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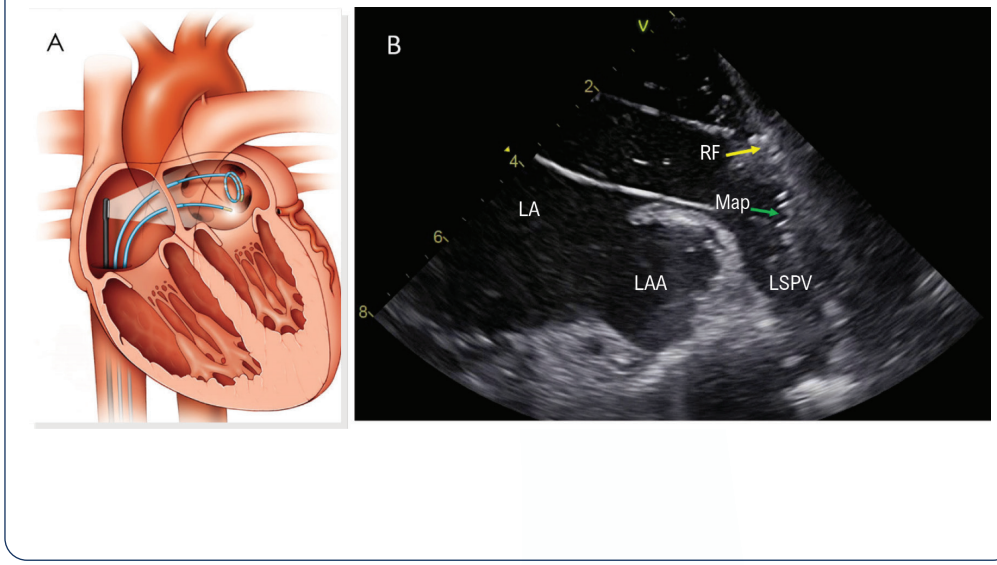

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JOURNAL OF BRAZILIAN SOCIETY OF CARDIOLOGY - Published since 1943

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Vaccinating Patients with Heart Disease Against COVID-19: The Reasons for Priority

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The COVID-19 pandemic

The World Health Organization recognized COVID-19 as a pandemic on March 11, 2020. Since then, this public health emergency has become the leading cause of death in the world and has made addressing it an unquestionable priority. At the time of writing this editorial, we counted 86 969 386 confirmed cases and 1 915 657 deaths from COVID-19 worldwide, of which, 8 013 708 cases in Brazil resulted in 201 460 deaths.[1] According to projections by the Institute for Health Metrics and Evaluation (IHME),[2] Brazil will have 248 476 deaths from COVID-19 on April 4, 2021. By March 19, 2021, 242 738 [232 202 – 255 044] deaths are estimated, and those numbers could be reduced to 241 668 [231 337 – 253 770], with the quick administration of vaccines, and to 223 910 [215 565 – 233 360], with a 95% level of face mask use in public. The magnitude of the number of cases and deaths from a single disease in such a short time is worrisome. Now, when there is a growth in the number of new cases and hospitalizations, starting to vaccinate will have an impact on reducing deaths and hospitalizations in a short interval. Despite the efforts of the scientific community, there is no specific treatment to block viral replication. In this sense, vaccination programs are powerful allies. In addition, due to the remarkable progress of science, we already have this resource.

Brazil, through its Unified Health System (SUS), has been known for the successful implementation of vaccination programs for its population. The institution of a public policy to vaccinate within the SUS principles, which are universality, integrality, and equity, is urgent. However, because of the antivaccine movements that have emerged worldwide, a strong effort to obtain the population's adhesion is required. In the past, in the Vaccine Revolt experienced by Oswaldo Cruz, we have successfully faced that disbelief. Let us be inspired by that episode to overcome this serious health crisis.

Keywords

Coronavirus Infections; Coronavirus, COVID-19; Betacoronavirus, Pandemics; Vaccination; Vaccines; Cardiovascular Diseases; Influenza, Human; Health Policy.

