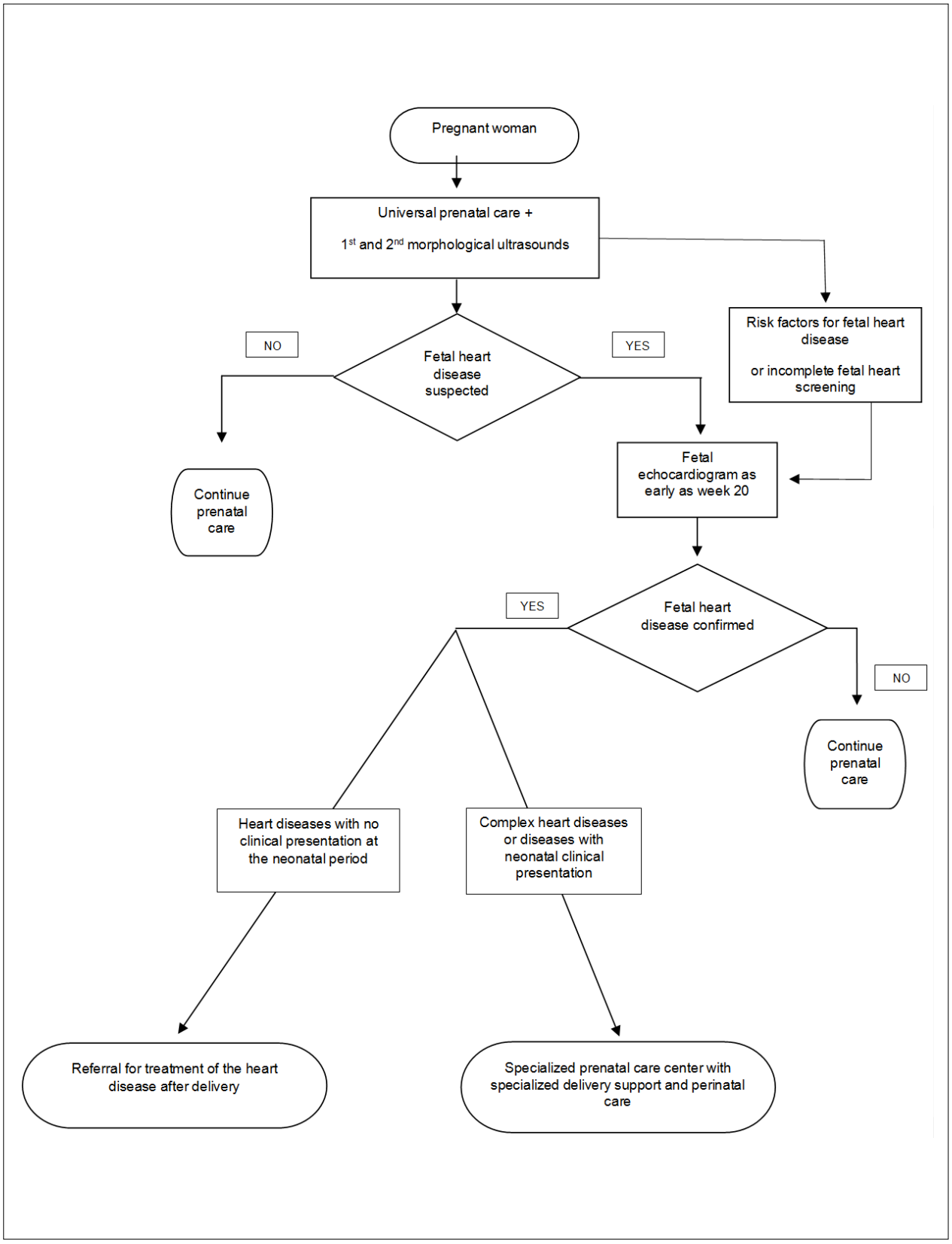

Figure 3.1 – *Fetal care flowchart according to the specific fetal heart condition. USG: ultrasound.*

Table 4.1 – Classification of fetal anomalies according to fetal outcome

Group	Fetal outcome
I	Heart diseases without fetal hemodynamic compromise A. Structural B. Functional
II	Heart diseases with fetal hemodynamic compromise A. Structural B. Functional
III	Heart diseases with poor postnatal prognosis

4.1.2. Functional

This group includes cardiac rhythm abnormalities such as isolated supraventricular extra beats and mild isolated tricuspid regurgitation.

4.2. Group II – Heart Diseases with Fetal Hemodynamic Compromises

4.2.1. Structural

This group includes cardiac defects that may compromise the development of cardiac structures throughout gestation, such as critical or total obstruction of the ventricular outflows,[42,43] defects that potentially trigger heart failure due to the presence of severe valvular insufficiency,[44] and anomalies that require patent foramen ovale to divert flow from one chamber to the other (atrioventricular valves atresia or stenosis), being the main examples HLHS and tricuspid atresia.[45] This group requires special attention, and some of the cases may benefit from a fetal cardiac intervention to increase the blood mixture at the atrial level (see the Fetal Interventions Chapter).[44]

4.2.2. Functional

Primary fetal myocardial dysfunctions have various etiologies. They may be caused by myocarditis (usually viral), structural changes in myocardial fibers (noncompacted myocardium, deposit diseases such as mucopolysaccharidoses or glycogenoses), and they may be related to maternal diabetes and genetic conditions.[46,47] Severe cardiac arrhythmias, such as sustained tachyarrhythmias and complete atrioventricular block (CAVB) lead to cardiac chambers dilation, atrioventricular valves regurgitation, and myocardial dysfunction.[48] Tachyarrhythmias are considered emergencies in Fetal Cardiology due to the risk of hydrops and fetal death; being the majority of cases possible to be treated with antiarrhythmic medication.[49]

Cardiac tumors are rare. The most prevalent in fetal life is rhabdomyoma. They may be single or multiple and their dimensions increase during fetal life.[50] Serial echocardiograms are indicated because of the risk of arrhythmias, ventricular outflow obstructions, or cardiac structures compression. Functional abnormalities of the intracardiac shunts may imbalance the distribution of fetal blood flow. Ductal arteriosus constriction, the most frequent, will be detailed discussed in a subsequent chapter.[51] Restrictions of blood flow through the foramen ovale and agenesis of the ductus venosus are rare conditions. Both evolve with right chamber dilation and may lead to fetal heart failure.[52,53] High-output fistulas may lead to cardiac chambers dilation and dysfunction and fetal hydrops. The most frequent are Galen's vein aneurysm, hemangioma, hepatoblastoma, pulmonary arteriovenous malformation, vascularized tumors such as sacrococcygeal or cervical teratoma, and the twin-twin transfusion syndrome.[54,55] Severe anemia resulting from viral infection or blood type incompatibilities may lead to heart failure. Fetal hemodynamics may also be compromised by extrinsic fetal heart compressions, such as diaphragmatic hernia, pulmonary cystic adenomatoid malformation, and pericardial tumors. This group needs serial fetal echocardiograms, ideally biweekly, and this interval may be reduced if needed. The cardiovascular profile score, published by Huhta et al should be employed to establish the outcome.[56]

4.3. Group III – Fetal Heart Diseases with Limited Postnatal Prognosis

This group corresponds to very severe heart diseases in which, any therapeutic measurements will result in nearly 100% chance of death. It includes severe forms of left atrial isomerism associated with CAVB, obstruction of both ventricular outflows tracts and myocardial disease, critical obstructive malformations associated with noncompacted myocardium, the worst spectra of Ebstein's anomaly or tricuspid valve dysplasia associated with lung hypoplasia, left ventricular aneurysms with fetal congestive heart failure, and heart diseases associated with chromosomal disorders with limited prognosis (trisomies of 13 and 18). In this group, multidisciplinary follow-up, including psychological support for parents must be prioritized, but delivery may be in a hospital with basic support (Table 4.2).

5. Management of the Main Fetal Heart Diseases

One of the main challenges for the ultrasound specialist and pediatric cardiologist is to know exactly

Table 4.2 – Distribution of fetal heart diseases according to their classification

Group	Cardiac anomalies
IA	Left to right shunt heart diseases: ASD, VSD, AVSD, and Ao-P window Diseases with mild outflow tract obstructions: PS, AS, and CoA Complex congenital heart diseases without significant obstructions of systemic or pulmonary outflow tracts: TOF, complex TGA, DORV, univentricular hearts, and CTGA
IB	Isolated extrasystoles; mild, isolated TR
IIA	Heart diseases with critical obstruction of systemic or pulmonary outflow tracts: PAIVS, Critical PS, Critical AS, and HLHS Heart diseases that need interatrial shunt: HLHS and variations, TGA, and TA Heart diseases with severe valve insufficiencies: Ebstein's anomaly and tricuspid valve dysplasia, pulmonary valve agenesis, severe primary or secondary MR, secondary TR, and truncal valve insufficiency
IIB	Cardiomyopathies and myocarditis, arrhythmias, obstructive tumors, extrinsic compressions, (CDH and CCAM), ductal constriction, restrictive foramen ovale, ductus venosous agenesis, AVMs, TTTS, and twin gestation with 1 acardiac fetus
III	Severe chromosomal disorders; multiple malformations, cardiac defects that are not correctable, very severe forms of Ebstein's anomaly or tricuspid valve dysplasia with lungs hypoplasia, LV aneurysms, or diverticula associated with fetal hydrops

Ao-P: aortic to pulmonary; AS: aortic stenosis; ASD: atrial septal defect; AVMs: arteriovenous malformations; AVSD: atrioventricular septal defect; CCAM: congenital cystic adenomatoid malformation; CDH: congenital diaphragmatic hernia; CoA: coarctation of the aorta; CTGA: corrected transposition of great arteries; DORV: double outlet right ventricle; HLHS: hypoplastic left heart syndrome; LV: left ventricle; MR: mitral regurgitation; PAIVS: pulmonary atresia and intact ventricular septum; PS: pulmonary stenosis; TA: tricuspid atresia; TGA: transposition of great arteries; TOF: tetralogy of Fallot; TR: tricuspid regurgitation; TTTS: twin-twin transfusion syndrome; VSD: ventricular septal defect.

what to do when they face a fetus with CHD. Because of the fetal physiology characteristics, the majority of cardiac anomalies have a benign outcome in utero. However, at birth, they may become devastating, and require specific treatment immediately after the umbilical cord clamping. On the other hand, mild fetal cardiac abnormalities may be overvalued and lead unnecessary attitudes regarding gestation and delivery conduction, just because of the lack of knowledge of the real impact of the anomalies to the baby's health after birth. Although prenatal diagnosis has been possible for more than 40 years, understanding the behavior of CHD during the pre- and postnatal periods has become clearer over the past last years, thanks to the diagnostic accuracy improvements and to the introduction of fetal therapy that lead to progressive understanding of their natural and modified history. For these reasons, in order to guide the need of delivery and/or treatment in specialized centers, cardiac anomalies were separated into several groups according to their perinatal outcome: with and without hemodynamic compromise, with and without in utero progression, and possible postnatal outcome (Tables 5.1 to 5.8).

6. Fetal Ductal Constriction: Treatment and Prevention

Fetal circulation has specific characteristics, differing morphologically and functionally from extrauterine circulation. Anatomically, the ductus arteriosus is part of the right ventricular outflow tract, playing a essential role in directing blood flow to lower portions of the fetus. Basically, the ductus arteriosus carries 80–85% of right ventricular output to the descending aorta.[60] It's histological structure is composed of a thick muscle layer, which increases with gestational age. Its constrictive mechanism is facilitated by the circumferential orientation of muscular fibers, especially those of the external layer.[61] Due to these histological characteristics, its patency is measured by multiple factors. Luminal abnormalities may cause severe fetal and neonatal complications, such as heart failure, hydrops, persistent neonatal pulmonary hypertension, and death.[62-64]

Typically, maternal use of indomethacin and/or other anti-inflammatory medications interferes with the metabolism of prostaglandins (PG), causing ductal constriction.[65-67] Many causes of ductal constriction and neonatal pulmonary hypertension, however, are not related to the use of these substances and are classified as idiopathic.[68]

A growing amount of evidence has recently shown that herbs, fruits, nuts, and a wide variety of substances commonly consumed as part of a daily diet affect the inflammatory cascade, culminating in reduced PG synthesis.[69,70] This anti-inflammatory action, especially of polyphenols, when ingested during the third trimester of gestation, influences the dynamics of the fetal ductus arteriosus.[71-78]

Table 5.1 – Group IA. Structural fetal heart diseases without in utero hemodynamic compromise, which do not require immediate neonatal care. Class of recommendation/level of evidence: IB.[17,41,57-59]

Heart disease	In utero outcome	In utero follow up	Delivery	Postnatal assessment
VSD AVSD ASD Ao-P window	Stable	Repeat the study a few weeks before birth is recommended	Delivery type according to obstetric indication Level 1 center	Maternity ward or outpatient clinic

Ao-P: aortopulmonary; ASD: atrial septal defect; AVSD: atrioventricular septal defect; VSD: ventricular septal defect.

Table 5.2 – Group IA. Structural fetal heart diseases without in utero hemodynamic compromise that may progress during fetal life and may or may not require immediate neonatal care. Class of recommendation/level of evidence: IB.[17,41,57-59]

Heart disease	In utero outcome	In utero follow up	Delivery	Postnatal assessment
TOF DORV Complex TGA CTGA TA	May progress to significant obstruction to systemic or pulmonary outflow tracts	After diagnosis, repeat the study every 4–6 weeks A new study a few weeks before birth is highly recommended	Delivery type according to obstetric indication Level 1; Level 2 or 3 centers in case the in utero hemodynamic condition worsens or precipitates immediate neonatal decompensation (significant obstruction of the systemic or pulmonary outflow tracts)	In all cases, before hospital discharge, cardiac assessment with echocardiogram is required

CTGA: corrected transposition of great arteries; DORV: double outlet right ventricle; TA: tricuspid atresia; TOF: tetralogy of Fallot; TGA: transposition of great arteries.

Table 5.3 – Group IB. Functional fetal heart diseases without in utero hemodynamic compromise, that not require immediate neonatal care. Class of recommendation/level of evidence: IB.[17,41,57-59]

Heart disease	In utero outcome	In utero follow-up	Delivery	Postnatal assessment
Atrial or ventricular extrasystoles Mild TR	Stable	Repeat the study a few weeks before birth is recommended	Delivery type according to obstetric indication Level 1 center	Maternity ward or outpatient clinic

TR: tricuspid regurgitation.

Table 5.4 – Group IIA. Structural fetal heart diseases with possible in utero hemodynamic compromise and chance of fetal treatment, which require immediate neonatal care. Class of recommendation/level of evidence: IB.[17,41,57-59]

Heart disease	In utero outcome	In utero follow-up	Delivery	Postnatal assessment
PS PAIVS AS Ebstein's anomaly	Risk of ventricular hypoplasia Risk of ventricular dysfunction or fetal hydrops Risk of circular shunt Risk of fetal arrhythmia	Repeat the study every 2 to 4 weeks is recommended If signs of in utero progression, consider fetal intervention between 22 and 32 weeks If circular shunt, consider induced ductal constriction	Without hydrops, induced vaginal delivery or programmed C-section With hydrops, programmed C-section Level 2 or 3 center	Immediate neonatal cardiac assessment PAIVS requires neonatal treatment Severe or critical PS and AS, may require neonatal treatment Ebstein's anomaly needs treatment if pulmonary atresia and lung hypoplasia

AS: aortic stenosis; PAIVS: pulmonary atresia with intact interventricular septum; PS: pulmonary stenosis.

Table 5.5 – Group IIA. Structural fetal heart diseases that inevitably require neonatal care. Class of recommendation/level of evidence: IB.[17,41,57-59]

Heart disease	In utero outcome	In utero follow-up	Delivery	Postnatal assessment
Simple TGA HLHS IAA Severe CoA TAPVR Truncus Complex heart diseases with severely restricted systemic or pulmonary outflow tracts	FO may be restrictive during gestation Although they are complex heart diseases, they tend to remain stable, without hemodynamic compromise during gestation	Repeat study every 4 to 6 weeks is recommended In HLHS or anatomical variations with restrictive ASD, consider fetal intervention Perform a new evaluation a few weeks before delivery	Induced vaginal delivery or programmed C-section Level 2 or 3 center	Immediate neonatal cardiac evaluation The majority are duct dependent CHD and require prostaglandin infusion + interventional or surgical treatment during the first week of life TAPVR and Truncus are diseases with early presentation of HF and PH, and thus require treatment during the first weeks of life, even when they are not duct dependent

CoA: coarctation of the aorta; FO: foramen ovale; HF: heart failure; HLHS: hypoplastic left heart syndrome; IAA: interrupted aortic arch; PH: pulmonary hypertension; TAPVR: total anomalous pulmonary venous return; TGA: transposition of great arteries.

Table 5.6 – Group IIB. Functional fetal heart diseases with hemodynamic compromise. Class of recommendation/level of evidence: IIb C.[17,41,57-59]

Heart disease	In utero outcome	In utero follow up	Delivery	Postnatal assessment
Restricted FO Ductal constriction Pericardial effusion Extrinsic compressions Anemia High-output AV fistulas TTTS	May evolve with ventricular dysfunction or fetal hydrops	Serial echocardiogram every 4 to 6 weeks is recommended May need fetal treatment	With hydrops, programmed C-section; Without hydrops, induced vaginal delivery or programmed C-section Level 2 or 3 centers Evaluate the need for preterm delivery	Immediate neonatal cardiac evaluation May require clinical, interventional or surgical treatment immediately after birth

AV: arteriovenous; FO: foramen ovale; TTTS: twin-twin transfusion syndrome.

Table 5.7 – Group IIB. Nonstructural fetal heart diseases which may evolve with hemodynamic compromise. Class of recommendation/level of evidence: I C.[17,41,57-59]

Heart disease	In utero outcome	In utero follow up	Delivery	Postnatal assessment
Cardiomyopathies Arrhythmias Tumors	May evolve with fetal hydrops May require medical treatment	Frequent follow-up (weekly or biweekly), depending on diagnosis and hemodynamic compromise	Vaginal delivery in a level 1 center if well controlled tachyarrhythmias or cardiomyopathies without fetal hemodynamic compromise; Programmed C-section in a level 2 or 3 center in cases of arrhythmia or hydrops which have not been resolved in utero	Cardiac management according to diagnosis Treatment is usually with medication, with the exception of some tumors which need to be removed due to obstructive or compressive character, which compromises hemodynamics

Table 5.8 – Group III. Fetal heart diseases associated with genetic syndromes or extracardiac malformations. Class of recommendation/level of evidence: IIb C.[17,41,57-59]

Heart disease	In utero outcome	In utero follow up	Delivery	Postnatal assessment
Multiple malformations Associative syndromes Trisomies Triploidy Other genetic anomalies	May evolve with fetal hydrops depending on the genetic of extracardiac anomaly	Depends on fetal or neonatal viability and extracardiac anomalies prognosis	For non-viable fetuses or newborns, delivery may be in a level 1 center, preferably by spontaneous vaginal birth. For viable fetuses or newborns, delivery may be vaginal or programmed C-section in a level 2 or 3 center Consider palliative care team support	Cardiac management according to prognosis of associated anomalies or chromosome diseases

6.1. Prevalence, Diagnosis, Clinical Consequences, and Prognosis of Fetal Ductus Arteriosus Constriction

The prevalence of ductal constriction detected in a convenience sample of 16,079 records of fetal echocardiograms performed during the third trimester of gestation, over a period of 11 years, excluding all other concomitant anomalies, in Porto Alegre, Rio Grande do Sul, Brazil was 2.7% (435 cases). During this period, there were 207,323 live births; the sample thus represented 7.75% of births.[79]

Experimental studies have shown that fetal ductal constriction results in an increase in the medial layer of the pulmonary artery, which leads to a secondary increase in pulmonary vascular resistance in utero.[80] Thus, the majority of studies on persistent pulmonary hypertension are based on the experimental model of fetal ductal constriction induced by the administration of indomethacin.[81] Moderate or chronic ductal constrictions lead to pulmonary hypertension due to the increase in the medial layer and consequent increase in pulmonary artery constriction. This sustained increase in right ventricular afterload may lead to morphological, functional, and histological modifications in the right ventricular myocardium.[82] Ventricular dysfunction in cases related to maternal medication ingestion may be completely reverted following its interruption. The persistence of the dysfunction, however, may even lead to myocardial ischemia with papillary dysfunction.[80,83,84] Fetal cardiac dysfunction is described as one of the characteristics of fetal ductal closure and, in severe cases, the possibility of anticipation the childbirth should be considered, once fetal pulmonary maturity is reached.[85] Postnatal clinical outcome depends on the severity of in utero right ventricular failure and response to the increased pulmonary vascular resistance.[86]

Long-term prognosis is uncertain; however, in cases with favorable initial outcome, there usually are no chronic complications. Nevertheless, after fetal heart failure, functional modifications may persist during the neonatal period, even in those with benign outcome.

Echocardiographic diagnosis of fetal ductal constriction is based on the presence of turbulent flow in the ductus, with an increase in systolic velocity (> 1.4 m/s), increase in diastolic velocity (> 0.3 m/s), and decrease in pulsatility index (PI) (< 2.2). In the first publication, the cutoff point for PI was 1.9.[87] Recent studies, however, have considered a higher threshold.[78,88] With the increased afterload secondary to ductal constriction, the heart shows symptoms of growth in earlier stages, hypertrophic response, with hyperplasia (substituted by apoptosis), increased right chamber proportions, increased pulmonary artery to aorta ratio, and interventricular septum bulging into the left ventricle.[89,90] It is important to highlight that the diagnosis of ductal constriction and the evaluation of its severity cannot be established solely in terms of categorical variables of the "yes/no" sort, but are based rather on continuous variables, with a spectrum of circulation compromise (mild, moderate, or severe) which has been summarized in Table 6.1.

The scores are classified as followed:

Mild constriction: 3–7 points, the first 3 criteria being required

Moderate constriction: 8–14 points, the first 3 criteria being required

Severe constriction: > 15 points, the first 3 criteria being required.

As the vasoconstrictor effect in the ductus arteriosus is dose-dependent,[91] the disappearance of hemodynamic abnormalities and non-development of fetal/neonatal cardiac dysfunction are common after the use interruption of constrictor substances.[89,92-95] Even in severe cases of ductal constriction following use of substances that

Table 6.1 – Diagnostic criteria and classification according to the severity of ductal constriction

Criteria	1 point each	2 points each	3 points each
Systolic velocity, m/s	1.40–1.69	1.70–1.99	≥ 2.00
Diastolic velocity, m/s	0.30–0.34	0.35–0.39	≥ 0.40
Pulsatility index	2.2–2.1	2.0–1.9	≤ 1.8
RV:LV ratio	1.30–1.59	1.60–1.79	≥ 1.80
PA:Ao ratio	1.30–1.59	1.60–1.79	≥ 1.80
Septal bulging to the left	0 – +/4	++/4	+++/4 – ++++/4
Tricuspid regurgitation	0 – +/4	++/4	+++/4 – ++++/4

Ao: aorta; LV: left ventricle; PA: pulmonary artery; RV: right ventricle.

inhibit PG, their use interruption reduces systolic and diastolic ductal velocities, with improvements of the abnormal hemodynamics.[89] There are no reports of important spontaneous reversal of ductal constriction without the removal of the causal factor.

In more severe cases, preterm delivery may be necessary, with immediate neonatal cardiopulmonary resuscitation measures. Although the relationship between the duration of the prenatal condition of ductal constriction and the prevalence and severity of neonatal pulmonary hypertension has yet to be defined, ideally it should be as short as possible. The moment of preterm delivery, thus, takes into account fetal pulmonary maturity, the severity of the of ductal constriction presentation and its progressive nature.[62] To allow for recovery and early resolution of the process, it is obviously crucial to remove the cause immediately.

6.2. The Role of Anti-Inflammatory Substances in the Genesis of Fetal Ductal Constriction

The action of non-steroidal anti-inflammatory drugs (NSAID) results from PG synthesis inhibition caused by the inactivation of the cyclooxygenase 1 (COX-1) and 2 (COX-2) enzymes.[96] This inhibitory effect reduces the formation of PGG2 and PGF2.[97,98] The use of this class of medication for treating premature birth, preeclampsia, and restricted growth in utero has made it possible to evaluate its effects on COX and ductal constriction.

Indomethacin is the most studied NSAID medication. Its effect on COX is reversible after excretion.[99,100] It crosses the placental barrier freely, as early as in the second gestational trimester.[101] Fetal response to indomethacin, however, is individual, varying in studies with twin fetuses.[102] Reports of constrictions before 27 weeks gestation are rare; however, they have occurred as early as week 22nd.[83] Other PG synthesis inhibitors are involved in fetal ductal constriction, with well documented dose-dependent effects, for example, in dipyrone, paracetamol, scopolamine, fluoxetine, paroxetine and sertraline.[66,91,103-111]

Glucocorticoids also affect ductal patency. Their effects occur through the reduction of PG formation and ductal sensitivity to PGE2, with dose-dependent effects.[112,113] Concomitant use with indomethacin has a synergetic effect that duplicates the incidence of fetal ductal constriction.[114]

6.3. Anti-Inflammatory and Antioxidant Action of Polyphenols

The main action of phenolic compounds or polyphenols is described in the literature as anti-inflammatory and antioxidant, demonstrating positive effects on cardiovascular health, cancer, diabetes, and neurodegenerative diseases.[115-117]

The antioxidant capacity of these compounds is essential to the organism in neutralizing the action of oxygen-reactive species,[118] which, when produced excessively and not destroyed by endogenous defense, may interact with DNA, proteins, and lipids, culminating in the development of diseases such as cancer.[119,120]

Polyphenols play an important role in inhibiting the inflammatory cascade, with actions similar to that of NSAID, and are able to interfere with PG synthesis. The inflammatory cascade is initiated by the activation of phospholipase A2 (PLA2), stimulated, for example, by compounds such as thrombin, bradykinin, or epinephrine, upon membrane receptor binding. Activated PLA2 hydrolizes arachidonic acid (AA), or other similar polyunsaturated fatty acids, from membrane phospholipids. AA, in its turn, through the action of the COX-2 enzyme, initiates the formation cascade of PG and thromboxane (TX). Some NSAID, such as indomethacin, for example, inhibit the inflammatory cascade via inhibitory action of COX-2, a mechanism that has been studied in order to explain the similar effect of polyphenols in this process.

Polyphenols have their anti-inflammatory effects through a variety of molecular targets, which may be divided into 2 pathways: AA-dependent and AA-independent. COX, lipoxigenase, and PLA2 are AA-dependent inflammatory mediators. The activation of these proteins leads to the release of AA (a starting point for general inflammatory response) which promotes the release of pro-inflammatory molecules.[114] On the other hand, nitric oxide synthase (NOS) nuclear factor-kappa B (NF-kB), and peroxisome proliferator activated receptor (PPAR) promote inflammation through AA-independent pathways.

6.4. Summary of Evidence for Ductal Constriction Management

A cornerstone of treating and preventing ductal constriction during fetal life is the reduction of fetal exposure to agents that interfere with the biosynthesis of PGE1, and PGE2.

The metabolic chain of PG production can be inhibited on different levels, such as in the decrease of AA production from phospholipids, by PLA2 inhibition, as is the case with corticosteroids, in the reduction of the transformation of AA to PGG2, measured by inhibition of COX-1 and COX-2, by maternal use of NSAID or consumption of polyphenol-rich foods, and by the inhibition of isomerase, which is responsible for the synthesis of PG, TX, and prostacyclin.

The inhibitory effect of NSAID on PG biosynthesis has been broadly demonstrated. Meta-analysis conducted in a systematic review of 25 randomized clinical trials, which evaluated the risk of fetal ductal constriction in pregnant women exposed and not exposed to NSAID, concluded that the risk of ductal constriction is 15 times greater in acutely exposed fetuses.[66]

Multiple randomized clinical trials, systematic reviews, and meta-analyses have established that polyphenols, in the various forms in which they are present in food, have a definite anti-inflammatory and antioxidant action, which culminates in the inhibition of circulating PG, with diversified clinical outcomes.

In 2015, the International Federation of Gynecology and Obstetrics (FIGO) published its official recommendations for gestational nutrition. One point in the section, "Exposures to avoid" reads:

"In late pregnancy, women **should avoid** high intakes of herbal teas and polyphenol-rich foods, which have been associated with effects on the fetal ductus arteriosus brought about by inhibition of prostaglandin synthesis." (italics ours)[106]

Specifically regarding the results of "abnormal ductal flow and ductal constriction" in fetuses exposed to a maternal diet rich in polyphenols, studies developed in Brazil, on all levels of the evidence pyramid, from experimental to case control studies, have unequivocally demonstrated the following:

• Consumption of green tea, yerba mate, and grape juice, which are sources of high concentrations of polyphenols, causes ductal constriction in experimental models of sheep fetuses in the final trimester of gestation.[121]

• There is a cause-effect relationship between maternal consumption of green tea and ductal constriction during the third trimester of gestation in experimental models of sheep fetuses.[74]

• High maternal consumption of polyphenols induces fetal ductal constriction in sheep, with increased urinary excretion of total polyphenols and abnormalities in oxidative stress biomarkers, which characterize the anti-inflammatory and antioxidant actions of polyphenols.[122]

• An experimental single-dose of cocoa administered to rats during the third trimester of gestation caused ductal constriction equivalent to that caused by indomethacin.[123]

• Normal human fetuses during the third trimester, when exposed to maternal consumption of polyphenols above the 75th percentile of the average population, exhibit worse ductus arteriosus flow dynamics and increased right-to-left ventricular diameter ratios (higher ductal flow velocities and larger right ventricular diameters), in comparison with those exposed to maternal consumption of polyphenols below the 25th percentile.[76]

• Normal human fetuses submitted to guided nutritional intervention (restriction of polyphenol-rich foods) in the third trimester showed, after 2 weeks, decreased ductal systolic and diastolic velocities, increased pulsatility index, and decreased right-to-left ventricular and pulmonary artery to aorta ratios, whereas these parameters did not change during the same period in control fetuses who were not submitted to the intervention.[77]

• Human fetuses with ductal constriction during the third trimester showed, in more than 95% of cases, reversion of the echocardiographic signs of this condition, as well as its hemodynamic compromise, after 3 weeks of a restricted in polyphenols diet, whereas there were no changes in the parameters evaluated in fetuses controls of the same gestational age, who did not receive a nutritional intervention with restricted maternal intake of polyphenols.[78]

• Polyphenol supplementation capsules inhibit physiological increase of PGE2 and other markers of inflammation and oxidative stress in women of childbearing age using combined hormonal contraceptives.[124]

• Dietary intervention to restrict maternal consumption of polyphenol-rich foods in the third trimester in cases of fetuses with ductal constriction is accompanied by an increase in plasma levels of PGE2, with improvements in the condition.[125]

• A 52-item food frequency questionnaire for quantifying consumption of polyphenol-rich foods in pregnant women, whose validity and reproducibility were evaluated in the South of Brazil, may be used in clinical practice.[71]

6.5. Conclusions

6.5.1. Recommendations for Ductal Constriction Treatment

When ductal constriction is diagnosed in the fetal echocardiogram, the complete use interruption of NSAID should be recommended, in addition to the restriction of polyphenol-rich foods, made up of products with a concentration ≥ 30 mg/100 g of food, in accordance with the recommendations in table 6.2, intending to maintain balanced diet that includes all necessary micronutrients during this gestational period, reducing, however, the concentration of total polyphenols below 125 mg per day, or to the 25th consumption percentile[78] (Class of recommendation: I; level of evidence: A). If possible, consumption of other medications with

potential anti-inflammatory actions (corticosteroids,[108] aspirin,[107] dipyrone,[105,110] fluoxetine,[109,126] paroxitine, sertraline,[109,111] isoxsuprine,[107] and naphazoline),[107] their use interruption may be considered (Class of recommendation: IIa; level of evidence: C). In cases in which there is no reversal of ductal constriction and its consequences after initiation of treatment, preterm delivery may be considered, provided that fetal pulmonary maturity has been established (Class of recommendation: IIb; level of evidence: C).

6.5.2. Recommendations for Ductal Constriction Prevention

In order to prevent fetal ductal constriction, pregnant women should be recommended not to use NSAID during the third trimester of gestation, regardless of the route of administration (Class of recommendation: I; level of evidence: A). It is also considered to recommend that they avoid using other medications with possible anti-inflammatory effects (corticosteroids,[108] aspirin,[107] dipyrone, fluoxetine,[109,126] paroxetine, sertraline,[109,111] isoxsuprine,[107] and naphazoline)[107] (Class of recommendation: IIa; level of evidence: C). It is sufficient to recommend moderate maternal polyphenol-rich foods consumption during the third trimester of gestation, i.e., below the 75th percentile of consumption,[76] or limiting consumption of foods with concentrations above 30 mg per 100 g, in accordance with the food pyramid shown in Figure 6.1. Reduced daily consumption of polyphenols below 1,089 mg (75th percentile) maintains an acceptable diet for nutritional needs during this period of gestation (Class of recommendation: IIa; level of evidence: C). Figures 6.2 and 6.3, respectively, show recommendations for treatment and prevention of fetal ductal constriction.

