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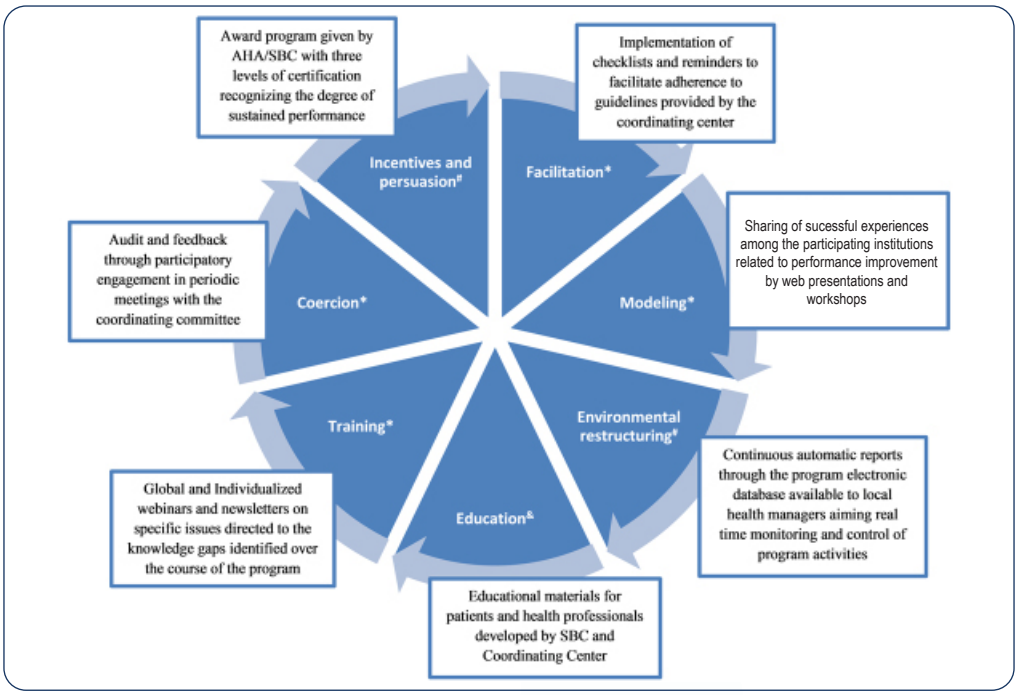

Figure 1 on page 95.

COVID-19: pregnancy and heart disease

Post-Exercise Hypotension: Interval Vs. Continuous

Effects of losartan in obesity

Resistant hypertension in afrodescendants

Hypertensive measures and childhood obesity

Parents' BP and young men autonomic impairment

Mechanism of decreased heart collagen I in obesity

Cardiovascular Imaging and Interventional Procedures

COVID-19 and Cardiac Injury

Pulmonary Thromboembolism in COVID-19

Circulatory System Diseases and COVID-19

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Contents

Editorial

COVID-19: A New Challenge in Pregnancy and Heart Disease
Walkiria Samuel Avila and Regina Coeli de Carvalho
.....page 1

Original Article

Acute Effect of Interval vs. Continuous Exercise on Blood Pressure: Systematic Review and Meta-Analysis
Raphael José Perrier-Melo, Eduardo Caldas Costa, Breno Quintella Farah, Manoel da Cunha Costa
.....page 5

Short Editorial

High-intensity Interval Training versus Continuous Exercise: Is There a Difference Regarding the Magnitude of Blood Pressure Reduction?
Filipe Ferrari and Vítor Magnus Martins
.....page 15

Original Article

AT_1 Receptor Blockade Improves Myocardial Functional Performance in Obesity
Silvio Assis de Oliveira-Junior, Nayara de Araújo Muzili, Marianna Rabelo de Carvalho, Gabriel Elias Ota, Camila Souza de Morais, Larissa Fregapani da Costa Vieira, Mateus Oliveira Ortiz, Dijon H. S. Campos, Marcelo Diacardia Mariano Cezar, Marina Politi Okoshi, Katashi Okoshi, Antonio C. Cicogna, Paula Felippe Martinez
.....page 17

Short Editorial

Targeting the Renin-Angiotensin-Aldosterone System in Obesity
Ariane Vieira Scarlatelli Macedo
..... page 29

Original Article

Clinical Characteristics of Resistant vs. Refractory Hypertension in a Population of Hypertensive Afrodescendants
Cristiano Macedo, Roque Aras Junior, Isabella Sales de Macedo
..... page 31

Short Editorial

Short Editorial: Clinical Characteristics of Resistant vs. Refractory Hypertension in a Population of Hypertensive Afro-descendants

Rui Póvoa

..... page 40

Original Article

Hypertensive Measures In Schoolchildren: Risk Of Central Obesity And Protective Effect Of Moderate-To-Vigorous Physical Activity

Tatiana Affornali Tozo, Beatriz Oliveira Pereira, Francisco José de Menezes Junior, Cristianne Morgado Montenegro, Carla Marisa Maia Moreira, Neiva Leite,

..... page 42

Short Editorial

Physical Activity in the Present Can Be the Recipe to Avoid the Ills of Obesity and Hypertension in the Future

Roberto Jorge da Silva Franco

..... page 50

Original Article

Family History of Hypertension Impairs the Autonomic Balance, but not the Endothelial Function, in Young Soccer Players

Walter Vargas and Katya Rigatto

..... page 52

Short Editorial

Heart Rate Variability as an Indicator of Cardiovascular Risk in Young Individuals

Breno Quintella Farah

..... page 59

Original Article

Decreased Collagen Type I Is Associated With Increased Metalloproteinase-2 Activity And Protein Expression Of Leptin In The Myocardium Of Obese Rats

Danielle Cristina Tomaz da Silva-Bertani, Danielle Fernandes Vileigas, Gustavo Augusto Ferreira Mota, Sérgio Luiz Borges de Souza, Loreta Casquel De Tomasi, Dijon Henrique Salomé de Campos, Adriana Fernandes de Deus, Paula Paccielli Freire, Carlos Augusto Barnabe Alves, Carlos Roberto Padovani, Antonio Carlos Cicogna

..... page 61

Original Article

Assessing Dynamic Atrioventricular Conduction Time to RR-interval Coupling in Athletes and Sedentary Subjects

Paulo Roberto Benchimol-Barbosa, Olivassé Nasario-Junior, Jurandir Nadal

..... page 71

Short Editorial

Atrioventricular Conduction System Disorders and Potential Risks of Arrhythmic Events in Endurance Athletes

Carlos Alberto Cordeiro Hossri

.....page 78

Original Article

Cost-effectiveness of Drug-Eluting Stents in Percutaneous Coronary Intervention in Brazil's Unified Public Health System (SUS)

João Addison Pessoa, Felipe Maia, Edirley Maia, Maurício Sales de Oliveira, Denizar Viana, Esmeralci Ferreira, Denilson Campos Albuquerque

.....page 80

Short Editorial

Drug-Eluting Stents for Everyone: Is the Price Worth It?

Marcos Danillo P. Oliveira, Vanessa Teich, Adriano Caixeta

.....page 90

Original Article

Implementation of a Best Practice in Cardiology (BPC) Program Adapted from Get with the Guidelines in Brazilian Public Hospitals: Study Design and Rationale

Fabio Papa Taniguchi, Sabrina Bernardez-Pereira, Suzana Alves Silva, Antônio Luiz Pinho Ribeiro, Louise Morgan, Anne B. Curtis, Kathryn Taubert, Denilson Campos de Albuquerque, Bernadete Weber, Pedro Paulo Magalhães Chrispim, Camila Pereira Pinto Toth, Erica Deji Moura Morosov, Gregg C. Fonarow, Sidney C. Smith Jr., Angelo Amato Vincenzo de Paola

.....page 92

Short Editorial

Implementation of Healthcare Quality Improvement Programs

Felix J. A. Ramires

.....page 100

Original Article

Quercetin Ameliorates Lipid and Apolipoprotein Profile in High-Dose Glucocorticoid Treated Rats

Hoda Derakhshanian, Mahmoud Djalali, Abolghassem Djazayery, Mohammad Hassan Javanbakht, Mahnaz Zarei, Azita Hekmatdoost, Ghazaleh Eslamian, Seyyedeh Somayyeh Mirhashemi, Ahmad Reza Dehpour

.....page 102

Short Editorial

Short Editorial: Quercetin Ameliorates Lipid and Apolipoprotein Profile in High-Dose Glucocorticoid Treated Rats

Bruna Paola Murino Rafacho

.....page 109

Review Article

Cardiovascular Imaging and Interventional Procedures in Patients with Novel Coronavirus Infection

Isabela Bispo Santos da Silva Costa, Carlos Eduardo Rochitte, Carlos M. Campos, Silvio Henrique Barberato, Gláucia Maria Moraes de Oliveira, Marcelo Antônio Cartaxo Queiroga Lopes, Cesar Higa Nomura, Alexandre A. Abizaid, Giovanni Cerri, Roberto Kalil Filho, Ludhmila Abrahão Hajjar

.....page 111

Review Article

Acute Cardiorenal Syndrome: Which Diagnostic Criterion to Use And What is its Importance for Prognosis?

Andréa de Melo Leite, Bruno Ferraz de Oliveira Gomes, André Casarsa Marques, João Luiz Fernandes Petriz, Denilson Campos Albuquerque, Pedro Pimenta de Mello Spineti, Antonio José Lagoeiro Jorge, Humberto Villacorta, Wolney de Andrade Martins

.....page 127

Viewpoint

Appropriate Use of Diastolic Function Guideline When Evaluating Athletes: It is not Always what it Seems to Be

Carlos Eduardo Suaide Silva

.....page 134

Image

Myocardial Injury in COVID-19: a Challenge for Clinical Cardiologists

Roberto Cintra de Azevedo Aragão, Mariana Carvalho Alves, Hellen Dutra Passos, Luiz Flavio Galvão Gonçalves, Leonardo Baumworcel, José Augusto Soares Barreto-Filho

.....page 139

Case Report

SARS-Cov-2 Infection and Pulmonary Thromboembolism – The Prothrombotic State in COVID-19

Hellen Dutra Passos, Mariana Carvalho Alves, Leonardo Baumworcel, João Paulo Cerqueira Vieira, Juliane Dantas Seabra Garcez, Antônio Carlos Sobral Sousa

.....page 142

Letter to the Editor

Does Existence of Prior Circulatory System Diseases Accelerate Mortality Due to COVID-19?

Carlos Dornels Freire de Souza, Thiago Cavalcanti Leal, Lucas Gomes Santos

.....page 146

Erratum

.....page 148

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COVID-19: A New Challenge in Pregnancy and Heart Disease

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The outbreak of coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a pandemic by the World Health Organization on March 11, 2020.[1] Although SARS-CoV-2 isolation, gene sequencing, and structural analysis have been completed, therapies for COVID-19.

The first epidemiological data have pointed to a worse outcomes and higher mortality of COVID-19 in patients with chronic diseases, such as heart disease and arterial hypertension. Subsequently, the Brazilian Health Ministry included in the high-risk group pregnant, puerperal and post-abortion women.[2]

Previous epidemiological evidence strongly suggests that pregnant women have an increased risk of serious illness and death from viral infections during pandemics, such as influenza.[3]

Physiological changes in pregnant women not only increase susceptibility to the viral infection but also increase the severity of this disease (*Table 1*).[4-6] During pregnancy, the immune response predominates through T-helper 2 (Th2) cells, which protect the fetus but make the mother more vulnerable to viral infections, which are more effectively fought by Th1 cells.[7]

Pregnant women infected with the H1N1 influenza virus and two other pathogenic coronaviruses [severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV)] had high morbidity and mortality during pregnancy and the postpartum period. It was estimate that 90% of pregnant women with these viral infections progressed to severe respiratory failure, with obstetric complications, such as abortion, premature birth, and intrauterine growth restriction. Maternal mortality in pregnant women infected with SARS-CoV or MERS-CoV has been reported to reach 25%, and no transplacental vertical transmission has been recorded.[8]

There are no data to inform whether pregnancy increases susceptibility to COVID-19. The evidence is still scarce, but COVID-19 during pregnancy appears to be less severe than infections by H1N1 influenza virus, SARS-CoV, and MERS-CoV.

Studies in pregnant women infected with SARS-CoV-2 are limited to small series. A systematic review[9] of 108 pregnant women with COVID-19 has shown cough and fever as their main complaints, present in almost 80% of the women, while only 12% had dyspnea. No maternal death has been reported. Of the three critical patients who required mechanical ventilation, two had obesity (body mass index > 35) as a morbidity factor.

Another study[10] assessing 116 pregnant women with COVID-19 pneumonia has concluded that clinical pneumonia characteristics of pregnant women were similar to those of the general population. Currently, there is no evidence that pregnant women with COVID-19 are more prone to develop severe pneumonia as compared to nonpregnant ones. Fortunately, there was neither increase in spontaneous abortion or in natural preterm birth, nor evidence of vertical transmission of SARS-CoV-2.

Perinatal transmission of COVID-19: Should we be concerned? Of 75 newborns of mothers with COVID-19, only one tested positive for the virus and had a satisfactory clinical outcome with mild changes in liver enzymes.[9] However, some babies testing negative for COVID-19 developed lymphocytopenia and radiological findings of pneumonia, and one had disseminated intravascular coagulation. All babies had a full recovery.[11,12] Based on these findings, we can exclude neither the possibility of subclinical response from fetuses and newborns to the maternal infection, nor transplacental vertical transmission. Thus, close monitoring of newborns of mothers with COVID-19 is recommended.

Should pregnant women with heart disease or arterial hypertension and SARS-CoV-2 infection be considered at greater mortality risk? The Brazilian Society of Cardiology Statement for the Management of Cardiac Diseases in Pregnancy,[13] which includes healthcare protocols, treatment, and prevention strategies for heart complications during pregnancy, has contributed to a reduction in maternal mortality in Brazil. However, we are facing the emergence of COVID-19, a disease that shakes that once improved situation. New clinical research and an integrated approach to the subgroup of pregnant women with heart disease or hypertension affected by SARS-CoV-2 are mandatory.

The optimistic perspective on the outcomes of the association of pregnancy and SARS-CoV-2 infection becomes uncertain in women with heart disease or hypertensive disorders, because these two heart conditions alone represent the main causes of maternal and fetal mortality during pregnancy.

It is important that clinical suspicion of COVID-19 in pregnant women with heart disease MUST be ruled out.

Keywords

Coronavirus; COVID19; Pandemics; Pregnancy; Pregnancy, high-risk; Severe Acute Respiratory Syndrome; Pneumonia; Hypertension/prevention and control; Risk Factors; Morbidity; Mortality.

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Table 1 – Impact of physiological changes of cardiovascular and respiratory systems of pregnancy in women with cardiac disease with SARS-CoV-2

• Downregulation of maternal immune system - Risk to Severe Respiratory Disease
• Oxygen consumption - hypoventilation, apnea or impaired gas exchange - Hypoxemia
• Decreased Functional Residual Capacity - (10 a 25%) - Hypoxemia
• Hyperemia and edema of the upper airway - Challenges to endotracheal intubation
• Increased breast volume and the need for crush induction due to impaired gastric emptying - Risk of aspiration
• Decreased systemic vascular resistance - Hypotension, Hypoxemia
• Incresead heart rate and stroke volume - Heart failure
• Mechanical ventilation carefulness
Hyperventilation and alkalosis - Uterine vasoconstriction
Hypoventilation and hypercapnia - Fetal respiratory acidosis
Matenal PaO_2 should be kept greater than 70 mmHg for adequate fetal oxigenation
• Increase thromboembolic risks
increase in coagulation factors (V, VIII, X, and von Willebrand factor)
Fall in protein S levels
Uterine compression of the inferior vena cava and the left iliac vein
Local trauma to pelvic veins during delivery
Pospartum period of cesarean section

Table 2 – COVID-19 / Heart Disease / Pregnancy - Features of trinity and Differential Diagnosis

	Covid-19	Cardiopathy	Normal Pregnancy
Symptoms	Fever (>37,8 ºC), myalgia, fatigue, anorexia, sore throat, nasal and conjuctival congestions, cough, Dyspnea, anosmia, anorexia, odynophagia, nausea, vomiting, diarrhea, abdominal pain	Dyspnea, palpitations, chest pain, syncope, hemoptysis, fadigue, lower limb edema, orthopnea, dry cough.	Náusea, vomiting, edema / dyspnea / fatigue, palpitations, dizziness, epistaxis, gestational rhinitis, headache and abdominal pain
Time of symptoms and age gestational	Any of gestational age	2nd and 3rd trimester	Any gestational age
History	Without previous heart disease	Previous heart disease	Without previous heart disease
Laboratory	COVID-19 Positive RT-PCR nasopharygeal Lymphocytopenia Increased aminotransferase- Alt/AST ureia / creatinine D-dimer -increased	High level of B-type natriuretic peptide BNP	D - dimer normal or slight increase
Imaging Exams	Normal echocardiogram Chest X-ray alterede or not Chest tomography - ground glass opacities image	Echocardiogram - structural cardiac lesion Chest X ray / Tomography altered: Cardiomegaly and / or pulmonary congestion	Normal echocardiogram Normal Chest-X ray

RT-PCR: reverse transcription polymerase chain reaction assay; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

Heart diseases and COVID-19 have symptoms in common, which can lead to a misdiagnosis (Table 2). In view of this and considering the current pandemic, tests for SARS-CoV-2 should be included in the good practice screening for pregnant women with heart disease.

Physiological changes in the cardiorespiratory system due to pregnancy do not increase susceptibility to infection by the virus but can induce worse maternal outcome[4-6] (Table 1). Respiratory changes in pregnancy result in decreased total lung capacity and chest compliance at the end of pregnancy. In addition, it is reasonable to consider that maternal hypoxia resulting from hypoventilation and impaired gas exchange reduces the offer of oxygen to the fetus, consequently, intra-uterine death. In this context, COVID-19 pneumonia progresses rapidly from focal to bilateral diffuse pulmonary consolidation and more readily predisposes to severe hypoxemic respiratory failure.

COVID-19 can result in cardiac injury by multiple mechanisms, resulting in an extreme inflammatory response with endothelial injury and myocarditis.[14] During pregnancy and the postpartum period, acute heart failure should be considered in some circumstances, such as peripartum cardiomyopathy, viral myocarditis, and noncardiogenic pulmonary edema. Pulmonary edema is also seen in healthy pregnant women, as a consequence of major changes in intravascular volume during labor and after delivery. Likewise, hemodynamic changes in pregnancy cause an increase in the gradient across the stenotic mitral valve and could lead to pulmonary congestion. Congenital cyanotic cardiopathy, obstructive injuries of the left side of the heart or serious systemic ventricular dysfunction present a greater risk of cardiac complications in pregnant women. The fall in systemic vascular resistance worsens hypoxemia in pregnant women with pulmonary hypertension and with uncorrected tetralogy of Fallot

Systemic coagulopathy is a critical aspect of morbidity and mortality in COVID-19.[14] The hypercoagulable state (Table 1) of pregnancy increases the risk of thromboembolism in women with heart disease. In this scenario, the combination of COVID-19 and mechanical valve prosthesis or atrial fibrillation in rheumatic valve disease increases the risk of thromboembolic events in pregnant women. It is worth noting that, as D-dimer levels increase as pregnancy progresses, it is not a good marker for the diagnosis of thromboembolism in pregnancy. Despite radiation exposure, chest computed tomography and complementary angiography should be indicated in pregnant women with heart disease and COVID-19, when pulmonary thromboembolism is suspected.

Systemic inflammation and coagulopathy in COVID-19 increase the risk of atherosclerotic plaque rupture and acute myocardial infarction.[14] The significant implication of SARS-CoV-2 infection for the cardiovascular system is evidenced by acute myocardial injury (high levels of highly sensitive troponin I and/or new ECG/echocardiogram abnormalities), complex cardiac arrhythmias, and cardiac arrest. During pregnancy, acute coronary syndromes are not common. However, infections, especially in the postpartum period, are a risk factor for myocardial infarction. The most frequent causes of myocardial infarction during pregnancy are spontaneous coronary artery dissection, atherosclerosis, coronary thrombosis, and normal arteries on angiography with impaired coronary microcirculation

According to recent studies, angiotensin-converting enzyme 2 (ACE2) is a functional receptor of SARS-CoV-2.[15] The renin-angiotensin system is a key player in blood pressure regulation, and ACE2 plays a critical role in cardiovascular physiology control in pregnant women. Angiotensin-(1-7) is significantly elevated in healthy pregnant women as compared to nonpregnant ones. In preeclampsia, plasma angiotensin levels (1-7) are reduced and plasma angiotensin II is consistently elevated, which contributes to the development of hypertension in these pregnant women. Moreover, pregnant women with chronic hypertension are at risk for preeclampsia or HELLP syndrome. Therefore, the relationship between positive regulation of ACE2 and SARS-CoV-2 in pregnancy requires further studies.

Finally, there are currently no data available on the outcome of pregnancy in patients with heart disease or arterial hypertension and COVID-19. However, those patients must be considered a high-risk group.

In view of the lack of specific therapy and vaccine for COVID-19, we have to be prepared to prevent and treat cardiovascular complications during pregnancy.[13] Integrated and multidisciplinary care should be aimed at optimizing therapy, guiding patients on the risks of COVID-19, and treating them in an occasional infection by SARS-CoV-2.

The severe consequences of COVID-19 compounded by the possible complications experienced by pregnant women with heart disease or arterial hypertension could result in poor maternal outcome and uncertain prognosis.

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Acute Effect of Interval vs. Continuous Exercise on Blood Pressure: Systematic Review and Meta-Analysis

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Abstract

Background: Continuous aerobic exercise (CE) is one of the main non-pharmacological recommendations for hypertension prevention and treatment. CE is safe and effective to reduce blood pressure chronically, as well as in the first few hours after its performance, a phenomenon known as post-exercise hypotension (PEH). Interval exercise (IE) also results in PEH.

Objective: This systematic review and meta-analysis sought to compare the magnitude of PEH between CE and IE in adults.

Methods: A systematic review of studies published in journals indexed in the PubMed, Web of Knowledge, Scopus and CENTRAL databases was performed until March 2020, which compared the magnitude of PEH between CE and IE. PEH was defined as between 45-60 minutes post-exercise. The differences between groups on blood pressure were analyzed using the random effects model. Data were reported as weighted mean difference (WMD) and 95% confidence interval (CI). A p-value <0.05 was considered statistically significant. The TESTEX scale (0-15) was used to verify the methodological quality of the studies.

Results: The IE showed a higher magnitude of PEH on systolic blood pressure (WMD: -2.93 mmHg [95% CI: -4.96, -0.90], p = 0.005, I2 = 50%) and diastolic blood pressure (WMD: -1,73 mmHg [IC95%: 2,94, -0,51], p= 0.005, I^2 = 0%) when compared to CE (12 studies, 196 participants). The scores of the studies on the TEXTEX scale varied from 10 to 11 points.

Conclusions: The IE resulted in a higher magnitude of PEH when compared to CE between 45 and 60 minutes post-exercise. The absence of adverse event data during IE and CE in the studies prevents comparisons of the safety of these strategies. (Arq Bras Cardiol. 2020; 115(1):5-14)

Keywords: Hypertension; Blood Pressure; Post-Exercise Hypotension; Exercise Therapy; Exercise; Review.

Introduction

Hypertension affects between 30 and 40% of the world's population.[1,2] In Brazil, its prevalence varies from 22.3 to 43.9%, affecting more than 60% of the elderly.[3,4] Hypertension is directly associated with the incidence of heart and cerebrovascular diseases,[3] responsible for approximately 20% of deaths in individuals over 30 years of age,[5] in addition to generating costs of around R$ 30.8 billion *reais* per year.[6] Changes in lifestyle, including physical activity, healthy eating habits, weight reduction and smoking cessation have been strongly recommended for the prevention and treatment of hypertension.[1,3] In fact, changes in lifestyle result in reductions in blood pressure (BP) levels, which reduce the risk of cardiovascular events.[3,7,8]

Regarding physical exercises, the guidelines for the prevention and treatment of hypertension recommend aerobic exercises performed continuously (CE), mainly of moderate intensity, as they are safe and effective for reducing BP levels, improving the cardiovascular and metabolic risk profile, in addition to increasing cardiorespiratory fitness.[3,9] The antihypertensive effects of CE can occur acutely,[10,11] a phenomenon known as post-exercise hypotension (PEH), or chronically, after several sessions of physical exercise over weeks or months.[12,13] In recent years, special attention has been given to exercises that can enhance the magnitude and duration of PEH, considering that this effect would reduce cardiovascular overload in the hours after the exercise session, thus decreasing the risk of cardiovascular events.[14,15] Additionally, more recent studies have shown that individuals with greater PEH after an exercise session, tend to have a greater reduction in resting BP after weeks of training (i.e., greater chronic effect).[16] Therefore, the magnitude of PEH seems to predict the magnitude of the chronic antihypertensive effect, which represents an important practical applicability.

PEH can occur with different "doses" of physical exercise, both aerobic and strength.[16] In relation to aerobic exercises, a systematic review and previous meta-analysis[11] showed that PEH occurs after performing CE

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and IE, despite being documented mainly after CE, which is the basis for hypertension prevention and treatment recommendations.[3,9] However, in recent years, IE, whether at vigorous or maximum intensity ("all out"), has been considered an alternative to CE for the improvement of several cardiovascular parameters, such as cardiorespiratory capacity,[17] vascular function[18] and clinical BP.[19]

However, it is important to highlight that no direct comparisons were made on the acute effects of CE and IE on BP. Thus, it is not clear whether there is a superiority of the acute antihypertensive effect between exercises, which is an important knowledge gap, as it can help professionals in both hypertension prevention and treatment. Therefore, the aim of this systematic review and meta-analysis was to compare the magnitude of PEH between CE and IE in adults.

Methods

Literature search strategy

The systematic review was carried out following the guidelines of the 'Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA)'.[20] The search for the articles was carried out in PubMed, Web of Knowledge, Scopus and CENTRAL electronic databases. The search strategy used the following descriptors and free terms: "high intensity interval training" [MeSH Terms] OR "high intensity interval exercise" [TIAB] OR "aerobic interval training" [TIAB] OR "aerobic interval exercise" [TIAB] OR "sprint training" [TIAB] OR "sprint" [TIAB] OR "sprint exercise" [TIAB] OR "sprint interval exercise" [TIAB] AND "blood pressure" [MeSH Terms] OR "post-exercise hypotension" [Mesh Terms] OR "post-exercise hypotension" [Mesh Terms] OR "hypotension" [Mesh Terms]. All processes for article search, selection and evaluation were carried out in duplicate and independently.

Eligibility criteria

The eligibility criteria were established according to the PICOS (Population, Intervention, Comparator, Outcomes and Study Design) question.

Population

This review included studies involving adults (18 years or older) of both genders, with no restriction regarding the level of physical activity and BP classification (normotensive, pre-hypertensive and hypertensive). Mean pre-exercise systolic and diastolic BP values were used to classify individuals regarding BP, following the same procedures as other systematic reviews[19,21] and the 7th Brazilian Guidelines on Hypertension.[3]

Intervention

The classification system for IE proposed by Weston et al.[22] was used to define the eligibility criteria for this intervention. According to this proposal, repeated stimuli at vigorous intensity (80-100% of peak heart rate - HRpeak) interspersed with periods of recovery (active or passive) are classified as high-intensity interval training, and maximum stimuli ("all out"; or above the peak oxygen consumption load -VO_2peak) interspersed with recovery periods (active or passive) are classified as sprint interval exercise. Studies that used the percentage of VO_2peak, VO_2 reserve or rating of perceived exertion (RPE) equivalent to 80-100% of HRpeak according to the American College of Sports Medicine,[23] were considered eligible, as well as the "all out" protocols. Studies that showed interventions associated with IE, such as another form of exercise (e.g., strength exercises) or nutritional strategy, were not considered for inclusion.

Comparator

The CE was considered as a comparator of the IE. Studies that used the percentage of VO_2peak, VO_2 reserve or RPE equivalent to moderate intensity (i.e., 64-76% of HRpeak) or vigorous intensity (i.e. 77-95% of HRpeak) were considered eligible. Studies that showed interventions associated with CE, such as another type of exercise or nutritional strategy, were not considered for inclusion.

Outcomes

The primary outcome of this review was clinical BP, measured between 45 and 60 minutes post-exercise. This post-exercise time was defined considering that most studies that investigated the effects of CE and IE included measures within that period. Therefore, even though the study analyzed BP beyond 60 minutes post-exercise, this measure was not considered for the meta-analysis.

Study Design

Crossover studies were considered, involving a session of CE and IE, randomized performance order, in English or Portuguese. The search was carried out without a date limit and ended in March 2020.

Data extraction

An electronic spreadsheet was used to extract data from the included articles, according to the eligibility criteria, in duplicate and independently. In case of disagreement, a meeting was held, and a consensus was established between the researchers. The characteristics of the study participants (age, gender, body mass index, level of physical activity, BP classification), characteristics of the exercise sessions (modality, environments, duration, intensity and time spent in the training session), method of BP measurement and post-exercise BP measurement period were extracted and recorded. Absent data in the texts were requested directly from the authors.

Evaluation of study methodological quality

The 'Tool for the assEssment of Study qualiTy and reporting in Exercise (TESTEX)' scale was used to assess the methodological quality of the included studies,[24] also in duplicate and independently. In case of disagreement, a meeting was held, and consensus was established between the researchers.

Quantitative synthesis

The changes (post and pre-intervention) in clinical BP were extracted from each study and expressed as mean ± standard deviation. The data were reported as weighted mean differences (WMD) and 95% confidence interval (95%CI). The heterogeneity (I^2) between the studies was calculated. Values > 75% and p <0.10 were used to indicate high heterogeneity.[25] The random-effects model was adopted in the presence of low or high statistical heterogeneity. Publication bias was assessed using the funnel plot (Figure 3). The meta-analysis was performed using the Review Manager software (RevMan 5.3, Nordic Cochrane, Denmark). Two studies did not report the standard deviation values in the pre- and post-intervention moments.[26,27] In this case, the values were estimated based on the recommendations of Follman et al.[28] For this purpose, the study by Costa et al.[29] was adopted as the basis. In all analyses, the level of significance adopted was 5%.

Results

Included studies

The search strategy identified 3,252 articles for the initial analysis. After screening the titles, abstracts and excluding duplicate results, 84 studies were selected for full-text analysis. Of these, 72 did not meet the eligibility criteria for inclusion in the study. Additionally, an unpublished study was included in the analyses.[30] Figure 1 shows the flowchart of the research results.

Characteristics of participants

The 12 articles included in the study analyzed clinical BP as the main outcome and none of them reported adverse effects (n = 196; age between 20-75 years; BMI between 21.2-33.0 kg/m²).[26,27,29-38] Of these, three studies involved 46 normotensive individuals (n = 23 women),[26,29,34] with a mean age of 32.67 years, and mean BMI of 24.52 km/m². The mean systolic and

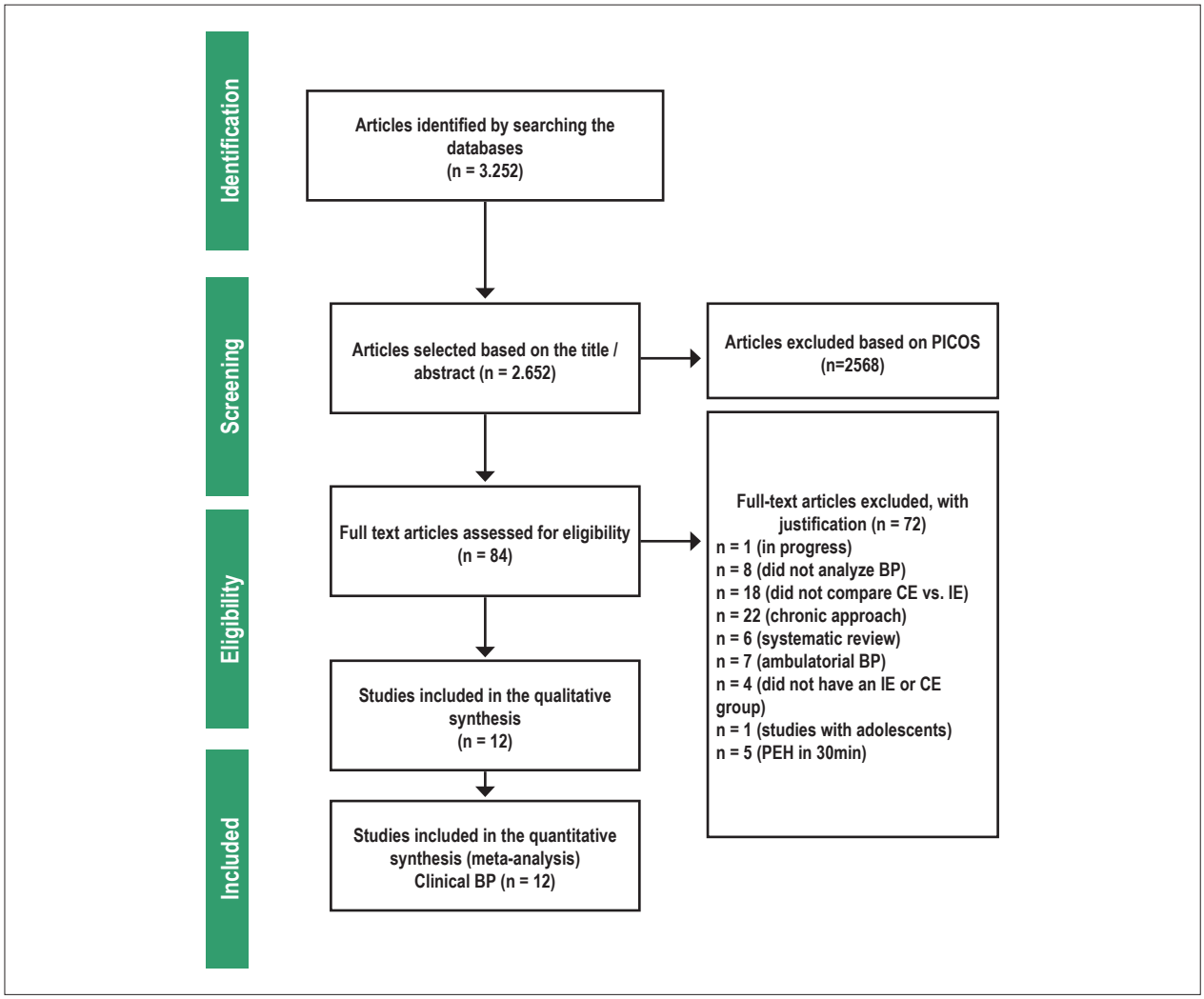

Figure 1 - *PRISMA flowchart of selected studies. BP: blood pressure; CE: aerobic exercises performed continuously; IE: interval exercise; PEH: post-exercise hypotension.*

diastolic BP at rest was 118/65.46 mmHg in IE and 117.27 / 64.73 mmHg in CE. Six studies involved 89 pre-hypertensive patients (n = 1 woman),[27,31-33,36,37] with a mean age of 29.15 years, and mean BMI of 24.68 km/m^2. Mean systolic and diastolic BP at rest was 127.22 / 73.12 mmHg in IE and 126.72 / 73.22 mmHg in CE. Four studies involved 61 hypertensive patients (n = 34 women),[30,34,35,38] mean age of 60,67 years, and mean BMI of 29,97 km/m^2 and all used antihypertensive medication.

Regarding the BP measurement, of the 12 included studies, four used the auscultatory method (~ 33%), while the others used the oscillometric method in an automatic equipment. All studies used inferential statistics, adopting a value of $p \leq 0.05$. Table 1 and 2 shows additional information on the characteristics of the studies and interventions.

Characteristics of interventions

Of the 12 studies included, seven (~ 58%) used a cycle ergometer,[26,27,31-35] and five used a treadmill[29,30,36-38] in the exercise sessions. When the IE session was performed on the treadmill, reductions in systolic and diastolic BP of ~ 9.8 and 4.4 mmHg were observed, respectively. When the IE session was performed on a cycle ergometer, the reduction in systolic and diastolic BP was ~ 7.6 and 3.7 mmHg, respectively. The reduction in systolic and diastolic BP after the CE session on the treadmill was ~ 6.2 and 2.5 mmHg, respectively, and the reduction in systolic and diastolic BP in the cycle ergometer was ~ 4.5 and 2.6 mmHg, respectively. The most frequently used IE protocol consisted of 4 minutes at high intensity, followed by 3 minutes,[27,34] 2 minutes[35] or 1 minute[31] of active recovery. The other protocols used shorter periods (30 seconds to 3 minutes) at high intensity. The CE protocols, on the other hand, had a constant stimulus, lasting between 30 and 70 minutes.

Table 3 shows the qualitative assessment of the included studies. According to the TESTEX scale (0-15 points), all studies had scores > 10 points. The weakest points in the studies were: lack of allocation concealment (92%),[26-29,31-37] blinding of the evaluator to evaluate the outcome (100%)[26,27,29–36] and absence of the reporting of adverse events (75%).[26,29-31,33-37]

Effect of IE versus CE on clinical BP

Figure 2 (panel A) shows the direct comparison between the effects of IE and CE on systolic BP. The meta-analysis showed a significant difference in favor of IE (WMD: -2.93 mmHg [95% CI: -4.96, -0.90], p = 0.005). Moderate heterogeneity was found for this analysis (I^2 = 50%; p = 0.01).

A sensitivity analysis showed that the effect in favor of IE on PEH persisted after the removal of each of the included studies.

The direct comparison between the effects of IE and CE on diastolic BP showed a significant difference in favor of IE (WMD: -1.73 mmHg [95% CI: -2.94, -0.51], p = 0.005). Low heterogeneity was found for this analysis (I^2 = 0%; p = 0.49), as shown in Figure 2 (panel B). In the sensitivity analysis, all studies (one by one) were removed and it was found that only the removal of the study by Maya et al.[36] from the analysis made the positive

Table 1 - Characteristics of participants included in the studies

Authors	Participants	Men (%) / Women (%)	Age (years)	BMI (kg/m^2)	Sample characteristic
Pimenta et al.[38]	n=20 (15 women)	25%/75%	51±8 years	30±6 kg/m^2	Hypertensive men and women
Costa et al.[30]	n= 19 hypertensive women	0/100%	67.6±4.7 years	27.2 kg/m^2	Physically active and inactive women
Boeno et al.[37]	n= 13 pre-hypertensive men	100%/0	22.7±2.6 years	25.3 kg/m^2	Pre-hypertensive and physically inactive men
Maya et al.[36]	n= 30 pre-hypertensive men	100%/0	23±6.5 years	23.9 kg/m^2	Pre-hypertensive and physically active men
Santos et al.[35]	n=15 hypertensive	NI	65.1±4.7 years	29.1 kg/m^2	Physically active men and women
Morales-Palomo et al.[34]	n=7 men and women with metabolic syndrome	57%/43%	55±9 years	29.1 kg/m^2	Normotensive men and women with metabolic syndrome
Morales-Palomo et al.[34]	n= 7 men	100%/0	59±6 years	33 kg/m^2	Hypertensive men with metabolic syndrome
Costa et al.[29]	n= 14 men	100%/0	24.9±4.1 years	24.2 kg/m^2	Normotensive and physically active men
Graham et al.[33]	n=12 men	100%/0	23±3 anos	24 kg/m^2	Pre-hypertensive and physically inactive men
Angadi et al.[27]	n=11 pre-hypertensive individuals	91%/9%	24.6±3.7 years	24.4 kg/m^2	Pre-hypertensive men and women
Lacombe et al.[32]	n=13 men	100%/0	57±4 years	28.6 kg/m^2	Pre-hypertensive and physically inactive men
Rossow et al.[26]	n= 15 men	100%/0	25.8±6.5 years	22.6 kg/m^2	Trained normotensive men
Rossow et al.[26]	n=10 women	0/100%	25±3.4 years	22.2 kg/m^2	Trained normotensive women
Mourot et al.[31]	n=10 men	100%/0	24.6±0.6 years	21.86 kg/m^2	Trained pre-hypertensive men

SOURCE: The author. Recife, 2019.

Table 2 - Characteristics of the CE and IE sessions of the included studies

Authors	Modality	Intervention site/ Supervision	IE Protocol	CE Protocol	Equipment and moment of analysis	Mechanisms related to PEH
Pimenta et al.[38]	Treadmill	Laboratory/Yes	5x 3 min – 85-95% resVO$_2$/ 2 min – 50-60% resVO$_2$	~35min – 60 - 70% res VO$_2$	Aneroid sphygmomanometer - 60min	Not investigated
Costa et al.[30]	Treadmill	Laboratory/Yes	10x 1 min – 80-85% RHR/ 2min – 40-45% RHR	30 min – 50-55% RHR	Oscillometric - 60min	**IE:** → CO, ↓ PVR, ↓ TVI, → AC; **CE:** → CO, → PVR, ↓ TVI, → AC
Boeno et al.[37]	Treadmill	Laboratory/Yes	5 km: 1 min- 90% HRmax/ 1min -60% HRmax	5 km – 70% HRmax	Digital sphygmomanometer - 60min	Not investigated
Maya et al.[36]	Treadmill	Laboratory/Yes	500 kcal: 3 min – 115%AT/ 1min 30s PR	500 kcal: 85% AT	Aneroid sphygmomanometer - 60min	Not investigated
Santos et al.[35]	Cycle ergometer	Laboratory/Yes	4x 4 min-85-90% RHR/ 2min - 50% RHR	40 min - 60-80% RHR	Aneroid sphygmomanometer - 60min	Not investigated
Morales-Palomo et al.[34]	Cycle ergometer	Laboratory/Yes	5 x 4 min-90% HRpeak/ 3 min 70% HRpeak (~460 kcal)	~70 min-60% HRpeak (~460 kcal)	Digital sphygmomanometer – 45min	**IE:** ↑ CO, ↓ SV, ↓ PVR; **CE:** → CO, → SV, → PVR
Morales-Palomo et al.[34]	Cycle ergometer	Laboratory/Yes	5 x 4min-90% HRpeak/ 3 min 70% HRpeak (~460 kcal)	~70 min-60% HRpeak (~460 kcal)	Digital sphygmomanometer – 45min	**IE:** ↑ CO, ↓ SV, ↓ PVR; **CE:** → CO, → SV, → PVR
Costa et al.[29]	Treadmill	Laboratory/Yes	10x 1 min-90% MAV/ 1 min - 30% MAV	20 min - 60% MAV	Digital sphygmomanometer – 60min	Not investigated
Graham et al.[33]	Cycle ergometer	Laboratory/Yes	5x 30 s – 0.075% BM - all out/4 min 30 s - AR – UULL ergometer	50 min-65% VO$_2$max	Aneroid sphygmomanometer - 60min	Not investigated
Graham et al.[33]	Cycle ergometer	Laboratory/Yes	5x 30s – 0.075% BM - all out/4 min 30 s - AR – LLLL ergometer	50 min-65% VO$_2$max	Aneroid sphygmomanometer - 60min	Not investigated
Angadi et al.[27]	Cycle ergometer	Laboratory/Yes	4 x 4min-90-95% HRmax/3 min –50% HRmax	30 min - 75-80% HRmax	Oscillometric - 60min	Not investigated
Angadi et al.[27]	Cycle ergometer	Laboratory/Yes	6 x 30s- (0.075% BM – all out) /4min – 50% HRmax	30 min - 75-80%HRmax	Oscillometric - 60min	Not investigated
Lacombe et al.[32]	Cycle ergometer	Laboratory/Yes	5x 2min - 85% VO$_2$max/ 2min-40% VO$_2$max	21 min - 60% VO$_2$max	Digital sphygmomanometer - 60min	**IE:** ↓BRS, → CO, ↓SV. **CE:** BRS, → CO, ↓SV
Rossow et al.[26]	Cycle ergometer	Laboratory/Yes	4x 30 s -0.07% BM – all out /4 min 30 s- AR	60 min-60% RHR	Digital sphygmomanometer - 60min	**IE:** ↑ CO, ↓ PVR; **CE:** CO, ↓ PVR
Mourot et al.[31]	Cycle ergometer	Laboratory/Yes	9x4 min-1stVT/ 1 min-Ppeak	48 min-1st VT	Digital sphygmomanometer – 60min	Not investigated

N: number of participants; IE: interval exercise; CE: continuous exercise; BMI: body mass index; AT: anaerobic threshold; VT: ventilatory threshold; RHR: reserve heart rate; HRmax: maximum heart rate; Wmax: maximum Watts; HRpeak: peak heart rate; Ppeak: peak power; MAV: maximum aerobic velocity on the treadmill; VO$_2$max: maximum oxygen consumption; VO$_2$res: reserve oxygen consumption; BM: body mass; M: men; W: women; UULL: upper limb; LLLL: lower limb; AR: active recovery; PR: passive recovery; NI: not informed; CO: cardiac output; PVR: peripheral vascular resistance; SV: stroke volume; BRS: baroreflex sensitivity; TVI: total vascular impedance; AC: arterial compliance; ↑ increase; ↓ reduction; → maintenance. SOURCE: The author. Recife, 2019.

Table 3 - Methodological quality analysis of the included studies

Authors	Study quality					Partial (0-5)	Study quality										Partial (0-10)	Total (0-15)
	1	2	3	4	5		6 a	6 b	6 c	7	8 a	8 b	9	10	11	12		
Costa et al. 2020	1	1	1	1	0	4	1	0*	-	1	1	1	1	NC	1	1	7	11
Pimenta et al. 2019	1	1	0	1	0	3	1	1	-	1	1	1	1	NC	1	1	8	11
Boeno et al. 2019	1	1	0	1	0	3	1	0*	-	1	1	1	1	NC	1	1	7	10
Maya et al. 2018	1	1	0	1	0	3	1	0*	-	1	1	1	1	NC	1	1	7	10
Santos et al. 2018	1	1	0	1	0	3	1	0*	-	1	1	1	1	NC	1	1	7	10
Morales-Palomo et al. 2017	1	1	0	1	0	3	1	0*	-	1	1	1	1	NC	1	1	7	10
Costa et al. 2016	1	1	0	1	0	3	1	0*	-	1	1	1	1	NC	1	1	7	10
Graham et al. 2016	1	1	0	1	0	3	1	0*	-	1	1	1	1	NC	1	1	7	10
Angadi et al. 2015	1	1	0	1	0	3	1	1	-	1	1	1	1	NC	1	1	8	11
Lacombe et al. 2011	1	1	0	1	0	3	1	1	-	1	1	1	1	NC	1	1	8	11
Rossow et al. 2010	1	1	0	1	0	3	1	0*	-	1	1	1	1	NC	1	1	7	10
Mourot et al. 2004	1	1	0	1	0	3	1	0*	-	1	1	1	1	NC	1	1	7	10

**- studies that did not report the number of dropouts; however, all ended with the same number of participants who started the intervention, 6c- does not fit, all studies show an acute analysis, NC - no control group. Quality of studies: 1 = Specific eligibility criterion; 2 = Type of randomization specified; 3 = Allocation concealment; 4 = Similar groups in the baseline; 5 = The evaluators were blinded (at least for one main result); 6 = Results evaluated in 85% of participants (6a = 1 point if more than 85% were concluded; 6b = 1 point if adverse events were reported; 6c = if exercise attendance is reported); 7 = Intention to treat statistical analysis; 8 = Statistical comparison between groups were reported (8a = 1 point if comparisons between groups are reported for the variable primary outcome of interest; 8b = 1 point if statistical comparisons between groups are reported for at least one secondary measure); 9 = Point measures and measures of variability for all outcome measures were reported; 10 = Monitoring of activity in the control group; 11 = The intensity related to the exercise remained constant; 12 = Exercise volume and energy expenditure were reported. SOURCE: The author. Recife, 2019.*

result in favor of IE disappear (WMD: -0.99 mmHg [95% CI: -2.30, 0.32], p = 0.14; I^2 = 0%; p = 0.97).

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis that directly compared the magnitude of PEH after a session of CE and IE in adults. The main finding of this study is that the IE shows a reduction in systolic and diastolic BP of ~ 3 and 1.3 mmHg, respectively, more than the CE (between 45-60 minutes post-exercise). However, it is important to highlight that this result on diastolic BP has considerable influence of a single study.[36]

Overall, the present study observed that IE showed a reduction of ~ 8 and 4 mmHg for systolic and diastolic BP, respectively, between 45-60 minutes post-exercise. The reduction observed after CE, however, was ~ 5 and 2.6 mmHg for systolic and diastolic BP, respectively, in the same post-exercise analyzed period. Therefore, a direct comparison (head-to-head) of the effects of these interventions confirmed the superiority of IE over CE in terms of the magnitude of systolic and diastolic PEH between 45-60 minutes. These data are similar to those found in a previous meta-analysis,[11] which observed a reduction in systolic BP of 7.1 and 4.0 mmHg and a reduction in diastolic BP of 2.5 and 3.2 mmHg, respectively, for interval and continuous exercise. However, it is important to highlight that not only the interval *versus* continuous nature was compared in the present meta-analysis, but interventions that specifically involved IE (at vigorous intensity and "all out") versus CE (at moderate and vigorous intensity), which was not performed in the previous study.[11]

Studies have shown that the magnitude of PEH can be related both to the intensity reached during the exercise session,[10,11,39] and to the exercise volume.[11,40] In the present meta-analysis, most of the included studies (~ 66%; n = 8) [29–32,34,36–38] equalized the volume, and / or average intensity, and / or total energy expenditure of IE with CE sessions, which can facilitate the understanding of the impact of the exercise nature (interval *vs*. continuous) and intensity of stimuli on the PEH magnitude. This aspect is important because studies show that when volume and/or mean intensity are equalized, PEH is similar between IE and CE.[41,42] However, of the studies included in this systematic review, those that showed volume, and / or mean intensity, and / or total energy expenditure equalized between the exercise protocols, mean reductions of -9.7 and -5 mmHg were observed in systolic BP and -4.3 and -2.2 mmHg in diastolic BP, for IE and CE, respectively. The IE protocols that showed lower volume, and/or mean intensity and/or energy expenditure,[26,27,33,35] showed mean reductions of -6.2 and -3.4 mmHg in systolic and diastolic BP, respectively, which was slightly higher than the mean

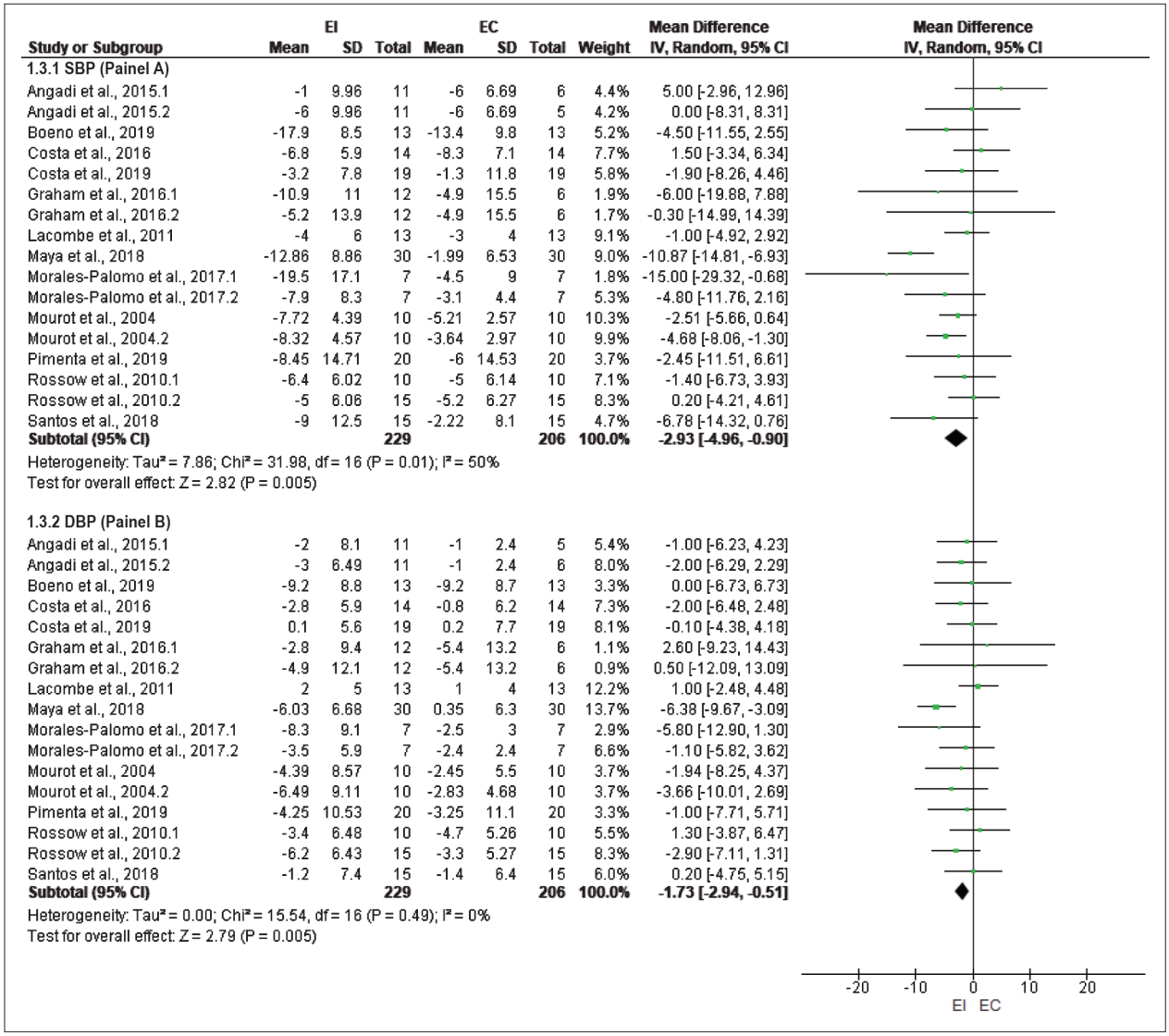

Figure 2 - *Forest plot of the comparison of the effects of interval exercise (IE) vs. continuous exercise (CE) on systolic (panel A) and diastolic (panel B) blood pressure (BP). Results are expressed in delta change (post-exercise blood pressure values - pre-exercise blood pressure values).*

reductions in systolic and diastolic BP observed in CE (-4.9 and -3.2 mmHg, respectively). Therefore, high-intensity stimuli seem to have a role in the magnitude of PEH, regardless of whether or not there was volume, and/or mean intensity and / or total energy expenditure equalization.

The mechanisms through which PEH occurs after a CE session are well documented.[13,16,43,44] The reduction in peripheral vascular resistance has often been attributed as one of the main mechanisms of acute post-exercise BP reduction,[45] which is aided by the reduction of sympathetic activity in the vessel due to baroreflex control, which generates prolonged vasodilation.[46,47] Additionally, local vasodilators, such as prostaglandins and nitric oxide, also play an important role in the occurrence of PEH.[48,49] In patients with vascular disorders (e.g., the elderly, peripheral arterial disease, and obese individuals), PEH occurs by reducing the stroke volume, due to a decreased preload, which is not compensated by increased heart rate.[26,45,50] The studies that directly compared the acute effects of CE and IE on BP showed that the mechanisms related to PEH between these exercise models seem to be different.[26,30,32,34]

In normotensive individuals, Rossow et al.[26] observed a greater reduction in peripheral vascular resistance and an increase in cardiac output (mediated by an increase in heart rate) after the IE protocol, when compared to the CE. In pre-hypertensive men, Lacombe et al.[32] demonstrated that IE resulted in greater changes in baroreflex sensitivity and heart rate variability than CE in the post-exercise period. Morales-Palomo et al.[34] observed, in individuals with metabolic syndrome (normotensive and hypertensive), greater reductions in stroke volume, peripheral vascular resistance, skin vascular resistance, higher blood flow in the skin and greater increases in heart rate after IE, when compared to CE. In middle-aged and elderly hypertensive

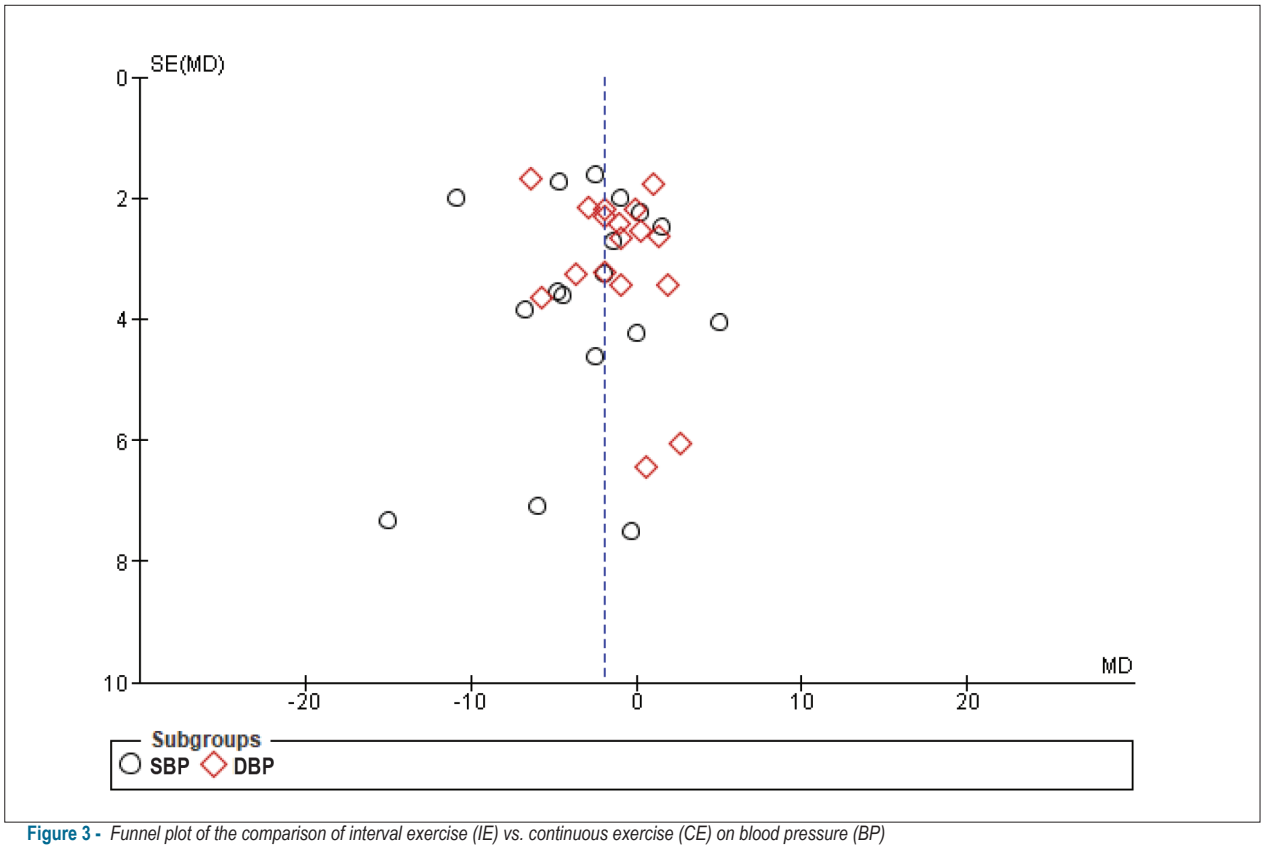

Figure 3 - *Funnel plot of the comparison of interval exercise (IE) vs. continuous exercise (CE) on blood pressure (BP)*

women, Costa et al.[30] found that there was a reduction in peripheral vascular resistance 60 minutes after IE, when compared to the control session, which did not occur after CE. Considered together, IE seems to induce a greater reduction in peripheral vascular resistance post-exercise, when compared to CE. It is important to emphasize that the studies that compared the hemodynamic determinants of PEH between IE and CE are few and involve different populations, which makes it difficult to understand the possible differences between these protocols.

From a clinical point of view, a chronic reduction of 2 mmHg in systolic BP reduces the risk of mortality from stroke by 6% and coronary artery disease by 4%, while a reduction of 5 mmHg decreases 14% and 9% of the risk, respectively.[15] A meta-analysis showed that the chronic antihypertensive effect of IE and CE is similar in individuals with prehypertension and hypertension, both on systolic (-6.3 *vs*. -5.8 mmHg) and diastolic BP (-3.8 *vs*. -3.5 mmHg) at rest.[19] Regarding the acute antihypertensive effect of exercise, the present review suggests the superiority of IE over CE for both systolic (~ 3 mmHg) and diastolic (~ 1.3 mmHg) BP. However, it is important to note that this effect was observed between 45-60 minutes after the exercise. Therefore, physical exercise must be performed regularly so that the chronic benefits can be attained.

The findings of this study demonstrated that a single session of aerobic exercise is capable of promoting PEH in adults, regardless of the performed stimulus (CE or IE). The magnitude of the PEH was associated to the intensity and interval nature of the exercise, so that the IE generated a greater PEH. However, it is important to emphasize that there are different forms of IE prescription, which makes it impossible to determine a protocol that maximizes PEH.

Despite the new and interesting results, this systematic review has some limitations: i) only four databases were searched for study inclusion; ii) few studies were included in this review; iii) the included studies involved a small number of participants (between 10 and 30 individuals); iv) different BP measurement methods were used in the studies; v) food and water intake control, level of physical activity and other confounding factors were seldom reported in the studies; vi) short post-exercise BP monitoring time, which makes it difficult to understand the duration of PEH between protocols.

Conclusions

This systematic review and meta-analysis of crossover studies suggests that IE induces a PEH of greater magnitude compared to CE, between 45-60 minutes post-exercise in adults, both in systolic (~3 mmHg) and diastolic BP (~1.3 mmHg). However, the clinical importance of these findings should be considered with caution. Future studies comparing the acute effect of IE and CE on ambulatorial BP are required in order to clarify whether, in fact, the difference between these types of exercises has clinical importance regarding acute BP control, both in wakefulness and in sleep.

Author contributions

Conception and design of the research and Acquisition of data: Perrier-Melo RJ. Costa EC; Analysis and interpretation of the data and Writing of the manuscript: Perrier-Melo RJ. Costa EC. Farah BQ; Critical revision of the manuscript for intellectual content: Perrier-Melo RJ. Costa EC. Farah BQ. Costa MC

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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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High-intensity Interval Training versus Continuous Exercise: Is There a Difference Regarding the Magnitude of Blood Pressure Reduction?

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Short Editorial related to the article Acute Effect of Interval vs. Continuous Exercise on Blood Pressure: Systematic Review and Meta-Analysis

Systemic arterial hypertension (SAH) is strongly associated with adverse cardiovascular events, including heart failure, ischemic heart disease and cerebrovascular diseases.[1] With a high prevalence worldwide, SAH is commonly associated with risk factors such as family history, obesity, high sodium intake and physical inactivity. Therefore, it is estimated that countries such as the United States and England have 1/3 of hypertensive individuals.[2] In Brazil, specifically in 2016, a prevalence rate > 32% of SAH (36 million) was reported in adult individuals, being > 60% in the elderly. SAH contributed, directly or indirectly, to 50% of deaths from cardiovascular diseases.[3]

A standardized and appropriate technique for measuring blood pressure (BP) is necessary. Ideally, several steps should be followed to achieve maximum accuracy. It is recommended to measure BP with the patient in the sitting position, with legs uncrossed, feet placed flat on the floor and supported back region; the arm should be at the heart level and the palm facing upwards.[3]

Adequate management of SAH comprises pharmacological and non-pharmacological interventions. Non-pharmacological ones, such as physical exercise, are an important mainstay of treatment, helping to reduce blood pressure levels, and potentially contributing to the reduction of the daily dose of antihypertensive medication. In addition to exercise, a balanced diet with a special reduction in salt consumption, stress control and alcohol consumption are also considered important behaviors.[4] Thus, lifestyle changes aiming at BP reduction are recommended for all individuals with SAH.[5]

Regarding physical exercise, it is postulated that high-intensity interval training (HIIT) is an alternative training protocol and even more efficient than continuous training (CT) of moderate intensity (MICT), which is the gold standard recommended in several guidelines.[6] HIIT intercalates vigorous activity (~ 85% to 95% of maximum heart rate [HR_{max}] and/or VO_{2max}) lasting 1 to 4 minutes, with recovery periods (resting or low intensity exercise).[7] It has been shown that HIIT can be superior to MICT in improving cardiorespiratory fitness, endothelial function, insulin sensitivity, markers of sympathetic activity and arterial stiffness,[8] factors that can influence a better post-exercise BP response.