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The epidemiology of cardiovascular diseases in COVID-19

In Brazil, between March 17 and May 22, 2020, there was a greater number of deaths in the capitals of the Northern, Northeastern and Southeastern regions, especially São Paulo, Rio de Janeiro, Fortaleza, Recife, Belém, and Manaus, and a lower number of reports of death in the capitals of the Southern and West-Central regions, and in the inner country cities. We observed an increase in the number of deaths due to non-specific cardiovascular causes in all regions, in the capitals and in the inner country, mainly in the Northern, Northeastern, and Southeastern regions. On the other hand, there was a percentage reduction in the reports of deaths from acute coronary syndrome (ACS) and stroke, with greater magnitude in the Northeastern region, followed by the West-Central and Southeastern regions (capital and inner country).[3]

In 2020, the COVID-19 pandemic in Brazil increased the number of general deaths and of deaths due to cardiovascular diseases (CVD) and non-specific causes, as well as that of sudden deaths at home. Regional differences express the socioeconomic and ethnic inequalities of a continental country, as well as the consequence of a health system with heterogeneous and poorly distributed resources.[3]

COVID-19 is the pandemic novelty and CVD are our endemic, consolidated, and irresolute reality. Both compromise health in all aspects, individually and collectively, physically, psychologically, socially, and economically. In common, they reap productive and promising lives.

We still lack double-blind, randomized, placebo-controlled studies that show the causal relationship between vaccination against COVID-19 and benefit for cardiac patients. Let us, then, use the best available evidence.

Vaccines and the impact on humanity

Despite having arisen even before immunologists, vaccines have had an impact on the control and even

eradication of once devastating diseases. Smallpox killed 29% of children in London in the 17th and 18th centuries, being declared extinct in 1980. Who among us diagnosed diphtheria myocarditis in a patient in the past ten years? How many cases of neonatal tetanus were admitted to your hospital in 2020? Vaccinations changed the natural history of some epidemics, such as that of diphtheria in 1940, of polio in 1956, of pertussis in 1950, of measles in 1968, of meningococcal disease in 1999. However, vacillation in campaigns has invariably resulted in recurrence.[4]

The influenza model

Influenza vaccination is the successful evidence-based experience closest to the current COVID-19 pandemic situation. Although influenza vaccination is recommended by the main guidelines in cardiology, that vaccination coverage is low and has increased little in the last decade.[5] Vaccination depends to a great extent on the cardiologist's recommendation. The cardiologist is "the clinician" of the patient with CVD, heard in several situations. The knowledge and consequent conviction about the need for a vaccine is crucial for its dissemination. The influenza vaccine is an unequivocal example: it is available, is easily accessed in campaigns, but its coverage does not exceed 25% of the patients with heart failure (HF).[5,6]

The need for influenza vaccination in cardiac patients has been first determined by historical reports of increased mortality in epidemics, and, later, by epidemiological studies.[5] Table 1 shows evidence that supported these recommendations.[7-15] Today, influenza vaccination is known to be an effective measure for secondary prevention because it reduces hospital admissions from HF, stroke, and ACS, in addition to reducing overall mortality more significantly than many medications or interventions.[5,6]

Infections and systemic inflammatory syndrome

Influenza predisposes to secondary bacterial pneumonia and, thus, decompensates patients with HF, and that is a fact. However, it should be noted that the systemic inflammatory syndrome secondary to influenza leads to changes in the coagulation factors and platelet hyperaggregability, and to an increase in inflammatory phase proteins, cytokines, and tumor necrosis factor. Consequently, there is an increase in thrombotic phenomena and fibrin deposition, cardiomyocyte hypocontractility, inflammation, acceleration of atherogenesis, and remodeling (Figure 1). Thus, this easily explains the reduction in ACS and stroke in

Table 1 – Main evidence that supported the recommendation of influenza vaccination in cardiac patients

Author	Year	n	Main conclusions
Nichol KL et al.[7]	2003	286 383 elderly	Influenza vaccine reduced overall mortality by 48%, hospitalizations for heart disease by 19%, and stroke by 16-23%
Yap FHY et al.[8]	2004	17 226 admissions for NCD	Influenza caused a 45.6% increase in hospitalizations for HF
Sandoval C et al.[9]	2008	5448 patients with systolic ventricular dysfunction	The risk of hospitalization for HF is 8-10% higher during the influenza season, regardless of how it is defined
Jorge JEL et al.[10]	2009	6596 hospitalizations for HF	The seasonality with the highest number of hospitalizations for decompensated HF also occurs in tropical regions
Estabragh ZR & Mamas MA[11]	2013	40 trials	Influenza leads to direct effect: myocarditis with cardiogenic shock, increased AMI, decreased cardiovascular mortality after vaccination
Wu WC et al.[12]	2014	107 045 patients with HF	Influenza vaccination reduced mortality of patients with HF in 30 days and 1 year
Caldeira D et al.[13]	2015	4 trials	Influenza vaccination is effective in secondary prevention in patients with cardiovascular disease. Data is lacking to prove the same action in primary prevention
Blaya-Nováková V et al.[14]	2016	227 984 patients followed for 5 years	Influenza vaccination reduced risk of global winter mortality by 41% per year
Fang YA et al.[15]	2016	4406 patients with CKD and age ≥55 years.	Elderly people with chronic kidney disease who received an annual influenza vaccination have a lower risk of hospitalizations for HF