7. Fetal Cardiac Arrhythmias: Diagnosis and Treatment

Screening programs for detecting prenatal cardiac abnormalities developed over the past 3 decades,

Table 6.2 – Recommendations for polyphenol-rich foods restriction after 28 weeks gestation for ductal constriction treatment

Restricted foods	Alternatives options
Raw beets: consume no more than 2 tablespoons/day	Cooked beets or carrots
Lettuce: consume no more than 10 medium-sized leaves/day	It is ideal to consume less
Red/purple plums, unpeeled: consume no more than 1 small unit/day	Pineapples, pears, and peeled red apples
Blackberries/mulberries: consume no more than 1/2 cup/day	Pineapples, acerolas, and limes
Red apples, unpeeled: do not eat the peel	Green apples or peeled red apples
Oranges/orange juice: do not consume	Pineapples, acerolas, limes, and tangerines*
Papaya: consume no more than 1 slice/day (formosa variety)	Guavas, acerolas, limes, and tangerines*
Strawberries: consume no more than 2 larges units/day	Pineapple, acerolas, limes, and tangerines*
Red/purple/pink grapes/grape juice: do not consume	White grapes, pears, and peeled apples
Green tea: do not consume	Fruit teas (teabags)
Black tea: do not consume	Fruit teas (teabags)
Boldo tea: do not consume	Fruit teas (teabags)
Coffee: do not consume	---
Yerba mate: do not consume	---
Dark/milk/bittersweet chocolate: do not consume	White chocolate
Cocoa powder: do not consume	
Olive oil: do not consume	Canola oil
Green herbs: consume no more than 12 teaspoons/day	Other natural spices

** Consume in moderation. When consuming a restricted food, consume no more than once daily, and do not exceed the quantities described in the table. Source: Adapted from Arnt et al.[127]*

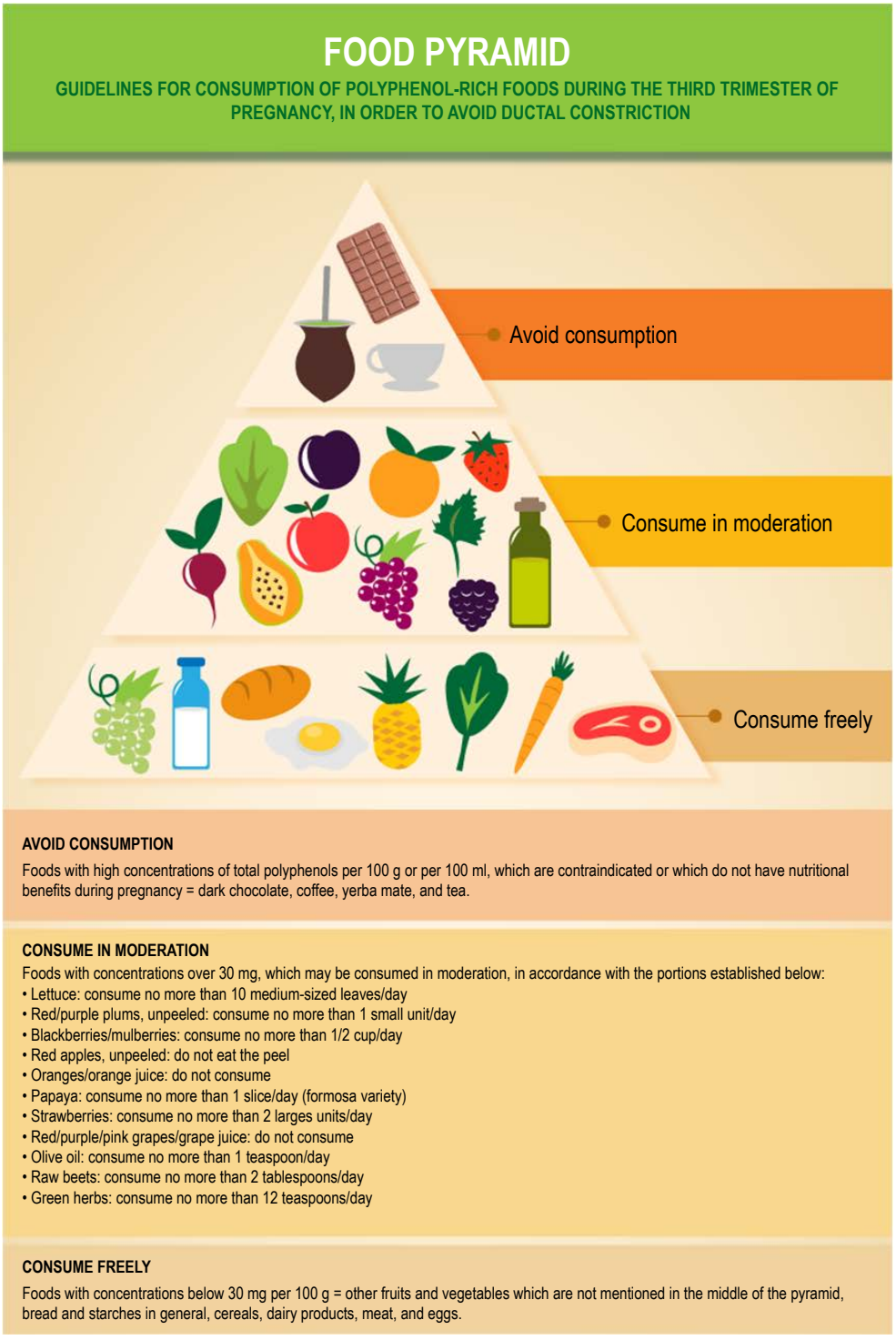

Figure 6.1 – *Food pyramid.*

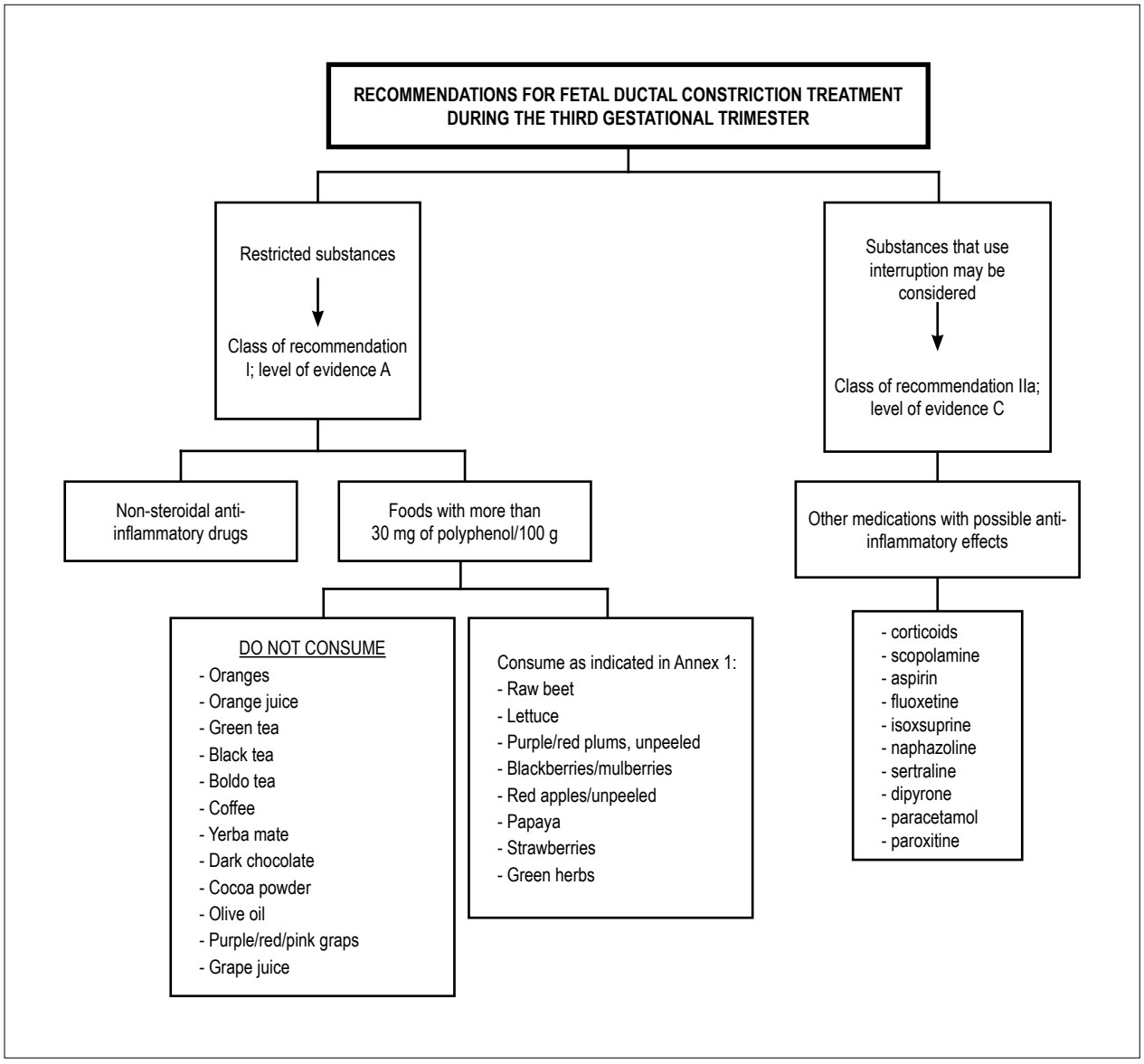

Figure 6.2 – *Recommendations for fetal ductal constriction treatment during the third gestational trimester. In cases in which there is no reversal of the ductal constriction and its consequences after initiation of treatment, preterm delivery may be considered, since fetal pulmonary maturity has been established. Class of recommendation: IIb; Level of evidence: C.*

improved the understanding of fetal cardiac rhythm abnormalities. Since fetal arrhythmias may severely compromise the gestation outcome, it is very important to diagnose, recognize the mechanisms, hemodynamic consequences, and the fetal cardiac morphology for perinatal therapy planning.

Fetal cardiac rhythm abnormalities affect approximately 0.5–2% of pregnancies, and are responsible for 10–20% of referrals for in utero cardiac examination. The ectopic beats are the most prevalent rhythm irregularities seen during fetal heart. They are usually benign however, may potentially trigger a sustained supraventricular tachycardia (SVT) especially when they are blocked. Some fetal cardiac arrhythmias, however, are considered emergencies in Fetal Cardiology, requiring early diagnosis and treatment and have determinant impact on perinatal morbidity and mortality. Complete heart block (CAVB), atrial flutter (AF), and SVT may have severe consequences for the fetus clinical status.[128]

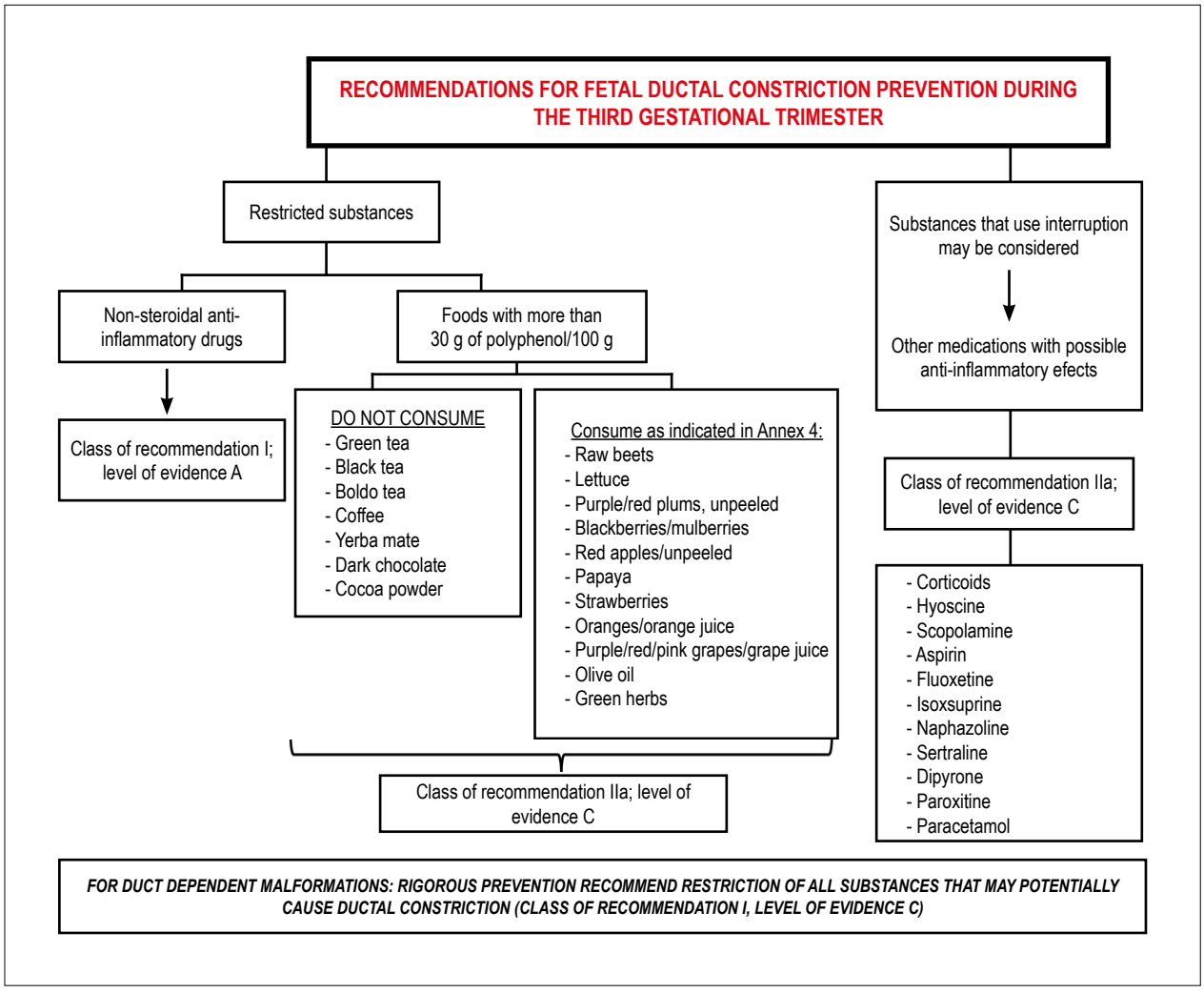

Figure 6.3 – *Recommendations for fetal ductal constriction prevention during the third gestational trimester.*

7.1. Fetal Cardiac Rhythm and Fetal Cardiac Arrhythmias

During fetal echocardiography, heart rate and rhythm are assessed with simultaneous examination of the atrial and ventricular systoles employing M-mode, two-dimensional echocardiography and pulsed-wave Doppler with or without color flow mapping. Cardiac rhythm is considered normal when the ratio of atrial and ventricular contractions is 1:1, with heart rate ranging from 120 to 180 bpm.[48,129-131]

M-mode allows to evaluate the movement of the posterior atrial wall (atrial systole or A wave), concomitantly with aortic valve opening (ventricular systole or V wave). This trace is obtained from the longitudinal two-dimensional image of the heart, with the cursor positioned crossing the right ventricle, the aortic valve and the LA. Sinus rhythm is identified when, for each movement of the left atrial wall (A wave), there is a corresponding opening movement of the aortic valve (V wave), i.e., 1:1 atrioventricular (A:V) conduction. Positioning the cursor simultaneously across the atrial (A wave) and ventricular (V wave) wall may also be employed. Color M-mode facilitates the identification of aortic flow during ventricular systole and may also be used to identify left atrial activity from mitral flow.

The atrioventricular sequence may also be assessed positioning the pulsed Doppler sample volume between the left ventricular inflow and outflow tracts, thus recording the mitral (A wave) and aortic (V wave) flows. Additionally, the sample volume may be placed between the SVC and the aorta in the 3 vessels view. The SVC "A" wave reversal flow represents the atrial contraction (A wave), and the aortic flow represents ventricular systole (V wave). The same concept can be used with

the Doppler sample volume placed at the same time reaching the pulmonary artery and vein flows.[48,129-138]

7.2. Extrasystoles

Extrasystoles occur in 1–3% of pregnancies. They are, usually, benign, with no consequences for the fetus. In the setting of bigeminy, trigeminy, or very frequent extrasystoles (1 for every 3–5 fetal heartbeats), differential diagnosis with ventricular extrasystoles, long QT syndrome, and second-degree atrioventricular block may be difficult. The presence of blocked bigeminy increases the risk of SVT triggering.[139-141]

7.2.1. Isolated Supraventricular Extrasystoles

Correspond to premature atrial contractions (A wave), that may or may not be followed by ventricular activity (conducted or blocked, respectively). They may occur with bi- or trigeminy, compensatory pauses, or in series. They are considered benign arrhythmias, and do not require treatment. About 1% of conducted ectopic beats may trigger tachyarrhythmias.[48]

7.2.2. Ventricular Extrasystoles

Ventricular extrassystoles are ventricular ectopic beats that are not related to atrial activity.

Table 7.1 shows the summary of in utero management of irregular rhythms.

7.3. Fetal Bradycardia

Fetal bradycardia is considered when the fetal heart rate of < 110 bpm. When treatment is necessary, it is important to identify its cause and mechanism.

7.3.1. Sinus Bradycardia

Sinus bradycardia is diagnosed when the heart rate is < 110 bpm with a 1:1 A:V conduction. It is usually a vagal response secondary to hypoxia or umbilical cord

Table 7.1 – In utero management of irregular rhythm

Diagnosis	Cause	In utero management	GOR/LOE	Comments
Second-degree AVB	Autoimmune	Dexamethasone	IIb/B	This may stop progression to CAVB
	Structural CHD	Weekly follow-up	I/C	If possible, perform FMCG to rule out LQTS
	Channelopathy	Weekly follow-up	I/C	
VPC or frequent APC	Idiopathic	Observation with obstetric evaluation of fetal HR weekly until the arrhythmia is resolved (bigeminy, trigeminy, or 1 ES at every 3–5 beats)	I/A	2% also have first- or second-degree AVB
	Oval fossa aneurysm			For APC, there is a 0.5–1% risk of developing SVT
				For VPC, the risk of developing VT is unknown
				Most episodes are benign and of short duration
				Evaluate secondary causes
Secondary causes				
VPC or frequent APC	Myocarditis	Observation with evaluation of FHR at weekly intervals	I/C	
		Frequent evaluation (every 1–2 week) of heart function and other parameters of fetal CHF		
	Cardiac tumors	Observation with obstetric evaluation of FHR weekly	I/C	
	Ventricular or atrial diverticula or aneurysm	Observation with FHR assessment by OB weekly	I/C	
	Maternal stimulants	Observation with FHR assessment by OB	I/C	

APC: atrial premature contractions; AVB: atrioventricular block; CAVB: complete atrioventricular block; CHD: congenital heart disease; CHF: congestive heart failure; FHR: fetal heart rate; FMCG: fetal magnetocardiography; GOR: grade of recommendation; LOE: level of evidence; LQTS: long QT syndrome; SVT: supraventricular tachycardia; VPC: ventricular premature contraction; VT: ventricular tachycardia. Source: adapted from Donofrio et al.[17]

compression by the transducer. It also may occur due to maternal illnesses. When transitory, they are commonly benign and do not require treatment. However, persistent bradycardia indicates fetal abnormality and its causes should be treated.[48,129,134,137,141]

7.3.2. Low Atrial Rhythm

The main mechanisms of low atrial rhythm include congenital displacement of atrial activation, acquired damage of the sinoatrial node, channelopathy, and secondary suppression of sinus node rate. Left and right atrial isomerism can occur, with fetal heart rate varying from 80 to 130 bpm. Situations that may cause sinus node fibrosis, such as maternal anti-Ro/anti-LA antibodies or viral myocarditis, may occur with progression to fetal death. Additionally, maternal use of medications, such as sedatives or betablockers, may reduce the sinus node rate. Low atrial rhythm does not require treatment.[137]

7.3.3. Blocked Atrial Bigeminy

Blocked atrial bigeminy occur with a heart rate ranging from 75 to110 bpm in a 2:1 atrioventricular conduction. They do not require treatment. It is known, however, that approximately 10–13% may evolve to SVT; weekly evaluation of fetal heartbeats is thus recommended by echocardiogram or sonar.[137,142]

7.3.4. Complete Atrioventricular Block

CAVB results in complete dissociation between atrial and ventricular activity, with heart rates usually below 60 bpm. In 50–55% of cases, malformation of the conduction system occurs, as a consequence of structural heart diseases, such as congenitally corrected transposition of great arteries and left atrial isomerism.[141,143-146] In about 40% of the cases, it occurs due to maternal autoimmune diseases that present with anti-SSA/SSB (anti-Ro/LA antibodies).[142-147]

The risk increases in the presence of anti-Ro 52-kd (sequence p200) antibodies, that cannot be tested in Brazil yet.[147-153] In a minority of cases, no etiology is identified. Fetuses without hydrops and with heart rate above 55 bpm have good prognoses. In immature fetuses, with very early hydrops and heart rates below 50 bpm, prognosis is more limited. Fetuses with CAVB and structural heart diseases, such as left atrial isomerism, have a poor prognoses.[145]

In mothers with autoimmune diseases, it is recommended to test maternal anti-SSA/RO antibodies. If positive, and the fetus is in sinus heart rhythm, weekly measurements of the AV interval (mechanical PR interval) are recommended, from weeks 18 to 26. This measurement should be taken employing pulsed-wave Doppler, evaluating mitral and aortic flows simultaneously, from the beginning of the mitral A wave ("A") to the beginning of the ventricular systole ("V").[142] Myocardial function should be monitored every 4 weeks up to delivery (grade of recommendation: I; level of evidence: C) (Figure 7.1).[154]

Although controversial, treatment with dexamethasone at a dose of 4–8 mg orally can be started to cases where the AV interval is > 150 milliseconds or when it increases progressively. Some groups have shown to be beneficial the treatment of immune CAVB with maternal dexamethasone (4–8 mg orally) and/or intravenous gammaglobulin infusion,[149-158] observing reduced inflammatory response, stabilization of first- and second-degree AVB, regression of endocardial fibroelastosis and hydrops improvement.[145-151]

However, the use of corticosteroids may be associated with complications, such as ductal constriction, maternal diabetes, restricted growth, and oligohydramnios.[149-161]

Dexamethasone may be used to treat first- and second-degree AVB associated with signs of myocardial inflammation (myocardial hyperechogenicity, valve regurgitation, cardiac dysfunction, and pericardial effusion) to prevent progressing to CAVB, however the efficiency of corticosteroids has not been completely established and one may consider its possible side effects.[140] In fetuses with CAVB without functional consequences, dexamethasone may also be used to reduce the prevalence of dilated cardiomyopathy.[152,162] Whenever significant side effects occur in the mother or the fetus, the use of the medication should be interrupted. Intravenous immunoglobulin associated with dexamethasone may improve survival in fetuses with endocardial fibroelastosis or systolic dysfunction.[149] It is not yet known, however, when is the ideal moment for administration and the ideal intervals between doses. There is no recommendation regarding the prophylactic use of immunoglobulin at the beginning of gestation for mothers with positive antibodies.[160]

The use of salbutamol, terbutaline, or isoprenaline is indicated when heart rate is < 55 bpm and/or in the presence of fetal heart failure and hydrops.[142,146,157] These medications are usually well tolerated. Maternal extrasystole and sinus tachycardia may appear.[161] There is an increase in fetal heart rate of approximately 10 to 15% of the basal frequency, and, although small, it may prolong the gestation to or close to term. There are no studies demonstrating that these medications modify fetal survival in these cases. In immature fetuses with hydrops, with very low heart rate, in utero implantation of a pacemaker may be considered. This procedure

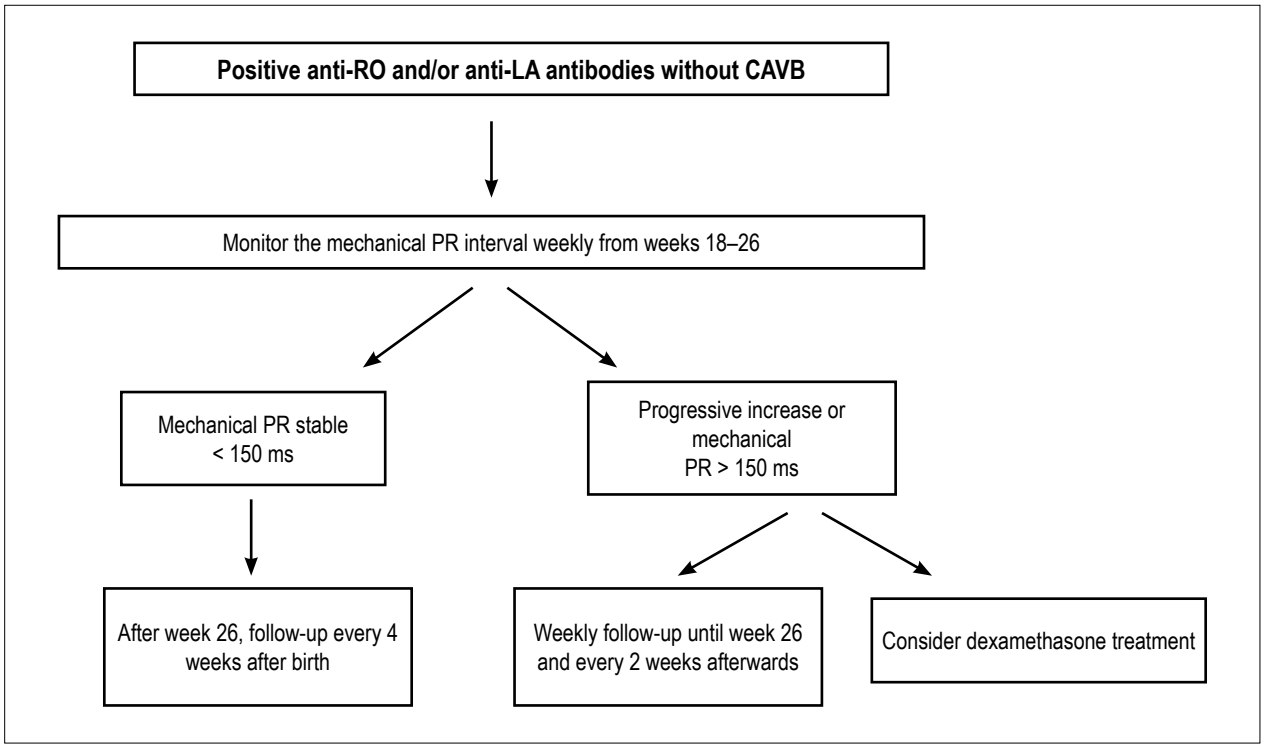

Figure 7.1 – *Suggested approach for pregnant women with positive antibodies, without fetal CAVB. CAVB: complete atrioventricular block; ms: miliseconds.*

continues to have technical limitations and is still undergoing experimental studies.

Indications for delivery should be analyzed based on the degree of fetal manifestations. In fetuses with significant hydrops, with ventricular rate < 50 bpm and pulmonary maturity (after week 34 of gestation), delivery should be considered, with immediate postnatal pacemaker implant.[163] In fetuses before week 26 of gestation, with heart rate < 45 bpm and hydrops, in utero pacemaker implant, still in experimental phase, may be a therapeutic option.[164-168] In fetuses between weeks 26 and 34 of gestation, the risks of prematurity and the manifestations of CAVB should be weighed together. The in utero suggested manaegment of fetal bradycardia is summarized in figure 7.2.

7.4. Fetal Tachycardia

Fetal tachycardia is diagnosed when fetal heart rate is > 180 bpm. In utero treatment depends on gestational age, etiology, degree of hemodynamic compromise (presence of hydrops), mother's clinical condition, and potential maternal risks of fetal treatment. The therapeutic decision should be based on fetal vs. maternal risks. Medical treatment is indicated for fetuses with sustained or intermittent tachycardias with hydrops and/or ventricular dysfunction, unless gestation is close to term, with fetal pulmonary maturity, thus minimizing the risks of preterm birth.[17,129,131-133,136,140,142,169,170]

Tables 7.3 and 7.4, respectively, demonstrate the management of tachyarrhythmias and antiarrhythmic drugs.[17] The suggested management approaches for fetal tachycardias are shown in Figures 7.3, 7.4, and 7.5.

7.4.1. Intermittent Tachycardias

Intermittent tachycardia is defined when it is present for less than 50% of the exam period, the minimum observation time being 30 minutes. Sinus tachycardia is determined by atrial and ventricular activation with 1:1 A:V conduction and heart rate over 160 bpm and, usually, below 180 bpm. It is frequently associated with an underlying fetal or maternal abnormal condition, such as fever, stress, or use of medication. Its cause should be treated. As an isolated finding, it does not have clinical significance and does not require treatment.[137,138,141]

Intermittent ventricular tachycardia, with ventricular rate over 200 bpm is extremely rare and may evolve to important hemodynamic impairment and hydrops; for this reason, treatment is indicated.

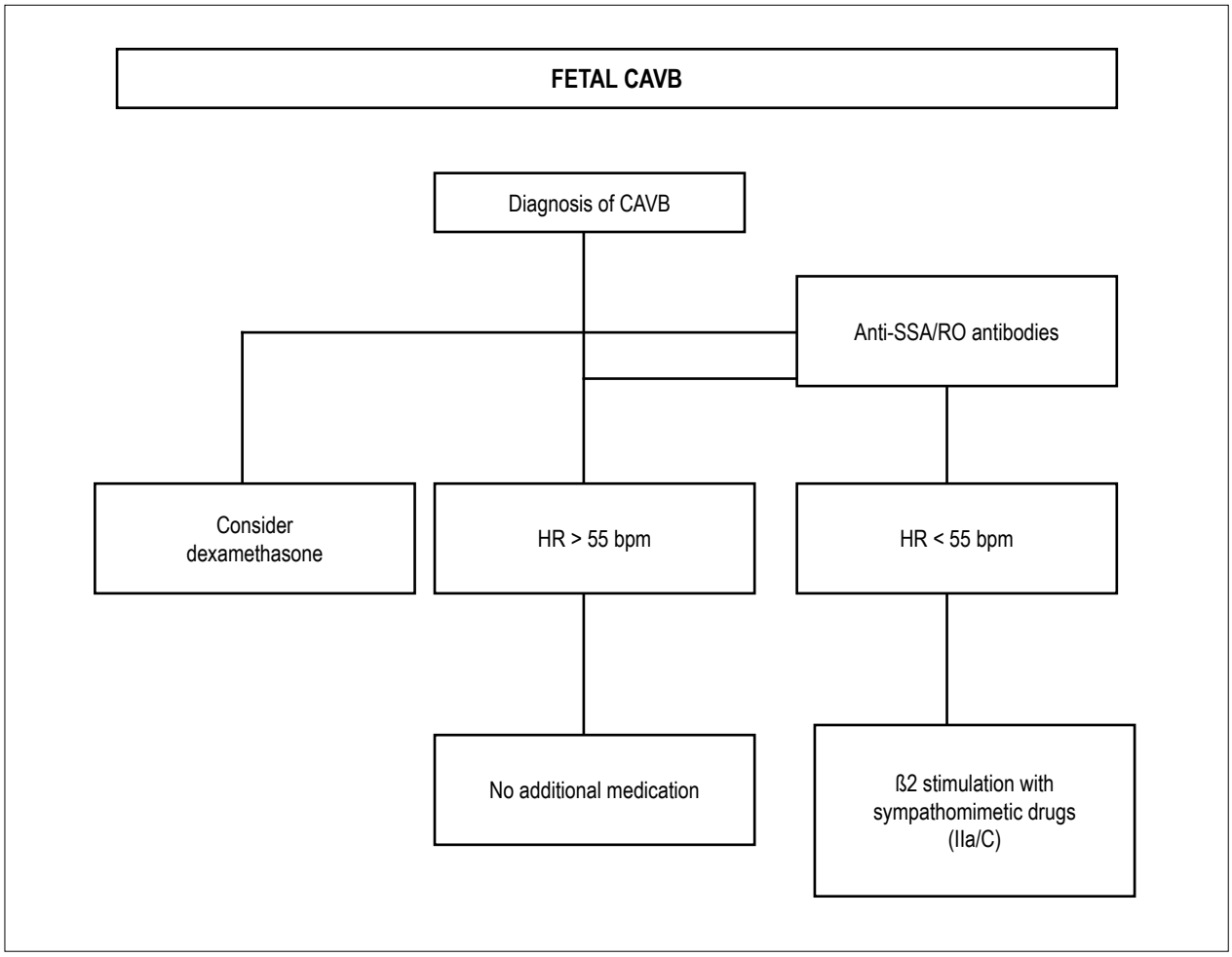

Figure 7.2 – *Suggested approach for fetuses who have CAVB. CAVB: complete atrioventricular block; HR: heart rate.*

Other intermittent tachycardias usually do not have signs of cardiac hemodynamic impairment, and there is no indication for treatment.[171] However, in isolated cases, it may evolve to sustained tachycardia, justifying its follow up.

7.4.2. Sustained Tachycardias

This group of fetal arrhythmias, identified by a period of more than 50% of exam duration, includes supraventricular tachycardias, AF, and ventricular tachycardias. The therapeutic goal is to bring the gestation to term, while improving secondary manifestations. Prognosis is good when they are reversed in utero and limited for immature fetuses with hydrops and cases of arrhythmia which were not successfully reversed. Prognosis should be considered favorable when fetuses continue with tachyarrhythmia, but with lower heart rates and improvement in hydrops.

7.4.2.1. Diagnosis

Sustained atrial tachycardia is characterized by a cardiac rhythm with 1:1 A:V conduction and heart rate above 180 bpm, usually above 220 bpm.[17,137,138,141] It is important to understand the underlying mechanism of the arrhythmia, assessing simultaneously the atrial and ventricular activity. Using Doppler flow tracing, it is possible to measure the AV (atrium → ventricle) and VA (ventricle < atrium) intervals, which correspond, analogously and respectively, to PR and RP intervals in an electrocardiogram. When the VA interval is greater than the AV, the most possible diagnosis is reentrant tachycardia (95%); when the VA interval is greater

Table 7.2 – In utero management of bradycardias

Diagnosis	Primary causes	In utero management	GOR/LOE	Comments
Sinus bradycardia	Ectopic atrial pacemaker	Rule out fetal distress as the cause of bradycardia	I/A	Can be seen in atrial isomerism
	Sinus node dysfunction (including immune mediated or infection)	Observation until bradycardia resolves	I/A	Test for anti-Ro/LA antibodies Maternal IgG/IgM for TORCH diseases and parvovirus
	Secondary causes: maternal medications, maternal hypothyroidism, fetal distress or fetal CNS abnormalities	Treat underlying cause of bradycardia	I/A	
Blocked atrial bigeminy	Atrial extrasystoles	Observe / reduce maternal stimulants	I/A	10% risk of fetal SVT Weekly auscultation of fetal HR until arrhythmia resolves
AVB	Maternal anti-Ro/La antibodies	Observation	I/A	Structurally normal heart
		Dexamethasone for second-degree block or first-degree block with findings of cardiac inflammation	IIb/B	Endocardial fibroelastosis, associated valvular or myocardial dysfunctions
		For CAVB to prevent death or cardiomyopathy	IIb/B	4–8 mg⁄day
		IVIG (note: IVIG as prophylaxis is not recommended)	IIa/C	
		Sympathomimetics for HR < 55 bpm or higher rates associated with fetal hydrops	Ib/C	
	CAVB not related to antibodies	Observation	I/A	Associated with structural defects such as CTGA, left atrial isomerism
	CAVB related to channelopathies	Observation	I/A	
		Avoid QT-prolonging drugs		

AVB: atrioventricular block; CAVB: complete atrioventricular block; CNS: central nervous system; CTGA: corrected transposition of great arteries; GOR: grade of recommendation; HR: heart rate; IVIG: intravenous infusion of gammaglobulin; LOE: level of evidence; mg: milligrams; SVT: supraventricular tachycardia; TORCH: toxoplasma IgG, Rubella IgG, Cytomegalovirus IgG, and Herpes. Source: adapted from Donofrio et al.[17]

than the AV, tachycardia due to ectopic atrial focus or junctional reciprocating tachycardia are the most frequent diagnosis.[132,133,136]

Atrial flutter presents with atrial rates above 400 bpm, with variable atrioventricular conduction (2:1, 3:1, 4:1) and ventricular rates (200–250 bpm).[17,137,138,141,169]

Ventricular tachycardia is identified as atrioventricular dissociation, with atrial rate lower than ventricular, varying from 100 to 400 bpm. When it coexists with bradycardia periods, the possible diagnosis is long QT syndrome, which may manifest as monomorphic ventricular tachycardia, torsade de pointes, ventricular dysfunction, atrioventricular valve regurgitation, and fetal hydrops.[138,172]

7.4.2.2. Treatment

The first choice for medical treatment of supraventricular tachycardias in most centers continues to be transplacental digoxin, given that it is safe and widely used during gestation.[17,137,138,141,173,174] The doses should be high, since only 50–70% crosses the placental barrier. The recommended loading dose is 3.0 mg during the first 48 hours of treatment, i.e., 0.50 mg every 8 hours. The maintenance dose is 0.25–0.75 mg/day, varying in accordance with isolated experience of each service and maternal serum level. Daily control of digoxin level is mandatory, and it should be kept between 1 and 2 ng/mL. If it is not possible to administer it orally, intravenous lanatoside C may be used as an alternative. If the arrhythmia has not reversed

Table 7.3 – In utero management of tachycardias

Diagnosis	In utero management	GOR/LOE	Comments
	Intermittent tachycardia		
SVT or AF	Observation	I/B	Frequent fetal HR auscultation
VT ≥ 200 bpm	Antiarrhythmic medication	IIa/C	
	Sustained tachycardia		
SVT or AF with hydrops or ventricular dysfunction	First or second line (transplacental) drugs:		See Table 7.4, for dosing ranges and monitoring recommendations
	Digoxin	I/B	
	Sotalol	I/B	
	Combination of drugs (transplacental)	IIb/B	Combination treatments are used for severe, drug-refractory cases. Consider preterm delivery if near term
	Third line (transplacental):		
	Amiodarone	I/B	
	Contraindicated: verapamil	III/A	
	Contraindicated: procainamide	III/B	
	Direct fetal treatment:		
	IM digoxin	IIa/B	
	Intracordal digoxin	IIb/B	
	Contraindicated: Intracordal adenosine	III/B	
SVT ≥ 200 bpm, without hydrops or ventricular dysfunction (usually SVT has HR ≥ 220 bpm; consider other causes if HR < 220 bpm).	First or second line:		
	Digoxin	I/B	See Table 7.4, for doses and monitoring recommendations
	Sotalol	I/B	Frequent monitoring of fetal well-being and maternal/fetal drug toxicity. Consider preterm delivery if near term.
	Third line:		
	Amiodarone	IIb/B	
	Contraindicated: verapamil	IIb/A	
	Contraindicated: procainamide	III/B	
	Observation	I/B	
SVT < 200 bpm, without hydrops or ventricular dysfunction	Sotalol	I/B	Digoxin increases AVB and decreases ventricular response. Consider preterm delivery if near term
AF	Digoxin	I/B	
	Amiodarone	IIb/B	
	Contraindicated: procainamide	III/B	
VT ± hydrops		I/C	
First line treatment	Magnesium IV Lidocaine IV Propranolol (oral)	I/C	FMCG (if available) to measure QTc interval. Start with magnesium IV, then lidocaine, load + maintenance. Note: maternal intravenous magnesium should not be used for > 48 h. Consider preterm delivery if near term.
Second line treatment	Mexiletina (oral) Sotalol	I/C	

AF: atrial flutter; GOR: grade of recommendation; IV: intravenous; HR: heart rate; IM: intramuscular; FMCG: fetal magnetocardiography; LOE: level of evidence; SVT: supraventricular tachycardia; VT: ventricular tachycardia. Source: adapted from Donofrio MT et al.[17]

Table 7.4 – Antiarrhythmic drugs

Drug	Therapeutic dose	Therapeutic serum level and effect	Toxicity
Digoxin	LD: 0.5 mg (2 capsules) every 8 h for 48 h – 1.5 mg/d for 2 days	0.7-2.0 ng/mL	Maternal nausea/vomiting, sinus bradyarrhythmia or AVB, proarrhythmia
	MD: 0.25–0.75 mg/day Fetal IM dose: 88 µg/kg every 12 h, repeat twice	Nausea, fatigue, loss of appetite, sinus bradycardia, first-degree AV block, nocturnal Wenckebach AV block (rare)	Fetal IM: sciatic nerve injury or skin laceration from injection
Sotalol	160–480 mg/day every 8–12 h PO	Levels not monitored	Nausea/vomiting, dizziness, QTc ≥ 0.48 s, fatigue, BBB, maternal/fetal proarrhythmia
		Bradycardia, first-degree AVB, P and QRS widening, QTc ≤ 0.48 s	
Amiodarone	LD: 1800–2400 mg/d divided every 6 h PO	0.7–2.0 µg/mL	Nausea/vomiting, thyroid dysfunction, photosensitivity rash, thrombocytopenia, BBB, QTc ≥ 0.48 s, maternal/fetal proarrhythmia, fetal torsades with LQTS, fetal goiter, neurodevelopmental concerns
	MD: 200–600 mg/d PO	Maternal/fetal sinus bradycardia, decreased appetite, first-degree AVB, P and QRS widening, QTc ≤ 0.48 s	
	Consider discontinuation of drug and transition to another agent once normal rhythm is reestablished or hydrops has resolved.		
Propranolol	60–320 mg/d divided every 6 h PO	25-140 ng/mL	Fatigue, bradycardia, hypotension, AV block, fetal growth restriction, increased uterine tone
		First-degree AVB, bradycardia, increased uterine tone	
Lidocaine	LD: 1–1.5 mg/kg followed by infusion of 1–4 mg/min continuous IV	1.5-5 µg/mL	Nausea/vomiting, neurological symptoms, proarrhythmia
Mexiletine	600–900 mg/d divided every 8 h PO	0.5-2 µg/mL	Nausea/vomiting, neurological symptoms, proarrhythmia
Magnesium sulfate	LD: 2–6 g IV over 20 min followed by 1–2 g/h	< 6 mEq/L	Fatigue, neurological symptoms If there is loss of patellar reflex and/or levels of> 6 mEq/L STOP infusion
	Treatment for > 48 h is not recommended but redosing may be considered if VT recurs	Monitor patellar reflex	Levels > 5 mEq/L associated with maternal changes on ECG and proarrhythmia

AV: atrioventricular; AVB: atrioventricular block; BBB: bundle-branch block; ECG: electrocardiogram; IM: intramuscular; IV: intravenous; LD: loading dose; LOE: level of evidence; LQTS: long QT syndrome; MD: maintenance dose; PO: orally; VT: ventricular tachycardia. Source: afapted from Donofrio et al.[17]

after 5 days, oral sotalol is initiated as second-choice drug.[175-177] This may be used with an initial dose of 80 mg every 12 hours, gradually increasing 40–80 mg every 3–5 day, until the arrhythmia is reversed or the maximum dose of 480 mg/day has been reached. In this case, the mother must remain in hospital for monitorization, with daily ECG control to measure the QTc interval, as well as serum levels of digoxin. In fetuses with significant hydrops and sustained tachycardia with elevated heart rate, sotalol may be initiated concomitantly with digoxin. Combined therapy has greater risks of maternal and fetal complications. If there is no therapeutic response in fetuses who are severely affected, the third-choice drug, amiodarone, may be used at a dose of 800–1,200 mg/day.[178-179] This drug, however, has a significant toxicity for both mother and fetus.[180]

If the fetal tachyarrhythmia continues, with important hemodynamic impairment and severe hydrops, direct fetal therapy may be necessary, via cordocentesis or direct intramuscular injection, given that, in this situation, there is a significant decrease in the transplacental passage of medications.[171,181,182] The risks and benefits of every situation must be weighed individually. Digitalis (dose of 0.03 mg/kg) or amiodarone (dose of 15 mg/kg) may be administered. Adenosine has not shown any effect in maintaining sinus rhythm, and it is not recommended for atrial flutter.