Clark et al.[9] studied the 6-week effects of HIIT versus MICT on BP assessed by ambulatory blood pressure monitoring (ABPM) and aortic stiffness in 28 overweight or obese men. The individuals performed exercise on a stationary bicycle 3x / week. HIIT showed a stronger correlation than MICT, reducing BP by about 3-5 mmHg, being more evident in those with higher baseline BP, but there were no statistical differences in effectiveness between HIIT and MICT on BP values.[9] In another study, 19 patients (8 normotensive and 11 hypertensive ones) with metabolic syndrome were divided into a group of HIIT (>90% HRmax, ~85% VO_{2max}), MICT (~ 70% HRmax, ~ 60% VO_{2max}) or control group without exercise. No differences were found regarding ABPM values in normotensive individuals, In hypertensive patients who practiced HIIT, the systolic BP showed a reduction of 6.1 ± 2.2 mmHg when compared to those of the MICT group and the control group (130.8 ± 3.9 *versus* 137.4 ± 5.1 and 136.4 ± 3.8 mmHg, respectively; $p < 0.05$). However, diastolic BP was similar in the three groups. Therefore, exercise intensity seems to influence BP reduction magnitude, with the HIIT being superior to the MICT.[10]

In this issue of the Brazilian Archives of Cardiology *(Arquivos Brasileiros de Cardiologia)*, Perrier-Melo et al.[11] compared the magnitude of post-exercise hypotension (PEH) – considering between 45 and 60 minutes post-exercise – in HIIT (~ 80 to 100% of HR_{peak}) *versus* CT in adult individuals. In this study, protocols with both moderate (64 to 76% of HR_{peak}) and vigorous intensity (77 to 95% of HRpeak) were considered eligible for the CT group. Twelve randomized clinical trials were included, 6 with prehypertensive, 2 with normotensive, 1 with hypertensive and normotensive, and 3 with hypertensive. As a method of measurement, four used the auscultatory method, while the others used the oscillometric method with automatic equipment. As a training protocol, seven studies used a cycle ergometer, while the other five used a treadmill. The researchers found a higher PEH in favor of HIIT both in systolic BP (WMD: -2.93 mmHg [95% CI: -4.96, -0.90]) and in diastolic BP (WMD: -1.73 mmHg [95%CI: -2.94, -0.51]), when compared to the CT group, suggesting a superiority of the HIIT when

Keywords

Hypertension; Exercise; Heart Failure; Risk Factors; Arterial Pressure; Post Exercise Hypotension; Exercise Therapy; Life Style.

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compared to CT on PEH in the 45-60 minutes after the end of the exercise.[11]

An important point to be mentioned in relation to the meta-analysis by Perrier-Melo et al.[11] is that, although HIIT significantly reduced diastolic BP, when the study by Maya et al.[12] was omitted from the analysis, the benefit disappeared. In this study, the assessed individuals were physically active and normotensive. Thus, the results found by Perrier-Melo et al.[11] should be viewed with caution regarding the pressure values of individuals with SAH, especially regarding diastolic BP. Despite the interesting study, some limitations should be recalled, such as the low number of studied patients and the heterogeneity of BP measurement methods. Moreover, the inclusion of normotensive, pre-hypertensive and hypertensive individuals in the same forest plots also does not allow a more assertive conclusion, since the magnitude of PEH may be different between these groups; although the authors carried out a sensitivity analysis, they found no differences after removing each of the included studies.[11]

Another recent meta-analysis compared the effects of HIIT and MICT in hypertensive individuals. Significant differences were found in systolic BP with both interventions, when compared to the control group: HIIT, 5.64 mmHg and MICT, 3.7 mmHg, as well as in diastolic BP: HIIT, 4.8 mmHg, and MICT, 2.41 mmHg, when compared to the control group. However, HIIT showed a greater magnitude of diastolic BP reduction when compared to MICT. When VO_{2max} (secondary outcome) was assessed, both interventions increased this important marker when compared to the control groups, but HIIT promoted an even more marked improvement.[13]

Although the mechanisms involved in BP reduction are not fully understood, it is postulated that the increase in shear stress (shear stress) with consequent improvement in nitric oxide release, in addition to the reduction of sympathetic nervous activity and peripheral vascular resistance, contribute to these results.[14] Moreover, by potentially increasing plasma levels of apelin and nitrite / nitrate, HIIT can be effective in reducing BP.[15]

Finally, although the evidence suggests a potential benefit in reducing training BP with greater intensities intercalated with recovery periods, further studies are required for a definitive conclusion and possible changes in current exercise prescription recommendations for the management of SAH. The results provided by this meta-analysis can contribute to the performance of further and larger studies, in a population consisting only of hypertensive patients, evaluating the acute and sustained reduction in BP with HIIT *versus* CT at different intensities as an outcome. Meanwhile, we must encourage all individuals, especially those diagnosed with SAH, to practice physical exercises, emphasizing the more appropriate and safer ones, according to the individuality and capacity of each individual.

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AT_1 Receptor Blockade Improves Myocardial Functional Performance in Obesity

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Abstract

Background: **Obesity has been associated with chronic activation of the renin-angiotensin-aldosterone system and with significant changes in cardiac performance.**

Objective: **To assess the impact of a blockade of angiotensin-II receptor type 1 (AT_1 receptor) on morphology and on myocardial functional performance in rats with high-fat diet- induced obesity.**

Methods: **Wistar rats (n=48) were submitted to control (2.9 kcal/g) or high-fat (3.6 kcal/g) diet for 20 weeks. After the 16th week they were divided into four groups: Control (CO), Obese (OB), Control Losartan (CL) and Obese Losartan (OL). CL and OL received losartan (30 mg/kg/day) in drinking water for four weeks. Subsequently, body composition, systolic blood pressure (SBP) and echocardiographic variables were analyzed. Papillary muscle function was assessed at baseline with 2.50 mM calcium concentration ($[Ca^{2+}]_o$) and after inotropic maneuvers: post-pause potentiation (PPP), $[Ca^{2+}]_o$ elevation, and during beta-adrenergic stimulation with isoproterenol. Analysis of the results was performed by the Two-Way ANOVA and by the appropriate comparison test. The level of significance was set at 5%.**

Results: **Although SBP change had been not maintained at the end of the experiment, obesity was associated with cardiac hypertrophy and with increased left ventricle posterior wall shortening velocity. In the study of papillary muscles in basal condition, CL showed lower developed tension maximum negative variation velocity (-dT/dt) than CO. The 60s PPP promoted lower -dT/dt and maximum developed tension (DT) in OB and CL compared with CO, and higher relative DT variation and maximum positive variation velocity (+dT/dt) in OL compared with CL and OB. Under 1.5, 2.0, and 2.5mM $[Ca^{2+}]_o$, the OL group showed higher -dT/dt than CL.**

Conclusion: **Losartan improves myocardial function in high-fat diet-induced obesity. (Arq Bras Cardiol. 2020;115(1):17-28)**

Keywords: **Cardiovascular Diseases; Obesity; Losartan/therapeutic use; Angiotensin II Type 1 Receptor Blockers/therapeutic use; Rats; Diet, High-fat/methods.**

Introduction

Obesity is a chronic and multifactorial disease resulting from interaction among many etiological factors.[1,2] This disease is a nutritional and metabolic dysfunction that may be associated with dyslipidemia, insulin resistance and cardiovascular diseases.[3] Clinical studies have shown obesity may cause morphological and functional changes in the heart.[4,5] Moreover, experimental research proved this condition is associated with myocardial hypertrophy,[6-8] interstitial fibrosis,[8,9] and several molecular changes.[10,11] These responses include disorders in expression and functioning of peptides involved with intracellular calcium handling during muscle contraction and relaxation.[7,12-14]

However, there are important divergences among studies regarding potential effects of high-fat diet induced obesity on myocardial performance. Jacobsen et al.[15] found increased contractile phase during inotropic maneuver of papillary muscle in obese rats after three weeks of diet; other authors have found higher myocardial shortening velocity

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in experiments of 20,[8] 30,[11] 33,[13] and 35 weeks.[16] Other investigations have reported impaired cardiac contraction, showed by *in vitro* papillary muscles analysis of obese rats in experimental models with15 weeks of diet.[7,17,18] There are also reports of unchanged cardiac function after 20,[9] 30,[19] and 32[14] weeks of dietary intervention. Therefore, cardiac performance should be further studied in high-fat diet-induced obesity experiments.

Obesity regards greater activity of the renin-angiotensin-aldosterone system (RAAS).[11,20,21] High levels of angiotensin-II (Ang-II) coupling to receptors type I (AT_1) exert a vasoconstrictor and a trophic effect on myocardium, stimulating several intracellular signaling cascades and multiple physiological responses.[21-23] RAAS activation is the main mechanism responsible for blood pressure disorders and cardiac remodeling in obesity; these effects were attenuated after AT_1 antagonism.[16,11,21,24] However, when considering the *in vitro* analysis of the papillary muscle, the association between RAAS activation and ventricular remodeling in obesity models based on high-fat diet administration is scarcely studied.

The *in vitro* preparation of papillary muscle allows myocardial contractile capacity measurements in terms of shortening and force generation, despite changes in load, heart rate and heart geometry; such conditions modify mechanical performance *in vivo*.[7,13,17,19] Using inotropic and lusitropic maneuvers, myocardial performance may also be studied to identify changes in contraction and relaxation that could not be observed under baseline conditions. The most used maneuvers are post-pause potentiation, extracellular [Ca^{2+}] elevation and beta-adrenergic stimulation.[7]

From this perspective, the objective of this study was to assess the influence of AT_1 blockade on cardiac morphology and performance using *in vitro* papillary muscle analysis in rats with saturated high-fat diet induced obesity. The initial hypothesis is that obesity is associated with changes in myocardial functional performance, sustained under different stimulation conditions; these responses are attenuated by AT_1 receptor antagonism.

Methods

Animal and experimental design

Male Wistar rats (n=48), aged 30 days-old were used from the Animal Center of São Paulo State University – UNESP – Botucatu/SP, Brazil. The sample size definition was based on a previous study,[19] developed with a similar experimental model and functional analysis of the isolated papillary muscle.

Firstly, animals were divided into two groups: control (CO), treated with control diet (2.9 kcal/g), and obese (OB), fed with high-fat diet with a predominance of saturated fatty acids (3.6 kcal/g).[9] The following ingredients were used for both dietary preparations: corn bran, soybean bran and hulls, dextrin, and palm and soybean oils, plus vitamin and mineral supplementation. In terms of saturated/unsaturated fatty acids content,[9,16] while the control diet presented 61.6/38.4%, the high-fat diet showed 64.8/35.2%.

After 16 weeks, the animals were allocated into four groups: CO, OB, CL and OL. For another four weeks, while CO and OB continued to receive their respective diets, CL and OL also received losartan in drinking water (30 mg/kg/day).[11] The animals were kept in individual cages at 22±2°C (room temperature), 55±5% humidity, and 12 hours light/dark lighting cycles. The experimental protocol was reviewed and approved by the Ethics Committee on Animal Experiments of the Botucatu Medical School (protocol 1000/2013).

Cardiovascular study

The cardiovascular study involved systolic blood pressure (SBP) measurement, cardiac morphology assessment, echocardiographic functional analysis and *in vitro* papillary muscle study. SBP and echocardiogram analysis were performed at 16 and 20 weeks of the experiment. SBP was obtained by plethysmography[26] using a sphygmomanometer (Narco Bio-Systems®, model 709-0610 - International Biomedical, Austin, TX, USA). For echocardiography, the animals were anesthetized with a mixture of ketamine hydrochloride (50 mg/kg) and xylidine hydrochloride (1 mg/kg) administered intramuscularly. After trichotomy in the anterior thorax, each animal was positioned in the left lateral position. For cardiac geometry analysis, one-dimensional images (M-mode) were obtained with the ultrasound beam adjusted in the two-dimensional mode, keeping the transducer on the parasternal position and smaller axis.

Left ventricle (LV) imaging was obtained by positioning the M-mode cursor below the mitral valve plane at the papillary muscles level.[27] Aortic and left atrial images were obtained with the M-mode cursor positioned at the aortic plane level. Images were recorded on a printer (model UP-890, Sony Co.). Cardiac structures were measured manually with a caliper. During the maximum ventricular cavity diameter, LV diastolic diameter (LVDD), LV posterior wall diastolic thickness (LVDT), and interventricular septum (IVDT) were measured. The LV systolic diameter (LVSD) was assessed during the minimum cavity diameter. The left atrium (LA) was measured at its maximum diameter. LV weight (LVW) was estimated according to the following formula: $LVW = [(LVDD+LVDT+IVDT)^3 - (LVDD)^3] \times 1.04$. The ratio between LVDD and tibia length was also considered.

LV systolic function was assessed by posterior wall shortening velocity (PWSV) and percentage of eendocardium fractional shortening (% ES) = [(LVDD-LVSD)/LVDD]. The diastolic function was analyzed by the following indexes: 1) ratio between the initial filling flow velocity peaks (E wave) and the atrial contraction (A wave) of the transmitral flow (E/A); 2) E wave deceleration time (EDT); 3) isovolumetric relaxation time (IVRT); 4) early mitral annulus diastolic displacement velocity peak (E') and late mitral annulus diastolic displacement velocity peak (A') obtained by tissue Doppler; and 5) ratio between the waves E and E' (E/E'). All measurements were performed by the same expert according to the American Society of Echocardiography[28] procedures, using an echocardiograph (General Electric Medical Systems, Vivid S6, Tirat Carmel, Israel), equipped with a multifrequency electronic transducer (5-11.5 MHz).

General characterization and *in vitro* analysis of myocardial performance

Caloric intake was assessed daily.[6-8] Feeding efficiency was obtained from the relationship between body weight variation and total energy intake.[6-8] Body weight was measured weekly, while weight gain was obtained from the difference between initial and final body weight values. Adipose tissue from the retroperitoneal, epididymal, and visceral regions was used to determine body fat content.[6-12]

Myocardial performance was assessed by *in vitro* study with papillary muscle isolated from LV.[7,16,18,29] After 20 weeks, animals were submitted to intraperitoneal anesthesia with ketamine hydrochloride (80 mg/kg), xylazine (5 mg/kg), and euthanasia. After median thoracotomy, the heart was removed and dissected. Atria, right ventricle (RVW) as well as left ventricle (LVW) were weighted for macroscopic morphological analysis. Dissected LV papillary muscles were placed between two stainless steel rings and positioned vertically within a glass chamber containing Krebs-Henseleit solution at 28°C, continuously oxygenated with O_2 (95%) and CO_2 (5%). The Krebs solution composition was the following: 118.5 mM NaCl; 4.69 mM KCl; 2.50 mM $CaCl_2$; 1.16 mM $MgSO_4$; 1.18 mM $KH2PO_4$; 5.50 mM glucose; and 24.88 mM $NaCO_3$. The lower end of the inferior ring was coupled to a 120T-20B force transducer (Kyowa, Tokyo, Japan) by a steel wire (1/15,000) running through a mercury-filled slot in the glass chamber floor.[7,16,18,29]

The muscles were kept on isotonic contraction against a light loading for 60 minutes; afterwards, they were then kept on isometric contraction and gradually stretched until the maximum developed tension (DT) was achieved. After 5 minutes under isotonic contraction, the muscles were placed back in isometric contraction to determine the tension-length curve (L_{max}) peak. The papillary muscles behavior was assessed at baseline with a 2.50 mM calcium concentration ($[Ca^{2+}]_o$) and after the following inotropic maneuvers: post-rest potentiation (PPP), extracellular $[Ca^{2+}]$ elevation since 0.5 until 2.5 mM, and during beta-adrenergic stimulation with 0.1 and 1.0 mM isoproterenol. Post-pause potentiation was studied in extracellular $[Ca^{2+}]$ equal to 1.50 mM, where the stimulus was stopped for 30 and 60 seconds before it restarted.[7,30]

After PPP, the papillary muscle response was assessed after extracellular $[Ca^{2+}]_o$ maneuver.[31] Isometric contractile parameters were recorded after 10 minutes with progressive calcium addition (0.5 to 2.5mM) in the extracellular solution. The beta-adrenergic system stimulation has also been studied to test beta-adrenergic complex integrity, troponin C sensitivity, and calcium absorption by the sarcoplasmic reticulum.[7,31] Beta adrenergic receptor stimulation was induced using cumulative isoproterenol concentrations (0.1 to 1.0 mM) in the presence of 1.0 mM $[Ca^{2+}]_o$.

Mechanical variables

Conventional mechanical responses at L_{max} were obtained in isometric contraction: maximum developed tension normalized by the transverse sectional area of the papillary muscle (DT [g/mm²]) and maximum positive variation velocities (+dT/dt [g/mm²/s]); and maximum negative variation velocity (-dT/dt [g/mm²/s]) of maximum developed tension (DT), normalized by the transverse sectional area of the papillary muscle. The measures used to characterize papillary muscle size included length (mm), muscle weight (mg) and transverse sectional area (TSA [mm²]). At the end of each experiment, L_{max} was measured with the *Gaertner* catheter (Gaertner Scientific Corporation, Chicago, IL, USA), and the muscle portion between the steel rings was cut and weighed. TSA was obtained from a ratio between muscle weight and length, assuming uniformity and a specific 1.0 gravity.

Statistical analysis

A Sigma-Stat version 3.5 software was used for data analysis. Firstly, the results were subjected to normality analysis by the Kolmogorov-Smirnov test. Since the variables had parametric distribution, measures were presented as mean and standard-deviation. Nutritional results, body composition, cardiac morphology and functional performance of the papillary muscle were analyzed using the two-way analysis of variance (*Two-Way* ANOVA) and the Tukey's multiple comparisons test. SBP and echocardiogram measurements were analyzed by *Two-Way* ANOVA in the repeated measures (RM) model, and Bonferroni multiple comparison test. The level of significance was set at 5%.

Results

Results of nutritional profile, body composition and cardiac macroscopic morphology are shown in Table 1. Although caloric intake was unchanged, OB and OL showed higher fat intake and feed efficiency than CO and CL, respectively. Obesity was characterized by higher measures of body weight and adiposity.

OB presented higher values of atria weight and respective relationships between atrial weight and LV weight with tibia length compared to CO regarding cardiac morphology. Losartan promoted lower atrial and LV measurements comparing OL with OB in absolute values and when normalized by tibia length, as shown in Table 1.

Table 2 presents SBP results, structure and performance of the heart, assessed by echocardiography. After 16 weeks, obesity was associated with higher SBP; losartan led to SBP reduction in CL and OL at the end of the experiment. The ratio between left ventricular diastolic diameter (LVDD) and tibia length was similar among groups and between the moments. At the end of the experiment, obesity culminated in a higher posterior wall shortening velocity (PWSV), as observed in OB and OL. Considering the diastolic performance, OL presented lower E/A ratio than CL at the 20th week. Tissue Doppler of late diastolic mitral valve annular velocity (A' average) was lower in CL than CO; S average and E' average were increased from week 16 to week 20 in OL.

The functional performance of the papillary muscles is shown in Figures 1 to 4. Under basal conditions, the DT and +dT/dt indexes were similar among groups (Figure 1A and 1B), while the -dT/dt was lower in CL than CO (Figure 1C). The effects of diverse calcium concentrations on papillary muscle performance are shown in Figure 2. Increasing $[Ca^{2+}]_o$ from 1.0 to 2.5 mM resulted in higher DT, +dT/dt and -dT/dt values in all groups. OL showed higher DT, +dT/dt and -dT/dt values compared to CL at calcium concentrations of 1.5,

Table 1 – Mean and standard deviation of nutritional variables, murinometry and cardiac morphology according with group

	Variable	Group			
		CO	OB	CL	OL
Nutritional Profile	Body weight (g)	451 ± 58	507 ± 64 *	456 ± 49	517 ± 50 ‡
	Caloric intake (Kcal)	81.9 ± 8.2	80.7 ± 7.5	80.3 ± 9.2	78.7 ± 7.9
	Total intake of unsaturated lipids (g)	122 ± 12	235 ± 22 *	120 ± 14	230 ± 23 ‡
	Total intake of saturated lipids (g)	196 ± 20	433 ± 40 *	193 ± 22	422 ± 43 ‡
	Feed efficiency (%)	26.82 ± 2.11	32.22 ± 4.38 *	28.43 ± 0.94	35.12 ± 4.78 ‡
	Adiposity (%)	3.48 ± 0.73	5.19 ± 1.47 *	3.61 ± 1.27	5.50 ± 1.48 ‡
Cardiac Morphology	Atria (g)	0.096 ± 0.015	0.113 ± 0.015 *	0.092 ± 0.009	0.100 ± 0.022 †
	Atria/ Tibia (mg/mm)	2.22 ± 0.33	2.59 ± 0.35 *	2.15 ± 0.21	2.29 ± 0.46 †
	RVW (g)	0.231 ± 0.029	0.241 ± 0.030	0.230 ± 0.039	0.245 ± 0.040
	RVW/Tibia (mg/mm)	5.36 ± 0.68	5.50 ± 0.70	5.34 ± 0.79	5.64 ± 0.86
	LVW (g)	0.844 ± 0.083	0.950 ± 0.099	0.800 ± 0.082 *	0.799 ± 0.087 †
	LVW/Tibia (mg/mm)	19.6 ± 1.7	21.7 ± 2.4 *	18.7 ± 1.5	18.4 ± 1.7 †

*RVW: right ventricular weight; LVW: left ventricular weight; CO: Control group; OB: Obese group; CL: Control Losartan group; OL: Obese Losartan group Group's effects: * p <0.05 compared to CO; † p <0.05 compared to OB; ‡ p <0.05 compared to CL; Two-Way ANOVA and Tukey test.*

2.0, and 2.5 mM. In the 2.5 mM $[Ca^{2+}]_o$ maneuver, DT (CO, 109±37; OB, 113±31; CL, 98±33; OL, 134±46%) and +dT/dt measures (CO, 118±43; OB, 122±27; CL, 109±37; OL, 153±49%) were higher in OL than OB (Figure 2A and 2B).

Figure 3 presents results of papillary muscles functional performance in response to PPP. In general, the PPP variation from 30 to 60s culminated in increased DT, +dT/dt and -dT/dt values. In the 60s PPP, OB group showed lower DT, +dT/dt and -dT/dt measurements than CO; OL showed higher DT (CO, 65.7±23.6; OB, 56.3±13.9; CL, 58.0±17.4; OL, 66.4±17.4%) than OB and CL, and higher +dT/dt values (CO, 70.0±14.9; OB, 59.3±15.9; CL, 62.7±20.0; OL, 70.7±20.7%) when compared with CL.

Regarding the β-adrenergic stimulation maneuvers, according to Figure 4, concentrations of 0.1 and 1mM showed an increase in DT when compared to basal conditions. The 1mM isoproterenol maneuver resulted in reduced +dT/dt in OB (Figure 4B) and increased the -dT/dt measurements in all groups when compared to baseline and 0.1mM concentrations (Figure 4C). Considering the group effect, CL showed higher DT (CO, 22.8±11.4; OB, 19.5±10.9; CL, 40.4±13.6; OL, 28.7±11.9%) and lower -dT/dt than CO (CO, 67.5±18.5; OB, 67.2±22.6; CL, 25.3±9.2; OL, 68.8±19.1%) in response to 0.1mM isoproterenol.

Discussion

This study aimed to assess potential effects of AT_1 receptor antagonism on cardiovascular characteristics in obese rats. Obese rats exhibited SBP changes, LV hypertrophy, alterations in systolic performance assessed by echocardiography, and disorders of papillary muscle function. Most of these effects have been attenuated by the losartan administration, an AT_1 receptor antagonist intervention.

This experimental model is characterized by the induction of obesity from the high-fat diet administration, with a predominance of saturated fatty acids.[9,16] In this context, despite the unchanged caloric consumption between groups, the obese animals showed higher measures of lipid intake and energy efficiency when compared to the respective control counterparts. As a result, body weight and adiposity values were also higher in obesity. Due to higher energy density of lipids, consumption of high-fat diets is associated with accumulation of body reserves and adipose tissue hypertrophy[9, 16-19]. Probably, the positive weight variation of obese animals resulted from increased adiposity, as previously reported.[9,11,19]

SBP was higher in obese after 16 experimental weeks. The association between obesity and blood pressure changes has also been confirmed by other studies.[8,11,17] Also, SBP was chronically increased after physical stress[32] and in response to experimental period,[8] even though baseline levels were unchanged at the end of the experiment. In general, inflammatory and/or neurohormonal factors regarding excess adipose tissue contribute to the occurrence of hemodynamic disorders in obese.[20,23] In the presence of losartan, SBP levels were reduced, confirming the RAAS participation in promoting obesity-derived hemodynamic pressure disorders.

In turn, persistent increase in SBP has been associated with higher afterload, parietal deformation and cardiac hypertrophy.[33,34] The results of this study confirmed ventricular hypertrophy and high systolic performance, as shown by the higher PWSV in obesity according to Table 2. Systolic function is affected by several factors, including heart rate, contractility, and changes in preload and afterload.[33] Although obesity did not change heart rate and ventricular geometry, larger wall measurements could preserve or decrease preload. However,

Table 2 – Mean and standard deviation of systolic blood pressure, measures of structure and functional performance of the heart analyzed by echocardiogram and left ventricular tissue Doppler, according to group and time of assessment

Variable	Moment	Group			
		CO	OB	CL	OL
SBP (mmHg)	16th Wks	119.4 ± 9.2	133.3 ± 12.3 *	119.5 ± 9.4	132.0 ± 9.6 ‡
	20th Wks	129.6 ± 9.3	139.3 ± 12.6	103.0 ± 13.2 * §	107.7 ± 7.4 †§
HR (bpm)	16th Wks	277 ± 41	272 ± 27	276 ± 48	273 ± 44
	20th Wks	285 ± 32	266 ± 39	265 ± 39	277 ± 39
LA (mm)	16th Wks	5.47 ± 0.79	5.80 ± 0.60	5.87 ± 0.74	5.81 ± 0.89
	20th Wks	5.69 ± 0.56	5.95 ± 0.55	5.70 ± 0.60	5.77 ± 0.67
LA/AO	16th Wks	1.37 ± 0.18	1.45 ± 0.14	1.48 ± 0.14	1.42 ± 0.18
	20th Wks	1.42 ± 0.16	1.44 ± 0.10	1.40 ± 0.11	1.42 ± 0.12
LVDT (mm)	16th Wks	1.317 ± 0.072	1.374 ± 0.044	1.313 ± 0.071	1.361 ± 0.058
	20th Wks	1.272 ± 0.067 §	1.305 ± 0.043 §	1.262 ± 0.085 §	1.271 ± 0.061 §
LVDD (mm)	16th Wks	7.95 ± 0.64	7.91 ± 0.37	7.80 ± 0.57	7.82 ± 0.44
	20th Wks	8.11 ± 0.41	8.15 ± 0.26	8.06 ± 0.54	8.08 ± 0.52
LVDD/ Tibia (mm/mm)	16th Wks	0.184 ± 0.015	0.180 ± 0.008	0.182 ± 0.012	0.180 ± 0.007
	20th Wks	0.188 ± 0.010	0.186 ± 0.007	0.188 ± 0.011	0.187 ± 0.012
LVSD (mm)	16th Wks	3.65 ± 0.68	3.56 ± 0.39	3.54 ± 0.65	3.69 ± 0.56
	20th Wks	3.66 ± 0.42	3.55 ± 0.50	3.86 ± 0.67	3.75 ± 0.62
PWSV (mm/s)	16th Wks	40.44 ± 4.70	43.63 ± 2.95	42.31 ± 5.11	39.29 ± 3.96
	20th Wks	42.92 ± 4.45	48.72 ± 4.81 * §	42.82 ± 3.60	47.96 ± 4.03 ‡§
EF	16th Wks	0.900 ± 0.039	0.907 ± 0.023	0.903 ± 0.037	0.892 ± 0.037
	20th Wks	0.907 ± 0.022	0.914 ± 0.033	0.887 ± 0.039	0.898 ± 0.037
ES (%)	16th Wks	54.32 ± 6.38	55.00 ± 3.72	54.83 ± 6.28	52.92 ± 5.41
	20th Wks	54.94 ± 3.58	56.49 ± 5.67	52.34 ± 5.73	53.83 ± 5.45
E/A	16th Wks	1.65 ± 0.35	1.49 ± 0.25	1.52 ± 0.25	1.43 ± 0.23
	20th Wks	1.60 ± 0.33	1.50 ± 0.23	1.74 ± 0.27	1.39 ± 0.26 ‡
EDT (ms)	16th Wks	50.09 ± 6.85	49.50 ± 4.56	47.64 ± 8.69	51.10 ± 6.19
	20th Wks	47.64 ± 7.47	50.58 ± 6.59	50.17 ± 5.84	54.40 ± 5.77
IVRT	16th Wks	58.88 ± 6.98	58.12 ± 4.22	55.38 ± 7.72	54.66 ± 5.26
	20th Wks	53.60 ± 4.22	52.47 ± 4.87	53.49 ± 7.17	52.72 ± 3.78
S'(cm/s)	16th Wks	3.57 ± 0.31	3.79 ± 0.28	3.72 ± 0.24	3.79 ± 0.45
	20th Wks	4.00 ± 0.24 §	4.05 ± 0.47	3.91 ± 0.29	4.19 ± 0.27 §
E' (cm/s)	16th Wks	4.62 ± 0.53	4.23 ± 0.40	4.25 ± 0.39	4.04 ± 0.53
	20th Wks	4.85 ± 0.57	4.80 ± 0.32 §	4.83 ± 0.38 §	4.92 ± 0.52 §
A' (cm/s)	16th Wks	3.75 ± 0.86	3.85 ± 0.59	3.78 ± 0.83	3.49 ± 0.50
	20th Wks	4.37 ± 0.87	3.78 ± 1.08	3.61 ± 0.75 *	4.31 ± 0.81 §
E/E'	16th Wks	16.80 ± 3.62	18.76 ± 3.13	18.12 ± 2.27	18.86 ± 2.61
	20th Wks	17.89 ± 2.59	18.79 ± 2.35	17.27 ± 1.52	17.22 ± 2.51

*SBP: systolic blood pressure; HR: heart rate; LA / AO: relationship between the diameters of the left atrium (LA) and the aortic artery (AO); LVDT: diastolic thickness of the posterior wall; LVDD: left ventricular diastolic diameter; LVSD: left ventricular systolic diameter; PWSV: posterior wall shortening velocity; EF: ejection fraction; ES: endocardial shortening; E / A: relationship between the E and A waves of the transmitral flow; IVRT: isovolumetric relaxation time; EDT: E wave deceleration time; S ': systolic velocity of the mitral valve ring at tissue Doppler (TDI); E ': TDI of the diastolic velocity of the mitral valve ring (mean between septal and lateral walls); A ': TDI of the late diastolic velocity of the mitral valve ring (mean of the septal and lateral walls); E / E ': relation obtained between the velocities of the initial mitral valve flow and the TDI of the mitral valve ring; CO: Control group; OB: Obese group; CL: Control Losartan group; OL: Obese Losartan group. Group's effects: * p <0.05 compared to CO; † p <0.05 compared to OB; ‡ p <0.05 compared to CL; Moment's effect: § p <0.05 compared to the 16th week (Wks); Two-Way RM ANOVA and Bonferroni test.*

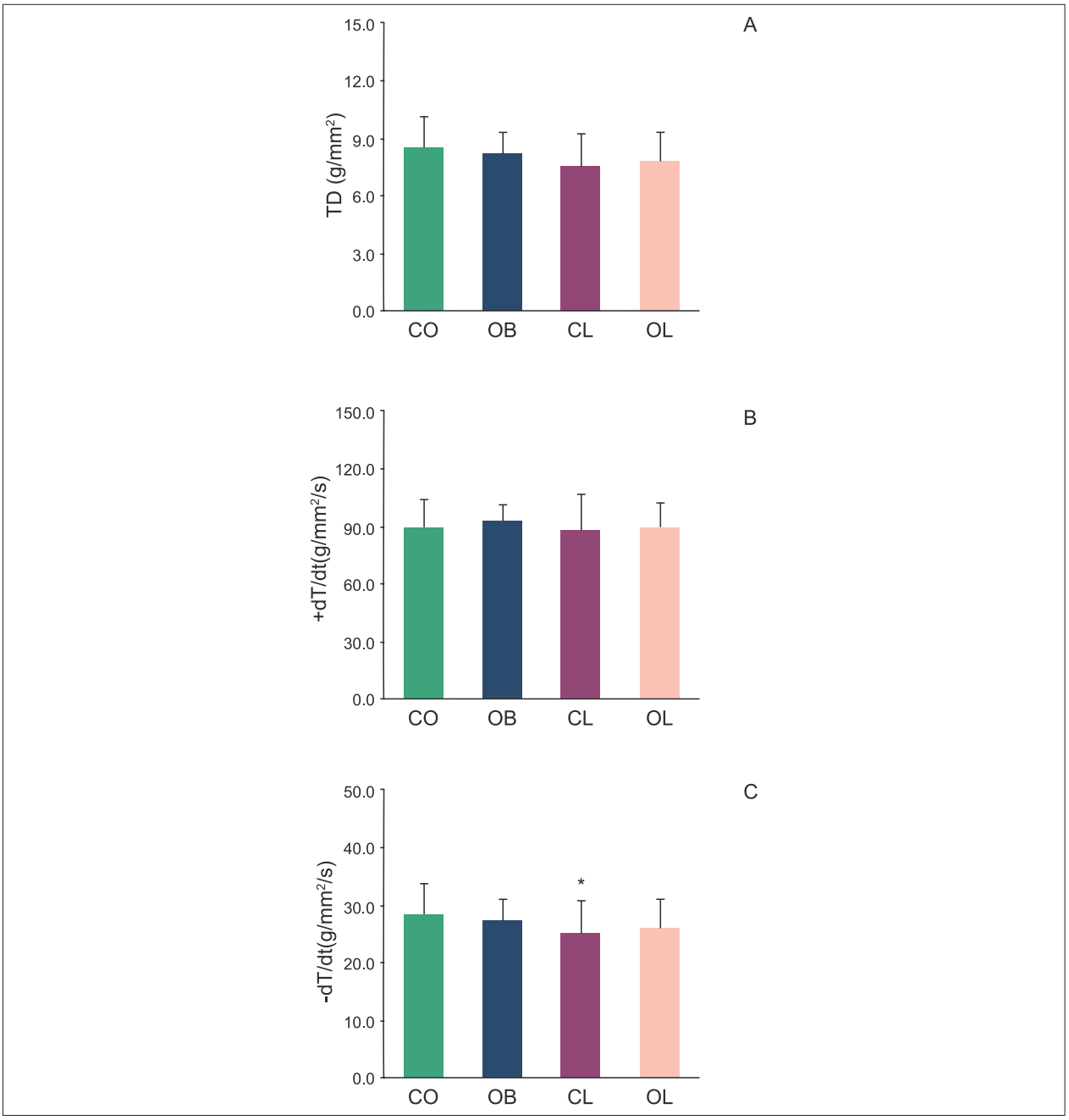

Figure 1 – *Functional papillary muscle assessment at baseline with extracellular [Ca $^{2+}$] equal to 2.5 mM; results in mean±SD; (A) DT: maximum developed tension; (B) +dT/dt: maximum DT variation speed; (C) –dT/dt: maximum DT decrease; CO: Control group; OB: Obese group; CL: Control Losartan group; OL: Obese Losartan group. * p<0.05 compared to CO; Two-Way ANOVA and Tukey Test.*

reduced preload could cause lower ejection,[11,33] which was not confirmed by the results. Likewise, increased systolic performance is associated with ventricular hypertrophy and/or changes in afterload in OB. The afterload is a mechanical variable directly influenced by changes in pressure and intraventricular diameter and inversely related to ventricular wall thickness.[33,34]

However, the papillary function assessment showed that obesity *per se* was not associated with basal changes, not only in response to various [Ca^{2+}] but also isoproterenol concentrations. A previous study showed decreased contractile strength and other functional disorders in basal conditions of obese papillary muscles.[35] Lima-Leopoldo et al.[7] showed that increased Ca^{2+} extracellular concentration resulted in lower values of myocardial parameters of contraction (DT) and relaxation (-dT/dt) in obesity. These divergences may regard differences in dietary compositions, including added sugar[7] and/or lipid profile from formulations.

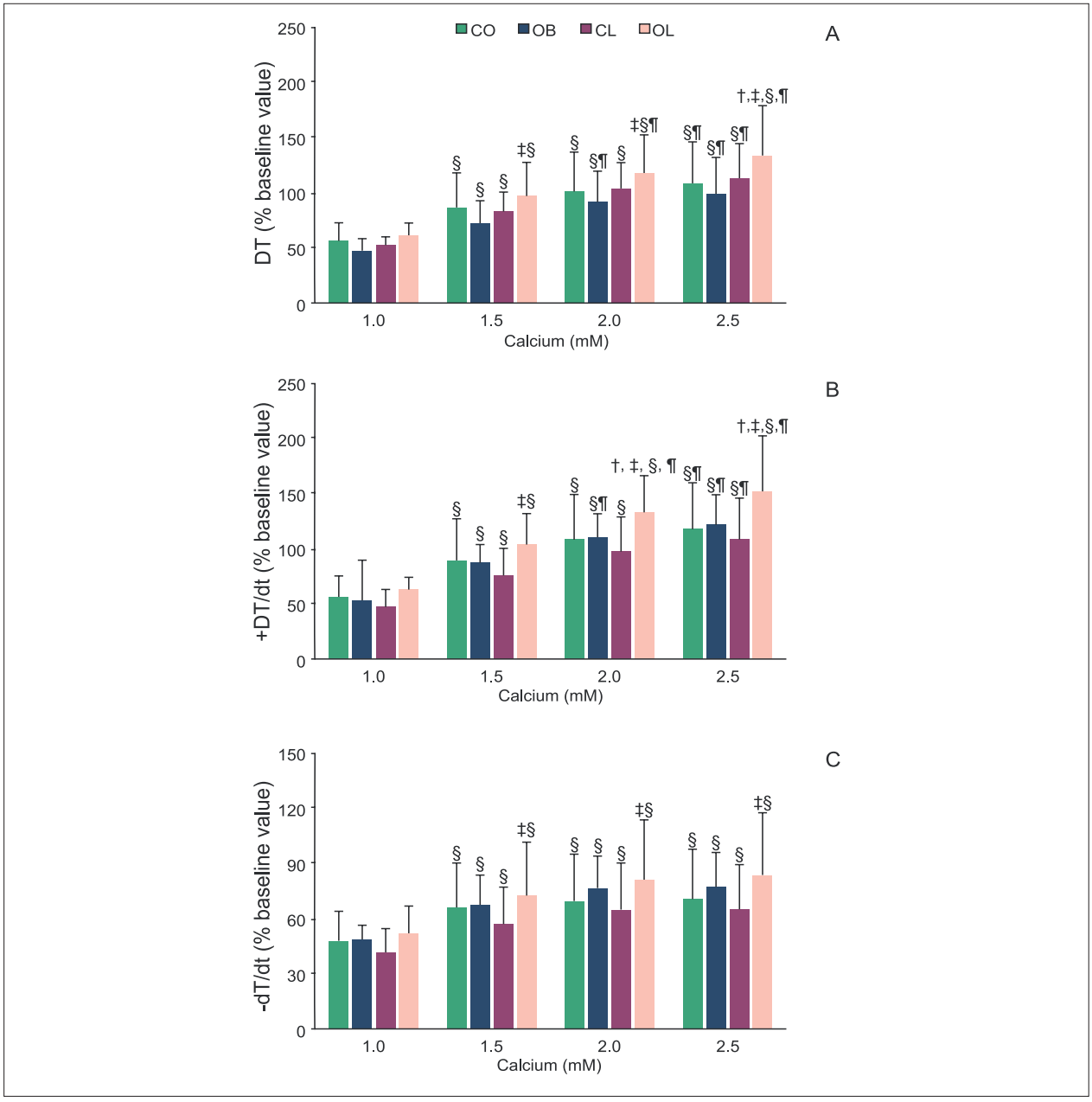

Figure 2 – *Functional papillary muscle assessment according to extracellular calcium concentration (1.0-2.5 mM). Results expressed regarding the baseline with extracellular [Ca 2+] equal to 0.5 mM value (mean±SD); (A) DT: maximum developed tension; (B) +dT/dt: maximum positive DT change; (C) -dT/dt, maximum DT decrease. CO: Control group; CL: Control Losartan group; OB: Obese group; OL: Obese Losartan group. Group's effect: † p<0.05 compared to OB; ‡ p<0.05 compared to CL. Calcium's Effect: §, p<0.05 compared to 1.0 mM; ¶, p<0.05 compared to 1.5 mM; Two-Way RM ANOVA and Bonferroni Test.*

Based on using a similar intervention to this study, Vileigas et al.[16] also found unchanged myocardial function in papillary muscle preparation at baseline and after isoproterenol addition.

Regarding the PPP assessment, obesity promoted myocardialdysfunction, most probably due to changes in intracellular Ca^{2+} handling. The 60s maneuver reduced DT, +dT/dt and -dT/dt values in myocardium of obese rats, as in Figure 3. The results agree with previous studies showing lower contractile response in obese Zucker rats after 60s of PPP[35]. As -dT/dt is influenced by the frequency of calcium ions absorption into the sarcoplasmic reticulum,[7] the lower Ca^{2+} recapture shown by -dT/dt in obese rats suggests that SERCA2 protein activity was reduced. Decreasing -dT/dt with high cytosolic Ca^{2+} concentrations suggests that activation of SERCA2 from Ca^{2+}/*calmodulin-dependent protein kinase* may be shortened by obesity. Important reduction in DT of obese rats could result not only from Ca^{2+} reduction in the sarcoplasmic reticulum, but also from a lower Ca^{2+} release through the *Rianodine* receptors.

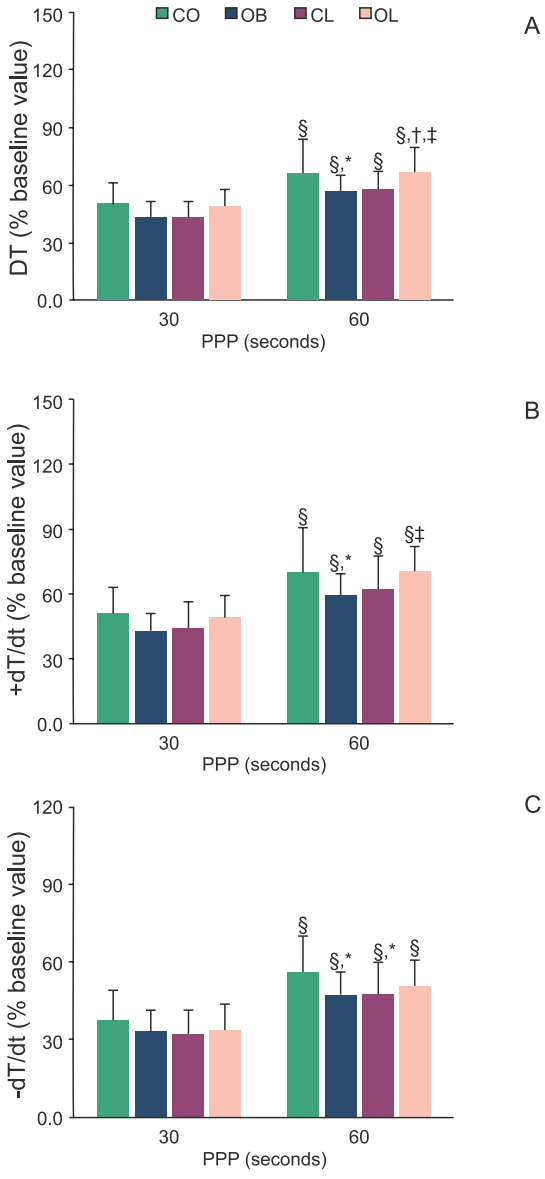

Figure 3 – *Isolated papillary muscle assessement, according to post-pause potentiation (PPP) time. Results are expressed regarding the baseline with extracellular [Ca 2+] equal to 0.5 mM value (mean±SD); (A) DT: maximum developed tension; (B) +dT/dt: maximum positive DT change; (C) –dT/dt: maximum DT decrease; CO: Control group; CL: Control Losartan group; OB: Obese group; OL: Obese Losartan group. PPP's effect: §, p<0.05 compared to 30s; Group's effect: * p<0.05 vs CO; † p<0.05 compared to OB; ‡ p<0.05 compared to CL. Two-Way RM ANOVA and Bonferroni Test.*

The disturbances in Ca^{2+} intracellular handling and myocardial contractility in obese rats probably result from the RAAS stimulation. When compared with OB and CL, OL animals showed better contractile performance in response to Ca^{2+}, PPP and isoproterenol elevation maneuvers (Figures 2-4). Considering the high PWSV maintenance and the mechanical behavior of the papillary muscle in response to losartan, it is likely that systolic performance was regulated by greater sensitivity to Ca^{2+} in OL. From this perspective, one cannot rule out a possible metabolic effect of AT_1 blockade, providing greater energy efficiency from improved combustion of macronutrients, especially lipids.[24,36] Excessive fatty acids supply may promote greater mitochondrial activity, stimulating mechanisms regarding increased Ca^{2+} handling.[19,23] In a previous experiment, intervention with losartan resulted in the inhibition of molecular mechanisms of myocardial insulin resistance, improving contractile heart performance in obese rats by cafeteria diet.[11] Recently, AT_1 blockade resulted in improved mitochondrial function in obese insulin-resistant rats.[37]

From this perspective, the clinical repercussions of the findings of this study are diverse. RAAS activation conditions have been associated with metabolic disorders and heart disease.[23] In this study, important contractile disorders were shown, which could be the focus of interventions for cardiovascular treatment in obese patients.

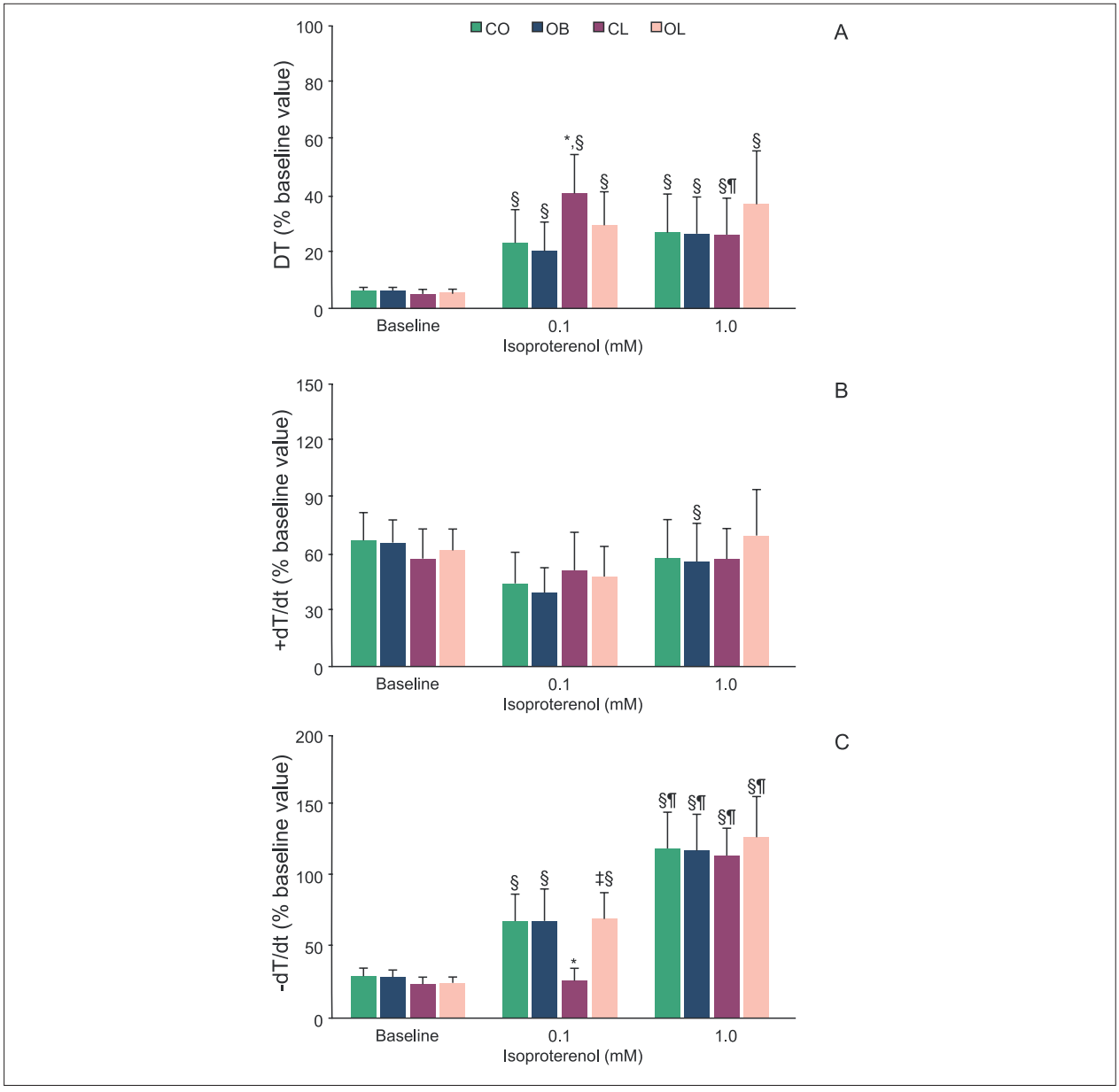

Figure 4 – *Functional assessment of the isolated papillary muscle, according to Isoproterenol concentration. Results expressed regarding the baseline with extracellular [Ca $^{2+}$] equal to 1.0 mM value (mean±SD); (A) DT: maximum developed tension; (B) +dT/dt: maximum positive DT change; (C) -dT/dt: maximum DT decrease; CO: Control group; OB: Obese group; CL: Control Losartan group; OL: Obese group under Losartan. Group's effect: * p<0.05 compared to C; ‡ p<0.05 compared to CL. Isoproterenol's Effect: §, p<0.05 compared to Baseline; ¶, p<0.05 vs 0.1 mM; Two-Way RM ANOVA and Bonferroni Test.*

However, isolated effects of dietary variables as a cause of cardiac remodeling cannot be ruled out, although these effects have been improved with AT_1 antagonism. In a previous study,[8] increased lipid consumption was shown to be directly related to characteristics of cardiovascular response in obesity. Therefore, this is an important study limitation and new investigations should be developed to better clarify the isolated role of saturated and unsaturated fatty acids in this experimental model.

Conclusion

In conclusion, high-fat diet-induced obesity promotes cardiac remodeling, sustained by ventricular hypertrophy and myocardial dysfunction. Considering that Losartan attenuated most of these disorders, the initial hypotheses of this investigation was confirmed, according to which the AT_1 receptor stimulation is associated with impaired myocardial function in obese rats.

Author contributions

Conception and design of the research: Oliveira-Junior SA, Okoshi MP, Martinez PF; Acquisition of data: Muzili NA, Carvalho MR, Ota GE, Morais CS, Vieira LFC, Ortiz MO, Campos DHS, Cezar MDM, Okoshi K; Analysis and interpretation of the data: Oliveira-Junior SA, Campos DHS, Cezar MDM, Okoshi MP, Okoshi K, Cicogna AC, Martinez PF; Statistical analysis and writing of the manuscript: Oliveira-Junior SA; Obtaining financing: Oliveira-Junior SA, Martinez PF; Critical revision of the manuscript for intellectual content: Okoshi MP, Okoshi K, Cicogna AC, Martinez PF.

Potential Conflict of Interest

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the UNESP under the protocol number 1000/2013. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

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Targeting the Renin-Angiotensin-Aldosterone System in Obesity

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Short Editorial related to the article: AT_1 Receptor Blockade Improves Myocardial Functional Performance in Obesity

Obesity has been increasing across the globe and markedly raising the prevalence of cardiovascular diseases (CVD).[1] Obesity, particularly severe obesity, causes hemodynamic alterations that contribute to changing cardiac morphology, which may predispose to impaired ventricular function and heart failure. These alterations include a high cardiac output state in most cases, as well as left ventricular hypertrophy (LVH) and left ventricular (LV) diastolic dysfunction. Experimental studies and some investigations on humans propose that specific neurohormonal and metabolic alterations generally associated with obesity may lead to changes in cardiac structure and function.[2]

Adipocytes are a rich source of angiotensinogen, angiotensin I, and angiotensin-converting enzyme, contributing to the production of angiotensin II. The generation of these hormones is additive to systemically-produced components of the renin-angiotensin-aldosterone system (RAAS).[3] Obesity is characterized by enhanced RAAS activation. Such activation has many implications concerning cardiac structure and function. The most critical is the vasoconstrictive effect of angiotensin II, which results in the development of hypertension (HTN) in obese patients, in addition to inducing an increase in LV afterload in normotensive-obese patients.[4]

Angiotensin II is a growth factor that affects both vascular smooth muscle and myocardium. Therefore, enhanced RAAS activation influences the development of vascular smooth muscle and myocardial hypertrophy.[2] Conditions related to RAAS activation have been associated with metabolic disorders and heart diseases. RAAS activation also seems to promote insulin resistance and hyperinsulinemia by various mechanisms. This scenario may lead to increased sympathetic nervous system (SNS) activity, further contributing to the development of LVH.[5] Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) are commonly used to treat obesity hypertension.

Keywords

Obesity; Cardiovascular Diseases; Prevalence; Heart Failure; Left Ventricular Hypertrofy; Renin-Angiotensin System.

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In a previous experiment, intervention with ARB (Losartan) resulted in the inhibition of molecular mechanisms of myocardial insulin resistance, improving heart contractility. Recently, the use of angiotensin II receptor type 1 (AT1) blockade resulted in improved mitochondrial function in obese insulin-resistant rats in an experimental model.[6]

Whether targeting the RAAS in normotensive obese patients improves cardiovascular outcomes to a greater extent than in normotensive lean patients is uncertain.

In this issue of ABC, Silva-Junior and co-authors[7] present the results of their animal study assessing the influence of AT1 blockade on cardiac morphology and performance using in vitro papillary muscle analysis in rats with high-fat diet-induced obesity. They hypothesize that obesity might be associated with changes in myocardial functional performance, sustained under different stimuli, and that these responses could be attenuated by AT1 receptor antagonism. Wistar rats were submitted to kcal/g control or high-fat diet for 20 weeks. Four groups were assessed: Control (CO), Obese (OB), Control Losartan (CL), and Obese Losartan (OL). The CL and OL groups received Losartan (30 mg/kg/day). Afterward, body composition, systolic blood pressure (SBP), and echocardiographic variables were analyzed. The authors found that obesity was associated with SBP changes and cardiac hypertrophy. They also identified changes in systolic performance and disorders of papillary muscle function in obese rats. The AT1 receptor antagonist intervention reduced most of these effects.

The results of this elegant experimental study reinforce the importance of cardiovascular interventions focused on obese patients.

A meta-analysis of 28 randomized clinical trials comprising 2,403 patients with HTN (mean age range 44–67 years) showed that LVH regression with antihypertensive drugs was greater in the overweight and obesity groups than in normal-weight subjects. Even with a smaller reduction in SBP, LVH improved in obese and overweight groups compared to the normal-weight group ($p<0.001$ at baseline in all groups). Renin-angiotensin system inhibitor therapy was the most effective treatment for reducing LVH in overweight and obese patients ($p<0.001$).[6]

Obesity is a complex adiposity-based chronic disease, whose management targets both weight-related complications and adiposity to improve overall health. Substantial voluntary weight loss can reverse many of the hemodynamic, neurohormonal, and metabolic changes associated with obesity.[8] Medical interventions, such as ARB, along with weight loss, may result in reverse cardiac remodeling and improve the ventricular function and the quality of life in obese patients.[9]

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Clinical Characteristics of Resistant vs. Refractory Hypertension in a Population of Hypertensive Afrodescendants

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Abstract

Background: Afrodescendants have been associated with a greater severity of arterial hypertension and a higher incidence of cardiovascular complications. Characteristics in the presentation of resistant hypertension (RH) or refractory hypertension (RfH), specifically in this ethnic group, have not been properly studied.

Objectives: The study compares clinical and epidemiological characteristics and prevalence of cardiovascular events in people of African descent diagnosed with RH or RfH.

Methods: Cross-sectional study carried out in a referral clinic for patients with severe hypertension. The level of significance was 5%.

Results: 146 consecutive patients were evaluated, of which 68.7% were female. The average age was 61.8 years, with 88.4% of Afrodescendants (mixed race or black). 51% had RfH. There was a high prevalence of cardiovascular risk factors: 34.2% of subjects had diabetes, 69.4% dyslipidemia, 36.1% obesity, and 38.3% history of smoking. Reduced renal function was seen in 34.2%. Previous cardiovascular events occurred in 21.8% for myocardial infarction and in 19.9% for stroke. The Framingham's risk score was moderate/high at 61%. RfH patients were younger (mean age 59.38±11.69 years versus 64.10±12.23 years, p=0.02), had more dyslipidemia (83.8 versus 66.7%, p=0.021), and stroke (30.4 versus 12.3%, p=0.011) when compared to those with RH. The use of a combination of ACEi/ARB+CCB+Diuretic, chlortalidone and spironolactone was also more frequent in individuals with RfH.

Conclusion: Africandescendant people with RH had a high cardiovascular risk, a high prevalence of RfH, a higher frequency of dyslipidemia and stroke, compatible with a high incidence of injury to target organs. (Arq Bras Cardiol.2020; 115(1):31-39)

Keywords: Hypertension/complications; African Continental Ancestry Grup/genetic; Comparative Stuy; Epidemiology; Myocardial Infarction; Stroke.

Introduction

The high proportion of individuals with systemic arterial hypertension (SAH) who do not reach the appropriate therapeutic goals has a direct impact on morbidity, mortality, disability and health costs.[1-3] Even with the proper use of antihypertensive drugs, a significant number of patients remain with high blood pressure (BP), a condition characterized as Resistant Hypertension (HR) and defined as the persistence of high BP despite the use of three antihypertensive drugs of different classes, or when BP control occurs only with the use of four or more drugs, always including a thiazide diuretic.[2-5] A subgroup of patients with HR exhibits a phenotypic presentation of apparently greater severity, in which BP is not controlled even with the use of five or more drugs, a situation currently defined as Refractory Hypertension (RfH).[2,6-8] The use of an association of Angiotensin Converting Enzyme Inhibitor (ACEI) or Angiotensin Receptor Blocker (BRA), Calcium Channel Blocker (BCC) and thiazide diuretic has been recommended as the basis of HR pharmacological therapy.[2,3,5,9]

The estimate of the real prevalence of RH is uncertain, hampered by the presence of factors that determine pseudoresistance, such as inadequate adherence to therapy and the white coat effect.[9-12] Some studies report a proportion of 11 to 33% of resistant hypertensive patients among those with SAH varying according to the characteristics of the population and the definition criteria.[9,13,14] The prevalence of RfH among patients with RH is even less known, estimated between 3 and 31% in some studies.[6]

Pathophysiological differences in the mechanisms involved in resistance to the treatment of hypertension in RH and RfH have been described.[14] Some studies point to an apparent worse prognosis, higher prevalence of injury to target organs and increased risk of cardiovascular events in patients with RH when compared to patients with non-resistant

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hypertension.[6,15,16] In black individuals, hypertension tends to manifest itself more severely, presenting greater difficulty in control and greater probability of complications and damage to target organs.[17] There is, however, a gap in the literature in the evaluation of the association between RH and individuals of African descent,[18] which can be attributed to genetic, environmental or even local factors.[7,19,20]

The present study aims, therefore, to compare clinical and epidemiological characteristics and prevalence of cardiovascular events in people of African descent diagnosed with RH or RfH. Improving the knowledge of these characteristics in this specific population, including demographic, social, ethnic aspects, conditions of access to health services and distribution of medicines, may contribute to the planning of strategies aimed at reducing the negative impact of this important clinical condition on the health of these individuals.

Methods

This is a cross-sectional study, carried out in a reference outpatient clinic for Severe Hypertensive Cardiovascular Disease at a University Hospital in the city of Salvador, Bahia. The population consisted of adult patients with a diagnosis of RH followed up regularly at the clinic between November 2012 and December 2015. The sample was made by convenience, being consecutively selected during routine visits all patients who agreed to participate in the study, signing an informed consent form. The study was approved by the local Ethics Committee, complying with resolution 466/12 of the National Supplementary Health Agency (*Agência Nacional de Saúde Suplementar* – ANS).

Patients with uncontrolled BP (systolic blood pressure – SBP 140mmHg and/or diastolic blood pressure – DBP 90mmHg) were considered as having HR, despite the use of three antihypertensive drugs with synergistic actions at the maximum recommended and tolerated doses, being one of them preferably a thiazide diuretic, or those with controlled BP, using 4 synergistic antihypertensive drugs and in adequate doses, including also a thiazide diuretic.[2] Patients with SBP≥140mmHg and/or DBP≥90mmHg using five or more classes of antihypertensive drugs were considered to have RfH.[7]

Blood pressure was measured during a routine medical consultation, after five minutes of rest, with the back supported in a sitting position, legs not crossed and the arm supported at heart level. Two measurements were taken, one before and one after the interview, with a minimum interval of five minutes. The average of the two measurements was used as a reference value for the patient's BP. The measurements were performed with an Omron HEM 711 DLX automatic oscillometric sphygmomanometer, validated by the British Hypertension Society (BHS) and the Association for Advancement of Medical Instrumentation (AAMI).[21,22]

A trained team collected, through a structured interview and review of medical records, information on demographic and clinical data, clinical-cardiological evaluation, history of cardiovascular events, medications, laboratory tests and factors related to lifestyle. Cardiovascular risk (CVR) was estimated by the Framingham risk score (FRS). Ethnicity was self-declared according to Brazilian standards of white, black or brown. The presence of previous cardiovascular events was defined by a positive history of stroke (stroke) or acute myocardial infarction (AMI) reported by the participant or family member and/or when present in the medical record. The glomerular filtration rate (GFR) was estimated using the Cockcroft-Gault equation (GFRe-CG).[23] For individuals with overweight or obesity, the correction factor suggested by Saracino et al. (GFRe-CGcorrected).[24] Renal function was considered abnormal when GFR<60 ml/min. For the classification of overweight and obesity, the value of body mass index (BMI) greater than 25 and 30 kg/m^2, respectively, was considered.

As part of the care and follow-up protocol, at least an Ambulatory Blood Pressure Monitoring (ABPM) is performed to assess the possibility of the white coat effect as a cause of possible pseudo-resistance to the treatment of SAH. The Morisky questionnaire (MMAS-8) was used to assess adherence to therapy. The level of adherence was determined by the score resulting from the sum of all correct answers: high adherence (8 points), average adherence (6 to <8 points) and low adherence (<6 points).[25,26]

Statistical analysis

For statistical analysis, Microsoft Office Excel 2010 software and SPSS (version 20.0) were used. A univariate descriptive analysis of the characteristics of the investigated population and a bivariate analysis (Pearson's χ^2 test) were performed to estimate the association between the dependent variable (RH or RfH) and the main independent variable (Presence of Atherosclerosis, Left Ventricular Hypertrophy and Events Cardiovascular – AMI or stroke). The continuous variables studied (SBP, DBP, time of diagnosis of SAH and time of outpatient follow-up) showed normal distribution by the Kolmogorov-Smirnov test and were compared between the RH and RfH groups using the unpaired Student's *t*-test. Categorical variables have their frequencies represented in percentages and continuous variables are presented in their means and standard deviation. The level of significance was set at 5%.