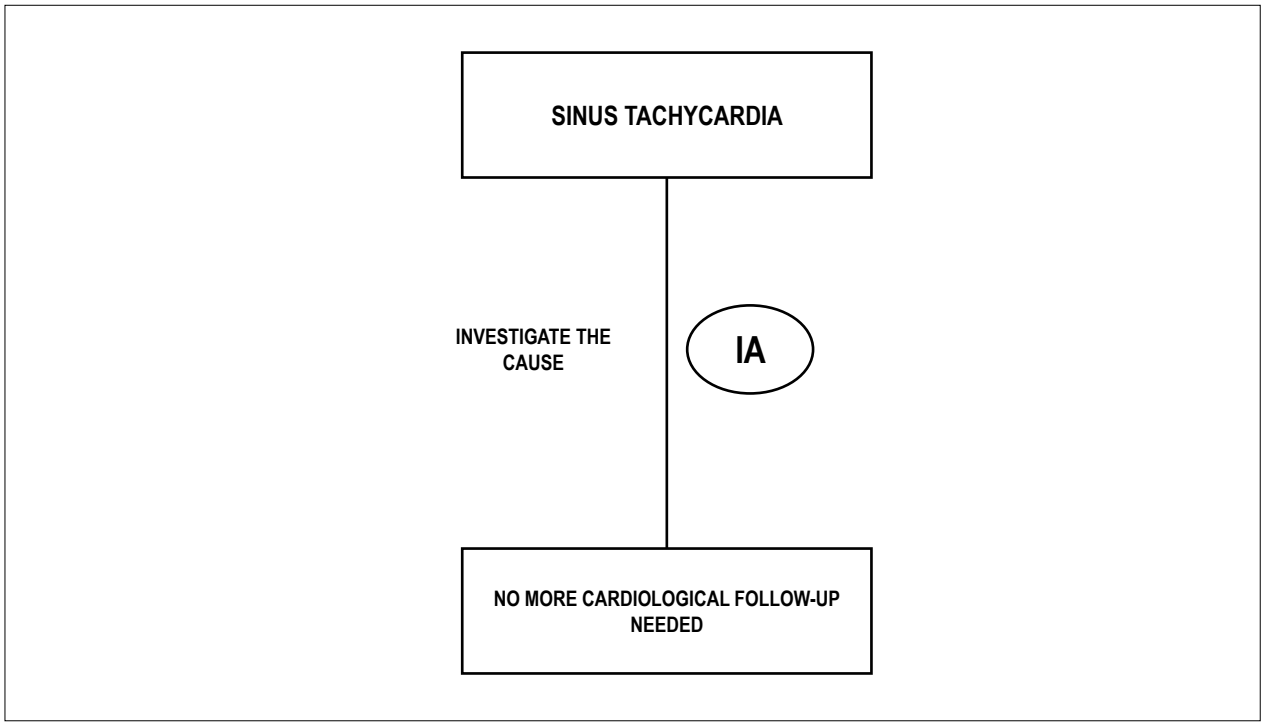

Figure 7.3 – *Sinus tachycardia clinical management.*

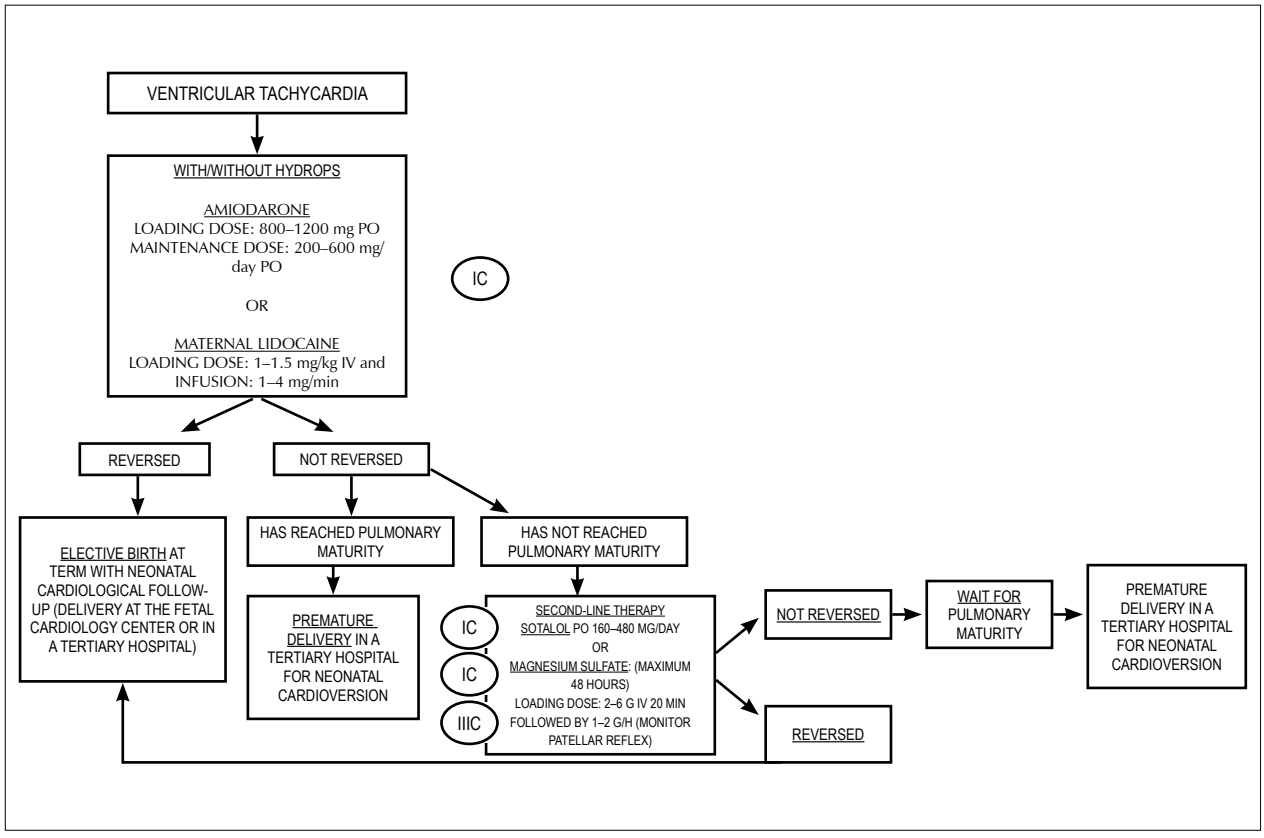

Figure 7.4 – *Treatment flowchart for ventricular tachycardia.*
IV: intravenous; PO: orally.

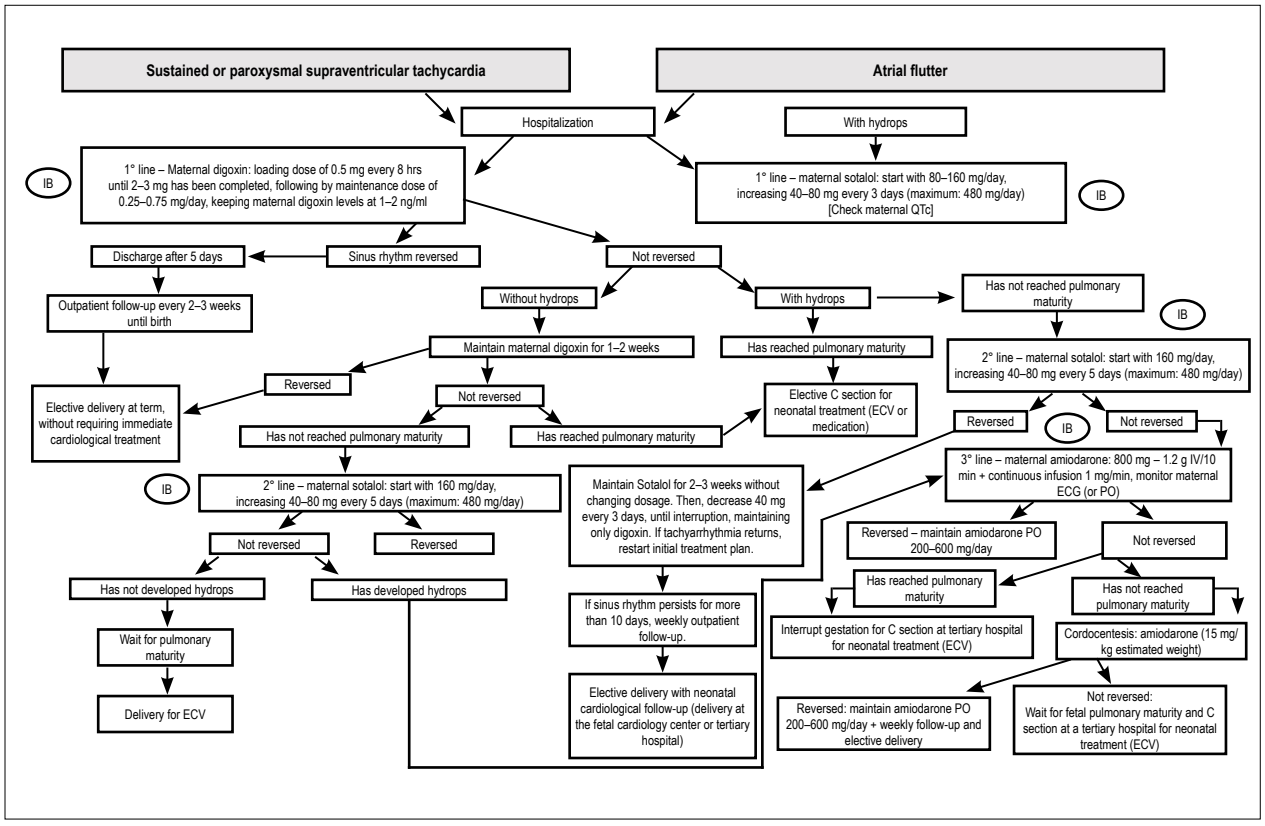

Figure 7.5 – *Flowchart treatment for supraventricular tachycardias. ECV: electric cardioversion; IV: intravenous; PO: orally.*

Some centers use flecainide (not commercially available in Brazil) or sotalol as first-choice drugs.[130,177,183,184] After birth, treatment should be based on the therapy used in utero and on the tachycardia mechanism. It is recommended to maintain therapy for 6 months to 1 year, in accordance with the outcome. About 50% of cases of fetal SVT do not recur after birth.[185]

For AF, recommended medication for initial treatment may be either digoxin and/or sotalol.[185] Sotalol is also safe and efficient with a reversal rate to sinus rhythm of 50–80%, without mortality.[177]

Doses and forms of administration for AF are as previously described for SVT. Following delivery, synchronized cardioversion is indicated when there is no in utero reversal. After birth, AF does not usually recur once it has been reversed and maintenance of medical treatment is not recommended.

Sustained ventricular tachycardia with ventricular rate < 200 bpm is usually well tolerated; when it exceeds this rate, transplacental magnesium is recommended. This infusion should not be administered for more than 48 hours.[172,186,187] If ventricular tachycardia recurs, a new dose of magnesium may be used, provided that maternal serum levels are < 6 mEq/L and there are no signs of toxicity. Therapeutic options for pharmacological treatment of sustained ventricular tachycardias include oral administration of amiodarone, propranolol, and mexiletine or maternal intravenous lidocaine. Amiodarone, sotalol, and flecainide cannot be used when there is long QT syndrome.[186,187] When ventricular tachycardia is secondary to myocarditis or maternal antibodies, intravenous dexamethasone and immunoglobulin may be administered to the mother. This treatment should be continued after birth.

One should consider that treatment of fetal sustained tachycardias is slow and its goal is to bring gestation to term. Total reversal of arrhythmia and hydrops may occur several weeks after initiation of medical treatment. A concomitant Doppler ultrasound, performed by the obstetrician, is essential to decide if the delivery should be anticipated. Delivery anticipation should be limited to fetuses with imminent risk of in utero death. If sustained tachycardia persists in fetuses with severe hydrops and proven pulmonary maturity (after week 34 of gestation), it

is recommendable to deliver the baby and begin postnatal treatment immediately.

8. Fetal Cardiac Interventions

The potential benefits of fetal cardiac interventions have been emphasized for many years. In the year 2000, Kohl et al.[188] published the worldwide experience of fetal aortic valvuloplasty, which, at that time, consisted of 12 cases, with 7 technically well-succeeded but only 1 survival. Since that time, the Boston Children's Hospital group has initiated an invasive intrauterine cardiac therapy program, stimulating vast progress in the field and disseminating technical application throughout various other centers around the world.[189,190]

The main reason for invasive procedures during fetal life is to improve outcome and postnatal prognosis, either because the fetus is at a risk of not surviving or because postnatal outcome is strongly unfavorable. Early therapy for CHD may improve the chances of myocardial and vascular remodeling and offer better chances of adapting the blood supply to the developing myocardium. Thus, provided that the technique is well established, the equipment is appropriate, and, above all, the medical team is trained in fetal surgery, pediatric interventions, and Fetal Cardiology, fetal percutaneous interventions represent another form of therapy in the field of Pediatric Cardiology.[189]

The main heart diseases that benefit from intervention in utero are HLHS with severe flow restriction through the interatrial septum, critical aortic valve stenosis with impending left ventricular hypoplasia, and pulmonary atresia with intact interventricular septum (PAIVS), or critical pulmonary stenosis with right ventricular hypoplasia.[191]

8.1. Indications

The main indications for fetal cardiac interventions are summarized in Table 8.1 and subsequently described.

8.1.1. Critical Aortic Stenosis with Impending Hypoplastic Left Heart Syndrome

Aortic stenosis is defined as the following morphological and functional characteristics: thick valve, little mobility, and turbulent or no antegrade

Table 8.1 – Main indications for fetal cardiac interventions

Aortic valvuloplasty	Gestational age between 22 and 30 weeks
Critical aortic stenosis with impending HLHS	Thick aortic valve with little mobility
	Minimal or no aortic anterograde flow
	Reverse flow in the transverse arch
	Reverse shunt at the atrial level (L→R)
	Monophasic LV inflow (single E wave of short duration)
	Moderate or severe LV systolic dysfunction (subjective analysis)
Critical aortic stenosis with giant LA	Same criteria as previously described
	LV function may not be very abnormal due to the presence of massive mitral regurgitation
	Giant LA
Pulmonary valvuloplasty	Gestational age between 22 and 30 weeks
Pulmonary atresia with intact interventricular septum/ critical pulmonary stenosis	Thick pulmonary valve with little or no mobility
	Minimal or no pulmonary anterograde flow
	Inverted flow in the ductus arteriosus, i.e., aorta→pulmonary
	Monophasic RV inflow (single E wave of short duration)
	Some degree of RV hypoplasia or no growth during 2–4 weeks of observation
Balloon atrial septostomy	Gestational age between 28 and 33 weeks
HLHS or variants with intact interatrial septum or minimal foramen ovale	Minimal or no flow at the atrial level
	Dilated LA and pulmonic veins
	Biphasic and bidirectional pulmonary vein Doppler tracing

HLHS: hypoplastic left heart syndrome; L: left; LA: left atrium; LV: left ventricle; R: right; RV: right ventricle.

flow across the valve assessed by Doppler techniques. Left ventricular to aorta Doppler gradient should not be used to classify the severity of the stenosis since, there is a frequent association of endocardial fibroelastosis and severe myocardial dysfunction in critical aortic stenosis. Reverse flow in the transverse arch, i.e., coming from the descending aorta to the ascending aorta; inverted flow at the atrial level (from left to right); monophasic left ventricular inflow (Doppler tracing across the mitral valve showing single A wave due to high filling pressures), and moderate or severe left ventricular dysfunction are the main functional parameters that suggest impending HLHS.[192-195] Ideally, when fetal intervention is considered to avoid left heart hypoplasia, left ventricular length Z score (long axis) should be > -2, meaning that the left ventricle is not hypoplastic yet. Occasionally, aortic valvuloplasty is performed in cases where the left ventricle has already some degree of hypoplasia (Z-score > -4 and < -2), and the main aim in these cases is to promote some anterograde aortic flow, which may improve coronary and encephalic perfusion and allow ascending aorta growth, knowing that the chances of left ventricular complete recovery are low.[192-195]

8.1.2. Hypoplastic Left Heart Syndrome with Intact Interatrial Septum or Significantly Restrictive Foramen Ovale

This situation is characterized by absent or minimal high velocity flow across the interatrial septum and bidirectional flow in the pulmonary vein with prominent reverse flow, with disappearance of the classic triphasic pattern.[196,197]

8.1.3. Pulmonary Atresia with Intact Interventricular Septum or Critical Pulmonary Valve Stenosis with Signs of Evolving Right Heart Hypoplasia

This disease is defined as membranous pulmonary atresia with identifiable pulmonary valve leaflets with intact interventricular septum, associated with minimal or no anterograde pulmonary blood flow; reverse flow in the ductus arteriosus, i.e., coming from the aorta to the pulmonary artery; some degree of right heart hypoplasia, with hypoplastic tricuspid valve annular diameter (Z score < -2), or evidence that the right ventricle has not grown during 2–4 weeks of observation. Cases with significant coronary to right ventricle fistulas are excluded.[198-200]

8.1.4. Critical Aortic Stenosis with Massive Mitral Regurgitation and Giant Left Atrium

This is a specific group of fetuses that has only recently been characterized as a subgroup of critical aortic stenosis. These cases present with left ventricular dilation, reverse flow in the transverse arch, and some degree of left ventricular dysfunction. Most of them are associated with fetal hydrops and may benefit from aortic valvuloplasty associated or not with atrial septostomy to reduce the risk of fetal or neonatal death.[44,201]

8.2. Technical Considerations

Pre-anesthesia fasting and tocolytic prophylaxis consist the main preparation for the procedure. Nifidipine, 20 mg orally, started 4–8 hours before the procedure, is the medication of choice for this purpose, since it has few side effects and is highly effective.[189] The intervention is performed under maternal regional block, preferably via spinal anesthesia. General anesthesia may also be used, but this has the disadvantage of hindering proper fetal positioning, given that maternal general anesthesia also anesthetizes the fetus.

The fetal positioning is obtained with manual maneuvers allowing the fetal specialist to reach the target cardiac structure percutaneously. The ideal fetal position is pelvic with the spine downwards, leading to proceed the puncture as close as possible to the uterine fundus.[189]

Fetal anesthesia may be intramuscular or intravenous via the umbilical cord. It is performed with a mixture of opioid (fentanyl), muscle blocker (pancuronium), and atropine at doses of 15 μg, 0.2 mg, and 0.02 mg per kilogram of fetal weight, respectively. A 20-G Chiba needle is used to administer this medication.[189,190,194]

The heart is also accessed with a Chiba needle, 15 cm in length ranging from 17 to 19 Gauge. The entire procedure is monitored by ultrasound, which may be operated by either the fetal specialist or the fetal cardiologist. Once the abdominal wall is crossed, the needle reaches the amniotic cavity and the fetal thorax.[194] The target structure (aortic valve, pulmonary valve, or interatrial septum) is reached by direct heart puncture.

Once the distal end of the needle has reached the target cardiac structure, a pre-assembled coronary angioplasty balloon catheter is advanced through the needle until the balloon is positioned across the structure to be dilated. The pressure with which the balloon is inflated varies, considering the diameter and the target structure. For semilunar valve dilation, the ideal balloon:annulus ratio is from 1.1 to 1.2.[193] After the balloon is completely deflated, the entire set (balloon, catheter, and puncture needle) is removed all together, at once. After the system is complete removed from the fetal heart, bradycardia and hemopericardium frequently occur.[190] Voluminous effusions should promptly be emptied via a new puncture with a

20-G needle.[194] Removal of 1–2 ml of blood from the pericardium is usually enough to treat the condition. In most cases, this does not cause fetal anemia.

These procedures are not exempt from risks involving the mother and/or the fetus. Maternal risks are currently extremely low and minimized, thanks to the increased experience in fetal surgery for noncardiac diseases. These complications include premature rupture of membranes, infection, hemorrhage, placental abruption, preterm labor, anemia, bradycardia, and fetal death.[202]

There are still some doubts regarding the ideal moment to perform fetal cardiac intervention. Due to the reduced number of candidates and the morphological variability that every pathology may present, it is difficult to establish when it should be considered too late for intervention.[203] It seems reasonable to perform intervention as early as possible, soon after the diagnosis. From the technical point of view, however, it is very difficult to act before gestational week 20, due to the small dimensions of the fetal heart. Interventions performed very early may result in orifice and valve closure before the fetus has reached term.[203] On the other hand, late interventions do not prevent ventricular hypoplasia or avoid vascular damage of the pulmonary circulation. It appears to be consensual that the adequate period would be between gestational weeks 22 and 30.[190]

8.3. Aortic Valvuloplasty

The goal of aortic valvuloplasty is to change the natural history of critical aortic stenosis, maintaining left ventricular size and function adequate for biventricular physiology at birth or after a rehabilitation process. Alleviating left ventricular outflow obstruction reduces the left ventricular myocardial damage, thus facilitating chamber growth and myocardial function improvement. This hypothesis is based on animal models studies, which demonstrated the impact of load and flow conditions abnormalities on the developing myocardium, which leads to abnormal cardiovascular growth and function conditions.[204-209] According to the study published by McElhinney et al.,[195] there are anatomical and functional characteristics that are predictive of technical success and progression to postnatal biventricular circulation, based on the experience of 70 fetal aortic valvuloplasty procedures performed by their group.[8] These criteria are shown in Table 8.2.

There is evidence that the transition from normal left ventricle to HLHS in fetuses with critical aortic stenosis almost always occurs during the second or third trimester of gestation.[210]

An interesting aspect observed by the authors is that the progressive growth of left structures during fetal life and early infancy may eventually result in biventricular correction during the first year of life. Applying the strategy initiated with fetal aortic valvuloplasty, treatment continues with neonatal hybrid procedure, which may or may not be associated with a new aortic valvuloplasty or Norwood procedure, with the maintenance of partially restrictive foramen ovale and aortic commissurotomy. This management is a bridge to biventricular correction following the process known as left ventricular rehabilitation.[189,201,211,212] Although diastolic dysfunction may be a problem in this group of patients, it is believed that this is better than the morbidity and mortality inherent in medium- and long-term of the univentricular pathways.[213]

8.4. Critical Aortic Stenosis with Giant Left Atrium

This is a very particular and severe presentation of critical aortic stenosis. In addition to obstructed left

Table 8.2 – Criteria for technical success (initial criteria) and criteria that indicate potential outcome to postnatal biventricular correction (modified criteria)

Initial criteria (all of which must be present)	Modified criteria*
LV long-axis Z-score > −2	Aortic stenosis or atresia (mandatory)
LV dysfunction capable of generating ≥ 10 mmHg pressure gradient across aortic valve or ≥ 15 mmHg mitral regurgitation jet gradient	LV long-axis Z-score > −2 (mandatory)
Mitral annulus Z-score > −3	Meet, at least, 4 of the following 5 parameters: • LV long-axis Z-score > 0; • LV short-axis Z-score > 0; • Aortic annulus Z-score > −3,5; • Mitral annulus Z-score > −2; • Aortic valve systolic gradient and/or LV-LA mitral regurgitation ≥ 20 mmHg

*LA: left atrium; LV: left ventricle. * Source: adapted from McElhinney et al.[195]*

ventricular outflow tract, the mitral valve is significantly abnormal, with annular dilation, resulting in severe mitral regurgitation and LA dilation. The foramen ovale is usually quite restrictive, or the interatrial septum is intact, and there is left ventricular endocardial fibroelastosis, which also compromises the subvalvular apparatus of the mitral valve. Most fetuses with this anatomical presentation have some degree of fetal hydrops, with a high risk of death in utero or of triggering premature labor with immediate neonatal death. This disease appears to be the worst spectrum of the mitral valve arcade, where the chordae tendineae are fused and shortened.

It is believed that this anatomical complex primarily compromises the mitral and aortic valves, associated with endocardial fibroelastosis, leading to dilation of left chambers. Restricted left to right flow at the atrial level contributes to significant LA dilation which compresses the right chambers and increases central venous pressure. This seems to be the physiopathology of fetal hydrops, which is present in 70–80% of cases, with polyhydramnios being observed in 100% of cases described by Vogel et al.[44]

Aortic valve opening, in these cases, may reduce the degree of mitral regurgitation and LA pressure, and may treat or improve fetal hydrops and bring the gestation closer to term.[201] Opening of the atrial septum may be considered for the same procedure, potentializing the effects of aortic valvuloplasty. Besides the intervention, this is a very severe clinical condition, which has a significant impact on fetal and neonatal mortality.

8.5. Fetal Pulmonary Valvuloplasty

PAIVS is associated with variable hypoplasia of the right ventricle, tricuspid valve, and right ventricular outflow. The disease's most severe spectrum presents fibromuscular atresia of the infundibulum and pulmonary valve, with significant hypoplasia of the right ventricular cavity and the tricuspid valve, associated with abnormal coronary circulation. Contrastingly, in the more favorable spectrum, the pulmonary valve atresia is membranous; the tricuspid valve annulus diameter and the right ventricular volume are close to normal, and there is an absence of abnormalities in the coronary arteries. Some cases of critical pulmonary stenosis observed during fetal life may evolve to total flow interruption between the right ventricle and the pulmonary artery, with consequent hypoplasia of the right ventricular chamber. These cases behave similarly to PAIVS with mild to moderate hypoplasia of the right ventricle.[214]

The goal of fetal intervention in cases of PAIVS and critical pulmonary stenosis is to promote growth and functional development of the right ventricle and to increase the chances of biventricular circulation during the postnatal period. The identification of potential candidates for the procedure should be based on the risks of the fetus' evolving to univentricular circulation without fetal intervention and the possibility of changing this progression.[198] The selection of candidates for intervention should follow the criteria previously described in the "Indications" section. Another important criterion in this decision is the presence of signs of fetal heart failure characterized by reverse "a" wave in the ductus venosus flow, which denotes increased right atrium pressure and possible fetal hydrops development. This hemodynamic condition is observed in fetuses who have significant tricuspid regurgitation and very reduced right ventricular compliance.[215]

From the technical point of view, this intervention is more difficult and challenging than aortic valvuloplasty. Due to the reduced dimensions and hypertrophy of the right ventricle, associated with its anatomical characteristics (outflow located anterior and far away from inflow), the positioning of the needle below the pulmonary valve requires very experienced and skilled fetal specialist. The RV puncture should be performed as far as possible from the outflow. In cases with valve atresia, the guidewire utilized should have a slightly firmer tip, in order to allow the interventionist to perforate the valve.[201] Some authors prefer to introduce a thinner needle through the first one to perforate the valve or proceed the valve perforation with the 17 G needle itself.[200] After reaching the pulmonary artery, the guide is positioned in one of the pulmonary branches or across the ductus arteriosus, to provide balloon support. For this intervention, the same balloon:annulus ratio as fetal aortic valvuloplasty is employed. The result of the intervention is evaluated by observing the anterograde flow through the pulmonary valve, the reduction of reverse flow through the ductus arteriosus, and the presence of pulmonary insufficiency. Pulmonary insufficiency is a marker of success, and it decreases as gestation advances. Restenosis during fetal life is commonly observed. Most cases will require a new valvuloplasty during the neonatal period.[200,216,217]

In many cases, total recovery of the right ventricle does not occur at birth, making accessory pulmonary flow necessary, either with ductus arteriosus stenting or surgical confection of a systemic to pulmonary shunt (modified Blalock-Taussig).[201]

8.6. Fetal Atrial Septostomy

Although HLHS neonatal survival continues to improve worldwide and, slowly in Brazil, some anatomical and functional aspects are risk factors for poor clinical outcome and neonatal or postoperative

death.[218] The presence of an intact atrial septum or severely restricted foramen ovale represents one of the worst risk factors of neonatal mortality. It causes deep hypoxemia after birth and pulmonary hypertension (venocapillary) triggered by pulmonary vein arterialization.[218]

In this condition, resuscitation maneuvers are usually ineffective. Some hospitals recommend emergency Norwood operation, with mortality affecting 83% of patients by the sixth month of life. Even in those who underwent immediate neonatal atrial septostomy, mortality exceeds 48%.[218,219] These deaths are usually not directly related to the procedure and end up occurring after the first week of life.[196] It is believed that, in addition to deep neonatal hypoxemia, anatomical abnormalities secondary to in utero venocapillary hypertension are related to mortality. In these cases, anatomopathological studies have demonstrated arterialization of the pulmonary veins associated with lymphatic vessel dilatation.[219-221] It is estimated that the incidence of severely restrictive foramen ovale or intact interatrial septum associated with HLHS occur in 6% of cases, with some degree of restriction affecting, at least, 22% of patients.[219]

Left atrial decompression during fetal life seems to be essential to the prevent poor immediate neonatal clinical presentation and the remodeling of the pulmonary vascular bed.[196] The main echocardiographic marker of significantly restricted foramen ovale during fetal life is the presence of high-velocity reverse flow in the pulmonary vein Doppler tracing, which shows an abnormal bidirectional pattern.[45] This finding indicates that blood is returning to the lungs during atrial contraction, because the LA cannot decompress to the left ventricle or the right atrium.[189]

It is very important to examine at least one pulmonary vein with pulsed-wave Doppler during the echocardiogram of a fetus with HLHS.[222] The echocardiographer must have in mind that this piece of information may significantly change these patients' outcome and the pre- and postnatal management. Other important features in this condition are pulmonary vein and LA dilation, atrial septum bulging into the right atrium, absent or minimal high-velocity flow across the interatrial septum.[189]

The ideal moment to perform atrial septostomy is discussed.[196,223] Intending to prevent definitive damage to the pulmonary circulation, the intervention should ideally be performed immediately after the diagnosis. On the other hand, from the technical point of view, it is rather difficult to create an orifice in the interatrial septum that lasts for multiple weeks and prevent severe neonatal hypoxemia. It appears to be consensual that the ideal moment is between the 28th to the 33rd weeks of gestation when the fetus is of good size. During this period, it is feasible to use larger balloons with greater capacity to open wider orifices in the interatrial septum.[190,197]

The use of stents in the interatrial septum has also been considered by some authors.[224,225] This procedure appears to be more challenging than atrial septostomy, mainly due to the difficulty of optimally positioning the stent in the septum. One of the main problems is to visualize the stent inside the metallic needle via ultrasound. Stent implantation is particularly interesting when the interatrial septum is very thick and, thus, does not allow for the opening of an orifice that is wide enough to alleviate pressure in the LA. Due to the profile of needles available for fetal interventions, the largest stent used is 3 mm, which may, in some cases, reach an internal diameter of 3.5 mm.[39,40] The rate of poor positioning and embolization is high, according to recent publications. In cases of embolization, the stent is buried in the atrium, without further complications, and the procedure may be completed with the septostomy.[224,225]

8.7. Final Considerations of Fetal Cardiac Interventions

With the development of fetal cardiac interventions, several important principles have been recognized. Technical success of the procedure does not always translate to clinical success after birth. Understanding the natural history of the malformation and continuously refining the criteria for patient selection are absolutely critical when one consider the creation of an invasive fetal cardiology program which includes potentially risky procedures. It is important to recognize that the majority of CHD are not fatal, and classic palliative treatment during the neonatal period is an option in many situations. However, for some anomalies whose natural history may be changed for the better, or for those with extremely severe prognoses, fetal intervention may be a therapeutic option. Table 8.3 indicates the class of recommendation and level of evidence for the different fetal cardiac interventions adapted form the Fetal Cardiology guidelines published by the AHA in 2014.[17]

9. Acknowledgments

These guidelines are the result of the work of many people whose intellectual, creative, "informatic," and executive efforts, combined with those of the authors, constitute the basis of this document. Unfortunately, because of editorial reasons, it is not possible for all of them to appear among the authors who represent each group. The authors thank them here formally for their

Table 8.3 – Aim and effects of fetal interventions

Anomaly	Intervention aim	Effect	GOR/LOE
CAS with impending HLHS	Open the Ao valve to promote anterograde flow, stimulate left structure growth, create possibility of biventricular correction	Disease modifying	IIb/B
HLHS with intact IAS or restrictive FO	Open IAS to alleviate left atrial hypertension, prevent pulmonary vasculopathy, improve oxygenation at birth	Lifesaving	IIb/C
CAS with significant mitral regurgitation and giant LA	Open Ao valve and/or IAS, alleviate left atrial hypertension and prevent pulmonary vasculopathy, improve oxygenation at birth	Lifesaving	IIb/C
PAIVS or CPS with evolving RV hypoplasia	Open pulmonary valve to promote right structure growth and lead to possible biventricular repair; treat fetal hydrops in cases of severe tricuspid regurgitation	Disease modifying and/or lifesaving	IIb/C

Ao: aortic; CAS: critical aortic stenosis; CPS: critical pulmonary stenosis; FO: foramen ovale; GOR: grade of recommendation; HLHS: hypoplastic left heart syndrome; IAS: interatrial septum; LA: left atrium; LOE: level of evidence; PAIVS: pulmonary atresia with intact interventricular septum; RV: right ventricle. Source: Adapted from Donofrio et al.[17]

invaluable contributions and consider them co-authors. Their names, in alphabetical sequence, are:

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Updated Geriatric Cardiology Guidelines of the Brazilian Society of Cardiology – 2019

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Note: The purpose of these Guidelines is to inform. They do not substitute the clinical judgment of doctors who, in final analysis, must determine which treatments are appropriate for their patients.

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Content

1. General Aspects of Old Age, Risk Factors, and Prevention

1.1. Demographic and Epidemiological Aspects

Since the second half of the 20th Century, survival has been democratized in numerous countries around the world. This means that more people are reaching more advanced ages. In Brazil, in 1980, of every 100 female live births, 30 could be expected to reach their 80th birthday; in 2013, this number increased to 55. The average lifespan of the Brazilian population, consequently, increased nearly 12 years during this period. One of the factors responsible for this phenomenon was the decrease in advanced age mortality, which was the result of the control of theretofore lethal diseases. However, many of these diseases that ceased to be lethal are still not curable. As a consequence, the aged population, which continues aging and becomes more heterogeneous, has grown. This heterogeneity is due to differentiated gender, age, and epidemiological profile, among other factors. For example, of the approximately 26 million people age 60 or over, 56.4% were women, and 13.8% were age 80 or over. It is worth highlighting that not only is the aging process expected to increase, but the aged populated itself is also expected to age further. Or be it, the population age 80 or over is the one that grows the most, given the reduced mortality in this age group[1] (Table 1). It is known that advanced age leads to the need to live with chronic, incapacitating diseases, which may compromise individual autonomy. In 2013, only 22.3% of elderly Brazilians declared that they had no chronic diseases. Approximately half, 48.6%, declared that they had 1 or 2 diseases, and 29.1% declared 3 or more. Women have a

higher likelihood of contracting a disease than men, 81.2%, compared to 73.1%. This higher proportion of women in the elderly age group means a higher proportion of people with chronic morbidity[1] (Table 2). Within diseases reported, cardiovascular diseases (CVD) are predominant. For example, 62.0% of men and 67.4% of women declare that they have hypertension, and 23.2% and 36.9% of men and women, respectively, declare high cholesterol. These diseases also constitute the main cause of death in the elderly population, accounting for 34.2% and 35.2% of deaths in men and women, respectively. Within CVD, acute myocardial infarction (AMI) and stroke stand out[2] (Tables 3 and 4).

This indicates a greater need for prevention, with lifestyle changes, alcohol and tobacco control, better diet, and physical exercise being able to contribute to a reduction in CVD. In summary, it is possible to affirm that humanity seems to be making the dream of long life come true, but it is necessary to avoid the Tithonus trap. Tithonus was a mythical Trojan hero who was granted eternal life; he forgot, however, to ask for eternal youth. Eventually he was transformed into a cricket. Ulysses, on the other hand, declined the gift of immortality, Ulysses, on the other hand, declined the gift of immortality, preferred remain owner of his destiny and his soul (Homero). Or be it, living a long life, with autonomy, should be humanity's dream.