Results

146 patients were evaluated, of which 68.7% were female and 88.4% were of African descent (mixed race and black), with a mean age of 61.8 ± 12.1 years. The mean time since the diagnosis of hypertension was 21.2 ± 12.5 years (median = 18 years), and patients had been followed at the clinic for an average of 11.1 ± 8.5 years (median = 10 years)). There was a high prevalence of risk factors for cardiovascular disease: 34.2% of individuals had *diabetes mellitus*, 69.4% dyslipidemia, 36.1% obesity, 38.3% history of smoking and 61% moderate risk/high risk for events cardiovascular diseases by the FRS. History of previous AMI was found in 21.8% of participants and stroke in 19.9%. Abnormality of renal function (GFR<60mL/min) was identified in 34.2%. SBP was considered controlled in 29.5% and DBP in 50.4% of

the total population studied, with an average of 152.1±28.0 and 88.0±7.6 mmHg, respectively, for SBP and DBP. Participants used an average of 4.8±1.1 antihypertensive agents, 80.8% of whom received a prescription for the recommended combination of ACE inhibitors or ARB + CCB + thiazide diuretic, regardless of the association with other drugs. Good or moderate adherence to therapy according to the MMAS-8 questionnaire was found in 61% of patients.

After evaluating the participants according to the phenotypic presentation of SAH, 51% were categorized as RfH. Age was significantly lower among patients with RfH when compared to patients with RH (mean age=59.4±11.7 years *versus* 64.1±12.2 years, respectively, p=0.02). Table 1 shows the distribution of patients according to the classification as RH or RfH. In our population, the RfH group had a higher proportion of individuals aged up to 60 years, dyslipidemia and a history of stroke. In addition, the RfH group had higher mean BP, and the mean time of diagnosis of SAH tended to be longer in patients with RfH; however, this did not reach statistical significance (Table 2).

Regarding the use of antihypertensive drugs, there was a higher proportion of use of ARB and, therefore, a lower proportion of use of ACEi. There was also a higher frequency of use of CCB and beta-blockers in individuals with RfH, when compared to RH (Figure 1). Figure 2 shows that the use of the ACEi/BRA+BCC+thiazide diuretic combination was significantly higher in patients with RfH. Spironolactone was used by 49.3% of the participants. Among patients who used a thiazide diuretic, 34.5% of patients used chlortalidone as an option. Figure 3 shows that the use of chlortalidone and spironolactone was also significantly higher among individuals with RfH.

Discussion

The group of individuals predominantly of African descent with RH is a population with high CVR, which is shown by a high proportion of participants (51%) categorized as RfH, a phenotypic presentation associated with greater severity of SAH according to previous studies.[7,8,16,27] The prevalence of RfH has been estimated in a limited number of studies, ranging from about 3% in a general population of individuals with SAH to up to 31%, in individuals with true RH with follow-up in a specialized clinic.[7,8,16] These studies, however, did not use a standard definition of RfH. It is known that the predominance of black and brown ethnicities is related to the severity of hypertension and probably contributed to the high prevalence of RfH in our sample.

Black ethnicity has often been associated with RH. Cushman et al.[28] reported an association between African American ethnicity and resistance to antihypertensive treatment, when evaluating data from the ALLHAT study.[28] This association was also described in the Brazilian study ELSA, where black ethnicity was associated with RH in a population undergoing treatment for SAH.[18] In turn, based on data from the REGARDS study cohort, where African-American ethnicity was the main predictor of RH, Calhoun et al.[7] reported that, compared to RH, the prevalence ratios for RfH were significantly higher in blacks (PR=3.00; 95% CI=1.68-5.37).[7] These data support our findings of a high prevalence of RfH in a population with the majority of individuals of African descent. The predominance of browns and blacks in our sample can be attributed to the fact that it is a public outpatient clinic, serving the low-income population, which in our region is composed of a majority of mixed and black ethnicities.

The prevalence of obesity (36.1%), history of smoking (37%), *diabetes mellitus* (34.2%), and dyslipidemia (69.4%) reflects a population with a high CVR, as would be expected in individuals with RH. This high CVR in our population is also demonstrated by the evaluation of the FRS, where 61% of individuals were categorized as at moderate/high risk. These findings are consistent with other studies that demonstrated an association of RH with female gender, advanced age, and obesity.[18,29] Calhoun et al.[7] reported an average FRS of 17.5% in patients with RfH and 11.7% in patients with RH, with risk of coronary events and stroke in 10 years of 20.8% in RfH and 16.2% in individuals with RH, respectively.[7]

Also contributing to the increase in CVR in the population of our study, there was a high prevalence of abnormal renal function, demonstrated by an estimated GFR of <60ml/min in 34.2% of the individuals and a high proportion of previous cardiovascular events (AMI and stroke). This suggests that the presence of target organ damage should be frequent in these patients. Muntner et al.,[30] by comparing ALLHAT study participants with and without RH, also observed a high risk of coronary disease (RR=1.44; 95% CI=1.18-1.76), stroke (RR=1.57; 95% CI= 1.18-2.08), and end-stage kidney disease (RR=1.95; 95% CI=1.11-3.41) in those with RH.[30]

In our study, like other publications,[7,8] there was a significantly higher prevalence of previous stroke in patients with RfH, who had significantly higher mean BP and a higher frequency of dyslipidemia. The frequency of other risk factors, as well as FRS and therapeutic adherence by MMAS-8 were similar in the two subgroups. These data suggest that the persistence of high BP, probably more than the other factors of CVR, seems to have a fundamental role in this unfavorable outcome in patients with RfH. Sympathetic hyperactivity, a mechanism proposed for the persistence of uncontrolled BP in patients with RfH,[14] could be associated with a higher incidence of stroke in these individuals. Dyslipidemia and its intimate association with atherosclerosis can also contribute negatively to the prognosis of patients with HRf and need to be better evaluated in other studies.

Despite the high average age, a significantly lower proportion of individuals over 60 years of age was observed among patients with RfH, despite the trend for longer time of SAH diagnosis among them. Similar findings have been described in other studies.[14,15,27] These data are probably associated with the possible mechanisms involved in the pathophysiology of RfH, attributing to this group of individuals characteristics that imply in the earlier development and greater severity of SAH.

Regarding the predominance of females, based on the ALLHAT study, Cushman et al.[28] found greater difficulty in

Table 1 – Sociodemographic and clinical characteristics of patients seen at a referral center, according to resistant or refractory hypertension

Characteristics			Hypertension		
			RH	RfH	
	N	%	%	%	p-value
Age (years)					
Up to 60	69	46.9	38.0	59.2	
60 or more	75	51.0	62.0	40.8	0.012*
Gender					
Male	46	31.3	32.9	31.0	
Female	100	68.7	67.1	69.0	0.724
Ethnicity					
White	12	8.2	12.9	4.3	
Black	60	40.8	41.4	41.4	
Brown	70	47.6	45.7	54.3	0.17†
BMI (kg/m²)					
Not obese	86	58.5	62.3	61.2	
Obese	53	36.1	37.7	38.8	0.898‡
Diabetes Mellitus					
No	86	58.9	56.9	69.0	
Yes	50	34.2	43.1	31.0	0.144
Smoking					
No	87	59.6	58.2	63.9	
Yes	54	37.0	41.8	36.1	0.869
Dyslipidemia					
No	34	23.1	33.3	16.2	
Yes	102	69.4	66.7	83.8	0.021
GFR<60mL/min					
No	79	54.1	65.5	65.6	
Yes	41	34.2	34.5	34.4	0.275
Framingham's risk score					
Low risk	45	30.8	31.3	33.8	
Moderate/high risk	89	61.0	68.7	66.2	0.753§
Adherence to therapy (MMAS 8)					
Low	44	30.1	33.8	32.4	
Moderate/High	89	61.0	66.2	67.6	0.855//
Previous AMI					
No	104	71.2	78.5	77.9	
Yes	29	19.9	21.5	22.1	0.942
Previous stroke					
No	105	71.9	87.7	12.3	
Yes	29	19.9	69.6	30.4	0.011
Use of the triad (ARB/ACEi+CCB+Diuretic)					
No	30	20.4	25.4	9.9	
Yes	116	79.6	74.6	90.1	0.015

*RH: resistant hypertension; RfH: refractory hypertension; BMI: body mass index; GFR: glomerular filtration rate; MMAS 8: morisky questionnaire; AMI: acute myocardial infarction; ARB: angiotensin receptor blocker; ACEi: angiotensin converting enzyme inhibitor; CCB: Calcium channel blocker. * P-value for distribution of subjects aged 60 years old or older or less than 60 years into RH versus RfH; † P-value for ethnicity distribution into RH versus RfH; ‡ P-value for the distribution of obese (BMI≥30) and non-obese (BMI<30) subjects into RH versus RfH; § P-value for low and moderate/high risk distribution using the Framingham's Risk Score into RH versus RfH; // P-value for low and moderate/high adherence distribution by the Morisky score into RH versus RfH.*

Table 2 – Systolic blood pressure, diastolic blood pressure, diagnosis time and follow-up time for patients seen at a referral center, according to resistant or refractory hypertension

Characteristics	Hypertension		p- value
	RH	RfH	
	Mean (SD)	Mean (SD)	
SBP (mmHg)	145.8 (24.8)	158.7 (29.6)	0.008
DBP (mmHg)	84.3 (14.1)	92.0 (20.0)	0.012
Time since SAH diagnosis (years)	19.2 (11.9)	23.12 (13.0)	0.078
Follow-up time (years)	10.7 (6.1)	11.38 (10.3)	0.665

SBP: systolic blood pressure; DBP: diastolic blood pressure; RH: resistant hypertension; RfH: refractory hypertension; SAH: systemic arterial hypertension; SD: standard deviation.

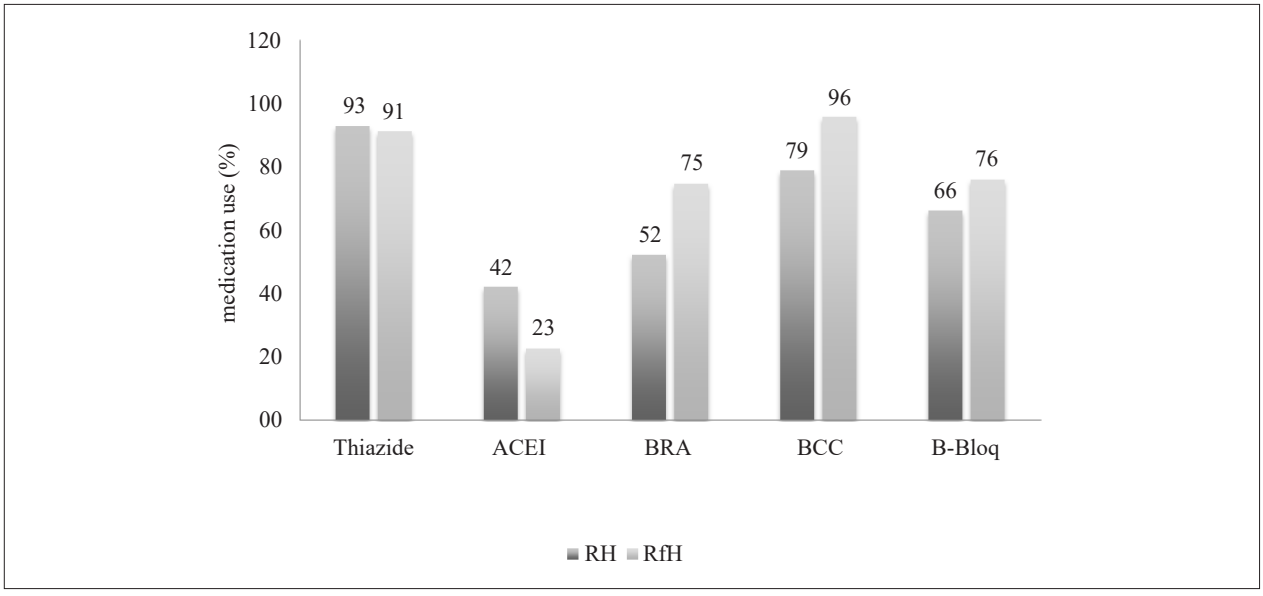

Figure 1 – *Proportion of use of antihypertensive medication, according to resistant or refractory hypertension. ACEI: angiotensin-converting enzyme inhibitor; BRA: angiotensin receptor blocker; BCC: calcium channel blocker; B-Block: beta blocker; RH: resistant hypertension; HRf: refractory hypertension.*

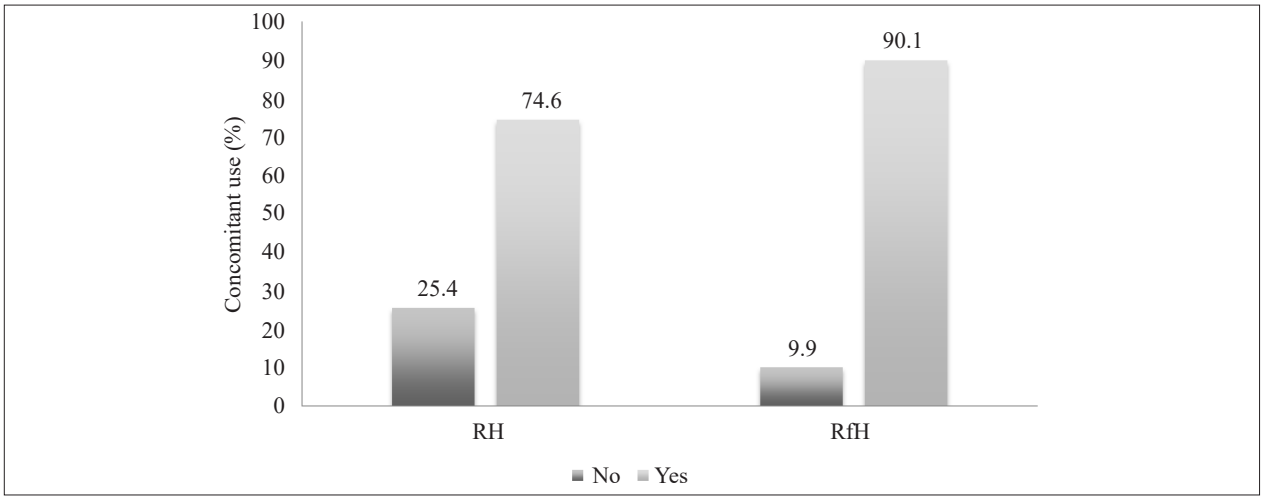

Figure 2 – *Proportion of concomitant use of antihypertensive drugs (Angiotensin Conversion Inhibitor triad or Angiotensin Receptor Blocker + Calcium Channel Blocker + Diuretic), according to resistant or refractory hypertension. HR: resistant hypertension; HRf: refractory hypertension; P = 0.015; for difference in distribution of the use of the triad of antihypertensive drugs (ACEI or BRA + BCC + Thiazide diuretic) between HR versus HRf.*

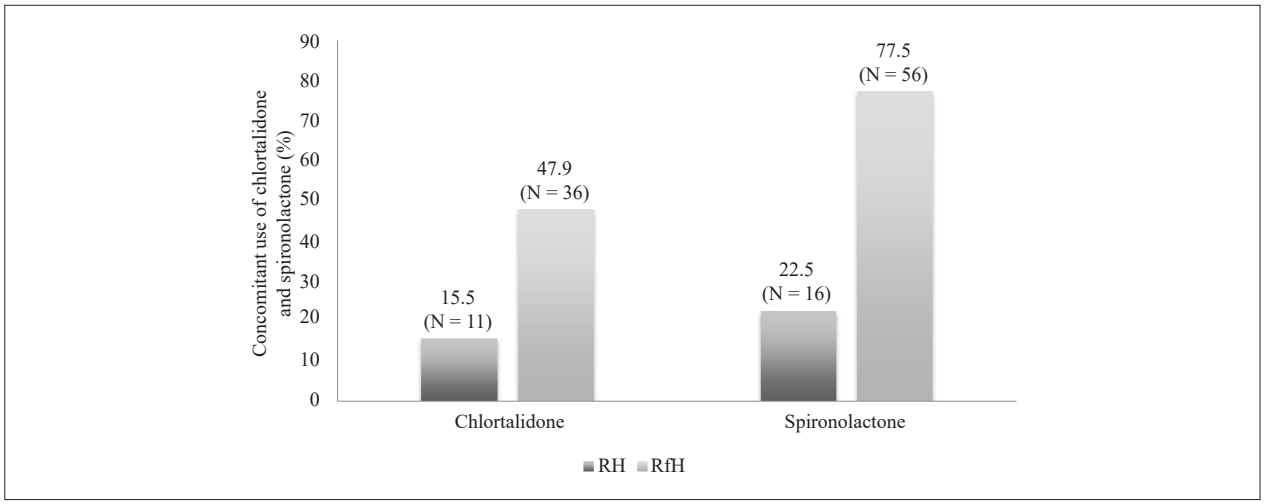

Figure 3 - *Proportion of concomitant use of chlortalidone and spironolactone, according to resistant or refractory hypertension. HR: resistant hypertension; HRf: refractory hypertension; P <0.001; for the difference in frequency of the use of chlortalidone between HR versus HRf; P <0.001; for difference in frequency of spironolactone use between HR versus HRf.*

controlling SAH in black women.[28] In a population study carried out in Sweden, Holmqvist et al.[31] also reported that women had a higher prevalence of RH, except when they specifically assessed the subgroup with controlled RH.[31] The present finding of a higher proportion of women in our sample of individuals with HR should be interpreted with caution, as it can be overestimated by Brazilian cultural aspects, since women tend to seek more health care.[18] However, this fact can identify a problem that deserves more attention, in order to encourage a better clinical evaluation and the antihypertensive therapy used in these individuals. In contrast, some authors reported a higher prevalence of RH among men.[32]

Regarding therapy, there was a wide use of the various classes of antihypertensive drugs available and a large proportion of participants used the combination of ACEi or ARB, CCB and thiazide diuretic, as recommended in the literature.[2,9] This combination was prescribed more frequently in patients with RfH, probably due to the greater difficulty in obtaining BP control in these patients. The prescriptions of spironolactone as the fourth drug to be introduced in antihypertensive therapy as well as the option of chlortalidone as the thiazide diuretic of choice, due to its longer duration, have also been recommended in the literature.[2,3,33,34] Some authors even suggest that the use of these drugs should participate in the definition criteria for RfH.[27] In our study, approximately one third of patients were receiving chlortalidone, while almost half were using spironolactone. Both were used significantly more frequently in patients with RfH (47.9% of patients with RfH used chlortalidone and 77.5% spironolactone, *versus* 11.5 and 22.5% of those with RH, respectively), which may corroborate a probable adequate RfH classification in a good number of patients. The relatively low preference for chlortalidone as a thiazide diuretic can be justified by the fact that it is a public service and the drug does not participate in the government list of free distribution of antihypertensive drugs, while hydrochlorothiazide is distributed free of charge. It is also possible that some of the participants are not using spironolactone due to adverse effects and/or contraindications for this medication. However, the frequency of use of chlortalidone and spironolactone in our work was somewhat similar to that of other studies.[7,8,14,16] However, there is a clear need to encourage more frequent use of these drugs, which, according to current evidence, would be more suitable for the treatment of RH.

Due to its transversal characteristic, our study has some limitations, since it is not possible to establish a causality and temporality relationship between some associations found, for example, a higher prevalence of stroke among those with RfH. The data presented here, however, have value in raising hypotheses to be proven in longitudinal studies with greater statistical power. This convenience sample is derived from a population seen at a referral clinic for severe hypertensive patients, with high CVR, and may have overestimated the prevalences and associations described. Another important aspect refers to the fact that some patients with pseudoresistance may have been included, which could also overestimate the prevalences found. However, these patients are followed up in a specific outpatient clinic, most of them for a long period (over 10 years, on average) and with an average time of diagnosis of hypertension for more than 20 years. They undergo frequent reassessments, including ABPM[35] and the Morisky score,[25] to assess the white coat effect and adherence to therapy, respectively. This could minimize the occurrence of individuals with pseudoresistance in this sample. Some other important studies, however, have evaluated patients with resistance to the treatment of SAH, defining them as resistant or apparent refractory hypertensive individuals and have found relevant associations.[10,36,37] The classification of individuals according to skin color was self-reported, as recommended in studies in Brazilian populations that involve this variable,[38] could lead to bias, due to the great ethnic mix of the Brazilian population. However, the ethnic profile of the sample studied is consistent with that of the local population and

that of those who historically attend the health unit where the study was conducted. The stratification of individuals as resistant or refractory took into account the control of BP and the number of drugs prescribed, disregarding whether or not they were using chlortalidone and spironolactone, which, according to some authors, may have overestimated the prevalence of RfH.

Conclusions

Individuals with RH followed up at this referral clinic for the treatment of severe cases of SAH were mostly of African descent, with a high prevalence of risk factors for cardiovascular diseases and, consequently, high cardiovascular risk according to the FRS. We found a high proportion of individuals with the most severe form of phenotypic resistance to the treatment of hypertension, defined as RfH, who had a higher frequency of dyslipidemia and a history of stroke compatible with a possibly higher frequency of damage to target organs. Further more comprehensive studies should be carried out to improve knowledge about the characteristics of this high-risk population, contributing to the definition of appropriate prevention and treatment strategies.

Author contributions

Conception and design of the research: Macedo C, Aras Junior R; Acquisition of data: Macedo C, Macedo IS; Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Macedo C, Aras Junior R, Macedo IS; Statistical analysis and writing of the manuscript: Macedo C.

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 Hospital Ana Nery under the protocol number 138.371. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Short Editorial: Clinical Characteristics of Resistant vs. Refractory Hypertension in a Population of Hypertensive Afro-descendants

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Short Editorial related to the article: Clinical Characteristics of Resistant vs. Refractory Hypertension in a Population of Hypertensive Afro-descendants

Differences in the clinical behavior of arterial hypertension (AH) in diverse ethnic groups have long been the object of intense scientific investigation. The American Heart Association statistics for 2015 found that Afro-descendants have the highest prevalence of hypertension worldwide. In black, non-Hispanic men and women, the prevalence was 44.9% and 46.1%, respectively.[1] Although such figures are not universal for all Afro-descendant populations, there are groups in which blood pressure levels are much higher, such as South-African blacks, in whom systolic blood pressure is 9.7 mmHg higher when compared to African-Americans.[2,3]

Target-organ lesions and complications are more prevalent in Afro-descendants, when compared to Caucasians or Hispanics for the same pressure levels, in addition to the fact that they are more resistant to treatment.[4,5]

Resistant (RH) and refractory (RfH) hypertension affect a non-negligible proportion of hypertensive patients. In Brazil, according to the ReHOT study, the prevalence is 11.7% of hypertensive patients.[6]

There is still much debate as to whether RH and RfH are different phenotypes or degrees of the same disease. Similarly to simple AH, which can be controlled with up to three drugs, the etiopathogenesis is multifactorial, and genetic and environmental factors are important. Among the environmental factors, salt intake and / or non-adequate saline excretion by the kidneys are preponderant elements of non-blood pressure control. This is corroborated in the elegant PATWAY-2 study, which evaluated the fourth drug in the antihypertensive therapy flowchart and singled out spironolactone as one of the most important drugs at this stage of treatment.[7] Subsequently, the PATWAY-2 Mechanistic study found similar effects with amiloride hydrochloride, both diuretic drugs.[8]

Considering this multifactorial aspect of AH, involving genetic and environmental causes, some particularities are evident, mainly regarding disease severity in certain ethnic groups. Afro-descendant individuals, in addition to having a higher prevalence of AH and more severe consequences of the disease, show greater damage to target-organs and greater morbidity and mortality from cardiovascular causes.[9] This is quite evident in African-American descendants; however, in our mixed population, there are no robust studies to ascertain such differences.

In this study by Macedo et al.,[10] "Clinical Characteristics of Resistant vs. Refractory Hypertension in a Population of Hypertensive Afro-descendants", it was found that RfH is common in this population, with a higher prevalence of dyslipidemia, history of stroke and greater damage to the target-organ.[10] The findings seem redundant and very similar to those of American Afro-descendants, but refer to a finding with a lot of epidemiological significance, which may raise hypotheses for other studies that can solve the great enigma of hypertension differences in different ethnic groups.

Brazilian Afro-descendants are believed to differ from African-Americans and to be very similar to native African blacks, with the exception of South Africa.[2] This probably has a strong association with the slave trade from Africa to America. It is known that some blacks have, genetically, some peculiarities in the renin-angiotensin-aldosterone system, with little renin activity and a smaller nephron mass, and thus, less sodium is excreted. Without being aware of any pathophysiological aspect, the English slavers tasted the black men's sweat to verify whether it was salty or not, and thus choose certain individuals for transportation in the ship holds, without food and water conditions.[11-13] Those who managed to survive the crossing of the Atlantic ocean were precisely those with a more efficient sodium and water retention system. Thus, in the New World, with an excess of salt in their diets, unlike in their homelands, they developed a more severe hypertension. This path of human trafficking from Africa to North America is almost twice the distance to Brazil and, therefore, the selection of Africans in Brazil was not as accentuated as the North-American one. However, there are no well-designed studies that can correctly answer such epidemiological questions.

It is estimated that heredity contributes 40% to 50% of the pathogenesis of hypertension, but little is known about its genetic architecture in the identification of the *loci* of genes responsible for high blood pressure. African-Americans have a lower renin and aldosterone index than Caucasians for the same level of sodium intake.[14] Salt sensitivity is a more common phenotype in blacks, and closely related to the pressure response with the sodium intake variation, even in those with low renin and aldosterone index.[15]

Keywords

Hypertension/complications; African Continental Ancestry Group/genetics; Comparative Studies; Epidemiology; Myocardial Infarction; Stroke.

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Therefore, this study by Macedo et al.[10] is important for the assessment of the characteristics of different ethnic groups that comprise the Brazilian population. The study was carried out in the city of Salvador, Bahia, where the Afro-descendant population represents a good portion of the inhabitants. The deeper knowledge of blood pressure characteristics, cardiovascular risk, more effective drugs, preferential target-organ lesions, etc., can lead to more accurate control, prevention and therapeutic plans. This cross-sectional study, with precise clinical and laboratory evaluation – including ambulatory blood pressure monitoring (ABPM) to rule out the white coat effect, a very common situation – allowed conclusions of epidemiological importance in our Afro-descendant population.

Many pathways will need to be traveled to unravel and fit all the parts of the multifactorial polygon of all hypertension phenotypes, mainly RH and RfH. We do not know yet what the precise roles of salt, the sympathetic nervous system, the endothelium and all the other related factors are in this complex disease called arterial hypertension.

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Hypertensive Measures In Schoolchildren: Risk Of Central Obesity And Protective Effect Of Moderate-To-Vigorous Physical Activity

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Abstract

Background: The proportion of arterial hypertension (AH) has increased in children and adolescents and is associated with several comorbidities.

Objective: To verify the association of arterial hypertension with central and general obesity as well as according to the level of physical activity in schoolchildren.

Methods: 336 children and adolescents aged 11 to 17 participated in the study. Height, body weight, waist circumference (WC) and blood pressure (BP) were measured. The body mass index z-score (BMI-z) was calculated. The level of physical activity was assessed by the short form of the International Physical Activity Questionnaire (IPAQ) according to the practice of moderate-to-vigorous physical activities (AF-mv). Students with systolic (SBP) and/or diastolic blood pressure (DBP) higher than the 95th percentile according to sex, age and height or ≥120/80 were considered hypertensive. Statistical tests of t-Student, Chi-square, Mann-Whitney and binary logistic regression model were used, considering the significance level of $p<0.05$.

Results: It was found that 40.5% of the students had AH, 35.11% were overweight (12.5% obese), 13.39% had high WC and 40.2% were considered insufficiently active in AF-mv. The chances of AH were related to high WC (OR = 6.11; 95% CI: 2.59¬–14.42) and overweight (OR = 2.91; 95% CI: 1.76–4.79). In addition, adolescents who practiced AF-mv had a lower risk of high DBP (OR = 0.33; 95% CI: 0.15–0.72).

Conclusion: Central obesity was the best predictor of AH in children and adolescents, as well as general obesity and males. The practice of AF-mv demonstrated a protective effect on high DBP in schoolchildren. (Arq Bras Cardiol. 2020; 115(1):42-49)

Keywords: Child; Adolescent; School Children; Physical Activity; Waist Circumference; Body Mass Index; Hipertension; Blood Pressure.

Introduction

The frequency of arterial hypertension (AH) has increased in all age groups and in several countries,[1] affecting children and adolescents, and tends to persist over time, with a high probability of progressing into adulthood,[2] mainly due to the increasing prevalence of obesity,[3] which is associated with the appearance of several comorbidities.[4]

The joint analysis of lifestyle habits that may predispose to the onset of cardiovascular diseases in adulthood plays an important role in preventing hypertension in children and adolescents.[5] Obesity has a multifactorial origin, involving aspects of behavior related to diet, physical activity and psychological factors.[6]

Therefore, early diagnosis of AH in children and adolescents is relevant to prevent the disease from advancing into adulthood, reduce the risk of cardiovascular problems[7] and recommend therapeutic programs to stop the process.[8] Thus, anthropometric measures such as body mass index (BMI) and waist circumference (WC) are efficient low-cost indicators for identifying cardiovascular risks.[9] BMI classified as overweight demonstrates general obesity,[10] while the largest WC is related to central obesity,[11] the latter being more associated with inflammation in adults and appearance of cardiometabolic comorbidities.[12]

Blood pressure should be measured on three different occasions[13] to confirm the diagnosis of AH, whereas in epidemiological studies it is usually measured on one day and the term hypertensive measures has been used.[14] Therefore, in children and adolescents, some studies show greater associations between AH with central obesity[15] and with general obesity,[16] which generates controversy

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as to the location of adiposity and blood pressure (BP) in this population.

In addition, evidence on the practice of physical activities with moderate-to-vigorous intensity (AF-mv) and BP is still limited, as well as the relationship between anthropometric measures and AF-mv as protectors of AH in children and adolescents. Thus, it is important to identify the risk of AH in adolescence to prevent the advancement of this condition in adulthood, which can increase the efficiency of treatment. Therefore, the present study aims to verify the association between AF-mv and anthropometric indicators of obesity with the diagnosis of AH in children and adolescents.

Methods

This is a descriptive cross-sectional quantitative study carried out in the city of São José dos Pinhais, Paraná (southern region of Brazil). The sample consisted of conglomerates, chosen for convenience, in which each private elementary and high school institution in the city was considered a conglomerate. Of the six institutions located in the central region that were invited, only two private schools agreed to participate in the study, to which all elementary and high school students were invited.

In the city, approximately 55,289 students were attending the final grades of elementary school and high school in 2018.[17] The prevalence of 12.5% of hypertensive children and adolescents in the southern region of Brazil was stipulated.[18] Based on the probabilistic sample selection, the total number of 111 adolescents for inference of the student population in the stipulated age range was obtained. 1.5x subjects were included regarding the design effect, taking into account a 5% sample error, and an additional 30% were included for possible dropouts, resulting in a total of 217 individuals aged between 11 and 17.

The study included 336 volunteer children and adolescents aged 11 to 17, of both sexes (173 girls). Pregnant women, individuals with limitations that prevented them from participating in any study procedure, and those who did not have signed the Free and Informed Consent Term (FICT) and the Free and Informed Consent Term for minors of age (TALE) were excluded from the study. All procedures were approved by the Research Ethics Committee of Pontifícia Universidade Católica do Paraná, PUC – PR, CAAE (71324017.1.0000.0020/2017).

Anthropometric measurements were collected at school, in a standardized manner, following the procedures recommended by the Anthropometric Standardization Reference Manual.[19] Height was measured using a portable stadiometer, with a resolution of 0.1 centimeters (cm); height was expressed in cm. Body weight was assessed with a portable scale model PLENA, with resolution of up to 100 grams and capacity of 150 kg.

BMI z-score (BMI-z)[20] was calculated using WHO Anthro Plus® version 1.0.4. Participants with BMI-z between ≥ -2 and <+1 were classified as overweight; between ≥ 1 and <2, obese; those with ≥2 were classified as eutrophic according to age and sex. Adolescents classified as overweight and obese (BMI-z ≥1) were considered with general obesity. In order to measure WC, an inelastic measuring tape was used at the midpoint between the last upper arch of the iliac crest and the outer face of the last rib. Adolescents with a ≥75 percentile were considered with central obesity according to sex and age group.[21]

Measurement of systolic blood pressure (SBP) and diastolic blood pressure (DBP) followed the recommendations of the 7th Brazilian Guideline on Hypertension[13] and were collected in a quiet isolated classroom using the automatic pressure device OMRON705-IT.[22] Two measurements of SBP and DBP were performed on the subject's right arm by volunteer nurses with an interval of five minutes between them. These measurements were classified according to age, sex and height percentile.[13] Thus, the criteria for classification were: values below the 90th percentile were considered adequate (normotensive), since they were lower than 120/80 mmHg; the percentiles between 90 and 95 were considered as prehypertensive (borderline); and equal to or greater than the 95th percentile were considered hypertensive.

The level of physical activity was assessed by the International Physical Activity Questionnaire — short form — (IPAQ).[23] The questions refer to the physical activities practiced in the week prior to the application of the questionnaire. The individuals were classified as sufficiently active (active or very active) or insufficiently active (irregularly active A, B or sedentary).[23]

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Science (SPSS), v. 24. The normality of the data was assessed by the Shapiro Wilk test. For comparison between sexes, nutritional status, WC classification and AF-mv, the independent Student's t test was used for parametric variables, and the Mann-Witney test for non-parametric variables. The Chi-square test was used to assess the proportions among students considered adequate, pre-hypertensive, hypertensive according to high SBP and DBP. The analysis of odd ratios for individuals considered adequate and hypertensive, based on anthropometric variables and AF-mv through binary logistic regression. The significance level of $p<0.05$ was considered for all analyses.

Results

Excess weight was found in 35.11% of the 336 schoolchildren evaluated, with 12.5% being classified as obese. Central obesity was present in 13.39% of the students; 59.8% were classified as sufficiently active in PA-mv practices and 52.97% had high BP; 12.5% were pre-hypertensive and 40.5% hypertensive. The sample distribution according to sex and age group is shown in table 1.

It was observed that mean SBP ($p <0.001$), BMI-Z ($p = 0.034$), body mass ($p=0.001$) and WC ($p<0.001$) were higher in boys than in girls. On the other hand, girls showed higher PAD ($p=0.009$). In addition, boys participated for longer in light and vigorous physical activities than girls ($p=0.007$; $p=0.009$) (Table 2).

Table 1 – Sample distribution by sex and age range

Age range (years)	Male (n)	Female (n)
12	33	29
13	38	29
14	34	36
15	23	36
16	**21**	**29**
17	**14**	**15**

In the total sample, it was identified that individuals with general obesity had higher SBP (p<0.001) and height-z (p=0.005) than eutrophic individuals (Table 3). According to sex, it was observed that both boys and girls with general obesity had higher SBP (p=0.003; p=0.001) and WC (p<0.001; p<0.001). However, only girls had higher values of height -z and greater participation in light and vigorous activities compared to eutrophic ones (p<0.05).

In the group with central obesity, the girls had higher SBP (p=0.026), body weight (p<0.001), height (p=0.038) and BMI-z (p<0.001) compared to the group considered adequate. In relation to boys, the group with central obesity showed higher SBP (p=0.002), DBP (p=0.003), body mass (p<0.001) and BMI-z (p<0.001) compared to the group considered adequate (Table 4). However, no differences were identified for the practice of physical activity.

Anthropometric and blood pressure measurements were also assessed according to AF-mv (Table 5). In the total sample, active individuals had higher values of body weight (p=0.002), BMI (p=0.016), height z (p=0.001), in addition to lower DBP (p=0.046) compared to those classified as insufficiently active. In relation to girls considered sufficiently active, higher values for body mass (p=0.005), height (p=0.048), WC (p=0.015), BMI (p=0.005) and height z (p=0.016) were identified compared to insufficiently active girls. Sufficiently active boys had higher z-stature (p=0.025) than insufficiently active boys.

Analyzing the anthropometric parameters CC, BMI and AF-mv with blood pressure (Table 6), the boys presented a higher proportion of prehypertension and arterial hypertension (p=0.033). The individuals considered active had a higher proportion of diastolic prehypertension, while sedentary individuals had a higher proportion of AH (p=0.015). It was observed that adolescents with central obesity, as well as those with overweight, had a higher proportion of prehypertension and hypertension and high SBP (p<0.001).

According to the odds ratio analysis (Table 7), there was no difference between sexes for high AH (OR = 1.40; CI = 0.88–2.22), SBP (OR = 1.35; CI = 0.85–2.14) and DBP (OR = 0.84; CI = 0.40–1.77). On the other hand, according to adiposity indicators, individuals with central obesity were 6.11 (CI = 2.59–14.42) times more likely to have AH than those with adequate WC, while obesity general analysis revealed that the probability of presenting AH is 2.91 (CI = 1.77 = 4.79) higher than those who presented adequate BMI z-score. In addition, it was observed that sufficiently active adolescents had a reduction of approximately one third in the risk of high DBP (OR = 0.33; 95% CI: 0.15–0.72).

Discussion

The main results revealed higher risk for the presence of AH in students with abdominal obesity (OR = 6.11) and general obesity (OR = 2.91). In addition, adolescents who practice AF-mv showed a 33% reduction in the risk of high DBP. The current literature has been consistent in showing that BMI-z and WC are strongly associated with AH in childhood and adolescence.[9] In addition, the findings of this study show a relevant protective factor of the practice of AF-mv for the presence of AH in adolescence, an aspect that has been little explored in population-based studies.

Table 2 – Sample characteristics

	Total (n=336)	Female (n=173)	Male (n=163)	W
Age (years)#	14.50[13.35–15.88]	14.74[13.52–15.99]	14.35[13.16-15.54]	0.103
Body weight (kg)#	56.25[47.90-64.60]	54.70[46.90-62.00]	58.90[49.35-70.50]	0.001
Stature (cm)	1.62[0.10]	1.59[0.07]	1.66[0.10]	<0.001
Stature -z#	0.49[0.29-0.78]	0.44[0.26-0.71]	0.57[0.34-0.82]	0.003
WC (cm) #	68.00[62.50-74.00]	65.00[60.00-70.00]	71.00[65.50-78.00]	<0.001
BMI (kg/m²)#	21.29[19.00-24.09]	21.55[19.17- 24.01]	20.79 [18.87. 24.80]	1.000
BMI-Z	0.51[1.22]	0.37[1.16]	0.65[1.27]	0.034
SBP (mmHg)#	124.00[113.50-132.50]	120.00[111.00-131.00]	127.00[118.00-135.25]	<0.001
DBP (mmHg)#	69.50[63.38-75.00]	70.00[65.00-76.50]	68.00[61.75-74.00]	0.009
PA-light (min/day)#	19.29[2.50-42.86]	14.29[0.00-38.57]	25.71[8.57-48.21]	0.007
PA- Moderate (min/day)#	17.14[6.43-34.64]	12.86[6.43-34.29]	17.14[6.79-37.14]	0.282
PA- Vigorous (min/day)#	7.14[0.00-17.14]	5.71[0.00-14.29]	8.57[0.00-25.71]	0.009

SD: standard deviation; # non-parametric; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI; body mass index; WC; waist circumference; BMI-Z: BMI z-score; PA: physical activity.

Table 3 – Anthropometric variables and blood pressure according to the classification of bmi z-score.

	EUTHROPHIC			OVERWEIGHT					
	Total (n=218)	Female (n=119)	Male (n=99)	Total (n=118)	Female (n=54)	Male (n=64)	pt	p ♀	p ♂
Age (years)#	14.66[13.41-15.90]	14.80[13.68-16.01]	14.49[13.16-15.48]	14.25[13.14-15.83]	14.62[13.14-15.86]	14.07[13.21-15.61]	0.232	0.356	0.573
Body weight (kg)#	51.60[43.92-57.77]	51.10[43.30-55.90]	52.20[45.65-59.15]	67.45[61.12-78.62]	64.00[59.70-71.15]	74.10[64.75-83.15]	<0.001	<0.001	<0.001
Stature (cm)	1.61[0.10]	1.58[0.08]	1.65[0.11]	1.63[0.09]	1.60[0.06]	1.66[0.10]	0.062	0.230	0.380
Stature z#	0.43[0.27- 0.73]	0.41[0.23-0.64]	0.54[0.32- 0.79]	0.57[0.35- 0.83]	0.52[0.35-0.74]	0.71[0.42-0.87]	0.005	0.027	0.083
WC (cm)#	64.50[60.00-69.00]	61.00[58.00-66.00]	66.50[63.75-70.20]	76.50[72.00-86.00]	72.50[67.25-76.50]	83.00[75.25-91.12]	<0.001	<0.001	<0.001
BMI (kg/m²)#	19.54[18.07-21.26]	19.69[18.18-21.65]	19.33[17.81-20.49]	25.34[23.88-27.91]	24.93[24.08-27.08]	26.04[23.64-29.03]	<0.001	<0.001	<0.001
BMI- Z	-0.18[0.85]	-0.19[0.90]	-0.17[0.78]	1.78[0.64]	1.60[0.56]	1.93[0.68]	<0.001	<0.001	<0.001
SBP (mmHg)#	121.00[111.50-130.50]	117.00[108.50-129.00]	124.00[116.50-132.00]	129.00[120.00-136.50]	124.00[116.62-136.25]	130.25[122.38-138.75]	<0.001	0.001	0.003
DBP (mmHg)#	68.50[62.50-74.00]	70.00[64.50-75.25]	67.50[61.25-73.25]	70.00[64.50-76.50]	70.50[66.12-77.88]	69.50[62.38-74.62]	0.075	0.255	0.096
PA-L (min/day) #	17.14[0.00-42.32]	11.43[0.00-36.43]	25.71[8.57-51.43]	24.29[6.96-51.43]	24.29[1.43-64.29]	23.57[8.57-43.39]	0.090	0.042	0.910
PA-Mod (min/day) #	14.29[6.43-34.29]	12.86[6.07-31.07]	17.14[6.79-37.14]	17.14[8.57-35.36]	13.57[8.57-35.36]	19.29[8.04-35.36]	0.532	0.768	0.734
PA-Vig (min/day) #	5.71[0.00-17.14]	4.29[0.00-13.57]	8.57[0.00-29.29]	8.57[2.14-17.14]	8.57[3.21-17.14]	10.71[1.39-17.14]	0.120	0.010	0.603

SD = standard deviation; # non-parametric; t: Total vs. Total; ♀: boys vs. girls; ♂: boys vs. boys; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; WC = waist circumference; BMI-Z: BMI z-score; PA-L: light physical activity; PA-Mod: moderate physical activity; PA-Vig: vigorous physical activity.

Table 4 – Anthropometric variables and blood pressure according to the classification of waist circumference.

	ADEQUATE			CENTRAL OBESITY					
	Total (n=291)	Female (n=163)	Male (n=128)	Total (n=45)	Female (n=10)	Male (n=35)	pt	p ♀	p ♂
Idade (anos)#	14.64[13.39-15.94]	14.74[13.64-16.01]	14.49[13.23-15.63]	13.81[12.99-15.52]	13.50[12.95-15.48]	13.94[13.02-15.31]	0.065	0.170	0.326
Peso corporal (kg)#	54.50[46.80-61.35]	53.80[46.45-60.80]	55.20[47.58-61.62]	78.40[68.90-89.30]	81.75[70.65-89.38]	78.40[68.80-88.20]	<0.001	**<0.001**	**<0.001**
Estatura (cm)	1.62[0.10]	1.59[0.07]	1.65[0.11]	1.66[0.08]	1.64[0.03]	1.67[0.09]	0.005	**0.038**	0.543
Estatura-z#	0.45[0.28-0.74]	0.43[0.24-0.68]	0.55[0.32-0.80]	0.74[0.49-0.89]	0.77[0.61-0.90]	0.73[0.46-0.89]	<0.001	**0.005**	0.064
CC (cm)#	66.00[61.00-71.50]	64.00[59.00-69.50]	69.50[64.50-72.50]	88.50[84.00-95.00]	81.00[79.00-88.50]	90.00[86.00-97.25]	<0.001	**<0.001**	**<0.001**
IMC (kg/m2)#	20.56[18.54-22.77]	21.40[19.13-23.38]	20.11[18.37-21.60]	28.67[26.40-31.40]	29.80[26.30-33.16]	28.67[26.66-30.23]	<0.001	**<0.001**	**<0.001**
IMC-z	0.22[1.02]	0.25[1.07]	0.17[0.95]	2.39[0.52]	2.35[0.53]	2.40[0.53]	<0.001	**<0.001**	**<0.001**
PAS (mmHg)#	122.50[112.75-131.00]	119.00[111.00-129.75]	124.25[117.50-132.88]	132.00[127.00-139.50]	136.25[129.00-138.25]	131.00[126.75-141.75]	<0.001	**0.026**	**0.002**
PAD (mmHg)#	68.50[62.50-74.50]	70.00[65.00-75.75]	67.00[61.00-73.50]	73.00[68.00-78.00]	76.50[68.88-84.38]	72.50[68.25-74.75]	0.009	0.101	**0.003**
AF-leve (min/dia)#	19.29[0.00-42.86]	14.29[0.00-38.57]	25.71[8.57-46.61]	21.43[5.71-51.43]	23.57[9.29-57.86]	21.43[5.00-47.14]	0.609	0.432	0.527
AF-moderada (min/dia) #	14.29[6.43-35.00]	12.86[6.43-33.21]	17.14[6.43-36.43]	17.14[8.57-34.29]	19.29[6.96-33.75]	17.14[9.64-34.29]	0.377	0.779	0.619
AF-vigorosa (min/dia)#	6.43[0.00-17.14]	5.71[0.00-14.29]	8.57[0.00-26.43]	10.71[2.86-17.14]	6.43[0.71-11.79]	12.86[3.57-22.14]	0.271	0.928	0.607

Abbreviations: SD = standard deviation; # non-parametric; t: Total vs. Total; ♀: boys vs. girls; ♂: boys vs. boys; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI = body mass index; WC = waist circumference; BMI-Z: BMI z-score; PA-L: light physical activity; PA-Mod: moderate physical activity; PA-Vig: vigorous physical activity.

Table 5 – Anthropometric variables and blood pressure according to the classification of level of physical activity. By sex

	SUFFICIENTLY ACTIVE			INSUFFICIENTLY ACTIVE					
	Total (n=201)	Female (n=93)	Male (n=108)	Total (n=135)	Female (n=80)	Male (n=55)	pt	p ♀	p ♂
Age (years)#	14.39[13.17-15.96]	14.48[13.28-15.99]	14.27[13.08-15.88]	14.64[13.56-15.80]	14.84[13.94-15.95]	14.45[13.38-15.10]	0.504	0.442	0.854
Body weight(kg)#	58.10[50.50-65.80]	57.40[50.70-63.40]	59.15[50.40-72.30]	53.70[43.90-62.05]	51.60[43.08-60.83]	58.50[48.45- 66.65]	0.002	0.005	0.300
Stature (cm)	1.63[0.10]	1.60[0.07]	1.67[0.11]	1.60[0.09]	1.58[0.08]	1.64[0.10]	0.002	0.048	0.114
Stature z#	0.56[0.34-0.80]	0.48[0.34-0.73]	0.68[0.35- 0.84]	0.41[0.23- 0.70]	0.38[0.22-0.62]	0.48[0.27-0.71]	0.001	0.016	0.025
WC (cm)#	69.50[64.00-75.00]	67.00[61.00-72.00]	71.25[66.38-79.25]	65.00[61.00-72.00]	63.00[59.00-67.00]	70.00[64.00-75.50]	0.001	0.015	0.226
BMI (kg/m^2) #	21.58[19.40-24.50]	22.27[19.69-24.26]	20.98[19.17-24.80]	20.35[18.23-23.56]	20.10[18.25-23.34]	20.39[18.29-24.62]	0.020	0.009	0.530
BMI$_{-z}$	0.64[1.11]	0.59[1.01]	0.67[1.19]	0.31[1.34]	0.11[1.26]	0.61[1.41]	0.016	0.005	0.748
SBP (mmHg)#	124.50[115.50-132.50]	120.50[112.50-131.00]	129.00[119.12-136.62]	123.00[111.50-130.75]	117.50[108.50-130.62]	124.00[118.00-130.75]	0.067	0.365	0.205
DBP (mmHg)#	69.00[62.50-74.00]	70.50[64.50-75.00]	67.75[61.38-73.00]	70.00[64.50-77.75]	70.00[65.00-77.62]	70.00[62.50-77.75]	0.046	0.599	0.063
PA-L (min/day) #	34.29[12.86-64.29]	34.29[14.29-64.29]	34.29[12.86-64.29]	8.57[0.00-17.14]	0.00[0.00-12.86]	12.86[2.86-25.71]	<0.001	<0.001	<0.001
PA-Mod (min/day) #	25.71[12.86-60.00]	25.71[12.86-60.00]	25.71[12.86-53.57]	8.57[0.00-12.93]	8.57[0.00-12.86]	8.57[0.71-17.14]	<0.001	<0.001	<0.001
PA-Vig (min/day) #	14.29[5.71-32.14]	12.86[5.71-25.71]	15.71[8.04-39.64]	0.00[0.00-5.71]	0.00[0.00-4.64]	1.86[0.00-5.71]	<0.001	<0.001	<0.001

SD: standard deviation; # non-parametric; t: Total vs. Total; ♀: boys vs. girls; ♂: boys vs. boys; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; WC: waist circumference; BMI-Z: BMI z-score; PA-L: light physical activity; PA-Mod: moderate physical activity; PA-Vig: vigorous physical activity.

Table 6 – Percentage distribution of blood pressure according to anthropometric values and level of physical activity

		BLOOD PRESSURE			p	SYSTOLIC BLOOD PRESSURE			p	DIASTOLIC BLOOD PRESSURE			p
		Adequate (n=158)	Pre (n=42)	Hypertensive (n=136)		Adequate (n=164)	Pre (n=40)	Hypertensive (n=132)		Adequate (n=287)	Pre (n=18)	Hypertensive (n=31)	
Sex (%)	Female	91(52.6%)	15(8.7%)	67(38.7%)	0.033	93(53.8%)	15(8.7%)	65(37.6%)	0.075	145(83.8%)	11(6.4%)	17(9.8%)	0.633
	Male	67(41.1%)	27(16.6%)	69(42.3%)		71(43.6%)	25(15.3%)	67(41.1%)		142(87.1%)	7(4.3%)	14(8.6%)	
PA-mv (%)	Suff. Active	91(45.3%)	27(13.4%)	83(41.3%)	0.685	93(46.3%)	27(13.4%)	81(40.3%)	0.412	179(89.1%)	11(5.5%)	11(5.5%)	0.015
	Insuff. Active	67(49.6%)	15(11.1%)	53(39.3%)		71(52.6%)	13(9.6%)	51(37.8%)		108(80.0%)	7(5.2%)	20(14.8%)	
WC (%)	Appropriate	151(51.9%)	34(11.7%)	106(36.4%)	<0.001	155(53.3%)	32(11.0%)	104(35.7%)	<0.001	252(86.6%)	16(5.5%)	23(7.9%)	0.103
	Central Obes.	7(15.6%)	8(17.8%)	30(66.7%)		9(20.0%)	8(17.8%)	28(62.2%)		35(77.8%)	2(4.4%)	8(17.8%)	
BMIz (%)	Eutrophic	121(55.5%)	25(11.5%)	72(33.0%)	<0.001	125(57.3%)	22(10.1%)	71(32.6%)	<0.001	190(87.2%)	13(6.0%)	15(6.9%)	0.114
	Overweight	37(31.4%)	17(14.4%)	64(54.2%)		39(33.1%)	18(15.3%)	61(51.7%)		97(82.2%)	5(4.2%)	16(13.6%)	

PA-mv: moderate-vigorous physical activity level; Insuff.: insufficiently; Suff.: sufficiently; Obes.: obesity; WC: waist circumference; BMI z: body mass index z score.

Table 7 – Odds ratios for the risk of high blood pressure between anthropometric variables and level of physical activity

	HA OR (CI 95%)	PAS elevada OR (CI 95%)	PAD elevada OR (CI 95%)
Sex=Boys	1.40(0.88-2.22)	1.35(0.85-2.14)	0.84(0.40-1.77)
PA-mv= sufficiently active	1.15(0.72-1.84)	1.21(0.76-1.93)	0.33(0.15-0.72)
WC= Central obesity	6.11(2.59-14.42)	4.64(2.10-10.23)	2.50(1.04-6.03)
BMI-z= General obesity	2.91(1.76-4.79)	2.75(1.68-4.52)	2.09(0.99-4.40)

M: male; AF-mv: moderate-vigorous physical activity; WC: waist circumference; BMI-z: body mass index z-score; AH: arterial hypertension; SBP: systolic blood pressure; DBP: diastolic blood pressure; OR: odds ratio; CI: confidence interval; p values with significance level at p <0.005.

In view of this situation, anthropometric measurements represent relevant predictors of AH, which are justified as a simple, quick, easily interpreted and cost-effective alternative.[24,25] Several reports demonstrate an association between blood pressure, BMI and WC, suggesting obesity as a strong risk factor for the development of AH in adulthood.[9,16] Excessive distribution of visceral fat is accompanied by changes in various inflammatory and endothelial markers,[26] which stimulate the increase of insulin resistance events, endothelial dysfunction and increased fluid retention, which can then stimulate variations in BP levels and growth of cardiovascular risk.[27]

It was found that 40.5% of the adolescents had AH, with half of overweight students and two-thirds with high WC diagnosed as AH, in a greater proportion in adolescent relationships with adequate measures. In a study of national and regional representativeness that evaluated 73,399 students aged 12–17 years in the southern region of Brazil, the estimated prevalence of AH was 12.5% and that of prehypertension was 17%;excess weight varied between 29.8%[1] and 35.5%[28] of South Brazilian adolescents. It is suggested that, in addition to genetic and environmental factors, obesity and AH may be related to metabolic disorders.[27] Regarding the differences between sexes, a prevalence of AH and similar SBP among boys and girls was identified, however, girls had higher mean DBP. Similar results have been found in the literature.[9] A possible explanation may the fact that girls practice less physical activities per day compared to boys, which demonstrated a protective effect for high DBP.

In addition, it was observed that overweight girls practice longer physical activities, as well as adolescents considered active had higher averages of anthropometric indicators. This data may reflect participation in physical activities as a strategy to reduce body weight.[14]

It was found that high WC and BMI-z were associated with higher risk of AH, however, those considered sufficiently active showed one-third reduction in the risk of high DBP, which suggests that AF-mv may interfere with blood pressure levels, in addition to reducing metabolic risk.[29] However, another study[30] demonstrated that only overweight and obesity were directly associated with AH, but not the practice of AF-mv.[31] Most adolescents were considered sufficiently active, which may be related to socioeconomic level, as physical activities are offered out of school periods.[32]

The urbanization process, technological advances in modern society and the increase in violence are associated with changes in behavior in children and adolescents.[33] The increase in time spent doing sedentary activities and less AF-mv practice favor weight gain and diseases associated with obesity, including HA.[1] At least 300 minutes of AF-mv per week is recommended to provide additional health benefits.[34]

In this regard, an aspect of relevance found in this study refers to the association between lower DBP in adolescents who practice AF-mv, suggesting that the practice of AF-mv may interfere with blood pressure levels in the juvenile population.[30] A recent study found that adolescents with better muscle skills exhibited lower levels of DBP.[35] Thus, interventions that encourage the transition from physical inactivity to activity promote immediate impacts on the increase of physical activity among schoolchildren,[36] which can be considered a protective factor for AH.

Therefore, effectively detecting risk factors early can contribute to the prevention of cardiovascular diseases in adulthood, since changing established habits and attitudes can represent complex tasks and often lead to unsatisfactory results. However, health policies directed at schoolchildren, as well as social investments to improve the practice of AF-mv, may eventually determine significant changes in the population. In this regard, the presence of education and support from health professionals is of great importance, contributing to the control and prevention of AH, among other risk factors associated with cardiovascular diseases.

The present study has some limitations, such as the small sample size, and measurement of blood pressure must be performed on at least three different occasions to better diagnose hypertensive students. Another limitation is the use of a recall questionnaire to assess the level of physical activity, however the IPAQ has an excellent association with AF-mv.[23] The variables of socioeconomic level, sexual maturity, dietary salt intake and family history of hypertension were not verified either. However, it is noteworthy that the strong point was to associate AH with the diagnosis of central and general obesity, as well as to highlight the importance of the practice of AF-mv as a protective factor against changes in BP in children and adolescents. Such assessments are important as a prevention in public health, as many children and adolescents do not have the opportunity to have their blood pressure assessed at school.

Conclusions

In this study, it was observed that half of the evaluated students demonstrated AH and one third had general obesity. In addition, the anthropometric measurements of WC and BMI-z were significantly related to the increased risk of the presence of AH, while the practice of physical activities appears as a protective factor of high DBP among children and adolescents. Thus, it is suggested to implement programs that encourage a healthy lifestyle in the school environment, to contribute to the reduction of central and general obesity indicators, as well as to add protection against AH by increasing the practice of AF-mv in the population of children and adolescents.

Author Contributions

Conception and design of the research: Tozo TA, Pereira BO, Moreira CMM, Leite N; Acquisition of data: Tozo T; Analysis and interpretation of the data: Tozo T, Pereira BO, Menezes Junior FJ, Montenegro CM, Moreira CMM, Leite N; Statistical analysis: Menezes Junior FJ; Obtaining financing: Pereira BO, Moreira CMM, Leite N; Writing of the manuscript: Tozo T, Pereira BO, Menezes Junior FJ, Montenegro CM; Critical revision of the manuscript for intellectual content: Pereira BO, Moreira CMM, Leite N.

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 under the protocol number 2.198.319- CAAE: 713240017.1.0000.0020. 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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Physical Activity in the Present Can Be the Recipe to Avoid the Ills of Obesity and Hypertension in the Future

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Short Editorial related to the article: Hypertensive Measures In Schoolchildren: Risk Of Central Obesity And Protective Effect Of Moderate-To-Vigorous Physical Activity

Arterial hypertension is one of the most important causes of premature death in the world. Nearly one billion are affected and it is estimated that by 2025, 1.5 billion adults will be living with AH.[1] Fortunately, AH is a major modifiable risk factor for cardiovascular diseases with roots in childhood making both the development of the disease and death to be preventable.

Nowadays, the prevalence of AH in children and adolescents has become a significant public health issue.[2] One example of how this scenario has become worse is the comparison of a study conducted by our group,[3] with two successive cohorts (1975–1976) of students aged 16 to 25 from the city of Botucatu, São Paulo state, which found the prevalence of AH of 5.0% and 6,2%, respectively, with another more recent study. Almost 40 years late, the Brazilian study of cardiovascular risks in adolescents (ERICA),[4] a national school-based study involving 73,999 adolescents aged 12 to 17, found an AH prevalence of 9.6%. Obese adolescents presented higher prevalence of hypertension — 28.4% — than overweight adolescents, with 15.4%, or eutrophic adolescents, with 6.3%. The portion of AH attributable to obesity was 17.8%.

Many reasons may explain the growing prevalence of AH in young people. Obesity is the main one, followed by consumption of salt and sugar, stressful environments, low level of physical activity and sedentary lifestyle. In Brazil, a cross-sectional study on food consumption[5] in a representative sample of a population aged 10 or older noted that higher consumption of ultraprocessed food was associated with higher content of fats in general, saturated fat, trans fat and free sugars.

Evidence of protection against both the development of AH and cardiovascular diseases and all-cause mortality by regular physical activity has become incontestable.[6] Most people in all industrialized societies are becoming less physically active in their daily lives, spending more and more time in sedentary activities. Not only will increased physical activity and higher levels of exercise capacity reduce the risk of cardiovascular outcomes and diabetes, but they will also prevent the development of hypertension.[7] The incidence of AH was reduced by 28% in men and 35% in women doing physical activities such as jogging or swimming in a prospective 11-year follow-up of over 12,000 Finish people.[8] In a prospective longitudinal study,[9] we evaluated the association between level of physical activity and mortality in 200 hypertensive and diabetic patients in 2012 and reassessed it in 2018. Over 6 years of follow-up, 80% of active patients survived compared to sedentary patients. Also, the benefit of physical activity was seen in irregularly active people, with 65% of chances to survive compared to patients who do not maintain this healthy practice.

The article "*Hypertensive Measures In Schoolchildren: Risk Of Central Obesity And Protective Effect Of Moderate-To-Vigorous Physical Activity*"[10] now reported in this journal has the aim of verifying the association of AH, central and general obesity and level of physical activity in schoolchildren and adolescents. The trial involved 336 children and adolescents aged 11–17. Height, weight, waist circumference (WC) and blood pressure (BP) were measured. Body mass index score Z (BMI-z) was calculated. The level of physical activity was evaluated by the short International Physical Activity Questionnaire (IPAQ), according to practice of moderate-vigorous physical activities (PA-mv). Schoolchildren with systolic blood pressure (SBP) or diastolic blood pressure (DBP) above the 95th percentile, according to sex, age and height, or over 120/80 mmHg, were considered hypertensives. Statistical analysis was evaluated by the Student's t test, Chi-square, Mann-Whitney and binary logistic regression model, where $p<0.05$ was the significant level. AH was found in 40.5% of this population, of which 31.1% were overweight and 12.5% were obese, and 13,4% had large WC. Schoolchildren insufficiently active in PA-mv accounted for 40.2%. AH was associated to higher WC (OR=6.1; 95% CI: 2.6 to 14.4) and to overweight (OR=2.9 95% CI: 1.8 to 4.5). Besides that, schoolchildren practicing PA-mv presented lower risk of high DBP (OR=0.33; 95% CI: 0.15 to 0.72) and risk reduction of 33%. In conclusion, central obesity, general obesity and male sex were better predictors of AH. Practicing PA-mv protects schoolchildren from developing diastolic hypertension.

Obesity in childhood and adolescence is followed by obesity in adult age and has been implicated in many chronic diseases, including type 2 diabetes, hypertension and cardiovascular diseases, and linked to mortality and premature death. For these reasons, we empathize with the paper by Tozo et al.,[10] who make clear the relevance of obesity and hypertension in childhood and adolescence. Although the prevalence of hypertension is not the focus of the study, it is

Keywords

Hypertension; Risk Factors; Cardiovascular Diseases/mortality; Adolecents; Adult; Obesity; Physical,Activity; Sedentarism.

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unusual compared to the ERICA study.5 However, the merit of the study is that it provides precious information, warning us and calling us to open our eyes to the near future stressing the importance of growing factors of cardiovascular diseases such as obesity, hypertension, sedentary lifestyle, bad eating habits and physical inactivity that adversely affect our youth. We have recently learned that the same risk factors for cardiovascular diseases are also the same for virus infection deseases.[11] It is time to move. The final message is: look to the future to make the right decisions at the right moment so as not to regret the consequences caused by obesity and hypertension in youth.

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Family History of Hypertension Impairs the Autonomic Balance, but not the Endothelial Function, in Young Soccer Players

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Abstract

Background: The family history of hypertension (FHH) imposes consistent risk for diverse chronic diseases that are accompanied by hypertension. Furthermore, the heart rate variability (HRV) and flow-mediated dilation (FMD) are both related to maximal oxygen uptake (VO_{2max}), and are usually impaired during hypertension

Objective: To compare the autonomic modulation, the endothelial function (EF) and maximum oxygen uptake (VO_{2max}) of young athletes, separated according to their parents' blood pressure (BP) history, in order to study the influence of their genetic background on those parameters.

Methods: A total of 46 young male soccer players (18±2 years of age) were divided into four groups: 1-normotensive father and mother (FM-N); 2-only father was hypertensive (F-H); 3-only mother was hypertensive (M-H); 4-father and mother were hypertensive (FM-H). Measurements of BP, FMD, HRV and VO_{2max} were performed. The significance level adopted in the statistical analysis was 5%.

Results: The standard deviation of normal RR intervals (SDNN; FM-N=314±185; FM-H=182.4± 57.8), the square root of the mean squared differences in successive RR intervals (RMSSD; FM-N=248±134; FM-H=87±51), the number of interval differences of successive NN intervals greater than 50ms (NN50; FM-N=367±83.4; FM-H=229±55), the ratio derived by dividing NN50 by the total number of NN intervals (pNN50; FM-N=32.4±6.2; FM-H=21.1±5.3) and the high (HF; FM-N=49±8.9; FM-H=35.3±12) and low-frequency (LF; FM-N=50.9±8.9; FM-H=64.6±12) components, in normalized units (%), were significantly lower in the FM-H group than in the FM-N group ($p<0.05$). On the other hand, the LF/HF ratio (ms^2) was significantly higher ($p<0.05$). We found no significant difference between the groups in VO_{2max} and FMD ($p<0.05$).

Conclusions: In young male soccer players, the FHH plays a potentially role in autonomic balance impairment, especially when both parents are hypertensive, but present no changes in VO_{2max} and FMD. In this case, there is a decrease in the sympathetic-vagal control, which seems to precede the endothelial damage (Arq Bras Cardiol. 2020; 115(1):52-58)

Keywords: Hypertension; Blood Pressure; Heredity/genetics; Soccer; Athletes; Youth Sports; Endothelium/function

Introduction

Cardiovascular disease is the leading cause of death worldwide.[1] The correlation between blood pressure (BP) and the risk of cardiovascular events is continuous and independent of other risk factors[2]. The latest Guidelines for the management of arterial hypertension established that the optimal values of systolic (SBP) and diastolic BP (DBP) are <120 and 80 mmHg, respectively.[2] Cardiovascular events, such as sudden coronary death, myocardial infarction and stroke might easily occur at pressure even below 139/89mmHg, a threshold considered as normal BP.[3,4] This fact indicates the importance of keeping the BP at lower values.

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In this context, family history of hypertension emerges as an important predictor of risk to be considered in creating prevention strategies. In fact, professional guidelines for health risk assessment already include the genetic family history.[5] Evidence suggests that the variation of 66% in SBP and 60% in DPB are due to genetic background.[6]

Data from the literature have shown that normotensive subjects with a family history of hypertension have lower cardiac parasympathetic modulation and also heart rate variability (HRV). These findings are accompanied by sympathovagal imbalance.[7] Moreover, it has been postulated that this imbalance is associated to increased sympathetic participation, which could be used as a marker for monitoring the cardiovascular system.[8] A decrease in sympathetic modulation helps preventing the risk of premature death, even in non-obese young adults,[9] and should be a goal for treating cardiovascular system diseases.

Nevertheless, in healthy young subjects, there is consistent evidence that enhanced parasympathetic activity is associated

with an increase in maximal oxygen uptake (VO_{2max}),[10] i.e., there is a relationship between the parasympathetic modulation and the functional capacity of the cardiovascular system. There is also a consensus that there is a strong relationship between VO_{2max} and arterial endothelial function (EF), since they are dependent variables.[11] However, data from our laboratory have shown, in a normotensive group of young soccer players, that a difference of 10 mmHg in mean BP is enough to change the autonomic balance, without changing VO_{2max} and EF.[12] Although it is not possible to conclude whether BP or autonomic balance is the cause or the consequence, this result indicates that the alteration in autonomic balance probably precedes the VO_{2max} or EF changes.

Thus, our study was designed to compare the autonomic modulation, the EF, and the VO_{2max} of young athletes grouped according to the parents' BP history. The objective was to access the influence of the genetic background in those parameters, and whether normotensive athletes would present differences in the cardiovascular system control that could compromise their performance. Additionally, our intention is also to drive attention for the importance of preventing cardiovascular diseases and finding out which system is the first to be compromised in normotensive subjects with a family history of hypertension.

Methods

The Ethics Committee of the Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA) approved the study (CEP/UFCSPA protocol number 562.572). The sample size was calculated with a confidence level of 95%, applying a tolerated measurement error estimated at 5% over the mean of variable standard deviation of normal RR intervals (SDNN) of anterior study.[11] Thus, in order to conduct this research project, a minimum number of 39 participants was required. Predicting losses and dropouts around 20% of the sample number, 46 individuals were invited to participate.

Forty-six young male soccer players (18±2 years of age) were submitted to: anthropometric and BP measurements, autonomic nervous system and EF evaluation, and exercise tests. All players had at least two years of previous soccer-specific training and lived in the club accommodations to avoid significant differences in lifestyle. Moreover, all meals were provided assuring similar diet and nutrients intake.

Before data collection, the athletes were fully informed about the tests to be performed and provided a written informed consent to participate. The data was collected during the soccer preseason, when the athletes were training, but not participating in any competitions. All evaluations were made on Tuesdays, before training, respecting the athletes' rest breaks. The athletes trained on Sundays, rested on Mondays, and returned to training on Tuesdays. To avoid any tendency in data interpretation, all data collection were performed before the subjects were allocated in the groups.

The athletes were instructed to attend the Laboratory of Physiotherapy/UFCSPA, at 7 a.m., fasting. The BP and HR were measured, followed by an evaluation of EF in the brachial artery. To avoid an excess of measurements in a single day, the anthropometric data (height, weight, age, body fat percentage, and time of training) and VO_{2max} were collected one week later. The athletes were grouped according to their family history of hypertension: 1- normotensive father and mother (FM-N), with 14 athletes; 2- only father was hypertensive (F-H), with 11 athletes; 3- only mother was hypertensive (M-H), with 10 athletes; and 4- father and mother were hypertensive (FM-H), with 11 athletes. Following the guidelines for this assessment,[13] the BP of the athletes was measured, as well as their parents'. The hypertensive status of the athletes' parents was previously defined by a physician (53.3% of those individuals were taking anti-hypertensive drugs and 3.3% were not treating their state). Individuals who showed changes in BP values were advised to seek medical attention.

Blood pressure measurement

An auscultatory method was used. The athletes were kept in a quiet environment for at least five minutes before BP measurements, seated with their feet on the floor, right arm supported at heart level and BP cuff covering at least 80% of the upper arm. To confirm the data, the BP measurement was repeated at least twice at 2-minute interval. When a difference of more than 6 mmHg was detected in two successive measurements, the measurements were repeated until the difference was less than 4 mmHg. For each athlete, an average of two measurements was used to obtain the SBP.[13]

Heart rate variability

A Polar model RS800CX heart-rate monitor (Polar Electro Öy, Kempele, Finland) was used to collect heart rate (HR) data at a sampling frequency of 1000Hz. For the evaluation of HRV, the athletes were instructed to lie quietly on a stretcher in the supine position. After 10 minutes, still in the supine position, the HR signal was recorded for 10 minutes followed by additional 10 minutes with the athlete standing in front of the stretcher.[13] The signal was automatically stored as an RR interval and analyzed with Kubios HRV software version 2.0 (University of Kuopio, Kuopio, Finland). A 1,000-Hz sampling rate was chosen to provide a temporal resolution of 1 ms for each RR interval, a standard deviation of normal RR intervals (SDNN, ms), the square root of the mean squared differences among consecutive RR intervals (RMSSD, ms), the number of interval differences of successive NN intervals greater than 50 ms (NN50, ms), and the proportion derived by dividing NN50 by the total number of NN intervals (pNN50; ms)[8].

An autoregressive method was used to determine HRV, based on the spectral power integrated in two frequency bands: (i) a high-frequency (HF) band from 0.15 to 0.4 Hz; and (ii) a low-frequency (LF) band from 0.03 to 0.15 Hz. The results were expressed in absolute values (HFa and LFa, ms^2) and their respective percentages (HFnu and LFnu, %). The LF/HF ratio (ms^2) was calculated according to the LFa and HFa.[8] This methodology had been previously reproduced in the soccer players.[11]

Endothelial Function Assessment

EF was assessed noninvasively by means of a brachial artery ultrasound probe (GE Medical Systems, Vivid I Ultrasound, Israel) and Doppler ultrasonography, using an instrument

equipped with a 7- 12-MHz high-resolution linear probe (L12-3, GE Medical Systems, Israel). The ultrasonography was performed in a silent, temperature-controlled room. At rest, the left brachial artery diameter was measured by B-mode ultrasound images to detect reactive hyperemia. Before BP cuff inflation, a resting scan was performed. After the resting measurement, the cuff was inflated for 5 min at 50 mmHg above SBP, to occlude the arterial flow. This procedure causes ischemia followed by vasodilation due to auto-regulatory mechanisms. After the cuff deflation, a second continuous scan was recorded from 30–120 seconds. The same experienced sonographer performed and analyzed all ultrasound scans without knowing the genetic history of each athlete. At a fixed position, the vessel diameter was measured offline with ultrasonic calipers at end-diastole, and coincident with the R wave on an electrocardiogram, which was continuously recording. After an interval of 10 seconds and during the period within 30–180 seconds, the dilatation was obtained by the difference from baseline. After the release of the sphygmomanometer cuff, the flow-mediated dilation (FMD, %) indicates the increase in blood flow.[14]

Maximal oxygen uptake

The Yo-Yo intermittent recovery test level 1 (Yo-Yo IR1) was used to infer the VO_{2max}. The athletes performed 2×20-minute shuttle runs at increasing speeds, interspersed with a 10-second period of active recovery. The test was controlled by audio signals from a compact-disc player and ended when the athlete was unable to maintain the speed for the test. The distance traveled at that point was the result of the test, as described by Bangsbo et al.[15] The indirect measurement of VO2max was calculated as follows:

VO_{2max} (ml/min/kg) = IR1 distance (meters) × 0.0084 + 36.4 [14]

Statistical analysis

All analyses were performed with the SPSS software version 10.0 (SPSS Inc., Chicago, IL). The data normality and equality were assessed through the Shapiro–Wilk and Levene's tests. The results of parametric data are presented as mean ± standard deviation, and the results of non-parametric data are described as median and interquartile range.

In the inferential statistical analysis, one-way ANOVA was used to compare the groups, followed by Tukey's post hoc test, when parametric data. The Kruskal-Wallis test was used to compare the groups when non-parametric data, and U of the Mann-Whitney test was used to verify the differences between the groups. A significance level of 0.05 was adopted for all the tests.

To detect a minimum 30% difference between the groups with a minimum probability of a type I error of 5% ($\alpha = 0.05$) and a probability of type II error of 20% ($\beta = 0.2$), the minimum number of individuals for each group was estimated at 10, based on a preliminary study.[11]

Results

Anthropometric, SBP, DBP, maximal oxygen uptake measurements and parents' BP

There was no significant difference among groups regarding the age (years; 17.65±0.7), weight (kg; 69.25±3.6), and height (cm; 175.2±5.7). Moreover, VO_{2max} (ml/min/kg) indicated that physical fitness was similar among groups, and SBP and DBP (mmHg) were not different among the groups either (Table 1). According to the definitions and classification of office blood pressure levels,[3] the blood pressure level in 15.3% (n = 7) of the athletes was optimal BP (BP<120 and 80mmHg), 39.1% (n = 18) of them presented normal BP (BP = 120-129 and/or 80-84mmHg), and 45.6% (n = 21) had high normal blood pressure (BP = 130-139 and/or 85-89 mmHg).

SBP: systolic blood pressure; DBP: diastolic blood pressure; VO_{2max}: maximal oxygen uptake. Blood pressure values are expressed as mean (confidence interval) and VO_{2max} values, as mean ± SD.

The parents' BP are shown in Table 2. The parents' systolic and diastolic blood pressures were higher in the hypertensive group when compared to the normotensive one.

Heart rate and time-domain and frequency-domain measurements of resting heart-rate variability

In our study, the HRV in the time domain was significantly lower in the FM-H than in the FM-N group (Table 3). The spectral analysis, using a frequency-domain method (HFnu) was significantly lower in the FM-H than in the FM-N group, and LFnu and the LF/HF ratio were significantly higher in the FM-H than in the FM-N group (Figure 1).

Endothelial function assessment

There was no significant difference between the groups regarding FMD or baseline brachial artery diameter upon reactive hyperemia, either before or after nitroglycerin-mediated vasodilatation (Table 4; P>0.05).

Table 1 – Measurements of systolic and diastolic blood pressure and maximal oxygen uptake

	FM-N (n=14)	F-H (n=11)	M-H (n=10)	FM-H (n=11)
SBP (mmHg)	124 (117-132)	128 (114-134)	128 (111-139)	128 (120-139)
DBP (mmHg)	72 (60-84)	76 (65-83)	79 (67-89)	78 (60-89)
VO2max (ml/kg/min)	53.5±2.5	52.3±2.9	53.4±1.1	51.4±1.6

SBP: systolic blood pressure; DBP: diastolic blood pressure; VO_{2max}: maximal oxygen uptake. Blood pressure values are expressed as mean (confidence interval) and VO_{2max} values, as mean ± SD.

Table 2 – Measurements of parents' systolic and diastolic blood pressure

	FM-N (n=14)		F-H (n=11)		M-H (n=10)		FM-H (n=11)	
	Father	Mother	Father	Mother	Father	Mother	Father	Mother
SBP (mmHg)	129 (120-188)	124 (120-130)	147 (130-177)	124 (120-127)	124 (120-127)	158 (143-184)	154 (130-193)	152 (130-184)
DBP (mmHg)	86 (75-105)	84 (77-90)	97 (85-110)	83 (77-88)	85 (80-89)	96 (80-120)	98 (85-110)	96 (80-120)

PAS: pressão arterial sistólica; PAD: pressão arterial diastólica. Os valores correspondem à média (inrervalo de confiança).

Table 3 – Heart rate, time-domain and frequency-domain measurements of resting heart-rate variability

	FM-N (n=14)	F-H (n=11)	M-H (n=10)	FM-H (n=11)
RMSSD (ms)	210.2 (229)	179.1 (187,9)	125.2 (164.2)	82.2 (65)*
NN50(count)	356±82	260±50	296±81.3	218.8±44*
pNN50 (%)	31.5±6.4	23.6±3.4	25.8±6.3	20.2±4.5*
HRV triangular index	26.6±7	21.9±6.1	20.8±7.4	17.2±2.5*
SDNN (ms)	256 (145)	211.1 (123.1)	185.3 (84.3)	162.4 (92.7)*
HFa (ms)	15935 (31705.1)	13822.5 (22099.8)	3421 (24564.2)	3025.1 (15568.9)
HFnu (%)	48.6±8.6	40.3±13	38.4±10.3	33.8±11.2*
LFa (ms)	13654 (54544.1)	11575.2 (53678.3)	2591.8 (9127.9)	3173.4 (13163.2)
LFnu (%)	51.4±8.6	59.7±13	61.6±10.3	66.2±11.2*
LF/HF (ms2)	1(0.5)	1.5 (1.4)	1.8 (0.3)	2.5 (1.3)*

*Values are expressed as mean ± SD when parametric data, or median (interquartile range) when non-parametric data. *A value of $p < 0.05$ was considered statistically significant when compared to the group FM-N.*
RMSSD: square root of the mean squared differences among consecutive RR intervals; NN50: the number of successive NN intervals greater than 50ms; pNN50; the ratio derived by dividing NN50 by the total number of NN intervals; HRV: heart rate variability; SDNN: standard deviation of normal RR intervals; HFa: absolute values of high-frequency components; nu: normalized units; LFa: absolute values of low-frequency components; LF/HF: ratio between low- and high-frequency power components.

Discussion

In the present study, there was no significant difference between the groups in terms of FMD, SBP, DBP or VO_{2max}. Thus, our results suggest that the differences found between the FM-N and FM-H groups in relation to cardiovascular autonomic modulation are due to the family history of hypertension of the athletes, regardless of the other variables studied.

According to the literature data, the prevalence of hypertension appears to affect about 30% to 45% of the general population.[13] In our study, we found a prevalence of 53.3% for the athletes' parents (Table 1), values above the world average. We believe that socioeconomic factors can explain the differences found in our sampling.

Our results provide, for the first time, evidence that family history of hypertension might be crucial to the progressive imbalance of autonomic regulation in healthy young athletes with normal BP. Based on our knowledge, this is the first study to show the possible early involvement of the autonomic modulation in the hypertensive process. Solanki et al.[16] examined sympathetic function tests of young nonathletic males, considering measures of obesity, PA and familial hypertension. Their results showed that the cardiac autonomic function is altered in individuals with a family history of hypertension. Autonomic imbalance changes due to increased sympathetic tone was more pronounced in subjects with a family history of hypertension. These findings by Solanki and co-workers[16] are in agreement with our results, and also highlight the importance of physical exercise, which countered the autonomic imbalance in favor of normal EF for all study subjects, regardless of the experimental group. At least partially, it is reasonable to believe that our results point out towards the fact that the first changes in the hypertensive process affect the sympathetic and parasympathetic systems. These conclusions are in agreement with Vargas et al.,[11] who also showed that in athletes a small increase in BP induces changes in the autonomic nervous system without changing the EF or VO_{2max}.

Considering that the autonomic regulation can be assessed with a non-invasive approach to evaluate the HRV in the time and frequency domains,[8] it could be useful to detect its impairment and provide the physicians with valuable information to assess the treatment efficacy or even to prevent diseases. Despite the enormous impact of a decrease in HRV over the cardiovascular risk, we did not find any researches in the literature showing a correlation between the family history of hypertension and these parameters in healthy subjects. We believe that our results may drive the attention to a method that is easy, of low cost and able to present data associated to a significant cardiovascular risk, such as HRV. They will contribute not only to prevent hypertension in subjects who are at genetic risk, but also to open up a new possibility of monitoring hypertensive patients.

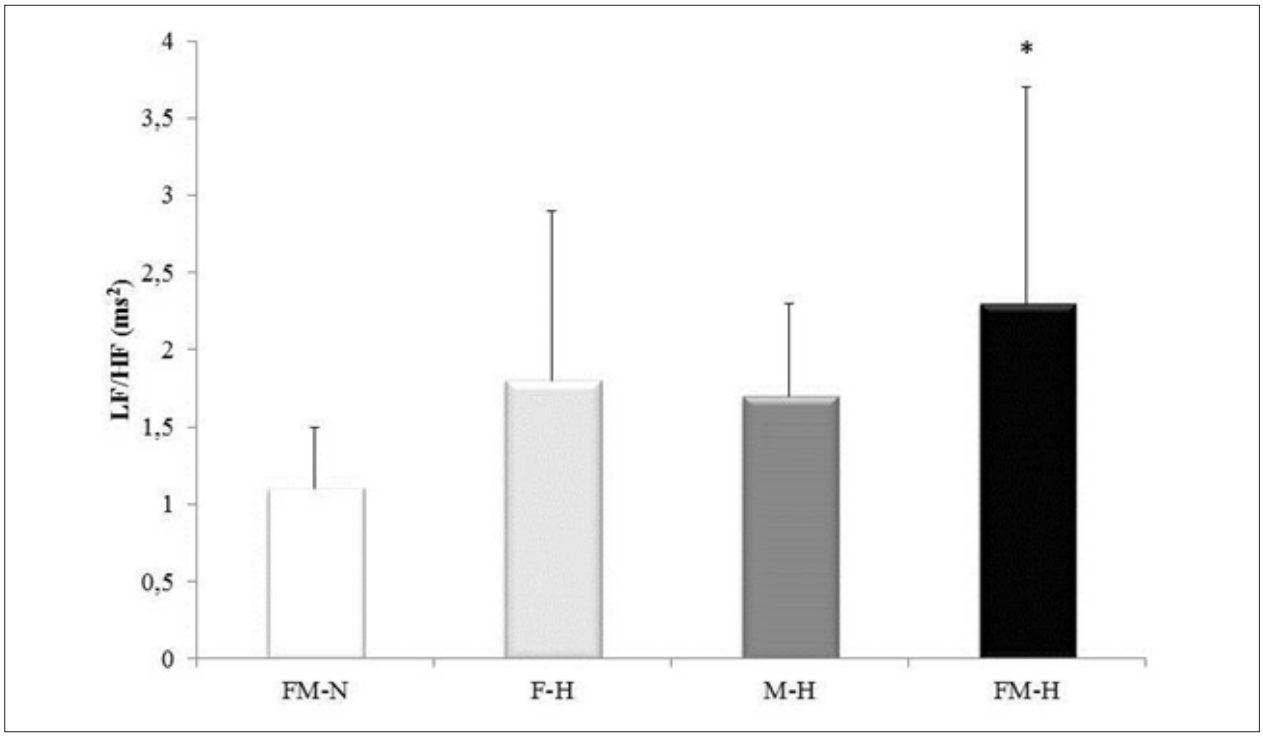

Figure 1 – *LF/HF= Ratio between low and high frequency power components, i.e., the autonomic balance of the FM-N, F-H, M-H and FM-H groups. *Differences between FM-H and FM-N groups (p<0.005).*

Table 4 – Brachial artery characteristics of athletes in supine position

	FM-N (n=14)	F-H (n=11)	M-H (n=10)	FM-H (n=11)
B-DIA (mm)	0.355±0.043	0.364±0.035	0.344±0.041	0.383±0.037
RH-DIA (mm)	0.387±0.042	0.387±0.028	0.366±0.042	0.402±0.045
FMD (%)	9.323±3.028	6.745±1.263	6.261±1.726	5.097±3.157
Before NTG (mm)	0.368±0.044	0.363±0.032	0.352±0.043	0.387±0.039
After NTG. (mm)	0.431±0.039	0.431±0.036	0.419±0.041	0.453±0.034
NTG (%)	17.639±7.086	18.920±3.991	19.472±6.456	17.678±7.503

B-DIA: basal brachial artery diameter; FMD: flow-mediated dilation; NTG: brachial artery diameter with nitroglycerin; RH-DIA: brachial artery diameter with reactive hyperemia. Values are expressed as mean ± SD.

In our study, the FM-H group showed higher LFnu and LF/HF ratio than the FM-N group. In addition, in the FM-H group, the HFnu, in the frequency-domain, and SDNN, RMSSD, NN50, pNN50 and HRV triangular index, in the time-domain, were significantly lower than those from the FM-N group. These results indicate that family history of hypertension is accompanied by an increase in cardiac sympathetic modulation and a decrease in parasympathetic modulation, regardless of the normal BP of each soccer player.

Moreover, Tozawa et al.[17] sought to determine whether the family history of hypertension was quantitatively associated with the prevalence of hypertension in a screened cohort. They concluded that the increasing number of family members with hypertension had a correlation with increased prevalence of higher BP, regardless of the conventional risk factors for hypertension. These findings are in agreement with ours, since we also found a significant difference in autonomic modulation only when both parents were hypertensive, emphasizing the importance of the genetic background for HRV, which is a predictor of cardiovascular risk.

There is no doubt that physical exercise is associated with beneficial effects on BP. Because exercising is a healthy method of cardiovascular diseases control,[3] we have chosen to study only athletes. Our results emphasize the importance of the genetic background. Healthy and young athletes, who had hypertensive father and mother, presented a significant increase in the LF/HF ratio, as well as a reduction in HRV.

There is also consistent evidence showing that enhanced parasympathetic modulation is associated with an increase in VO2max in healthy young subjects.[10] However, in the present study we have found no differences in VO_{2max}, BP and EF between all groups. This is probably due to the fact that, being composed of young athletes who had similar diets and nutrients intake, our groups had a high physical performance, which attenuated the differences.

Although we have found a significant difference in cardiac autonomic modulation between the FM-H and FM-N groups, we have not found significant differences in VO_{2max} and EF which, ultimately, kept BP in normal values despite the family history of hypertension.

In agreement with Lucini et al.,[9] our results demonstrated that the autonomic changes possibly precede endothelial dysfunction. They showed that, in subjects with BP in the upper normotensive range, the HRV was impaired. These authors also reported that these changes might suggest that the disturbance in the autonomic regulation precedes the hypertensive state,9 as seen in neurogenic hypertension.

A point of criticism to our method is the fact that we did not separate the groups according to the parents' type of hypertension. On the other hand, we know that the probability to have only parents with neurogenic hypertension in the FM-H group is very low. Thus, it is reasonable to believe that, regardless of the cause of hypertension, the EF was preserved.

According to our results, strengthened by previous studies that also looked for answers concerning the beginning of the arterial hypertensive process,[9,12,17] it appears that the autonomic dysfunction precedes the endothelial dysfunction. Thus, it is a challenge to discover a treatment for sympathovagal imbalance and reduce cardiovascular risk.

Conclusion

Although our study has the limitation of a small sample size, it suggests that HRV, in the time and frequency domains, may provide a useful functional outcome to assess the cardiovascular system control earlier. This advantage is useful for healthy young people, as young soccer players, and is probably more important for sedentary people at risk. Doing exercise, more than treating borderline hypertension, represents an alternative to prevent the increase in BP through strategies that treat the mechanisms by which normal BP, eventually, becomes hypertension. However, further studies are needed to confirm these conclusions.

Author contributions

Conception and design of the research, Analysis and interpretation of the data, Statistical analysis, Obtaining financing, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Vargas W, Rigatto K; Acquisition of data: Rigatto K.

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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Heart Rate Variability as an Indicator of Cardiovascular Risk in Young Individuals

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Short Editorial related to the article: Family History of Hypertension Impairs the Autonomic Balance, but not the Endothelial Function, in Young Soccer Players

The autonomic nervous system, which consists of the sympathetic and parasympathetic systems, plays an important role in regulating the functions of several systems in the human body, such as the cardiovascular system. Neural control of the heart is directly related to changes in heart rate and baroreceptor reflex activity, of which oscillation results from environmental stimuli.[1,2] These stimuli can lead to heart rate reduction through the parasympathetic nervous system, by decreasing the frequency of sinus node depolarization through the effect of acetylcholine on the cardiac neuroeffector junction. In turn, the sympathetic nervous system promotes an increase in heart rate through the norepinephrine release, which acts through the connection with β-adrenergic receptors, increasing the depolarization rate of the sinus pacemaker.[1,2]

Healthy individuals or athletes, with an intact autonomic nervous system, show a predominance of parasympathetic modulation to the detriment of sympathetic modulation to the heart. On the other hand, in individuals with cardiovascular diseases, such as arterial hypertension, this pattern is reversed, with greater sympathetic modulation and less parasympathetic modulation being observed, which characterizes a picture of cardiac autonomic dysfunction.[1-3] This is particularly important, considering that changes in cardiac autonomic modulation and, consequently, in heart rate, can have a direct impact on cardiac output, which can result in BP changes.[1]

Specifically in the young population, several studies have also shown an association between cardiac autonomic dysfunction and increased BP. In a previous study by our group,[4] we observed, in a sample of 1152 male adolescents (aged 14 to 19 years), that high BP levels are directly associated with greater sympathetic modulation and less cardiac parasympathetic modulation, irrespective of the level of physical activity and the nutritional status, which also affect cardiac autonomic modulation.[5-7]

The study "Family History of Hypertension Impairs the Autonomic Balance, but not the Endothelial Function, in Young Soccer Players"[8] sought to compare autonomic modulation, endothelial function and maximum oxygen consumption (VO_{2max}) in young (healthy) athletes, divided according to their parents' blood pressure (BP) history, aiming to investigate the influence of genetic inheritance on these parameters. For that purpose, a cross-sectional study was carried out, in which 46 soccer players (18 ± 2 years old) were divided according to their parents' BP levels: 1) normotensive father and mother; 2) hypertensive father only; 3) hypertensive mother only; and, 4) hypertensive father and mother. One of the highlights of the study is the athletes' BP control, as well as their excellent health status. In this sense, no difference was found among the athletes regarding endothelial function and VO_{2max}. On the other hand, the authors found that athletes whose parents are hypertensive had autonomic dysfunction, while athletes with normotensive parents had an intact cardiac autonomic system.

The novelty of the aforementioned study is the suggestion that before the BP impairment, common in children of hypertensive patients,[9] there is autonomic dysfunction with maintenance of endothelial function even in young athletes with good health status. It had been previously shown in the general population that children of hypertensive patients have cardiac autonomic dysfunction,[10] but the association with healthy young athletes had not been demonstrated.

These results suggest that the cardiac autonomic modulation evaluation can be used to assess cardiovascular risk in young individuals, aiming at establishing preventive measures. Among the different ways of assessing cardiac autonomic modulation, heart rate variability (HRV) stands out, because it is a simple and non-invasive method of assessing the autonomic nervous system based on oscillations in the intervals between consecutive heartbeats (RR-intervals)[11] with good intra-individual, and inter- and intra-evaluator reproducibility.[12] For HRV analysis, the parameters can be obtained using linear methods, in the time and frequency domain, as well as non-linear methods.[11]

In this context, given the many parameters that can be evaluated in HRV and the lack of universally accepted cutoff points, the use of HRV in clinical practice is still incipient, even though, in 1996, a task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology[11] sought to standardize and establish the clinical use of HRV parameters. Specifically with adolescents, our group[4] and others[13,14] described reference values in representative samples of the general adolescent population, as well as the establishment of a cutoff point for the HRV linear parameters in the identification of cardiovascular risk,[15] thus facilitating the use in clinical practice.

Keywords

Hypertension; Blood pressure; Heredity / genetics; Soccer; Athletes; Youth Sports; Endothelial / function.

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That said, the importance of assessing cardiac autonomic modulation is evident, given its association with cardiovascular risk factors even in a healthy sample. The study "Family History of Hypertension Impairs the Autonomic Balance, but not the Endothelial Function, in Young Soccer Players"[8] reinforces this finding. However, being a cross-sectional study with a small sample, it obviously has some limitations. Thus, further studies may consider expanding this investigation by increasing the number of athletes in the sample, including female ones.

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Decreased Collagen Type I is Associated with Increased Metalloproteinase-2 Activity and Protein Expression of Leptin in the Myocardium of Obese Rats

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Abstract

Background: **Obesity is a risk factor for medical complications, including the cardiovascular system. There is limited information on collagen in the heart in obesity. Our previous study showed decreased protein levels of myocardial collagen type I in obese rats fed a high-fat diet for 34 weeks. However, the mechanisms responsible for low levels are not fully elucidated.**

Objective: **The purpose of this study was to test the hypothesis that the reduction in collagen type I is associated with increased metalloproteinase-2 (MMP-2) activity, which is linked to elevated leptin in the myocardium of obese rats.**

Methods: **Thirty-day-old male Wistar rats were randomized into two groups, control (standard diet) and obese (high-fat diet), and fed for 34 weeks. The general animal characteristics and metabolic and endocrine profiles were evaluated. Myocardial protein expressions of collagen I, leptin, tissue inhibitors of metalloproteinases (TIMP), and MMP-2 activity were assessed. Pearson correlation was employed to determine the associations between variables. The level of significance was 5%.**

Results: **The obese animals had increased adiposity index compared to control. Comorbidities such as glucose intolerance, hyperinsulinemia, insulin resistance, hyperleptinemia, and hypertension were observed in obese rats. Obesity reduced collagen I, TIMP-1, and TIMP-2, and it increased leptin and MMP-2 in the myocardium. There was a negative correlation between collagen I and MMP-2 and a positive correlation between leptin and MMP-2.**

Conclusion: **The hypothesis was confirmed; the reduction in collagen type I is associated with increased MMP-2 activity and leptin expression in the myocardium of obese rats. (Arq Bras Cardiol. 2020; 115(1):61-70)**

Keywords: **Cardiovascular Diseases/physiopathology; Obesity; Collagen Type 1; Rats; Leptin; Adiposity; Tissue Inhibitor of Metalloproteinases; Metaloproteinase-2.**

Introduction

Obesity is a chronic metabolic disorder characterized by excessive accumulation of adipose tissue. The prevalence of obesity has increased worldwide, representing a major public health problem that affects both developed and developing countries.[1,2]

The adipocytes are influenced by several substances, and they secrete numerous peptides that act directly or indirectly on the cardiovascular system. Therefore, adipose tissue is not simply an energy deposit, but also an active endocrine, paracrine and autocrine organ with multiple functions, including the ability to synthesize and release mediators, like leptin, that participate in multiple biological processes, including those that occur in the heart.[3]

The heart is composed of myocytes, nerves, vessels, and the extracellular matrix (ECM). The main component of the ECM is collagen, predominantly type I and III, with type I being the most abundant, corresponding to approximately 80% of total myocardial collagen.[4] This protein is produced by fibroblasts and degraded by the family of matrix metalloproteinases (MMP).[5] In a stable condition, it contributes to the maintenance of cardiac architecture and function.[6] Several mechanisms act to ensure that the components of matrix degradation by MMP are precisely controlled, including tissue inhibitors of metalloproteinases (TIMP).[7] Cardiac collagen changes in response to neuro-hormonal and mechanical stimuli,[6,8] due to elevated synthesis and decreased degradation or vice versa.

Several studies have analyzed the expression of collagen type I in different tissues in experimental models of obesity.[9-11] There is limited information on the behavior of this type of collagen in the heart in obese animals. Although Carroll et al.[12] have shown elevated myocardial collagen type I in obese

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rabbits fed a high-fat diet for 12 weeks, a previous study by our group, Silva et al.,[13] found decreased cardiac collagen type I in obese rats fed an unsaturated high-fat diet for 30 weeks.[13] The mechanisms responsible for the decreased myocardial collagen type I, however, were not studied.

One of the possible mechanisms involved in myocardial type I collagen regulation is the increased leptin hormone.[5,14-16] Supporting this hypothesis, most studies *in vitro* have shown that leptin increases MMP-2 activity,[5,15,16] which is involved in the degradation of collagen type I. Therefore, the purpose of this study was to test the hypothesis that the reduction in myocardial collagen type I, associated with increased activity of MMP-2, is linked to elevation of leptin in obese rats.

Materials and methods

Animals and Experimental Protocol

After one week for acclimatization, 30-day-old male Wistar rats were randomly assigned, by lottery, to one of two groups: control (n = 20) and obese (n = 21). The sample size used in this study was based on the literature and on our previous studies.[13,17-19] The control group was fed standard rat chow (RC Focus 1765, Agroceres®, Rio Claro, SP, Brazil) containing 12.3% of kilocalories from fat, 57.9% from carbohydrates, and 29.8% from protein, whereas the obese group was fed one of four alternating high-fat diets (RC Focus 2413, 2414, 2415, and 2416, Agroceres®, Rio Claro, SP, Brazil) containing 49.2% of kilocalories from fat, 28.9% from carbohydrates, and 21.9% from protein. The four high-fat diets had the same nutritional composition, except flavoring additives, namely, cheese, bacon, chocolate, or vanilla. Each diet was changed daily, and the rats were maintained on their respective diets for 34 consecutive weeks. The high-fat diet was calorically rich compared to the standard diet (3.65 kcal/g vs. 2.95 kcal/g) due to the higher fat composition. The high-fat diet consisted of saturated and unsaturated fatty acids, which provided 20% and 80% of the fat-derived calories, respectively.

Rats were housed in individual cages in an environmentally controlled clean-air room at 23 (± 3)ºC with a 12-hour light/dark cycle and 60% (± 5%) relative humidity. All experiments and procedures were conducted according to the Guide for the Care and Use of Laboratory Animals, published by the National Research Council (1996),[20] and they received approval from the Botucatu Medical School Ethics Committee (UNESP, Botucatu, SP, Brazil, Protocol: 861-2011).

Animal general characteristics and metabolic and endocrine profiles

Animal general characteristics and metabolic and endocrine profiles were evaluated according to the following parameters: body weight, body fat (BF), adiposity index (AI), food consumption, caloric intake, feed efficiency, glucose tolerance, insulin resistance, serum lipid profile, and serum leptin and insulin concentrations. A criterion based on the AI was used to determine obesity. The AI is an easy and consistent method used by several authors to evaluate the amount of BF in rodents.[21-23]

The animals' food intake and body weight were measured weekly. Caloric intake was determined by multiplying the energy value of each diet (g × kcal) and weekly food intake. To analyze the animals' capacity to convert consumed food energy to body weight, feed efficiency was calculated, dividing the total body weight gain (g) by total energy intake (Kcal).

Glucose tolerance was evaluated by the oral glucose tolerance test one week before euthanasia. After a 6-hour fast, blood samples were collected by puncture from the tail tip at baseline and after intraperitoneal administration of 30% glucose solution (Sigma-Aldrich®, St Louis, MO, USA), equivalent to 2.0 g/kg body weight. Blood glucose concentrations were analyzed at 0 minutes (baseline) and after 15, 30, 60, 90, and 120 minutes of glucose infusion, using a handheld glucometer (Accu-chek Advantage; Roche Diagnostics Co., Indianapolis, IN, USA). Glucose intolerance was assessed by the area under the curve (AUC) for glucose.

At the end of the experimental protocol, after fasting for 12 hours, animals were anesthetized (sodium pentobarbital 50 mg/kg, intraperitoneal injection), decapitated, and thoracotomized; the adipose tissue fat pads were dissected and weighed. BF was calculated as the sum the weight of the individual fat pads as follows: BF = epididymal fat + retroperitoneal fat + visceral fat. AI was calculated by the following formula: AI = (BF/final body weight) × 100. Blood samples were collected in heparinized tubes, centrifuged at 3,000 × g for 10 minutes at 4°C, and stored at −80°C for later analysis. Triacylglycerol, total cholesterol, and high- (HDL) and low-density lipoprotein (LDL) concentrations were determined using specific kits (BIOCLIN®, Belo Horizonte, MG, Brazil). Hormone levels of leptin and insulin were determined by enzyme-linked immunosorbent assay (ELISA), using commercially available kits (EMD Millipore Corporation, Billerica, MA, USA).

The homeostatic model assessment of insulin resistance (HOMA-IR) was used as an insulin resistance index, calculated according to the formula: HOMA-IR = [fasting glucose (mmol/L) × fasting insulin (μU/mL)]/22.5.[24]

Cardiovascular profile

The cardiovascular profile of the animals was also assessed according to the following parameters: systolic blood pressure (SBP); cardiac tissue morphology; myocardial protein expression of collagen type I, TIMP-1, TIMP-2, and leptin; and MMP-2 activity.

Systolic blood pressure

At the end of the experiment, one week before euthanasia, SBP was measured in conscious rats using the non-invasive tail-cuff method with an electro-sphygmomanometer, Narco BioSystems® (International Biomedical, Austin, TX, USA).[25] Arterial pulsations were recorded in a computerized data acquisition system (Biopac Systems Inc., CA, USA). The average of two readings was recorded for each measurement.

Morphological study

The hearts were removed and dissected following euthanasia and thoracotomy. Atria, left and right ventricles weights, and their respective relations with final body weight were determined to evaluate the presence of cardiac remodeling (i.e., presence or absence of hypertrophy).

Myocardial protein levels of collagen type I, TIMP-1, TIMP-2, and leptin

Left ventricular tissue was analyzed by Western Blot to quantify protein levels of collagen type I, TIMP-1, TIMP-2, and leptin. Six samples were used in each group to ensure that all samples were analyzed in the same electrophoresis run in order to avoid inter-gel variations. Briefly, frozen left ventricle samples were homogenized using a Polytron device (Ika Ultra TurraxTM T25 Basic, Wilmington, USA) in a lysis buffer containing 10 mM Tris, pH 7.4, 100 Mm NaCl, 1 mM EDTA, 1 Mm EGTA, 1% Triton X-100, 10% glycerol, 0.1% sodium dodecyl sulfate (SDS), 0.5% deoxycholate, and phosphatase and protease inhibitors (Sigma-Aldrich). The homogenate was centrifuged at 4ºC for 20 minutes at 12,000 rpm. The supernatant was collected, and total protein content was determined by the Bradford Method. Samples (50 μg) were subjected to SDS-polyacrylamide gel electrophoresis (SDS-PAGE) in polyacrylamide gels (6% or 10% depending on molecular protein weight). After electrophoresis, proteins were electro-transferred to nitrocellulose membrane (BioRad Biosciences; NJ, USA). The blotted membrane was then blocked (5% nonfat dry milk, 10 mmol/L Tris-HCl, pH 7.6, 150 mmol/L NaCl, and 0.1% Tween 20) for 2 hours at room temperature and incubated with specific antibodies overnight at 4ºC. Subsequently, the blotted membrane was incubated for 1.5 hours at room temperature with peroxidase-conjugated anti-rabbit or anti-mouse secondary antibody (1:10,000 dilution), and then incubated with enhanced chemiluminescence (Amersham Biosciences, NJ, USA) and detected by autoradiography. Quantification analysis of the blots was performed using Scion Image software (Scion, based on NIH Image). Mouse monoclonal antibodies to collagen type I (1:10,000), TIMP-2 (1:1,000), and leptin (1:1,000) and rabbit monoclonal antibodies to TIMP-1 (1:1,000) and β-actin (1:1,000) were obtained from Abcam (Cambridge, USA) and Cell Signaling (Danvers, USA), respectively. Targeted bands were normalized to the expression of cardiac β-actin.

Myocardial metalloproteinase-2 activity

Myocardial MMP-2 activity was determined as reported by Tyagi et al.[26]. Six samples were used in each group to ensure that all samples were analyzed in the same electrophoresis run in order to avoid inter-gel variations. In brief, left ventricular tissues were homogenized in a buffer containing the following: Tris 50 mM, pH 7.4, NaCl 0.2 M, Triton-X 0.1% and CaCl2 10 mM. The homogenate was centrifuged at 4ºC for 20 minutes at 12,000 rpm. The supernatant was collected, and total protein content was determined by the Bradford Method (Bradford 1976). Samples were diluted in application sample buffer consisting of 0.5 M Tris, pH 6.8, 100% glycerol, and 0.05% bromophenol blue. The samples were loaded into the wells of 8% SDS-polyacrylamide containing 1% gelatin. Electrophoresis was carried out in a Bio-Rad apparatus at 80 V for 2 hours. The gel was removed and washed two times with 2.5% Triton-X-100 and then washed with 50 mM Tris pH 8.4. The gel was then incubated at 37°C overnight in an activation solution consisting of 50 mM Tris, pH 8.4, 5 mM CaCl2 and ZnCl2. Staining was performed for 2 hours with 0.5% Coomassie blue, and destaining was performed in 30% methanol and 10% acetic acid until clear bands were observed over a dark background. The gels were photographed, and the intensity of gelatinolytic action (clear bands) was analyzed in UVP, UV, and a White Darkhon image analyzer.

Statistical analysis

Prior to statistical analysis, all data were tested for normality using the Shapiro-Wilk test. Results were expressed as mean ± standard deviation and submitted to Student's t-test for independent samples. Pearson correlation was used to evaluate the association between the variables collagen I, MMP-2, TIMP, and leptin. All statistical analyses were performed using SigmaStat for Windows (Version 3.5). The level of significance considered was 5 % ($\alpha = 0.05$).

Results

Animal general characteristics

The general animal characteristics are displayed in Table 1. Final body weight; deposits of epididymal, retroperitoneal, and visceral fat; total BF; and AI were significantly higher in the obese group than in the control group. During the experimental period, animals in the obese group ate less food and calories than those in the control group; however, the feed efficiency was higher in obese animals.

Metabolic and endocrine profiles

The metabolic and endocrine profiles are summarized in Figure 1. Long-term obesity induced by high fat led to significant metabolic and hormonal changes. There was a significant increase in the glucose AUC, as well as in insulin and leptin levels in the obese group, compared to control. The obese animals presented increased AUC, serum insulin, and HOMA-IR. The serum measurements of glucose, triacylglycerol, total cholesterol, HDL, and LDL were similar between groups.

Systolic blood pressure and cardiac morphological profile

Table 2 shows that SBP was higher in the obese animals, and there were no significant differences between the groups for any of the studied parameters concerning morphological profile, except for the right ventricle, suggesting that obesity did not trigger left ventricular hypertrophy.

Table 1 – Animal general characteristics

Variables	Groups		
	Control (n = 20)	Obese (n = 21)	p value
IBW (g)	151 ± 11	151 ± 11	0.290
FBW (g)	480 ± 51	534 ± 58	0.009
Epididymal fat (g)	9.3 ± 2.3	14.2 ± 3.4	< 0.001
Epididymal fat/100gFBW	1.9 ± 0.5	2.7 ± 0.6	< 0.001
Retroperitoneal fat (g)	10.5 ± 3.3	21.7 ± 5.9	< 0.001
Retroperitoneal fat/100gFBW	2.2 ± 0.7	4.1 ± 1.1	< 0.001
Visceral fat (g)	6.3 ± 1.4	11.2 ± 4.2	< 0.001
Visceral fat/100gFBW	1.3 ± 0.3	2.1 ± 0.8	< 0.001
BF (g)	26.1 ± 6.2	47.2 ± 12.3	< 0.001
Adiposity index	5.6 ± 0.9	8.8 ± 1.6	< 0.001
Food consumption (g/day)	22.8 ± 2.1	17.0 ± 2.3	< 0.001
Caloric intake (kcal)	67.4 ± 6.3	62.1 ± 8.2	0.03
Feeding efficiency (%)	2.1 ± 0.2	2.7 ± 0.2	< 0.001

Values are means ± SD. IBW: initial body weight; FBW: final body weight; BF: body fat. Student's t-test.

Myocardial protein levels of collagen type I, TIMP-1, TIMP-2, and leptin

Figure 2 reveals that obesity promoted a reduction in protein levels of collagen type I, TIMP-1 and TIMP-2; however, there was an increase in leptin protein levels in the obese group compared to the control group.

Myocardial MMP-2 activity

Figure 3 shows the identification of two weak bands of degradation corresponding to MMP-2 in electrophoresis gel: inactive MMP-2 (pro-MMP-2) with a molecular weight of approximately 72 kDa and active MMP-2 with a molecular weight of approximately 64 kDa. Between the two bands mentioned, it was possible to identify the strong band of MMP-2 intermediate degradation. There was a significant increase in MMP-2 in the obese animals.

Linear association between cardiac variables

Table 3 reveals that there was a significant correlation between the decrease in collagen type I and increased MMP-2 activity, as well as between the elevation of MMP-2 activity and leptin. Moreover, a correlation was observed between the increase in MMP-2 and the decrease in TIMP-1 and -2, as well as between decreased TIMP-1 and increased leptin protein levels. There was no significant correlation between decreased TIMP-2 and increased leptin.

Discussion

This study aimed to investigate whether a reduction in collagen type I is associated with increased MMP-2 activity and elevated levels of leptin in the myocardium of obese rats. The main results confirmed this hypothesis.

The continuous feeding of a high-fat diet was effective to promote obesity in 34 weeks, given that the rats showed higher levels of body and fat weight and AI compared to rats fed a standard diet; these data are in agreement with other studies.[27,28]

The major causes of obesity are a more abundant supply of food, higher intake of energy-dense, palatable food, and reduction in energy expenditure. The high-fat diet used in the current study was rich in mono- and polyunsaturated fatty acids with an energy content of 3.65 kcal/g, while the standard diet fed to the control group consisted of 2.95 kcal/g, generating a difference of 24% in caloric content. Authors have shown that consumption of a high-fat diet promotes less satiety and thus increased food intake.[29]

These data differ from our results since the obese animals ate a lower amount of food and calories compared to control. However, feed efficiency was higher in obese rats, likely due to the thermic effect of food. Dietary fat requires less energy (2% – 3%) to be metabolized, and the excessive fat is thus easily deposited in the form of triglycerides in adipocytes, resulting in obesity.[30]

Several studies have reported some comorbidities related to experimental obesity,[29,31,32] such as glucose intolerance, insulin resistance, dyslipidemia, hyperinsulinemia, hyperleptinemia, and arterial hypertension. In the present study, the obese animals exhibited higher AUC in the oral glucose tolerance test and higher serum insulin levels than controls, indicating that obesity promoted glucose intolerance and hyperinsulinemia. Glucose intolerance, associated with increased serum insulin, indicated that obese rats presented resistance to the action of insulin. These results are further supported by the increased HOMA-IR in obese rats. All these findings are in accordance with previous reports that used rats fed a high unsaturated fat diet.[13,27,28,33] Different studies

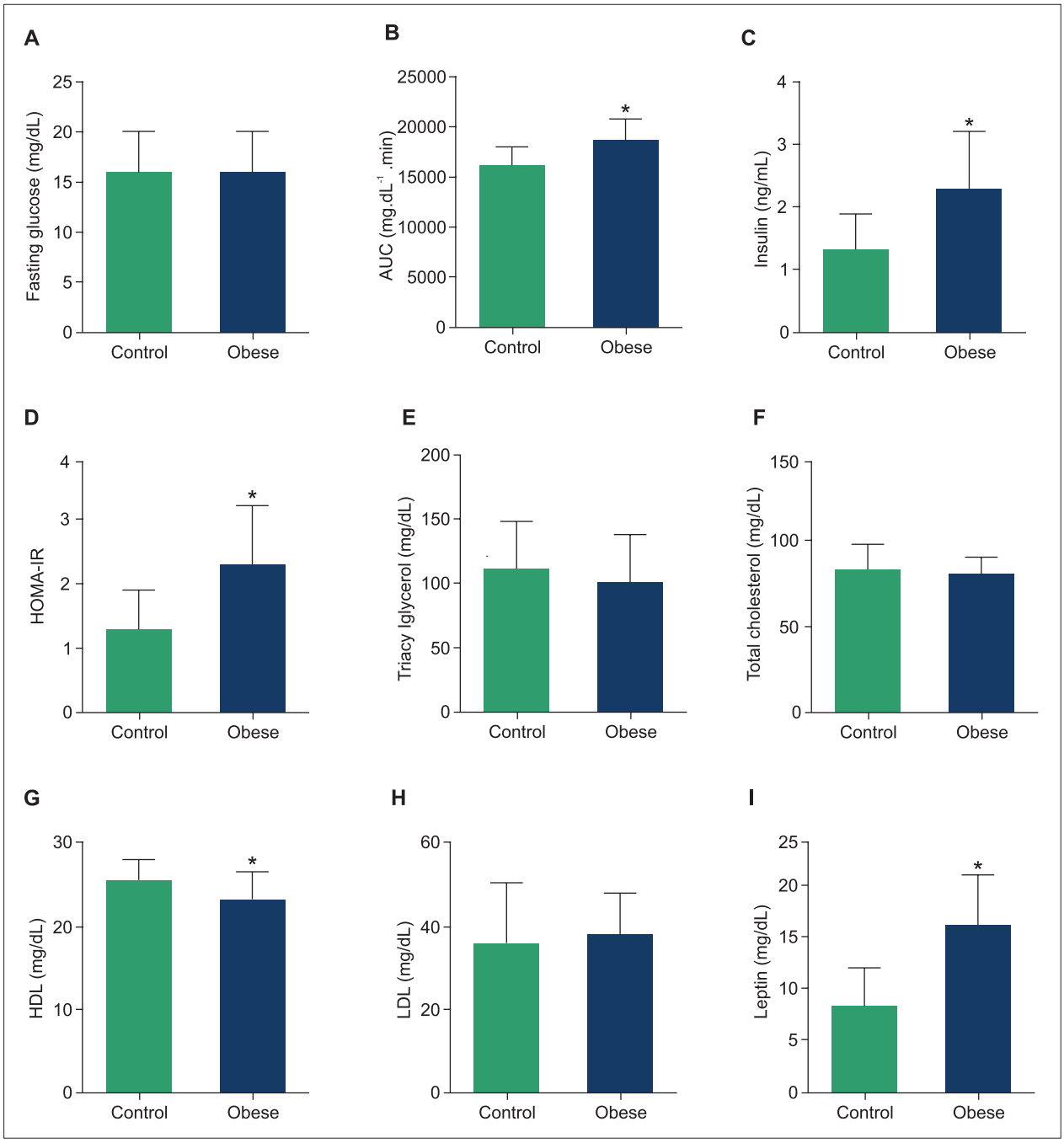

Figure 1 – *Metabolic and hormonal profile. (A) Fasting glucose, (B) Area under curve (AUC) of intraperitoneal glucose tolerance test, (C) insulin, (D) homeostasis model assessment of insulin resistance (HOMA-IR), (E) triacylglycerol, (F) total cholesterol, (G) high-density lipoprotein (HDL), (H) low-density lipoprotein (LDL) and (I) leptin in control and obese rats. (n= 15 – 21 per group). Data are presented as mean ± SD; Student's t-test. *: p < 0.05.*

have shown that high-fat diet-induced obesity leads to dyslipidemia,[19,34,35] whether due to changes in triacylglycerol, LDL, or HDL, in agreement with our study, which observed decreased serum HDL levels. Leptin is a hormone produced by adipose tissue, which participates in energy balance, by regulating food intake and the oxidation of lipids,[36] and in the biology of collagens.[5,14-16]

Concerning the effects of obesity on the cardiovascular system, obesity did not promote left ventricular cardiac remodeling. However, SBP increased in obese animals. As SBP control involves the neurohumoral system, such as the sympathetic nervous system and the renin-angiotensin-aldosterone system, which are increased in obesity,[37] it may be inferred that the neurohumoral system is activated in

Table 2 – Systolic blood pressure and cardiac morphological profile

Variables	Groups		
	Control (n = 20)	Obese (n = 21)	p value
SBP	127 ± 11.0	134 ± 12.0	0.04
Heart (g)	1.10 ± 0.10	1.17 ± 0.13	0.06
ATW (g)	0.093 ± 0.018	0.094 ± 0.021	0.80
LVW (g)	0.81 ± 0.09	0.82 ± 0.10	0.62
RVW (g)	0.22 ± 0.03	0.24 ± 0.03	0.04
ATW/FBW. $^{10-3}$	0.20 ± 0.03	0.18 ± 0.03	0.14
LVW/FBW. $^{10-3}$	1.72 ± 0.11	1.71 ± 0.12	0.44
RVW/FBW. $^{10-3}$	0.48 ± 0.09	0.47 ± 0.05	0.64

Values are means ± SD. SBP: systolic blood pressure; LVW: left ventricle weight; RVW: right ventricle weight; ATW: atrial weight; FBW: final body weight; ATW/FBW; LVW/FBW; RVW/FBW ratio; 10^{-3} = 0.001. Student's t-test.

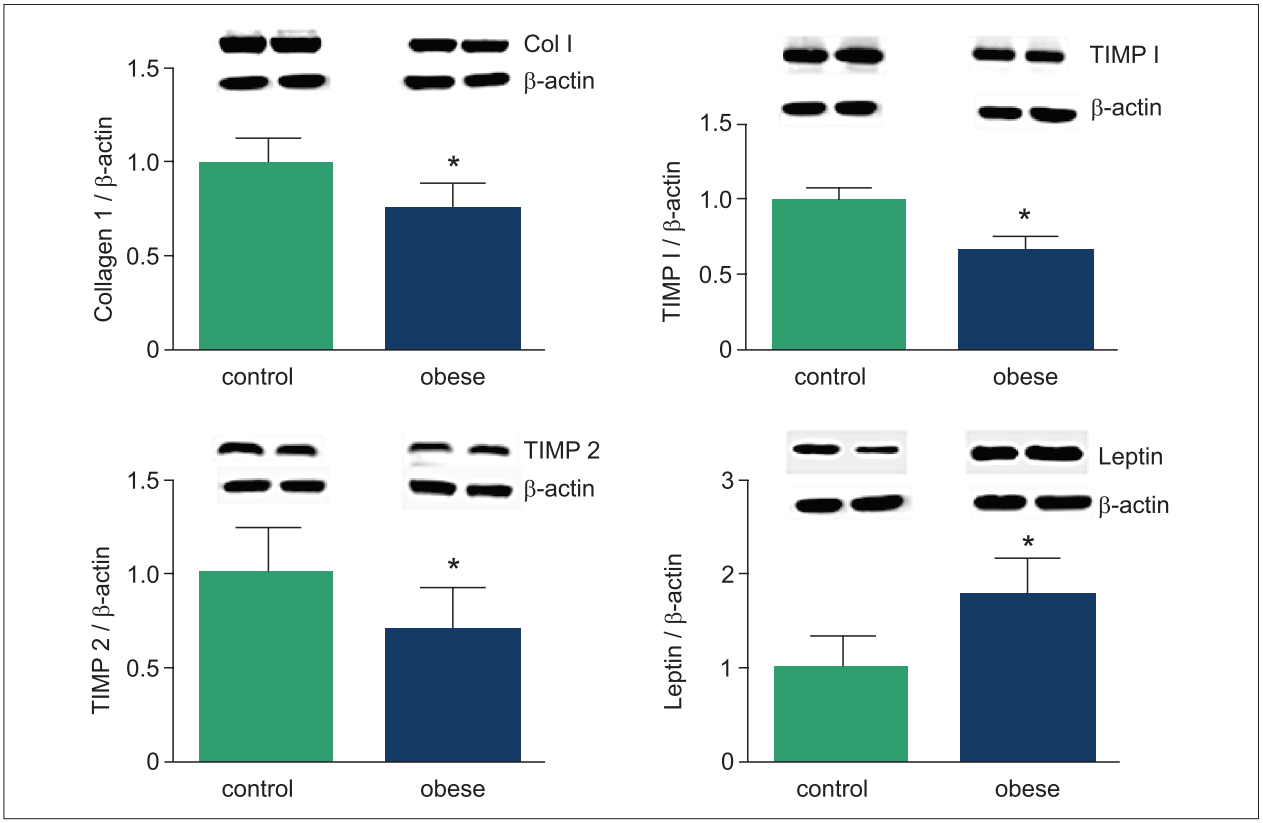

Figure 2 – *Representative western blots and quantification of myocardial collagen type I, TIMP-1, TIMP-2, and leptin from control and obese rats (n = 6 per group). Western blot bands were normalized to β-actin. Data are presented as mean ± SD. Student's t-test. *: p < 0.05.*

obese animals. This finding is consistent with some previous researchers who investigated SBP in obese animals fed a high-fat diet[38] and in disagreement with others.[27]

The main objective of this study was to investigate whether increased MMP-2 activity by leptin is responsible for the reduction in myocardial collagen type I in obese rats. The results of this investigation indicated that there was a reduction of protein levels of collagen type I accompanied by an increase in MMP-2 activity and leptin protein levels and a decrease in TIMP-1 and TIMP-2 protein levels in the heart. As previously stated, few studies have evaluated the behavior of collagen type I in the myocardium of animals with obesity induced by a high-fat diet; while Carroll[12] and Martínez-Martínez[39] found an increase, Silva et al.[13] found a decrease in myocardial type I collagen.

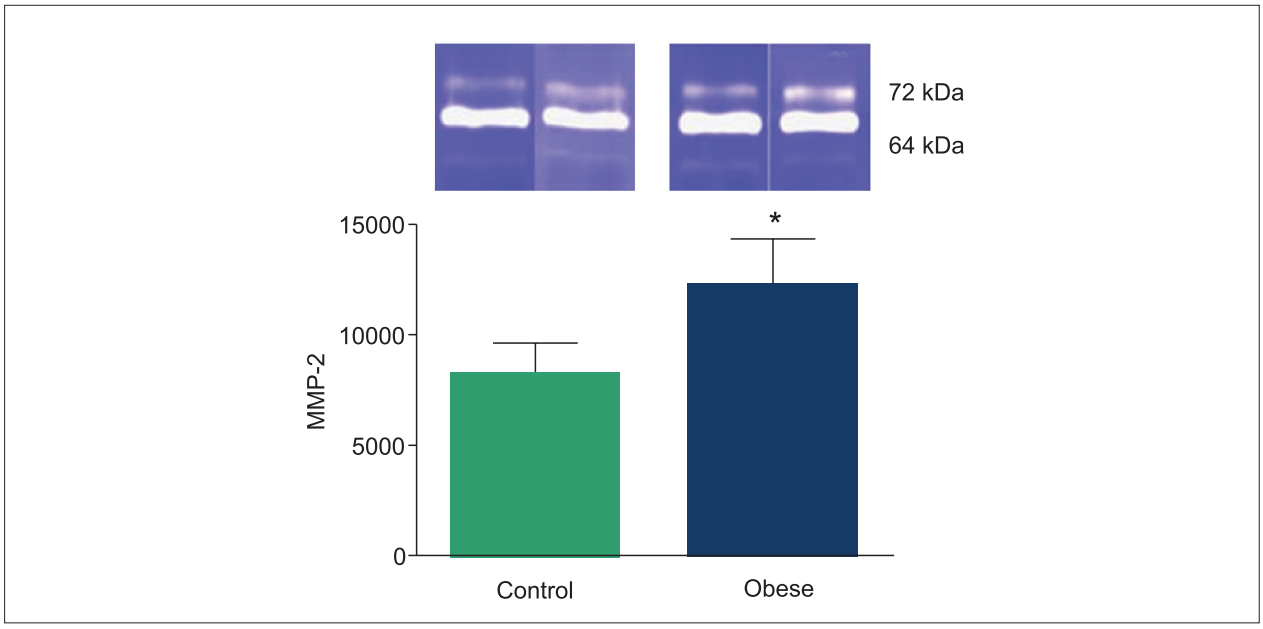

Figure 3 – *Relation between active (active and intermediate active) and inactive MMP-2 in control and obese rats (n = 6 per group). Inactive MMP-2 = 72 kDa and active MMP-2 = 64 kDa. Data expressed as mean ± standard deviation. Student's t test. *: p < 0.05.*

Table 3 – Linear association between cardiac variables

Association	Coefficient of correlation	p value
Collagen I × MMP-2	−0.723	0.008
MMP-2 × Leptin	0.766	0.004
MMP-2 × TIMP-1	−0.815	0.001
MMP-2 × TIMP-2	−0.597	0.040
TIMP-1 × Leptin	−0.656	0.020
TIMP-2 × Leptin	−0.273	0.390

MMP: metalloproteinase; TIMP: tissue inhibitor of metalloproteinases. Pearson's correlation test. Control, n = 6 and obese, n = 6.

The changes in myocardial collagen may result from an elevation of the synthesis or decreased degradation. The data from this study showed that the degradation of collagen type I may have prevailed in obese rats, as there was a significant association between reduced collagen type I and increased MMP-2 activity. Although some studies show that the increase in MMP-2 activity enhances collagen synthesis,[40] most information in the literature indicates the opposite behavior, i.e., the increase in MMP-2 activity promotes the degradation of collagen type I.[5,39,41] Although Martínez-Martínez et al.[39] and Zibadi et al.[14] have found that leptin reduced the MMP-2 activity *in vitro*, other studies have shown that leptin increases MMP-2 activity,[5,15,16] and our results further support this latest finding. Thus, the elevation of MMP-2 may have been consequent to increased cardiac leptin, because there was a close association between these two variables, although these findings do not necessarily reflect a cause-and-effect relationship. Nevertheless, several studies have reported a direct relation between leptin and MMP-2 activity in cardiomyocytes.[5,15,16]

Despite the fact that increased MMP activity is associated with elevated cardiac leptin, another modifying factor of this enzyme is the behavior of TIMP. The results of the present study showed a decrease in TIMP-1 and TIMP-2 protein levels in obese animals, which may have influenced the increase of MMP-2, given that there was a significant association between MMP-2 and TIMP-1 and TIMP-2. The reduced TIMP-1 may be related to the increase in leptin, as there was a significant association between these variables. This finding is consistent with Schram et al., who found a substantial reduction in TIMP-1 mRNA expression after the elevation of leptin concentrations in cultured cardiac cells.[15] To our knowledge, this is the first study that evaluated the association between collagen type I, leptin, MMP-2, and TIMP-1 and TIMP-2 in the myocardium of obese animals fed an unsaturated high-fat diet. However, further analyses are required to confirm the cause-and-effect relationship.