1.2. Interpretation of Frailty

Frailty is a biological syndrome characterized by decreased homeostatic reserve and resistance to various stressors. It results in cumulative decreases in multiple physiological systems and leads to increased vulnerability and unfavorable clinical outcomes, such as falls, impaired mobility and functional decline, hospitalization, institutionalization, and a higher risk of death.[3] This state of vulnerability causes an apparently minor injury (e.g., infection, introduction of a new medication, or even a small surgery) to lead to an evident, disproportional change in the patient's state of health; these changes may by exemplified as alterations from independent to dependent status, from able to move to immobile, from balance and stable gait speed to risk of falling, or from lucid to delirious.[4,5]

There is an overlap, but not a concurrence in the incidence of frailty, incapacity, and multimorbidity (coexistence of two or more chronic diseases). Although they are less frequent, there are frail individuals who have neither incapacity nor multimorbidity.[4] Sarcopenia (decreased muscle mass and function) is a component of the syndrome of frailty, which is more multifaceted and complex than sarcopenia alone.[5]

Clinical presentation results not only from a single well defined disease, but rather from the accumulation of impairments in multiple organic systems, and it occurs when the accumulated effects of these impairments compromises the organism's compensatory capacity. A systematic review demonstrated that the prevalence of frailty among community-dwelling elderly people was 10.7% (varying from 4.0% to 59.1%).[6]

In CVD patients, frailty confers a 2-fold risk of death, and this effect continues after adjusting for comorbidities and age. Numerous studies have also demonstrated an increase in the prevalence of frailty among patients with CVD, such as coronary artery disease (CAD), heart failure (HF), heart valve

Table 1 – Percentage distribution of the elderly population by sex and age[1]

	Men	Women	Total
60 to 69	56.5	56.3	56.4
70 to 79	30.7	29.4	30
80 to 89	10.8	12.2	11.6
90 or over	2	2.1	2
Total	100	100	100

Brazil, 2013.

Table 2 – Proportion of elderly people with chronic diseases by number of pathological conditions[1]

	Men	Women	Total
None	26.9	18.8	22.3
1 to 2	49.4	48	48.6
3 or more	23.7	33.3	29.1

Brazil, 2013.

Table 3 – Main causes of death in the elderly population by age[2]

	Men	Women
Circulatory system diseases	34.2	35.2
Neoplasm	19	15.5
Respiratory system diseases	14.3	14.7
Endocrine, nutritional, and metabolic diseases	6.5	8.9
Poorly defined	6.2	6.2
Others	19.9	19.5
Total	100	100

Brazil, 2013.

Table 4 – Main causes of death due to circulatory system disease by sex[2]

	Men	Women
Acute myocardial infarction	26	21.4
Strokes not specified as hemorrhagic or ischemic	13.7	13.7
Heart failure	8.2	9.4
Others	52	55.5
Total	100	100

Brazil, 2013.

disease, etc. A higher risk of complications and mortality has also been identified in frail elderly patients who undergo cardiovascular interventions such as surgery and angioplasty.[7]

Frailty may potentially be prevented or treated, and many studies have demonstrated that exercise, protein/caloric supplementation, vitamin D supplementation, and reduction and optimization of polypharmacy may decrease levels of frailty, thus minimizing adverse outcomes and risks of interventions.[5,8]

The identification of frail elderly patients is advocated so that multidimensional interventions may be implemented, mainly physical and nutritional rehabilitation, which reduces or postpones adverse outcomes and provides risk prognosis. It is necessary to emphasize that the identification of frailty does not need to be seen as a reason to exclude or suspend treatment, but rather as a means of programming individualized, patient-centered interventions.[5,7]

Fried et al. (2001), in a longitudinal cardiovascular cohort study, identified the following manifestations for this syndrome: unintentional weight loss, muscular weakness, exhaustion (fatigue), decreased gait speed, and decreased degree of physical activity. Based on this, they proposed diagnostic criteria known as the "Fried et al. Frailty Phenotype",[3] or "Cardiovascular Health Study Frailty Screening Scale".[3,5] These criteria have been criticized, insofar as those referring to exhaustion and decreased physical activity are not objective and are difficult to evaluate in daily practice with elderly patients. Other indexes and scales for diagnosis have been proposed, such as Rockwood Clinical Frailty Scale,[9] the Gérontopôle Frailty Screening Tool,[10] the FRAIL scale proposed by Van Kan and Morley,[11] the Groningen Frailty Indicator,[12] the Tilburg Frailty Indicator,[13] the PRISMA-7 questionnaire,[14] the VES-13 Scale,[15] and the Edmonton Frailty Scale.[16] The latter five instruments have been transculturally adapted and/or validated in Brazil. Studies have demonstrated that the 5-meter gait speed test is a useful tool for evaluating frailty in elderly patients referred for percutaneous aortic valve implantation.[17,18] The incorporation of this tool into the Society of Thoracic Surgeons (STS) score improved its ability to predict adverse events. For a given STS score, the risk of mortality or morbidity was 2–3 times greater in patients with slow gait speed.[17,18] Regardless of the instrument used to screen and identify, the syndrome of frailty should be investigated in all individuals over age 70 and in elderly patients with CVD, even if they are below this age group, and prevention and treatment measures should be put into practice.[5,7,8]

1.3. Particularities in the Evaluation of Elderly Patients

Aging is a risk factor for most CVD, as well as numerous comorbidities, making the elderly the most heterogeneous and most complex adult age group.[19] Generally speaking, the healthcare system is poorly prepared to attend patients with multimorbidities, given that they require greater individualization, as well as assistance from a multiprofessional team that works integratedly.[20,21]

Interventions which are clearly beneficial in adults are, generally, also beneficial for elderly patients. However, the peculiarities which exist regarding evaluation of elderly patients are fundamental for their individual treatment. The evaluation of elderly patients should be performed using the Broad Geriatric Assessment (*Avaliação Geriátrica Ampla*, AGA).[22] This is a multidimensional, generally interdisciplinary, diagnostic process for determining impairments, inabilities, and disadvantages in elderly patients and, thus, planning their medium- to long-term care and assistance. The AGA prioritizes functional status and quality of life, facilitating communication between interdisciplinary team members. It should be applied to frail elderly patients and patients with multimorbidities. The AGA is also an important predictor of unfavorable outcomes, i.e., it has prognostic value for surgery, oncology, and orthopedic patients.[22] The AGA is fundamental in the context of evaluating elderly patients. It includes, at least, 4 principal dimensions, which are functional capacity, medical conditions, social functionality, and mental health.[22]

Independent elderly patients with a long life expectancy should be treated comprehensively in a manner that combines prevention and intervention. On the other hand, pre-frail and frail patients require more attention regarding their individual needs and priorities, as well as risk-benefit assessment for individualized therapeutic decisions.[19,20] Goals to be reached should, equally, depend on functional status, without contraindicating any treatment whatsoever exclusively on account of age.

Considering the high prevalence of multimorbidities and the high evolution of therapeutic options, polypharmacy has become very frequent in elderly patients, posing further challenges to case management.[19,20] Understanding the advantages and disadvantages of every treatment is fundamental to adequate elderly treatment. This may only be scaled through the AGA. Familiarity with the AGA is, thus, essential to the evaluation and introduction of a determined treatment in an elderly patient.[21,22]

1.4. Particularities in the Treatment of Elderly Patients

In treating elderly patients, priority is given to the patient who is ill, rather than to the illness, and to controlling the disease, rather than curing it. It is essential to know the disease, the patient who has the disease, and the treatment. CVD is frequent, and, even when there are few manifestations, it brings increased risks; elderly patients with diseases present comorbidities and high biopsychosocial vulnerability; treatments are more susceptible to undesired effects. Thus, evaluation of multiple clinical and psychosocial domains is fundamental. Owing to the fact that evidence is often lacking, conduct should be individualized. Decisions should be shared, and it is necessary to consider risk-benefit ratio and life expectancy. In elderly patients, treatment indication requires more caution. Although therapeutic goals are less precise, excluding them solely on the basis of age implies omission.[23-26]

Orientations regarding lifestyle changes are recommended, as in younger age groups. This may, however, cause undesired effects, especially if the changes are misunderstood or misapplied. Changing old habits requires attention.

Pharmacological treatments should: prioritize conditions and restrict number of medications, simplify posology, evaluate and stimulate satisfactory adherence even in secondary

prevention following AMI,[26] provide orientation regarding problems related to self-medication, consider modifications in pharmacology related to age which, generally, recommend reducing doses, and evaluate possible drug interactions, given that "polypharmacy" is common. Beers Criteria, informally known as the "Beers List," are a reference on safety in prescribing medications to the elderly. They were created in 1991, by the geriatrician Mark H. Beers, and they are periodically revised, the 2015 version being the most recent.[27]

In the United States, more than one third of emergency room visits due to adverse effects of substances occur in individuals over age 65. They imply hospitalization of more than 40% of cases, and this frequency is increasing over time. Of these visits, nearly 60% were related to the use of anticoagulants, antidiabetic agents, and opioid analgesics, and nearly 2% were related to restricted use medications, in accordance with the Beers Criteria.[28]

Recently, the Food and Drug Administration Adverse Event Reporting System (FAERS) drew attention to evaluating the eventual need for regulatory action for the following: the anticoagulants apixaban, edoxaban, rivaroxaban, and dabigatran, due to reports of vasculitis; ivabradine, due to potential signs of ventricular arrhythmias; and midodrine, due to reports of interactions with monoamine oxidase inhibitors (MAOI) which could trigger a stroke.[29]

Interventional treatments should be carefully based on criteria, with the participation of heart teams, and performed by experienced and qualified teams, given that they present more frequent and severe complications.

A noteworthy example of this scenario is the need for hospitalization and admission to skilled nursing facilities in 4 of every 5 elderly patients who received an implantable cardioverter-defibrillator for secondary prevention of sudden cardiac death, even though they survived at least 2 years.[30]

1.5. Diabetes Mellitus in Elderly Patients

The National Health Survey conducted by the Brazilian Institute of Geography and Statistics (IBGE, 2013) showed a 19.9% prevalence of diabetes mellitus in individuals in the 65–74 age group.[1] In diabetic adults, there is an increase in mortality and a decrease in functional capacity with consequent increase in the risk of institutionalization.[31] The presence of multimorbidities and comorbidities associated with this group's high heterogeneity means that the elderly are often excluded from randomized clinical trials, making disease management more difficult in this population.[31,32]

Diagnostic criteria for diabetes mellitus in the elderly are similar to those in younger populations: (1) fasting blood glucose ≥ 126 mg/dL; or (2) random blood glucose ≥ 200 mg/dL, associated with disease symptoms; or (3) blood glucose 2 hours after a 75-g glucose load ≥ 200 mg/dL; or (4) glycated hemoglobin (HbA1C) ≥ 6.5% (provided that the laboratory is standardized). The American Diabetes Association (ADA) recommends that individuals who are overweight as a risk factor and all adults ≥ age 45 be screened for diabetes every 1 to 3 years, with fasting blood glucose, glycated hemoglobin dosage, or oral glucose tolerance test, for the benefit of early diagnosis, early treatment, and prevention of complications.[31]

Elderly individuals with diabetes are at a higher risk of developing geriatric syndromes, such as polypharmacy, cognitive impairment, urinary incontinence, falls, and chronic pain. When individuals with these syndromes develop diabetes, their clinical condition worsens. Thus, in addition to screening for complications, multidimensional evaluation of elderly diabetic individuals is also fundamental. It becomes imperative to perform AGA with mental, functional, nutritional, and social evaluations for these individuals in order to define goals to be met for each patient.[32] The objective should be defined between two options: intensive blood glucose control, with less progression of chronic complications; or standard blood glucose control, in order to avoid only symptoms of hyperglycemia and acute complications.

The United Kingdom Prospective Diabetes Study (UKPDS), although it excluded elderly patients, showed the benefits of intensive blood glucose control in individuals as they age, with posterior follow-up.[33,34] There are 3 main randomized clinical trials with the participation of elderly patients and intensive blood glucose control. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study was interrupted due to mortality in the youngest group; however, hypoglycemia and other adverse effects of treatment were more common in elderly patients;[35,36] in the Action in Diabetes and Vascular Disease: Preteraax and Diamicron MR Controlled Evaluation (ADVANCE) study, the risk of hypoglycemia and hospitalization increased significantly;[37] and in the Veterans Affairs Diabetes Trial (VADT) study, there were no benefits, with the exception of decreased progression of microalbuminuria.[38] Two retrospective studies (U.K. General Practice Research Database, 2009[39] and The Diabetes and Aging Study, 2011) show a U-shaped curve relating mortality and blood glucose levels.[40] Individualization of treatment is, thus, imperative in elderly patients in accordance with their clinical, functional, and life expectancy profile, as demonstrated in Table 5, with treatment goals for arterial hypertension and dyslipidemia in elderly patients with diabetes.

1.6. Tobacco Use

The influence of tobacco use in elderly individuals occurs due to anatomical and physiological alterations in a cumulative process which leads to endothelial dysfunction, increased platelet adhesion, decreased high-density lipoprotein cholesterol (HDL-c), and increased low-density lipoprotein cholesterol (LDL-c), among other alterations.[41] Tobacco use is common in the elderly population, and it is an important cause of morbidity and mortality, including CVD, peripheral vascular disease, cerebrovascular disease, cancer, and obstructive pulmonary disease. On the other hand, the tobacco cessation has benefits, even in elderly patients, with respect to the prevention of these diseases or, at least, to slowing the decline of pulmonary function.[42] The Systolic Hypertension in the Elderly Program Study[43] observed patients with an average age of 72 and showed a significant increase in AMI, sudden death, and stroke in smokers, compared with non-smokers. Exposure to long periods of passive tobacco use increases the risk of developing CAD. Kawachi et al. (1997)[44] followed 32,000 non-smoking women, between the ages of 36 and 71, for 10 years, and found that the relative risk of developing coronary heart

Table 5 – Treatment goals regarding blood glucose, and dyslipidemia in elderly patients with diabetes

Patient characteristics/ health status	Rationale	Reasonable HbA1C goal	Fasting or preprandial blood glucose (mg/dL)	Bedtime blood glucose (mg/dL)	Blood pressure (mmHg)	Lipids
Healthy (few coexisting chronic diseases, cognitive and functional state intact)	Long life expectancy	< 7.5%	90–130	90–150	< 140/90	Statin, provided there is no contraindication or intolerance
Complex/intermediate (multiple coexisting chronic diseases, impaired IADL, or mild to moderate cognitive impairment)	Intermediate life expectancy, high treatment burden, vulnerability to hypoglycemia, fall risk	< 8.0%	90–150	100–180	< 140/90	Statin, provided there is no contraindication or intolerance
Very complex/ poor health (long-term care or end-stage chronic disease, moderate to severe cognitive impairment, or 2+ BADL dependencies)	Limited life expectancy makes benefit uncertain	< 8.5%	100–180	110–200	< 150/90	Consider the probability of benefits of statin (secondary prevention, rather than primary)

BADL: basic activities of daily living; HbA1C: glycosylated hemoglobin; IADL: instrumental activities of daily living. Source: American Diabetes Association. Older adults. Diabetes Care. 2017; 40 (suppl.1):S99-S104.[32]

disease increased in women exposed to smoking. Occasional exposure to cigarettes increased their relative risk by 1.58, and regular exposure increased the relative risk by 1.91.[45] Tobacco use constitutes a risk factor for dementia, and cessation may reduce the burden of dementia. Passive exposure to smoking may also increase the risk of dementia.[46] Studies show that elderly smokers have a lower intention of quitting in comparison with younger smokers; they have, on the other hand, a higher likelihood of success when they do try to stop smoking.[47,48] Success in stopping is frequently achieved after an acute coronary event, aggravation of chronic obstructive pulmonary disease (COPD), or symptomatic and limiting peripheral arterial disease. Medical advice to cease smoking should be firm, with emphasis placed on the short- and medium-term benefits. Aggressive practices related to tobacco cessation should be adopted.[49,50] Evidence shows the efficiency of using the 4 As method in elderly patients, namely: ask, advise, assist, and arrange follow up.[51,52] Different approaches, such as interventions through individual counseling performed by healthcare professionals, age-appropriate self-help material, use of nicotine (transdermal patches or chewing gum), or use of specific medications, e.g. bupropion), have also been shown to be efficient in treating tobacco use.[53-55]

Recommendations	Grade of recommendation	Level of evidence
Tobacco use is a modifiable risk factor for CVD in elderly individuals and cessation is recommended	I	C
Use of multidisciplinary approaches, with the 4 As Method, is recommended: ask, advise, assist, and arrange follow up	I	C
Nicotine/bupropion transdermal patches or chewing gum may be used to cease tobacco use	IIa	C

CVD: cardiovascular disease.

1.7. Obesity

The prevalence of overweight status and obesity has increased over the past decades in all age groups, including the elderly.[56,57]

Both obesity and overweight status have been associated with the risk of all cause and CVD mortality, in the general population.[58-60]

The majority of these studies mainly involved young adult patients, making this relationship less evident in the elderly.[61-64]

Some meta-analysis studies have reported that overweight and obese elderly individuals, when compared with elderly individuals within the normal weight range, had lower mortality rates and lower or no risk of CVD. This effect has been called the "obesity paradox".[65-67]

In addition to possible confounding factors in these studies, other reasons may be involved. The index used to measure and classify body mass was the body mass index (BMI). Degrees of obesity adopted by the World Health Organization (WHO), with respect to BMI, are: overweight (25.0 to 29.9 kg/m^2) and obese (over 30.0 kg/m^2).[68] Variables such as age, sex, and race may affect BMI. With aging, changes in body composition occur, such as increased visceral fat and decreased muscle mass. Loss of height may also occur, owing to compression of vertebral bodies or kyphosis. In this manner, BMI becomes less precise in measuring fat mass. When used alone, it is not able to be an accurate predictor of CVD risk in elderly patients. For instance, some elderly individuals may be considered overweight by body fat patterns without having a BMI over 25 kg/m^2.

Using BMI alone, we may be underestimating the degree of adiposity in individuals who lost muscle mass. Central obesity and nutrition are factors which seem more important in relation to mortality and CVD risk in this population. Some authors suggest that waist circumference (WC) could be a particularly important measure for elderly patients,

which would be better than BMI at evaluating risk, given its association with visceral adiposity.[69,70]

Another study indicates that the presence or absence of metabolic syndrome is more important than BMI in obese elderly patients, thus dividing this population into "healthy obese" (without metabolic syndrome) and obese with metabolic syndrome. The latter group has been strongly associated with increased risk of CVD regardless of BMI.[71]

More studies are necessary to clarify the interrelation between aging, obesity, and cardiovascular risk and what the best measures parameter(s) would be. Weight management in the elderly and efforts to promote healthy aging should be based on an individual approach, taking into consideration the maintenance of muscle mass and strength, comorbidities, functional and social status, physical activity, and quality of life. Intentional weight loss in obese elderly patients improves their cardiovascular risk profile, reduces chronic inflammation, and is correlated with improved quality of life. Unintentional weight loss requires careful clinical assessment of the underlying cause. Furthermore, the identification of elderly patients with sarcopenic obesity is relevant to prognosis. Sarcopenia and sarcopenic obesity have been associated with a higher risk of CVD, especially in elderly men with this type of obesity.

1.8. Sedentarism

Regular physical activity is essential to healthy aging. Considering that aging in inevitable, the rhythm and magnitude of decline in physiological function may be influenced by an intervention comprising exercise/physical activity (Table 6).[72,73]

Aging is associated with skeletal muscle mass loss; reduced muscle strength, flexibility, cardiac output, and pulmonary function; changes in hormonal and immune system regulation; reduced bone density, and higher prevalence and incidence of sedentarism.[74]

In sedentary elderly patients, walking may be a practical solution, evaluating heart rate (HR) before and after exercise. It is necessary to recognize that elderly people do not represent a uniform group of patients and chronological age in itself does not identify this special group.[75]

Sedentarism is an important risk factor for CAD in elderly individuals. Some studies demonstrate that the relative risk of CAD attributable to sedentarism is comparable to that of hypertension, hyperlipidemia, and tobacco use. Sedentarism, as an important risk factor, is, in most cases, directly or indirectly associated with the causes or aggravation of various diseases, such as obesity, diabetes, arterial hypertension, anxiety, depression, dyslipidemia, atherosclerosis, respiratory disease, osteoporosis, and cancer.[76,77] Systematic physical exercise helps control systemic arterial hypertension (SAH), by reducing peripheral arterial resistance, increasing HDL-c, reducing obesity and triglycerides, improving blood glucose control, preventing coronary disease, and decreasing mortality.[77,78]

Furthermore, it improves sleep quality, cognitive function, and short-term memory; decreases degree of depression; reduces or slows the onset of dementia; reduces the risk of colon, breast, prostate, and rectal cancer; increases bone density; and decreases the incidence of femur and vertebrae fractures.[77]

In elderly patients, pre-exercise clinical evaluation is very important. The goal of exercise and cardiovascular rehabilitation in elderly patients is to improve their functional capacity as much as possible. These objectives are reached through programs that aim to increase aerobic capacity, muscle strength, and flexibility.[72,79-82]

The amount of physical activity should be individualized, considering each patient's comorbidities and peculiarities.[73,74,79]

Elderly individuals should spend more time warming up before and cooling down after activity. The warm-up phase includes flexibility and movement exercises, which facilitate musculoskeletal biomechanics. The post-exercise cool-down phase allows for the gradual dissipation of body heat and consequent peripheral vasodilatation. Musculoskeletal injuries may be decreased by avoiding high impact activities, such as running and jumping. Extreme care is necessary for activities using free weights, given the risk of accidents, especially in less skilled or more frail elderly patients.[72,80] Walking briskly is an excellent way to obtain physical conditioning, with gradual increases in pace and distance covered.[81] Elderly patients should be instructed to reduce exercise intensity on humid or hot days, given that skin blood flow decreases with age, consequently lowering the efficiency of sweating and thermal regulation.[77] Practicing resistance exercise twice weekly is also recommended.

Pre-participation assessment should begin with patient history and clinical exam, focusing on the particularities of this population, which often has silent atherosclerotic disease. Complementary investigation should be oriented by clinical data, avoiding high costs, which are sometimes prohibitive and may discourage physical exercise. Resting electrocardiogram

Table 6 – Centers for Disease Control and Prevention exercise guidelines for adults over age 65

Substantial health benefits	2 hours and 30 minutes (150 minutes) of moderate-intensity aerobic activity per week Muscle strengthening activities 2 or more days per week 1 hour and 15 minutes (75 minutes) of vigorous-intensity aerobic activity
Additional health benefits	5 hours (300 minutes) of moderate-intensity aerobic activity per week Muscle strengthening activities 2 or more days per week 2 hours and 30 minutes (150 minutes) of vigorous-intensity aerobic activity

Adapted from: Centers for Disease Control and Prevention (CDC). Physical activities for older adults. Available at: www.cdc.gov/features/activity-older-adults/index.html. Accessed: 18/02/2016.

(EKG) for the elderly has limited application as a pre-selection exam for physical activity.

If possible, an exercise test (ET) should be performed in all elderly patients before initiating physical activity. The prevalence of coronary disease increases with age; the rationale behind the ET in this population may, thus, be even greater than in the general adult population.[72,79,80] The ET is a procedure during which the patient undergoes programmed and individualized exercise, with the aim of evaluating clinical, metabolic, hemodynamic, autonomic, electrocardiographic, and, eventually, ventilatory responses to exercise. In elderly patients, modified protocols are used to perform the ET.[79] If there are contraindications to performing the ET, stress EKG or scintigraphy should be performed. A Holter monitor is used to stratify risk in elderly patients with arrhythmias detected during EKG or ET, as well as those with a history of syncope.[72,82]

Adherence to physical activity in this group has been increasingly positive. It is always necessary to consider that an active or latent pathological process may by present in an elderly individual and that the ET may contribute to defining it.[83,84]

Recommendations	Grade of recommendation	Level of evidence
Clinical exam and electrocardiogram	I	C
Electrocardiogram, exercise test, or myocardial scintigraphy in medium-risk patients or in moderate to intense exercise	IIa	C
Physical exercise	I	A
Resistance exercise	IIa	C

1.9. Dyslipidemia in Elderly Patients

Dyslipidemia is a frequent diagnosis in elderly patients, mainly in women, owing to the fact that LDL-c levels tend to rise as they advance in age, especially after menopause; in men, however, LDL-c tends to decrease after age 55. Unlike in young adults, cases of de novo dyslipidemia are rare, and cases of dyslipidemia secondary to hypothyroidism (especially in women), diabetes mellitus, glucose intolerance, nephrotic syndrome, obesity, alcoholism, or use of medications such as thiazide diuretics and non-selective beta-adrenergic receptor blockers, are more common.[85]

In relation to treatment, as elderly patients are often already at high risks (owing to the factor of age), the approach to dyslipidemia, regarding therapeutic decisions, should give greater consideration to the patient's good general and mental state, his or her socio-economic conditions, family support, comorbidities present, and the use of other drugs that may influence adherence to and maintenance of therapy. Non-pharmacological orientations should follow the same principals of indication for young adults, more carefully observing caloric, protein, and vitamin intake needs and physical conditions for practicing exercise (recommendation I, evidence B). It is necessary to reiterate the importance of ceasing habits of smoking and excessive consumption of alcoholic beverages. After 90 days, if there is no response, drug treatment may be initiated, with the following precautions: (1) always start with low doses and, if necessary, increase, progressively; (2) analyze the cost-benefit ratio; and (3) verify the existence of socioeconomic conditions for maintaining long-term treatment and performing periodical clinical and laboratory exams, due to the higher likelihood of collateral effects and drug interactions.[85]

For hypercholesterolemia, statins are the first choice.[86] Tolerance is good; there is not a high incidence of undesired effects, even though muscle pain, cramps, and weakness, which are sometimes confounded with osteomuscular disease, may occur, even in low doses. Evidence from subgroup analyses in primary and secondary prevention studies and the Pravastatin in Elderly Individuals at Risk of Vascular Disease (PROSPER) study,[87] specially designed for elderly patients with or without previous manifestations of atherosclerosis, demonstrated the following benefits to treatment for this age group: reduction of coronary events (grade of recommendation IIa, level of evidence B), stroke (grade of recommendation IIa, level of evidence B), and preservation of cognitive functions (grade of recommendation IIb, level of evidence B). When maximum statin dosages are not sufficient to meet recommended LDL-c goals, ezetimibe may be associated with the statins (grade of recommendation IIb, level of evidence B).[88]

In cases of hypertriglyceridemia, fibrates are used (provided there are no gallstones or renal insufficiency). Fibrates and statins may be associated in cases of mixed dyslipidemia (elevated LDL-c and triglycerides), mainly with reduced HDL-c (grade of recommendation IIb, level of evidence D).[88]

In secondary dyslipidemias, the fundamental concern is treating the triggering disease and substituting or removing inductor drugs. We should remember that elderly individuals, generally, use other drugs metabolized by cytochrome P450 (CYP450), which have the possibility of interacting with lipid-lowering agents, thus altering their blood concentration (grade of recommendation IIb, level of evidence D).[88]

1.10. Depression and Cardiovascular Disease

Depression and anxiety are highly prevalent in individuals with CAD and other CVD. They have been also been considered independent risk factors for CAD and CVD, in addition to altering their natural history.[89,90]

Depression is disproportionally more frequent among CAD patients, with prevalence between 20% and 40%. It has also been reported that depression is prospectively associated with an increased risk of developing CAD,[91,92] including AMI,[93] at some point during life, as well as an increased risk of mortality.[94] A 60-month follow-up study of 158 patients who suffered AMI revealed that greater depression was a significant predictor of mortality and adverse cardiac events.[95]

Collateral effects of antidepressants on the cardiovascular system have been reported. These include bradycardia, tachycardia, hypertension, hypotension, orthostatic hypotension (OH), EKG alterations, altered electrolytes, reduced cardiac conduction, arrhythmias, and sudden cardiac death.[96]

1.10.1. Treating Depression and Anxiety in Patients with Cardiovascular Disease

First generation antidepressants include MAOI and tricyclic and tetracyclic antidepressants (TCA and TeCA, respectively); second-generation antidepressants include selective serotonin reuptake inhibitors (SSRI), selective norepinephrine reuptake inhibitors (SNRI), and atypical antidepressants.[89,96]

Even though MAOI (phenelzine, tranylcypromine, moclobemide, selegiline, etc.) are effective, they present several unfavorable collateral effects, mainly OH, tachycardia, and hypertensive crises; the latter are also associated with stroke and acute aortic dissection and should, thus, be avoided in patients with CAD.[89,96]

The cardiovascular collateral effects of TCA (imipramine, amitriptyline, nortriptyline, desipramine, clomipramine, doxepin, maprotiline, etc.) are fairly well known, namely, increased HR, OH, slowed cardiac conduction, and increased QT interval variability.[89,97] These effects, which have been reported not only in patients with CVD but also in people without previous cardiac disease, in addition to their anticholinergic action, make this class of drugs inappropriate for treating depression in elderly patients.[96]

SSRI (fluoxetine, sertraline, paroxetine, citalopram, escitalopram, fluvoxamine, etc.) are considered the medications of choice for treating depression and anxiety in most cases, due to their acceptable safety profile and higher margins of non-toxic levels in comparison with other classes of antidepressants.[89,96]

Regarding efficacy of SSRI in decreasing symptoms of depression, all meta-analyses of selected indicators have shown that these antidepressants are more effective than placebo.[98]

SSRI may cause prolonged QT intervals (reported mainly with fluoxetine and citalopram), but they do not generally lead to life-threatening arrhythmias in therapeutic doses. Citalopram appears to be the most cardiotoxic SSRI (conduction disturbances and arrhythmias).[96]

Most causes of prolonged QT interval and subsequent torsade de pointes (TdP) induced by SSRI are observed in patients with underlying vulnerabilities, such as congenital long QT syndrome, recent AMI, hypokalemia, or hypomagnesemia, or in cases of substance overdoses.[96]

Within this class, there is some evidence that escitalopram and sertraline have the best balance between effectiveness and acceptability for pharmacological treatment of depression in cardiac patients.[99]

In summary, SSRI probably do not cause adverse effects when used according to the recommended dosages, and it has been suggested that, through complex mechanisms, they may bring some benefits to the cardiovascular system, such as lower rates of AMI in comparison with other types of antidepressants, especially TCA.[96]

As there are still no robust clinical orientations, patient treatments should be individualized in relation to potential risks and benefits. Additional studies are necessary to verify the exact cardiovascular safety profile.[96]

Regarding selective serotonin and norepinephrine reuptake inhibitors (SSNRI) (venlafaxine, desvenlafaxine, reboxetine, duloxetine, etc.), venlafaxine is associated with severe cardiotoxicity, only when given in high doses. Left ventricular (LV) failure, even in patients with no prior history of CVD, has also been reported in the literature.[89,96] It is recommended to monitor blood pressure (BP) in patients who take SSNRI (especially venlafaxine), given that it has been reported to increase in epidemiological studies.[96]

Regarding atypical antidepressants (mirtazapine, agomelatine, nefazodone, trazodone, etc.), mirtazapine, in high doses, may cause hypotension and affect HR. Trazodone has minimal cholinergic activity; it may cause OH, and, in excess, prolonged QT and slowed atrioventricular conduction.[96]

In addition to pharmacological treatment, psychotherapy and the prescription of non-medical treatments, such as physical activity, especially aerobic exercise and cardiac rehabilitation, are also indicated. These improve prognosis and patient quality of life and reduce risks of evolution of CAD and CVD.[89,99]

1.11. Other Cardiovascular Risk Factors

Traditional risk factors explain only half of CVD cases, which present high morbimortality rates. Several studies have been developed to look for possible new risk factors, known as emerging risk factors, as well as means of early diagnosis of CVD by investigating signs of subclinical atherosclerosis. The emerging risk factors covered in these Guidelines are hyperuricemia, C-reactive protein (CRP), vitamin D, genetic factors, coronary calcium score (CCS), and investigation of subclinical atherosclerosis.

1.11.1. Hyperuricemia

Recent epidemiological studies have demonstrated that hyperuricemia is frequently observed in patients with CVD or high risks thereof, such as arterial hypertension, CAD, peripheral vascular disease, HF, and stroke.[100]

A recent meta-analysis of observational prospective studies on hyperuricemia and risk of stroke demonstrated a significant increase in the risk of stroke incidence and mortality, based on studies that adjusted traditional stroke risk factors, such as age, sex, hypertension, hypercholesterolemia, and blood glucose. Several pathophysiological mechanisms have been postulated, including endothelial dysfunction, oxidative metabolism, and platelet adhesiveness and aggregation. The role of hyperuricemia as an independent risk factor for CAD, however, remains controversial.[101]

1.11.2. C-Reactive Protein

The role of inflammation in the propagation of atherosclerosis and susceptibility to adverse cardiovascular events is well established. Even though CRP is involved in the immunological process which triggers vascular remodeling and platelet deposition and is associated with increased CVD risk, there is no definitive evidence for its role as a causal factor of atherothrombosis. The Jupiter study analyzed 9,261 elderly patients of both sexes, using ultrasensitive CRP (US-CRP) levels to determine whether or not they would receive rosuvastatin; the results were similar to those found in younger individuals, namely, a reduced occurrence of cardiovascular events.[102]

Notwithstanding the publication of guidelines on the use of US-CRP for predicting CVD risk by several professional organizations, there is still a lack of consensus regarding optimal clinical use of US-CRP.[103]

1.11.3. Vitamin D

Recent studies show evidence of a strong association between vitamin D deficiency and the presence of SAH, metabolic syndrome, diabetes, and atherosclerosis. It is thus considered an emerging risk factor for CVD.[104]

The mechanisms by which vitamin D exercises its role as a cardiovascular protector are still not well established. In the Third National Health and Nutrition Examination Survey (NHANES III), which involved 3,408 elderly patients, followed up for 7 years, after adjusting for cardiovascular risk, season of the year, and demographic data, verified that vitamin D levels are negatively associated with mortality risk, with this association being even stronger for cardiovascular mortality.[105]

A meta-analysis of 19 prospective studies with more than 65,000 patients demonstrated that the risk of all CVD, as well as cardiovascular death and CAD, was lower in patients with higher levels of vitamin D.[106,107]

1.11.4. Genetic Factors

Aging is characterized by the complex interaction of cellular and molecular mechanisms that lead to a series of functional problems. These problems are intimately associated with one another; they include poor vasodilatation, increased arterial stiffness, and evident extracellular matrix remodeling, diffuse carotid intimal thickening, and endothelial dysfunction.

The mechanisms by which age truly contributes to cardiovascular risk continue to be the object of speculation. Although this paradigm explains vascular aging, considering classic risk factors as causal mechanisms, a recently proposed alternative view on vascular aging has emerged, which presents new mechanistic alternatives for understanding the vascular aging process. In this new paradigm, causal mechanisms of the aging process in itself, most notably genomic instability, including telomeric wear, drive the harmful changes that increasingly occur with biological aging.[108]

1.11.5. Coronary Calcium Score

CCS represents an important risk marker for cardiovascular events, especially in predicting risk of AMI in subsequent years, with a score of 0 demonstrating an almost null possibility of coronary events in subsequent years. A score above 100, however, is considered an aggravating risk factor, and scores over 400 indicate a high risk of coronary events.[109]

Recommendations	Grade of recommendation	Level of evidence
Coronary calcium score	IIa	C

1.11.6. Investigating Subclinical Atherosclerosis

This is indicated to better stratify cardiovascular risk in elderly patients, with the aim of better identifying cases that will require more aggressive therapy. The Cardiovascular Health Study followed up elderly patients for 10 years and demonstrated that the subclinical atherosclerosis index was a better predictor of cardiovascular events than traditional risk factors in asymptomatic elderly adults. This index is composed of the ankle-brachial index (ABI), carotid artery stenosis, carotid intima-media complex thickness, altered EKG or echocardiogram, positive response to the Rose questionnaire or the intermittent claudication questionnaire.[110] Carotid artery ultrasonography is an important resource for evaluating elderly patients. Patients with carotid blockage of 50% or more are considered at a high risk of coronary events.[111]

Recommendations	Grade of recommendation	Level of evidence
Investigating subclinical atherosclerosis	I	C

1.11.6.1 Ankle-brachial index

Peripheral arterial obstructive disease (PAOD) is strongly related to coronary events, and it may be assessed by the ABI, a low-cost, easily applicable exam. ABI < 0.9 is positively associated with a higher number of coronary events and with death of cardiovascular etiology. Its indication is always applicable when there are alterations in the clinical exam which suggest peripheral arterial disease, as well as excluding intermittent claudication (grade of recommendation IIa, level of evidence C). The recommendations of a recent American scientific statement highlight the strong, consistent association of advanced age with PAOD prevalence and incidence. Age > 70 is an independent risk factor for developing PAOD involving lower extremities, notwithstanding other risk factors, with a prevalence rate of $> 20\%$ in men and women in this age group. Given the strong effect of age on the prevalence of PAOD, the statement endorses the use of ABI as a class I recommendation (level of evidence C).[112]

1.12. Aorta and Carotid Artery Disease

1.12.1. Thoracic Aortic Aneurysm

Bicuspid aortic valve (BAV) is the most frequent modality of congenital heart disease (1% to 2%), and it may occur with thoracic aortic aneurysm (TAA), with a high risk of undergoing expansion. As many as 50% of patients with BAV develop ascending aorta dilation. Factors that contribute to progression of TAA in the presence of SAH include obesity and increase in age. As these 3 conditions are frequently present together in elderly adults, TAA has been underdiagnosed in this age group. It is estimated that TAA is present in at least 3% to 4% of elderly individuals.

Patients with TAA are in primary prevention. One of the complications of TAA is acute dissection, whose frequency is 2 times higher in men than in women. Rupture, however, is responsible for 60% of deaths attributed to TAA.