Conclusion

The findings confirmed the hypothesis that the reduction in collagen type I is associated with increased MMP-2 activity, which is in turn linked to an elevation of leptin in the myocardium of obese rats. This study allowed for evaluation of mediators involved in cardiac remodeling, which can trigger impaired heart function in obesity. The identification of these deleterious factors may enable possible therapeutic targets.

Author contributions

Conception and design of the research: Silva-Bertani DCT, Padovani CR, Cicogna AC; Acquisition of data: Silva-Bertani

DCT, Vileigas DF, De Tomasi LC, Campos DHS, Deus AF, Freire PP, Alves CAB; Analysis and interpretation of the data: Silva-Bertani DCT, Vileigas DF, Mota GAF, Souza SLB, De Tomasi LC, Campos DHS, Deus AF, Freire PP, Alves CAB, Cicogna AC; Statistical analysis: Silva-Bertani DCT, Padovani CR, Cicogna AC; Obtaining financing: Silva-Bertani DCT, Cicogna AC; Writing of the manuscript: Silva-Bertani DCT, Vileigas DF, Mota GAF, Souza SLB, Cicogna AC; Critical revision of the manuscript for intellectual content: Silva-Bertani DCT, Vileigas DF, Mota GAF, Souza SLB, Cicogna AC.

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 master submitted by Danielle Cristina Tomaz da Silva-Bertani, from Faculdade de Medicina de Botucatu (UNESP).

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Faculdade de Medicina de Botucatu under the protocol number 861-2011. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

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Original Article

Assessing Dynamic Atrioventricular Conduction Time to RR-interval Coupling in Athletes and Sedentary Subjects

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Abstract

Background: **Atrioventricular conduction time (*AVCT*) is influenced by autonomic input and subject to physiological remodeling.**

Objective: **To evaluate beat-by-beat *AVCT* and *RR-interval* variability in athletes and healthy sedentary subjects.**

Methods: **Twenty adults, including 10 healthy sedentary (Controls) and 10 elite long-distance runners (Athletes), age, weight and height-adjusted, underwent maximal metabolic equivalent (MET) assessment, and 15-min supine resting ECG recording seven days later. The interval between P-wave and R-wave peaks defined the *AVCT*. Mean (M) and standard deviation (SD) of consecutive *RR-intervals (RR)* and coupled *AVCT* were calculated, as well as regression lines of RR vs. *AVCT (RR-AVCT)*. Concordant AV conduction was defined as positive *RR-AVCT slope* and discordant otherwise. A multivariate linear regression model was developed to explain MET based on *AVCT* and *RR-interval* variability parameters. Significance-level: 5 %.**

Results: **In Athletes, *M-RR* and *SD-RR* values were higher than in Controls, whereas *M-AVCT* and *SD-AVCT* were not. *RR-AVCT* slopes were, respectively, 0.038 ± 0.022 and 0.0034 ± 0.017 ($p < 0.05$). Using a cut-off value of 0.0044 (AUC 0.92 ± 0.07; $p < 0.001$), *RR-AVCT* slope showed 100% specificity and 80% sensitivity. In a multivariate model, *SD-RR* and *RR-AVCT* slope were independent explanatory variables of MET (F-ratio: 17.2; $p < 0.001$), showing 100% specificity and 90% sensitivity (AUC 0.99 ± 0.02; $p < 0.001$).**

Conclusion: **In elite runners, *AVCT* to *RR*-interval dynamic coupling shows spontaneous discordant *AV* conduction, characterized by negative *AVCT* vs. *RR*-interval regression line slope. *RR*-intervals standard deviation and *AVCT* vs. *RR*-interval regression line slope are independent explanatory variables of MET (Arq Bras Cardiol. 2020; 115(1):71-77)**

Keywords: **Athletes; Adults; Resistance Training; Physical Fitness; Ventricular Remodeling; Sedentarism; Electrocardiography/methods; Heart Ventricles; Ventricular Function.**

Introduction

Cardiac adaptation secondary to physical fitness is reflected in mechanical, electrical and autonomic remodeling of the heart, as a consequence of repeated high-demand activities. Well-trained athletes often have slight ventricular mass gain, increased ECG wave amplitude, early repolarization, reduction of resting heart rate and increased heart rate variability, related to the conditioning status.[1-7]

Particularly, most autonomic heart remodeling in well-conditioned athletes is a consequence of increased vagal tonus and reduced sympathetic stimulation over the sinus and the atrioventricular (AV) nodes.[1,6] Although increased vagal tonus may be straightforwardly detected by measuring the resting heart rate, to differentiate between increased parasympathetic activity over the sinus node and the AV node on surface ECG may not be that simple.

Frequently, high-demand athletes have atrioventricular (AV) node remodeling, characterized by several degrees of AV conduction block, non-sinus low atrial or junctional rhythm and, more rarely, complete AV block.[8-10] Those AV conduction disturbances depend on physical conditioning status and are related not only to increased parasympathetic activity over the AV node, but also to secondary remodeling of the AV node fibers and cell-to-cell coupling.[11-13]

Although *AV* conduction disturbances have been repeatedly documented in athletes, the dynamic *AV* conduction adaptation to the cardiac cycle in this population still needs clarification. In the general population, *AV* duration varies dynamically according to *RR-interval* duration, characterizing a concertina-like effect. However, in athletes, autonomic remodeling may influence dynamic *AV* conduction to *RR-interval* adaptation, leading to a distinct behavior of *AV* conduction, in a time-related response to *RR-interval* variation.

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The present study evaluated beat-by-beat *AV* conduction time (*AVCT*) and *RR-interval* variabilities in elite runners and healthy sedentary subjects, at rest, aiming at assessing the effect of physical fitness status on spontaneous *AVCT* to *RR-interval* duration coupling.

Methods

Detailed information about study protocol, Ethics Committee approval, and ECG data acquisition has been described elsewhere.[6] The present study analyzed raw high resolution ECG data from the ECG data bank of the Biomedical Engineering Program, using a novel technique for extraction of atrioventricular conduction time and *RR-intervals*.[14] Data sampling procedure was described elsewhere.[6]

The study population comprised 20 volunteers divided in two groups: the 'Athlete' group, comprising ten elite long-distance runners (≥ 16.0 maximal metabolic equivalents [MET] calculated as the maximal oxygen consumption achieved during stress test divided by 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$, [mean ± SD] 19.5 ± 1.3 MET; aged 25.1 ± 7.1 years), and the 'Control' group, comprising ten male healthy sedentary volunteers (≤ 11.5 MET; 8.7 ± 1.9 MET; aged 29.0 ± 5.4 years). It is worth mentioning that the term 'MET' is employed throughout the text as the maximal metabolic equivalent achieved during stress test. The athletes' training program consisted of six to eight training sessions/week; 90 to 120 min/session; 90 to 110 km/week. The waves and fiducial point detection were carried out on ECG acquired using *XYZ* modified *Frank* leads, in the resting supine position, using low-pass filter at 15 Hz (*Butterworth*, 4th order). For the analysis of the *RR-interval* duration, artefacts and ectopic beats were adequately excluded.[15,16]

The distance between the peak of the *P*-wave and the peak of the *R*-wave in normal beats defined the *PR-peak* interval and was employed to analyze instantaneous *AVCT* adaptation over the cardiac cycle.[14] The *PR-peak* to *RR-intervals* coupling was assessed in a beat-by-beat basis throughout the whole ECG recording, using the lead showing the tallest *P*-wave, usually the *Y* lead. The *RR-interval* was assessed as the time between the peaks of the R-waves of two consecutive normal beats. The *PR-peak* interval was assessed immediately before the second beat of the respective *RR-interval*. For each subject, the mean *(M)* and standard deviation *(SD)* of all consecutive normal *RR-intervals* (*M-RR* and *SD-RR*) and respective *PR-peak* interval (*M-AVCT* and SD-*AVCT*) were calculated. *PR-peak* intervals were correlated to the respective *RR-intervals* and calculated regression line slopes ($RR\text{-}AVCT_{slope}$).

Statistical Analysis

The variables were expressed as mean ± SD or median and interquartile range, when appropriate. Data normality was assessed using Kolmogorov-Smirnov test, and all analyzed variables had their normality assumption accepted. Variables were compared between groups using non-paired Student's t-test. To assess the optimal cut-off values, ROC curves were calculated from the regression line slopes (*AVCT* vs. *RR*-interval) in both groups. A multivariate linear regression model was developed to explain the MET based on significant *AVCT* and *RR-interval* parameters. Pearson's correlation coefficient r was tested for significance (significance level was set at 5%). A concordant AV conduction was arbitrarily defined as *AVCT* and *RR-interval* increased and decreased in the same direction in consecutive cardiac cycles, and discordant otherwise. *AVCT* was assessed as *PR-peak-interval*.

A validation bootstrap resampling procedure applied to the multivariate model was carried out using two different approaches. In the first approach, 1100 replications with replacement were carried out in the whole sample of both groups to assess mean and SD estimates of independent variables. In a second approach, both groups were split in a test group, comprising 67% of subjects of each group, and a validation group, with the remaining 33%. The MET estimated by the multivariate model was employed to classify Controls and Athletes in all sets of bootstrap procedures. Raw ECG signals were processed using custom-made programs written in Matlab R2007a (The MathWorks, Inc) language. Statistical analysis was carried out using MS-Excel 360 (Microsoft Corporation) and Medcalc version 11 (Medcalc Software bvba). The significance level adopted in the statistical analysis was 5%.

Results

The Athletes had significantly higher *M-RR* and *SD-RR* values than the Controls, whereas there were no significant differences between *M-AVCT* and *SD-AVCT* values (Table 1). Examples of subjects from the Control (a) and Athlete (b) groups are shown in Figure 1, where regression lines and respective r of *AVCT* vs *RR-intervals* scatterplots are shown. $RR\text{-}AVCT_{slope}$ values are positive in Controls (Figure 1-a), whereas they are negative in Athletes (Figure 1-b). Overall, $RR\text{-}AVCT_{slope}$ in Controls and Athletes resulted in significant between-groups' differences (Table 1).

Variables showing significant intergroup differences were entered into a multivariate linear regression model, taking MET as the dependent variable in the bootstrap procedure. *SD-RR* ($p = 0.0099$) and $RR\text{-}AVCT_{slope}$ ($p = 0.006$) were independent explanatory variables of MET, showing 90% specificity, 100% sensitivity and 95% total accuracy (Table 2). The average C-statistic in test and validation groups were, respectively, 0.97 ± 0.06 and 0.87 ± 0.13; $p < 0.001$ for both. The multivariate linear regression analysis and respective bootstrap procedures results are summarized in Table 2.

The $RR\text{-}AVCT_{slope}$ values for each group, including interquartile range and 95% confidence intervals (CI) are shown in figure 2-a. Sensitivity, specificity and total accuracy were computed utilizing the optimal cutoff value shown in table 1, and exhibited as inset. To highlight the association between spontaneous decremental conduction and physical status, a regression line of $RR\text{-}AVCT_{slope}$ vs. MET is shown in figure 2-a. It shows a significant correlation ($r = 0.70$; $p < 0.05$) and a negative slope, demonstrating that $RR\text{-}AVCT_{slope}$ decreases as MET increases. An example of a short sequence of sinus beats showing spontaneous decremental conduction, registered during supine rest in a 19 y.o. athlete (MET 16.8 METs) is shown in Figure 2-b.

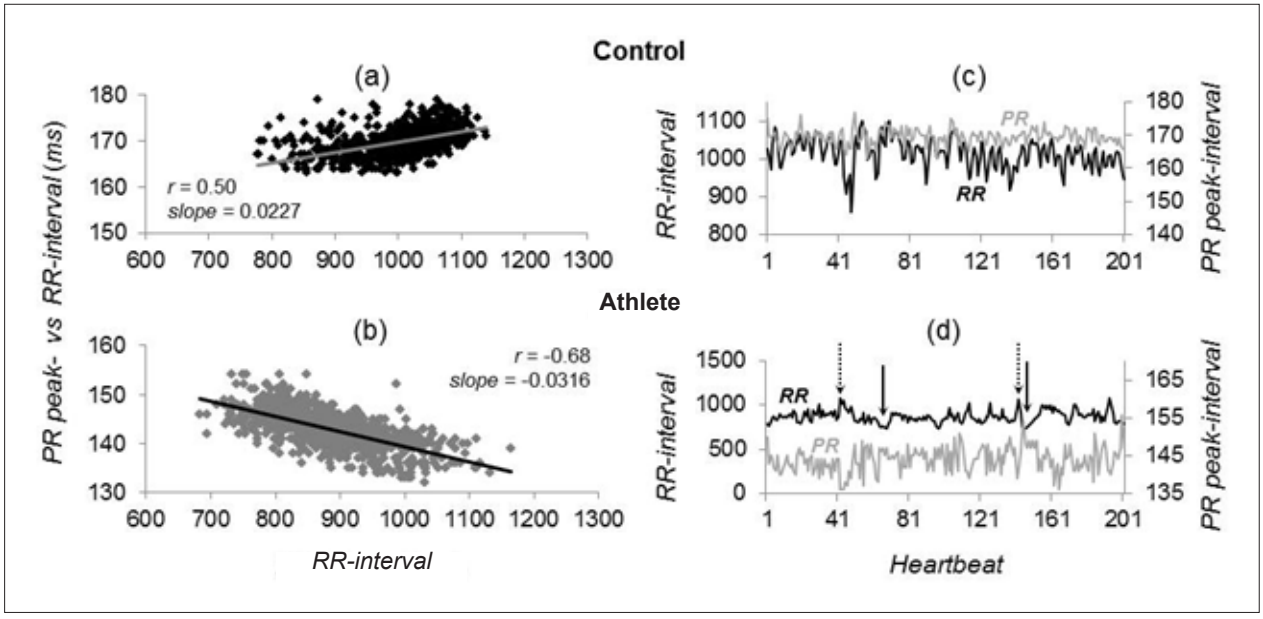

Figure 1 – *Scatterplot and regression line of beat-by-beat RR-interval as a function of respective PR-peak interval of a 30 y.o. Control subject (a) and a 19 y.o. Athlete (b). Two hundred heartbeat sequences of respective RR- and PR-peak intervals series are shown in (c) and (d). In (a), PR-peak interval increases as RR interval increases (positive slope: 0.0227; r = 0.50; p < 0.01), clearly observed in (c) (spontaneous concordant condition). Conversely, in (b), PR-peak interval decreases as RR interval increases (negative slope: -0.0316; r = -0.68; p < 0.01). In (d), note periods of reciprocal variation in RR- and PR-peak intervals (spontaneous discordant conduction): PR-peak interval shortens as RR-interval increases (dotted arrow) and PR-peak interval increases as RR-interval shortens (decremental conduction, solid arrow) (see text for details).*

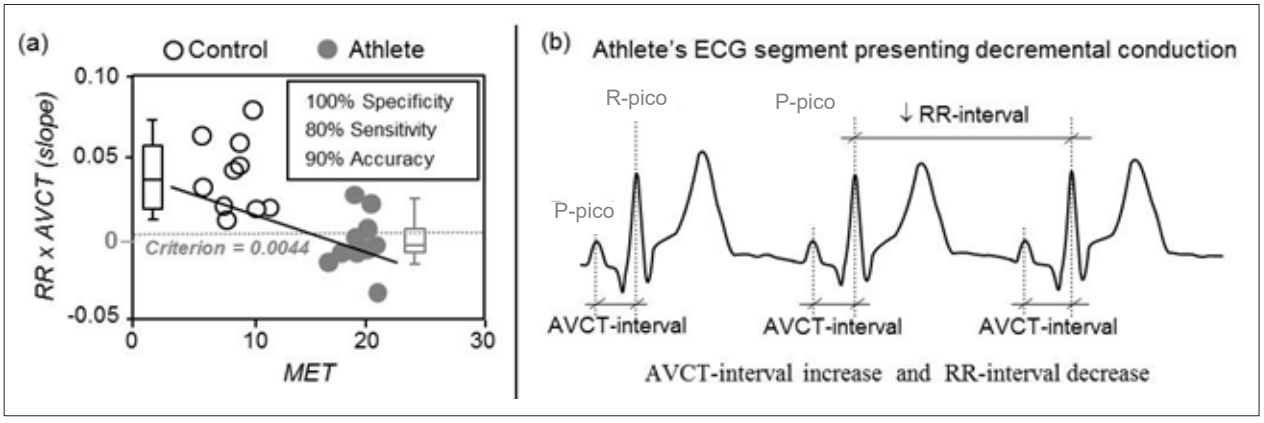

Figure 2 – *(a) Regression line slope values of pooled AVCT vs. mean RR-intervals (RR-AVCTslope) as a function of VO2 consumption expressed as maximal metabolic equivalent (MET) achieved during stress test and respective boxplot. Note that RR-AVCTslope tends to be more negative as physical conditioning status increases (grey dots), when compared to sedentary individuals (white dots). Box-plots showing median, interquartile range and 95% confidence intervals are shown in the vicinity of the respective group points. Specificity, sensitivity and accuracy values were computed utilizing RR-AVCTslope = 0.0044 as a cut-off criterion. (b) Illustration of 19 y.o. Athlete's ECG segment depicting a sequence of normal sinus beats showing AVCT lengthening as RR-interval decreases, indicating AV decremental conduction. Note P-wave and R wave peaks taken as the fiducial points for assessment of the PR-peak interval. AVCT was assessed as PR peak interval. AVCT – atrioventricular conduction time (see text for details).*

Discussion

Atrial ventricular conduction is the most important determinant of the *PR-interval* duration, which undergoes dynamic fluctuations depending on autonomic and health statuses, age, instantaneous HR, medications, stance and respiratory frequency.[17] The evaluation of the *PR-interval* by using either *P* wave-onset or *P* wave-peak approaches as fiducial points has been shown to provide accurate and precise results, and, thus, are both appropriate to assess *AVCT* inter-beat variations.[14,17]

In the present study, highly trained longdistance runners and healthy sedentary subjects had their maximal aerobic power assessed, and *AVCT* coupled to the preceding *RR-*

Table 1 – Univariate analyses of studied variables (mean ± SD)

	M-RR	*SD-RR*	*M-AVCT*	*SD-AVCT*	*RR-AVCT$_{slope}$*
Control group (mean ± SD)	853.9 ± 94.0	44.5 ± 10.1	134.0 ± 17.7	2.8 ± 1.1	0.0376 ± 0.0219
Athlete group (mean ± SD)	1079.1 ± 207.9	76.4 ± 21.0	143.3 ± 27.6	3.8 ± 2.2	-0.0034 ± 0.0172
p Significance level	0.0084	0.0008	0.3820	0.2032	0.002
ROC statistics					
Area under the ROC curve (AUC)	0.89	0.9	0.56	0.61	0.92
Standard Error	0.07	0.08	0.14	0.14	0.06
95% Confidence Interval	0.67–0.98	0.68–0.98	0.32–0.78	0.37–0.82	0,71–0.99
z statistic	5.5	5.2	0.4	0.8	6.7
p Significance level (area=0.5)	< 0.0001	< 0.0001	0.6721	0.4177	< 0.0001
Cut-off value	917.3	60.9	124.1	3.8	0.0044
Specificity	80 %	100 %	40 %	50 %	100 %
Sensitivity	80 %	80 %	90 %	80 %	80 %
Accuracy	80 %	90 %	65 %	65 %	90 %

M-RR: mean of all normal RR-intervals; SD-RR: standard deviation of all normal RR-intervals; M-AVCT: mean of PR-peak intervals respective to normal RR-intervals; SD-AVCT: standard deviation of PR-peak intervals respective to normal RR-intervals; RR-AVCTslope: slope of the linear regression line between PR-peak intervals and respective RR interval

Table 2 – Multivariable explanatory model of the maximal VO_2 consumption; 1100 bootstrap resampling procedure results and Internal validation of the maximal VO2 consumption multivariable explanatory model using bootstrap 2:1 'Test' vs 'Validation' procedure results

	Multivariate model		Bootstrap procedure		Bootstrap test-validation	
Model Variables	**Coefficients ±**	***p***	**Coefficients ±**	***p***	**Coefficients ±**	***p***
PR to RR slope (15 Hz)	-100.36 ± 31.97	0.006	-105.76 ± 33.93	0.0009	-101.42 ± 29.39	0.0003
SD RR	0.115 ± 0.040	0.0099	0.115 ± 0.041	0.003	0.115 ± 0.036	0.0007
Constant	8.88		8.75 ± 3.22	0.003	8.85 ± 2.83	0.0009
ROC statistics					Test group	Validation group
Area under the ROC curve (AUC)	0.99		0.99		0.97	0.87
Standard Error	0.02		0.02		0.06	0.13
95% Confidence Interval	0.94–1.00		0.94–1.00		0.85–1.00	0.61–1.00
z statistic	42.1		42.1		16.7	6.5
p Significance level (area=0.5)	< 0.001		< 0.001		< 0.001	< 0.001
Cut-off value	12.3		12.0		14.2	
Specificity	90%		90%		90.2%	81.0%
Sensitivity	100%		100%		96.7%	80.4%
Total accuracy	95%		95%		93.4%	80.7%

** Procedimento de bootstrap realizado sem restituição. O modelo explicativo multivariado foi calculado no grupo Teste e validado no grupo Validação; ± = (média ± DP).*

interval variability, assessed on resting supine ECG. It was hypothesized that, at rest, AV conduction would be affected by AV remodeling induced by high-end training, causing *AVCT* to *RR-interval* coupling to behave differently from sedentary conditions. In a linear model, *AVCT* to *RR-interval* coupling showed an average negative regression line slope in the Athlete group and, conversely, an average positive slope in the Control group, indicating that AV node remodeling due to training induces decremental conduction enhancement. A potentially distinguished measure of physical fitness, *AVCT* to *RR-interval* regression slope correctly identified 90% all subjects' related physical fitness status. Although identification of decremental conduction in athletes is a common finding, the application of a linear modeling to quantify *AVCT* and its relation to *RR-interval* in highly trained athletes has not been yet reported, to the best of our knowledge.

Previous studies evidenced a high prevalence of Mobitz I 2nd degree AV block in long distance runners at rest.[8-10] In the present study, the occurrence of spontaneous *PR-peak-interval* lengthening related to *RR-interval* shortening was a major finding,

making the average slope negative in the Athletes group (Figure 2b). Conversely to these studies, no blocked *P*-wave was found after a carefully revision of signals. Spontaneous episodes of decremental conduction were frequent in the Athletes group (57.9% of aggregated ECG recording time of Athletes) and rare in the Control group (7.9% of aggregated ECG time recording of Controls). Furthermore, when the *AVCT* vs. *RR-interval* regression slope was plotted against MET, it was observed that the higher the MET, the more negative the RR-$AVCT_{slope}$, showing that spontaneous decremental AV conduction becomes more frequent as physical conditioning status improves (Figure 2a). Noteworthy was that the decremental conduction was more frequently observed when *RR-interval* was larger than 1022.0 ms. *PR-peak* interval reduction related to RR interval increase was also observed in Athletes (Figure 1d). A possible explanation for this latter finding is the common occurrence of vagal-induced spontaneous para-sinus pacing activity.

It has been shown that the resting ECG of endurance athletes may show distinctive features from demographically equivalent healthy sedentary subjects, bearing similarities to those observed in elderly individuals and/or patients with cardiovascular disease.[18] However, in athletes, AV conduction abnormalities have been related to higher parasympathetic activity, differently from the elderly.19 Contemporary studies have shown that athletic training could induce intrinsic physiological adaptations in the conduction system, contributing to the higher prevalence of AV conduction abnormalities.[11-13] The physiological mechanisms by which endurance training induces those intrinsic changes in the cardiac conduction system are limitedly understood and may be multifactorial, but anatomic changes such as atrial and ventricular dilation has been shown to create a mechanical-to-electrical remodeling necessary to cause intrinsic AV electrophysiological adaptations.[7,11]

Limitations of the present study include the sample size of two distinct groups regarding the physical conditioning status. Raw ECG signals were obtained from the ECG database available in the Biomedical Engineering Program (convenience sample). *Peak-P* to *Peak-R* interval was employed as a surrogate of conventional *PR-interval* measurement. Although it has been shown that *Peak-P* to *Peak-R* interval appropriately describes *PR-interval* dynamicity, the duration of the actual *PR-interval* may be larger than the one observed in the present study. It was observed that both *M-AVCT* and *SD-AVCT* were larger among athletes when compared to controls, although statistical significance was not reached. The explanation of this finding may be twofold: i) although *AVCT* variability was expected to be higher among athletes, no true Mobitz I block was in fact observed after careful signal revision. This indicates that *AVCT* variability was expected to be increased to a limited extent, and ii) the sample size of the present sample was designed to determine differences related to ventricular activation total energy[6], thus limiting its statistical power to detect *AVCT* variation between groups. Subjects were kept on supine rest for 10 minutes before ECG acquisition, aiming at preventing orthostatic memory effect on AV conduction to influence AV conduction to *RR-interval* coupling dynamicity, in a controlled temperature and acoustically isolated environment. However, it cannot be completely ruled out that some orthostatic memory effect might still be present. In this study, we observed the occurrence of spontaneous *PR-peak* interval enlargement as *RR-interval* decreased, and vice-versa. This phenomenon was interpreted as a manifestation of decremental conduction during the transit of the cardiac activation wave-front through the AV node. However, due to the nature of this study, no invasive electrophysiological test was carried out to further characterize decremental conduction or para-sinus pacing activity. It is still necessary to investigate the potential impact of the present findings on clinical settings, such as a marker for supraventricular tachyarrhythmia, particularly AV nodal reentrant arrhythmia and atrial fibrillation.

Conclusion

The atrioventricular node undergoes substantial physiological remodeling in elite long-distance runners, characterized by spontaneous AV decremental conduction at supine rest, rarely observed in healthy sedentary subjects under the same resting conditions. The linear regression line slope of *PR-peak* to *RR-interval* coupling is a strong and independent explanatory variable of maximal metabolic equivalent achieved during stress test in this population.

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Author contributions

Conception and design of the research: Benchimol-Barbosa PR, Nasario-Junior O, Nadal J. Acquisition of data: Benchimol-Barbosa PR. Analysis and interpretation of the data: Benchimol-Barbosa PR, Nasario-Junior O, Nadal J. Statistical analysis: Benchimol-Barbosa PR, Nadal J. Obtaining financing: Nadal J. Writing of the manuscript: Benchimol-Barbosa PR, Nasario-Junior O, Nadal J. Critical revision of the manuscript for intellectual content: Benchimol-Barbosa PR, Nasario-Junior O, Nadal J.

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 Nacional de Cardiologia under the protocol number 0026/20.02.04. 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.

Errata

Ahead of Print

In the original article published in ahead of print with the title "Avaliação do Tempo de Condução Atrioventricular Dinâmica para Acoplamento ao Intervalo RR em Atletas e Indivíduos Sedentários", with DOI number: https://doi.org/10.36660/abc.20190281, published in the periodical Arquivos Brasileiros de Cardiologia, consider the title correct: "Avaliação da Dinâmica do Acoplamento da Condução Atrioventricular à Variação dos Intervalos RR em Atletas e Indivíduos Sedentários".

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Atrioventricular Conduction System Disorders and Potential Risks of Arrhythmic Events in Endurance Athletes

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Short Editorial related to the article: Assessing Dynamic Atrioventricular Conduction Time to RR-interval Coupling in Athletes and Sedentary Subjects

Some disorders found on electrocardiograms are commonly seen in endurance or high-performance athletes and often have characteristics that are similar to those observed in elderly individuals or in those with cardiovascular disease.[1-4]

High-intensity training done by high-performance athletes can induce intrinsic physiological adaptations to the cardiac stimulus conduction system and, consequently, a higher prevalence of abnormalities in atrioventricular (AV) conduction.[3,5]

The physiological or even pathophysiological mechanisms by which athletic training induces such intrinsic changes in the cardiac conduction system still have limited understanding, and are likely to be multifactorial. However, the anatomical changes observed, such as atrial and ventricular dilation, demonstrated the creation of a mechanical-electrical remodeling necessary to cause intrinsic AV electrophysiological adaptations.[4-6]

Among the most common electrocardiographic expressions, resulting from cardiac changes induced by high-performance sports and high levels of training, include sinus bradycardia and AV block. They do not usually require special care or attention as long as they are asymptomatic or do not produce pauses longer than 4 seconds. First-degree AV block is more common, followed by 2nd degree Mobitz I AV block. Mobitz II and 3rd degree atrioventricular blocks are more unusual findings, even in athletes, and should be considered a sign of potential organic injuries.

The occurrence of complex ventricular forms of arrhythmia should always lead to cardiological examination in search of cardiogenic substrate, especially hypertrophic or dilated cardiomyopathy. The presence of ventricular arrhythmias with no evidence of underlying heart disease does not appear to indicate any special or increased risk of sudden cardiac death. Higher incidence of right and/or left ventricular hypertrophy, reversible ST-segment elevation on exercise and reversible abnormalities on exercise on T waves (T negativity, sudden and/or excessive T waves) can be considered physiological abnormalities in the athletes' ECG scans.

Endurance or major physical training exposes the heart to intense overloads over time. These constant exposures to intense training can generate cardiac automatism disorders as described, in addition to atrioventricular conduction disorders, depolarization and ventricular repolarization.[1,2,6]

Besides, these cardiac structural adjustments can be remarkable and lead to increases of up to 85% in left ventricular mass. Although these functional and structural abnormalities are documented, their actual limits within standards considered normal, as well as their long-term consequences, are still unknown.

Stein et al.[5] described high-performance training actions as a corollary of their effects on sinus node, where increased parasympathetic tone, reduced sympathetic tone and non-autonomic components can contribute to sinus bradycardia and adaptations to the special system of cardiac conduction. Such mechanisms lead to a higher prevalence of abnormalities in intrinsic atrioventricular conduction observed in athletes.

In elite athletes, in addition to the predominance of vagal tone and, consequently, bradycardia at rest, which increase absolute QT interval duration,[7,8] an increase in left ventricular mass is considered a benign physiological phenomenon, also known as "athlete's heart". Observations made, such as a slightly prolonged isolated QT interval in athletes, may reflect the late repolarization resulting from increased ventricular wall thickness[8,9] and/or bradycardia, both as a reflex of training and ultimately as a form of impairment to the special conduction system of the cardiac stimulus.[10,11] These endurance athletes often present AV node remodeling, characterized by varying degrees of AV conduction block, low non-sinus atrial or junctional rhythm and, more rarely, complete AV block.[1,2,6,9] These AV conduction disorders depend on the fitness status and are related not only to increased parasympathetic activity on the AV node, but also to the secondary remodeling of the AV node fibers and to cell-to-cell coupling.[8,9]

Thus, the analysis of autonomic contributions to the dependence of the variability in the dynamic duration of ventricular repolarization (DVR) can be a valuable tool to assess the adaptation of DVR to the cardiac cycle duration in this population.[12]

In a previous study, Nazario and Benchimol-Barbosa[13] described the variability in the duration of beat-by-beat ventricular repolarization assessed by phases of cardiac

Keywords

Keywords: Athletes; Resistance Training; Physical Fitness; Ventricular Remodeling; Sedentarism; Arrhythmias, Cardiac; Eletrocardiography/methods; Ventricular Function.

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acceleration and deceleration in athletes. The duration of dynamic ventricular repolarization (DVR) and coupling with RR interval are related to autonomic control and electrical myocardial stability. The phase rectification of the series with RR interval separates the acceleration and deceleration phases, reflecting sympathetic and parasympathetic influences on heart rate, respectively, where they observed that these have a longer ventricular repolarization duration for all RR interval durations.

In athletes, DVR variability decreases as the RR interval increases, indicating a beneficial effect of physical fitness on the stability of repolarization and also the evaluation of RR interval using a start or peak wave approach as fiducial points providing proper accurate results for the analysis of physiological variation of the beat-to-beat interval.[13,14]

Although AV conduction disorders have been repeatedly documented in athletes, the dynamic adaptation of AV conduction to the cardiac cycle in this population still needs clarification. In the general population, AV duration varies dynamically according to the RR interval duration, characterizing an accordion-like effect. However, in athletes, autonomic remodeling can influence dynamic AV conduction in the adaptation of the RR interval, leading to a different behavior from AV conduction, in response to the variation of the RR interval related to time. The study by Benchimol-Barbosa et al.[15] evaluated beat-by-beat variability of AV conduction time (AVCT) and RR interval in elite runners and in healthy sedentary individuals, at rest, with the objective of evaluating the effect of physical fitness on the duration of spontaneous coupling of AVCT to the RR interval. In this study, athletes had mean RR values and RR standard deviations significantly higher than controls and the RR-AVCT slope on controls and athletes resulted in significant differences between groups, demonstrating that this RR-AVCT slope decreases as metabolic capacity (MET) increases.

We believe that some mechanism of intrinsic organic protection is activated when the individuals suffer, due to chronic intense exercising, these physiological adaptations and develop, through this discrepant response, a defense to maintain specialized cardiac conduction.

It is still necessary to investigate the potential impact of current findings in clinical settings, such as a marker for supraventricular tachyarrhythmias, particularly AV nodal reentry arrhythmia and atrial fibrillation.

Finally, we observed that the intriguing finding in the Benchimol-Barbosa[15] study was precisely the disagreement between the dynamic coupling of AVCT and denoting the different responses between athletes and sedentary people regarding the behavior of PR and RR intervals. Such observations deserve further investigation and follow-up on the potential effects of high-intensity training and improvements in the clinical guidelines for this population.

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Cost-effectiveness of Drug-Eluting Stents in Percutaneous Coronary Intervention in Brazil's Unified Public Health System (SUS)

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Abstract

Background: **The use of drug-eluting stents (DESs), compared with bare-metal stents (BMSs), in percutaneous coronary intervention (PCI) has reduced the rate of restenosis, without an impact on mortality but with an increase in costs. Medical literature lacks randomized studies that economically compare these 2 stent types within the reality of the Brazilian Unified Public Health System (SUS).**

Objective: **To estimate the incremental cost-effectiveness ratio (ICER) between DES and BMS in SUS patients with single-vessel coronary artery disease.**

Methods: **Over a 3-year period, patients with symptomatic single-vessel coronary artery disease were randomized in a 1:2 ratio to receive a DES or BMS during PCI, with a 1-year clinical follow-up. The evaluation included in-stent restenosis (ISR), target lesion revascularization (TLR), major adverse events, and cost-effectiveness for each group. P-values <0.05 were considered significant.**

Results: **In the DES group, of 74 patients (96.1%) who completed the follow-up, 1 developed ISR (1.4%), 1 had TLR (1.4%), and 1 died (1.4%), with no cases of thrombosis. In the BMS group, of 141 patients (91.5%), ISR occurred in 14 (10.1%), TLR in 10 (7.3%), death in 3 (2.1%), and thrombosis in 1 (0.74%). In the economic analysis, the cost of the procedure was R$ 5,722.21 in the DES group and R$ 4,085.21 in the BMS group. The effectiveness by ISR and TLR was 8.7% for DES and 5.9% for BMS, with an ICER of R$ 18,816.09 and R$ 27,745.76, respectively.**

Conclusions: **In the SUS, DESs were cost-effective in accordance with the cost-effectiveness threshold recommended by the World Health Organization (Arq Bras Cardiol. 2020; 115(1):80-89)**

Keywords: **Myocardial Infarction; Percutaneous Coronary Intervention; Drug-Eluting Stents; Coronary Reestenosis; Cost-Benefit Analysis; Unified Health System (SUS).**

Introduction

Data extracted from the 2013 Brazilian National Health Interview Survey[1] estimated that 72.1% of the population would use the Unified Public Health System (SUS) for medical or dental treatment. According to the number of deaths per cause between 2004 and 2014 in Brazil, it was estimated that 1,069,653 (8.8%) individuals died from acute myocardial infarction (AMI) or other ischemic heart diseases. In this respect, it is important to develop sustainable measures for the prevention and treatment of these illnesses in the SUS.[2]

In Brazil, the first drug-eluting stents (DESs) were restricted to the supplementary health system due to their high cost. Initial studies, conducted both in Brazil and abroad, have not demonstrated cost-effectiveness for DESs in all cases, suggesting their use in situations of greater risk for restenosis.[3-6]

The limitations described above led to the development of new DESs, called second-generation DESs. With new antiproliferative drugs and improved platform with thinner metal struts (chromium-cobalt, platinum-cobalt alloys), they provided better stent apposition and less contact area for endothelialization. Biocompatible polymers reduced the local inflammatory process, reducing the occurrence of late thrombosis.[7,8]

More than a decade after the beginning of their marketing, the use of DES in the SUS remained limited despite lower cost and more favorable results. In 2014, the Brazilian National Committee for Health Technology Incorporation (CONITEC)[9] recognized the cost-benefit of DES implantation in patients with diabetes, small vessels (<2.5 mm), and long lesions (>18 mm). Although the market price of DESs is higher than that of bare-metal stents (BMSs), the price suggested in the SUS (R$ 2,034.50 / code 070204061-4)

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was the same for both stent types, hindering the systematic use of DESs in private services involved in agreements with the Brazilian Ministry of Health.

According to data from the DATASUS,[10] in 2008, 44,138 percutaneous coronary interventions (PCIs) were performed with or without stenting. Eight years later, 79,997 PCIs were performed. With this significant increase in procedures (72.84%), it is possible to project an increase in cases of restenosis that could potentially be reduced with more liberal use of DESs in the SUS.

Despite the favorable scenario for the full incorporation of DESs into the SUS, scientific evidence based on the Brazilian reality is lacking. Therefore, this study aimed to analyze and estimate the incremental cost-effectiveness ratio (ICER) between DESs and BMSs in SUS patients.

Objectives

To evaluate the cost-effectiveness and major adverse events of DESs compared with BMSs in patients with single-vessel coronary artery disease undergoing PCI.

Methods

We conducted a randomized clinical study of patients undergoing PCI from November 2013 to October 2016 at Hospital Universitário Pedro Ernesto (HUPE) and at Hospital São Lucas de Nova Friburgo (HSL), Brazil. The study was approved by the Research Ethics Committees of both institutions, under number 923660. Written informed consent was obtained from each study participant, in accordance with the Brazilian National Health Council Resolution No. 466/2012.

A total of 231 patients of both sexes with single-vessel lesions, an indication for PCI after preliminary coronary cineangiography, and symptoms of angina or noninvasive tests showing myocardial ischemia were assessed. The inclusion criteria were (1) age ≥18 years, (2) angiographically significant lesions (>70%) in a coronary artery of great anatomical importance, with irrigation of a large area of cardiac muscle, related to the presence of ischemia or typical angina symptoms, (3) single-vessel coronary artery disease, with a lesion amenable to treatment with a single stent, (4) presence or not of diabetes, and (5) stable coronary disease or acute coronary syndrome. The exclusion criteria were (1) multivessel coronary artery disease, (2) injury that required an approach with more than one stent, (3) previous coronary angioplasty with stenting, (4) allergy to aspirin and/or clopidogrel, (5) recent intestinal or genitourinary bleeding (in the last 6 months), (6) active peptic ulcer, (7) major surgery in the past 6 weeks, (8) stroke in the last year or permanent neurological sequelae, (9) pregnancy, and (10) presence of lesion >50% in the left main coronary artery.

Participants were recruited sequentially and randomly assigned in a 1:2 ratio to receive a DES or BMS, according to a computer-generated list of random numbers (Program R 2.11). The DES group consisted of 77 patients who underwent PCI with implantation of a zotarolimus-eluting stent (Endeavor Sprint and Resolute, Medtronic) in single lesions with stenosis of >70% by visual estimation on angiography. The BMS group consisted of 154 patients who underwent PCI with implantation of a BMS in single lesions with stenosis of >70% by visual estimation on angiography. The BMSs used were Integrity (Medtronic), Tsunami (Terumo), and Tango (Microport).

In-hospital evaluation included the assessment of clinical variables, angiographic variables, clinical complications, major vascular complications, major cardiac events (death, acute or subacute occlusion, and AMI), and costs. The 1-year clinical follow-up included the assessment of the following parameters: death, AMI, angina, in-stent restenosis (ISR), target lesion revascularization (TLR), late thrombosis, and costs related to re-intervention, if any. Follow-ups were conducted at the HUPE outpatient clinic and at HSL.

The aim of PCI was always to obtain a residual lesion <10% on angiography in each treated artery, without signs of dissection or thrombus that would compromise the flow of the vessel. Patients in whom the procedure failed or who required additional stent implantation were excluded from the study. During intervention, any adjuvant medication was administered at the physician's discretion. After intervention, patients in both groups received dual antiplatelet therapy (DAPT) with aspirin (100 mg/day) and clopidogrel (75 mg/day), tailoring the duration of DAPT according to the type of stent used, the indication of the physician, and the clinical condition of the patient.

Cost-effectiveness Analysis

The study population was selected for a clinical trial considering 2 alternatives: PCI with DES or PCI with BMS. An analytical model was constructed by using a decision tree (Figure 1) based on these initial procedures, in a short-term version (1 year). Each avoided ISR was considered for the calculation of effectiveness. The model used probabilistic data from clinical outcomes of a systematic review of randomized clinical trials involving coronary angioplasty with stenting, extracted from the study by Polanczyk et al. [3]

The cost of angioplasty was calculated from the perspective of the SUS, using as a reference the amounts reimbursed for previous hospitalizations, with monetary values expressed in Brazilian currency (R$).[3] The cost of BMS was defined as the amount reimbursed by the SUS (R$ 2,034.00). The cost of DES was defined as the average market price of zotarolimus-eluting stents (R$ 3,600.00).

ICER was calculated by dividing the difference in costs (hospitalization, complementary tests, percutaneous procedures, and stent price) between the 2 groups by the difference in effectiveness (restenosis-free survival) between the 2 groups. The incremental value suggested by the World Health Organization (WHO) was used as a reference: up to 3 times the value of the GDP per capita,[11] which, according to the Brazilian Institute of Geography and Statistics (IBGE), was R$ 31,587.00 in 2017.[12]

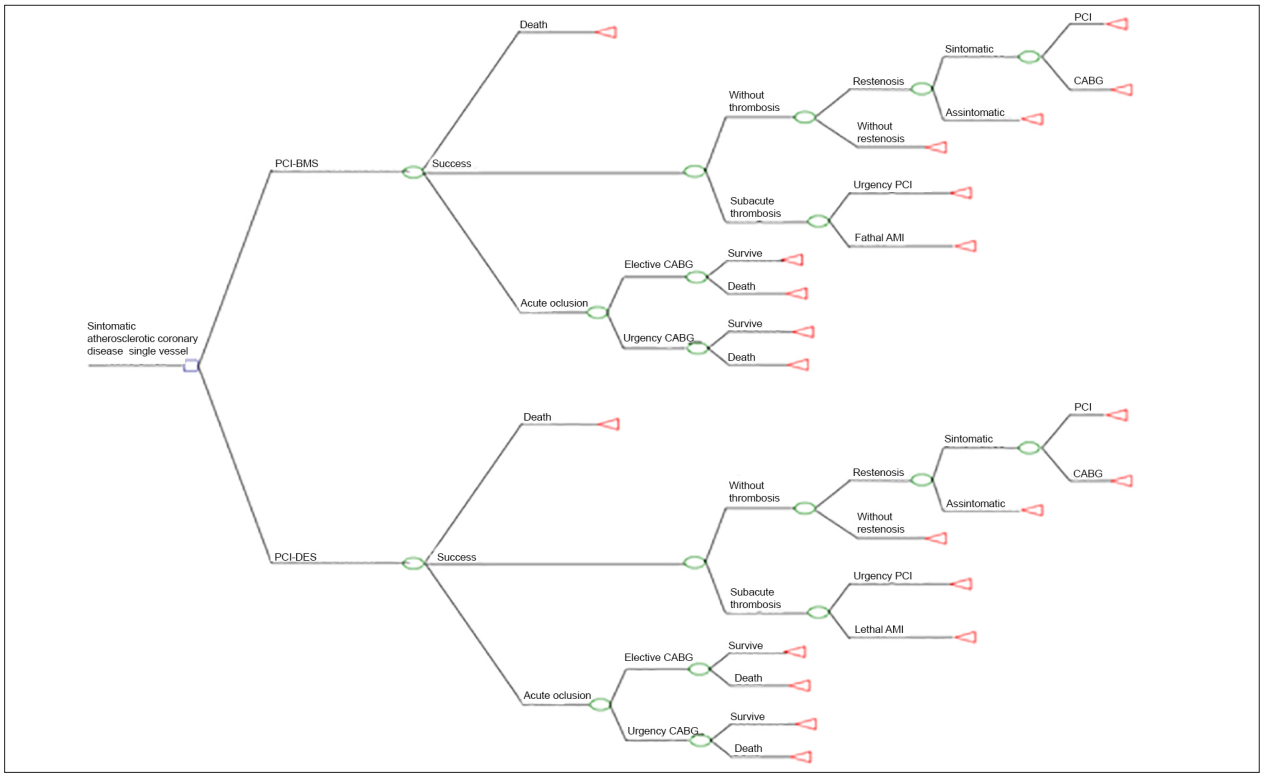

Figure 1 – *CABG:coronary artery by-pass graft; PCI-BMS:percutaneous coronary intervention witn bare metal stent; PCI-DES: percutaneous coronary intervention with drug elution stent. Source: Polanczyk et al(2007)[3]*

Statistical Analysis

Numerical data were expressed as measures of central tendency and dispersion (mean, standard deviation, median, and interquartile range). Categorical data were expressed as frequencies (n) and percentages (%). Numerical variables with non-normal distribution (normality hypothesis rejected by the Shapiro-Wilk test) were analyzed using nonparametric tests. Numerical and categorical variables were compared considering the use of DES or BMS. Student's *t* test for independent samples or the Mann-Whitney (nonparametric) test were used for the numerical variables, whereas the chi-square test or Fisher's exact test were used for the categorical variables. The statistical analysis was performed using SAS System, version 6.11 (SAS Institute, Inc, Cary, North Carolina). The level of significance was set at 5% for all analyses.

The association of the variables under study with ISR was determined by univariate and multivariate analyses, according to the independent predictors identified by the forward stepwise binary logistic regression analysis. A Kaplan-Meier curve was used to analyze differences in ISR-free survival between the 2 groups, which were compared by the log-rank test.

A decision tree model using TreeAge Pro Healthcare, version 2010 (TreeAge Software, Inc., Williamstown, MA, USA), was developed for cost analysis. A multivariable probabilistic sensitivity analysis was conducted with the variables with the greatest impact on the model in order to test the robustness of the result.

Results

Of 231 patients initially included in the study, 16 (6.9%) were lost after randomization. In the BMS group (n=154), 141 (91.5%) patients completed 1 year of follow-up, with 3 (2.1%) deaths: 2 from cardiac causes and 1 from stroke. In the DES group (n=77), 74 (96.1%) patients completed 1 year of follow-up, with 1 (1.4%) death from cardiac causes.

During follow-up, invasive stratification was indicated after the onset of typical angina or after functional assessment suggestive of ischemia. In the BMS group, 32 (23.2%) patients were stratified with a second catheterization: 14 (10.1%) with ISR, 3 with new obstructive lesions, and 15 without obstructive lesions. Of 14 ISR cases, 4 were treated clinically: 1 patient had moderate restenosis associated with the development of a new lesion in another artery (treated with BMS implantation), and 3 patients had a diffuse, occlusive lesion that did not affect the anterior descending artery and were treated conservatively. Of the 10 remaining ISR cases, 5 were treated with DES implantation, 1 was treated with implantation of another BMS, 1 underwent coronary artery bypass grafting (CABG), and 3 underwent balloon angioplasty. Of the 3 patients treated with balloon angioplasty, 1 underwent a second PCI with DES implantation. In the DES group, 14 (18.9%) patients repeated catheterization: 1 with ISR (treated with implantation of another DES), 1 with a new lesion in another vessel (treated with BMS implantation), and 12 without obstructive lesions.

A similar distribution was observed for the 2 groups, except for more frequent unstable angina in the BMS group (46.5% vs 30.9%; p = 0.027). In the DES group, 31.0% of patients had diabetes, against 27.7% in the BMS group (p = 0.59), without statistically significant difference between the groups (Table 1).

Regarding angiographic variables, the rate of type C lesions was 25.4% in the DES group and 19.9% in the BMS group, with no between-group difference. In both groups, there was a slight predominance of short lesions (<20 mm): 59.5% in the DES group and 54.6% in the BMS group (p = 0.49). Vessels with a diameter of <3.0 mm were more frequent in the DES group (47.3% vs 34.0%; p = 0.058) (Tables 2 and 3) .

The 2 groups did not differ in the occurrence of thrombosis, infarction, stroke, angina, or death. The BMS group had more cases of ISR (10.1% vs 1.4%; p = 0.018) and, consequently, more cases of TLR (7.3% vs. 1.4%; p = 0.058) (Table 4).

Figure 2 shows the Kaplan-Meier restenosis-free survival curve during follow-up (in days), stratified by stent type (DES × BMS) and compared by the log-rank test. Restenosis-free survival was significantly higher in the DES group than in the MBS group (p = 0.019).

Table 1 - Clinical variables and comorbidities of the study groups

Clinical variables	DES		BMS		p-value
Mean age (years) ± SD	61.8 ± 10.7		61.9 ± 9.7		0.98 *
Male sex n (%)	44	59.5	94	66.7	0.30
White color n (%)	50	73.5	90	67.2	0.35
Comorbidities n (%)					
Hypertension	58	78.4	115	81.6	0.58
Diabetes mellitus	23	31	39	27.7	0.59
Obesity	18	25.0	31	22.6	0.92
Dyslipidemia	43	58.9	75	54.0	0.49
Smoking	13	17.8	29	21.2	0.17
Family history	50	68.5	77	56.6	0.094
Previous AMI	9	12.3	19	13.6	0.80
CRF	3	4.1	4	2.9	0.46
Hemodialysis	1	1.4	1	0.7	0.58
EF <40%	6	9.0	11	8.5	0.91
Silent ischemia	1	1.4	3	2.2	0.56
Stable angina	23	32.4	46	33.8	0.84
Unstable angina	33	46.5	43	30.9	0.027
NSTEMI	5	6.9	19	14.0	0.13
STEMI	12	16.4	31	22.6	0.29

*Categorical data were expressed as frequency (n) and percentage (%) and compared by the X^2 test or Fisher's exact test. Numerical data with normal distribution were expressed as mean ± standard deviation and compared by Student's t test * for independent samples.*
Legend: DDES - drug-eluting stent; BMS - bare-metal stent; SD - standard deviation; EF - ejection fraction; AMI - acute myocardial infarction; CRF - chronic renal failure; STEMI: ST-segment elevation myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction. Source: The Author, 2018.

Table 2 - Angiographic variables of the study groups

Variables	DES			BMS			p-value
	n	median	Q1-Q3	n	median	Q1-Q3	
Stent diameter (mm) **	74	2.95	2.75 - 3.1	141	3.1	2.75 - 3.50	0.018 **
Stent length (mm)	74	18.0	15.0 - 24.0	141	18.0	15.0 - 26.0	0.97 **
QCA							
RDV **	46	2.90	2.58 - 3.19	88	2.89	2.49 - 3.64	0.56 **
% Lesion	45	82.6	72.5 - 87.9	88	87.1	74.1 - 93.1	0.069 **
Lesion extension (mm)	46	7.96	6.37 - 10.3	86	9.34	6.80 - 12.7	0.12 **
MLD – pre	46	0.805	0.685 - 1.07	85	0.870	0.610 - 1.05	0.88 **
MLD – post	46	2.76	2.22 - 3.26	85	2.86	2.42 - 3.39	0.32 **

*Data with non-normal distribution were expressed as median and interquartile range (Q1-Q3) and compared by the Mann-Whitney ** (nonparametric) test. DES - drug-eluting stent; BMS - bare-metal stent; MLD - minimal lumen diameter; RDV - reference diameter of the vessel; QCA - quantitative coronary angiography; Q1-Q3 - interquartile range. Source: The Author, 2018.*

Table 3 – Procedure-related variables of the study groups

		DES		BMS		p value
		n	%	n	%	
CASS	A	4	5.6	5	3.7	0,68
	B1	34	47.9	74	54.4	
	B2	15	21.1	30	22.1	
	C	18	25.4	27	19.9	
Treated vessel	Vessel <3.0 mm	35	47.3	48	34.0	0,058
	Lesion <20 mm	44	59.5	77	54.6	0,49
	Right coronary artery	12	16.2	48	34.3	0,014
	Circumflex artery	4	5.4	13	9.3	
	LADA	52	70.3	68	48.6	
	Branch	6	18.2	11	7.8	
Access	Radial	66	98.5	126	96.97	descriptive only
	Femoral	1	1.5	3	2.27	
	Ulnar	0	0	1	0.77	
Complication	Dissection	0	0	1	0.72	0,67
Follow-up	New coronarography	14	18.9	32	23.2	0,47

Categorical data were expressed as frequency (n) and percentage (%) and compared using the X^2 test or Fisher's exact test. DES: drug-eluting stent; BMS: bare-metal stent; ACCL: angiographic classification of coronary lesions (American Heart Association); LAD: left anterior descending artery. Source: The Author, 2018.

Table 4 – Outcomes at 1-year follow-up for the study groups

Outcomes	DES		BMS		p-value
	n	%	n	%	
Bleeding	1	1.4	2	1.4	0.73
TLR	1	1.4	10	7.3	0.058
CABG	0	0	1	0.72	0.66
Angina	16	21.6	39	28.3	0.29
AMI	0	0	1	0.72	0.66
Stroke	0	0	3	2.2	0.28
ISR	1	1.4	14	10.1	0.018
New injury	1	1.4	6	4.4	0.23
Death	1	1.4	3	2.1	0.58

Categorical data were expressed as frequency (n) and percentage (%) and compared using the x^2 test or Fisher's exact test. DES: drug-eluting stent; BMS: bare-metal stent; CABG: coronary artery bypass graft; AMI - acute myocardial infarction; CRF - chronic renal failure; ISR - in-stent restenosis; TLR - target lesion revascularization. Source: Author, 2018.

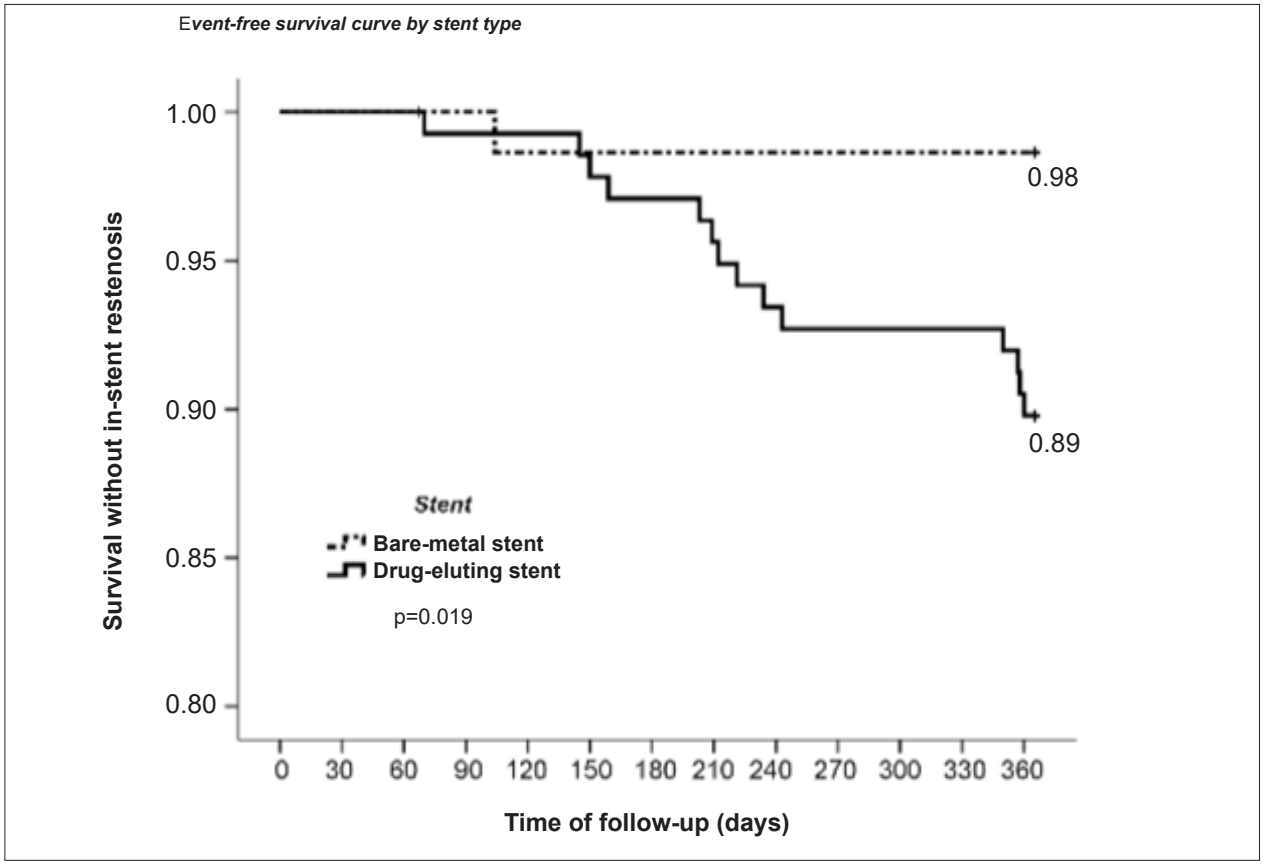

Figure 2 – *Event-free survival curve by stent type.*

Cost-effectiveness Analysis

The costs of the procedure and the effectiveness of each stent were calculated according to the type of stent implanted (DES or BMS). BMS had a cost of R$ 4,085.21 and DES of R$ 5,722.21. Considering the occurrence of ISR, DESs were 8.7% more effective than BMSs, with an ICER of R$ 18,816.09. Regarding TLR, DESs were 5.9% more effective than BMSs, with an ICER of R$ 27,745.76.

Discussion

Population Analysis

In the present study, as previously reported in the literature,[13,14] there was no difference between the use of DESs and BMSs in major adverse events (death, AMI, thrombosis), but a significant difference was observed in restenosis (DES: 1.4 % vs BMS: 10.1%; p = 0.018). The rate of TLR in 1 year was 1.4% in the DES group and 7.3% in the BMS group (p = 0.058). In this study, the only documented case of thrombosis occurred in the DES group (0.0% vs. 0.74%; p = 0.65), but without statistical significance.

In accordance with national and international guidelines for PCI,[15,16] the use of radial access minimized the occurrence of bleeding, with no major bleeding requiring blood transfusion or surgical intervention. Although small-diameter vessels, long lesions and diabetes mellitus are risk factors for restenosis,[17] this was not confirmed in the present study. Presence of diabetes did not differ between the 2 groups (DES: 31.0% and BMS: 27.7%; p = 0.59). Of patients with ISR, 40.0% had diabetes; however, 27.7% of patients who did not develop ISR also had diabetes, with no statistical significance (p = 0.22) (Table 5). Regarding lesion length, lesions <20 mm were found in 60.0% of patients with ISR and in 56.6% of patients without ISR, without statistical significance (p = 0.8).

Therefore, the only independent predictor of restenosis was the use of a BMS (RR: 8.14; 95% CI: 1.05-63.2; p = 0.045), where 93.3% of ISR cases occurred in patients who received a BMS.

Table 5 - Clinical variables and comorbidities according to the ISR outcome

Clinical variables	WITH ISR		WITHOUT ISR		p-value
Mean age (years) ± SD	59.9 ± 8.4		61.9 ± 10.1		0.45 *
Male sex n (%)	9	60.0	127	64.8	0.71
White color n (%)	10	66.7	128	69.6	0.51
Comorbidities n (%)					
Hypertension	13	86.7	156	79.6	0.39
Obesity	4	26.7	44	23.0	0.74
Diabetes mellitus	6	40	54	27.6	0.22
Dyslipidemia	8	53.3	106	54.9	0.91
Smoking	3	20.0	38	19.8	0.079
Smoking (ex + current)	13	86.7	116	60.4	0.043
Family history	9	64.3	116	60.4	0.77
Previous AMI	3	20.0	24	12.4	0.30
CRF	0	0	6	3.1	0.64
Hemodialysis	0	0	2	1.03	0.86
EF <40%	0	0	16	8.9	0.26
Silent ischemia	1	6.7	3	1.6	0.26
Stable angina	2	13.3	66	35.1	0.086
Unstable angina	8	53.3	67	35.1	0.16
NSTEMI	3	21.4	21	11.1	0.22
STEMI	1	7.1	40	20.8	0.19

*Categorical data were expressed as frequency (n) and percentage (%) and compared by the X^2 test or Fisher's exact test. Data with normal distribution were expressed as mean ± standard deviation and compared by Student's t test * for independent samples. Legend: ISR - in-stent restenosis; SD - standard deviation; EF - ejection fraction; AMI - acute myocardial infarction; CRF - chronic renal failure; STEMI: ST-segment elevation myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction. Source: The Author, 2018.*

Cost-effectiveness Analysis

In Brazil, the use of DESs for PCI is a rule in the supplementary health system, as this economic model bases its cost-effectiveness threshold on demand, considering how much the insured is willing to pay for it. However, the unrestricted use of DESs in the SUS is still a matter of controversy. As their use does not have an impact on mortality, with a decrease only in the number of re-interventions due to a reduction in restenosis, the cost-effectiveness threshold needs to be based on supply, that is, on how much more the State is willing to pay to obtain such a benefit.

Polanczyk et al.,[3] in a previous non-randomized study conducted in Brazil for the economic analysis of DESs, reported that the cost in the first year of implantation was R$ 5,788.00 for BMSs and R$ 12,708.00 for DESs, with a 13.8% higher effectiveness in favor of DESs. Using a cost-effectiveness threshold of USD 10,000.00 per avoided event, extracted from the North American and Canadian systems, it was concluded that the ICER of R$ 47,643.00 for DESs per avoided restenosis was not cost-effective in the SUS.

The present randomized study calculated the ICER of DESs in relation to BMSs only in the SUS. According to the SUS's reference values, the annual cost of DESs was R$ 5,722.21 and the annual cost of BMSs was R$ 4,085.21, which has changed little since the study by Polanczyk et al.[3] The effectiveness by ISR and TLR was 8.7% for DESs and 5.9% for BMSs, with an ICER of R$ 18,816.09 and R$ 27,745.76, respectively. Based on these results, can we consider DESs cost-effective?

In Brazil, there has never been an explicit threshold value for cost-effectiveness as a reference for assessing the economic viability of a technology to be implemented. CONITEC,[9] an adviser to the Ministry of Health for the incorporation of any treatment into the SUS, often uses the value of the GDP per capita in its reports to estimate this threshold.[18-20] The use of the GDP per capita as a threshold for cost-effectiveness has recently been abandoned by the WHO[19] due to lack of specificity for decision-making on resource allocation. Because of a scenario of uncertainty, there is a bill in the Senate that proposes the creation of cost-effectiveness parameters to assist in the approval of drugs, orthoses, and prostheses in the SUS.[21] In the absence of a better alternative, the GDP per capita was the parameter used to define cost-effectiveness in the present study.

The DES price has dropped dramatically. At the time of the study by Polanczyk et al.,[3] the reference price of rapamycin-eluting stents was R$ 10,320.00, whereas, in the present study, the price of zotarolimus-eluting stents was around R$ 3,600.00. The price of BMSs decreased as well, while incorporating the same technological advances of the platform used in DESs. Interestingly, SUS has a peculiarity: the amounts paid for the procedures have changed little over recent years, where, although the price of DESs in the SUS remained unchanged, they are currently more expensive in relation to the market price. Despite the decrease in their cost, the latest CONITEC report[9] recommended the use of DESs in the SUS only for patients at greatest risk for restenosis, purchasing them at a price below the market price.[9] Their use in the SUS, therefore, is still restricted.