Current guidelines consider a cutoff point for surgery indication for ascending TAA of 5.5 cm for patients without Marfan or BAV and 5.0 cm in the presence of one of these clinical conditions (Table 7). TAA with diameters ≥ 4 cm

require annual measurement, preferably by angiotomography (gold standard, but subject to radiation) or magnetic angioresonance. In non-genetic cases of TAA of ≥ 5 cm, measurements should be performed biannually. EKG tends to underestimate aorta caliber.[113-116]

Elective TAA surgery mortality in highly specialized centers is 2.9%. The risk of stroke or paraplegia is much higher in descending aorta. In this case, the option of endovascular intervention, with stent collocation, presents lower risk of paraplegia.

1.12.2. Abdominal Aortic Aneurysm

Abdominal aortic aneurysms (AAA) tend to affect elderly individuals (≥ age 65) and are atherosclerotic in nature; in this manner, AAA places patients in secondary prevention. Tobacco use is the main etiological factor of AAA, which is 3 to 5 times more common in smokers than in non-smokers. AAA is also common in patients with peripheral arterial disease (PAD).[115]

AAA is found in 1.3% of men between the ages of 45 and 54, and in 12.5% of those between the ages of 75 and 84. In women, the maximum prevalence was 5.2% in the elderly age group, being found in 0% of young women. The fact that men smoke more than women likely contributes to this pronounced difference between age groups by sex. This notwithstanding, evolution and prognosis of AAA are worse in women.[113-115]

Initial discriminatory evaluation by ultrasonography is recommended, especially in male patients who have been smokers, starting at age 65. In the event that the result is normal, there is no need for periodic reevaluation.[113-115]

AAA with diameters of ≥ 4 cm require annual measurement, which may only be performed by abdominal ultrasonography, which, in this area, has excellent sensitivity and specificity. If it is ≥ 5 cm, screening should be performed biannually. The cutoff point for indicating intervention is 5.5 cm. Open surgery poses a higher risk, but it lasts longer and should preferably be indicated in younger individuals with longer life expectancy. Endovascular intervention has evolved considerably and should preferably be indicated in older patients or patients considered high risk for surgery.[113-116]

1.12.2.1. Carotid Arteries

There is no solid evidence regarding the eventual advantage of interventional treatment in intensive clinical control of cardiovascular risk factors, especially if we consider the use of full dosages of latest generation of statins, although many services opt for aggressive treatment, based only on registers and specialist opinion.[117,118]

Table 7 – Threshold diameters for indicating aortic aneurysm surgery, according to current guidelines

Aorta	Marfan/BAV	Non-marfan
Ascending	5.0 cm	5.5 cm
Descending	6.0 cm	6.5 cm

BAV: bicuspid aortic valve.

Routine carotid ultrasonography is only indicated for patients who have suffered stroke/transient ischemic attack (TIA), or when physical examination identifies decreased, absent, or asymmetric pulse or carotid murmur.

1.12.3. The Original and 10-Year CREST Studies

The original Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST) study (n = 2,502) aimed to observe the medium- and long-term reduction in risk of ischemic stroke associated with carotid endarterectomy (CEA) and angioplasty with carotid-artery stenting (CAS) in patients with significant carotid atherosclerotic disease. The proportion of cerebrovascular asymptomatic patients and of those who had suffered stroke/TIA was very similar. The main study objective was to evaluate the risk of death, AMI, or stroke during the first 30 days after the procedure and of ipsilateral stroke during the following 4 years. They did not, however, find an optimized clinical treatment group. The risk of minor stroke was higher in the CAS group during the first 30 days, whereas the risk of AMI was higher in the CEA group. At the end of the 4-year period, the risk of stroke was low and similar in both groups analyzed (2.0% and 2.4%; p = 0.85). The main conclusion was that both CEA and CAS may be alternatively indicated as interventional carotid treatments. Additional findings suggest that CEA seems to be more beneficial in elderly patients, while CAS would be more useful in subpopulations under age 65.[117]

The main lesson of the 10-year CREST study was that, once the initial critical phase was over, patients who underwent interventional treatment tended to evolve very well long-term. The 10-year risk of stroke was 6.9% in the CAS group and 5.6% in the CEA group, with no significant statistical difference (p = 0.96). The primary composite endpoint (death, AMI, and stroke) occurred in 11.8% of participants in the CAS group and in 9.9% of those in the CEA group, with no statistical difference (p = 0.51). Nevertheless, the primary composite endpoint death/stroke over 10 years was worse in the CAS group (11.0% vs. 7.9%; hazard ratio [HR]: 1.37%; p = 0.04).[118]

The Asymptomatic Carotid Trial (ACT) 1 study (n = 1,453) included patients with significant asymptomatic carotid disease, randomized into interventional treatment by CEA (n = 364; 25%) or CAS (n = 1,089; 75%). Elderly patients > age and those who had suffered stroke/TIA during the past 180 days were excluded. The carotid anatomical pattern was required to be viable for both procedures, with a minimum degree of stenosis of 70% diagnosed by either ultrasonography or angiography.[119,120]

The main objective was to demonstrate the noninferiority of CAS to CEA in relation to a composite endpoint, represented by death, AMI, and stroke during the first 30 days and ipsilateral stroke within 1 year. The results during 30 days showed that the incidence of this endpoint was only 2.95%. There were more cases of stroke and stroke or death in the CAS group and more cases of AMI in the CEA subgroup. The risk of major stroke was low (0.4%) and mortality was 0.2%. Medium- and long-term survival free of stroke was excellent in both groups, 97.5% over 1 year and 93.9% over 5 years. In 5 years, 97.5% of participants did not require carotid reintervention, and total mortality was 11.8%.[119]

1.12.4. Precautions and Recommendations

The main problem with interventional carotid treatment lies in the risk of death, AMI, or stroke inherent in the procedures per se, which extends to 30 days after intervention. Once this phase has passed, the annual risk of stroke or need for reintervention is considered low.

Intervention by CEA or CAS in patients with asymptomatic carotid disease dos not have a solid base for recommendation in comparison with optimized clinical treatment, and it should preferably be avoided at this moment until studies currently underway help to definitively answer this important question (CREST 2 and ACST-2).[121-123]

More than 90% of carotid interventions in the USA currently involve asymptomatic cerebrovascular patients. In Germany and Italy, these indexes are 60%; in Australia and Canada, 15%; and in Denmark, 0%.

The annual risk of stroke in asymptomatic patients with significant carotid disease receiving only clinical treatment has reached values as low as 0.5%, or be it, the same index documented in the ACT-1 and the 5 and 10 year CREST studies.[122,123]

Contrary to what has been admitted by some guidelines, it is here suggested that interventional carotid treatment be reserved for symptomatic patients (stroke/TIA over the past < 6 months), and that it be indicated for asymptomatic patients only when the degree of stenosis is between 70% and 99% in spite of optimized clinical treatment, and when there is proof that a large cerebral area is at risk or plaque-related microembolism, obtained by imaging exams and cerebral blood flow evaluation.[121-123]

1.13. Evaluation of Surgical Risk In Elderly Patients

The elderly population is currently growing more than any other. For this reason, a significant increase has been observed in the number of surgical procedures in this age group. The number of surgical procedures in people over age 65 is estimated to be 4 times higher than in the younger population.[124] The prevalence of symptomatic and asymptomatic CVD increases progressively with age, as shown in the results of many studies which suggest that age ≥ 80 is an independent predictor of perioperatory complications and death in patients who undergo non-cardiac or cardiac surgery.[125] Few studies, however, include elderly individuals over age 70 and the results are, generally, extrapolated from younger to older populations, ignoring the latter's particularities.[126]

Clinical evaluation in the elderly population should consider biological processes underlying so-called normative aging, such as physiological decrease in multiple organic functions which may cause inadequate responses to anesthetics, analgesics, and other substances administered and also lead to the appearance of cardiovascular complications, hemorrhagic or neuropsychiatric accidents, et al. It is mandatory to evaluate associated comorbidities and their repercussions on nutrition, overall functionality, independence, and healthy life expectancy, as well as all medication in use, in order both to prevent possible complications and to choose the most adequate procedure for each case.[127]

As a general rule, the establishment of a patient's surgical risk should be individualized and the bioethical principle of patient autonomy should be respected in all patient decisions or, in the event of impossibility, those of the patient's legal representative, following adequate clarification regarding the risks inherent in the disease and the surgical procedure, during the intraoperative and immediate and late postoperative periods, and the quality of life expected to result from the treatment. It is necessary to document the patient's and/or legal representative's decision in the medical records.[128]

With these considerations, surgical risk should be established based on a "tripod" comprising: (1) nature and character of the surgery; (2) functional capacity; (3) patient risk profile.

The new guidelines have established that elective and minor surgeries where the possibility of heart attack or major adverse cardiovascular events is ≤ 1% are low risk; when the possibility is ≥ 1% they are considered high risk. More recent publications have incorporated intermediate or high risk.[129] Patients indicated for urgent surgery should have their risks established when possible, using information provided by the family or the patients themselves, and then be referred to the surgical center. In the event of elective surgeries where the patient's hemodynamic conditions are not stable, they must be treated before establishing status and choosing the most opportune moment to perform the operation.

Patient functional capacity is a valuable indicator of risk of complications during the course of surgery and the postoperative period. The ability to ascend 2 stories by stairs or by ramp or to walk at a velocity of approximately 4 mph on a level surface corresponds to a metabolic equivalent (MET) ≥ 4, which indicates a good cardiovascular reserve and regular physical capacity; MET ≥ 10 is considered very good.

The last step in this strategy is to establish the patient's risk profile based on his or her clinical history, symptoms, signs, and laboratory data. In the presence of unstable coronary syndromes, decompensated HF, symptomatic valve disease, severe arrhythmias, or pulmonary embolisms which may compromise the course of the perioperative period, non-invasive exams are indicated in order to improve comprehension. When non-invasive exams are suggestive of coronary insufficiency, it is necessary to indicate scintigraphy stress testing, eventual coronary angiography, and even myocardial revascularization, provided that performing this may substantially change patient management or survival, taking the severity of the underlying disease into account.[130]

1.14. Vaccination in Elderly Patients

1.14.1. Brazilian Immunization Society (SBIm) Recommendations – 2015/2016[131]

Influenza [indicated for all elderly individuals] – Influenza is a highly infectious acute respiratory infection, caused by *Myxovirus influenzae*, a virus that is not specific to humans (The virus infects different domestic and wild vertebrates which may, in turn, infect humans). There are 3 known types, A, B, and C, and there is no crossed immunity between them. Type A is the most virulent. It causes the largest epidemics, and is

subdivided into subtypes in accordance with the characteristics of its superficial molecules (designated by the abbreviations HA and NA). There are currently 2 subtypes of influenza A in circulation among humans: H1N1 and H3N2.

The mortality associated with this virus may be elevated in more elderly and very young individuals, as well as in those with respiratory, cardiovascular, or renal pathologies, or diabetes, for example. The severity of the illness may be due to the virus itself or, more frequently, overlapping bacterial infections that follow influenza. There are 2 types of influenza vaccine, trivalent (3V) and quadrivalent (4V). The 3V protects against the H1N1 and H3N2 strains (both influenza A) and against a 1 type of the influenza B virus. The 4V protects against the forenamed strains and, additionally, against a second influenza B virus. Provided that it is available, the 4V influenza vaccine is preferable to the 3V, as it provides greater protection against circulating strains. If it is not possible to use the 4V vaccine, the 3V vaccine should be used. The vaccine offered by the public system is the 3V. Contraindications include known systemic hypersensitivity to any medication or substance, including neomycin, formaldehyde, triton-X-100 (octoxinol 9), eggs, or chicken protein, either following the administration of this vaccine or a vaccine containing the same composition. People with acute febrile diseases should not, normally, be vaccinated until these symptoms have disappeared.

Pneumococcal vaccine [indicated for all elderly individuals] – This vaccine protects against invasive infections (sepsis, meningitis, pneumonia, and bacteremia) and acute otitis media (AOM), caused by some serotypes of *Streptococcus pneumoniae*. It starts with a dose of VPC13, followed by a dose of VPP23 6 to 12 months later, and a second dose of VPP23, 5 years after the first. For those who have already received VPP23, an interval of 1 year is recommended for the application of VPC13. A second dose of VPP23 should be given 5 years after the first, maintaining an interval of 6 to 12 months after the dose of VPC13. For those who have already received 2 doses of VPP23, a dose of VPC13 is recommended at a minimal interval of 1 year after the latest dose of VPP23. If the second dose of VPP23 was applied before age 65, a third dose is recommended after this age, with a minimum interval of 5 years after the latest dose. This vaccine is available through the public system for risk groups (COPD, diabetes, etc.)

Diphtheria, tetanus, and acellular pertussis (DTaP)/ diphtheria and tetanus (DT) [indicated for all elderly patients] – This vaccine protects against diphtheria, tetanus, and acellular pertussis (DTaP) or diphtheria and tetanus (DT). A DTaP booster is necessary, regardless of previous DT or tetanus interval. For elderly patients who intend to travel to countries where polio is endemic, the combined DTaP inactivated poliovirus vaccine (DTaP-IPV) is recommended. The combined DTaP-IPV vaccine may substitute the DTaP. When the basic vaccination schedule for tetanus is complete, a DTaP booster is recommended every 10 years. When the basic vaccination scheme for tetanus is incomplete, a DTaP dose is recommended at any moment, completing basic vaccination with 1 or 2 doses of adult DT vaccine, in a manner that totals 3 doses of tetanus vaccine. This vaccine is recommended, even in individuals who have already had pertussis, given that protection provided by the infection is not permanent. It is possible to consider anticipating a DTaP booster, containing the pertussis component, to 5 years after the latest dose in elderly individuals who are in contact with breastfeeding infants. The DT is available through the public system.

Herpes zoster [indicated for all elderly patients] – This vaccine is recommended even in patients who have already had herpes zoster. In these cases, a minimum interval of 1 year is necessary between the acute phase and the vaccine application. In cases of patients with a history of ophthalmic herpes zoster, there are still not enough data to indicate or contraindicate the vaccine. Regarding use in immunocompromised patients, the vaccine should not be used in individuals with primary or acquired immunodeficiency states or those undergoing drug therapy at doses considered immunosuppressive. This vaccine is not available through the public system.

1.14.2. Other Vaccines (Non-Routine)

Hepatitis A, B, or A+B – Hepatitis A: 2 doses, in 0 and 6 month schedule. Hepatitis B: 3 doses, 0, 1, and 6 month schedule. Hepatitis A and B: 3 doses, 0, 1, and 6 month schedule. For hepatitis A, in the over 60 population, susceptible individuals are not commonly found. Vaccination is, thus, not a priority in this group. Serology may be requested in order to determine whether or not to vaccinate. In patients who have contact with hepatitis A or during an outbreak of the disease, vaccination should be considered. Regarding hepatitis A, B, and A+B, the combined hepatitis A and B vaccine is an option, and it may substitute isolated vaccination for hepatitis A and B.

Yellow fever – The vaccine is necessary in residents of risk areas and in those who intend to travel to these areas, at least 10 days before travel. If the risk persists, 10 years later, a second dose is necessary. This vaccine is contraindicated in immunocompromised individuals; however, when the risks of acquiring the disease outweigh the potential risks associated with vaccination, the physician should evaluate its use. There are reports of a higher risk of serious adverse events in patients over 60 years of age; therefore, if it is the primary vaccination, it is necessary to assess the risk-benefit ratio.

Measles, mumps, and rubella – Individuals are considered protected when they have, at some point in their lives, over 1 year of age, received 2 doses of the measles, mumps, and rubella vaccine with a minimum interval of 1 month between them. The vaccine is indicated in increased risk situations, given that the majority of people in this age group are not susceptible to these diseases. In the over 60 population, individuals susceptible to measles, mumps, and rubella are not commonly found. In this group, vaccination is thus, not routine. Nonetheless, according to medical criteria (during outbreaks, before travel, et al.), it may be recommended. It is contraindicated in immunocompromised individuals.

1.15. Palliative Care

Palliative care (PC), which was initially focused on oncology, has been incorporated into diverse practice areas, one of which is cardiology, with discussions on PC in the area of

CVD, especially involving the most elderly population. For this reason, this topic deserves to be covered in this document.

According to the WHO, PC is defined as a mode of assistance provided by a multidisciplinary team with the objective of improving patient and family member quality of life, when faced with a life-threatening disease, through prevention and relief of suffering.[132] PC requires early identification, evaluation, and treatment of pain and other physical, social, psychological, and spiritual issues.[132,133]

PC should be individualized; it is not an approach to "terminal" patients, but rather to a life-threatening clinical condition.[133] Its indication should be early, at the moment of diagnosis, in a manner that promotes understanding, acceptance, and progressive expansion of the means of support over time. The possibility of whether or not to implement disease-modifying treatments should be discussed in a manner that does not allow for the idea that "there's nothing to do."[133]

The principles that guide PC in accordance with the WHO consist of:[132]

1. Relieve pain and other distressing physical symptoms.
2. Affirm life and consider death as a normal life process.
3. Neither hasten nor postpone death.
4. Integrate psychological and spiritual aspect into patient care.
5. Offer a support system that makes it possible for the patient to live as actively as possible, until the moment of death.
6. Offer a support system that helps family members cope with the disease and bereavement.
7. Improve quality of life and positively influence the course of the disease.
8. Initiate care as early as possible, in conjunction with other life-prolonging measures, such as chemotherapy and radiotherapy, and include all necessary investigations to better comprehend and control existing clinical situations.

From the theoretical point of view, all patients with serious, incurable, and progressive diseases that are life-threatening should receive PC.[133] If this reference were put into practice, the number of patients indicated for PC would be enormous, and it would not be possible to provide this type of assistance to all of them. For this reason, the National Academy of Palliative Care (Academia Nacional de Cuidados Paliativos, ANCP)[133] recommends the adoption of the criteria used by Medicare in the United States,[134] which establishes expected survival time as a criterion for indicating PC. Adapting the Medicare criteria, we may suggest the following conditions for indicating PC:[133,134]

1. Patient with life expectancy less than or equal to 6 months.
2. Diagnosis with an incurable and irreversible disease.
3. The patient must opt for PC, giving up life-prolonging treatments.
4. The implementation of PC should be operationally available.

Prognostic evaluation of patients receiving PC is a complex process involving physiological and social judgments. The ANCP recommends some instruments for evaluating patient functionality, as well as measuring functional and clinical decline, such as the Karnofsky Performance Status Scale and the Palliative Performance Scale. These scales and their methods of evaluation are detailed in the ANCP's Palliative Care Manual, which is available on their virtual library (http://paliativo.org.br/).[133]

In relation to CVD, they are known to be the main cause of death in Brazil, as well as in other parts of the world. They may occur at any age, but their prevalence is higher with advanced age.[133] Among CVD, HF represents a challenge to prognostic evaluation, given that many patients die suddenly, even when they are in higher functional classes. Diverse criteria have sought to identify patients with HF at a risk of sudden death, such as left ventricular ejection fraction (LVEF), type B natriuretic peptide, end-diastolic LV diameter, presence of nonsustained ventricular tachycardia, diabetes mellitus, thromboembolic phenomena, history of previous cardiorespiratory arrest, and AIDS diagnosis.[133] The difficulty of prognosis in patients with HF makes it challenging to discuss care preferences with patients; for this reason, these patients have been considered those with the least comprehension of their clinical condition and the least involved in the decision making process related to their care.[133] Patients with CVD suffer severely, and they are among those who least receive home healthcare and PC; for this reason, these Guidelines agree with the idea that PC should be considered earlier during the evolutionary course of CVD and in routine cardiology practice.

2. Chronic Coronary Disease

2.1. Peculiarities of Diagnosing Chronic Coronary Artery Disease in Elderly Patients

Clinical history and detailed physical examination are essential when evaluating an elderly patient with suspected chronic CAD; however, in routine practice, this constitutes a challenge, considering the occurrence of comorbidities, atypical symptoms, and alterations in cognition and locomotion.

Ischemia is frequently present in the form of anginal equivalents, such as fatigue, dyspnea, and epigastric discomfort, with the presence of typical angina being rare.[135] Physical examination, generally non-specific, may provide some leads, such as SAH, abnormal heart rhythms such as atrial fibrillation (AF), and peripheral arterial disease.

Resting EKG may be non-specific in 50% of cases, even in those with severe coronary disease;[136] alterations such as pathological Q waves, T-wave inversions, left ventricular hypertrophy (LVH), His bundle branch blocks, and AF are common in elderly patients. These alterations complicate diagnosis. EKG is particularly useful during episodes of angina, when ST segment depression or pseudonormalization may be observed in up to 50% of cases.

Chest radiography should be performed when there is a suspected coexistence of congestive HF, valvulopathy, or respiratory disease.

Transthoracic echocardiography provides information which is relevant to diagnosis and management of chronic:

(a) LV status – systolic and diastolic function, parietal mobility, and hypertrophy; (b) presence of valvulopathy; (c) situation of the aortic root.

The use of functional tests for ischemia (ET, stress echocardiography and myocardial perfusion scintigraphy [MPS]) or anatomical tests (coronary computed tomography angiography [CCTA] and coronary cine angiogram [CCA]) depends on pre-test estimates on the likelihood of obstructive CAD.[137] When the probability is low (< 20%), it is not necessary to continue investigation. On the other hand, when the probability is high, (> 80%), negative results of non-invasive exams cannot exclude obstructive CAD; invasive strategies may, thus, be considered. In patients with intermediate pre-test probability, a stress test is indicated.

In elderly patients, the diagnostic sensitivity and specificity of ET have been questioned,[138] as a result of low exercise capacity (reduced muscle mass, deconditioning, comorbidities) and the presence of alterations in baseline EKG; nevertheless, this method may be useful in clinical management, offering relevant information on symptoms, exercise capacity, chronotropic response, arrhythmias, etc.

Both stress tests and MPS may be used in association with the ET to increment sensitivity and specificity for ischemia.[139,140] Diagnosis and prognosis of both modalities are similar and the preference for a determined method depends on the experience and/or equipment available at the investigating center. For elderly patients incapable of exercising, pharmacological stress may be used both in the stress test (dobutamine) and the MPS (vasodilatory agents).

The CCS, obtained in conjunction with CCTA, is useful for risk stratification in asymptomatic elderly patients, due to its high negative predictive value;[141] its value, however, is limited in symptomatic patients with suspected CAD. Due to the high prevalence of coronary calcification in the elderly, CCTA has shown to be of reduced accuracy in demonstrated obstructive CAD.[142]

CCA continues to be the "gold standard" for definitive evaluation of epicardial CAD; it is generally recommended for patients whose clinical characteristics and/or non-invasive test results indicate a high likelihood of severe coronary disease, with a high risk of coronary events or death. Even though it is well tolerated, it deserves attention due to the risk of bleeding, stroke, and contrast-induced nephropathy.

2.2. Peculiarities of Treating Chronic Coronary Artery Disease In Elderly Patients

During the last decades, the treatment of coronary disease has been founded on general clinical measures related to the development of healthy habits, such as a balanced diet, weight control, regular practice of physical activity, vaccination schedule completion, tobacco cessation, intensive BP control, and appropriate use of antiatherosclerotic medications such as statins, antiplatelet medications, and renin-angiotensin system inhibitors, in addition to antianginal agents.[143-145] Additionally, well selected cases are treated with myocardial revascularization procedures, through percutaneous coronary intervention or surgery. In elderly patients, these principles are largely applicable with evidence which it has been possible to extrapolate from randomized clinical trials, that have begun to include "young" elderly individuals (ages 60 to 75) in their observations, with less frequently evaluation of "truly elderly" individuals (ages 75 to 85) are scarce evaluation of "very elderly" individuals (over age 85).[143-145]

Regarding diet, the Lyon, Dietary Approaches to Stop Hypertension (DASH), and, more recently, *Prevención con Dieta Mediterránea* (PREDIMED) studies have validated the concept of a healthy diet; the PREDIMED included patients up to age 80. Weight control represents a particular consideration in the elderly owing to the apparent existence of a paradox between BMI and age.[146] In a more conclusive analysis of the topic of CAD, the reduction of obesity is associated with better results.

Regular practice of activities which are appropriate for the elderly individual's physical conditions bring innumerable psychological benefits that impact improvements in general healthcare and which justify their implementation.

Inflammation caused by infections plays a recognized role on the emergence of coronary disease complications, and influenza and pneumococcal vaccination is a recommendable measure in elderly coronary disease patients.[147]

Analysis of the Coronary Artery Study (CASS) registry has been definitive in demonstrating the benefits of tobacco cessation in elderly coronary disease patients.[148]

A systolic blood pressure (SBP) control goal of < 140 mmHg has been established for the elderly population. A recent study, the Systolic Blood Pressure Intervention Trial (SPRINT), recommends that this goal be even more intensive, even in elderly coronary disease patients (< 130 mmHg, if tolerated), without verifying the J curve or undesired events in relation to reduced diastolic BP. Special caution needs to be taken in this population when comorbidities are present.[149]

Antiatherosclerotic medications such as statins have confirmed demonstration, in clinical trials, up to age 79. If tolerated, they should be used to stimulate an LDL-c goal of < 70 mg/dL. Acetylsalicylic acid (ASA) is recommended, as well as the use of angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), even in the absence of SAH or HF, notwithstanding the fact that both of these conditions are frequently associated with CAD in the elderly.

Anti-ischemic medications, such as beta-blockers (and calcium channel blockers, when beta-blockers are not possible, or in association with them) for control and nitrates for crises, as well as new anti-ischemic medications, such as trimetazidine, should be used with due caution regarding progressive doses, due to the higher incidence of side effects. Ivabradine may be considered for HR control when it is not possible to use beta-blockers.[150]

In relation to revascularizing elderly patients without frailty by either percutaneous or surgical intervention, this should be considered with the aim of controlling refractory symptoms or in cases with severe ischemic burden. With respect to deciding which procedure should be performed, whether percutaneous intervention or surgery, this depends wholly on the feasibility of using the techniques, it being necessary to consider that age adds a considerable weight to risk of both procedures and that scores that include

associated comorbidities tend to affect the surgical procedure even more.[151]

In conclusion, in addition to the previously mentioned facts, therapeutic recommendations must consider many other relevant factors such as biological aspects of frailty, psychological competence, economic and social support, among others. This makes this choice an optimal example of personalized therapy centered on the elderly individual who is affected by CAD.

2.3. General Recommendations – Chronic Coronary Artery Disease in Elderly Patients

Diagnostic evaluation of chronic coronary disease in elderly patients

Method	Positive aspects	Possible limitations	Grade of recommendation	Level of evidence
EKG	Easily obtained. Detection of inactive zones and conduction disorders	Low accuracy	I	B
Ergometric test	Availability. Moderate accuracy in detecting ischemia	Locomotive difficulties. Resting EKG alterations	I	B
Stress echocardiography (exercise, dobutamine, or dipyridamole)	Detection and evaluation of the extent of ischemia. Evaluation of LV function	Echocardiography window. Cost	I	B
Scintigraphy	Detection and evaluation of the extent of ischemia. Does not depend on preexisting electrocardiographic alterations. Evaluation of LV function	Lower availability. Cost	I	B
Coronary computed tomography angiography	Detection of obstructions	Calcification in the elderly patient decreases diagnostic accuracy	IIa	B
Coronary magnetic resonance angiography	Detection of obstructions	Lower accuracy. Difficult to obtain	IIb	C
Cardiac magnetic resonance	LV function. Areas of fibrosis	Difficult to obtain	IIb	C

EKG: electrocardiogram; LV: left ventricle.

Treatment of chronic coronary disease in elderly patients

General measures	● Balanced diet ● Weight control ● Regular practice of physical activity ● Vaccination schedule completion ● Tobacco cessation ● Intensive blood pressure control
Antiatherosclerotic medications	● Statins ● Antiplatelets ● Renin-angiotensin system inhibitors (ACEI/ARB)
Antianginal medications	● Beta-blockers ● Calcium channel blockers ● Nitrates ● Trimetazidine
Myocardial revascularization	● Percutaneous coronary intervention ● Myocardial revascularization surgery

ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blockers.

Recommendations for general measures and antiatherosclerotic use

Procedure/medication	Grade of recommendation	Level of evidence
Balanced diet	I	A
Weight control	I	B
Physical activity	I	B
Vaccination against influenza	I	B
Tobacco cessation	I	A
BP control < 140 mmHg	I	A
BP control < 120 mmHg	IIa	B
Statins	I	A
Antiplatelets	I	A
ACEI/ARB	I	A

ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blockers. BP: blood pressure.

Recommendations for antianginal medications		
Medication	**Grade of recommendation**	**Level of evidence**
Beta-blockers	I	A
Calcium channel blockers	IIa	B
Nitrates for anginal crises	I	A
Nitrates for chronic use	IIb	B
Trimetazidine	IIa	B
Ivabradine	IIa	B

Indication for revascularization in elderly patients refractory to clinical treatment		
PCI – Patients with angina	**Grade of recommendation**	**Level of evidence**
PCI feasible and easily applied	I	C
Low SYNTAX score	I	B
High SYNTAX score	IIb	B
Surgery – Patients com angina	**Grade of recommendation**	**Level of evidence**
Multivascular, with low surgical risk	I	B
Low SYNTAX score and moderate to high surgical risk	IIb	B

PCI: percutaneous intervention; SYNTAX: Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery.

Indication for revascularization in asymptomatic elderly patients		
Severe ischemic load	**Grade of recommendation**	**Level of evidence**
Percutaneous intervention	IIa	C
Surgery	IIa	C

3. Acute Coronary Disease

3.1. Diagnostic Peculiarities

Elderly patients have a higher incidence of acute coronary syndrome (ACS), and their prognosis is worse in comparison with younger patients. The causes of this unfavorable evolution include: (a) delayed arrival at the hospital; (b) diagnostic difficulties; (c) lower likelihood of receiving interventional treatment; (d) less use of beta-blockers; (e) previous HF; and (f) comorbidities.[152] As age increases, the effects of risk factors such as hypertension, diabetes, and tobacco use decreases, and the importance of associated comorbidities, such as stroke and renal and cardiac insufficiency increases.[153,154] Atypical presentation is more common in this age group; chest pain is present in 40% of patients ≥ age 80, compared to 80% in those ≤ age 65. In elderly heart attack patients, 8.4% do not present precordial pain (43.3% in patients ≥ 75 years old, compared to 29.4% in those ≤ 65 years old). More common symptoms include: dyspnea (29.4%), sweating (26.2%), nausea and vomiting (24.3%), and syncope and pre-syncope (19.1%), which are denominated ischemic equivalents.

Although physical examination may be normal, the presence or absence of signs of peripheral hypoperfusion, vital signs, presence or absence of arterial pulses, jugular vein distention, cardiac auscultation (blowing, friction, third heart sound), and pulmonary auscultation with signs of congestion are important data to evaluate. Initial EKG is less solicited and more delayed, in elderly patients: 40% of patients ≥ age 85, compared to 25% of those ≤ age 65, do not have diagnostic EKG. The presence of non-specific EKG alterations and blocks is more frequent in elderly patients, increasing diagnostic difficulties in this age group, especially in the presence of left bundle branch block.[102,155] Elevated myocardial necrosis markers unrelated to ACS are common in other situations, such as increased plasma N-terminal brain natriuretic propeptide (NT-pro-BNP), diabetes, renal insufficiency, anemia, dehydration, metabolic and hydroelectrolytic disorders, infections, and echocardiography abnormalities in chronic heart diseases.[156-159]

Risk scores, such as the Thrombolysis in Myocardial Infarction (TIMI) Risk[160] and the Global Registry of Acute Coronary Events (GRACE),[161] are important for risk stratification of elderly ACS patients, ensuring better strategy in diagnostic and therapeutic approach, increasing the use of antithrombotic and anticoagulant medications and myocardial revascularization, with a consequent decrease in risk of death, heart attack, and recurring ischemia.[162,163] Being over age 70 confers a moderate (ages 70 to 75) to high (> age 75) risk of coronary disease.

Frailty is an important independent predictor of mortality, longer hospital stays, increased risk of bleeding and morbidity in the elderly population with ACS.[164,165] Functional decline in elderly patients is a predictor of poor evolution.[166] The Gold Standards Framework (GSF) score, which associates end-stage disease criteria, has shown to be an independent predictor of non-cardiovascular events in ACS, while the GRACE score has demonstrated that it is an excellent predictor of cardiovascular events in elderly patients.[167] Chest radiography, resting transthoracic echocardiography, myocardial scintigraphy, coronary angiotomography, cardiac magnetic resonance, and CCA follow the same indications as in younger patients for diagnosis of ACS in this age group.[156,157]

3.2. Peculiarities of Treatment

Even though the elderly population is the one that most benefits from more aggressive strategies, they have a higher risk of bleeding, with a 2-fold risk of mortality compared to younger patients (< 75 years old). Higher intra-hospital mortality and higher bleeding rates with thrombolytic therapy are part of this scenario. Approach to ACS in elderly patients should be individualized, based on risk of complications, estimated life expectancy, comorbidities, quality of life, and the patient's wishes and preferences.[153,154,156,157,168-170] Elderly patients (> age 75) with acute coronary syndrome with ST-segment elevation (ACS-STE) and without ST-segment

elevation (ACS-NSTE) should follow the same diagnostic and therapeutic approach as in younger patients, based on guidelines and consensuses, it being necessary to evaluate particularities of pharmacokinetics, sensitivity, and collateral effects and collateral effects of drugs, always taking weight and creatinine clearance into account.[102,153,154,156,157,168-170]

During the past 15 years, there has been a significant increase in the rates of pharmacological therapy use based on evidence for ACS patients in all age groups. However, in cases of ACS-STE, elderly patients have a lower chance of receiving primary angioplasty or thrombolysis, as well as the prescription of ASA, clopidogrel, beta-blockers, statins, or ACEI.[171] The Study of Global Ageing and Adult Health (SAGE) compared the effects of intensive (atorvastatin 80 mg) versus moderate statin therapy (pravastatin 40 mg) on reducing myocardial ischemia in elderly patients between the ages of 65 and 85. Both statin regimens were equally effective in reducing the frequency and duration of ischemia; intensive therapy with atorvastatin, however, was demonstrated to be more effective in the reduction of lipids and all-cause mortality, in comparison with pravastatin.[170,172] However, due to the prevalence of collateral effects and intolerance to this medication in this age range, lower doses of statins are suggested for ACS patients, until LDL-c < 70 mg/dL has been reached, maintaining the tolerated dose.

After age 85, studies suggest that there are benefits associated with reperfusion strategies for ACS-STE. The choice between fibrinolytic drugs and angioplasty is determined by the presence or absence of cardiogenic shock, presentation time, and comorbidities, which often tend toward angioplasty in elderly patients. The safety and efficacy of reperfusion, especially fibrinolytic therapy, in very elderly patients (≥ 85 years old) are questions which require deeper investigation.[173] The After Eighty study investigators evaluated 457 patients over the age of 80 with ACS-NSTE (AMI and unstable angina) who were randomized to an invasive or a conservative strategy, suggesting that invasive therapy is superior, with a higher incidence of death, myocardial infarction, and stroke in the conservative therapy group. The same results were obtained in the subgroup of elderly patients over age 90.[174]

3.3. General Recommendations – Acute Coronary Syndrome in Elderly Patients

With elderly ACS patients, cardiologists face the following 3 challenges:

1st Challenge: summary of diagnostic challenges in elderly patients
Atypical presentation: less typical pain and more anginal equivalents (dyspnea, syncope, stroke, HF, etc.)
Greater severity: present with more HF and cardiogenic shock
Higher prevalence of morbimortality: reinfarction, stroke, more severe hemorrhage, and death
Lower effects of risk factors and greater importance of comorbidities
Non-specific EKG in 43% of elderly patients > 85 years old
Myocardial infarction (ACS-STE) should be strongly suspected in women, diabetes patients, and elderly patients with atypical symptoms
Due to frequent atypical presentation, elderly patients (> 75 years old) should be investigated for ACS-NSTE with a lower level of suspicion

2nd Challenge: summary of challenges regarding approach individualization
Heterogeneous population
Moderate to high risk in the most utilized risk stratification scores (TIMI, GRACE)
Treatment should consider overall health, comorbidities, cognitive status, life expectancy, frailty, patient's wishes and preferences
It is necessary to pay attention to pharmacokinetic alterations and sensitivity to hypotensive drugs

3rd Challenge: summary of treatment challenges
Treat elderly patients (≥ 75 years old) with medical therapy, early invasive strategy, and revascularization, as indicated, in accordance with guidelines
It is necessary to pay attention to adjustments in doses of antithrombotic drugs in elderly patients and patients with renal insufficiency
Antithrombotic treatment should be adapted in accordance with weight and creatinine clearance
Intensive medication strategies and revascularization intervention strategies should always be considered, observing the adverse effects of these therapies
Adjustments in doses of beta-blockers, ACEI, ARB, and statins should be considered, with the aim of decreasing or avoiding collateral effects
Consider invasive strategies and, if appropriate, revascularization, following careful evaluation of potential risks and benefits, estimated life expectancy, comorbidities, quality of life, frailty, and patient preferences
It is reasonable to choose myocardial revascularization surgery over angioplasty in more elderly patients, especially those with diabetes or multiple vessel disease, due to increased survival and reduction of cardiovascular events

ACEI: angiotensin converting enzyme inhibitors; ACS-NSTE: acute coronary syndrome without ST-segment elevation; ACS-STE: acute coronary syndrome with ST-segment elevation; ARB: angiotensin receptor blockers; GRACE: Global Registry of Acute Coronary Events; HF: heart failure; TIMI: Thrombolysis in Myocardial Infarction.

4. Heart Failure

4.1. Diagnostic Peculiarities of Heart Failure in Elderly Patients

Elderly patients may have atypical presentations of HF due to cognitive alterations, sedentarism, functional limitations, and the presence of comorbidities. These factors contribute to late diagnosis, thus making complementary exams important (Figure 1).[175] The use of biomarkers, such as outpatient values of brain natriuretic peptide (BNP) below 35 ng/mL, excludes the presence of HF in symptomatic individuals. In individuals with acute dyspnea in the emergency room, however, BNP values over 250 ng/mL or pro-BNP over 1,800 ng/mL indicate HF as the cause of the symptoms. Elderly patients have higher natriuretic peptide levels, as well as comorbidities which may increase these values, such as renal insufficiency.[176] Normal EKG results may be useful in making the hypothesis of HF less likely, while findings of AF, complete left bundle branch block, inactive areas, and LVH, increase the probability of this disease.[176,177] Alterations in cardiac geometry and structure occur with aging, including decreases from the base to the apex, right deviation, aortic annulus dilation, and increased interventricular septum thickness, which leads to so-called Sigmoid septum and may cause outflow obstruction.[176] Even

Updated

Intervention	Recommendation	Grade of recommendation	Level of evidence
Oxygen	In patients with arterial saturation below 90%, respiratory failure, or a high risk of hypoxemia, it is necessary to maintain during the first 6 h or until hemodynamic stabilization is reached	I	C
Nitrates	In sublingual form, it is recommended for patients with ischemic type chest pain. It may be used in intravenous form in elderly patients with persistent pain and conditions associated with hypertension and heart failure. It should be avoided in cases of hypotension, right ventricular infarction, and severe aortic stenosis	I	C
Morphine	This should be reserved for patients with unacceptable pain levels. The initial dose is 2 to 4 mg, with 2 to 8 mg increments repeated in 5 to 15 minute intervals	I	C
Beta-blockers	Great benefits in comparison with younger groups, regarding prevention of ACS and death. Intravenous administration should only be used in specific cases	I	B
ACEI	Benefits especially in CHF or LV dysfunction	I	A
Statins	Dyslipidemia treatment in elderly patients up to age 75 should follow the same orientations as in non-elderly patients	I	A
	After age 75, doses of lipid-lowering agents should be individualized according to the presence of comorbidities, life expectancy, and polypharmacy	I	B
ASA	Indicated for all elderly patients, if there are no contraindications. Benefits are greater in elderly patients	I	A
Clopidogrel	Indicated for elderly ACS patients with high risks, especially those who will undergo angioplasty. Loading doses are not recommended in elderly patients who are eligible for thrombolytic therapy	I	A
Ticagrelor	Better evolution than clopidogrel, comparing groups over and under age 75, with no differences in bleeding in either of the 2 groups	I	B
Prasugrel	Contraindicated in patients ≥ 75 years old, weight < 60 kg, and stroke/TIA history	III	A
Antithrombins	Should be administered with caution in ACS patients. Enoxaparin may be administered at reduced doses in patients > 75 years old (0.75 mg/kg, SC, 12/12h)	I	A
Glycoprotein inhibitor IIb/IIIa	Indicated in the most elderly subgroups at the moment of intervention, excluding renal insufficiency:	I	A
	ACS-NSTE – Early intervention strategies, when thienopyridine is not administered	IIa	C
Thrombolysis	When indicated, evaluate with attention to contraindications, as they are more frequent in elderly patients. In the event of tenecteplase use in elderly patients > age 75, administer a half-dose	I	A
Primary angioplasty	Better risk-benefit compared to thrombolytic drugs	I	A
Early catheterization	Improved short- and long-term evolution. Evidence from randomized, controlled studies are limited in elderly patients and should take risk of bleeding into account. Data are lacking in the ≥ age 80 subgroup	IIa	B
	ACS-STE – Elderly patients should be considered for early invasive strategies, with the possible option of revascularization	I	A
Cardiac rehabilitation	The same benefits as in younger groups regarding death prevention	I	B

ACEI: angiotensin converting enzyme inhibitors; ACS: acute coronary syndrome; ACS-NSTE: acute coronary syndrome without ST-segment elevation; ACS-STE: acute coronary syndrome with ST-segment elevation; ASA: acetylsalicylic acid; CHF: congestive heart failure; LV: left ventricle; TIA: transient ischemic accident.

though patients with HF with reduced ejection fraction (HFrEF) (LVEF < 40%) and HF with preserved ejection fraction (HFpEF) (LVEF > 50%) are well defined, there is some uncertainty in elderly patients with moderate HF (LVEF 41% to 49%). A recent study demonstrated that this intermediate profile is a distinct entity and it should be categorized as HFrEF due to the elevated prevalence of coronary disease and to the similar benefits of using the standard of treatment indicated for this biomarker.[178] Echocardiography study allows for evaluation of indexed left atrial (LA) volume, the presence of LV hypertrophy, analysis of filling pressures (E/A ratio, E/E' ratio, and pulmonary flow), diastolic function, inferior vena cava variation, pulmonary BP evaluation, degree of mitral regurgitation, and the presence or absence of aortic stenosis (AS) (especially the low-flow, low-gradient phenotype with normal ejection fraction). It also allows for investigation of etiology, where senile amyloidosis is currently a growing condition in individuals over the age of 70.[176,177,179] In clinical practice, evaluation of functional state using ergospirometry aids prognostic evaluation and cardiac rehabilitation planning.

The presence of fibrosis, cardiac hypertrophy, cardiac chamber dilation, intracardiac thrombus, pericardial thickening, in addition to the study of right ventricle (RV) function, may be evaluated by cardiac resonance. This has become an integral part of the evaluation of myocardial disease patients, as it identifies the cause (inflammation [myocarditis], amyloidosis, sarcoidosis, Chagas disease), cardiomyopathies, and ischemic disease.[176] Myocardial scintigraphy is a useful method in individuals with suspected ischemic heart disease with systolic dysfunction; it is requested to investigate ischemia and/or myocardial viability. Technetium pyrophosphate bone scintigraphy may be useful in diagnosing transthyretin cardiac amyloidosis in elderly hypertrophy and HF patients.[176]

4.2. Peculiarities of Heart Failure Treatment in Elderly Patients

HF is prevalent among the elderly, affecting up to 20% of patients > 75 years old.[1] It is characterized by the presentation of systolic dysfunction (HFrEF) or diastolic dysfunction (HFpEF) and high mortality (2-fold risk of all-cause mortality adjusting for age and sex and 4-fold risk of cardiovascular death).[180,181] Over the past decades, HFpEF has become the main clinical phenotype.[2]

Polypharmacy is extremely common in this context, with a strong impact on drug interactions, higher rates of adverse effects and poor adherence; however, multidisciplinary and adherence programs have been shown to be useful in this group of patients.[182] Exercise training, in comparison with habitual care, in elderly HFrEF patients in New York Heart Association (NYHA) classes II and III, was shown to be safe, without an increase in mortality and hospitalization and with improvements in the walking test.[183]

The objectives of pharmacological treatment of HF are: reducing mortality and hospitalization; improving functional capacity and quality of life; and including the use of ACEI, ARB, beta-blockers, and aldosterone antagonists. Elderly individuals have frequently been excluded or under-represented in studies performed on HF patients.[184]

Several influential clinical trials have demonstrated the efficacy of ACEI in younger patients (average age of 60/66); however, subgroup analysis of the Heart Outcomes Prevention Evaluation (HOPE) study demonstrated a higher risk reduction in patients > 65 years old, in comparison with the younger group.[184]

ARB have been little evaluated in elderly patients; however, subanalysis of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM-Alternative) study, with 23.3% of its study population ≥ age 75, demonstrated benefits similar to those reported for the general group.[185]

Regarding beta-blockers, a recent meta-analysis of 12,719 patients did not find any differences in benefits between those defined as "elderly" in the clinical trials included and their younger counterparts. It is important to underline the fact that the oldest patient from the individual clinical trials analyzed was 71 years old.[5] The Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure (SENIORS) demonstrated the efficacy of nebivolol in CHF patients > 70 years old. Subanalysis of the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) study provided evidence that beta-blockers may be associated with beneficial effects in patients ≥ 75 years old.[186,187]

The Euro Heart Failure Survey II has suggested that the use of ACEI and/or beta-blockers is associated with a significant decrease in short-term mortality in octogenarians. The Euro HF Survey II, on the other hand, did not show improvements in mortality during 1 year with the use of beta-blockers; this is possibly related to the higher number of elderly HFpEF patients in this study.[188]

In the most important studies with aldosterone antagonists, the Randomized Aldactone Evaluation Study (RALES) and the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), the average patient age was 67 and 64, respectively. Their use, in elderly patients, however, should be carefully monitored in accordance with renal dysfunction and the underlying drug interaction. In the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM) study, symptomatic hypotension in patients > age 75 was more frequent in the sacubitril/valsartan group (18%) than in the enalapril group (12%).[189]

In summary, current orientations recommend a therapeutic approach similar to the one applied to younger patients for HF treatment, with caution regarding interactions and tolerance.[176,190]

4.3. General Recommendations for Elderly Heart Failure Patients

Complementary diagnostic methods of CHF in elderly patients	Grade of recommendation	Level of evidence
Transthoracic echocardiogram recommended for evaluating structure and function in HF and establishing diagnosis of HFrEF and/or HFpEF	I	C
Transthoracic echocardiogram recommended for evaluating resynchronization/ICD candidates	I	C
Repeat evaluation of ventricular function and measures of structural remodeling in patients with CHF, change in clinical status, or decompensation	I	C
MR with delayed enhancement should be considered in patients with dilated cardiomyopathy to differentiate between ischemic and non-ischemic etiology	IIa	C
MR recommended for cardiac tissue characterization when myocarditis, amyloidosis, sarcoidosis, or non-compacted myocardium are suspected	I	C
Non-invasive stress exams (resonance, echocardiogram, SPECT, PET) are recommended for evaluating myocardial ischemia and viability in patients with CAD and CHF before deciding on revascularization	IIb	B

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Cinecoronariography recommended in patients with CHF and angina for diagnosis of CAD	I	C
Coronary angiotomography in patients with CHF and pre-test likelihood indicating low or intermediate risk and in patients whose non-invasive stress exams suggest CAD, with the objective of excluding invasive exams	IIb	C
Hemogram, sodium, potassium, urea, creatinine (clearance), hepatic function, glucose, glycated hemoglobin, TSH, ferritin	I	C
Natriuretic peptides	IIa	C
Electrocardiogram recommended for evaluating rhythm, heart rate, morphology and QRS duration	I	C
Chest radiography recommended to exclude pulmonary alterations. In cases of acute decompensation to detect edema/pulmonary congestion	I	C
Endomyocardial biopsy should be considered for diagnosing specific causes in cases of rapid and progressive worsening in spite of standard therapy	IIa	C

CAD: coronary artery disease; CHF: congestive heart failure; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; ICD: implantable cardioverter-defibrillator; MR: magnetic resonance; PET: positron emission tomography; SPECT: single photon emission computed tomography; TSH: thyroid-stimulating hormone.

Treatment of comorbidities

Recommendation	Grade of recommendation	Level of evidence
Iron deficiency – IV iron replacement in patients with ferritin < 100 ng/ml or ferritin between 100 and 199 ng/ml and transferrin saturation < 20% with the objective of improving symptoms and quality of life	IIa	A
Diabetes – metformin use	IIa	C

IV: intravenous.

Grade of recommendation for pharmacological treatment of HFrEF FC II to IV

Recommendation	Classification of recommendation	Level of evidence
ACEI in conjunction with beta-blockers with the objective of reducing mortality and hospitalization	I	A
ARB in conjunction with beta-blockers with the objective of reducing hospitalization and mortality in patients with ACEI intolerance	I	B
Addition of aldosterone blockers in symptomatic patients, with LVEF ≤ 35%, associated with ACEI (or ARB) and beta-blockers	I	A
Diuretics to improve symptoms in patients with congestion	I	B
Angiotensin receptor-neprilysin inhibitor (sacubitril/valsartan), to substitute ACEI in order to reduce mortality and hospitalization in patients who continue to be symptomatic in spite of treatment with ACEI (or ARB) and beta-blockers	I	B
Hydralazine and isosorbide dinitrate in African-American patients with EF < 35% or EF < 45% with ventricular dilatation who continue to be symptomatic, with FC III-IV, in spite of treatment with ACEI (or ARB) and beta-blockers to reduce mortality and hospitalization	IIa	B
Hydralazine and isosorbide dinitrate in symptomatic patients with HFrEF who do not tolerate ACEI or ARB to reduce mortality	IIb	B
Digoxin in symptomatic patients with sinus rhythm in spite of treatment with ACEI (or ARB) and beta-blockers to reduce hospitalization	IIb	B
An If channel inhibitor (ivabradine) may be used in symptomatic patients with sinus rhythm, EF < 35%, and HR > 70 bpm, in spite of treatment with ACEI (or ARB) and beta-blockers to reduce hospitalization and mortality	IIa	B

ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blockers; EF: ejection fraction; FC: New York Heart Association functional class; HFrEF: heart failure with reduced ejection fraction; HR: heart rate; LVEF: left ventricular ejection fraction.

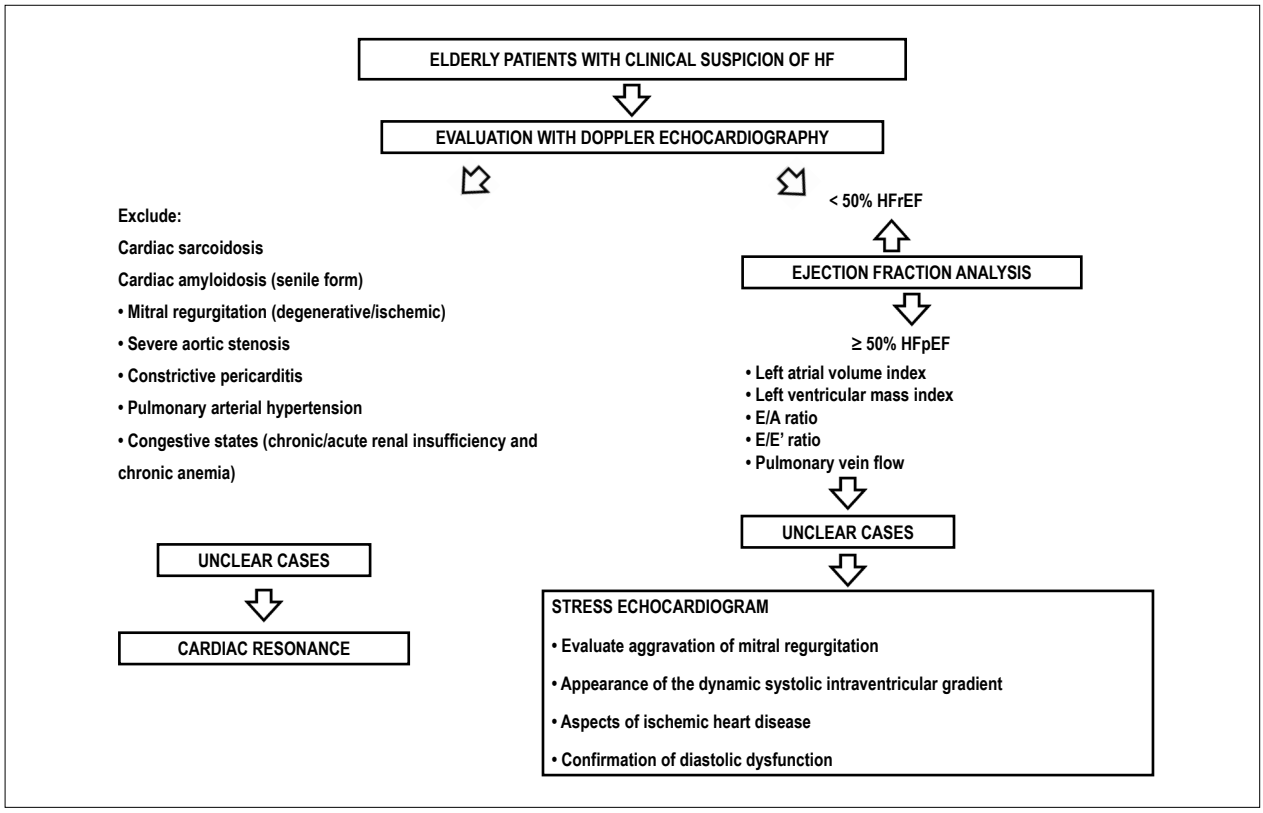

Figure 1 – *Diagnostic flowchart. HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction.*

Available drugs, initial and target doses, dose adjustments, and safety in elderly patients

Drugs	Initial dose	Maximum dose	Dose adjustment for elderly patients	Safety in elderly patients
Captopril	6.25 mg 3×/day	50 mg 3×/day	None	Increase in orthostatic hypotension Take before bedtime Decrease diuretics
Enalapril	2.5 mg 2×/day	10–20 mg 2×/day	None	More susceptible to renal dysfunction
Lisinopril	2.5–5.0 mg 1×/day	20–40 mg 1×/day	None	Avoid use of NHAI drugs
Perindopril	2.0 mg 1×/day	8,0–16 mg 1×/day	None	
Ramipril	1.25–2.5 mg 1×/day	10 mg 1×/day	Adjust according to renal function	
Candesartan	4.0–8.0 mg 1×/day	32 mg	None, but elevated AUC and Cmax	Similar to that of ACEI
Losartan	25 mg 1×/day	50–100 mg	None	
Valsartan	40 mg 2×/day	320 mg	None	
Bisoprolol	1.25 mg 1×/day	10 mg 1×/day		Water retention: - Monitor weight daily - Adjust diuretic dosage Risk of hypotension and bradycardia: - Start with a low dose and increase progressively - Adequate hydration Increased fatigue: - Improves over time - Consider comorbidities anemia

Carvedilol	3.12 5mg 2×/day	50 mg/day	None	
Metoprolol succinate	12.5–25 mg	200 mg/day	None	
Nebivolol	1.25 mg	10 mg	None	
Spironolactone	12.5–25 mg	25–50 mg	None	Increased risk of hyperkalemia and renal dysfunction Monitor K and creatinine
Furosemide	20–40 mg/day 1 or 2×/day	600 mg (usual 40–240 mg/day)	Start 20 mg/day	Frequent monitoring Increased risk of alterations in water balance and electrolyte disturbances
Bumetanide	0.5–1 mg 1 or 2×/day	10 mg Usual (1–5 mg/day)	None	Frequent monitoring Increased risk of alterations in water balance and electrolyte disturbances
Hydrochlorothiazide	25 mg	200 mg/day Usual (12.5–100 mg/day)	Start 12.5 mg–25 mg	Monitor fluid volume and electrolyte status
Chlorthalidone	12.5–25 mg	100 mg	None	Monitor fluid volume and electrolyte status

ACEI: angiotensin converting enzyme inhibitors; AUC: area under curve; NHAI: non-hormonal anti-inflammatory.

5. Arterial Hypertension in The Elderly

5.1. Diagnostic Peculiarities

A Brazilian epidemiological study titled the Multicenter Study of Elderly Patients in Outpatient Clinics of Cardiology and Geriatric Brazilian Institutions (EMI, acronym in Portuguese)[191] demonstrated that SAH is the main risk factor among elderly Brazilians. It is found in 65% of elderly outpatients and 80% of women > 75 years old. Aging produces vascular alterations, such as arterial stiffening, reduced elasticity and vascular compliance, reduced vasodilation capacity, increased SBP, decreased sensitivity to volume changes, slowed ventricular relaxation, increased cardiac workload, loss of myocytes, and compensatory hypertrophy.[192] These alterations lead to peculiarities in diagnosing and treating SAH in elderly patients.

5.1.1. Peculiarities in Measuring Blood Pressure

In elderly patients, BP has high variability. It is necessary to take special care in measuring BP, owing to the possible presence of the following factors:

a) OH: defined as a drop in SBP of > 20 mmHg or in diastolic blood pressure (DBP) of > 10 mmHg, following 3 minutes in the orthostatic position. BP should be checked in the sitting, lying, and standing positions, given that atherosclerotic alterations in the carotid sinus regions may reduce baroreceptor sensitivity, leading to reduced postural reflexes and, thus, predisposing the patient to OH.[3] Furthermore, comorbidities, such as peripheral polyneuropathy and Parkinson's disease, as well as the use of diuretic, antidepressant, vasodilator, and beta-blocker drugs may also lead to OH in up to 34% of elderly patients > age 75.

b) Auscultatory gap: a sitution in which, after auscultation of the first Korotkoff sound, the sound disappears completely and only reappears after the decrease in SBP, but before the beginning of the last phase of Korotkoff sounds. This leads to errors in diagnosing SBP at lower levels and false diagnoses of normotension. In order to avoid this measurement error, it is necessary to estimate systolic pressure using the radial pulse palpatory method, raising cuff pressure 20 to 30 mmHg above this point.[193]

c) Pseudo-hypertension: pseudo-hypertension may appear in elderly patients with pronounced atherosclerosis, arterial wall calcification, and vessel stiffening. In this situation, it is sufficient to inflate the cuff in order to collapse the brachial artery.[193] Osler's maneuver is used to identify this. The maneuver consists of inflating the cuff above systolic pressure levels and, concomitantly, palpating the radial artery. If it continues to be palpable, this suggests that the artery is stiff and indicates that the index obtained by auscultation does not express the true SBP. Pseudo-arterial hypertension may also be suspected when SBP is elevated in patients who do not present injuries in target organs or in those who manifest hypotension following treatment with low doses of anti-hypertensive drugs.

d) Arterial hypertension during exercise: although BP is habitually higher during physical exercise, this increase is greater in elderly adults, due to arterial stiffness. Values for diagnosing SAH during exercise are not clear. Physically deconditioned patients respond with greater increases in BP than conditioned patients.

e) White coat hypertension: this occurs when BP increases during a clinical visit but remains normal during daily activity. This can be better evaluated by 24-hour ambulatory blood pressure monitoring (ABPM) or home blood pressure monitoring (HBPM).[193] Serial measurements may minimize this condition.

f) Masked arterial hypertension: this is the opposite of white coat hypertension, namely, pressure is high during daily activities and normal during the clinical visit.[193] This may also be evaluated by 24-h ABPM or HBPM.

g) Isolated systolic hypertension (ISH) and pulse pressure (PP): ISH and PP are cardiovascular risk factors in elderly patients.[191] ISH is due to lower distensibility and elasticity in the large capacitance vessels, such as the aorta, which results in increased pulse wave velocity (PWV). This increase in PWV

is accompanied by an increase in reflex wave velocity, which returns from peripheral to central circulation.[191,192] In elderly patients, the reflex wave reaches the ascending aorta during systole, leading to an even higher increase in SBP. Loss of reflex wave in protodiastole makes diastolic pressure remain equal or decrease.[192] The final effect consists of a predominant increase in SBP, with DBP remaining normal or even low. Characteristics of ISH include SBP ≥ 140 mmHg and DBP < 90 mmHg.[193] PP is defined as the difference between SBP and DBP. This occurs due to the progressive loss of arterial elasticity, with a consequent decrease in vascular complacency. DBP tends to remain normal or even low. Limits for abnormal PP values have yet to be defined.[191] The Framingham study demonstrated a higher cardiovascular risk associated with higher PP, in patients between the ages of 50 and 79, as well as an important role of low DBP in this association.[3] In addition to the factors mentioned, target organ injuries should be investigated (eye fundus changes, LV hypertrophy, and peripheral and renal atherosclerosis), and the possibility of secondary SAH should be evaluated. The following are suspicious factors:[193]

a) Sudden onset of SAH or acute worsening

b) Abdominal murmur

c) SAH resistant to 3 or more drugs

d) Creatinine increase over 30% with the use of ACEI or ARB

e) Systemic atherosclerotic disease in smokers and patients with dyslipidemia

f) Recurrent hypertensive pulmonary edema

g) Pheochromocytoma and hyperaldosteronism should be adequately investigated with more specific exams, because, even though they are less frequent in elderly patients, once they are diagnosed and treated, they may result in the patient being cured.

Among secondary causes of SAH, the following stand out: aortic regurgitation (AR), hyperthyroidism, renovascular atherosclerosis, and use of drugs that increase pressure, such as non-hormonal anti-inflammatory agents, antihistamines, decongestants, corticosteroides, MAOI, and TCA.

5.1.2. Peculiarities of Clinical Laboratory Investigation

The objective of clinical laboratory investigation is to confirm that BP is increased; identify causes of SAH, target organ injuries, and associated diseases; and stratify cardiovascular risk. In addition to clinical history, cognitive tests, and physical examination including BMI and abdominal circumference, the following should be performed:

a) Resting EKG.

b) Urine examination (biochemical and sediment)

c) Blood tests: complete blood count, creatinine, blood glucose, potassium, fasting blood glucose, glycohemoglobin, total cholesterol and fractions, triglycerides, and uric acid. Blood levels of creatinine may be normal, in spite of declined renal function. This fact results from the progressive loss of muscle mass, a determining factor of creatinine production. Thus, creatinine levels > 1.5 mg/dL are considered abnormal in elderly patients. The formula most used to calculate estimated glomerular filtration rate (eGFR) is the Cockroff-Gault (mL/min): (140 – age) × weight (kg)/plasma creatinine (mg/dL) × 72, with a coefficient of 0.85 for women. Interpretation: normal renal function, > 90 mL/min; slight renal dysfunction, 60 to 90 mL/min; moderate renal dysfunction, 30 to 60 mL/min; severe renal dysfunction, < 30 mL/min.

d) ABPM and HBPM: to investigate white coat SAH and masked SAH, in cases where it is necessary to investigate episodes of arterial hypotension, or to evaluate the efficacy of SAH therapy.[193]

5.2. Treatment Peculiarities

5.2.1. Therapeutic Goals for Elderly Patients

Treating SAH in elderly patients represents a great challenge, as it involves a heterogeneous group, with multiple comorbidities, cognitive problems, risk of falling, polypharmacy, and frailty syndrome. Therapeutic goals for elderly patients should thus be individualized based on multidisciplinary team judgment, and they should consider patient preferences.[193,194] Dose adjustments should occur every 4 weeks, in order to avoid abrupt reductions of BP. The Hypertension in the Very Elderly Trial (HYVET) randomized, placebo-controlled study[194] included 3,845 patients with SBP ≥ 160 mmHg over the age of 80, with an average age of 83.6. Target blood pressure was 150/80 mmHg. They demonstrated that treatment with indapamide, with or without perindopril, was beneficial in octogenarians. In the intention-to-treat analysis, there was a 30% reduction in rate of fatal or non-fatal stroke, 39% reduction in the rate of death from stroke, a 21% reduction in death from any cause, a 23% reduction of in the rate of death from cardiovascular causes, and a 64% reduction in the rate of HF. Fewer severe adverse events occurred in the active treatment group (358 versus 448 in the placebo group). There is evidence that greatly lowering BP in elderly patients may be harmful; this fact is known as the J- or U-curve.[191] The recent SPRINT study[149] sought to evaluate two different BP goals. In the standard group, the goal was SBP < 140 mmHg and, in the intensive treatment group, the goal was SBP < 120 mmHg. The intensive treatment group had a significant reduction in primary events (infarction, other acute coronary syndromes, stroke, HF, or death from cardiovascular causes) in comparison with the standard treatment group. Although the initial impression may be that more intensive goals may be more beneficial, it is necessary to consider that there was an increase in the number of severe adverse events, such as hypotension, syncope, electrolytic disorders, and acute renal insufficiency, in the intensive treatment group. Another important study was the ACCORD,[35] performed with 10,251 diabetic patients, ages 40 to 79, 4,733 of which were also randomized for BP reduction < 140 mmHg or < 120 mmHg. However, BP reduction with more intensive goals did not succeed in significantly reducing the risk of the study's primary outcome (death from CVD, nonfatal infarction, and nonfatal stroke). Thus, to date, the III Geriatric Cardiology Guidelines recommends SBP levels ≤ 130 mmHg for elderly patients ≥ age 65, who are considered robust and who do not have frailty criteria.[195,196] For patients ≤ 80 years old, without frailty, SBP levels < 140 mmHg may be considered;[195] in patients ≥ age 80 with SBP ≥ 160 mmHg, an initial reduction to SBP

between 150 and 140 mmHg may be considered;[7] in fragile elderly patients or patients with multiple comorbidities, the therapeutic goal should be individualized, considering each case's risk-benefit ratios.[196]

5.2.2. Medical and Non-Medical Treatments

Salt reduction should be cautious and well accompanied by the doctor, given that the elderly patient's diminished taste sensitivity may make food appear blander, causing the patient to eat less and thus bringing about the risk of malnutrition. It is also necessary to remember that elderly patients rarely present only one chronic disease. The evaluation of multimorbidities generally defines what the best treatment is and what drugs should be avoided in each specific case. Treatment should be initiated with low doses, and dose adjustments should be gradual. Adherence needs to be stimulated, if possible, by monthly control at the beginning of treatment and at each dose adjustment. The most commonly used drugs in elderly patients are:

a) Diuretics: thiazides and correlates (hydrochlorothiazide, chlorthalidone, indapamide) are considered first-line drugs in elderly patients without comorbidities. Their use is preferential in osteoporosis patients, as they decrease urinary excretion of calcium, and in initial phases of congestive heart failure (CHF), as they reduce preload, volume, and pulmonary congestion. Recommended doses of hydrochlorothiazide: 6.25 to 25 mg/day, maintaining efficacy and reducing adverse metabolic effects.[191] In most cases, diuretics are associated with therapeutic schedules. However, they should be avoided in elderly patients with incipient urinary incontinence, gout (because they increase uric acid) and prostatism.[191] Attention should be paid to blood glucose in elderly patients with concomitant use of thiazides and oral antidiabetics or insulin, given that thiazides may increase blood glucose and interfere with diabetes control.

b) Calcium channel blockers: they include both dihydropyridine and non-dihydropyridine derivatives. Dihydropyridine derivatives have major vasodilatory effects. The most recent generation provokes less edema. They are very commonly used in elderly SAH and symptomatic coronary disease patients. Non-dihydropyridine derivatives, especially verapamil, have fewer vasodilatory effects, and they are not usually prescribed to elderly patients, as they may alter electrical impulses of atrioventricular conduction. Verapamil may, furthermore, provoke intestinal constipation.

c) ACEI: they continue to be efficacious in elderly patients, notwithstanding the decrease in renin with aging. They decrease cardiovascular events and should be used in elderly patients with SAH and HF or asymptomatic ventricular dysfunction. Adverse effects include changes in taste, especially with captopril, which may reduce food intake, and dry cough, which limit their use. It is fundamental to check potassium, due to frequent reductions in renal function.

d) Angiotensin II receptor antagonists (ARA-II): they are effective in HF, and they have an established renal and cardiac protective action in type 2 diabetes with nefropathy.[191] ARA-II have a favorable tolerability profile, with few adverse effects (occasional dizziness and, rarely, hypersensitive skin reaction). They are well used in cases of ACEI intolerance.[193]

e) Beta-blockers: they are not used as initial monotherapy in elderly patients without comorbidities, due to their lower effects on BP reduction; however, in association with diuretics, they present good results. They are mainly used in elderly patients with SAH and coronary insufficiency or HF. Less liposoluble beta-blockers, such as atenolol, metoprolol, and bisoprolol, are recommended for elderly patients because they have lower risks of collateral effects on the central nervous system (depression, drowsiness, confusion, sleep disturbances).[193]

In summary, elderly patients have particularities regarding SAH diagnosis and approach. It is necessary to consider each patient's comorbidities and particularities, including functional status, which may be determining factors for setting BP goals and for patient decision making.

Recommendation	Grade of recommendation	Level of evidence
SBP ≤ 130 mmHg for elderly patients ≥ age 65, without frailty	I	A
SBP < 140 mmHg for elderly patients ≤ age 80, without frailty	IIb	C
For elderly patients > age 80, with initial SBP ≥ 160 mmHg, initial SBP reduction between 150 and 140 mmHg	I	B
In fragile elderly patients or patients with multiple comorbidities, the therapeutic goal should be individualized, considering risk-benefit ratios	IIa	C

SBP: systolic blood pressure.

6. Valvulopathies

6.1. Mitral Stenosis

6.1.1. Diagnostic Peculiarities

Mitral stenosis (MS) is rare in elderly patients (present in 6% of patients with mitral annulus calcification).[197]

Etiology – Sequel of rheumatic carditis or calcification of the mitral valve apparatus in patients > 85 years old.[198]

Symptoms – similar to those observed in non-elderly patients. Symptoms may be absent. The most frequent are dyspnea and cough, which may be accompanied by hemoptoic sputum. It may manifest as systemic embolism or AF.

Physical examination – Hyperphonetic first heart sound and apical mid-diastolic murmur with thrill may be absent. The opening snap of the mitral valve is rarely auscultated. Most patients > age 80 present AF with elevated HR which, in association with a greater anteroposterior thorax diameter, makes auscultation difficult. The more fibrosis and calcification are present in the mitral valve, the less audible the auscultatory signs of MS will be. Diagnostic suspicion may be established based on signs of pulmonary arterial hypertension (P2 hyperphonesis in the second heart sound, RV insufficiency,

pulmonary and tricuspid regurgitation). In elderly pulmonary arterial hypertension patients without any other evident cause, it is important to investigate MS.[199-202]

Complementary exams – EKG, chest radiography, and echocardiogram are sufficient, in most cases, to confirm diagnosis and estimate severity. The following may be found in the EKG: left atrial overload (LAO), RV hypertrophy, and AF. Chest radiography findings include: increased LA, mitral valve calcification, and posterior displacement of the barium-filled esophagus. Echocardiography data include: mitral annulus calcification (in 60% of elderly patients > age 85),[4] mitral valve area (Table 8), pulmonary BP, and status of the valvular apparatus (mobility, thickening, and subvalvular impairment).[5]

6.1.2. Treatment Peculiarities

Clinical treatment – Patients with mild MS are generally asymptomatic, and they do not need to receive medication,[203] unless they also suffer from AF. Unlike younger patients, elderly MS patients who develop AF have a higher chance of showing symptoms of HF, owing to the concomitant present of diastolic dysfunction. Thus, in cases of paroxysmal AF with hemodynamic deterioration, even if MS is mild, electrical cardioversion is indicated. Patients with MS and AF, be it permanent, persistent, or paroxysmal, should constantly use warfarin, regardless of risk scores, with the aim of keeping the international normalized ratio (INR) between 2 and 3, unless there is a formal contraindication.[204] Although some publications recommend the use of new oral anticoagulants in this situation, these data have yet to be evaluated in comparative studies.[205] The finding of LA thrombus or the occurrence of a systemic embolic event, even in the presence sinus rhythm (SR), also indicate the need for anticoagulant use. In MS of rheumatic etiology, prophylaxis for rheumatic fever is not necessary, given that elderly patients rarely have relapses of this disease.[206] Early treatment of bacterial infections is recommended with the aim of protecting the patient from the risk of infective endocarditis (IE). Chemoprophylaxis against IE in elderly MS patients is not indicated.[207] In symptomatic patients with moderate to severe MS, loop diuretics are the best option for controlling pulmonary or systemic congestion, and beta-blockers are indicated for reducing HR and facilitating atrial emptying. There is no evidence that the use of beta-blockers is beneficial in patients with SR who do not have elevated HR.[208] In the presence of AF with elevated ventricular response, beta-blockers are the drugs of choice for reducing HR. In cases where they are contraindicated, nondihydropyridine calcium channel blockers or digitalis may be used. In the presence of signs of RV failure with associated hepatomegaly, due to the frequent coexistence of secondary hyperaldosteronism, elevated doses of spironolactone (100 mg/day) are an option.[209] Caution is necessary with the risk of hyperkalemia.

Options for correcting MS – When evaluating an elderly patient with MS who has been indicated for intervention, the following should be considered and discussed with the patient and/or family members: etiology, whether rheumatic or degenerative; patient life expectancy; evaluation of functionality; and the presence of multimorbidities. There are 2 options for correcting rheumatic MS: percutaneous balloon mitral valvuloplasty (PBMV) or extracorporeal circulation surgery. Randomized clinical trials have shown that, in selected cases, PBMV offers immediate and long-term results similar to those of open commissurotomy.[210] For this intervention, presence of favorable valve morphology is important. This may be evaluated by several proposed echocardiography criteria, the Wilkins and Block score being the most widely used.[211] It is, additionally, necessary to respect contraindications to this procedure (presence of LA thrombus or mitral regurgitation with more than a mild degree of severity). Unfortunately, elderly patients frequently have valve morphologies which are unfavorable for this procedure, whether the etiology be rheumatic or degenerative.[212] In the latter case, owing to the fact there is no commissural fusion, as occurs in rheumatic disease, the success of PBMV is restricted, and mitral valve replacement surgery is the procedure of choice. As degenerative MS patients frequently have multimorbidities that elevate their risks, clinical treatment should be attempted initially; mitral valve replacement surgery is indicated only in cases that do not respond to clinical treatment.[213] There are reports of small series of percutaneous implants of mitral prostheses in degenerative MS patients, with relative success.[214]

Table 8 – Severity of mitral stenosis

	Pressure gradient (LA-LV) in mmHg	Mitral valve area (cm²)
Mild	< 5	> 1.5
Moderate	5 a 10	1 a 1.5
Severe	> 10	< 1

LA: left atrium. LV: left ventricle.[202]

Medical treatment of elderly mitral stenosis patients

Recommendation	Grade of recommendation	Level of evidence
Regardless of severity, MS patients who have AF, be it permanent, persistent, or paroxysmal, should receive warfarin indefinitely, with the aim of keeping INR between 2 and 3, unless this is contraindicated	I	B
MS patients indicated for warfarin may use direct oral anticoagulants	IIb	C
Elderly rheumatic MS patients should receive prophylaxis to prevent rheumatic fever	III	C
Elderly MS patients with MVA less than or equal to 1.5 cm²; FC II, III, or IV; and/or signs of RVF should receive loop diuretics to alleviate symptoms	I	C
Elderly MS patients with MVA less than or equal to 1.5 cm²; FC II, III, or IV; and SR, who continue to be symptomatic in spite of diuretic use, if HR is over 60 bpm, should receive beta-blockers, unless there are contraindications	IIa	B

Elderly patients with mild MS who develop AF with elevated ventricular response should receive beta-blockers to control ventricular response, unless there are contraindications	IIa	C
In the previously described cases, nondihydropyridine calcium channel blockers or digitalis may be used, in the event that beta-blockers are contraindicated	IIa	C
MS patients with signs of RVF and hepatomegaly, without adequate response to loop diuretics, should receive spironolactone.	IIb	C

AF: atrial fibrillation; bpm: beats per minute; FC: New York Heart Association functional class; HR: heart rate; INR: international normalized ratio; MS: mitral stenosis; MVA: mitral valve area; RVF: right ventricle failure; SR: sinus rhythm.