In Europe, where the health care system is mostly public, DESs have been widely used for 5 years. In 2013, in France,[22] 72.5% of implanted stents were DESs; in the United Kingdom, 89.0%; in Italy, 78.0%; in Germany, 77.0%; and in Spain, 74.0%. Barone-Rochette et al.,[23] in a cohort study of patients who received sirolimus-eluting stents at different time points (2008 and 2012), demonstrated their cost-effectiveness after the price drop. The cost difference between DESs and BMSs was € 1200 in 2008 and € 400 in 2012.

In 2018, the new European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS)[16] guideline for myocardial revascularization recommended the unrestricted use of DESs, regardless of the type of injury, planning for non-cardiac surgery, or concomitant anticoagulation. In short, the constant improvement of DESs and the variety of models available on the market tend to further reduce their price and increase their use. Technological advances in DESs tend to ultimately eliminate the use of BMSs in clinical practice, but a change of attitude of government managers is still lacking to implement their use more broadly, as in developed countries.

Conclusions

DESs were cost-effective in the SUS patients participating in the study, compared with BMSs. There was no difference in mortality or other major adverse events between DESs and BMSs. Patients who received a DES had a significantly lower rate of ISR compared with those who received a BMS.

Study Limitations

Due to the random selection of patients with single-vessel coronary artery disease without previous angioplasty or history of CABG, less complex cases were probably selected, with a lower probability of developing restenosis, which may have influenced the difference in effectiveness between the groups. In addition, due to the small sample size, the number of adverse events was low, and the use of BMSs was the only independent predictor of restenosis, but with a wide confidence interval.

Author contributions

Conception and design of the research: Pessoa JA, Maia F, Oliveira MS, Araújo DV, Ferreira E, Albuquerque DC; Acquisition of data: Pessoa JA, Maia E, Maia F, Oliveira MS; Analysis and interpretation of the data and Statistical analysis: Pessoa JÁ; Obtaining financing: Araújo DV, Ferreira E, Albuquerque DC; Writing of the manuscript: Pessoa JA, Ferreira E; Critical revision of the manuscript for intellectual content: Pessoa JA, Araújo DV, Ferreira E, Albuquerque DC.

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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Drug-Eluting Stents for Everyone: Is the Price Worth It?

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Short Editorial related to the article: Cost-effectiveness of Drug-Eluting Stents in Percutaneous Coronary Intervention in Brazil's Unified Public Health System (SUS)

Despite their initial revolutionary role for the interventional cardiology development, bare-metal stents (BMS) have as main drawback in-stent restenosis (ISR), which occurs in a significant proportion (up to 44%) of patients undergoing to percutaneous coronary interventions (PCI).[1]

Drug-eluting stents (DES) became first available in the year 2,000. By locally releasing antiproliferative and anti-inflammatory drugs, there is an inhibition to the proliferation of smooth muscle cells, thereby mitigating a key factor to ISR. The introduction of second-generation DES, including everolimus-eluting and zotarolimus-eluting stents, has led to claims of improved safety with non-inferior efficacy compared with first generation DES devices, supported by numerous clinical trials.[2]

Bangalore et al.[3] published a meta-analysis comparing BMS versus DES in terms of stent thrombosis (ST), target vessel revascularization (TVR), death and myocardial infarction (MI), with 117,762 patient-years of follow-up, from 76 international randomized trials. While they found the risk of death was not significantly different between the two stent types, there was a lower risk on short-term and on long-term outcomes in favor of DES, except for the first-generation paclitaxel-eluting stent, not anymore available nowadays.

Baschet et al.[2] performed a cost-effectiveness analysis in the French National Health Insurance setting. The main effectiveness criterion was major adverse cardiac event-free survival. Effectiveness and costs were modelled over a 5-year horizon. Incremental cost-effectiveness ratios (ICER) and a cost-effectiveness acceptability curve were calculated for a range of thresholds for willingness to pay per year without major cardiac event gain. Base case results demonstrated DES were dominant over BMS, with an increase in event-free survival and a cost-reduction of €184, primarily due to a reduction of future revascularizations, and an absence of MI and ST. No differences in overall survival were predicted. These results were robust for uncertainty on one-way deterministic and probabilistic sensitivity analyses. Using a cost-effectiveness threshold of €7000 per major cardiac event-free year gained, DES had a >95% probability of being cost-effective versus BMS.

More recently, the randomized study EXAMINATION[4] evaluated 1,498 patients with STEMI, who were allocated for PCI with new-generation DES 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. Over the life-long time horizon, the DES strategy was €430 more costly than BMS (€8,305 vs. €7,874) but went along with incremental gains of 0.10 quality-adjusted life-years (QALYs). Thus, this resulted in an average ICER over all simulations of €3,948 per QALYs gained and was below a willingness-to-pay threshold of €25,000 per QALYs gained in 86.9% of simulation runs. Hence, despite the higher initial cost in the index procedure, DES present better cost-effectiveness compared to BMS on the long-term.

Accordingly, the recent *"2018 European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS) guidelines on myocardial revascularization"* recommend (class I, level A) DES over BMS for any PCI, irrespective of clinical presentation, lesion type, planned non-cardiac surgery, anticipated duration of dual antiplatelet therapy or concomitant anticoagulant therapy.[5]

Nonetheless, despite the large body of evidences in favor of DES, much debate still exists over risk-benefit and cost-effectiveness ratios of DES over BMS. To date, DES have not yet been incorporated as default device for any PCI in the setting of the Brazilian Public Health System—despite the official approval by Ordinance No. 29 issued by the Ministry of Health in 2014+[6] Costs of DES have decreased in recent years and their second-generation development raises a need for evaluation of the cost-effectiveness of DES versus BMS.

Pessoa et al.[7] must be congratulated by performing a thoroughly randomized 2:1 comparison of BMS versus second-generation DES PCI strategies for 231 consecutive patients with single-vessel coronary disease plus symptoms and/or significant ischemia burden, for whom planed single stent PCI was sought to be feasible, in the setting of Brazilian Public Health System. The aim was to evaluate the ICER and major adverse events of DES versus BMS. Despite no relevant differences related to ST, MI, stroke, angina *pectoris* or death, there was a significant reduction of ISR (10,1% vs. 1,4%; p=0.018) and, consequently, of target lesion revascularization (TLR) (7,3% vs. 1,4%; p=0.058) with DES, thus avoiding repeated procedures. The differences of effectiveness in favor to DES, for ISR and TLR, were 8.7% and 5.9%, respectively, with ICER of R$ 18.816,09 and R$ 27.745,76. The study has

Keywords

Myocardial Infarction; Percutaneous Coronary Intervention; Drug-Eluting Stents; Coronary Reestenosis; Unified Health System (SUS); Cost-Benefit Analysis.

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been performed in a 1-year time horizon and increasing the analysis for 5 years could further improve the cost-effectiveness of DES. The authors concluded that, in the setting of the Brazilian Public Health System, second-generation DES were cost-effective, in accordance with the recommendations of the World Health Organization. Policymakers in health care systems face difficult decisions about how to allocate scarce resources. While ICER are undoubtedly informative in assessing value for money they also need to be considered alongside affordability, budget impact, fairness, feasibility and any other criteria considered important in the local context. ICER threshold values of £20,000 to £30,000 and $50,000 have been conventionally applied in the United Kingdom (UK) and the United States (US), respectively, to guide policymakers in resource allocation decisions.[8,9] If the ICER for a new technology falls below £20 000 (UK) or $50,000 (US) per QALYs gained, that technology is generally recommended for purchase by the national health system. Nonetheless, as stated by Pessoa et al.,[7] there is no clear ICER threshold in Brazil as a guidance to incorporate drugs and devices in the public health system. Indeed, the cost-effectiveness thresholds suggested by the WHO for use in low- and middle-income countries is 1 to 3 times GDP per capita[10] by disability adjusted life year (DALY) saved, which is not the outcome considered by the autors. Yet the threshold of R$ 31.587,00 used by Pessoa et al.[7] was initially developed for analysis by DALY saved, then became used as a threshold for the cost-effectiveness limit of analysis by QALY saved and even by life-year saved. But it has not be used as a threshold for cost-effectiveness analyses that consider other outcomes not directly related to survival. Although analyzing a different outcome, Pessoal et al.[7] highlights that the cost increase for providing access to DES is not as high as it has been previously considered. Finally, efforts have recently been made by the Brazilian government to further improved analysis of cost-effectiveness of our major Universal Health Care system in the world.

In conclusion, in the light of DES decreasing costs, constant development of new-generation devices and favorable outcomes of recent robust meta-analyses, DES appears to be cost-effective and should, therefore, be adopted as default for routine PCI in the setting of Brazilian Public Health System, like in most developed countries worldwide.

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Implementation of a Best Practice in Cardiology (BPC) Program Adapted from Get With The Guidelines® in Brazilian Public Hospitals: Study Design and Rationale

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Abstract

Background: **There are substantial opportunities to improve the quality of cardiovascular care in developing countries through the implementation of a quality program.**

Objective: **To evaluate the effect of a Best Practice in Cardiology (BPC) program on performance measures and patient outcomes related to heart failure, atrial fibrillation and acute coronary syndromes in a subset of Brazilian public hospitals.**

Methods: **The *Boas Práticas em Cardiologia* (BPC) program was adapted from the American Heart Association's (AHA) Get With The Guidelines (GWTG) Program for use in Brazil. The program is being started simultaneously in three care domains (acute coronary syndrome, atrial fibrillation and heart failure), which is an approach that has never been tested within the GWTG. There are six axes of interventions borrowed from knowledge translation literature that will address local barriers identified through structured interviews and regular audit and feedback meetings. The intervention is planned to include at least 10 hospitals and 1,500 patients per heart condition. The primary endpoint includes the rates of overall adherence to care measures recommended by the guidelines. Secondary endpoints include the effect of the program on length of stay, overall and specific mortality, readmission rates, quality of life, patients' health perception and patients' adherence to prescribed interventions.**

Results: **It is expected that participating hospitals will improve and sustain their overall adherence rates to evidence-based recommendations and patient outcomes. This is the first such cardiovascular quality improvement (QI) program in South America and will provide important information on how successful programs from developed countries like the United States can be adapted to meet the needs of countries with developing economies like Brazil. Also, a successful program will give valuable information for the development of QI programs in other developing countries.**

Conclusions: **This real-world study provides information for assessing and increasing adherence to cardiology guidelines in Brazil, as well as improvements in care processes. (Arq Bras Cardiol. 2020; [online].ahead print, PP.0-0)**

Keywords: **Cardiovascular Diseases/physiopathology; Heart Failure; Atrial Fibrillation; Acute Coronary Syndrome; Quality Improvement/trends; Guidelines as Topic.**

Introduction

The Brazilian public health system serves about 70% of the country's population and functions as Brazil's primary health care delivery system.[1] Despite a number of initiatives taken by the federal government to improve the efficiency of the Brazilian public health system, results have been inconsistent, indicating a great need for improvement.[1,2] Furthermore, little has been done to control the under- or overutilization of healthcare resources and barriers that prevent evidence-based therapies from being implemented at the national level.[2]

Significant variability in the quality of care, assessed through performance measures by Brazilian health institutions with the support of the Brazilian Society of Cardiology (SBC), has been observed.[3-5] Educational initiatives and programs for quality improvement (QI) have been shown to help improve

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care provided to patients with cardiovascular disease (CVD).[6,7] Thus, a well-aligned clinical intervention such as a multiyear QI program like the American Heart Association (AHA) Get With The Guidelines (GWTG) program, if adapted to the guidelines and health care delivery system of Brazil, might have a significant impact on treatment and outcomes of CVD patients and practice patterns of their caregivers.

GWTG is a QI program created by the AHA and the American Stroke Association (ASA) with the aim of improving the care of patients hospitalized with CVD. It was created to assist hospitals in redesigning the care delivered for heart conditions of high economic burden such as acute coronary syndrome (ACS), atrial fibrillation (AF), heart failure (HF) and stroke and has been validated in the United States over the past 17 years. It has been shown to improve in-hospital quality of care, patient outcomes, and costs.[8]

It is within this context, after appropriate adaptation to the Brazilian healthcare system, that this novel program is being launched. Its main objective is to assess the adherence rates of hospital health professionals to the latest AHA/SBC guidelines' recommendations on HF, AF and ACS and its effect on patient outcomes and quality of life before and after the implementation of a Best Practice in Cardiology (BPC) program adapted from the GWTG initiative. This initiative in Brazil is the result of a tripartite collaboration of the AHA, the SBC and the Brazilian Ministry of Health, with participation of the Hospital do Coração (HCor), to be tested in selected public hospitals and if proven effective, to be further implemented countrywide.

Methods

BPC is a QI program that was adapted from GWTG and approved by the Institutional Review Board (IRB) of the Coordinating Center under the number 48561715.5.1001.0060. It will be implemented in selected tertiary hospitals of the Brazilian public health system in the five macro-regions of Brazil. The study steering committee and coordination groups are described in Appendix 1.

After acceptance to participate and local IRB approval, the project management group will make an initial visit to make sure that the center meets the infrastructure requirements to participate in the program and to present it to local leadership.

The effect of the program on measures of institutional performance, quality of life and clinical outcomes will be evaluated in a cohort quasi-experimental study design combined with a cohort design, through data collection before and after the implementation of the BPC Program.

Before the intervention, evaluation will occur over a period of approximately two months prior to the implementation of the BPC program in the institution or after the inclusion of the first 15 patients in each arm. Post-intervention evaluation will be conducted after the first intervention and will last approximately 18 months. Patients will be followed through telephone contact at one and six months after discharge by local trained interviewers.

A multidisciplinary team composed of a local leader, doctors, nurses, and patient educators will be responsible for establishing local strategies for improvement and driving the efforts to the local program.

Population

Eligible patients will be consecutive patients aged 18 years or older, admitted to the selected hospitals with a primary diagnosis of acute HF (ICD-10 code I50; I50.0; I50.1 or I50.9), ACS (ICD10 codes: I20.0 to I21.9 and I22.0 to I22.9) or AF/Atrial Flutter (ICD-10 code I-48), regardless of a previous history of any of these conditions, and agree to participate in the study by signing an informed consent form. Screening for AF/flutter patients may be performed in the outpatient clinic. The details of eligibility criteria can be found in Appendix 2.

Definition of performance measures and quality metrics

Performance measures and quality metrics were selected from the American College of Cardiology (ACC)/AHA care metrics on HF,[9] ACS[10] and AF[11] to compose two sets of indicators for each of these conditions. As previously reported, the former set of indicators were derived from class I recommendations of the latest ACC/AHA guidelines and included public comment and a peer review process whereas the latter was derived from other recommendations not following a strict methodology.[12,13] These performance and quality metrics have then been reviewed and adapted to be consistent with current guidelines in Brazil.

Twenty-one performance measures were selected, five for HF, nine for ACS and seven for AF (Table 1). Twenty-two other quality metrics were included in the three arms of the program, nine for HF, six for ACS and seven for AF (Appendix 3). Eligible patients are defined as those patients without documented intolerance or contraindications for that specific measure.

The overall rates of adherence to recommendations will be measured using an opportunity-based approach according to ACC/AHA methodology.[14]

Outcome measures

Length of stay, in-hospital mortality, cardiac mortality at one month and at six months, and readmission within one month and six months due to a cause related to the index admission will be computed.

In addition, quality of life and health perception will be measured using the WHOQOL-BREF questionnaire[15] and the Numering Rating Scale (NRS),[16] respectively, at discharge and at six months.

Identification of barriers at baseline

Possible causes of non-adherence to guidelines that require specific interventions will be identified through discussion with the institutions, via a semi-structured interview (Appendix 4). The semi-structured interview will be held before the start of the project for mapping institutional processes and flow of care in each arm in which the institution is enrolled. These interviews aim to identify specific behavioral changes needed to encourage participation in the BPC program as well as adherence to guideline recommendations. Thus, when care processes lead to failure to implement recommended therapies, changes can be implemented to improve a specific process or care.

Table 1 – Performance measures

Time	Performance measure	Definition	HF	AF	ACS
Within 24h of arrival	Early Aspirin*	Proportion of ACS patients receiving aspirin within 24 hours of hospital arrival			●
	Proper reperfusion therapy	Proportion of STEAMI patients submitted to thrombolysis within 30 min or primary angioplasty within 90 min from hospital arrival			●
During hospitalization	Assessment of thromboembolic risk factors	Proportion of non-valvular AF/Flutter patients with a documented CHADS2-VASc risk score assessment		●	
	Bleeding risk assessment	Proportion of patient with a documented HAS-BLED risk score assessment.		●	
	Assessment of left ventricle function	Proportion of HF patients with a documented LV function either in the medical records or other reports accessible in hospital charts in the 12 months before admission or during hospitalization or with a scheduled evaluation planned to be performed after discharge	●		
At discharge	Aspirin*	Proportion of ACS patients with aspirin prescribed at discharge			●
	ACEI/ARB*	Proportion of HF patients with LVEF < 40% or AF patients with LVEF ≤ 40% or ACS patients with LVEF < 45% with an ACEI/ARB prescribed at discharge	●	●	●
	Beta blockers*	Proportion of HF patients with LVEF ≤ 40% and a proven efficacious beta blocker (Bisoprolol, Carvedilol, Metoprolol Succinate CR/XL) prescribed at discharge			
		Proportion of ACS patients with a beta blocker prescribed at discharge	●	●	●
		Proportion or AF patients with either LVEF ≤ 40% or CAD with a beta blocker prescribed at discharge			
	Anticoagulants*	Proportion of AF patients at high risk for thromboembolism according to the CHADS2_VASc taking anticoagulants		●	
	Statin*	Proportion of AF patients with CAD, stroke/TIA, PVD or diabetes who were prescribed a statin at discharge		●	●
		Proportion of ACS patients without contraindications with statin prescribed for LDL control at discharge			
	Aldosterone inhibitors*	Proportion of HF patients with LVEF ≤ 35% taking aldosterone inhibitors	●		
	Blood pressure control	Proportion of ACS patients under medication for blood pressure control			●
	Smoke cessation counseling	Proportion of ACS patients, who are active smoker within the past 12 months, who receive smoking cessation advice during hospitalization or at discharge			●
	Returning visit appointment	Proportion of AF patients discharged on Warfarin who had an INR follow up planned prior to hospital discharge		●	
	Post-discharge appointment	Proportion of HF patients for whom a follow-up appointment was scheduled and documented	●		

** Only eligible patients, without contraindications, will be computed in the denominator. ACS: acute coronary syndrome; ACEI: angiotensin-converting enzyme inhibitor; AF: atrial fibrillation; ARB: angiotensin receptor blocker; CAD: coronary artery disease. CVA: cerebrovascular accident; HF: heart failure; INR: international normalized ratio; LDL: low density lipoprotein; LV: left ventricle; LVEF: left ventricle ejection fraction; PVD: peripheral vascular disease; STEAMI: ST elevation acute myocardial infarction; TIA: transient ischemic attack.*

Data collection

Clinical data from the patients included will be registered on a web database (MySQL version 5.7 or higher) developed specifically for this project. Each hospital will be responsible for its own data collection by a trained local team of data abstractors who will work under the supervision of their local leadership. Data will be abstracted from medical charts and structured interviews made directly with the patients during hospitalization and at one and six months of follow-up.

Data will include demographics, comorbidities and risk factors, symptoms on arrival, health literacy, risk profile according to international standards for each arm of the program,[17-21] in- and out-of-hospital treatment and procedures, discharge medications and secondary prevention, discharge counseling and patients' adherence to recommendations.

Data Management and Quality Control

All data will be treated as protected health information and securely stored centrally in a password-protected web server, accessible in real time by any approved user through a web browser.

Data accuracy and completeness will be ensured by following the same methodologies of the GWTG.[22,23]

QI Interventions and Hospital Recognition

As opposed to the approach taken in the U.S., the Brazilian program uses a didactic framework based on Michie et al.[24] Interventions were grouped in seven domains aiming to cause behavioral change (facilitation and restriction; modeling; environmental restructuring; education; incentives

and persuasion; coercion; and training). These groups of interventions will be implemented in all participating institutions and can be emphasized individually throughout the study according to the barriers identified at baseline and to the monthly reports on overall and specific adherence to recommendations. The description of the interventions embedded in each of these groups is available in Figure 1.

Coordination of these activities will be made by a nurse, member of the Management Group, and will include checklists and reminders, webinars, automatic and real time reports through an electronic database, educational materials, quarterly meetings for audit and feedback, and hospitals' recognition and training on QI methodologies for the implementation of rapid improvement cycles by the use of the Institute for Healthcare Improvement (IHI) 's tools.[25,26] Concepts of improvement such as training of a QI team and establishment of goals based on the barriers that need to be overcame and monitoring and analysis of results will be used throughout the study.

The electronic reports will capture real time information when completed in the study's electronic database. The reports will include specific run charts describing the temporal trends on a monthly basis of the overall and specific adherence rates of the institution in relation to an established goal of 85% and to the median rates observed in the selected period for that same institution.[27] Each institution will be able to see, in real time, their own run charts and the charts showing average rates of the other participating (anonymous) institutions. The coordinating center will be able to follow all the participating institutions concomitantly.

For the purposes of this project, we established as a goal a threshold of 85% based on previously reported GWTG results, where clinical outcomes improved when institutions reached this threshold.[28] Hospitals will be recognized by SBC with a bronze award if they reach this threshold for at least three consecutive months, with a silver award if they sustain these results for at least six months and with a gold award if they continue on the threshold or above it for 12 consecutive months.

Data analysis

Data will be analyzed using R program version 3.4.0 or higher.

Hospitals will be excluded from the analysis of a performance measure if less than 10 patients are noted in the denominator for that measure.

Continuous variables with normal distribution will be summarized as mean and standard deviation, and those with skewed distribution as median and 25th and 75th percentiles. Ordinal or categorical variables will be reported as absolute frequencies, percentages and 95% confidence intervals. Missing data will be addressed on an analysis-specific basis and considered non-compliance for the specific measure.

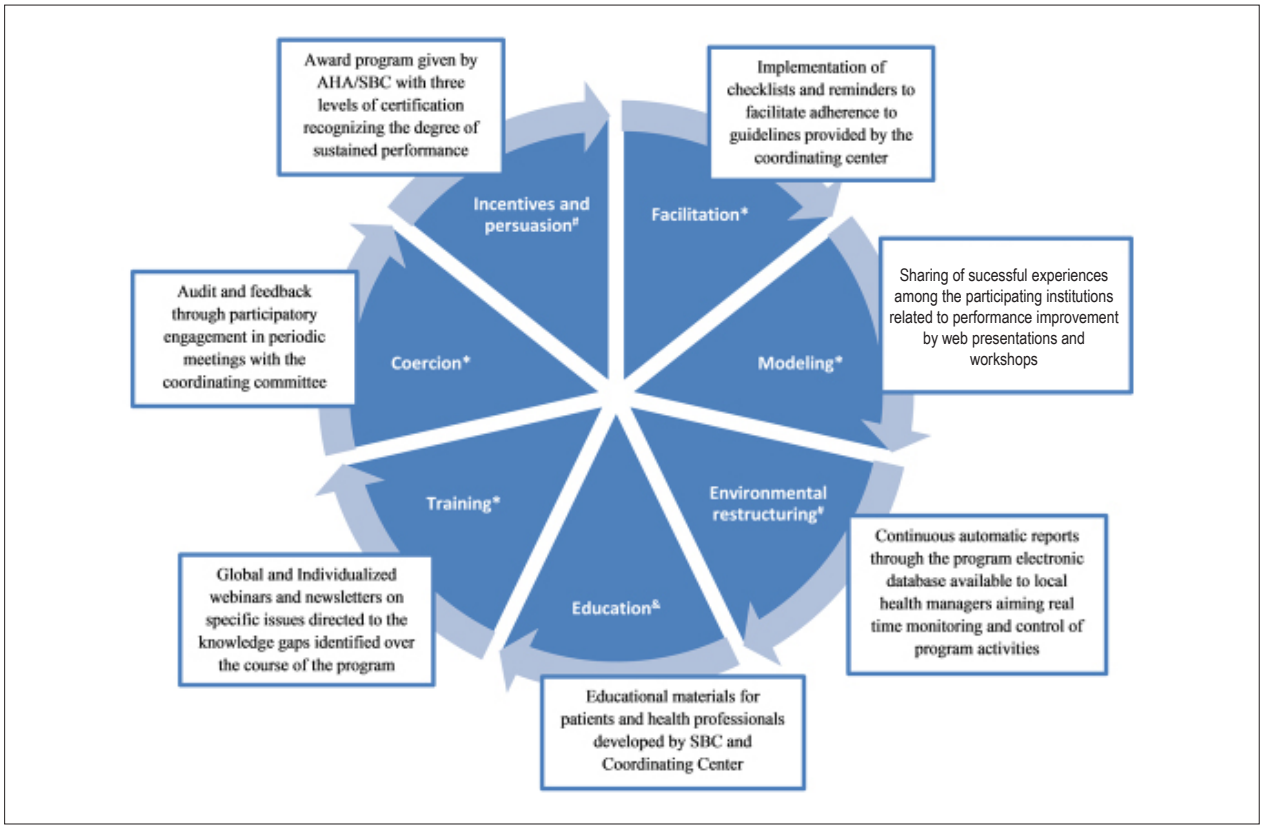

Figure 1 – *Intervention axes *Target of behavior change: health professionals &Target of behavior change: Patients and health professionals # Target of behavior change: Health managers.*

The longitudinal effect of the program on HF, ACS and AF will be assessed by comparing the overall rates of adherence to the recommendations before and after its implementation in the participating institutions on a quarterly basis, using a generalized linear mixed-effect model (GLMM) for time trend analysis over a time horizon of 18 months. It will be expressed by means of proportions and their respective 95% confidence intervals. It is expected that the random effect approach used by GLMM will account for between-site differences at baseline.[29]

Quality of life scores will be calculated using the methodology reported in the WHOQOL-BREF questionnaire manual.[30] The total score consists of the average of the scores of the four domains of the instrument (physical health, psychological health, social relationships and environment).[30] The internal consistency of the instrument will be calculated using the Cronbach's alpha coefficient. It shall be considered appropriate a value above 0.7.

The results observed over time in the participating institutions on the dependent variables of mortality, readmission rate, length of stay, variation in quality of life and in health perception will be adjusted by multivariable GLMM for demographic, clinical and socioeconomic variables, disease severity, risk factors, initial self-perception of health (NRS), level of health literacy and degree of specific and overall adherence of the institution to clinical recommendations. The variables will be included in the model when associated in the univariate or bivariate analysis ($p < 0.20$) and according to clinical relevance. Odds ratios or relative risks will be calculated, as appropriate, with respective 95% CI.

All analyses will be two-tailed and performed independently for each arm of the protocol using a 0.05 significance level.

Discussion

Why is this project needed?

In Brazil, a large country with a complex universal healthcare system,[1] the quality of cardiovascular care has been the subject of evaluation and concern. Patient access to the various levels of healthcare varies throughout the country and the quality of care delivered is highly heterogeneous.[1,2]

As in other parts of the world and in spite of medical society efforts in publishing clinical guidelines, mortality related to CVD remains high, reflecting the difficulty of patients having access to recommended therapies and care at appropriate times.[31,32]

Registries performed by SBC in multiple regions of Brazil have shown a high variation in the quality of care delivered for cardiovascular conditions of high economic burden,[32,33] such as coronary artery disease (CAD)[3,34] HF,[4] stroke, and AF.[35] These registries have shown that adherence to evidence-based therapies remains suboptimal and, at least for HF, the lack of optimal therapies is more critical in the public non-academic institutions of the poorest regions of Brazil.[4] It was also observed that morbidity and mortality related to HF are much higher than those observed in developed countries, even when adjusting for region, number of hospital beds and type of institution. The Brazilian registries have contributed enormously in demonstrating how these highly prevalent conditions are being approached across the country, but they have not addressed the gap in the implementation of interventions that may have prevented improvements in the quality of care. Furthermore, they have not controlled for situations where specific therapies are not recommended or are contraindicated.[3,4,34,35]

The two randomized trials (BRIDGE-ACS and IMPACT-AF) performed in Brazil for testing multifaceted interventions to promote adherence to guideline recommendations have shown that the implementation of QI interventions is feasible and can be effective.[6,7] However, these studies did not consider barriers related to local context, did not test if the results observed on adherence to recommendations are sustained over time or the effect of the interventions on patients' quality of life.[6,7] The BRIDGE-ACS trial, for example, which was performed mostly in academic institutions,[36] achieved at most 68% adherence to acute therapies and only 51% adherence if all acute and discharge therapies were considered, with no impact on 30-day mortality.[6] The GWTG program show that hospitals achieving at least 85% of compliance to evidence-based therapies reached better results on clinical outcomes.[37,38]

These findings provide a compelling argument in support of the implementation of a QI initiative in Brazilian hospitals that considers the complexity of the local reality and that has already been tested and proven effective elsewhere. The GWTG program, implemented in nearly 50% of all U.S. hospitals, has shown a sustained effect on mortality, length of stay and costs.[39] There is thus the potential to decrease the economic burden imposed by ACS, HF and AF on the Brazilian health system.

What is different in the Brazilian program?

Despite the fact that the GTWG program has been deployed in the U.S. for more than 15 years, only as recently as 2016 has another country (China) taken advantage of a similar ACS program.[36] In Brazil we are starting the program in three different dimensions: ACS, AF and HF. A nationwide quality program focusing on multiple conditions, including outpatient clinics has never been tested within the GWTG experience.[8,22] Also, the notion of patient-reported outcomes including quality of life has been contemplated for the BPC program and may help ministries and cardiology societies in directing health policies to local needs.

The identification of barriers and facilitators in each hospital is considered one of the key steps in the success of clinical implementation strategies. In this project, we are using as a conceptual model a didactic framework proposed by Michie, Stralen and West,[24] which integrates dynamic and interactive mechanisms to promote behavioral changes resulting from the interaction between the individual (capability and motivation) and the environment (opportunities).[24] This model will also help the coordinating center in identifying and acting on specific institutional needs during the course of the project. In doing so, in some institutions, intervention will be focused on improving capacity, in others on increasing

motivation, and still in others to increase or to restrain the supply of opportunities, individually or jointly, depending on the objectives of each institution. Interventions such as the award program that was considered one of the keys for success in the GWTG experience will be emphasized in all participating institutions.[40]

Lessons learned from the IHI open school experience, such as shaping the audit and feedback intervention with run charts, will be also used in this project.[41] These approaches consider institutional longitudinal data on the several quality metrics not only in relation to the average benchmarks of the other participating institutions, but also to the goal established for that institution by the median line of the scores obtained for the entire period of observation.[27,41] This feedback loop allows the institution to continuously evaluate itself and redesign processes in rapid improvement cycles,[25,26] considering how their performance differs from the objective and whether adjustments made in their multidisciplinary interventions are resulting in sustained improvement.

Conclusion

This novel QI program will be provided to selected public institutions in Brazil addressing issues pertaining to the local context that will allow for the identification of specific barriers to the adoption of standards of care. It has the potential to provide solutions that can result in sustained improvement in adherence to evidence-based therapies and patient outcomes.

It is hoped that the implemented strategies will contribute to creating an organizational culture focused on the construction and exchange of knowledge among the institutions nationwide, thereby advancing the quality of cardiovascular health care in Brazil.

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Author contributions

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Ethics approval and consent to participate

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*Supplemental Materials

For additional information, please click here.

Implementation of Healthcare Quality Improvement Programs

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Short Editorial related to the article: Implementation of a Best Practice in Cardiology (BPC) Program Adapted from Get with the Guidelines in Brazilian Public Hospitals: Study Design and Rationale

The incidence and prevalence of cardiovascular disease are increasing worldwide.[1-3] This is partly due to population aging and the accumulation of risk factors associated with these diseases. In Brazil, the life expectancy of the population in 2019 was estimated at 76.6 years in a population of 211,652,819 people, assessed by IBGE. In the same year, approximately 12,168,390 hospitalizations were registered in the public healthcare system (in Brazil, SUS) — Ministry of Health — with approximately 1,200,000 due to cardiovascular diseases (10% of the total).[4] In addition, the mortality related to cardiovascular diseases remains high, around 29% of the annual causes of death.[5] Therefore, we observe the great impact of these diseases with regard to the occupation of hospital beds and mortality in Brazil. In this scenario, chronic disease management programs have shown that monitored and multidisciplinary monitoring improves adherence to pharmacological and non-pharmacological treatment determines optimization of therapy, decreases the number of hospitalizations directly related to the disease, promoting an important improvement in the quality of life and reduction of hospital costs.[6-8] Brazilian records have shown adherence to extremely low medical guidelines.[9] The reasons for poor performance in implementing clinical guidelines include barriers related to the health system itself, medical commitment and improvement, multidisciplinary involvement and the patient's own involvement in healthcare. Some studies suggest that about 30%–40% of patients do not receive healthcare according to the current scientific evidence, while 20% or more of the healthcare provided are not necessary or potentially harmful. The strategies developed to optimize adherence to current guidelines have demonstrated success in the management of these patients. This chronic disease management, focused on the quality of evidence-based care, can promote the reduction of clinical events. Some studies on management and quality improvement have shown reduced rates of hospital readmission in 30 days with the adoption of these measures.[10,11] Other models, in performance monitoring associated with strategies for implementing guidelines, promote the improvement of healthcare and reduction of outcomes. The encouragement of healthcare and quality measures are heterogeneous in different regions and among Brazilian institutions, resulting in extremely varied outcomes. The association of performance measures, detection of opportunities for improvement and development of strategies to increase adherence to good health practices are fundamental to optimize results.

In this scenario, the development of national protocols and studies on the management of cardiovascular diseases, focusing on the implementation of models and tools to improve the quality of healthcare and implementation of adherence to best practices, has a fundamental role in assessing feasibility and results.[12]

Keywords

Cardiovascular Diseases/mortality; Prevalence; Guidelines as Topic; Aging; Risk Factors; Bed Occupancy; Drug Therapy; Quality Improvement; Cost Savings.

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Quercetin Ameliorates Lipid and Apolipoprotein Profile in High-Dose Glucocorticoid Treated Rats

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Abstract

Background: **Glucocorticoids (GCs) are widely prescribed for the treatment of numerous clinical disorders due to their anti-inflammatory and immune-modulatory properties and one of the most common untoward effects of these drugs is dyslipidemia.**

Objective: **To evaluate the effect of quercetin, a plant-derived flavonoid, on the lipid profile of high-dose glucocorticoid treated rats.**

Methods: **A total of 32 Sprague-Dawley rats, were randomly distributed among four groups (8 rats per group) and treated for 6 weeks with one of the following: (i) normal saline; (ii) 40 mg/kg methylprednisolone sodium succinate (MP); (iii) MP + 50 mg/kg quercetin; (iv) MP + 150 mg/kg quercetin. MP was injected subcutaneously, and quercetin was administered by oral gavage 3 days a week. At the end of the study, the animals' lipid profile was measured by enzymatic kits. Data were analyzed and statistical significance was set at $p<0.05$.**

Results: **The mean serum total cholesterol (TC), triglyceride (TG) and LDL levels were drastically increased in GC-treated animals compared with the control group. Both doses of quercetin (50 and 150 mg/kg) ameliorated TC (43% and 45%), LDL (56% and 56%) and TG (46% and 55% respectively). Apo B/A1 ratio decreased more than 20% following quercetin intake and the decline in TC/HDL, TG/HL, LDL/HDL ratios were significant.**

Conclusions: **These data suggest that quercetin intake with both doses of 50 and 150 mg/kg could be considered as a protective agent for glucocorticoid-induced dyslipidemia. (Arq Bras Cardiol. 2020; 115(1):102-108.)**

Keywords: **Rats, Sprague-Dawley; Anti-Inflammatory Agents; Quercetin; Glucocorticoids; Dyslipidemias; Triglycerides; Cholesterol.**

Introduction

Glucocorticoids such as prednisone, methylprednisolone, and dexamethasone are widely prescribed for the treatment of numerous clinical disorders, including pulmonary, gastrointestinal, hematological, skin, and renal diseases, as well as organ transplants, particularly due to their anti-inflammatory and immune-modulatory properties.[1] Although these drugs have such benefits, their adverse effects such as hyperglycemia, hypertension, hyperlipidemia, osteoporosis, muscle atrophy and obesity must be taken seriously.[2] Impaired lipid metabolism, as one of the most common undesirable reactions, in high-dose or long-term GC users, resembles Cushing's syndrome. In other words, hypercholesterolemia and hypertriglyceridemia are highly prevalent in patients undergoing GC therapy for prolonged periods and may ultimately lead to risks for atherosclerosis.[3-4] However, when the administration of these immunosuppressive drugs is inevitable, one should look for some drugs or natural products to minimize their untoward effects.

Quercetin, 3,3',4',5,7-Pentahydroxyflavone, 2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one, C15H10O7, is a plant-derived flavonoid, isolated from onions, apples, grapes, leafy vegetables and tea.[5,6]

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This naturally occurring polyphenol compound is generally known for its antioxidant and anti-inflammatory properties and is reported to enhance the antioxidant defense system, and decrease the incidence of cardiovascular, neoplastic and inflammatory diseases.[7-9] Since the oxidant-antioxidant balance and inflammation status play an important role the etiology of many diseases, flavonoid compounds have been in the spotlight as natural preventive or therapeutic agents.[10,11] In addition, some previous studies reported the beneficial impact of quercetin on metabolic syndrome and lipid metabolism.[12,13] The aim of this study is to evaluate the effect of quercetin on lipid profile of rats treated with high-dose glucocorticoid.

Materials and methods

Animals

A total of 32 Sprague-Dawley rats, aged 6-7 months, weighing 210±30 grams were obtained from the Razi Institute (Karaj, Iran). The animals were acclimatized to the standard laboratory conditions (temperature 20-25°C, and a 12-h light/dark cycle) for 10 days before the beginning of the main experiment. Clean water and pelleted standard chow diet (Danbehparvar, Thran, Iran) were provided *ad libitum*. The experimental protocol was in accordance with the Principles of Laboratory Animal Care.[14] The sample size was calculated with 80% power, using a two-sided test at the 5% significance level and based on the effect size of 0.5.

Chemicals

Methylprednisolone sodium succinate (MP) was used as the glucocorticoid (SOLU-MEDROL, Pfizer Pharmaceuticals, NY, U.S.A) for generating GC-induced dyslipidemia.[15] Quercetin, with a purity of 95%, was obtained from Sigma-Aldrich Chemicals (St. Louis, MO, U.S.A) and the quercetin suspension was prepared by adding quercetin to 0.05% aqueous carboxymethyl cellulose (CMC) solution immediately before being administered by oral gavage.

Experimental procedure

Thirty-two animals were randomly distributed into four groups, using the block randomization scheme. Each experimental group contained eight rats, which were treated for six weeks. All groups were injected subcutaneously (s.c.) with MP (40 mg/kg body weight), except the control group, which received normal saline solution three days a week. Each of the three glucocorticoid-injected groups received one of the following treatments: CMC as placebo, 50 mg/kg quercetin or 150 mg/kg quercetin. All treatments were given three days a week *per os*. At the end of the study all animals were anesthetized with an intra-peritoneal (i.p.) injection of ketamine together with xylazine (50 mg/kg and 30 mg/kg respectively).[15,16] Blood samples were collected by cardiac puncture and were immediately centrifuged at 3000 rpm for 10 min for serum isolation and stored at -80°C until analysis of the lipid profile. The rats were fasted for 12-14 hours and all blood samples were collected between 8 and 10 am. Commercially available enzymatic kits were used to measure the serum concentrations of total cholesterol (TC), high density lipoprotein (HDL), and triglycerides (TG) in duplicate tests (Pars Azmoon Co., Tehran, Iran) and Apo A and Apo B were measured by immunoturbidimetric methods (biorexfars LTD, Iran). Low-density lipoprotein (LDL) level was calculated using the Friedewald equation.[17] Animals were weighed at the beginning and end of the study.

Statistical analysis

All data were presented as mean ± standard deviation (SD) and analyzed by the Statistical Package for Social Sciences (version 23.0; SPSS Inc., Chicago, USA). The Kolmogorov-Smirnov test was used to assess the normality of the data. Statistical differences between groups were evaluated using analysis of variance (one-way ANOVA) followed by Bonferroni *post hoc* test. Statistical significance was set at $p<0.05$.

Results

Although the average body weight of rats was the same in all groups at the beginning of the experiment, after six weeks of intervention, all glucocorticoid-treated animals showed a significant weight reduction compared with their own initial weights and with their age-matched controls (Table 1).

Following six weeks of methylprednisolone injection, the mean plasma cholesterol and triglyceride levels were drastically increased in glucocorticoid-treated animals compared with the control group. Both doses of quercetin (50 and150 mg/kg) improved the hypercholesterolemia and hypertriglyceridemia in comparison with the MP group, and the same trend was observed for LDL levels. In addition, the MP injection caused a moderate increase in HDL levels, which was not significantly changed following quercetin supplementation. However, the reduction in TC/HDL, TG/HDL and LDL/HDL ratios were statistically and clinically significant. Moreover, Apo B/A1 ratio decreased more than 20% following quercetin intake (Table 2; Figures 1-3). It seems that a higher dose of quercetin does not have a conspicuous superiority for cholesterol and apolipoprotein level improvement. However, a negative correlation was found between the quercetin dose and TG, as well as TC/HDL (-0.87 and -0.75 respectively).

Discussion

Our findings revealed that the administration of high-dose glucocorticoid for 6 weeks drastically increased serum concentrations of total cholesterol, LDL and triglycerides. However, oral supplementation with two different doses of quercetin, as a naturally occurring flavone that was previously reported to be beneficial in metabolic syndrome, conspicuously reversed the undesirable effects of methylprednisolone. Different doses of quercetin were chosen, since the lower one can be provided by a quercetin-rich diet and the higher one might be taken as commercially available supplements.[18] Needless to say, the different metabolic rates of rats and humans were taken into account for dose determination.[19] The final results indicated that 150 mg/kg quercetin were not much more effective than 50 mg/kg to improve lipid profile, except

for TG concentrations, which decreased to the control level as a result of high dose quercetin administration. Methylprednisolone also caused a moderate increase in HDL levels, which was not significantly changed following quercetin supplementation.

Although the hyperlipidemic impact of GCs has been noticed for the last decades, the molecular mechanisms are not well recognized yet. Some *in vitro* and *in vivo* studies demonstrated that these anti-inflammatory drugs can directly increase hepatic HDL production, up-regulate lipoprotein lipase activity and impair LDL catabolism by reducing hepatic LDL receptors expression and activity.[15,20] Consequently, they contribute to fatty liver development by increasing fatty acid synthesis and decreasing β oxidation.[21]

On the other hand, flavonoids have been described as lipid metabolism modulators. They mostly act through the inhibition of phosphodiesterase, alteration of hepatic cholesterol absorption and triglyceride production and secretion.[22-25] In addition, quercetin as a potent antioxidant distributed in both the lipid bilayer and aqueous phase of the cell, can suppress lipid peroxidation by radical scavenging activity.[26] Large studies have shown that ApoB/Al ratio is superior to the total cholesterol and TG for cardiovascular risk prediction in both genders and at all age ranges.[27] Given that the ApoB/Al ratio is a measurement of the number of ApoB atherogenic particles over the number of ApoAl anti-atherogenic particles, there is also a possibility that it is a more important factor than the amount of lipids carried per particle. In the present study, quercetin intake significantly decreased ApoB/Al ratio, which might be an important indicator of lower cardiovascular risk in the future.[27,28]

At the end of intervention, all glucocorticoid-treated animals showed a significant weight reduction compared to their controls, which might be due to glucocorticoid-induced anorexia in rats, which has been previously reported,[29] or to severe proteolysis and muscle loss.[30] One of the limitations of this study was the lack of precise data about the animals' food intake, which could be very useful for the interpretation of GC-induced weight loss in rats. Overall, our findings are in accordance with previous studies reporting the beneficial effects of flavonoids on lipid metabolism.[31] This is the first research evaluating the impact of quercetin on GC-induced hyperlipidemia. However, the hypolipidemic effect of some other flavonoids has been reported in GC-treated rats.[32] Other favorable properties of quercetin in improving bone density and modifying blood glucose, make this flavonoid an excellent choice to control glucocorticoid side effects.[33]

Conclusion

Quercetin administration, at both doses of 50 and 150 mg/kg, was able to reverse the untoward effects of high-dose glucocorticoids on the lipid profile of rats, and might be considered for combination therapy with GCs to minimize the resulting dyslipidemia.

Table 1 – Initial and final body weight (gram) of experimental groups

Body weight	Control	MP	MP+Q50	MP+Q150
Initial	212±29	212±27	210±28	212±28
Final	214±30†	182±22*,‡	185±20*,‡	180±16*,‡

*Data are presented as Mean±SD. N=8 for all groups. MP, methylprednisolone; Q50, quercetin 50 mg/kg; Q150, quercetin 150 mg/kg; Analysis of variance (ANOVA) followed by Bonferroni test. * p<0.05 compared with control group, † p<0.05 compared with MP group, ‡ p<0.05 compared with the initial weight of same group.*

Table 2 – Lipid profile of experimental groups after six weeks of intervention

	Control	MP	MP+Q50	MP+Q150	p value
TC (mg/dl)	89.12±3.35	193.50±12.77*,‡	108.75±15.47*,†	105.87±11.25*,†	<0.001
HDL (mg/dl)	34.25±3.69	41.37±5.75*	38.25±4.77	39.00±4.07	=0.03
LDL (mg/dl)	41.87±3.79	119.22±12.70*,‡	52.72±15.15†	52.22±10.87†	<0.001
TG (mg/dl)	65.00±4.34	164.50±9.36*,‡	88.87±12.93*,†	73.25±11.33†,‡	<0.001
TC/HDL	2.62±0.27	4.76±0.86*,‡	2.86±0.42†	2.74±0.47†,‡	<0.001
TG/HDL	1.92±0.29	4.05±0.71*,‡	2.33±0.34†	1.92±0.51†	<0.001
LDL/HDL	1.24±0.23	2.95±0.73*,‡	1.39±0.43†	1.36±0.38†	<0.001
Apo B/ Al	0.93±0.16	1.63±0.19*,‡	1.25±0.30†	1.06±0.28†	<0.001

*Data are presented as Mean±SD. n=8 for all groups. MP: methylprednisolone; Q50: quercetin 50 mg/kg; Q150: quercetin 150 mg/kg; TC: total cholesterol; TG: triglyceride; HDL: high-density lipoprotein; LDL: low-density lipoprotein; ApoB/Al: apolipoprotein B to apolipoprotein Al ratio; Analysis of variance (ANOVA) followed by Bonferroni test. * p<0.05 compared with control group, † p<0.05 compared with MP group, ‡ p<0.05 compared with MP+Q50.*

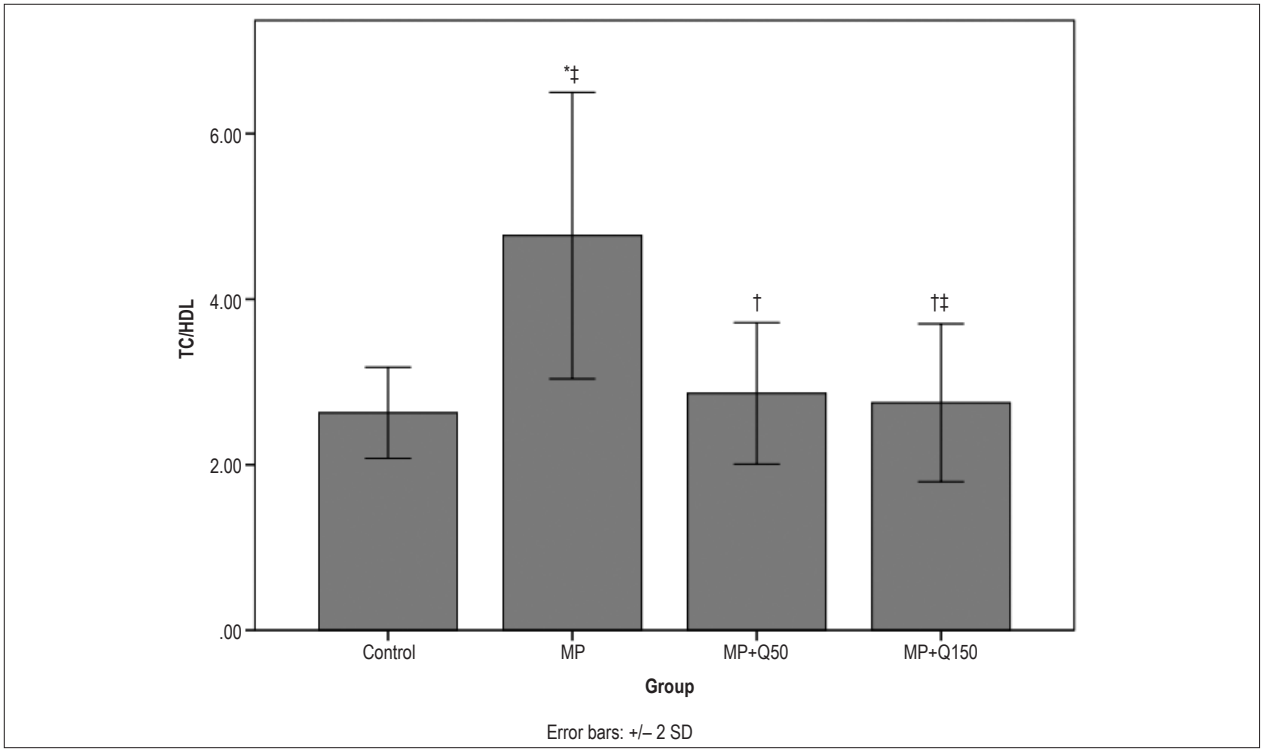

Figure 1 – *Mean of the total cholesterol to HDL ratio in the different groups. Data presented as Mean±SD. N=8 for all groups. MP: methylprednisolone; Q50: quercetin 50 mg/kg; Q150: quercetin 150 mg/kg; TC: total cholesterol; HDL: high-density lipoprotein; * p<0.05 compared with control group, † p<0.05 compared with MP group, ‡ p<0.05 compared with MP+Q50.*

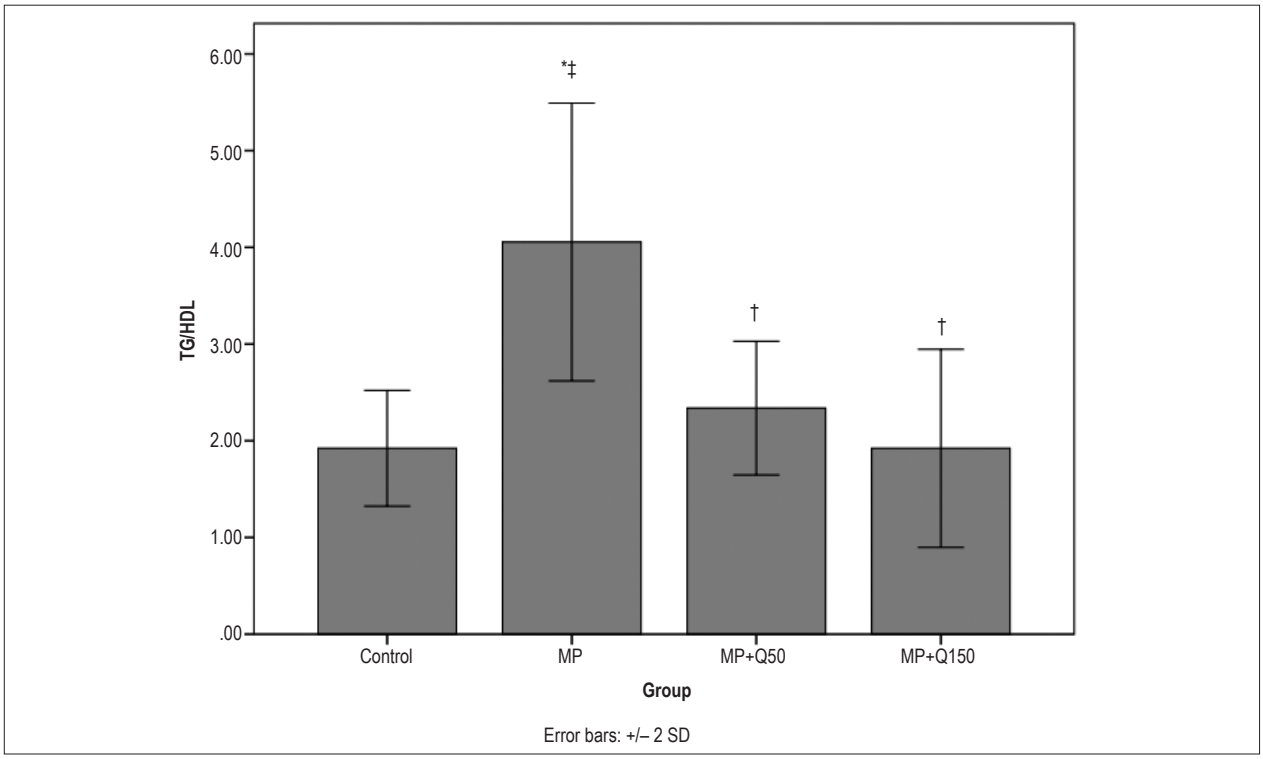

Figure 2 – *Mean of triglycerides to HDL ratio in the different groups. Data presented as Mean±SE. n=8 for all groups. MP: methylprednisolone; Q50: quercetin 50 mg/kg; Q150: quercetin 150 mg/kg; TG; triglyceride; HDL: high-density lipoprotein; * p<0.05 compared with control group, † p<0.05 compared with MP group, ‡ p<0.05 compared with MP+Q50.*

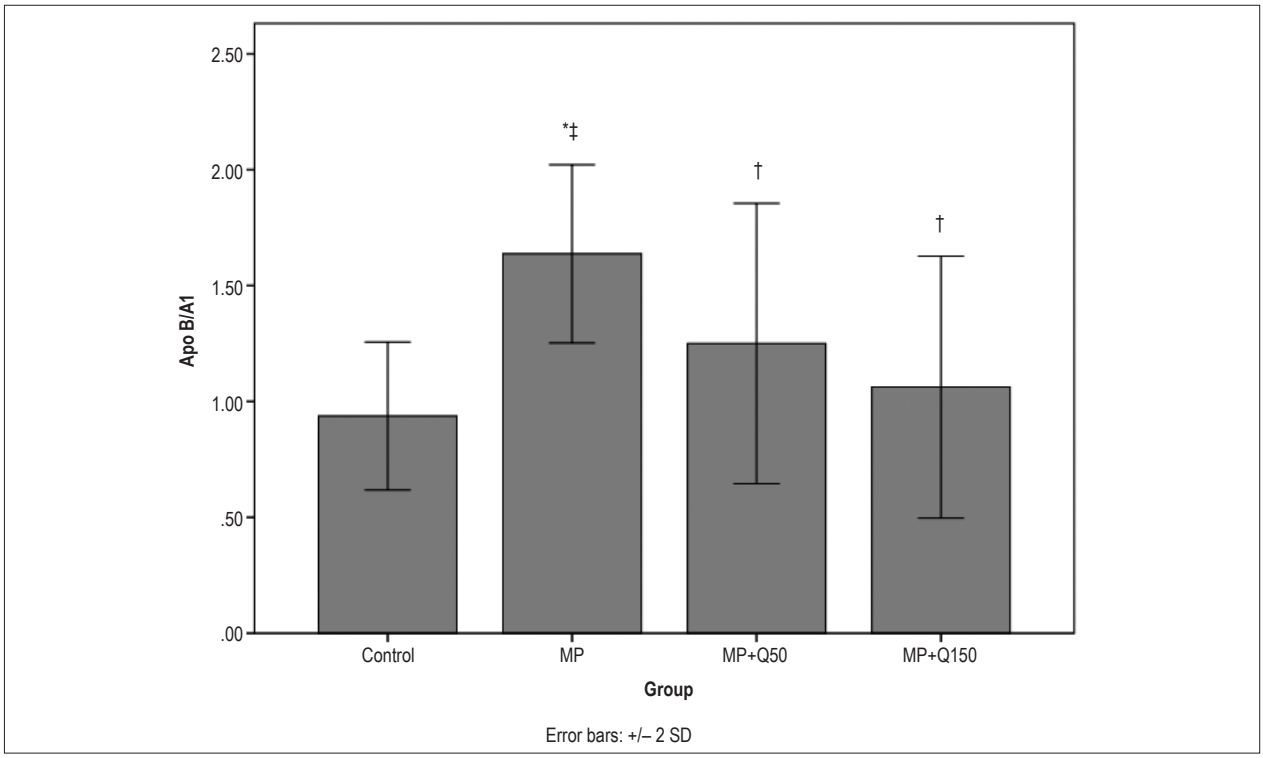

Figure 3 – *Mean of apolipoprotein B to apolipoprotein AI ratio in the different groups. Data presented as Mean±SE. n=8 for all groups. MP: methylprednisolone; Q50: quercetin 50 mg/kg; Q150: quercetin 150 mg/kg; ApoB/AI: apolipoprotein B to apolipoprotein AI ratio; * p<0.05 compared with control group, † p<0.05 compared with MP group, ‡ p<0.05 compared with MP+Q50.*

Author contributions

Conception and design of the research: Derakhshanian H, Djalali M, Djazayery A, Javanbakht MH, Dehpour AR; Acquisition of data: Derakhshanian H, Zarei M, Eslamian G; Analysis and interpretation of the data: Derakhshanian H, Javanbakht MH, Zarei M, Eslamian G, Mirhashemi SS; Statistical analysis: Derakhshanian H, Mirhashemi SS, Mirhashemi SS, Mirhashemi SS, Mirhashemi SS, Mirhashemi SS, Mirhashemi SS; Obtaining financing: Derakhshanian H, Djalali M, Djazayery A; Writing of the manuscript: Derakhshanian H; Critical revision of the manuscript for intellectual content: Derakhshanian H, Djalali M, Djazayery A, Javanbakht MH, Hekmatdoost A, Dehpour AR.

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This study was approved by the Ethics Committee of the Tehran University of Medical Sciences under the protocol number 11157. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

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Original Article

Short Editorial: Quercetin Ameliorates Lipid and Apolipoprotein Profile in High-Dose Glucocorticoid Treated Rats

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Short Editorial related to the article: Quercetin Ameliorates Lipid and Apolipoprotein Profile in High-Dose Glucocorticoid Treated Rats

Flavonoids, such as anthocyanins, flavonols, flavanols, flavanones, flavones, and isoflavones are the most abundant polyphenols in the human diet. The flavonol quercetin is one of the most studied among these compounds.[1-3] Quercetin is a secondary plant metabolite of the flavonol subclass of flavonoids present in many fruits and vegetables, e.g. apples, grapes, onions and peppers.[3,4]

In the past years, evidence showed that quercetin is a potent antioxidant and anti-inflammatory natural product.[4] Quercetin is able to protect cells from oxidative damage caused by reactive species and activate antioxidant enzymes, such as heme oxygenase and nuclear factor erythroid 2–related factor 2 in different models.[5-7] Regarding cardiovascular health, in vitro, animal and human studies have reported beneficial effects, including improving lipid profile,[4,5,8-10] as explored in the study of Derakhshanian et al. presented in this section.

The study by Derakhshanian et al.[11] addresses the effect of quercetin on hypercholesterolemia induced by high doses of methylprednisolone in rats, novel use of this bioactive compound.[11] Glucocorticoids (GC) such as methylprednisolone are widely used in the treatment of different diseases. However, high dose GC can lead to adverse effects, including changes in lipid metabolism.[12] The authors tested two doses of quercetin for six weeks and obtained a reduction in total cholesterol (CT), low-density lipoprotein cholesterol (LDL), triglycerides (TG) and high-density lipoprotein cholesterol (HDL), CT/HDL, TG/HDL and LDL/HDL ratios and Apolipoprotein B (Apo B)/ Apolipoprotein (A1) ratio, an indicator of plasma atherogenic balance[13] and a potential cardiovascular risk marker.[14] The authors also discuss that little is known about the mechanisms by which GCs alter blood lipids, and suggest that the effect of quercetin could be attributed to its antioxidant property and glucose-modulating potential.[11] An interesting point of Derakhshanian et al.[11] work is that both doses produced a protective effect on glycosteroid-induced hypocholesterolemia, excluding a superior effect of the higher dose employed. It is important to note that previous research about human intake estimative ranges from 3 - 40mg in Western diet pattern to 250mg in high fruit and vegetable diet.[3] Thus, the lowest dose could be obtained from a diet rich in quercetin sources, as pointed by the present paper.[11]

The interest in natural compounds for the management of different conditions has grown in recent years due to their safety potential in comparison to synthetic compounds.[4] Although there are still many questions about the use of flavonoids in human health, the study by Derakhshanian et al.[11] adds data about the adjuvant role of quercetin in metabolic disorders.

Keywords

Quercetin; Antioxidants; Anti-Inflamatórios Agents; Flavonoids; Rats; Glucocorticoids.

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Cardiovascular Imaging and Interventional Procedures in Patients with Novel Coronavirus Infection

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic is a huge challenge to the health system because of the exponential increase in the number of individuals affected. The rational use of resources and correct and judicious indication for imaging exams and interventional procedures are necessary, prioritizing patient, healthcare personnel, and environmental safety. This review was aimed at guiding health professionals in safely and effectively performing imaging exams and interventional procedures.

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a huge challenge worldwide. The rapid spread of the infection has grown into a global level pandemic. As by May 20th, COVID-19 had already reached 185 countries, with 4,995,127infected individuals and 160,706 deaths.[1] Despite underreporting due to test unavailability, Brazilian statistics have shown increasing numbers, with 291,579 infected patients and 18,859 deaths registered to date.[2]

Keywords

Coronavirus; COVID-19; Pandemics; Communicable Diseases, Emergency; Cardiovascular Diseases/prevention and control; Diagnostic Imaging; Medical Examination/methods; Diagnostic Techniques and Procedures.

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The most effective strategy to control COVID-19 spread is home confinement, via quarantine and social distancing.[3] Hospitals, clinics and medical offices have been following the recommendations of national and international medical societies to protect patients without COVID-19 from the risk of infection, while, at the same time, providing adequate care to those with COVID-19.[4,5] In light of this, procedures considered elective should be timely rescheduled.[6]

The proper management of infected patients requires the adoption of a series of measures involving the interaction of several hospital sectors and the training of multidisciplinary teams. The majority of patients with the most severe COVID-19 forms have comorbidities, cardiovascular diseases being frequent.[7-9] In addition, cardiovascular complications of COVID-19 occur in 7% to 40% of the cases, manifesting as myocardial injury, thrombosis, ventricular dysfunction, myocarditis, arrhythmias, and shock.[10-12] These complications have significant prognostic implications, such as a high mortality rate.[11]

The diagnosis and follow-up of patients with those complications usually require performing imaging tests, such as electrocardiography, transthoracic echocardiography (TTE), computed tomography (CT), in addition to cardiac magnetic resonance imaging (CMRI) and coronary computed tomography angiography (CCTA). These tests should not be performed routinely in all infected patients, their indication being preferably based on the benefit added to the patient's care and considering the safety of the staff conducting the tests. The need for rational, responsible, and thorough use of resources reinforces the importance of the clinician not only in identifying patients who need the test, but also in selecting the proper tests and in accurately interpreting their findings.

This review was aimed at: a) helping physicians to properly indicate and implement cardiovascular tests and interventional procedures in their clinical practice for patients with suspected

or confirmed COVID-19; b) guiding physicians to safely perform the tests and procedures, preventing environmental and healthcare personnel contamination.

2. Approach to patients with suspected or confirmed COVID-19

The approach to patients with suspected or confirmed COVID-19 should begin with the proper characterization of their signs and symptoms. Those with mild symptoms, such as cough, fever, and sore throat, can be followed up in low-complexity units or at their homes. Those with more severe symptoms (oxygen saturation <94% in room air, respiratory distress, tachypnea, hypotension, acute respiratory failure) should be referred to specialized centers. On the initial contact, symptomatic individuals should be given a surgical mask and directed to a specific room aimed at respiratory isolation; in addition, they should receive instructions on hand hygiene to prevent contamination of the environment and other individuals.[4]

The identification of at-risk patients should comprise the assessment of clinical comorbidities known to be associated with a more severe course of the disease.[7,13] Patients with arterial hypertension (AH), chronic cardiovascular disease, diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), or chronic kidney disease, in addition to immune suppressed or elderly patients, are more susceptible to develop complications, being considered a risk group.[4]

Patients with severe symptoms and/or of the risk group are prone to develop COVID-19-related cardiovascular complications.[8,9] Zhou et al.,[9] in a cohort with 191 patients, have reported high prevalence of AH (30%), DM (19%), coronary arterial disease (CAD - 8%), and COPD (3%).[9] Of the 54 deceased patients (28%), 67% had a comorbidity, AH being identified in 48%, DM in 31%, and CAD in 24%. Advanced age was an independent predictor of mortality.9

Other important markers of severity in those patients are high serum levels of troponin, NT-proBNP, and D-dimer. Those with troponin elevation had more severe forms of COVID-19, with a higher incidence of acute respiratory distress syndrome (ARDS) and death.[11] High troponin levels are accompanied by an elevation in markers of inflammation, thrombosis and cardiac dysfunction, patients with those characteristics being more likely to develop acute heart failure and shock.[8,9,11]

On admission, patients with clinical or laboratory findings suggestive of more severe disease should have their cardiovascular function evaluated via clinical assessment, measurement of biomarkers, and imaging tests.[12,14] The most often performed imaging tests and interventional procedures are described in the following sections.

3. Echocardiography

Echocardiography has a well-established role in the diagnosis, prognostic assessment, and therapeutic guidance of several cardiovascular diseases. However, because it requires a close contact between examiner and patient, it poses a high risk of contamination. The pandemic has called for the urgent reorganization of echocardiography laboratories to minimize the exposure to COVID-19 and ensure the protection of patients and healthcare personnel.[5] In light of this, the Brazilian Society of Cardiology Cardiovascular Imaging Department has issued a document to aid healthcare professionals during this pandemic.[5]

Echocardiography should not be performed routinely during the pandemic, especially in patients with confirmed COVID-19. However, echocardiography professionals will continue to be exposed in certain clinical scenarios in which that exam can play a decisive role in the differential diagnosis and clinical management of more severely ill patients. COVID-19 is known to cause severe cardiovascular manifestations; in addition, previous cardiovascular disease is common in patients with COVID-19, being associated with worse prognosis.[9,14,15]

3.1. General Precautions

The provision of patient care amidst the pandemic should meet the following safety recommendations to minimize the risks of healthcare personnel and patient exposure to COVID-19: (a) to define whether the test is deemed essential on the occasion; (b) to assess in advance the risk of contamination; (c) to respect the general hand hygiene and contact restriction rules; and (d) to observe the rational and strict use of proper personal protective equipment (PPE) according to the test type and contamination risk.[5]

When the likelihood of COVID-19 is low (low-risk areas and negative SARS-CoV-2 test), TTE in an asymptomatic patient requires the echocardiographer to perform thorough hand hygiene and wear gloves and surgical mask, and the patient to wear surgical mask as well, during the test. When the risk is moderate to high (symptomatic patients with suspected or confirmed COVID-19), the safety measures include hand hygiene and use of gloves, surgical mask (or N95 mask, when available), gown, hair covers and eye protection (goggles or face shield) by the examiner. The patient must wear a surgical mask. When transesophageal echocardiography (TEE), an aerosol-generating procedure, is necessary, the N95 mask or similar must be added to the aforementioned PPE, for respiratory protection. In addition, shoe covers, as well as a protective cover for the transducer, are recommended. For patients with suspected or confirmed COVID-19 on non-invasive or invasive mechanical ventilation, respiratory protection should also be adopted when performing a TEE.[16] For inpatients, bedside echocardiography should be preferred, taking proper protective measures and reducing the number of individuals in the room to the lowest possible. The devices and transducers should be thoroughly cleaned and disinfected right after use according to the manufacturer's specifications. Echocardiography laboratory staff with the following characteristics should be kept away: aged over 60 years, immunosuppressed, pregnant, and with chronic diseases.[5,17]

3.2. Indications for Echocardiography in Patients at Low Risk of COVID-19

During the pandemic, the indication for echocardiography in patients at low risk of COVID-19 should be based on the proper use of the exam; in addition, the exam should only be performed if the resulting information is deemed essential for

the management of the case.[5] All elective echocardiographies, such as, TTE, TEE, stress echocardiography (SE) and fetal echocardiography (FE), should be postponed until such time as the pandemic has waned. The need for urgent echocardiography on an outpatient setting should be assessed on a case-by-case basis; however, an urgent exam is the one whose result can prevent an adverse event or hospitalization within 2 to 4 weeks.[17] In light of this, urgent echocardiography is recommended in the following situations: suspicion of new symptomatic heart disease [New York Heart Association (NYHA) functional class III/IV]; worsening of preexisting heart failure with severe symptoms (syncope, chest pain, NYHA functional class III/IV); cancer therapy with cardiotoxic drugs and suspected heart failure or previous reduction in ejection fraction; suspected severe symptomatic aortic stenosis; high pretest probability of infective endocarditis in a patient with valvular prosthesis and acute symptoms.[17] Routine echocardiography for the follow-up of patients without severe symptoms or noneligible individuals for urgent clinical, surgical or invasive therapy should be deferred or canceled. For inpatients, the indications for urgent echocardiography are usually the same as before the pandemic.

3.3. Indications for Echocardiography in Patients with Suspected or Confirmed COVID-19

Echocardiography remains an essential imaging technique during the coronavirus pandemic. The considerations "in whom", "how" and "where" to use it are fundamental to reduce the risks of contamination, and, at the same time, to ensure high-quality medical care. Some authors advocate the use of TTE in all patients with complicated COVID-19 (electrocardiographic changes, increased troponin levels, moderate to severe symptoms requiring hospitalization),[12,18] specially in the presence of previous cardiovascular disease. Although there is no formal indication supported by solid scientific evidence, it is worth noting the importance of assessing cardiac function because of the potential simultaneous occurrence of previous and acute cardiovascular disease in patients with severe COVID-19.

Zhou et al.[9] have reported heart failure in 23% of patients with COVID-19 and associated it with higher mortality (51.9% versus 11.7%).[9] It is not clear whether that heart failure rate was due to aggravation of a previous ventricular dysfunction, new heart disease or both. Patients with previous ventricular dysfunction can develop severe heart failure decompensation in severe COVID-19, accompanied by hypotension and/or cardiogenic shock. Several possibilities have been suggested for acute myocardial injury, such as direct viral effect (myocarditis), hypoxic injury, toxic effect via "cytokine storm", vasospasm, thrombosis, myocardial stunning due to stress cardiomyopathy, and hemodynamic instability.[19-21] The possibility that SARS-CoV-2 causes myocarditis has been widely discussed. In a series of 150 patients with COVID-19, the retrospective analysis of 68 deaths has attributed 53% of them to respiratory failure, 7% to myocarditis with circulatory shock, 33% to a combination of both, and 5% to unknown causes.[15] The authors have used clinical data to diagnose fulminant myocarditis, with no biopsy confirmation. Similarly, fulminant myocarditis has been reported in patients with and without fever, who had chest pain, ST-segment elevation with no coronary obstruction, and severe ventricular dysfunction, and who responded to salvage therapy with corticoid and immunoglobulins.[22,23] Although in these two studies CMRI had shown findings compatible with myocarditis, there was no histological confirmation.[22,23]

The differential diagnosis with myocarditis and stress cardiomyopathy necessarily includes acute coronary syndromes, which have also been reported in patients with COVID-19.[24,25] The intense inflammatory response and hemodynamic changes associated with severe COVID-19 might increase the risk of rupture of atherosclerotic plaques and/or thromboembolic phenomena in susceptible patients.[14] Even for those with neither fever nor cough, who have typical cardiac manifestations, COVID-19 should be considered in the differential diagnosis during the pandemic, and echocardiography can aid clinical judgment.

Cardiac arrhythmias are common in inpatients with COVID-19, being described in 16.7% of the cases in a Chinese cohort with 138 patients.[7] Echocardiography can be useful, especially for malignant ventricular arrhythmias, by diagnosing left ventricular dysfunction or preexisting structural heart disease.

Regarding severe pneumopathy and ARDS, association with pulmonary hypertension and right ventricular dysfunction should be assessed. Pericardial infusion has been reported as an exam finding associated with myocarditis (myopericarditis), usually without significant hemodynamic repercussion.[22,23]

In the following clinical scenarios, the indication for echocardiography in patients with COVID-19 seems defensible:[12,17,18,26]

- Suspected heart failure
- Enlarged heart on chest X-ray
- Clinically significant arrhythmias
- Chest pain with electrocardiographic changes and/or troponin elevation
- Hemodynamic instability and/or shock
- Suspected pulmonary hypertension and/or right ventricular dysfunction

For patients with severe COVID-19 admitted to the intensive care unit, bedside, and preferably point-of-care, echocardiography is recommended on admission and during the course of disease.[5,12]

3.4. Special Protocols During the Pandemic

3.4.1. Transthoracic echocardiography: the exam should have its length reduced to a minimum and be targeted at the suspected diagnosis. Because the risk of contamination increases as the duration of the exam lengthens, the use of focused echocardiography, rather than complete TTE, has been recommended.[5,17,26] Nevertheless, unnecessary repetition of exams should be avoided, and, according to the complexity of the case, complete TTE might be required to meet clinical demand. Images should be stored aiming at performing the off-line measurements, and electrocardiographic monitoring can be dismissed. Ideally one exclusive echocardiography device

should be dedicated to patients with COVID-19, and it should remain in the contaminated areas. Additional protective measures can be adopted, such as plastic film wrapping of the device and/or interposition of an acrylic (or plastic) barrier between the examiner and the patient. Portable or pocket ultrasound devices can be easily covered, transported, and disinfected; however, their diagnostic resources are limited (point-of-care). Echocardiographic contrast agents might be useful, and their use should be anticipated to prevent additional circulation in the exam room.[26] It is worth noting that contrast agents should not be used for critical patients with circulatory instability and severe pulmonary impairment.

3.4.2. Focused (point-of-care) echocardiography: may be important for the care of critical patients during the COVID-19 pandemic. Although not equivalent to complete TTE, focused echocardiography can confirm or exclude a specific diagnosis, supporting therapeutic decisions.[27] It can be performed by properly trained physicians already providing direct care to the patient in the intensive care unit, thus contributing to reduce the exposure of the echocardiographer. Portable or pocket ultrasound devices should be preferably used to facilitate access to bed and further disinfection.

3.4.3. Transesophageal echocardiography: there is special concern regarding TEE, because of the high risk of equipment and healthcare personnel contamination with droplets and aerosols. Thus the incremental value of TEE over TTE should be carefully assessed, and TEE should be avoided in most cases.[16] Whenever possible, other alternatives should be considered, such as repeating TTE or using another imaging technique with less contact between examiner and patient, such as CT and CMRI. To perform urgent TEE in hospitalized patients, the examiner should use complete PPE for respiratory protection, in addition to protective cover for the transducer.

3.4.4. Stress echocardiography: exercise stress echocardiography can increase the risk of contamination via droplets and should, thus, be deferred (patients at low risk of COVID-19) or not performed (patients with suspected or confirmed COVID-19). When there is proper indication and deferral is not possible or recommended, pharmacological stress echocardiography should be preferred for patients at low risk of COVID-19 (patient with cancer waiting for surgery and with high pretest probability of obstructive CAD). In addition, during the pandemic, selected cases of chronic CAD could be investigated by use of CCTA.

3.4.5. Fetal echocardiography: proper indication for FE remains the same during the pandemic, which is pregnancy with high risk of fetal heart disease;[16] the exam should be performed outside the hospital setting. At the moment, there is no indication for routine FE in mothers with suspected or confirmed COVID-19.

3.4.6. Lung ultrasonography: is an agile tool to assess lung involvement and to follow up the result of bedside therapeutic interventions. The following findings have been reported in COVID-19: thickening and irregularity of the pleural line with loss of continuity; several patterns of B lines (focal, multifocal, confluent); and lung consolidations (frequently subpleural).[28] Although those abnormalities are unspecific and found in other types of pneumonia, they are valuable to track the evolution of COVID-19 pneumonia. Pleural effusions are not frequent, and A lines appear during the recovery phase.

4. X-ray, Computed Tomography and Cardiac Magnetic Resonance Imaging

Pulmonary and cardiovascular imaging tests play an important role in the accurate diagnosis of COVID-19 complications. Chest X-ray is the most used exam, but CT might be necessary.[16] The CMRI might be required in patients with suspected myocarditis and/or Takotsubo syndrome.[16] However, before indicating CT and CMRI, some considerations should be made. Such tests pose a significant risk of contamination for patients and health professionals, not only those related to patient's transportation but also to direct contamination during the exam. The CMRI and CT should only be performed if the information resulting from the tests could help the patient's clinical management. Those exams should be indicated for stable patients with a minimum transportation risk, if performed at a safe environment, with strict adherence to local safety rules, and with the use of PPE by the professionals involved in patient's transportation and image acquisition.[16]

4.1. Chest X-ray

Chest X-ray is usually the first imaging test performed in patients with COVID-19 because of its low cost and ease of access, mainly in hospitalized patients who cannot be safely transported.[29] Chest X-ray has low sensitivity. In addition, X-ray findings are not specific to COVID-19, because they can also be associated with the flu syndrome, such as consolidations (47%), low-density opacities (33%), and pleural effusion (3%).[30] The imaging findings are predominantly peripheral, occurring most often within 10 to 12 days.[30] Figure 1 summarizes the major chest X-ray findings.

4.2. Chest Computed Tomography

Chest CT is a tool to support the diagnosis, while COVID-19 confirmation is based on viral reverse transcriptase polymerase chain reaction (RT-PCR) or serological tests. Performing screening CT for the identification of COVID-19 should not be encouraged.[29] Asymptomatic or mildly symptomatic patients should not undergo CT; however, for mildly symptomatic patients with access to neither RT-PCR nor serological tests, the benefit of performing CT is uncertain. For severely symptomatic, hospitalized patients, who can be transported safely, such as using a mask, CT should be considered when complications are suspected (pulmonary thromboembolism, pleural effusion, and superimposed bacterial infection).[29] Figure 1 summarizes CT findings and recommendations for performing CT.

The protocol recommends the use of low radiation doses, preferably with no contrast medium administration, which should be reserved for specific indications, such as to discard pulmonary thromboembolism.[29] In the first days after symptom onset, CT can be normal, which does not exclude COVID-19. The CT sensitivity and specificity reported for COVID-19 vary widely (60% to 98%, and 25% to 53%, respectively), probably

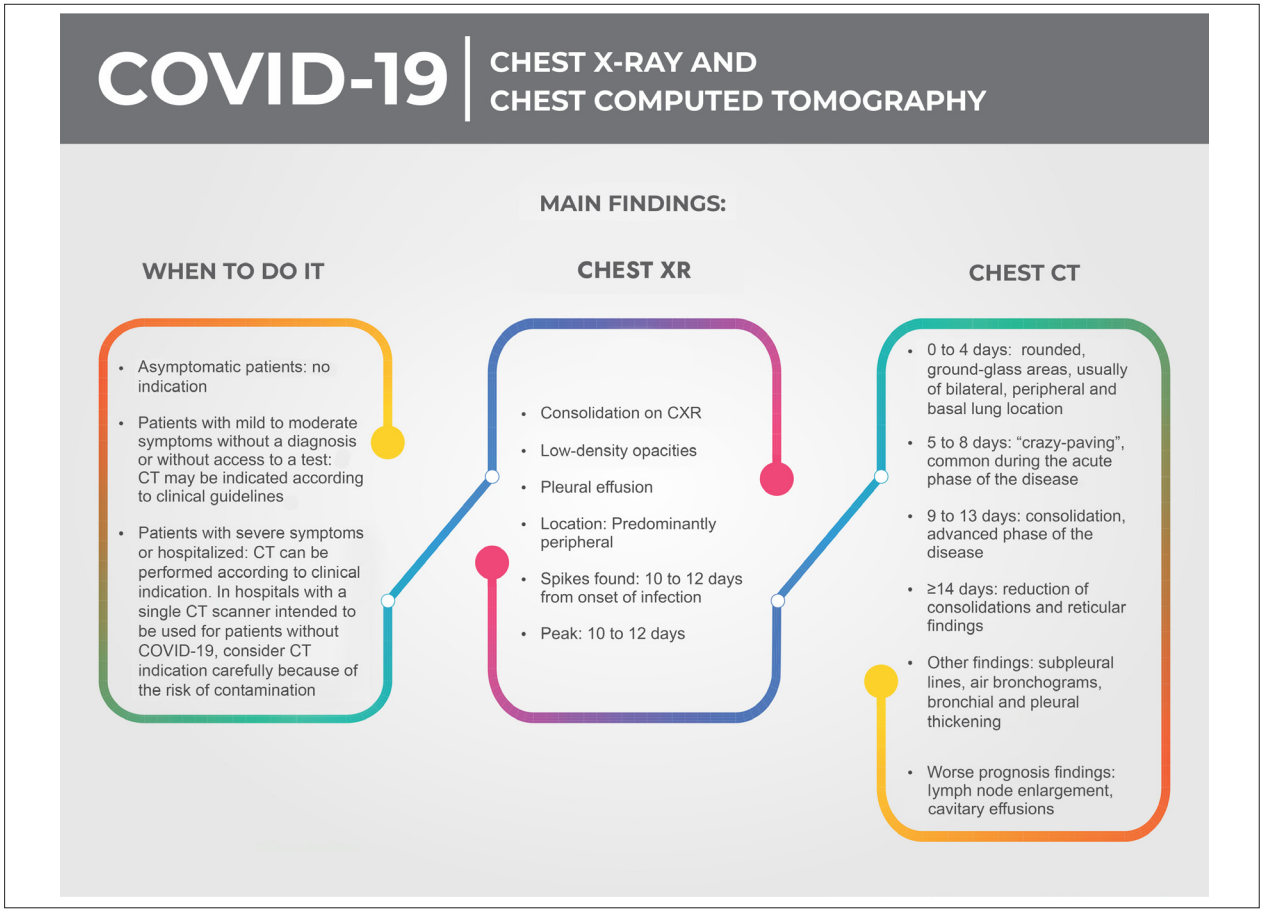

Figure 1 – *Chest X-ray (XR) and computed tomography (CT) in COVID-19.*

because of the retrospective nature of the studies published, including the lack of strict criteria for imaging diagnosis and procedural differences for confirming infection.[31]

The CT findings depend on when infected patients are imaged. In the initial phase, 57-98% of the patients will present usually bilateral, peripheral and rounded ground-glass opacities.[32] From 5% to 36% of the patients will have a 'crazy paving' pattern at disease peak (5 to 8 days after symptom onset). Consolidations are present in 2% to 64% of the patients, commonly in the elderly and those with the disease severe form. Later in the course of the disease, a reticular pattern is observed in 48% of the patients, as is the gradual resolution of the consolidations.[33,34] Other CT findings, although less frequent, in COVID-19 are as follows: subpleural lines, air bronchograms, lymph node enlargement, pleural thickening and effusion, and pericardial effusion.[35,36]

4.3. Coronary Computed Tomography Angiography

CCTA can be performed in patients with COVID-19 and high troponin levels to exclude CAD. In that situation, CCTA can be extremely helpful to exclude or confirm acute coronary syndrome if the clinical findings are uncertain, replacing invasive coronary angiography and the exposure of all cardiac catheterization laboratory (CCL) staff that comes with it. Another important and emerging role of CCTA during the pandemic is to replace TEE in ruling out a thrombus in the left atrial appendage before electrical cardioversion, limiting the exposure of the echocardiographer.[16]

The Society of Cardiovascular Computed Tomography has offered guidance with recommendations to help physicians when performing CCTA during the pandemic, considering the need to prioritize urgent exams and chest CT in patients with COVID-19.[37] These are urgent indications, in which scanning should be performed within hours to 4 weeks:[37]

- Acute chest pain with clinical suspicion for CAD;
- Stable CAD at high risk for events or when there is concern for high-risk coronary anatomy;
- Patient requiring urgent structural correction of heart disease;
- Assessment of left atrial appendage in patients with acute atrial fibrillation prior to restoration of sinus rhythm;
- Assessment of cardiomyopathy in low pretest probability of CAD, only if CCTA will change management;
- Assessment of ventricular assist device dysfunction;

- Symptomatic prosthetic heart valve dysfunction, endocarditis, perivalvular extension of endocarditis, and possible valve abscess;
- New cardiac tumor suspected to be malignant;
- Need to rule out intracavitary thrombus.

Outpatient procedures considered elective can be rescheduled timely, within 4-8 weeks.[37] However, the decision about which procedures defer should be carefully made. Telemedicine can help in decision making and criteria assessment. Figure 2 summarizes the recommendations to support the decision about performing or deferring the exams.

Stable patients should be considered for CCTA, which usually requires the administration of heart rate control drugs and coronary vasodilators. Ideally, low radiation and contrast dose protocols should be chosen.[38] It is worth observing and describing in the exam report the pulmonary findings that might aid the patient's clinical management.

4.4. Cardiac Magnetic Resonance Imaging

CMRI can be important the etiological investigation of new ventricular dysfunction in COVID-19. Patients with high troponin levels, myocardial dysfunction and severe arrhythmia/

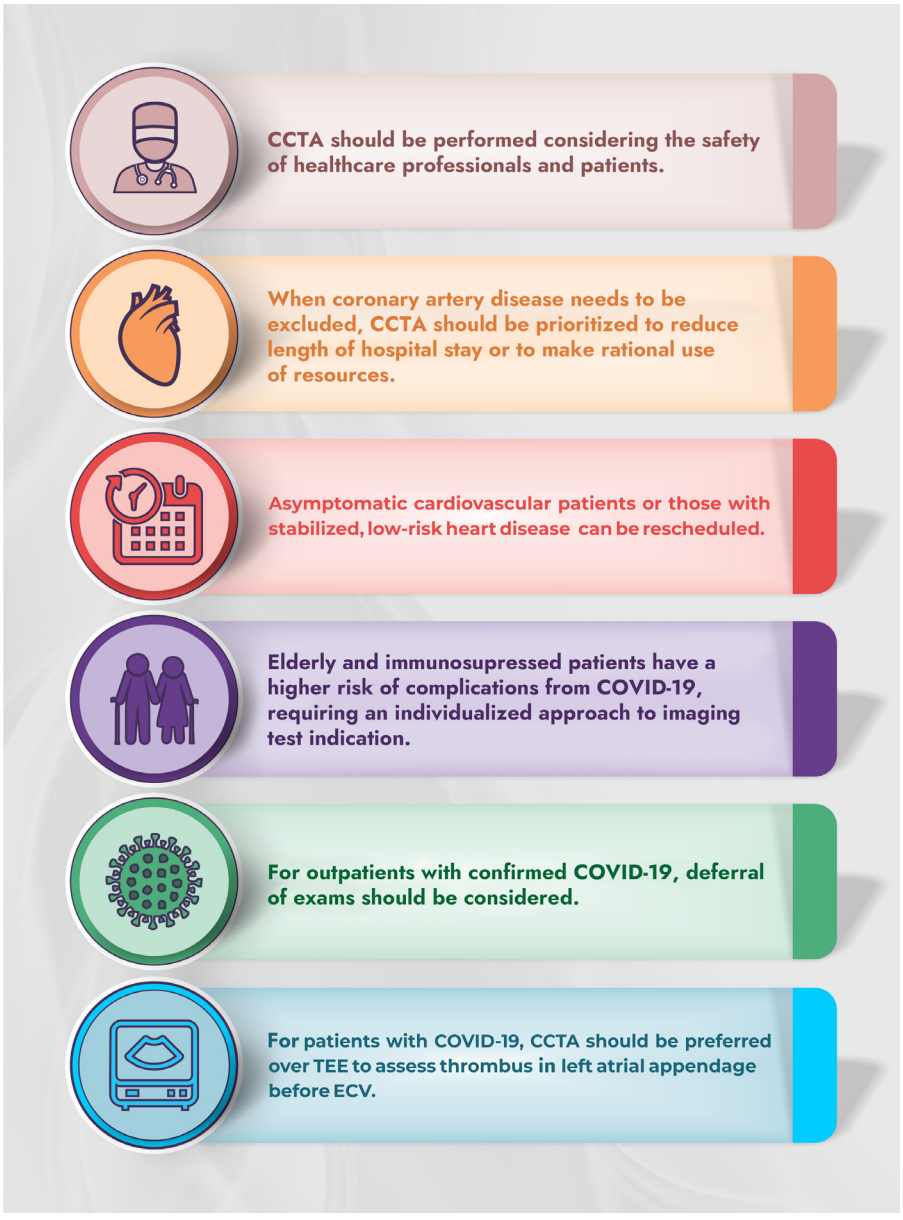

Figure 2 – *Recommendations for performing coronary computed tomography angiography during the COVID-19 pandemic. CCTA, coronary computed tomography angiography; TEE, transesophageal echocardiography; ECV, electrical cardioversion.*

electrocardiographic changes not explained by use of other methods can be candidates to undergo CMRI.[16] Myocarditis and Takotsubo syndrome are suggested etiologies of the SARS-CoV-2-related ventricular dysfunction.[23,25,39,40]

The diagnosis of myocarditis follows the same criterion of the other etiologies, usually using the Lake Louise diagnostic criteria, which comprise the presence of regional or global ventricular dysfunction, myocardial edema, pericarditis and/or non-ischemic delayed enhancement.[41-43] Left ventricular function can be preserved in some patients with myocarditis.[43] The protocol recommended should be the shortest possible, aimed at answering the clinician's questions.[44]

Regarding an elective exam already scheduled, its deferral can be considered if the requesting physician understands that does not increase the risk to the patient. The physician in charge of the exam should decide together with the requesting one about the safety for the patient of postponing the exam (Figure 3). If deciding upon performing the exam, the lowest number of professionals should be in contact with the patient. Safety measures should be taken during the entire procedure and patient's transportation.[16] Healthcare professionals should be well educated on the proper use of PPE. Whenever possible, one imaging device should be dedicated to patients with suspected or confirmed COVID-19. Device and room cleaning should be performed after the exam.[45]

5. Interventional Procedures

The COVID-19 pandemic has imposed an unprecedented stress to healthcare systems worldwide. More than ever, the situation calls for extraordinary efficiency in the use of resources and increases the need for fair, consistent, ethical, and efficient healthcare provision. The decision about performing an interventional cardiology procedure amidst a pandemic should balance the risk of healthcare staff's exposure to the virus, the unnecessary use of resources, and the potential benefit to the patient.

5.1. Human Resources

Each service should take proper measures to separate workers into groups, so that possible quarantines can be applied to groups inside each service and not to the entire service. The elderly (age > 65 years), individuals with chronic heart or pulmonary disease, DM or AH are at higher risk of severe disease after COVID-19. Thus, minimizing the direct exposure of healthcare personnel with those characteristics to cases of presumed or confirmed COVID-19 might be advisable.

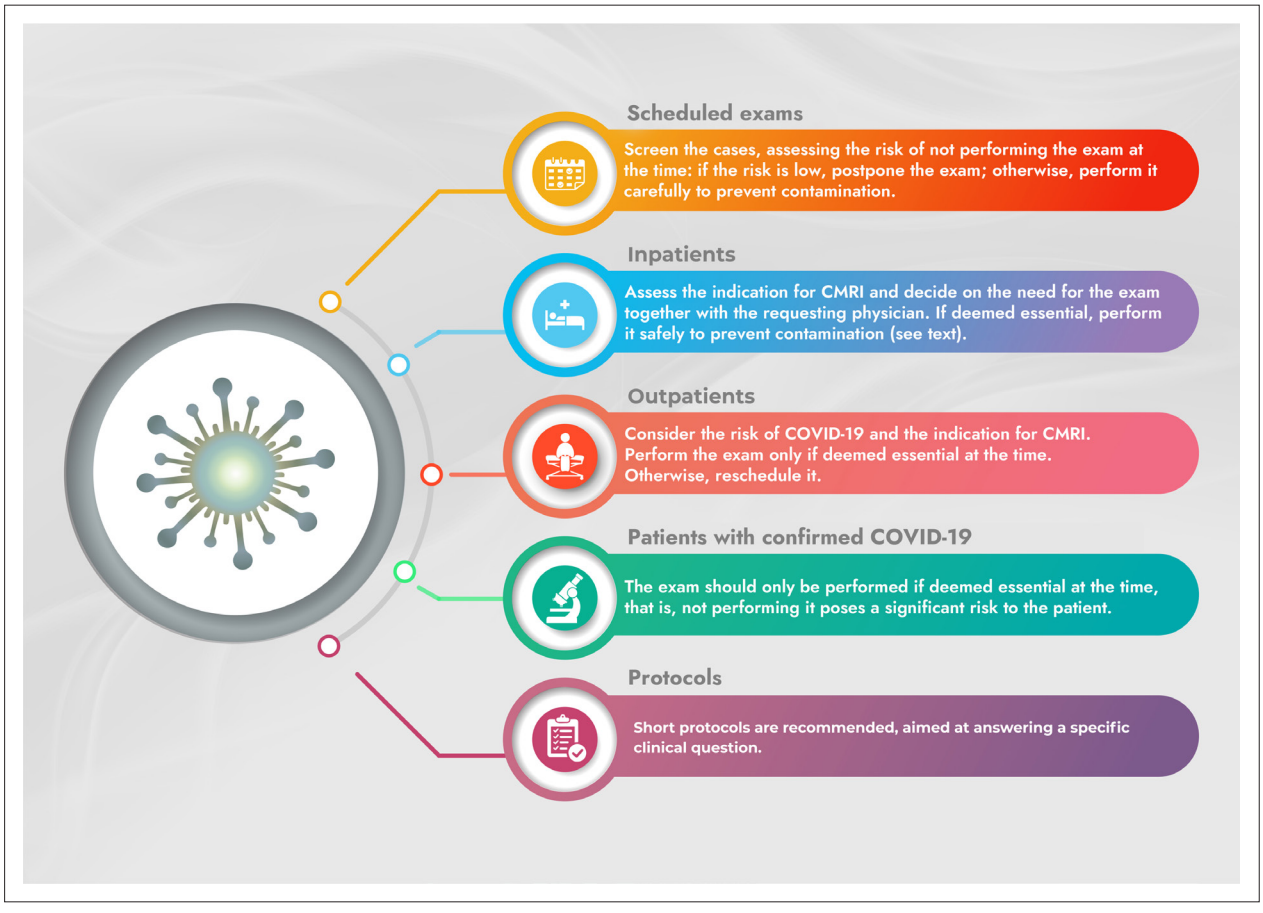

Figure 3 – *Recommendations for performing cardiac magnetic resonance imaging (CMRI) during the COVID-19 pandemic.*

5.2. Indication for a Procedure

Thorough assessment of the clinical urgency of an interventional procedure during the pandemic is essential. Ideally, that should be a joint decision of the physician performing the procedure, the clinical cardiologist, and the patient.

5.3. Stable Coronary Artery Disease

Risk profile assessment should be individualized, considering clinical findings, complementary tests and symptoms. Usually, elective procedures for stable CAD should be postponed until after the pandemic. Patients with stable CAD, as those assessed in the ISCHEMIA study, have a favorable outcome with optimized clinical treatment. It is worth noting that the ISCHEMIA trial has not included patients with the following characteristics: estimated glomerular filtration rate lower than 30mL/min/1.73m^2 of body surface area; recent acute coronary syndrome; unprotected left main coronary artery stenosis of at least 50%; left ventricular ejection fraction lower than 35%; NYHA functional class III/IV heart failure; and unacceptable angina despite the use of optimized medical therapy.[46] The ISCHEMIA trial has shown a higher incidence of acute myocardial infarction in patients with stable CAD under conservative treatment as compared to those submitted to revascularization. That, however, has occurred only after a six-month follow-up, corroborating the deferral of interventional procedures in that subgroup of patients.[46]

5.4. Non-ST-elevation Acute Coronary Syndrome (NSTE-ACS)

It is worth noting that 7-22% of the patients with COVID-19 have myocardial injury with significant elevation in myocardial necrosis markers, which might correspond to type 2 acute myocardial infarction or myocarditis.[7,10] Type 2 acute myocardial infarction should be distinguished from "primary" acute coronary syndrome, and deferral of invasive stratification considered in the former, mainly if the patient is hemodynamically stable.

For most patients with NSTE-ACS and suspected COVID-19, diagnostic tests for COVID-19 might be performed before cardiac catheterization, allowing to a more sensible decision-making about infection control. Unstable patients with NSTE-ACS, whose instability is due to acute coronary syndrome, should follow the urgent care flow. Figure 4 shows a flowchart for the care of confirmed cases of NSTE-ACS according to the diagnosis of COVID-19.

Readiness to discharge after revascularization might be important to maximize the availability of hospital beds and reduce the patient's exposure inside the hospital. Follow-up via telemedicine can be an additional tool in a time when restriction to people circulation is recommended.[47]

5.5. ST-elevation Acute Myocardial Infarction (STEMI)

STEMI has high morbidity and mortality, and primary percutaneous coronary intervention (PPCI) should be deemed the therapy of choice.[48] However, in face of the current burden imposed to health systems by COVID-19, some centers have recommended fibrinolysis as the first-line treatment of STEMI.[49] This is a controversial issue that should take into account the COVID-19 diagnosis probability, the patient's clinical severity, the availability of resources, and the estimated time to perform PPCI.

At the time this article was written, PPCI was recommended as the treatment of choice for STEMI in patients with COVID-19. If resources become scarce, the clinical severity hinders patient's transportation to the CCL, and the door-balloon time is inadequate, the cardiology staff might decide to use thrombolytics, rather than PPCI, for patients with COVID-19 and STEMI. In hospitals with no access to a CCL, fibrinolysis remains the standard treatment.[50] Figure 5 presents an algorithm with the care for STEMI in the current pandemic scenario. Because of the need for emergency care, all patients with STEMI should be considered initially as having COVID-19, and the cardiovascular findings should be prioritized until the infection can be properly investigated.

It is worth noting that patients with COVID-19 can have diffuse or regional ST-segment elevations, with no obstructive lesion justifying the alteration.[51] Those with obstructive CAD have higher levels of troponin and D-dimer.[51] Thus, caution is recommended in interpreting the electrocardiogram, mainly in patients with severe pulmonary findings, whose transportation conditions are not safe. In that scenario, echocardiography can be considered, as long as it does not delay CCTA, when indicated.[51]

5.6. Procedures for Structural Heart Disease Management During the COVID-19 Pandemic

a) **Transaortic valve implantation (TAVI):** Aortic stenosis (AS) is a progressive disease that affects patients with advanced age vulnerable to death from infection. The importance and clinical urgency of TAVI require a joint decision-making by a multidisciplinary team (clinical and interventional cardiologists and surgeon). That decision should weigh the risk of patients' exposure to COVID-19 contamination against their risk of an acute, potentially fatal event.[52] Patients with indication for TAVI should be closely followed up by telemedicine during this pandemic. Asymptomatic patients with significant AS can be followed up on an outpatient basis. Those with complicating echocardiographic findings (Vmax > 5.0 m/s, valvular area < 0.7 cm^2, mean left ventricle/aorta gradient > 60 mm Hg), syncope, reduced left ventricular ejection fraction due to AS and NYHA functional class III/IV, who are at higher risk for events,[53] ideally should not have their TAVI postponed. Compared to open-chest surgery for aortic valve replacement, TAVI can reduce the need for intensive and anesthesia care during a pandemic. If TAVI is to be performed, preprocedural screening with PCR for COVID-19 might reduce the risk for the healthcare personnel.

b) **Mitral valve clip:** mitral valve clip procedure can be considered for unstable patients if resources allow and should be postponed for lower-risk patients.

c) **Closures of patent *foramen ovale* and atrial septal defect:** should be postponed.

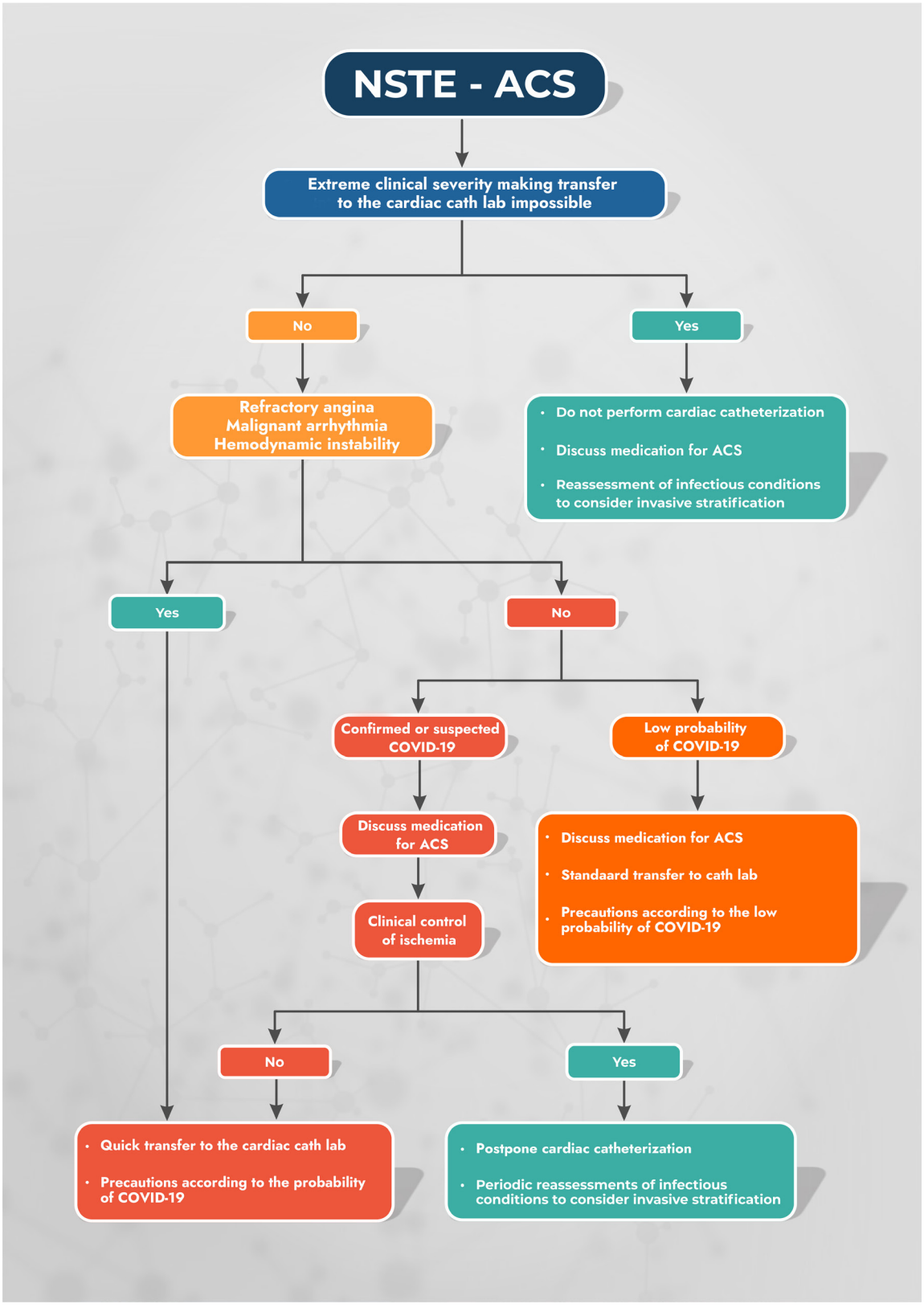

Figure 4 – *Flowchart for the treatment of non-ST-elevation acute coronary syndromes. NSTE-ACS, non-ST-elevation acute coronary syndrome; ACS, acute coronary syndrome.*

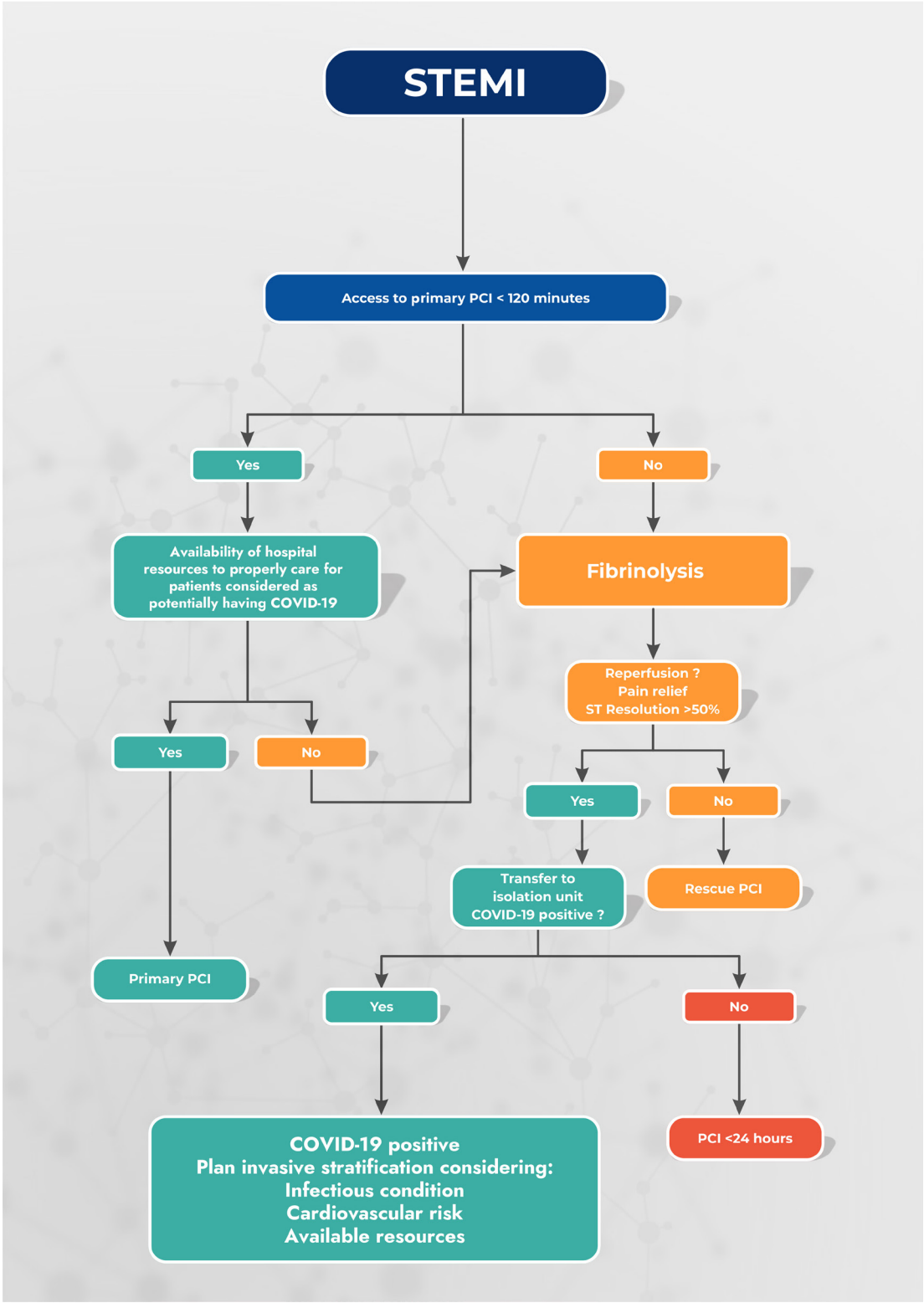

Figure 5 – *Flowchart for the treatment of ST-elevation acute myocardial infarction (STEMI). In addition to cardiovascular risk stratification, consider readiness to perform reperfusion, ischemia time, and resources available for patient's proper care. Because of the need for emergency care, all patients with STEMI should be considered as potentially having COVID-19 and treated according to the proper isolation measures until the infection can be thoroughly investigated. PCI, percutaneous coronary intervention.*

d) **Left atrial appendage closure:** should be postponed.

e) **Other procedures:** should be postponed unless urgent hospitalization is required.

5.7. Reducing the Spread of COVID-19

5.7.1. Reducing droplets spreading: Involves measures such as the use of surgical mask by patients with suspected or confirmed COVID-19. All nonessential equipment should be moved out of the CCL procedure room or covered with clear drapes before the patient's arrival to the room. In addition, it is worth emphasizing the importance of reducing circulation in the procedure room to minimize exposure and infection spread.[50] Deep cleaning and thorough disinfection of the room after CCL procedures involving patients with COVID-19 are important to control the infection. In addition, disinfection with ultraviolet radiation can be used. Thorough cleaning might require an extra time; thus, if feasible, a procedure in a patient with COVID-19 should be performed as the final one of the day. Whenever possible, the patient with suspected or confirmed COVID-19 should undergo bedside procedures (transient pacemaker, intra-aortic balloon) aiming at minimizing the need for moving the patient out from an isolation room and preventing the risk of additional exposure via transportation to the CCL.[50]

5.7.2. Patients requiring intubation, aspiration or cardiopulmonary resuscitation: Intubation, aspiration and active cardiopulmonary resuscitation can generate aerosol particles from respiratory secretions, increasing the likelihood of personal exposure.[54] Patients already intubated pose a lower contamination risk to healthcare personnel, because they are on closed-loop ventilation.[55] For patients with suspected or confirmed COVID-19 who need orotracheal intubation, this intervention should be performed before arrival to the CCL. In addition, intubation should be considered as early as possible in borderline patients to avoid the need for an urgent intubation in the CCL.[55] The cooperation of the intensive care and anesthesia staffs for airway management is fundamental to prevent the infection spread.

5.8. Dedicated Catheterization Laboratory

Having a dedicated room for the care of suspected/positive COVID-19 cases is aimed at reducing the risk of infection for health professionals and minimizing the viral contamination of other rooms. In CCLs with more than one procedure room, one should be dedicated to COVID-19 and another to 'clean' procedures. This is no guarantee that the 'clean' CCL will not be contaminated at any time but can minimize the risks and optimize the flow of patients in the CCL, mainly of those at "low risk for exposure". It is advisable to consult with the hospital engineering about the possibility of having "negative air pressure" procedure rooms. Understanding the air conditioning system is important, because one single procedure might expose other hospital areas to viral contamination.[50]

5.8.1. Measures of management control. Suppliers, visitors, observers, research coordinators and any nonessential individual for the CCL operation should refrain from entering the CCL during the pandemic.[55]

5.8.2. Approaching the patient. It is worth noting the importance of assessing the risk of SARS-CoV-2 infection before submitting the patient to the interventional procedure. Organization is recommended to minimize the waiting times in the hospital common areas before and after the procedure.[7] All patients should be asked about respiratory symptoms, fever or close contact with suspected/positive cases before entering the CCL room, in addition to undergoing temperature check.[55]

- **Approach to patients without confirmed SAR-CoV-2 infection:** Given the current situation and the likelihood of treating asymptomatic or undiagnosed patients, careful protective measures are recommended. Patients should wear surgical mask before arrival to the room. The interventional cardiologist should adopt safety measures that include proper hand hygiene and the use of sterile and water-resistant gown, sterile gloves, goggles, hair covers, and surgical mask. Technologists, nurses and circulating technicians should use goggles, gloves, hair covers, and surgical mask.[55]
- **Approach to suspected or confirmed COVID-19 patients:** Procedures involving airway and/or esophageal manipulation should be considered of high risk. Only essential personnel should be granted access to the CCL room, whose doors should remain closed all time. Avoid exiting the room with contaminated equipment (gown, gloves, mask) to get material (stents, catheters). Ideally the material used in the procedure should remain outside the room. A circulating technician will remain outside the room exclusively providing the material necessary for the procedure to another circulating technician remaining exclusively inside the room. Medications should be prepared before patient's arrival to the room.

The patient should wear a surgical mask, which acts as a barrier to secretions. The staff responsible for moving the COVID-19 patient from the litter to the CCL table should wear PPE, including water-resistant gown, hair covers, gloves covering the wrists, eye protection, and FFP2/N95 mask.56 At the end of transfer, the PPE should be removed as indicated in the following topic, noting that the mask should never be removed inside the CCL room.[55]

5.8.3. Putting on PPE: The interventional cardiologist should perform hand hygiene with soap and water, wear a reinforced water-resistant gown (if not impermeable, a plastic gown needs to be added), two pairs of gloves, protective lead goggles or conventional eye glasses, face shield, and high-efficiency filter mask of the FFP2/N95 type.[56] Technologists, nurses and circulating technicians should use gloves, hair cover, water-resistant gown and FFP2/N95 mask. A surgical mask should be put on over the FFP2/N95 mask. Closed shoes are recommended.[56]

Figure 6 – *Steps for putting on the personal protective equipment in cases of suspected or confirmed COVID-19.*

5.8.3.1.Steps for putting on PPE in cases of suspected or confirmed COVID-19 (Figure 6)

Outside the CCL procedure room

- Remove any personal items
- Hold hair fully back
- Put on the lead gown and shoe covers
- Perform proper hand hygiene
- Put on the FFP2/N95 mask, securing ties or elastic bands at middle of head and neck, fit flexible band to nose bridge and snug to face and below chin, to ensure isolation and no leak.
- Put on hair cover
- Put on surgical mask over the N95 mask
- Put on goggles and face shield
- Perform hand disinfection with alcohol gel or foam
- Put on the first pair of gloves
- Enter the CCL procedure room

Inside the CCL procedure room

- Put on the water-proof gown
- Put on the second pair of gloves

5.8.3.2. Steps for removing PPE in cases of suspected or confirmed COVID-19 (Figure 7)

Inside the CCL procedure room

- Disinfect the external pair of gloves with alcohol gel or foam
- Remove the gown and simultaneously the external pair of gloves, discarding them in a waste container marked with the biological hazard symbol (do not push to avoid generating aerosol particles, because they can be infected)
- Disinfect the internal gloves with alcohol gel or foam
- Remove hair cover, face shield and shoe covers
- Remove the internal pair of gloves
- Perform hand disinfection with alcohol gel or foam
- Exit the procedure room

Limitations of the present document

It is worth noting that this document is being written in a time when we do not completely understand COVID-19 transmission, severity, and proper treatment. The strategies herein suggested are based on limited evidence and recommendations might be subject to change.

Figure 7 – *Steps for removing the personal protective equipment in cases of suspected or confirmed COVID-19.*

Conclusions

The exponential growth in the number of patients with COVID-19 has been a huge burden on health services, requiring the urgent adoption of measures that can contain the virus and restrain its spread. Patients with COVID-19 have cardiovascular complications and often require diagnostic imaging tests and procedures to support their management. The correct identification of patients who need imaging tests and interventional procedures should be judicious, careful, and ethical, prioritizing the patient's health and the rational use of resources.

Author Contributions

Conception and design of the research: Costa IBSS, Rochitte CE, Campos CM, Barberato SH, Oliveira GMM, Lopes MACQ, Abizaid AA, Hajjar LA; Data acquisition: Costa IBSS; Writing of the manuscript: Costa IBSS, Rochitte CE, Campos CM, Barberato SH, Lopes MACQ, Hajjar LA; Critical revision of the manuscript for intellectual content: Costa IBSS, Rochitte CE, Oliveira GMM, Lopes MACQ, Abizaid AA, Cerri G, Kalil Filho R, Hajjar LA.

Potential Conflict of Interest

The authors report no conflict of interest concerning the materials and methods used in this study or the findings specified in this paper.

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Study Association

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Acute Cardiorenal Syndrome: Which Diagnostic Criterion to Use And What is its Importance for Prognosis?

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Abstract

The absence of a consensus about the diagnostic criteria for acute cardiorenal syndrome (ACRS) affects its prognosis. This study aimed at assessing the diagnostic criteria for ACRS and their impact on prognosis. A systematic review was conducted using PRISMA methodology and PICO criteria in the MEDLINE, EMBASE and LILACS databases. The search included original publications, such as clinical trials, cohort studies, case-control studies, and meta-analyses, issued from January 1998 to June 2018. Neither literature nor heart failure guidelines provided a clear definition of the diagnostic criteria for ACRS. The serum creatinine increase by at least 0.3 mg/dL from baseline creatinine is the most used diagnostic criterion. However, the definition of baseline creatinine, as well as which serum creatinine should be used as reference for critical patients, is still controversial. This systematic review suggests that ACRS criteria should be revised to include the diagnosis of ACRS on hospital admission. Reference serum creatinine should reflect baseline renal function before the beginning of acute kidney injury.

Introduction

Heart failure (HF) is a clinical challenge and a growing epidemiological problem worldwide, with high morbidity and mortality.[1] In the ARIC study,[2] the case fatality rates within 30 days, 1 year and 5 years from hospitalization due to HF were 10.4%, 22.0% and 42.3%, respectively. The I Brazilian Registry of Heart Failure (BREATHE),[3] an observational study with 1263 patients from different Brazilian regions, has shown in-hospital mortality of 12.6%.

Keywords

Cardiorenal Syndrome; Renal Insufficiency; Creatinine; Prognosis; Heart Failure; Systematic Review.

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Cardiorenal syndrome, defined as kidney injury caused by HF, was first described in 1951[4] and categorized into five types in 2008 (Table 1).[5] Type 1 cardiorenal syndrome or acute cardiorenal syndrome (ACRS) is characterized by acute kidney injury (AKI) caused by decompensated HF (DHF). Some authors refer to ACRS as acute worsening of renal function in patients with HF, which is a frequent condition, present in 11% to 40% of hospitalizations due to DHF.[6,7]

Worsening of renal function is defined as an absolute increase in serum creatinine by 26.5 μmol/L, equivalent to 0.3 mg/dL, and/or a 25% increase in creatinine or a 20% decrease in glomerular filtration rate (GFR).[8] The criterion of absolute 0.3-mg/dL increase in creatinine has been adopted by most authors as the cutoff point to define ACRS.

The North American ADHERE registry[9] is an observational study with more than 100,000 patients hospitalized with DHF, 35% of whom had moderate to severe renal dysfunction.

Worsening of renal function occurs in 30% to 50% of patients with DHF, depending on the definition used, and is associated with longer length of hospital stay, as well as higher health care costs and mortality.[10-14] However, the absence of a consensus definition of ACRS contributes to the lack of clarity in its diagnosis and treatment.[15] The choice of reference serum creatinine to anchor the diagnostic criteria for ACRS is a challenge. Ideally, reference serum creatinine should reflect the baseline renal function before AKI begins. Most of the time, however, that information is not available, leading to the use of surrogate reference values, which can

Table 1 – Types of cardiorenal syndrome

Type	Name	Mechanism
1	Acute CRS	AKI induced by acute cardiac dysfunction
2	Chronic CRS	Progressive CKF secondary to chronic HF
3	Acute renocardiac syndrome	Acute HF precipitated by AKI
4	Chronic renocardiac syndrome	HF secondary to CKF
5	Secondary CRS	Myocardial and renal dysfunction due to systemic diseases

CRS: cardiorenal syndrome; AKI: acute kidney injury; CKF: chronic kidney failure; HF: heart failure. Source: Di Lullo et al.[40]

result in misclassification of ACRS regarding its diagnosis and severity.[16]

Methods

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology.[17] Data search in the MEDLINE, EMBASE and LILACS databases included the full texts of original publications, such as clinical trials, cohort studies, case-control studies and meta-analyses, issued from January 1998 to June 2018, written in English, Spanish and Portuguese. The database search was conducted with the following descriptors: (*cardiorenal syndrome*) OR *(worsening renal function)* AND (*heart failure*) AND (*diagnosis*) AND (*prognosis*).

This study used the PICO (Population, Intervention, Control and Outcome) framework for literature search and reviewed the diagnostic criteria for ACRS and their prognostic implication for the outcomes 'in-hospital mortality', 'mortality after hospital discharge', and 'length of hospital stay'. Case reports and experimental animal models were excluded.

Results

Regarding database search, 368 abstracts met the established criteria. Other 9 articles were retrieved in other sources, while 278 duplicate abstracts were removed. Of the 99 abstracts left, 61 were selected, 35 of which were excluded for not meeting the previously established criteria (PICO). The full text of the resulting 26 articles was then assessed regarding their scientific quality, and 4 articles were excluded for not meeting the criteria. The remaining 22 articles were analyzed in this study (Figure 1).

Temporal classification of acute cardiorenal syndrome

Studies with access to pre-admission serum creatinine have revealed AKI in one third of the patients presenting to the emergency department,[18] while 50% of patients have been reported to develop AKI within the first 48 hours from admission. Tayaka et al.,[19] in a study comparing renal function changes up to the fourth day of hospitalization with those from the fifth day onward, have reported higher mortality within 1 year from hospital discharge in patients with late renal injury. A *post hoc* analysis of the Pre-RELAX study has shown that the drop in systolic blood pressure in the first 48 hours of vasodilator therapy was an independent predictor of AKI up to the fifth day of hospitalization.[20] Those results suggest that therapy-related reduction in renal perfusion pressure is one of the major mechanisms leading to AKI in the first days of hospitalization.

Acute cardiorenal syndrome can be classified into intermittent or persistent. Intermittent ACRS occurs when serum creatinine levels vary during hospitalization with a reduction in its values up to discharge time. Persistent ACRS occurs when either creatinine elevation or GFR decrease persist up to discharge time.[21,22]

Incidence of acute cardiorenal syndrome

Studies have shown a large variation in the incidence of ACRS, whose estimates range from 19% to 45%. That variation can be attributed to differences among the studies regarding

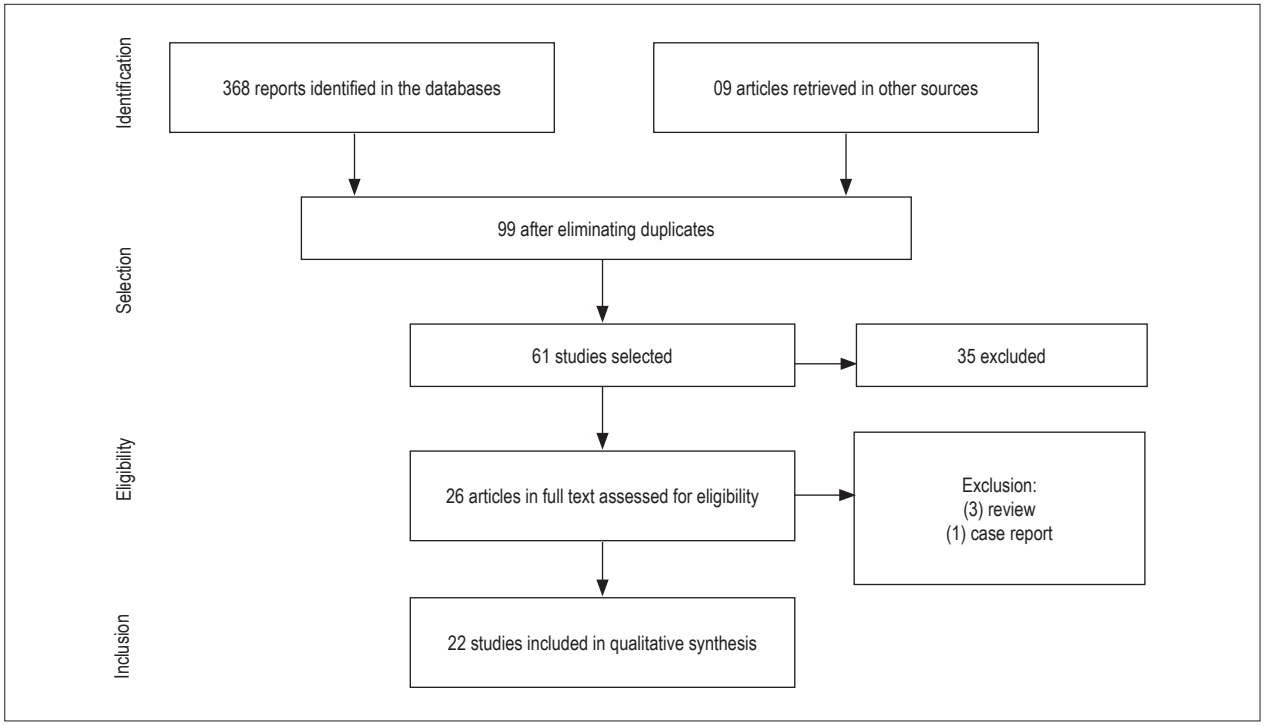

Figure 1 – *Flowchart of the studies assessed (PRISMA methodology[17]).*

their diagnostic criteria, their inclusion and exclusion criteria, their sample sizes, and the clinical findings of the populations studied. Most studies involve retrospective, secondary and/or *post hoc* analyses of large databases[10-12,23-25] or clinical trials of drug therapy.[26]

Diagnostic criteria for acute cardiorenal syndrome

The first study to assess the impact of worsening renal function on the elderly admitted with DHF, published in 2000, adopted the 0.3-mg/dL increase in creatinine as the criterion.[10] Another study has shown that 0.1-mg/dL increases in creatinine during hospitalization were associated with higher in-hospital mortality and longer length of hospital stay. In addition, that study reported that creatinine increase ≥0.3 mg/dL had higher sensitivity and specificity to predict both death (81% and 62%, respectively) and length of hospital stay longer than 10 days (64% and 65%, respectively).[11]

Absolute creatinine increase by 0.3 mg/dL has been adopted by most authors as the criterion defining ACRS.[27] Some authors, however, disagree, because that criterion does not consider the previous degree of renal dysfunction, and they suggest using one of three different classifications to define AKI,[28] which, however, are not specific for DHF and have been developed to define and classify AKI in different clinical scenarios.

The RIFLE (Risk, Injury, Failure, Loss and End-stage renal disease) classification[29] was proposed in 2004 to define and stratify the severity of AKI, which is determined by the most altered parameter (creatinine variation, GFR and urine output).

The classification proposed by the Acute Kidney Injury Network (AKIN)[30] excludes the stages of 'renal function loss' and 'end-stage renal disease', as well as the 'GFR-based criteria". Staging should be performed after correcting the patient's blood volume, excluding urinary tract obstruction, and considering the most altered criterion. In 2012, the *Kidney Disease – Improving Global Outcomes* (KDIGO)[31] group proposed a classification modifying the previous one by adding to its third stage GFR reduction to values below 35mL/min/1.73m^2 in patients under the age of 18 years and excluding the need for the minimum 0.5-mg/dL increase for patients with creatinine greater than 4 mg/dL.

A cohort study assessing 637 hospitalizations due to DHF with 30-day and 1-year follow-up assessments has compared the diagnostic criterion of creatinine increase ≥0.3 mg/dL with those from KDIGO, RIFLE and AKIN regarding prediction of the following outcomes: 'death', 'readmission due to HF' or 'initiation of dialysis'. Regarding the ability to determine adverse events, the four criteria performed similarly. The benefit of using the AKI classification systems (RIFLE, AKIN, KDIGO) is the possibility to identify patients with more severe AKI who will have adverse events in 30 days and 1 year.[32] Table 2 summarizes the different diagnostic criteria for AKI found in the literature.