Indications for intervention in elderly rheumatic mitral stenosis patients

Recommendation	Grade of recommendation	Level of evidence
Elderly symptomatic rheumatic MS patients (FC II-IV), with MVA ≤ 1.5 cm^2, who have favorable valve morphology and no contraindications, should undergo PBMV	I	A
Elderly rheumatic MS patients who, although they are very symptomatic (FC III/IV) with MVA ≤ 1.5 cm^2, but with unfavorable valve morphology or contraindication to PBMV, without elevated surgical risk or low life expectancy, should be referred for open valvuloplasty or valve replacement surgery	I	B
If the MS patient is in FC II with MVA ≤ 1.5 cm^2, but is not a candidate for PBMV, it is prudent to maintain medical treatment as long as the patient does not become more symptomatic	IIb	C
Rheumatic MS patients with MVA ≤ 1.5 cm^2 who are indicated for AVR, ascending aorta surgery, or MRS, should also undergo valvuloplasty or mitral valve replacement	I	C
PBMV is indicated for rheumatic MS patients, with MVA ≤ 1.5 cm^2, even if they are asymptomatic, notwithstanding pulmonary arterial hypertension (PASP > 50 mmHg), whose probably etiology is MS, when valve morphology is favorable, in the absence of contraindication	IIa	C
Severe rheumatic MS patients (MVA ≤ 1.0 cm^2), who are asymptomatic and who have favorable valve morphology for PBMV and no contraindications, should undergo the procedure	IIb	C

AVR: aortic valve replacement; FC: New York Heart Association functional class; MS: mitral stenosis; MRS: myocardial revascularization surgery; MVA: mitral valve area; PASP: pulmonary artery systolic pressure; PBMV: percutaneous balloon mitral valvuloplasty.

Indications for intervention in elderly degenerative mitral stenosis patients

Recommendation	Grade of recommendation	Level of evidence
MVR in elderly degenerative MS patients who do not respond adequately to clinical treatment and who have low surgical risk and high life expectancy	IIa	C
PBMV in elderly degenerative MS patients, FC III/IV, who do not respond to clinical treatment, with high surgical risk	IIb	C
Percutaneous implants of mitral prosthesis in very symptomatic patients who do not respond to clinical treatment and who are not candidates for open surgery or PBMV	IIb	C

FC: New York Heart Association functional class; MS: mitral stenosis; MVR: mitral valve replacement; PBMV: percutaneous balloon mitral valvuloplasty.

6.2. Mitral Regurgitation

6.2.1. Diagnostic Peculiarities

From the etiological point of view, mitral regurgitation (MR) may be: (a) primary: when there are histological changes in the valve, for example, myxomatous degeneration, degenerative fibroelastic disease, and IE; or (b) secondary: when MR is functional and the valve is histologically normal, for example, poor leaflet coaptation with dilated cardiomyopathy. MR is common in elderly patients; the degenerative cause is the most frequent, followed by ischemia, and, less frequently, rheumatic disease and IE.[215,216] Acute MR is mainly linked to CAD by papillary muscle dysfunction or chordae tendineae rupture, with condition of acute HF.

Symptoms – symptoms of chronic MR are related to severity, rate of disease progression, pulmonary BP, presence of arrhythmias (e.g., AF), and associated diseases. The most common symptoms are stress dyspnea and fatigue.

Physical examination – The following are present: protosystolic murmur in mitral focus, variable intensity, and displaced ictus, with characteristics of volumetric overload. Thoracic deformities, which are common at this age, may modify ictus, sounds, and murmurs.[102,202]

Complementary exams – During EKG, frequent abnormalities are LAO, AF and left ventricular overload (LVO).[217] In the presence of ischemic MR, electrocardiographic signs of coronary insufficiency, such as electrically inactive zones and alterations in ventricular repolarization, may occur.[218] In cases of acute MR, EKG may be normal, or it may show only sinus tachycardia.[217,219] Chest radiography aids detection of comorbidities, evaluation of pulmonary congestion, and distinction between acute and chronic cases. In cases of acute MR, the heart may have normal dimensions, and pulmonary congestion may, nevertheless, be present. In cases of chronic MR, there will be an increase in the LA and LV.[217,218,220] Transthoracic echocardiography is indispensable for diagnosing and evaluating degree of mitral regurgitation, chamber size, and ventricular function. The sizes of the LA and LV and measurements of pulmonary

artery pressure are especially important. Identification of the cause and detailed evaluation of valvular apparatus impairment, leaflet morphology, and reflux mechanism are important for deciding whether the most adequate treatment is mitral valve replacement or plasty.[202,221,222] Transesophageal echocardiography (TEE) may be used when there are technical difficulties to acquiring an adequate echocardiography window. Cardiac catheters are indicated for diagnosis of CAD in patients referred for surgery and in cases where there are doubts regarding the severity of the lesion.[102,202,221,222] ET/ergospirometry may be used to evaluate the reproduction of symptoms and changes in tolerance to exercise. They are less used with very elderly patients with physical limitations.[202,217,221,222] Magnetic resonance and computerized tomography are not routinely used in patients with mitral disease, but they may be indicated when the severity of MR or LV function have not been adequately evaluated by echocardiogram or when there are discrepancies.[221,222]

6.2.2. Treatment Peculiarities

Treatment of MR should consider its etiology and severity. AF, pulmonary hypertension, and symptoms are relevant factors in the decision making process. Elderly patients > age 75 have elevated surgical risks. Surgical management in this age range will aim to improve and maintain quality of life. Thus, the symptoms present are a determining factor for surgical indication. Patients with ventricular dysfunction who are asymptomatic should continue clinical treatment.[221] Therapeutic decisions for MR should be guided by presentation (acute or chronic), clinical hemodynamic profile, and severity of symptoms. Echocardiography parameters, such as LVEF, left ventricular end-systolic diameter (LVESD), and the presence of dyspnea are indicators for surgical therapy (See the following recommendations table). Mitral plasty is the preferred surgical treatment. Currently, mitral clips are an incipient and promising alternative.[221,223]

Treatment of acute MR – In patients with acute, severe MR, immediate surgical treatment is recommended. Some patients with moderate MR may develop hemodynamic compensation due to LV dilation, thus making lower filling pressure and normalization of cardiac output possible. In cases of chordae tendineae rupture, mitral repair is preferable to mitral replacement, and surgery may be scheduled according to the patient's clinical and hemodynamic status.[221,223,224] Medical treatment of acute MR must by implemented as a support therapy for the definitive surgical correction.[221] In the presence of severe manifestations, such as acute pulmonary edema or shock, vasoactive drugs, such as intravenous vasodilators, sodium nitroprusside, nitroglycerin, and vasopressin amines, in addition to an intra-aortic balloon for hemodynamic support, should be used up to the moment of the indicated surgical procedure.[223]

Treatment of chronic MR – Patients with chronic, asymptomatic MR and normal LVEF are not indicated for medical treatment. There is no evidence that long-term treatment with vasodilators presents therapeutic benefits.[221] In symptomatic patients, treatment with ACEI, beta-blockers, such as carvedilol, and diuretics should be implemented.[224,225] Biventricular pacemakers in patients classified as "responders" show improvements in MR in reverse LV geometry.[226] Patients with symptomatic chronic primary MR should undergo surgical treatment, preferably plasty, regardless of LV function. Asymptomatic patients who have progressive dysfunction (LVEF < 0.60) and/or increased ventricular diameters (LVESD > 45 mm), should also be considered surgery. Indication for valve surgery in elderly patients > age 75 has not been consistently evaluated in clinical trials, it being necessary to prioritize the presence of symptoms as an indication for invasive intervention. In valve replacement surgery, bioprostheses are indicated in elderly patients owing to their lower rates of prosthetic dysfunction and to the inherent risks of anticoagulant therapy.[227,228]

Percutaneous treatment of mitral regurgitation – Percutaneous treatment of MR has been performed, particularly in Europe. In Brazil, MitraClip® is the only commercially available device, and it is used only in select cases, owing to the high cost. The use of this device is indicated in patients whose primary chronic MR is degenerative in etiology and whose surgical risks are high or prohibitive. Furthermore, patients with chronic MR secondary to ventricular dilation who are refractory to optimized clinical treatment and cardiac resynchronization may eventually benefit from this procedure. In symptomatic patients with severe MR due to degeneration of a bioprosthesis or previously implanted valve rings and prohibitive surgical risks, percutaneous mitral replacement via the valve-in-valve procedure at a specialized center is an alternative. Percutaneous mitral replacement for symptomatic patients with severe native valve MR and prohibitive surgical risks is at an advanced phase of development and should be available in Brazil in the coming years.[229]

Recommendations for MR surgery

Recommendation	Grade of recommendation	Level of evidence
Symptomatic patients with severe acute MR	I	C
Symptomatic patients with severe chronic primary MR and normal left ventricular function	I	B
Asymptomatic patients severe chronic primary MR and left ventricular function (EF 30-60% and/or end-systolic diameter ≥ 40 mm)	I	B
Plasty is preferable to mitral replacement in severe chronic primary MR patients	I	B
Plasty or mitral replacement is indicated in patients with severe chronic primary MR and patients undergoing concomitant heart surgery	I	B
Mitral replacement is preferable to plasty in patients with chronic secondary MR of ischemic etiology	I	A
Mitral plasty may be considered for chronic primary (non-rheumatic) MR, normal ventricular function, and new atrial fibrillation or pulmonary hypertension (resting PASP > 50 mmHg)	IIa	B

Plasty or mitral replacement may be considered for symptomatic patients with chronic primary MR and FE ≤ 30%	IIb	C
Mitral plasty via catheter may be considered for symptomatic patients (FC III/IV) with chronic primary MR and prohibitive surgical risk	IIb	B
Mitral plasty may be considered for symptomatic patients (FC III/IV) with chronic secondary (functional) MR who are refractory to clinical treatment and cardiac resynchronization	IIb	C
For symptomatic patients with severe MR due to degeneration of a bioprosthesis or previously implanted valve rings and prohibitive surgical risks, percutaneous mitral replacement at a specialized center may be considered	IIb	C
Asymptomatic patients with severe MR and preserved left ventricular function (LVEF > 60% and end systolic diameter < 40 mm)	III	C
Plasty or mitral replacement may be considered for patients with moderate MR who are undergoing concomitant myocardial revascularization surgery	III	A

EF: ejection fraction; FC: New York Heart Association functional class; LVEF: left ventricular ejection fraction; MR: mitral regurgitation; PASP: pulmonary artery systolic pressure.

6.3. Aortic Stenosis

6.3.1. Diagnostic Peculiarities

In order to diagnose AS, the most frequent valvulopathy in elderly patients, it is necessary to consider clinical history, which may be difficult in this age range due to possible cognitive and sensory alterations.

Symptoms – Patients may be asymptomatic or present dyspnea, angina pectoris, or syncope.

Physical examination – Findings may include: (a) impulsive type *ictus cordis*, which may be absent in elderly patients due to increased anteroposterior diameter of the rib cage; (b) the *parvus et tardus* pulse (reduced amplitude and longer duration time), which is characteristic of AS in younger patients, may be absent in elderly patients, due to the stiffening of arterial walls which promotes an increase in PWV, thus masking this semiological finding; (c) mid-systolic murmur in crescendo and decrescendo which radiates toward the neck and clavicles. Gallavardin's phenomenon is frequently auscultated. This is a radiation of the AS murmur to the apical region; (d) hypophonetic second sound.

Complementary exams – EKG may present findings compatible with LAO and LVO. Chest radiography may be normal, in approximately half of elderly patients examined, or there may be aspects of hypertrophy, which may or may not present post-stenotic aortic dilatation. Echocardiography is a fundamental exam for diagnosing and classifying this valvulopathy. Three echocardiography parameters are frequently used to classify severity of AS: (a) peak aortic jet velocity; (b) mean transvalvular gradient; (c) valve area (Table 9). The ET has been indicated for asymptomatic patients with severe AS in order to verify the hemodynamic response to effort; on the other hand, its use in elderly patients should be individualized, owing to the presence of multimorbidities which may impede the procedure.

6.3.2. Treatment Peculiarities

Medical treatment – Arterial hypertension is common in elderly AS patients. It contributes to increased total afterload, in conjunction with obstruction, thus promoting LV overload. In elderly patients, it is necessary to begin antihypertensive treatment with low doses and gradually increase posology. It is necessary to be cautious when using diuretics, due to the risk of hypotension. ACEI may be advantageous due to their effect on ventricular fibrosis, and beta-blockers are appropriate in patients with CAD. Statin use is not indicated for preventing the progression of AS.[203] In the presence of HF, beta-blockers should be initiated with low doses, and the same precautions should be taken in prescribing aldosterone antagonists, ACEI, and ARB, and especially with digitalis drugs, as their toxicity and therapeutic thresholds are close.[203] In elderly patients, it is important to evaluate creatinine clearance in order to adjust dosages and thus avoid drug intoxication.

Surgical treatment – Indicating surgery, whether aortic valve replacement or transcatheter aortic valve implantation (TAVI), depends on a set of factors, including: severity of valve lesion; complementary exam data; evaluation of multimorbidities; risk scores, for example the STS score; and functional evaluation (frailty and cognitive function). Deciding on percutaneous implantation requires a multidisciplinary team for integrated action.[203,230] The first step in deciding on surgery is establishing that the patient has a severe aortic valve lesion, which, associated with the presence of symptoms, presents a high grade of recommendation. Surgical treatment may still be offered to asymptomatic patients with ventricular dysfunction (LVEF < 50%) or who have already scheduled another cardiac surgery.[203] In relation to the risks of surgical procedures, patients are classified as low risk: STS < 4%, without frailty, without comorbidity; intermediate risk: STS 4% to 8%, mild frailty, affected organic system; high risk: STS > 8%, moderate to severe frailty, more than 2 affected organic systems; prohibitive risk: pre-operative risk > 50% in 1 year, 3 affected organic systems, or extreme frailty.[203,231] In most cases, the decision is complex, making it necessary to involve family and the medical and multidisciplinary team and, above all, to respect the patient's own wishes. When the benefits are considered less than the risks, palliative care may be the patient's best option.

Table 9 – Diagnosis and classification of aortic stenosis severity

Indicator	Mild	Moderate	Severe
Jet velocity (m/s)	< 3.0	3.0 to 4.0	> 4.0
Mean gradient (mmHg)	< 25	25 to 40	> 40
Valve area (cm^2)	> 1.5	1.0 to 1.5	< 1.0

Recommendations for medical treatment of AS		
Recommendation	**Grade of recommendation**	**Level of evidence**
Systemic arterial hypertension should be treated in asymptomatic AS patients, starting with a low dose of anti-hypertensive and gradually increasing, as necessary, with frequent clinical follow-up	I	B
Vasodilator therapy may be used in association with invasive hemodynamic monitoring to treat patients with severe decompensated AS, with New York Heart Association class IV symptoms of HF	IIb	C
Statin use is not indicated to prevent the progression of AS in patients with mild to moderate calcified lesions	III	A

AS: aortic stenosis, HF: heart failure.

Recommendations for surgical treatment of AS		
Recommendation	**Grade of recommendation**	**Level of evidence**
Symptomatic patients with severe AS	I	B
Asymptomatic patients with severe AS and LVEF < 50%	I	B
Patients with severe AS scheduled to undergo other cardiac surgeries	I	B
Asymptomatic patients with very severe AS (transvalvular jet velocity ≥ 5.0 m/s) and low surgical risk	IIa	B
Asymptomatic patients with severe AS and diminished exercise tolerance or	IIa	B
effort hypotension	IIa	C
Patients with moderate AS scheduled to undergo other cardiac surgeries	IIb	C

AS: aortic stenosis; LVEF: left ventricular ejection fraction.

The choice between surgical aortic valve replacement and TAVI		
Recommendation	**Grade of recommendation**	**Level of evidence**
Surgical aortic valve replacement is recommended in patients who have indications for surgical treatment and who have low or intermediate surgical risks	I	A
In patients under consideration for TAVI and in those with high surgical risk for valve replacement, members of a Heart Team should collaborate to provide the patient with the best care possible	I	C
TAVI is recommended for patients indicated for surgical aortic valve replacement, with prohibitive surgical risk and post-TAVI life expectancy of more than 12 months	I	B
TAVI is a reasonable alternative to surgical aortic valve replacement in patients who meet indications for surgical treatment and who have high surgical risks	IIa	B
Balloon aortic valvuloplasty may be considered as a bridge to surgical or percutaneous valve replacement in severely symptomatic patients with severe aortic stenosis	IIb	C
TAVI is not recommended for patients whose existent comorbidities would impede the benefits expected from correction of aortic stenosis	III	B

TAVI: transcatheter aortic valve implantation.

6.4. Aortic Regurgitation

6.4.1. Diagnostic Peculiarities

AR is less common in elderly patients than AS and MR.

Etiology – The most common causes of chronic AR in elderly patients are ascending aorta dilation due to SAH, primary aortic disease, calcified valve disease, and, rarely, atrioventricular block (AVB). Another cause is rheumatic cardiac disease (especially in developing countries).[232]

Symptoms – Chronic AR evolves slowly and insidiously in most cases, with very low morbidity during the asymptomatic phase. After this phase, some patients present progression of the regurgitant lesion, with subsequent LV dilation, systolic dysfunction, and, eventually, HF.[233] Mortality rates for patients with severe AR with NYHA class II symptoms are approximately 6% yearly and almost 25% in patients in NYHA classes III or IV.[234]

Physical examination – The murmur is diastolic, decrescendo, blowing, and high frequency, and it is best heard in the left sternal border or in aortic focus. Its severity is more related to duration of murmur than to intensity. The ictus is dislocated, revealing LV volumetric overload, and its dimension is related to lesion severity. Peripheral alterations, which are characteristics of severity in young patients (increased PP, arterial neck pulsation, and systolic pulsation in the head), may be exacerbated in elderly patients, given that alterations resulting from the loss of elasticity of the great arteries may accentuate them.

Complementary exams – EKG is not very specific in AR, and the routine finding is LVO in cases with long duration. Chest radiography helps detect comorbidities, evaluate pulmonary congestion, and distinguish between acute and chronic cases. Acute cases present pulmonary congestion and normal or slightly enlarged cardiac area. Chronic cases present increased cardiac area secondary to LV dilation. Ascending aorta dilation, on the other hand, suggests that the AR is secondary to aneurysmal dilatation of the aorta. Echocardiography is the pillar of serial monitoring and evaluation of chronic AR patients. It is useful for confirming diagnosis, evaluating cause and valve morphology, estimating lesion severity, and evaluating LV dimensions, mass, and systolic function, as well as aortic root dimensions.[203] For patients with suspected moderate or severe AR, cardiovascular magnetic resonance (CMR) provides precise quantification

of regurgitant volume and fraction, in addition to precise measurements of LV volumes and function. CMR is particularly useful when the degree of LV dilatation in echocardiography seems to be greater than what would be expected. Cardiac catheterization should be performed routinely in all patients referred for surgical correction or coronary disease evaluation, or when clinical and laboratory tests are unclear or divergent regarding AR severity.[203]

6.4.2. Treatment Peculiarities

In cases of severe acute AR, surgical treatment should be implemented as early as possible, especially if there are signs and symptoms of low cardiac output. In these cases, clinical treatment is inferior to surgical treatment. Inotropic drugs and vasodilators may aid clinical control while the patient is waiting for surgery.[203,235]

Clinical treatment – Clinical treatment of AR patients with vasodilators is applied to those with associated SAH and those with severe symptomatic AR and high surgical risks, especially owing to comorbidities, in order to alleviate symptoms. They are not routinely recommended for patients with mild, moderate, or severe asymptomatic chronic AR and normal systolic function.[203,235] Studies have not demonstrated the efficacy of these drugs in slowing surgical indication in AR patients, and they do not substitute surgery when it is indicated.[236]

Surgical treatment – Patients with severe symptomatic AR, as well as some asymptomatic patients, have reduced quality of life and life expectancy without surgical treatment. Selecting the appropriate moment for and type of procedure is paramount for a satisfactory surgical result; it is, naturally, necessary to observe and respect functionality and associated comorbidities in this group of patients.[235] Surgical treatment is indicated for patients with severe symptomatic AR or for asymptomatic patients with reduced LVEF or significant LV dilatation.[203,235] There has recently been some speculation regarding aortic valve repair for this pathology, given that complications resulting from anticoagulant use in patients who receive mechanical prostheses are not uncommon. Scientific studies have demonstrated that valve repair is an independent predictor of better survival, with a great reduction in the need for reoperation.[237] Few centers, however, have the experience necessary to perform this procedure, and, in elderly patients, thickened, deformed, or calcified leaflets are common findings, which complicate the procedure.[203]

Percutaneous treatment – Percutaneous aortic valve implantation is an effective option for AR patients with moderate or high risks for conventional valve replacement surgery. The use of TAVI is still off-label for AR patients, but studies have demonstrated that it is feasible and will be able to be a treatment alternative.[238]

Recommendations for surgical treatment of aortic regurgitation

Recommendation	Grade of recommendation	Level of evidence
Symptomatic patients with severe AR, regardless of LV systolic function	I	B
Asymptomatic patients, with severe AR and LVEF < 50%	I	B
Patients with severe AR scheduled to undergo other cardiac surgeries	I	C
Asymptomatic patients with severe AR, normal LV systolic function (LVEF ≥ 50%), and significant LF dilatation (LVSD > 50 mm)	IIa	B
Patients with moderate AR scheduled to undergo other cardiac surgeries	IIa	C
Asymptomatic patients with severe AR, normal LV systolic function (LVEF > 50%), progressive severe LV dilatation (LVEDD > 65 mm), and low surgical risk	IIb	C

AR: aortic regurgitation; LV: left ventricle; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVSD: left ventricular systolic diameter.

6.5. Infective Endocarditis

6.5.1. Diagnostic Peculiarities

IE, which was previously prevalent in young and middle-aged patients, owing to its association with rheumatic valve disease, has progressively increased in the elderly population.[239] In Europe and the United States, more than half of cases occur in patients > age 60. Diagnosis of IE in elderly patients may be more difficult owing to the fact that signs and symptoms such as mental confusion, fatigue, weight loss, and murmur may be attributed to age itself. The forms in which IE is present in elderly patients, such as clinical signs of stroke, HF, pneumonia, and abdominal pain, may also confuse the initial diagnosis. In some case registries, fever appears in only 2% of cases in elderly patients, in comparison with 90% of patients < age 60. Other not very specific symptoms, such as anorexia, weight loss, arthralgia, dyspnea, and headache, similarly appear in elderly patients. Classic peripheral signs of IE such as Osler's nodes, Roth spots, and petechiae, are less frequent in elderly patients, being found in 1% to 14% of cases.[240]

Laboratory and echocardiography data – hemogram may be normal or present leucocytosis, with the frequent presence of normochromic, normocytic anaemia. Erythrocyte sedimentation rate (ESR) may be elevated in 90% of cases. Positive rheumatoid factor is found in 50% of cases, and the majority of patients have proteinuria and microscopic hematuria.[241] Blood cultures: at least 3 blood samples should be collected during the first 24 hours, with intervals of less than 15 minutes between samples, and they must be collected before beginning antibiotic therapy, given that antibiotic use is the leading cause of failure to identify the germ responsible for endocarditis. In the most developed countries, blood cultures reach 80% to 95% positivity. Echocardiogram: with the advent of echocardiography in the 1980's,[242] the probability of diagnosing IE has increased, given that it is used to confirm the presence of vegetations, which are one of the 3 diagnostic pillars of IE, along with identification of the germ in blood culture and signs of affected valves, such as murmurs. In elderly patients, the sensitivity and specificity of transthoracic echocardiography is lower owing to the higher frequency of

calcified lesions and valve prostheses, as well as the presence of obesity and thoracic deformities.[243] TEE improves diagnostic accuracy, and it may be performed in elderly patients as safely as in younger patients.

Diagnostic criteria – In various cases of IE, diagnosis is uncertain due to the impossibility of demonstrating the existence of vegetations and to unspecific clinical manifestations, resulting in diagnostic errors. The Duke criteria, modified by Li et al.[244] (Table 10), are the most widely used to establish IE diagnosis. Nevertheless, IE diagnosis is a difficult process, but the inclusion of clinical, laboratory, and echocardiography data reduces the chance of error.

6.5.2. Treatment Peculiarities

As the population ages, IE affects more and more elderly individuals. More than a third of IE patients in Western countries are over age 70.[245] Mortality in elderly patients is also higher when compared to the general population.[246] Aging is a heterogeneous process, and it is always recommended to use AGA, which considers nutritional, functional, and cognitive status to better define prognosis as well as treatment options for this population.[247] The majority of elderly IE patients have multimorbidities, and the most common entryways for bacteria are the digestive and urinary tracts. Furthermore, these patients have predisposing factors, such as AS, valve

Table 10 – Criteria for diagnosing IE

Major criteria	
Microbiological	**Comments**
Typical isolated microorganism from two separate blood cultures: *Streptococcus viridans*, *Streptococcus bovis*, HACEK group, *Staphylococcus aureus*, or community-acquired enterococcal bacteremia, in the absence of a primary focus	In patients with possible IE, at least 2 blood cultures must be obtained in 2 different veins during the first 2 hours. In patients with septic shock, 3 blood cultures must be collected at 5–10 min intervals, after which point empirical antibiotic therapy should be initiated.
Or	
Persistently positive blood cultures consistent with isolated IE	
Or	
Blood culture positive for *Coxiella burnetii* or antibody titre (IgG) > 1:800 for *C. burnetii*	*C. burnetii* is not cultivated in most laboratory analyses
Evidence of endocardial involvement	
New valvular regurgitation (increases and changes in preexisting murmurs are not sufficient)	
Or	
Positive echocardiogram (TEE recommended for patients with prostheses, possible IE based on clinical criteria, or complicated IE)	Three TTE findings are considered major criteria: discrete oscillating intracardiac mass located on a valve or subvalvular structure, periannular abscess, and new dehiscence of prosthetic valve
Minor criteria	**Comments**
Predisposition to IE, including certain heart conditions and IV drug use	Cardiac abnormalities that are associated with IE are classified into 3 groups: ● High risk: previous IE, aortic valve disease, rheumatic valve disease, prosthetic valve, coarctation of the aorta, and complex cyanotic heart diseases ● Medium risk: mitral valve prolapse with leaflet insufficiency or thickening, isolated mitral stenosis, tricuspid valvulopathy, pulmonary stenosis, hypertrophic cardiomyopathy ● Low risk: Ostium secundum IAC, ischemic disease, previous revascularization surgery, and mitral valve prolapse without previous regurgitation, and mitral valve prolapse without regurgitation and with thin leaflets
Fever	Temperature > 38° C
Vascular phenomena	Except petechiae and hemorrhagic suffusions
	No peripheral lesions are pathognomonic of IE
Immunologic phenomena	Rheumatoid factor, glomerulonephritis, Osler nodes, Roth spots
Microbiological findings	Positive blood cultures that do not meet major criteria. Serological evidence of active infection, isolation of coagulase-negative staphylococci and organisms that rarely cause IE are excluded from this category
Cases are clinically defined as "definite IE" if they meet 2 major criteria, 1 major criterion and 3 minor criteria, or 5 minor criteria and "possible IE" if they meet 1 major criterion and 1 minor criterion or 3 minor criteria.	

HACEK: Haemophilus aphrophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens and Kingella kingae; IAC: interatrial communication; IE: infective endocarditis; IgG: immunoglobulin G; IV: intravenous; TEE: transesophageal echocardiography; TTE: transthoracic echocardiography.

prostheses, and intracardiac devices.[248] In defining treatment, the international literature makes no considerations regarding age and its consequences for treatment choice.[248-250] AGA data and the presence of frailty syndrome are factors which should be considered in deciding on a proposed treatment.[207,240,250,251] Table 11 shows examples of possible adaptations for elderly patients. The majority of elderly patients have decreased renal function; nephrotoxic antibiotics should, thus, be used carefully and, in some cases, even avoided in this population.[252] Treatment of IE often entails prolonged hospital stay, which is associated with functional and cognitive decline in the elderly population. The use of outpatient parenteral antibiotic therapy should be encouraged in this population, thus avoiding the complications of prolonged hospital stay; this requires that the patient's infection be controlled and the clinical situation stabilized, in addition to long-term venous access. In the event of difficult venous access, the subcutaneous or even the oral route may be considered, depending on the antibiotic in use.[252] Regarding surgical treatment, the indications are the same as in the general population (severe valvular lesion with HF, large vegetation with a risk of systemic embolism, and uncontrolled infection); in this context, however, AGA becomes more important in deciding on surgical treatment due to the fact that the risks of existing multimorbidities may interfere with the planned procedures. In these cases, a careful risk-benefit assessment of the procedures must be performed in an individualized manner.[253] When surgery is indicated, the decision should be made in a multidisciplinary fashion, and, when possible, it should involve the opinion of an infectologist, cardiologist, cardiac surgeon, anesthesiologist, and geriatrician, in order to define patients who may or may not benefit from a surgical procedure with the highest possible accuracy.[252]

7. Cardiac Arrhythmias

Arrhythmias and conduction disorders are common in elderly patients, and they are an important cause of emergency room visits and hospitalization in this age group.[1] Structural alterations in the cardiovascular system, which are promoted by aging and are associated with a higher incidence of comorbidities such as LVH, CAD, degenerative valvulopathy, SAH, LV dysfunction, and pulmonary disease, in addition to polypharmacy, are responsible for the increased prevalence of arrhythmias in this population.[254-258] Clinical evaluation should be meticulous, as many elderly patients have atypical manifestations such as unexplained falls, intermittent mental confusion, thromboembolic events, and syncope; some are even asymptomatic and are casually detected during routine EKG.[257] Multimorbidities, frailty syndrome, and impaired functionality and cognitive function interfere with the management of arrhythmias in this group, which should be individualized.

This section will discuss the diagnostic and treatment peculiarities of the main cardiac arrhythmias in elderly patients.

7.1. Syncope and Bradyarrhythmias

7.1.1. Syncope and its Differential Diagnoses in Elderly Patients

Syncope has a multifactorial etiology in elderly patients. Postural hypotension, also known as orthostatic hypotension (OH) is common, secondary to medication use and severe arrhythmias. It has an average prevalence of 6%, increasing exponentially with age.[254] It has a recurrence rate of 25% to 30% per year, in the first 2 years.[255] It is an independent predictor of morbimortality, reduced functional capacity and institutionalization,[257] as well as a frequent cause of hospital admission. Cardiogenic syncope has the worst prognoses, accounting for up to 20% of cases in elderly patients.[258] Bradyarrhythmias (sinus node disease or advanced AVB) are commonly related to syncope in elderly patients. Tachyarrhythmias manifest with syncope less frequently; they are "on-off" type manifestations, with sudden onset and without short-duration prodromes. They are unrelated to orthostatic position and characterized by fast recovery. It is worthwhile to remember that AS is a possible cause of effort-induced syncope in elderly patients. The following are considered to be predictors of cardiogenic syncope, according to the Evaluation of Guidelines in Syncope Study 2 (EGSYS-2) score: EKG abnormalities, structural heart disease, palpitations before syncope, syncope during effort or in the supine position, absence of autonomic prodromes, and absence of triggering or precipitating factors (≥ 3 points suggest cardiogenic syncope).[259] The presence of dyspnea before

Table 11 – Adaptations of the 2015 guidelines for elderly patients in accordance with comorbidities and functional status[252]

	Guidelines	Suggestion for elderly patients
Transesophageal echocardiography	Consider in all cases, in accordance with clinical suspicion	Assess risk-benefit of the procedure
Aminoglycosides	Combined to penicillin or vancomycin as first choice	Avoid, due to nephrotoxicity. Evaluate alternatives
Vancomycin	First-line treatment in beta-lactam allergic patients or in cases of MRSA	Consider daptomicine to avoid nephrotoxicity
Monitoring of antibiotic serum levels	Vancomycin and aminoglycosides	Consider also for all beta-lactam antibiotics
Intravenous therapy	All cases	Consider oral or subcutaneous route
Outpatient parenteral therapy	Only in compliant patients who have easy access to a hospital	Consider for patients for whom prolonged hospital stay may be deleterious to functional and cognitive status

MRSA: Methicillin-resistant Staphylococcus aureus. Adapted from Forestier et al., 2016.[252]

syncope also suggests cardiogenic etiology.[258] Syncope due to postural hypotension is common in dehydrated patients and patients with diminished intravascular volume. Its prevalence increases with age, varying from 6% in population studies to 70% in hospitalized, institutionalized, or Parkinson's disease patients.[260] In patients with dementia, 48% of syncope episodes occur due to OH.[261] Syncope episodes up to 2 hours after a meal should lead to a diagnosis of postprandial hypotension. Neuromediated syncope is common in elderly patients, of which the most prevalent types are situational (associated with urination, defecation, coughing, and carotid sinus hypersensitivity).[258,259] The presence of nausea, blurred vision, and sweating suggests a non-cardiogenic cause (OH or neurocardiogenic).[258] Neurological syncope, due to preexisting bilateral vertebrobasilar insufficiency is often accompanied by symptoms such as vertigo and ataxia, and it has a lower prevalence. It is also necessary to consider syncope an atypical manifestation of severe diseases such as AMI, which occurs in 3% of elderly patients > age 65[262] and is common in patients > age 85 with prevalence reaching 20%,[263] as well as of pulmonary thromboembolism (PTE) (24% of elderly patients > age 65)[264] and acute aortic dissection (5% to 10%).[265]

7.1.1.1. Stratifying Risk of Death

The San Francisco Syncope Rules (SFS) are simple rules that evaluate risk of adverse events in syncope patients. It has 74% to 98% sensitivity and 56% specificity.[266] The low specificity is owing to the fact that it is not very specific for cardiogenic syncope, but it makes it possible to discharge low-risk patients and hospitalize more severe cases. The following mnemonic device is used for the SFS:

C – History of CHF.

H – Hematocrit < 30%.

E – EKG abnormalities.

S – Shortness of breath.

S – SBP at admission < 90 mmHg.

(A) – Age > 75.

In a patient with syncope, any one of these findings is considered a high risk for events such as death, AMI, arrhythmia, PTE, stroke, subarachnoid hemorrhage, or emergency room re-admission and hospitalization related to a new syncope episode. When age is included, sensitivity increases to 100%, while specificity is reduced.

In conjunction with the SFS, the Short-Term Prognosis of Syncope (STePS) Study is another useful score,[267] which evaluates the risk of events 10 days after a syncope episode. It includes only 4 independent risk factors:

- EKG abnormalities (the best predictor).
- Concomitant trauma.
- Absence of prodromes.
- Male sex.

Predictors of poor long-term (1-year) prognosis include: EKG abnormalities, ventricular arrhythmia, HF, and age > 45. The 1-year event rate (severe arrhythmia or death) varies from 0% for patients with none of the 4 risk factors to 27% in patients with ≥ 3 factors. We may, thus, consider a high risk of short-term (7 to 10 days) and long-term (1 year) events for elderly patients who have syncope and:

- Are male.
- Do not have prodromes and have syncope with concomitant trauma.
- Have dyspnea or sustained hypotension associated with the syncopal event.
- Have previous diagnosis of HF and/or ventricular arrhythmias.
- Have altered EKG at admission.

7.1.1.2. General Recommendations

Elderly patients with unexplained recurrent falls, which are not witnessed by third parties and which are associated with trauma, should be interpreted as possible cardiogenic syncope. Investigation should occur in a hospital environment for episodes which occurred < 1 week prior, with trauma or in patients with known heart disease. Patients with a single episode, which occurred > 1 week prior, without trauma, may be investigated as outpatients. All elderly patients > age 75 with previous heart disease diagnosis and abnormal EKG should be investigated in a hospital environment, due to the high probability of cardiogenic syncope. The flowchart in Figure 2 suggests investigation routes, based on risk stratification, clinical history, and physical examination, which will define investigation strategy and treatment.