The most used diagnostic criterion is serum creatinine increase by at least 0.3 mg/dL or 25% in the first five days of hospitalization, which differs from the current KDIGO definition for AKI.[33] In addition, the definition of worsening renal function does not include AKI on admission, which is associated with mortality and cardiovascular events.[34]

Common approaches to the ACRS diagnosis include the use of the following reference values of baseline creatinine, from which the creatinine increase defines ACRS: a) serum creatinine on admission; b) the lowest creatinine during hospitalization; c) serum creatinine levels of other hospitalizations; or d) outpatient measurements of serum creatinine. The original criteria of the RIFLE classification do not specify the reference creatinine but recommend its calculation from an estimated GFR of 75mL/min/1.73m^2. Other approaches include the assessment of creatinine variation in the first 48 hours from admission, to reduce the need for the pre-hospital value (AKIN), and the lowest serum creatinine during hospitalization, when the outpatient measurement of serum creatinine is absent (KDIGO).[35]

Table 2 – RIFLE[34], AKIN[35], KDIGO[36] and WRF[11] criteria for definition of AKI

Criteria	WRF	RIFLE		AKIN	KDIGO
Years	2002	2004		2007	2012
Classification	sCr increase	sCr increase	GFR decrease	sCr increase	sCr increase
Stage 1 / Risk	≥ 0.3 mg/dL	≥ 1.5x bCr	≥ 25%	> 1.5-1.9x bCr or ≥ 0.3 mg/dL	≥ 1.5x bCr or ≥ 0.3 mg/dL
Stage 2 / Injury	-	≥ 2x bCr	≥ 50%	> 2-2.9x bCr	≥ 2x bCr
Stage 3 / Failure	-	≥ 3x bCr	≥ 75%	≥ 3x bCr	≥ 3x bCr
	-	Or sCr ≥ 4mg/dL and a 0.5-mg/dL increase		Or sCr ≥ 4mg/dL and a 0.5-mg/dL increase or initiation of dialysis	Or sCr ≥ 4mg/dL
Minimum time for AKI to occur	sCr can increase at any time during hospitalization	sCr changes over 1-7 days for more than 24 h		Acute sCr changes within a 48-h period during hospitalization	SCr changes ≥ 1.5x bCr within 7 days, or 0.3-mg/dL minimum increase in sCr within a 48-h period

WRF, worsening renal function; AKI, acute kidney injury; sCr, serum creatinine; GFR, glomerular filtration rate; bCr, baseline creatinine. Source: Adapted from Roy et al.[32]

Siew et al.,[36] studying 4,863 in-hospital patients, have assessed three reference values of baseline creatinine: MDRD (*Modification of Diet in Renal Disease*), serum creatinine on admission, and the lowest creatinine during hospitalization. The use of MDRD and *nadir* creatinine inflated the incidence of AKI by about 50%; in contrast, the use of the admission value underestimated it by 46%. The use of the admission creatinine value as reference has the lowest sensitivity for the diagnosis of AKI acquired at the hospital and does not include the diagnosis of pre-admission AKI. Some authors consider as reference the pre-admission creatinine (outpatient measurement) when available, but only some of them have defined the time of maximum validity of the outpatient measurement up to admission. However, the outpatient value of creatinine is rarely available.

The RIFLE classification[29] does not define specifically reference baseline creatinine. The most recent AKI criterion, KDIGO, recommends the lowest serum creatinine during hospitalization to be used as reference.[35] Few studies have considered baseline renal function correlated with increasing creatinine during the AKI episode.

The use of biomarkers to characterize acute cardiorenal syndrome

Although creatinine is the pillar of the diagnosis of ACRS, it has limitations as a marker of renal function, mainly in critical patients. Its serum level is influenced by factors, such as sex, age, body weight, and muscle mass. In addition, creatinine increases only 24 hours after kidney injury and its concentration does not increase significantly until half of renal function is impaired. Thus, creatinine is considered a slow marker of AKI.[37] The definition of baseline creatinine in critical patients is controversial because those patients have nutritional alterations, muscle mass loss and fluid overload.

Useful biomarkers are those with clinical applicability and a recognized role in the pathophysiology of ACRS. The search for more reliable biomarkers for the early diagnosis of ACRS is encouraged, and kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), interleukin 18 (IL-18), and cystatin C (Cys-C) are some of the new markers of kidney injury targeted in studies. However, none of the three renal tubular markers cited could predict accurately worsening renal function in patients with DHF.[38]

Microalbuminuria is estimated to be present in 20% to 30% of patients with HF. Two studies have shown association with mortality in patients with micro- or macroalbuminuria as compared to those with normal albumin excretion.[39]

The clinical condition of patients with ACRS deteriorates and they develop oliguria, despite the high levels of natriuretic peptides, which are known to have a diuretic effect. It is worth noting that NT-proBNP levels are reduced in patients undergoing hemodialysis with high-flux membrane.[40]

The suppression of tumorigenicity-2 (ST2), a biomarker of congestion less influenced by renal function than NT-ProBNP, might be helpful for diagnostic and prognostic information.[41]

Imaging methods for the diagnosis of acute cardiorenal syndrome

Renal imaging with assessment of the waves of venous and arterial renal flows can signal worsening renal function before serum creatinine levels increase, providing a feasible and non-invasive assessment of renal hemodynamics.[42,43]

Prognostic implications of acute cardiorenal syndrome

Acute cardiorenal syndrome is associated with the following: higher all-cause and cardiovascular mortality in the short and long run; prolonged length of hospital stay;[10,11,44-46] re-admissions;[27,47] progression to chronic kidney disease;[48] and higher health care costs.[10]

Acute cardiorenal syndrome is apparently more severe in patients with reduced left ventricular ejection fraction (LVEF) as compared to those with preserved LVEF, reaching the incidence of 70% in patients with cardiogenic shock.[49] In addition, renal function impairment is an independent risk factor for 1-year mortality in patients with acute HF, including those with ST-elevation myocardial infarction.[23] Moreover, an acute decline in renal function not only acts as a marker of disease severity, but also speeds cardiovascular alterations up by activating inflammatory pathways.[48]

Two studies have shown that the risk of poor prognosis remains independently of the ACRS type (intermittent or persistent)[45,47] and that even mild renal function changes can alter the risk of death.[49] Some studies have shown that persistent ACRS, as compared to intermittent ACRS, has worse prognosis after hospital discharge and that transient creatinine elevations did not relate to worse prognosis.[50-52]

In the ADHERE study,[9] 59% of the men and 68% of the women had moderate to severe renal dysfunction on admission, and those with worsening renal function during hospitalization had higher in-hospital mortality. Patients whose hospitalization is precipitated by ACRS have higher in-hospital mortality, longer length of hospital stay, more re-admissions and higher mortality rates after discharge as compared to patients with other precipitating factors.[53-55] Persistent ACRS within 1 year from hospital discharge was a strong predictor of cardiovascular and all-cause mortality.[56]

At least one fourth of the patients hospitalized with DHF can develop ACRS, depending on the diagnostic criterion used. Among patients hospitalized with HF, serum creatinine increase is one of the major predictors of survival,[10,57] and mortality increases progressively as serum creatinine increases.[11,27,58,59]

Not all changes in renal function have the same prognostic relevance. Serum creatinine elevation concomitantly with symptom improvement and body weight loss is not associated with an unfavorable outcome.[60] The presence of AKI indicates that a reversible or irreversible kidney lesion has occurred, while worsening renal function markers can represent a functional decline in GFR not directly related to an adverse outcome.[61]

Intermittent ACRS reflects a reversible reduction in GFR and seems less harmful than persistent ACRS. Paradoxically, in cases of ACRS on admission, the decrease in creatinine during hospitalization can be associated with adverse outcomes.[28,53,62] Considering renal congestion as the major pathophysiological mechanism of ACRS, diuretics are expected to have a beneficial effect on prognosis. A *post hoc* analysis of the DOSE trial[63] has shown that renal function improvement when associated with inadequate decongestive strategies had a worse prognosis.

Other studies have shown that, with diuretic therapy and hemoconcentration, worsening renal function has a lower impact on prognosis than in patients with persistent congestion and no hemoconcentration.[28,64] Those findings are partially due to confounding factors in serum creatinine assessment. In the context of measures of decongestion, the increase in serum creatinine can result from other mechanisms regardless of GFR reduction, such as hemoconcentration that reduces the distribution of creatinine. That renal change is harmless and transient, and named pseudo-AKI. The concept of pseudo-AKI can explain why biomarkers of tubular lesion were poor predictors of ACRS, considering that previous studies have made no distinction between AKI and pseudo-AKI.[62,65] During aggressive diuretic therapy, serum creatinine increased in 22% of the patients with DHF without increase in biomarkers, suggesting a potentially high proportion of pseudo-AKI.[65]

It is not easy to determine whether the therapy is effective and pseudo-AKI can induce inadequate discontinuation of treatment. It is worth assessing the clinical parameters of perfusion, urine output, body weight loss and hemoconcentration. In addition, biomarkers seem to be good to guide therapy.[66] Measuring cardiac output and other hemodynamic parameters can help ensure an adequate and directed diuretic therapy,[67] in addition to enabling better understanding of ACRS.

Conclusions

The different references of baseline serum creatinine limit the capacity of accurate comparisons between studies and interfere with the estimates of ACRS diagnosis, overestimating or underestimating it.

This study suggests that the ACRS criteria should be revised to include the diagnosis of ACRS on hospital admission. Reference creatinine should reflect baseline renal function before AKI begins.

Author contributions

Conception and design of the research: Leite AM, Gomes BFO, Albuquerque DC, Spineti PPM, Martins WA; Acquisition of data and Writing of the manuscript: Leite AM; Analysis and interpretation of the data: Leite AM, Gomes BFO, Marques AC, Petriz JLF, Albuquerque DC, Spineti PPM, Villacorta H, Martins WA; Critical revision of the manuscript for intellectual content: Leite AM, Gomes BFO, Marques AC, Petriz JLF, Albuquerque DC, Spineti PPM, Jorge AJL, Villacorta H, Martins WA.

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Appropriate Use of Diastolic Function Guideline When Evaluating Athletes: It is not Always what it Seems to Be

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The complete echocardiographic evaluation of the diastolic function has always been a great challenge for cardiologists and sonographers, either because of frequent changes found in every new guideline, due to a great amount of recent information about this complex subject, or because of some confusion created by the guidelines themselves, which are many times contradictory or not explanatory.[1] However, we are moving towards a better understanding of what really happens on this important phase of the cardiac cycle. The last published guideline of 2016, despite presenting some inconsistencies and still not making certain situations clear, clarified several points and corrected some distortions of the previous one.[2]

As usual in Medicine, every time we have a paradigm shift or a new clinical entity appears, we pass first through a moment of overdiagnosis followed by some discredit to finally reach a balance with the maturity and the knowledge acquired over time. The same happened with mitral valve prolapse, which showed an incidence of more than 30% in young women in the early 1970s, but nowadays it is known of about 2.5% in both sexes.[3] Ventricular non-compaction and many other diseases followed the same pattern, as well as diastolic disfunction. How many healthy elderly people were diagnosed with mild diastolic disfunction (or grade I) due to presence of E/A inversion on spectral Doppler of the mitral inflow? Almeida et al.[4] tested the impact of using the 2009 guidelines against 2016 for diagnosing diastolic disfunction in 1,000 elderly individuals (over 45 y/o). They found that only 1.4% had some degree of diastolic disfunction according to the 2016 guideline. On the other hand, if the 2009 guideline had been used, this number would rise to 38.2%.

Thus, with this new guideline, we seem to have come to this balance and by using the correct application of its criteria we can significantly reduce the excessive diagnosis of diastolic disfunction, mainly in the elderly. However, we may still fail to diagnose, fortunately in a much lower amount of cases, in another clinical situations. Particularly in athletes, diastolic function needs to be evaluated more carefully.

Keywords

Ventricular Dysfunction; diagnostic Imaging; Echocardiography/methods; Guidelines as Topic; Sports; Exercise; Athletes.

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Exercise is a strong stimulus for muscle adaptation, and there is plenty of evidence proving that it is responsible for changes in shape and cardiac output.[5]

The adaptations imposed to the heart depend, of course, on the type of performed exercise. Therefore, didactically, athletes that perform dynamic exercises and work out at a high heart rate, such as marathon runners or swimmers, suffer different adaptations from those who perform isometric (static) exercises, in which the heart rate is lower and there is predominant increase in blood pressure as it happens with bodybuilders. In practice, most exercises are mixed as in cyclists and rowers, for example.

In the first group (marathon runners), in which the cardiac output can reach ten times the resting value, the heart needs to adapt in a variety of manners, whether starting from a very low basal heart rate (bradycardia), increasing left ventricular volume (eccentric hypertrophy) or even making its pump more effective, by extracting the maximum of its diastolic and systolic functions. The diastole of these athletes must be extremely efficient because tachycardia shortens this phase and the heart has much less time to be filled. Thus, as soon as the mitral valve opens, the left ventricle must fill up quickly, show an extremely effective relaxation and "suck" as much blood as possible to generate an effective systole. It explains the big E wave on mitral Doppler followed by a small A wave (because there is little blood left to fill the ventricle on the end of diastole), thus showing a flow pattern similar to restrictive, but reflecting, in fact, a supernormal diastole[6] (Figure 1).

In the second group (bodybuilders), in which the heart is subjected to high pressures without increasing its frequency too much, we can find predominant increase in wall thickness without dilatation (concentric hypertrophy, augmented muscle stiffness, and longer relaxation period leading to a prolonged deceleration time of mitral E wave and an inverted E/A ratio).

These situations are exaggerations, and the examples used herein are only for better understanding, but in the real world, diastolic evaluation in athletes is usually much more complex. We will show, with two clinical examples, how the rational use of the new guideline along with advanced echocardiographic techniques and clinical history can lead to a correct and refined analysis of diastolic function on this population.

Example 1: 16-year-old male soccer player (same patient of Figure 1). If we look only for the mitral flow pattern of this athlete, we will find an E/A ratio of 2.25 and an E wave deceleration time of 138 ms, which could resemble a restrictive pattern that is incompatible with the status of a young athlete. Tissue Doppler velocity shows septal e' of 0.17 m/s and lateral e' of 0.18 m/s. It leads to an E/e' ratio of 7.01. Tricuspid regurgitation velocity was 1.33 m/s and there was left atrium volume indexed of 27.9 mL/m^2 (Figure 2). All measurements

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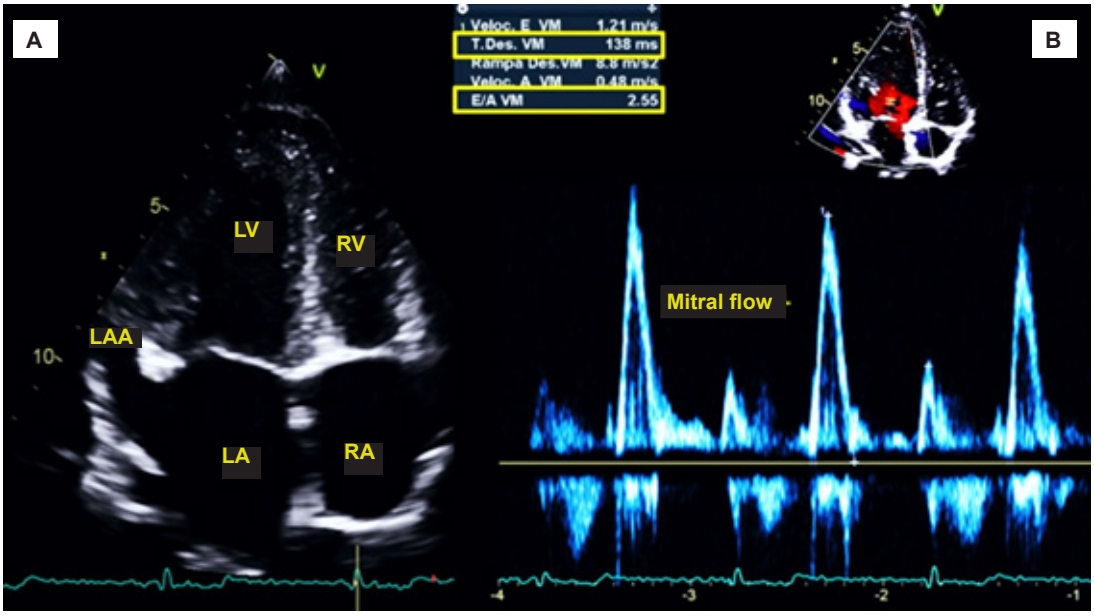

Figure 1 – *Left: Apical four-chamber view on 2D echo. Right: Doppler mitral flow on a young athlete. LAA: left atrial appendage; RA: right atrium; LA: left atrium; E/A VM: mitral valve E/A ratio; T.Des. VM: mitral valve deceleration; RV: right ventricle; LV: left ventricle..*

were within the normal limits, setting up a supernormal mitral flow pattern often found in youth and athletes.

Example 2: 48-year-old male bodybuilder and runner. Initial 3D echo study did not show any significant abnormalities. The diastolic evaluation showed an E/A ratio of 1.12, a septal and lateral e' velocity of 0.05 and 0.07 m/s, respectively, an E/e' ratio of 10.3, indexed left atrium volume of 17.9 mL/m^2 and tricuspid regurgitation peak velocity of 2 m/s (Figure 3). After analysis of these data, according to the 2016 guideline, only one criterium, out of four, was not normal (mitral septal and lateral annulus velocity), which should lead to a normal diastolic function.

However, attention was drawn to abnormal mitral annulus velocity in an asymptomatic athlete. After a more careful anamnesis, the patient reported that he was on anabolic androgenic steroids (testosterone propionate 30 mg, testosterone phenpropionate 60 mg, testosterone isocaproate 60 mg, testosterone decanoate 100 mg – Durateston®). After evaluation of the myocardial deformation with speckle tracking, we found an abnormal global longitudinal strain value of -15.4%. (Figure 4). This finding completely modifies the diastolic function analysis on this patient. Documented systolic disfunction lead to the second algorithm of 2016 guideline (patients with depressed LVEFs and patients with myocardial disease and normal LVEF after consideration of clinical and other 2D data). Such a low strain value points to some degree of myocardial impairment caused by the steroids, compromising both systolic and diastolic functions. According to this guideline, we should not expect to have systolic disfunction without, at least, some degree of diastolic disfunction, due to the intricated relationship between them. This has not been a new concept. Since 2008 Lester et al.[7] reported that: "traditionally, parameters of diastolic function have been derived from Doppler and those of systolic function from two-dimensional variables. This may create the illusion that individuals have isolated diastolic dysfunction". Thus, instead of normal diastolic function, according to the 2016 guideline, this athlete already has mild diastolic disfunction.

Extremely active people and competitive athlete populations are increasing day by day.[8] Recent reports extrapolate the causes of cardiac remodeling induced by exercises beyond the ventricular structure, including now changes in diastolic function,[9] right ventricle morphology,[8] and left atrium structure.[10-12]

All forms of vigorous physical exercise, whether in professional athletes or in highly active people, involve a combination of static and dynamic exercises. Static and dynamic refer to the skeletal muscular activity pattern and its consequence in the cardiovascular system. Static activity is characterized by vigorous short contractions of certain muscular groups. During pure static activity events (or predominantly), like in weightlifting/throwers, we find an acute increase in vascular resistance and blood pressure. The main purpose of cardiovascular system in these athletes is to preserve the cardiac output in face of the sudden and exaggerated increase in afterload. In contrast, dynamic exercises (endurance) are characterized by repetitive contractions and relaxations, often rhythmic, of big muscular groups that require an increase in the oxidative metabolism. The dynamic activity intensity can be quantified by the oxygen consumption (VO_2). The primary response of the cardiovascular system to dynamic exercise is to increase the cardiac output to ensure the arrival of nutrients to the active muscular bed. Increase of cardiac output is reached by increasing both stroke volume and heart rate and decreasing peripheral vascular resistance.

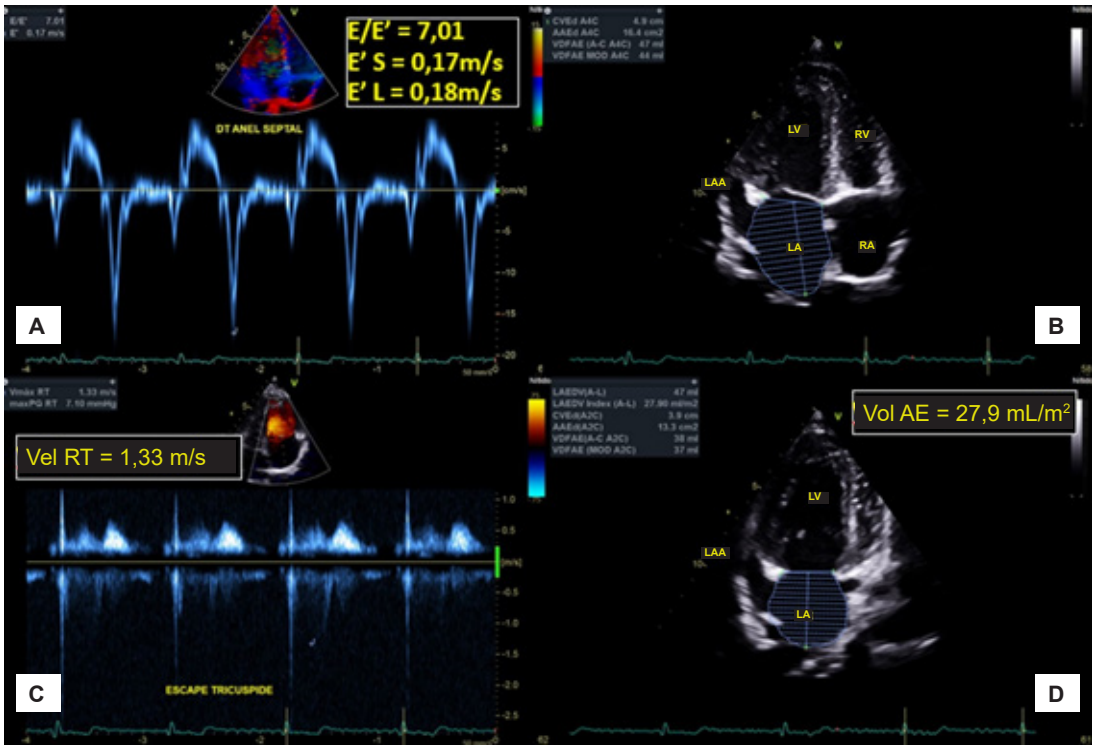

Figure 2 – *A) mitral annular tissue Doppler; B) apical four-chamber view on 2D echo bidimensional; C) continuous Doppler of tricuspid regurgitation; D) apical two-chamber view on 2D echo. LAA: left atrial appendage; RA: right atrium; LA: left atrium; E'L: lateral e' velocity; E'S: septal e' velocity; RV: right ventricle; LV: left ventricle; Vol AE: left atrium indexed volume.*

Diastolic function in athletes and in highly active people should be normal or increased, and any pieces of diastolic disfunction evidence should alert us for any pathology.[13] Large metanalysis data pointed that exercises promote an increase in diastolic function through the combination of a more effective early diastolic relaxation and increased ventricular compliance.[14] The type of physical activity is also related to the changes observed in athletes' diastolic function. Dynamic exercises lead to a more effective ventricular relaxation besides biventricular enlargement, while static exercises may be related to a certain degree of diastolic disfunction,[15] which usually happens with an increase in wall thickness and left ventricular concentric hypertrophy.

Therefore, it is essential while evaluating ventricular function in athletes, whether they are professionals, amateurs or only "weekend players," that we use all available tools in the echocardiographic arsenal. Ejection fraction should always be quantified by 3D echo, and evaluation of myocardial deformation (strain measurement) should be taken with the speckle tracking technique. Strain quantification can show incipient impairment in systolic function much earlier than any change in ejection fraction or 2D echocardiographic contractile abnormality could be verified. Routine evaluation of myocardial deformation would allow the detection of some underlying myocardial injury in this population. In addition, a comprehensive analysis of diastolic function must be done according to the recent guideline.

It is quite common to find athletes on formulas and anabolic androgenic steroids without any prescription or medical advice, and a complete echocardiographic evaluation could detect early ventricular systolic and diastolic disfunction, thus allowing correct treatment to avoid any larger myocardial damage.

Author contributions

Conception and design of the research, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Silva CES

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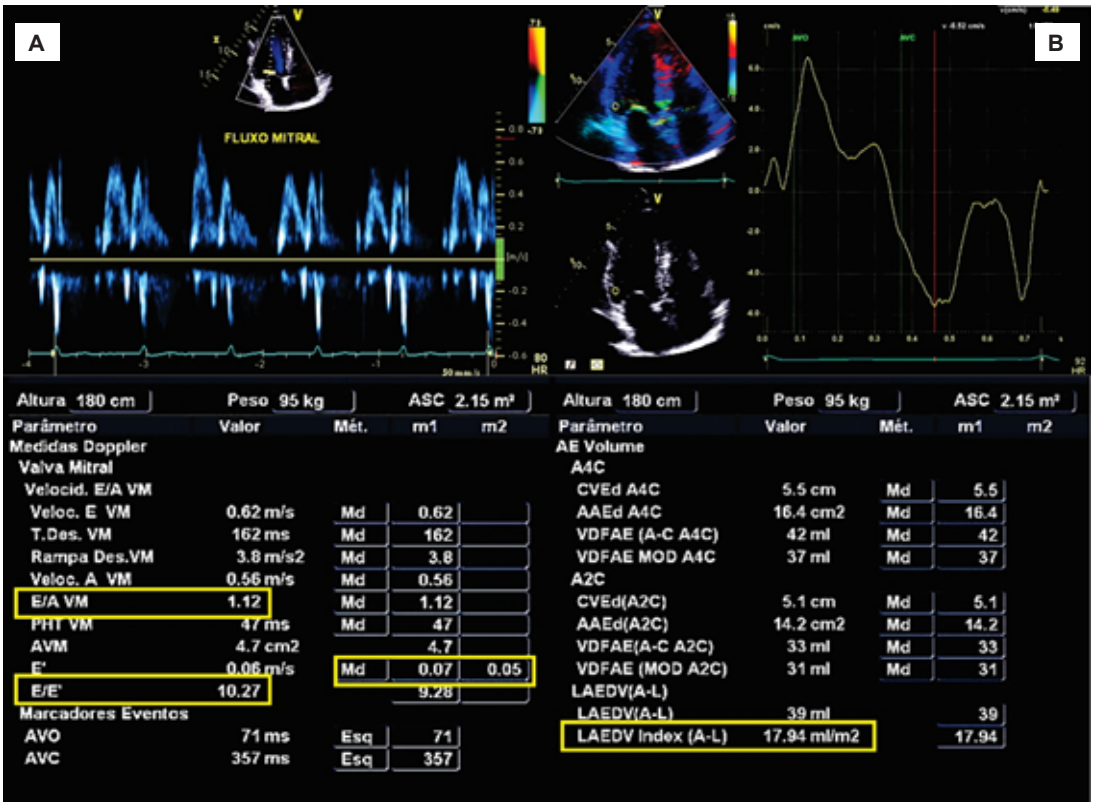

Figure 3 – *A) pulsed Doppler curve of mitral valve; B) tissue Doppler curve of mitral lateral annulus. E/A VM: mitral valve E/A ratio; LAEDVindex(A-L): left atrium indexed volume.*

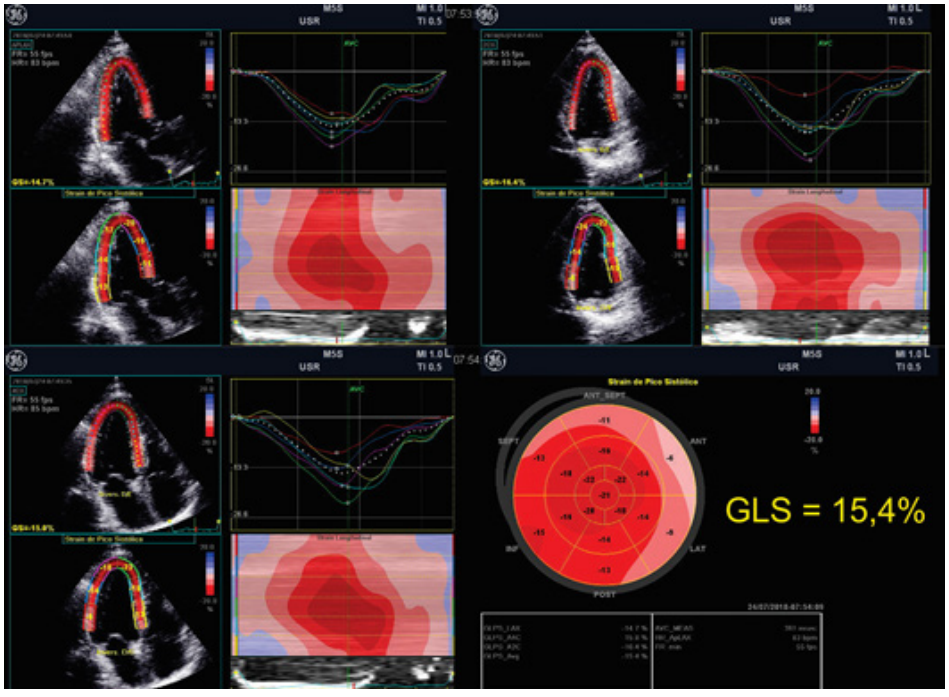

Figure 4 – *Quantification of myocardial strain by speckle tracking.GLS: global longitudinal strain*

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Myocardial Injury in COVID-19: a Challenge for Clinical Cardiologists

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A 39-year-old male patient, with no previous comorbidities, was admitted to the emergency department presenting intense chest pain, associated with nausea, sweating, and mild respiratory distress. The pain was oppressive, and it radiated to both shoulders. The patient reported onset of asthenia, lack of appetite, and fever (38.9 ºC) 2 days prior, and he presented with polymorphic erythematous skin lesions on his back 1 day after admission.

Physical examination revealed the following: blood pressure = 140/100 mmHg, heart rate = 90 bpm, no fever, SpO_2 = 98% in room air, regular cardiac rhythm with 2 beats, no murmurs, clean lungs, good peripheral perfusion, and no edema.

Electrocardiogram revealed sinus rhythm and ST-segment elevation in precordial leads V2 to V6 (Figure 1).

Laboratory exams revealed the following: troponin I: 25.20 ng/mL (normal value [NV]: ≤ 0.034 ng/ml), brain natriuretic peptide (NT-ProBNP): 1,460 pg/mL (NV: ≤ 125 pg/ml), D-dimer 104 ng/ml (NV: ≤ 400 ng/ml), hemoglobin 14.3 g/dl, leukocytes 7,020 mm^3 (78.1% neutrophils and 9.7% lymphocytes), platelets 145,000, and creatinine 0.6 mg/dl. Sorology for HIV and cytomegalovirus were negative, as was NS1 antigen test.

The patient was started on dual antiplatelet therapy with acetylsalicylic acid 200 mg and ticagrelor 180 mg, and he was referred to the hemodynamic service, where he underwent coronary cineangiography, which showed coronary arteries with mild diffuse parietal irregularities, without significant atheromatosis.

Chest computed tomography showed tenuous focal areas with ground-glass opacity, isolated on the periphery of the posterior basal segment of the right lower lobe (impairment < 25%). This finding may be observed in cases of viral pneumonia; it is, however, non-specific.

Echocardiogram showed hypokinesia of the middle segment of the antero-septal wall, with preserved ejection fraction (62%) and minimal diffuse pericardial effusion. Cardiac chambers were within normal limits.

Keywords

Cardiovascular Diseases; Chest Pain; Cardiac Injury; Myocarditis; Coronavirus; COVID-19; Pandemic.

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On the third day after onset of symptoms, oral and nasal swabs were collected for RT-PCR for COVID-19, the results of which were positive.

To clarify the diagnosis, cardiac magnetic resonance imaging was performed, which showed meso-epicardial late enhancement in the inferior, inferolateral and anterolateral walls, associated with hypersignal in T2, with slight extension to the adjacent pericardium, compatible with acute myopericarditis (Figure 2).

The patient was initially admitted to the intensive care unit. He progressed in good general condition; he was asymptomatic, and, on the eighth day, he was discharged, using a betablocker and an AT1 angiotensin receptor blocker.

Faced with the novel coronavirus pandemic, it has already been possible to see evidence of the correlation between COVID-19 and cardiovascular complications caused by this disease.[1,2] In this context, cardiovascular involvement, a condition with high morbimortality, has shown great variability regarding clinical presentation, overlapping with manifestations of COVID-19,[3-5] thus making initial cardiological evaluation and regular follow-up of infected patients necessary in order to minimize unfavorable outcomes.

This case indicate that young patients without risk factors may also suffer from cardiac complications during the course of infection with the novel coronavirus. Larger studies will be necessary in order to further clarify predictive factors and outcomes related to cardiac involvement.

Author contributions

Conception and design of the research and Acquisition of data: Aragão RCA, Alves MC, Passos HD; Analysis and interpretation of the data and Writing of the manuscript: Aragão RCA, Barreto-Filho JAS; Critical revision of the manuscript for intellectual content: Aragão RCA, Gonçalves LFG, Baumworcel L, Barreto- Filho JAS.

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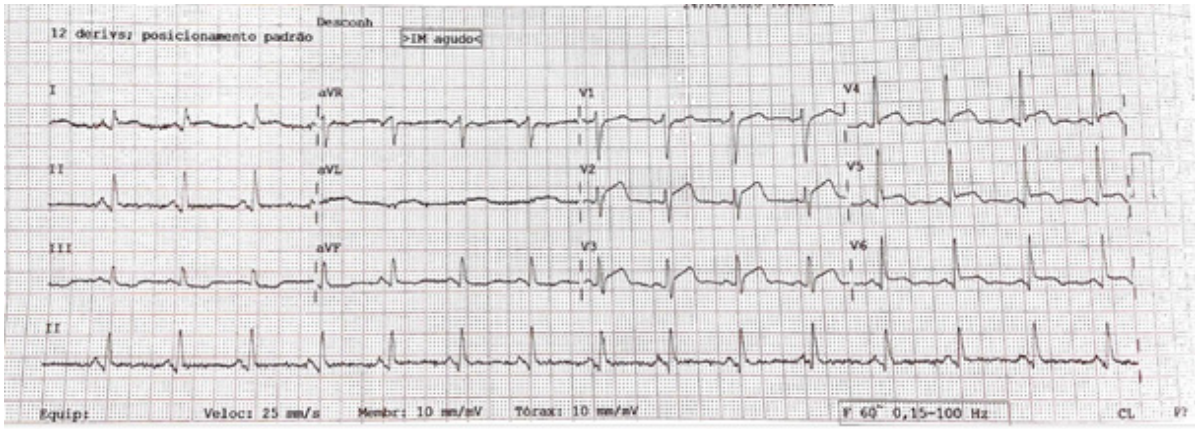

Figure 1 – *Electrocardiogram showing the presence of ST-segment elevation on leads V2 to V6.*

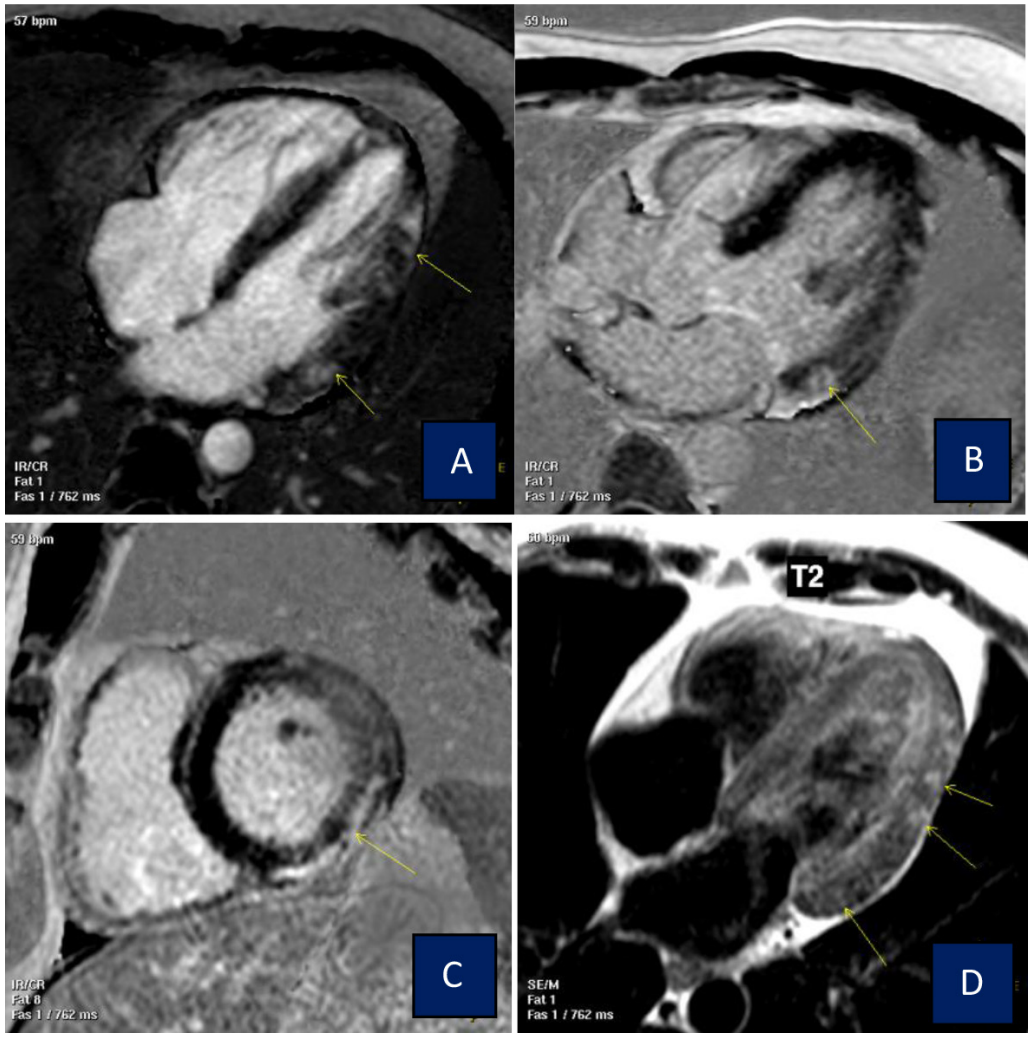

Figure 2 – *Post-contrast sequences (A, B, and C), demonstrating meso-epicardial late enhancement, involving inferior, inferolateral and antero-lateral walls, with slight extension to the adjacent pericardium and associated hypersignal, in black-blood sequences, predominantly in T2 (D).*

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SARS-Cov-2 Infection and Pulmonary Thromboembolism – The Prothrombotic State in COVID-19

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Introduction

The COVID-19 caused by new coronavirus, named by the World Health Organization as Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2), has spread all over the world with astonishing speed.[1] In Brazil, the spread risk (R0) of COVID-19 has been 3.0, which explains its rapid dissemination all over the states.[2]

Individuals with cardiovascular diseases, systemic arterial hypertension, diabetes mellitus, chronic obstructive pulmonary disease, and immunosuppressed patients are at higher risk for adverse outcomes.[3]

A relatively high incidence of thrombotic and thromboembolic disease has been observed in COVID-19 carriers, probably due to direct effects of the SARS-CoV-2 or indirect mechanisms of the infection. Interactions between COVID-19 therapies and antiplatelet agents or anticoagulants and the inadvertent use of anticoagulants may contribute to the prothrombotic state of the disease.[4]

Objectives

Here we describe a patient diagnosed with SARS-CoV-2 progressing with pulmonary thromboembolism and no evidence off peripheral thrombosis.

Methods

The data here reported were obtained by review of electronic medical records, complementary tests, and literature review.

Keywords

Coronavirus; COVID-19; Pulmonary Embolism; Severe Acute Respiratory Syndrome; Anticoagulants; Diagnostic, Imaging.

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Case Report

Patient I.M.S., male, aged 66 years, self-referred to the emergency department of a general hospital in Aracaju, Brazil, on March 28, 2020, with nasal congestion, dry cough, asthenia, nausea and fever (40ºC) for eight days, with worsening in the last 48 hours. The patient reported having been to Rio de Janeiro for a dental implant surgery in the beginning of March and returned to Aracaju on March 18, 2020. History of osteosynthesis of the left humerus 16 years before, former smoker (quit > 10 years ago), physically active. On physical examination, the only abnormal finding was diffuse inspiratory snoring and siblings on pulmonary auscultation. The patient had normal skin color and breathing, and hemodynamically stable. The hypothesis of COVID-19 was raised and the following tests were performed: 1) laboratory routine tests, showing slightly elevated C-reactive protein levels and the other parameters within normal ranges (including myocardial injury markers); 2) RT-PCR by oropharyngeal swab; and 3) chest tomography (Figure 1) which revealed ground-glass opacities, mainly in peripheral areas and more evidently in lower segments, affecting less than 50% of the pulmonary parenchyma. Electrocardiogram (ECG) with normal sinus rhythm and heart rate of 65 bpm.

Since the patient was an elderly man and had impaired pulmonary function, the patient stayed in isolation of an intensive care unit, with diagnosis of viral pneumonia, probably caused by the SARS-CoV-2 infection.

A therapy with Oseltamivir (150 mg/day), Azithromycin 500 mg/day and Ceftriaxone 2g/day was initiated, combined with prophylactic enoxaparin 40mg/day for venous thrombosis. After 24 hours of hospitalization, the patient showed progressive worsening of respiratory function, culminating with acute respiratory failure, requiring orotracheal intubation on the second day of hospitalization. The patient also developed shock, and vasoactive drug was used.

With worsening of hemodynamics and the negative RT-PCR for SARS-CoV-2, a transesophageal echocardiogram (TEE) was performed to rule out the possibility of infectious endocarditis. The TEE, performed on April 02, 2020, revealed: a) enlargement of the left ventricle, which showed diffuse hypokinesis predominantly of the antero-apical wall and apical septum, grade 1 diastolic function and moderated global diastolic dysfunction, with ejection fraction of 41%; b) enlargement of the right chambers, with diffuse hypokinesis of the right ventricle, and moderate global systolic dysfunction by subjective evaluation; c) mild-to-moderate pulmonary hypertension (pulmonary artery systolic pressure of

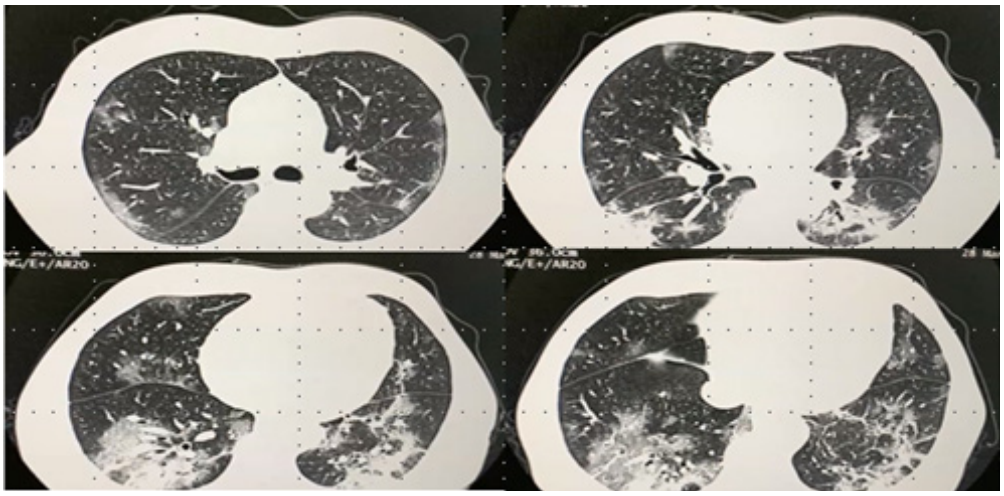


Figure 1 – *Chest computed tomography without contrast on hospital admission. Ground-glass opacities, mainly in peripheral areas and more evidently in lower segments, affecting less than 50% of the pulmonary parenchyma.*

48 mmHg); d) degenerative changes of aortic and mitral valves; e) absence of vegetations and/or thrombus. The hypothesis of myopericarditis was then raised, but both electrocardiographic findings and myocardial lesion markers were normal. Cardiac magnetic resonance imaging, which is a valuable test in these situations, was delayed due to ongoing infection.

Subsequently, an exponential increase in D-dimer and C-reactive protein levels was observed, while troponin and NT-pro-BNP levels remained within normal ranges, as described in Table 1. It is worth pointing out that the negative RT-PCR may be explained, at least in part, by the fact that the specimens were collected on the ninth day of symptom onset, when virus release is known to be falling. Due to the high suspicion of COVID-19, the regimen of antibiotics was maintained; also, a serological test was ordered, which yielded a positive result for the disease (IgG - / IgM + SARS-Cov-2).

Considering the echocardiographic changes and significant elevation of D-dimer (5,000 ug), a lower extremity venous duplex scan was performed to investigate venous thrombosis, and the result was negative. Computed tomography angiography of the chest was then carried out (Figure 2), which revealed filling defect of the distal right pulmonary artery, extending to segmental branches of the right upper lobe, compatible with pulmonary thromboembolism. Then, an anticoagulation was initiated with enoxaparin 120 mg/day for 72 hours, substituted with rivaroxaban 30 mg/day due to improvement in hemodynamics and mechanical ventilation weaning plan.

From the eight day on, the patient showed progressive improvement with concomitant decrease in dimer-D levels, as shown in Figure 1. The patient was extubated on the tenth day of hospitalization. Four days after, the patient was discharged, with rivaroxaban 30mg/day for further 17 days and when 21 days are completed, 20mg/day for 3-6 months, according to outpatient follow-up visits.

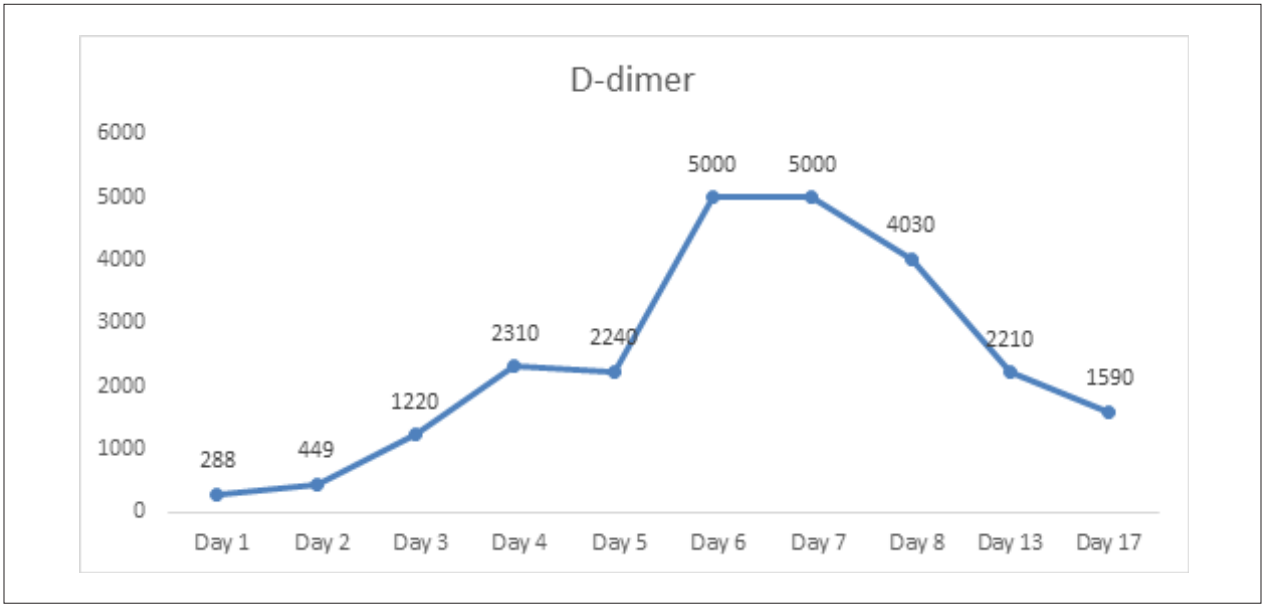
Discussion

There have been remarkable and variable cardiovascular complications of the coronavirus infection.[5] In severe manifestations of COVID-19, increased D-dimer and its association with increased mortality have been observed.[5] Studies have suggested that an exacerbate systemic inflammatory response plus hypoxia may cause endothelial dysfunction and increased procoagulant activity, contributing to thrombus formation. This prothrombotic state, associated with systemic infection, is commonly known as sepsis-induced coagulopathy.[6-9]

It is worth mentioning that the data available on thrombotic risk are limited; most of the cases reported have been derived from case series in China, Holland and Fance.[10] However, most experts agree that one sign of increased thrombotic risk is sufficient to recommend pharmacological prophylaxis

Table 1 – D-dimer, troponin, and NT-ProBNP levels during hospitalization

Hospitalization day	D-dimer (ug)	Troponin (ug/ml)	NT - ProBNP (ug/ml)
Day 1	288	<0.012	-
Day 2	449	< 0.012	
Day 3	1220	< 0.012	
Day 4	2310		
Day 5	2240		
Day 6	5000		
Day 7	5000	< 0.012	111
Day 8	4030		104
Day 13	2210		
Day 17	1590		416



Graph 1 – *D-dimer profile during hospital course.*

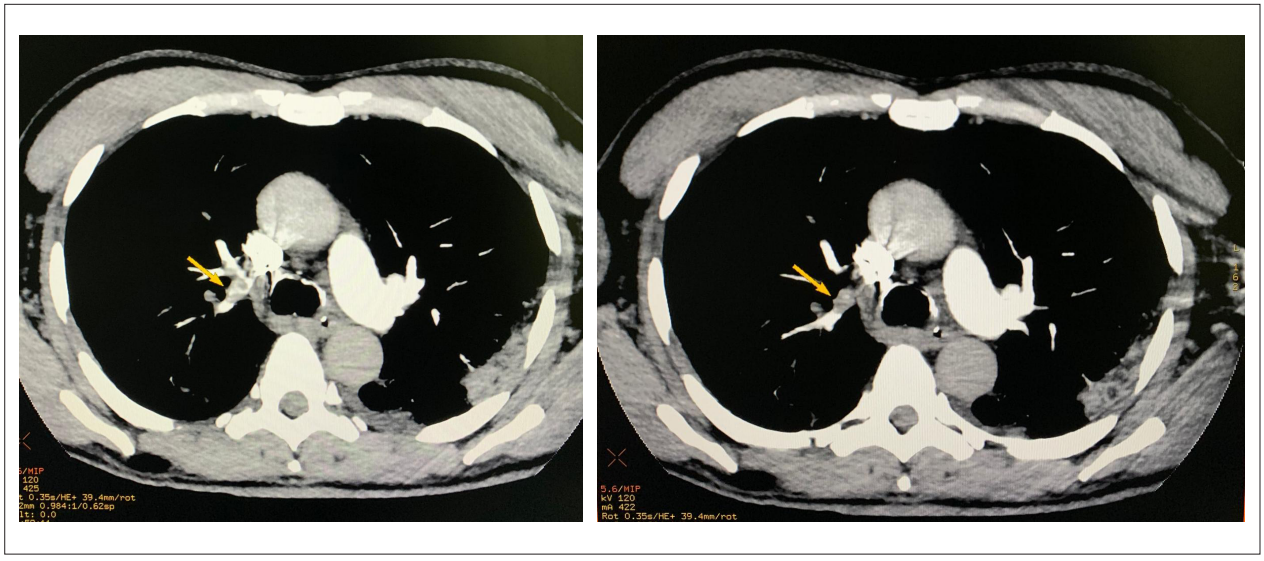


Figure 2 – *Computed tomography angiography of the chest: (yellow arrow) filling defect of the distal right pulmonary artery, extending to segmental branches of the right upper lobe, compatible with pulmonary thromboembolism.*

of venous thromboembolism in patients hospitalized for COVD-19. In addition, anticoagulation should be considered in critically ill patients under intensive therapy, even with no clinical or imaging evidence of thrombosis, taking into consideration the risk of bleeding and potential benefit of interrupting the prothrombotic cascade, based on experts' opinion and case series. Prospective studies are needed to confirm this benefit.[9,10]

The elevations in D-dimer levels in severe forms of COVD-19 and superposition of respiratory symptoms over pulmonary thromboembolism symptoms make it difficult to early diagnose the latter. Special attention must be paid to refractory hypoxemia, electrocardiographic alterations, sinus tachycardia that is not explained by current clinical condition and left ventricular dysfunction for diagnosis of pulmonary thrombosis and initiation of adequate anticoagulant therapy.

Conclusion

The SARS-Cov-2 infection has a variable phenotype, with common manifestations of cardiovascular complications and a prothrombotic state, by mechanisms not fully elucidated. Attention should be given to superposition of respiratory symptoms

of COVID-19 and eventual occurrence of pulmonary embolism, even in the absence of evidence of deep venous thrombosis. Further studies are still needed to elucidate the pathophysiological mechanisms of thromboembolic events in COVID-19.

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To the healthcare professionals engaged in the defense of life, against the Coronavirus. Paraphrasing Winston Churchill, "never was so much owed by so many to so few."

Author Contributions

Conception and design of the research and Analysis and interpretation of the data: Passos HD, Sousa ACS; Data acquisition: Passos HD; Writing of the manuscript and Critical revision of the manuscript for intellectual content: Passos HD, Alves MC, Baumworcel L, Vieira JPC, Garcez JDS, Sousa ACS.

Potential Conflict of Interest

The authors report no conflict of interest concerning the materials and methods used in this study or the findings specified in this paper.

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Study Association

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Ethics Approval and Consent to Participate

Informed consent was obtained from the participant included in the study.

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Does Existence of Prior Circulatory System Diseases Accelerate Mortality Due to COVID-19?

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Dear Editor,

The first cases of coronavirus disease 2019 (COVID-19) were identified in the metropolis of Wuhan, the capital of the province of Hubei, in the People's Republic of China.[1] An outbreak of rapidly progressive pneumonia of undetermined origin associated with common exposure to the city's seafood market was observed.[1] On December 31, 2019, China notified the World Health Organization (WHO) of the outbreak.[1] One month later, on January 30, 2020, the WHO declared the situation an international emergency, and, on March 11, the disease was declared a pandemic.[2]

In Brazil, the first case was confirmed on February 26, 2020, in São Paulo. On March 17, the first death in the country was registered, and, three days later, on March 20, the Ministry of Health recognized community transmission throughout Brazilian territory. On May 15, Brazil held sixth place worldwide in total cases, with more than 200,000 individuals infected and more than 13,000 deaths.[3]

The most relevant aspects that should be observed during the course of the pandemic include the groups at greatest risk; in this group, individuals over the age of 60 and those with cardiovascular comorbidities stand out, as these factors are associated with worse prognosis and greater lethality when patients are infected with the novel coronavirus.[4]

The objective of this study was to analyze the association between the existence of previous circulatory system diseases and time (in days) from onset of first symptoms to date of death due to COVID-19.

This is a case-control study, involving data from 374 deaths due to COVID-19, registered in the state of Pernambuco, Brazil. Data were obtained from the state's COVID-19 monitoring webpage (https://dados.seplag.pe.gov.br/apps/corona.html), on May 7, 2020. After collection, the database underwent adjustment of variables, which consisted of evaluation of signs/symptoms and comorbidities. Following adaptation, 197 individuals had prior circulatory system disease, 187 of which included date of onset of symptoms and date of death. These individuals constituted the case group. To form the control group, 187 deaths without related comorbidities were selected. Selection of these deaths was random, following the date of onset of symptoms.

In this study, the following variables were considered: existing comorbidities (none, one, two, and three or more) and time (in days) from onset of symptoms to death due to COVID-19. For statistical analysis, the Kolmogorov-Smirnov test was used for initial evaluation of data normality. When violation of the presupposed Gaussian distribution was found, association between variables was evaluated by nonparametric Mann-Whitney U test. Analyses considered a significance level of 5%, and they were carried out with the help of SPSS software, version 24.0 (IBM Corporation). Given that the study used public domain data, wherein it is not possible to identify the individuals, approval by the Research Ethics Committee was waived for this study.

Average and standard deviation (average ± SD) and median and interquartile range (median – IQR) of days from onset of first symptoms to date of death for the whole study population (n = 374) were 11.52 (± 7.75) and 10 (IIQ 10), respectively. In the case group, 38 (20.3%) had only one circulatory system disease; 79 (42.2%) had two comorbidities/risk factors, and 70 (37.5%) had three or more comorbidities/risk factors. It is worth highlighting that at least one of the comorbidities was related to the circulatory system (Figure 1).

A significant difference was observed regarding the number of days from onset of first symptoms to death when comparing the two groups. The values observed in the control group (average ± SD = 13.32 ± 7.2; median – IQR = 11 – 11) were higher than those in the group with reported comorbidities (average ± SD = 9.73 ± 7.8; median – IQR = 7 – 9) (Figure 1).

This study indicates more rapid progression of COVID-19 in patients with cardiovascular comorbidities; average number of days from onset of first symptoms to death was lower by almost four days (3.9 days for average and 4.0 days for median), when comparing the group that had prior cardiovascular disease to the control group. This process results from the effects of SARS-CoV-2 in the human body, such as the binding of the virus to angiotensin-converting enzyme 2 (ACE2) found in the surface of heart, kidney, and lung cells.[4]

Exposure of glycoproteins related to the novel coronavirus to ACE2 promotes internalization together with the virus, which diminishes the density of ACE2 in the membrane[5,6] and, consequently, the cardioprotective effect related to cardiac hypertrophy, myocardial fibrosis, and inflammation. Accordingly, the reduction of ACE2 is associated with the exacerbation of existing heart diseases, such as heart

Keywords

Coronavirus, COVID-19, Pandemics; Severe Acute Respiratory Syndrome/complications; Comorbidity; Risk Factors; Diabetes; Hypertension; Dispnea.

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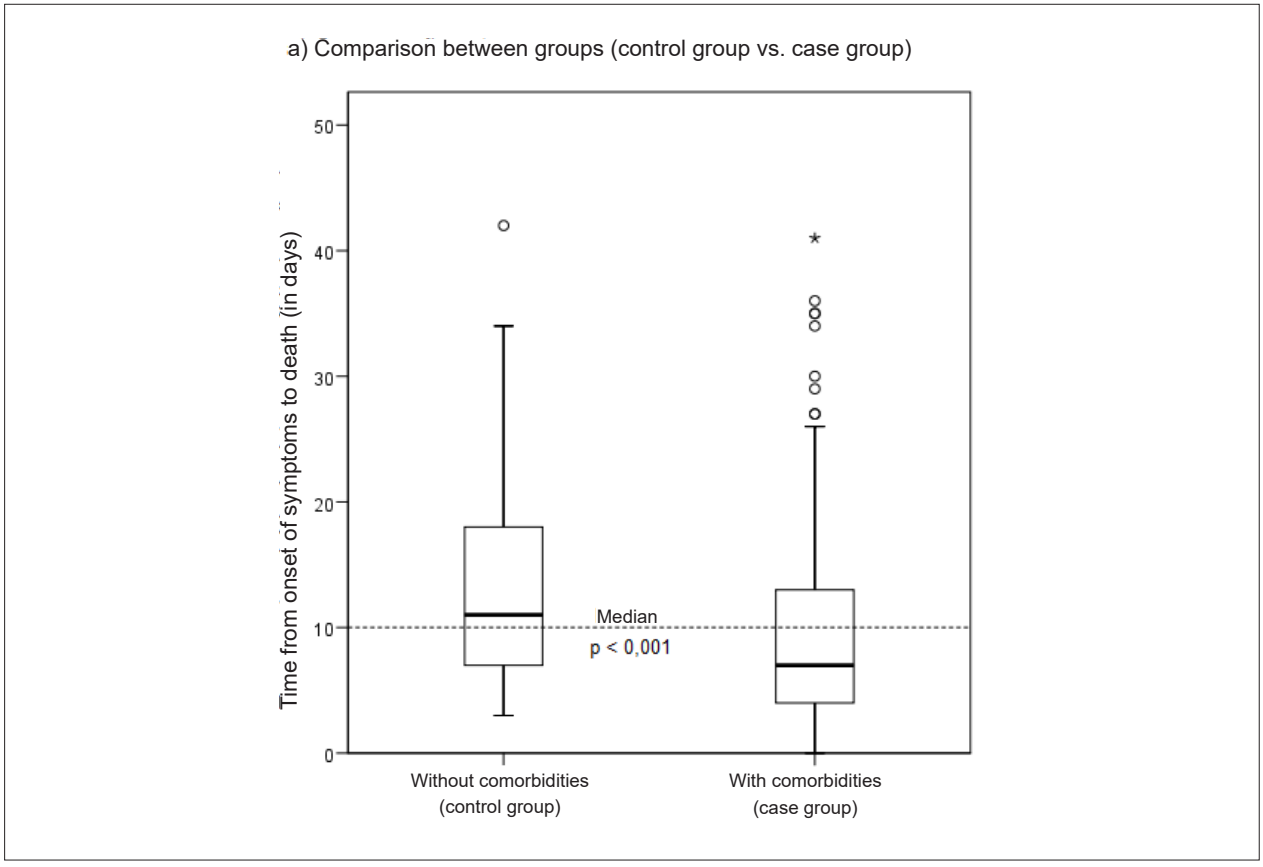

Figure 1 – *Comparison between number of days from onset of first symptoms to death due to COVID-19, according to presence or absence of comorbidities. Brazil, 2020.*

failure and arterial hypertension, contributing to more rapid progression and worsening of respiratory and cardiovascular condition of individuals with COVID-19.

Based on the observed results, the presence of cardiovascular comorbidities accelerates mortality due to COVID-19. Furthermore, future studies need to be performed with the aim of measuring the impact of each cardiovascular disease on risk of mortality.

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Erratum

April 2020 Issue, vol. 114 (4), pages 732-735

In the Brief Communication "Inotropic and Antiarrhythmic Transmural Actions of Ranolazine in a Cellular Model of Type 3 Long QT Syndrome", with DOI number: https://doi.org/10.36660/abc.20190220, published in the periodical Arquivos Brasileiros de Cardiologia, 114(4):732-735, on page 732: consider Danilo Roman-Campos as the correct form for the name of the author Danilo Roman Campos.

May 2020 Issue, vol. 114 (5), pages 849-942

In the Statement "Brazilian Cardiology Society Statement for Management of Pregnancy and Family Planning in Women with Heart Disease – 2020", with DOI number: https://doi.org/10.36660/abc.20200406, published in the periodical Arquivos Brasileiros de Cardiologia, 114(5): 849-942, on page 851, in the conflict of interests of Dr. Fernando Souza Nani, in the item " Spoke at events or activities sponsored by industry related to this statement", consider the company CSL Behring to be correct instead of Boehringer.

March 2020 Issue, vol. 114 (3), page 582

In the Statement "Posicionamento Brasileiro sobre Hipertensão Arterial Resistente – 2020" with DOI number: https://doi.org/10.36660/abc.20200198, published in the periodical Arquivos Brasileiros de Cardiologia, 114(3): 576-596, on page 582: in the figure 1 of the Portuguese version, where "hipertensão segundária" is mentioned, the correct is "Hipertensão arterial pseudorresistente". In the English version, where "abnormal" is mentioned, right side of the figure 1, the correct is "normal".

Ahead of Print

In the original article published in ahead of print with the title "Avaliação do Tempo de Condução Atrioventricular Dinâmica para Acoplamento ao Intervalo RR em Atletas e Indivíduos Sedentários", with DOI number: https://doi.org/10.36660/abc.20190281, published in the periodical Arquivos Brasileiros de Cardiologia, consider the title correct: "Avaliação da Dinâmica do Acoplamento da Condução Atrioventricular à Variação dos Intervalos RR em Atletas e Indivíduos Sedentários".

DOI: https://doi.org/10.36660/abc.20200730