7.1.2. Diagnostic Peculiarities of Bradyarrhythmias

First-degree AVB have a prevalence of 6% to 8% in individuals ≥ age 70, and, like Mobitz I second-degree AVB, they are not predictive of cardiovascular events. Mobitz II second-degree AVB and third-degree AVB, on the other hand, have worse prognoses and require treatment. Extreme bradycardia (< 35 bpm), sinus pauses > 2 seconds, and advanced AVB are associated with structural heart disease, and they are frequently symptomatic. The association of bradycardia induced by negative chronotropic drugs, acetylcholinesterase or anticholinesterase inhibitors (rivastigmine, donepezil, and galantamine) and central alpha-blockers used for prostatic symptoms or SAH is common. Many cases are asymptomatic and are casually diagnosed during a routine check-up, especially in sedentary patients or patients with functional limitations.[268] Common symptoms include non-rotatory dizziness, effort-induced dyspnea or fatigue, caused by chronotropic deficit. The classic "on-off" syncope (Stokes-Adams syndrome) caused by total or intermittent high-degree AVB is an alert symptom.[269] Diagnosis may be performed via 12-derivation EKG, 24-h Holter, loop event monitor, and electrophysiological studies (EPS). Holter is indicated for bradycardia patients who have daily symptoms. Event monitors (implantable or portable) are indicated for detecting symptoms which occur rarely, but which have significant hemodynamic impairment and prolonged duration and which place the elderly patient's life at risk.[270-274] In cases of effort-induced symptoms, treadmill ET may clarify diagnostic suspicion (chronotropic incompetence or advanced degree of AVB). EPS is indicated for patients

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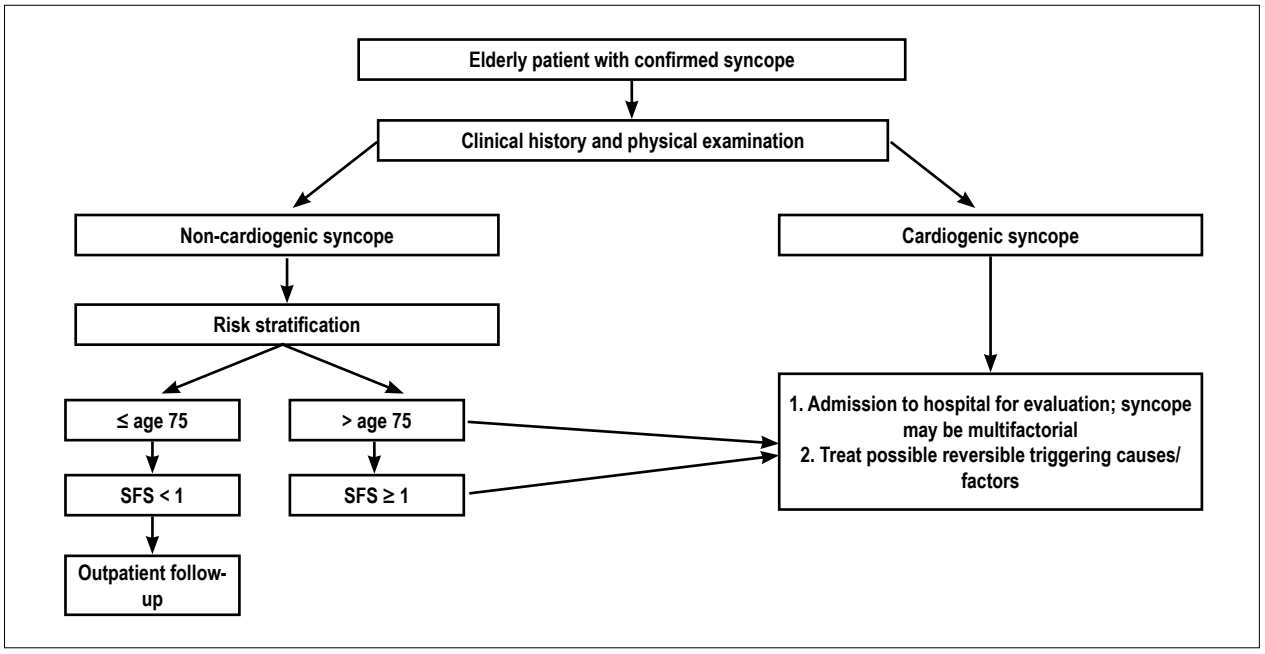

Figure 2 – *Flowchart for investigating syncope in elderly patients. SFS: San Francisco Syncope Rules.*

with inconclusive 24-h Holter or loop monitor results and unexplained recurrent syncope.

General recommendations for diagnosing bradyarrhythmias in elderly patients		
Recommendation	**Grade of recommendation**	**Level of evidence**
12-derivation EKG for patients with suspected bradyarrhythmia	I	C
Investigate negative chronotropic drug use and effort-induced symptoms in asymptomatic patients with bradycardia	I	C
24-h Holter for electrocardiographic correlation of symptoms with bradycardia (pre-syncope, syncope, palpitations, effort dyspnea, fatigue disproportionate to effort, or non-rotatory dizziness)	I	C
24-h Holter for patients with resting sinus bradycardia, asymptomatic patients	IIb	C
24-h Holter for patients with resting sinus bradycardia with effort symptoms to evaluate advanced degrees of block or pauses	I	C
24-h Holter for patients with high-degree AVB or total intermittent AVB, asymptomatic patients without negative chronotropic drugs	I	C
24-h Holter for patients with syncope, pre-syncope, and dizziness, whose probable cause (with the exception of bradyarrhythmias) has been identified, but whose symptoms persist in spite of treatment of the probably cause, and patients recovered from CRA	IIa	C
24-h Holter for electrocardiographic correlation of unspecific symptoms such as rotatory dizziness, dyspnea, and sweating in patients with documented bradycardia	III	C
24-h Holter for patients with dizziness	III	C
7-day Holter or loop monitor for patients with infrequent pre-syncope, syncope, palpitations, effort dyspnea, fatigue disproportionate to effort, or non-rotatory dizziness	I	C
7-day Holter or loop monitor for patients with infrequent syncope, pre-syncope, and dizziness, whose probable cause (with the exception of bradyarrhythmias) has been identified but whose symptoms persist in spite of treatment of the probably cause	IIa	C
7-day Holter or loop monitor for electrocardiographic correlation of unspecific symptoms such as rotatory dizziness, dyspnea, and sweating in patients without documented bradycardia	III	C
Treadmill ergometric test for patients with effort-induced symptoms and resting sinus bradycardia to evaluate de chronotropic incompetence	I	C
Treadmill ergometric test for patients without symptoms and resting sinus bradycardia	IIa	C
Electrophysiological study for patients with clinical suspicion of bradyarrhythmia and inconclusive non-invasive exams to measure AH intervals, HV intervals, and sinus node recovery time (investigating sinus node disease and degenerative disease of the AV node)	IIa	C

AVB: atrioventricular block; CRA: cardiorespiratory arrest; EKG: electrocardiogram.

7.1.3. Treatment Peculiarities

Treating syncope – Syncope treatment in elderly patients must be multifactorial, with an approach that covers various components which may be involved in the syncopal episode. Cases of cardiogenic syncope in no way differ from the approach used in younger patients. Treatment of baseline heart disease is in accordance with specific recommendations, respecting the elderly patient's specificities.[254] It is necessary to avoid hypovolemia and substitute vasodilatadory medications which may promote OH, by accentuating the dysautonomic response, such as beta-blockers with alpha and beta blocking action, calcium channel blockers, and central alpha-blockers. Centrally acting drugs (tricyclics, fluoxetine, acepromethazine, haloperidol, L-dopa, et al.) are also associated with risk of syncope and should be substituted.[275] The non-pharmacological measures commonly prescribed to treat neuromediated syncope have conflicting results in the elderly population, and they also present difficulties in adherence. Not limiting sodium intake and stimulating water intake are effective, but with low adhesion.[276] Avoiding heavy meals and meals in hot environments, as well as standing up immediately after a meal, may reduce the occurrence of postprandial hypotension. Classical medical treatment of neuromediated syncope has also not been shown to be effective in the elderly.[277] Regarding drugs, fludrocortisone has proven efficacy in this age range, at the expense of more collateral effects, mainly edema, hypokalemia, metabolic alkalosis, weight gain, and supine hypertension.[277,278] Treatment of cardioinhibitory syncope with pacemakers was shown to reduce syncope recurrence in a randomized clinical trial carried out in the elderly population (5% versus 61% recurrence in the pacemaker and control groups, respectively, $p = 0.00000$).[279]

Treating bradyarrhythmias – Treatment of bradyarrhythmias in the elderly follows the same recommendations as in younger patients.[280,281] The suspension of negative chronotropic drugs is fundamental. In patients with symptomatic sinus bradycardia, resting HR < 40 bpm, or symptomatic pauses, indicating definitive pacemaker implant reduces symptoms and improves quality of life, but it does not interfere with prognosis.[282,283] In patients with sinus bradycardia and dementia who need to initiate cholinesterase inhibitors, this may aggravate their bradyarrhythmia, the effect being dose dependent. Indication for a pacemaker in these patients should be individualized, as there is no evidence regarding the efficacy of this approach. In patients with advanced AVB, indication for a definitive pacemaker is associated with reduced mortality and should follow the same indications as in younger patients.[280,281]

General recommendations – With relation to treating syncope and bradyarrhythmias in the elderly, multiprofessional evaluation is important regarding the functional aspect and prognosis of comorbidities. Generally speaking, there is no specificity regarding the treatment efficacy of interventions with respect to bradyarrhythmias, and the same treatment recommendations used for younger patients should be followed. It is necessary to be attentive to non-cardiovascular use of drugs with negative chronotropic properties, as they may aggravate preexisting bradycardia.

7.2. Tachyarrhythmias in Elderly Patients

7.2.1. Diagnostic Peculiarities

Supraventricular tachyarrhythmias (SVT) – SVT are frequent in elderly patients, and their prevalence increases with age. The most common in this age range are: atrial tachycardia, flutter, and AF.[284] Atrial extrasystoles (AES) in patients ages 60 to 86 have an approximate prevalence of 80%, and supraventricular paroxysmal tachycardia (SVPT) has a prevalence from 10% to 15%. In individuals ≥ age 80, the prevalence of AES may reach 100%, and that of SVPT is from 25% to 30%. Effort-induced atrial arrhythmias in patients > age 80 reach a prevalence of > 10%.[285,286] In spite of their high prevalence, SVT (with the exception of AF) are not associated with increased morbimortality.[285,286] AES and non-sustained SVT (duration < 30 seconds) are not very symptomatic, observed with palpitation, "lightheadedness," dizziness, neck pounding, and "shortness of breath." Occasionally, dyspnea, chest pain, and syncope may occur, especially in patients with acute sustained arrhythmias, significant diastolic dysfunction, severe AS, HF, or CAD. The higher the HR, the less tolerated the arrhythmia, as a consequence of reduced cardiac output, which results in manifestations of cerebral and myocardial ischemia, arterial hypotension, and pulmonary congestion.[287]

Some arrhythmias are peculiar in elderly patients:[288,289]

a) Atrial tachycardia with AVB: presents high atrial frequency associated with slow ventricular response due to an AVB. Digitalis toxicity and hypokalemia are common causes.

b) Multifocal atrial tachycardia: is common in the presence of COPD.[285,287] Treatment focuses on the baseline disease, considering pre-fibrillatory rhythm.

c) Accelerated junctional rhythm: digitalis toxicity and inferior wall AMI are the most common causes in elderly patients.[285,287] Diagnosis is suggested for regular bradycardic rhythm, in the presence of AF.

d) Atrial flutter: habitually indicates structural heart disease. CAD and COPD are the most common causes in elderly patients. Elderly patients with atrial flutter have a higher chance of degeneration to AF; they are at a high risk for thromboembolic events, and they should receive a similar approach to AF cases.

Ventricular tachyarrhythmias – Ventricular extrasystoles are common in the elderly, with an incidence of 70% to 90%.[284,287,288] They do not generally produce symptoms, unless they are very frequent. Symptomology is variable; patients may perceive repetitive heart beats or the sensation that their "heart is going to stop," due to compensatory pauses. They are associated with risk of death in the presence of structural heart diseases. Treating arrhythmia in an isolated manner, however, does not reduce risk in elderly patients with CAD.[286,289] Pre-syncope, syncope, low output, pulmonary congestion, behavior disorder, and disorientation are frequent clinical manifestations of poor prognosis. Ventricular tachycardia (VT) is frequently associated with structural heart disease. LVH is an important determinant of ventricular arrhythmia,[287] as well as HF, which increases the incidence of VT from 2% to 4%, in patients without HF, to 20% to 80%.[287] In these patients, the presence of complex ventricular arrhythmia is associated

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with an increase in total mortality, cardiac mortality, and sudden death. The worse the ventricular dysfunction, the more complex and severe the ventricular arrhythmia will be. Thus, patients with LV dysfunction or LVH with complex ventricular arrhythmia should be considered at a high risk of sudden death, even if they are asymptomatic. In elderly patients without heart disease, the finding of tachyarrhythmias on Holter has no prognostic implications.[286]

Based on these premises, with respect to diagnostic evaluation of tachyarrhythmias in elderly patients, these Guidelines recommend:

Recommendation	Grade of recommendation	Level of evidence
Inquiry about all medications in use and risk analysis of induced arrhythmias or prolonged QT	I	C
12-derivation EKG in all patients at each clinical visit, even in the absence of symptoms	I	C
Calculation of QTc interval for all patients who report palpitation	I	C
Calculation of QT interval for all patients with polymorphic VT	I	B
24-h Holter to evaluate symptoms of palpitation, syncope, and unexplained falls	I	B
24-h Holter for asymptomatic patients with normal LV function and EKG with LVH	IIa	B
24-h Holter for asymptomatic patients with depressed LV function and EKG with LVH	I	A
24-h Holter for patients recovered from VF/VT before hospital discharge	IIa	C
24-h Holter for patients recovered from VF/VT during outpatient follow-up to evaluate therapy efficacy	IIb	C
24-h Holter for asymptomatic patients with simple ventricular arrhythmia during the initial exam, with normal LV function and EKG with LVH, during outpatient follow-up to evaluate therapy efficacy	III	C
24-h Holter for asymptomatic patients with complex ventricular arrhythmia during the initial exam, with normal LV function and EKG with LVH, during outpatient follow-up to evaluate therapy efficacy	IIb	C
24-h Holter for asymptomatic patients with simple ventricular arrhythmia during the initial exam, with depressed LV function and EKG with LVH, during outpatient follow-up to evaluate therapy efficacy	III	C
24-h Holter for asymptomatic patients with complex ventricular arrhythmia during the initial exam, with depressed LV function and EKG with LVH, during outpatient follow-up to evaluate therapy efficacy	IIa	C
24-h Holter for asymptomatic patients with normal LV function and EKG	III	B
Ergometric test in patients without contraindications who have effort-induced palpitations	I	C
Ergometric test in patients without contraindications who have palpitations associated with chest angina	I	C
Ergometric test in patients without contraindications who have resting palpitations	III	C
Ergometric test in asymptomatic patients without contraindications to investigate arrhythmia	III	C
Echocardiogram in all patients with palpitations	IIb	B
Echocardiogram in patients with LVH on EKG, asymptomatic patients	IIa	B
Echocardiogram in patients with palpitation and dyspnea	I	B
Echocardiogram in patients with LVH and cardiac murmur, asymptomatic patients	I	B
Investigation of ischemic etiology in all patients with supraventricular tachycardia	III	C
Investigation of ischemic etiology in all patients with supraventricular tachycardia and angina	I	C
Investigation of ischemic etiology in all patients with complex ventricular tachycardia	I	C
Magnetic resonance in patients with complex ventricular arrhythmia, whose other exam results are normal, to investigate arrhythmogenic RV dysplasia, myocardial fibrosis, and asymmetric apical hypertrophy	I	C
Magnetic resonance in all patients with VT	III	C
Magnetic resonance in all patients with SVT	III	C
EPS in patients with high SD risks (unexplained syncope and complex ventricular arrhythmia on Holter or trifascicular block, in order to clarify syncope etiology)	I	C

EKG: electrocardiogram; EPS: electrophysiological study; LV: left ventricle; LVH: left ventricular hypertrophy; RV: right ventricle; SD: sudden death; SVT: supraventricular tachyarrhythmia; VF: ventricular fibrillation; VT: ventricular tachycardia.

7.2.2. Treatment Peculiarities

Treatment principles for tachyarrhythmias in the elderly are similar to those in younger patients; however, treatment is more frequently influenced by the presence of baseline heart diseases such as CAD, LV dysfunction, LVH, and comorbidities such as chronic renal insufficiency (CRI) and COPD.[290] Non-sustained atrial arrhythmias (supraventricular extrasystoles and atrial tachycardias), generally, do not require treatment. In most cases, they are associated with baseline respiratory diseases, whose treatment, associated with avoiding stimulants such as caffeine, cigarettes, soft drinks, black tea, and fast-acting beta-agonist drugs, is normally sufficient to reduce the number of events and symptoms. Otherwise, the use of calcium channel blockers in patients with COPD (contraindicated in cases of LV dysfunction) or beta-blockers (in low doses and selectively, such as bisoprolol or metoprolol), in patients without contraindication, may be indicated. SVPT is usually caused by reentrant mechanisms, and may be interrupted by vagal maneuvers, such as the Valsalva maneuver, coughing, and vomiting. Due to the risk of arterial embolism, carotid sinus massage should be avoided in all elderly patients unless the presence of significant carotid disease has been excluded. If the attempted vagal maneuvers do not succeed in reversing arrhythmia, chemical cardioversion should be attempted. The first-choice drug should initially be adenosine, with electrocardiographic monitoring. Second-line drugs are calcium channel blockers (verapamil, diltiazem), if LV function is normal, and beta-blockers, in the presence of CAD. Digoxin should be restricted to patients with depressed LV function. In cases that do not respond to first- and second-line agents, class III antiarrhythmic drugs (amiodarone or sotalol) should be used. Beta-blockers and calcium channel blockers are equally effective in maintaining SR and avoiding recurrence of arrhythmia[290] (Table 12). In the event of hypotension, signs of low cerebral blood flow, pulmonary congestion, or chest angina, electric cardioversion should be performed at 50 to 75 J. Catheter ablation for treating sustained SVPT whose mechanism is nodal reentrant or an accessory pathway is as effective in elderly patients as it is in younger patients, with a success rate of > 95%.[291-295] Elderly patients have a higher risk of complications such as perforation, vascular lesion, renal insufficiency, a higher tendency to develop AF, and thromboembolic events after the procedure. Nevertheless, larger complications occur in < 3% of elderly patients.[292,293] It should be considered the treatment of choice for patients with frequent episodes (> 2 events/year, in spite of medical treatment) or patients with contraindications to the previously cited drugs, such as sinus bradycardia, hypotension, broncospasms, and severe LV dysfunction, as well as for patients who do not wish to undergo medical treatment.

General recommendations – Treatment of tachyarrhythmias in elderly patients: treatment of tachyarrhythmias in elderly patients, especially those between the ages of 65 and 75, should be similar to that in younger patients. In patients > age 75, individualization of conduct is recommended with multiprofessional evaluation that takes into consideration not only age, but also comorbidities, cognitive function, functional capacity, patient preferences, and severity of symptoms.[296,297]

7.3. Atrial Fibrillation

7.3.1. Diagnostic Peculiarities

AF is the most common persistent arrhythmia in elderly patients.[298] Its prevalence and incidence double every decade after age 60, affecting as many as 8% to 10% of patients > age 80 and 27% of patients > age 90.[287-301] It may occur isolatedly as a consequence of morphological and electrophysiological alterations inherent in aging of the atrial myocardium and sinus node, known as "isolated AF" or "lone atrial fibrillation." Truly isolated AF is, however, rare in elderly patients.[302] In general, it is associated with structural heart diseases: CAD, SAH, mitral valvulopathy, and HF.[303] Subclinical hyperthyroidism triples the risk of AF.[300] Patients with clinical hyperthyroidism may present episodes of paroxysmal AF. Other causes of AF in elderly patients include: obstructive sleep apnea-hypopnea syndrome (commonly called paroxysmal AF),[303] sinus node disease, and dilated cardiomyopathy, which are generally associated with AF with low ventricular response. Special attention should be paid to sinus node disease represented by tachycardia-bradycardia syndrome, where recurring paroxysmal AF is observed with a sudden stop followed by a long or asystolic pause, which is a frequent cause of unexplained syncope in the elderly. After adjusting for coexisting CVD, mortality in patients with AF is 1.5 to 1.9 times higher that in patients of the same age without AF.[299] This higher rate of mortality is mainly due to the 4- to 5-fold increase in the occurrence of stroke, a risk which proportionally increases after age 50 (< 1.5% in patients < age 50 and approximately 23.5% in patients > age 80).[304,305] Diagnosis of AF in elderly patients is initially made by physical examination, anamnesis, and EKG. As many as 20% of AF diagnoses in elderly patients occur casually, during clinical visits, in patients without complaints, especially in cases of permanent AF and ventricular response < 100 bpm, which occurs on account of concomitant AV nodal disease or use of beta-blockers.[287] The most frequent symptoms in elderly patients are: dyspnea, asthenia, dizziness, easy fatigue, decreased tolerance to exercise, sweating, polyuria, syncope, and palpitation. Permanent AF is related to silent thromboembolic events which, associated with chronic decreased cerebral blood flow and cerebrovascular alterations inherent in aging, are responsible for cognitive and motor impairments, such as slowing, motor incoordination, and dementia, which are initially discrete, but progressive and which may go unnoticed and delay diagnosis.[306]

General recommendations regarding AF diagnosis in the elderly

Recommendation	Grade of recommendation	Level of evidence
Inquiry about all medications in use and risk analysis of induced arrhythmias or prolonged QT	I	C
12-derivation EKG in all patients with irregular rhythm to diagnose AF, even in the absence of symptoms	I	C
12-derivation EKG in all patients with diagnosis of AF, at each clinical visit	IIb	C

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Table 12 – Drugs used to treat SVPT in elderly patients[290]

Cardioversion in the emergency room					
	Drug	**Initial dose**	**Repeat**	**Total dose**	**Precautions**
1st choice	Adenosine	6 mg in rapid bolus IV over 10 seconds	12 mg every 15 minutes	30 mg	Patients with CAD and active bronchial asthma
2nd choice	Verapamil	5 mg IV over 3 to 5 minutes	5 mg after 15 minutes	10 mg	LV dysfunction and hypotension
Patients with severe LV dysfunction	Amiodarone	300 mg IV over 30 minutes diluted in 0.9% saline solution or 100 to 250 mL 5% glucose solution	-	300 mg in bolus IV and 900 to 1,200 mg over the following 24 h	May be associated with digitalis IV to better control HR
Drugs used for maintenance following reversion to sinus rhythm					
Calcium channel blockers	Diltiazem (start with short half-life formulations and, if tolerated, substitute with extended release formulations, following dose adjustment)	30 mg 3×/day	Increase the dose by 50% every 14 days, if well tolerated, until the desired resting HR (60 to 70 bpm) has been reached	180 to 240 mg/day	Use caution with tachycardia-bradycardia syndrome and LV dysfunction
Beta-blockers	Verapamil	120 mg/day	Idem	240 mg/day	Idem
	Metoprolol	50 mg/day		Double the dose until the desired HR of 60 to 70 bpm has been reached	200 mg/day
	Atenolol	25 mg/day			200 mg/day
	Propranolol (In this order of preference, on account of liposolubility)	40 mg/day			240 mg/day
	Carvedilol	3.125 mg 2×/day		Double the dose every 2 weeks	25 mg 2×/day
Digoxin	Preferential in patients with HF	0.125 mg/day	Take care with patients > age 75 and creatinine > 1.5 mg/dL		0.25 mg/day (In the most elderly patients, debilitated patients, and patients with ERD, the dose should be adjusted in accordance with response and maintained at lower doses to 0.125 mg, 2–3×/week)
Amiodarone	Pay attention to collateral effects, especially those that are thyroid-related	600 mg/day for 10 days	Reduce to 400 mg/day for 10 days and maintain 200 mg/day	Monitor hepatic function, thyroid function, QTc interval, and eye fundus every 6 months	Maintain 100 to 200 mg/day

DAC: doença arterial coronariana; FC: frequência cardíaca; IC: insuficiência cardíaca; IRC: insuficiência renal terminal; IV: via intravenosa; TPSV: taquicardia paroxística supraventricular; VE: ventrículo esquerdo.

24-h Holter for evaluation of HR control	IIa	B
24-h Holter as follow-up, after rhythm control, in asymptomatic patients	IIa	C
24-h Holter for patients who complain of palpitations and for those with sinus rhythm following rhythm control	I	C
24-h Holter for patients with sinus rhythm, after stroke, to investigate paroxysmal AF	I	C
Transthoracic echocardiography in all patients with AF, with no prior diagnosis of CHF	I	C
Transthoracic echocardiography in all patients with AF	IIa	C
Transesophageal echocardiography in patients with AF > 48 h, for reversion to SR	I	C
Transesophageal echocardiography in patients with AF, after stroke, to investigate emboligenic focus	IIb	C

AF: atrial fibrillation; CHF: congestive heart failure; EKG: electrocardiogram; HR: heart rate; SR: sinus rhythm.

7.3.2. Treatment Peculiarities

Treatment of AF in elderly patients does not differ from that in younger patients. Oral anticoagulation (unless contraindicated) and the elimination of precipitating or reversible factors that induce paroxysmal AF or loss of ventricular frequency control in patients with persistent or permanent AF are the bases of AF treatment in elderly patients.[307,308] The decision to control HR or SR should be individualized; however, as an initial routine strategy, rhythm control has no benefits over HR control in asymptomatic patients in this age range.[309,310]

7.3.2.1. Heart Rate Control

Lenient strategies for HR control (target baseline HR < 110 bpm) is as effective for controlling symptoms as restrictive HR control (target resting HR < 80 bpm), except in cases of ventricular dysfunction, where caution is necessary to avoid significant bradycardias (HR < 50 bpm).[311,312] Beta-blockers, used alone, manage to adequately control HR in 42% of elderly patients,[312] and they should be the first-choice drug for this purpose. Combination with non-dihydropyridine calcium channel blockers should be used cautiously and only in patients without LV dysfunction. Attention should be paid to the condition worsening or to constipation appearing with their use, notably with verapamil, in addition to bradycardia and inferior member edema. Digoxin is less effective when used alone for controlling HR during effort. It is an acceptable choice for physically inactive patients, patients > age 80, and patients in whom other treatments have been ineffective or are contraindicated, and it should be used with due caution.[311,313] In cases of tachycardia-bradycardia syndrome and in patients who do not tolerate pharmacological HR control, pacemaker implant or atrioventricular node ablation followed by pacemaker implant may be indicated.[314,315] Rhythm control should be reserved for specific circumstances, particularly when symptoms cannot be contained by HR control, given that it is related to a higher number of hospitalizations due to the collateral effects of antiarrhythmic drugs (AAD) and the complications of invasive procedures, mainly in persistent AF with long duration. The strategy of rhythm control does not dispense with anticoagulation.[316] Control may be via AAD, electric cardioversion, or interventional procedures. Electric cardioversion restores SR and is indicated for acute cases of AF that do not respond to pharmacological therapy and that have hemodynamic instability. The basis for choosing AAD either for chemical cardioversion or for maintenance of rhythm depends on the baseline heart disease and the comorbidities, taking the occurrence of major collateral effects into consideration, due to decreased physiological function and the interactions between multiple medications common in elderly patients. Propafenone, sotalol, and amiodarone may be used for patients with minimal or no structural heart disease, bearing in mind that there is a higher risk of collateral and proarrhythmic effects in elderly patients when using propafenone and sotalol. For patients with structural heart disease (LVH with interventricular septum > 12 mm or coronary disease), sotalol or amiodarone are indicated. Amiodarone is reserved for elderly patients with reduced HF and LVEF.[317] Catheter ablation may be useful in healthy elderly patients who are symptomatic, without many comorbidities, without underlying heart disease, with AF paroxysms, and patients who are refractory to treatment or patients who do not wish to use AAD and who have no renal dysfunction. This procedure should be performed in a center with a great deal of experience.[318]

7.3.3. Oral Anticoagulants in Elderly Atrial Fibrillation Patients

The most feared complication in AF is thromboembolic events, notably stroke, whose incidence and severity increase with age.[319] It is the cause of up to 25% of strokes in elderly patients.[320] Oral anticoagulant therapy reduces the risk of stroke in elderly patients with non-valvular AF by 64%. It is thus superior to aspirin, which reduces the risk by only 22%, and is no longer recommended for stroke prevention in AF patients.[319,320] Double antiplatelet aggregation has not demonstrated benefits for preventing thromboembolic events in patients with AF and is not recommended.[321] The risk of thromboembolism in AF may be calculated using risk factor scores.[322] For evaluation of thromboembolic risk, the congestive heart failure, hypertension, age ≥ 75, diabetes mellitus, prior stroke, or transient ischemic attack ($CHADS_2$) score has been the most used. Its variables are age (≥ 75) and the presence of comorbidities (HF, SAH, diabetes mellitus, and previous history of thromboembolism). Thromboembolism is worth 2 points, and the other variables are worth 1. Anticoagulation is indicated for patients with scores ≥ 2, as they are at a high risk of events.[323] In 2010, the CHA_2DS_2-VASc score was proposed, considering a higher risk for female patients over age 65 and patients with peripheral arterial disease (1 point for the following variables: HF, hypertension, age between 65 and 74, diabetes mellitus, and peripheral arterial disease; 2 points for age 75 or over and previous

thromboembolic event), resulting in higher scores for more elderly patients, women, and peripheral arterial disease patients. These Guidelines, following the recommendations of the most recent guidelines[324,325] for treating AF, recommend the use of the CHA_2DS_2-VASc clinical score for defining start of anticoagulation in men with scores of 2 or more and women with score of 3 or more. In low-risk patients (men with scores of 0 and women with scores of 1), we recommend the use of echocardiography parameters, such as increased LA and auricular flow velocity, the presence of moderate to accentuated spontaneous contrast, or LA/auricular thrombus as an additional stratification for CHA_2DS_2-VASc. If a patient presents any one of these findings, anticoagulation is indicated.[326,327] After defining the risk of a thromboembolic event, it becomes necessary to stratify the risk of bleeding, before beginning anticoagulant therapy. The most used risk score for bleeding during anticoagulation is the HAS-BLED, where a score > 3 indicates a high risk of hemorrhage due to oral anticoagulants and includes, in addition to age range (> 65), variables such as SAH with SBP > 160 mmHg (1 point), renal or hepatic dysfunction (1 point each), prior history of stroke (1 point), bleeding (1 point), labile INR (1 point), and drug or alcohol use (1 point each).[328] Data on the isolated influence of age on the risk of bleeding are conflicting; for this reason, age should not be used to contraindicate anticoagulation.[329] Vitamin K antagonists, especially warfarin, are the pillar of oral anticoagulation in patients with AF, significantly reducing stroke and mortality attributed to AF.[330] Variability of INR with warfarin use depends not only on the dose used, but also on other medications and certain types of foods.[331] In an observational study, labile INR has been described in 21.3% of patients ages 40 to 89,[328,329] according to which the risk of INR ≥ 5 increases by 15% with each 10-year increment. As a result of this greater risk, it is necessary to monitor INR in elderly patients (especially those > age 75) more regularly and at more frequent intervals (grade of recommendation I, level of evidence B). These Guidelines recommend the use of low initial doses for elderly patients < age 85 (3 to 4 mg) and 2.5 mg for elderly patients ≥ age 85, patients with frailty syndrome, malnutrition, or hepatic disease and moderate to advanced renal insufficiency (creatinine clearance < 30 mL/min). The INR is at 3 days, with a new dose at 7 days, if there is dose adjustment, and 14 days, if the dose remains stable. It is weekly during the first 90 days in patients with greater risks, whatever they may be, > age 85, frailty, hepatic or renal insufficiency, history of falls, cognitive impairment, low level of education, and initial treatment. In other patients, evaluation of INR may occur every 15 days during the first 90 days of treatment, and may be monthly afterwards, in cases with stable INR. Oral anticoagulation with warfarin is, thus, safe in elderly patients, provided that precautions in indication and follow-up are respected. Warfarin is the least expensive oral anticoagulant, and its antagonist (vitamin K) is widely available to reverse the drug's anticoagulant effect.

Recently, non-vitamin K antagonist oral anticoagulants have become available with the advantages of not requiring constant monitoring of blood coagulation and presenting fewer drug interactions. They include direct thrombin inhibitors (dabigatran) and direct inhibitors of factor Xa (rivaroxaban, apixaban, and edoxaban). A meta-analysis of the main randomized clinical trials with non-vitamin K antagonist oral anticoagulants[330] has shown a significantly lower risk of stroke or systemic embolism compared with warfarin (relative risk [RR] = 0.81, 95% confidence interval [95% CI] = 0.73 to 0.91), as well as a lower risk of intracranial bleeding (RR = 0.48, 95% CI = 0.39 to 0.59), but not of major bleeding (RR = 0.86, HF 95% = 0.73 to 1.00). Findings were similar to those described in a second meta-analysis[331] with participants ≥ age 75. Notwithstanding the clear benefit of non-vitamin K antagonist oral anticoagulants, as well as the fact that they are safer regarding intracranial bleeding, this complication has relatively low rates (< 1%/year) even with warfarin (0.76% to 0.85% with warfarin and 0.26% to 0.49% with non-vitamin K antagonists).[331] The new oral anticoagulants are, thus, the safest option for anticoagulation in elderly patients with higher risks of bleeding, patients with difficulties in adhering to INR monitoring, patients using multiple medications, or patients who individually opt for them. It is, nonetheless, necessary to adjust doses according to renal function and age (< or > 75)[330,331] (grade of recommendation I, level of evidence B). Until recently, there were some concerns due to the lack of a specific antidote for reversing the anticoagulant effects of non-vitamin K antagonists; idarucizumab, however, has been introduced and was recently approved for use in humans in order to reverse the effects of dabigatran.[332]

7.3.3.1. General Recommendations

1. Unless there are formal contraindications to anticoagulation, elderly AF patients should begin anticoagulation, if their $CHADS_2VCAS_2$ scores are ≥ 2 for men and ≥ 3 for women (grade of recommendation I, level of evidence A).[324,325] If the $CHADS_2VCAS_2$ score is < 2 for men or < 3 for women and LA size is > 5.0 cm (or area indexed by body surface > 30 mm/m^2) on transthoracic echocardiography, anticoagulation should also be initiated (grade of recommendation IIa, level of evidence B). Elderly patients < age 65, with $CHADS_2VCAS_2$ = 0 for men or 1 for women should only start anticoagulation if LA > 5.0 cm or in the presence of moderate to severe spontaneous contrast or thrombus on transesophageal echocardiography (grade of recommendation IIa, level of evidence B).

2. The HAS-BLED score is recommended to evaluate risk of bleeding during anticoagulation (grade of recommendation I, level of evidence B). Elderly patients are considered at higher risks if they are > age 85, are fragile, have renal or hepatic insufficiency, have moderate to severe cognitive impairment, or have low levels of education, as well as during the first 90 days of treatment with anticoagulants. In these patients, anticoagulation is recommended with dose adjustment and more regular follow-up; however, it should not be contraindicated (grade of recommendation I, level of evidence C).

3. In parallel, the risk of hemorrhagic complications may further be reduced by controlling SAH and the risk of falls, as well as by paying attention to the introduction of new drugs in association with antiplatelet medications and antibiotics, which may interfere with serum levels or increase the risk of bleeding.

Recommended doses for elderly patients

	Dabigatran	Rivaroxaban	Apixaban	Endoxaban
Commercial presentation	150 mg 110 mg	20 mg 15 mg 10 mg	5 mg 2.5 mg	30 mg 60 mg
Dose	150 mg CrCl > 50 ml/min	20 mg CrCl > 50 ml/min	5 mg CrCl > 30 ml/min	60 mg CrCl > 50 ml/min
	110 mg CrCl between 30 and 50 ml/min	15 mg CrCl between 30 and 50 ml/min	2.5 mg CrCl 15-30 ml/min or Two of the following criteria: ≥ 80 years old Weight ≤ 60 kg Creatinine ≥ 1.5 mg	30 mg CrCl 15-50 ml/min or weight ≤ 60 kg
Posology	2 x day	1 x day	2 x day	1 x day
Particularities	Dyspepsia is common	Higher risk of GI bleeding than warfarin		
	Avoid if CrCl < 30 ml/min), recent stroke, and severe active hepatic disease	Avoid if CrCl < 15 ml/min) and severe active hepatic disease	Avoid if CrCl < 15 ml/min) or Creatinine > 2.5 mg and severe active hepatic disease	Avoid if CrCl < 15 ml/min or severe hepatic disease

CrCl: creatinine clearance; GI: gastrointestinal. Source: European Heart Journal.[324]

4. For warfarin patients, INR is recommended 5 to 7 days after beginning antibiotic therapy (grade of recommendation I, level of evidence C).

5. Regarding the choice of anticoagulant, current evidence demonstrates that direct oral anticoagulants (DOAC) are preferable to warfarin, except in patients with moderate to severe mitral stenosis and patients with valve prostheses (grade of recommendation I, level of evidence A).[324,325] These Guidelines, however, also recommend warfarin use, in situations of availability or preference, owing to the fact that it is an oral drug that is well known, inexpensive, and widely available to patients through the public system in Brazil, as well as to the fact that it has an antagonist (vitamin K) available to reverse its anticoagulant effect (grade of recommendation I, level of evidence A).

6. DOAC are a safe option for anticoagulation in elderly patients with higher risks of bleeding, in patients with difficulties in adhering to INR monitoring, patients using multiple medications, or patients who individually opt for them. It is, nonetheless, necessary to adjust doses according to renal function and age[330,331] (grade of recommendation I, level of evidence A). Rivaroxaban and edoxaban are the DOAC of choice given their use practicality (taken once a day). In patients with dyspepsia, dabigatran should be avoided (grade of recommendation I, level of evidence B). No DOAC have been tested with severe renal insufficiency.[324] For this reason, these Guidelines do not recommend using them in patients with creatinine clearance < 30 ml/min, in which case warfarin is preferable (grade of recommendation I, level of evidence B).

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In “Brazilian Guidelines for Vehicular Direction in Implantable Cardiac Devices and Cardiac Arrhythmias” (portuguese: Diretrizes Brasileiras para Direção Veicular em Portadores de Dispositivos Cardíacos Eletrônicos Implantáveis e Arritmias Cardíacas), page 2, second paragraph, consider correct for the phrase “suspension of driving for six months” (portuguese: suspensão da direção por seis meses) three months in place of six months.

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