NCD: chronic noncommunicable diseases; HF: heart failure; AMI: acute myocardial infarction; CKD: chronic kidney disease.

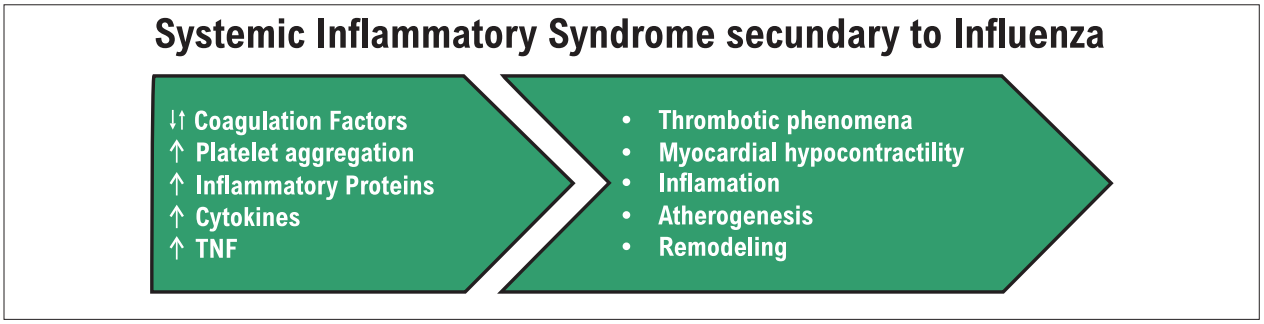

Figure 1 – *Pathophysiology of cardiovascular changes secondary to systemic inflammation in Influenza infection. Source: The authors.*

vaccinated patients as compared to controls in clinical trials and epidemiological observations.[5,16]

COVID-19 brought up the discussion of the same mechanisms and manifestations already well studied for influenza. It is undeniable that the COVID-19 inflammatory response is more exuberant and severe, and associated with the risk of thrombosis. Therefore, we are aware of the peculiarities of immunization in that subgroup of individuals and recommend efficient measures to increase the chances of success of the immunization program against COVID-19.

COVID-19 and risk groups

Since the first series published from China and Italy, the severity of COVID-19 has stood out in patients with chronic noncommunicable diseases, most likely because of the chronic systemic inflammation they have in common.[17] Discounting the confusions caused by inadequate interpretations of ecological studies, the concept of risk group has remained in subsequent publications, which has been an already known fact since the studies about influenza. The patient with HF is an undoubted example of a priority group, and the Brazilian Society of Cardiology (SBC) has already expressed its opinion.[18]

Recently, the SBC has been invited by the Ministry of Health to join the Technical Chamber and review the National Immunization Program against COVID-19. The SBC has pointed out suggestions regarding vaccination in patients affected by all CVD, defining and specifying priority groups for vaccination (Table 2).

The current perspectives with the different vaccines against COVID-19

There are still few vaccines tested in phase 2 or 3 studies. However, the results are positive and impactful, both in terms of safety and effectiveness. It is worth mentioning that the vaccines supported by Pfizer,[19] Moderna,[20] and AstraZeneca[21] have included the elderly, cardiac patients,

Table 2 – Cardiovascular and cerebrovascular diseases priority to COVID-19 vaccination. Suggestions offered by the Brazilian Society of Cardiology to the National Immunization Program of the Brazilian Ministry of Health

Cardiovascular or cerebrovascular syndrome / disease	Definition
Heart failure	• HF with reduced, intermediate or preserved ejection fraction, in stages B, C or D, regardless of New York Heart Association functional class • Post-heart transplantation (using inactivated virus vaccines)
Cor pulmonale and pulmonary hypertension	Chronic cor pulmonale, primary or secondary pulmonary hypertension
Resistant arterial hypertension	When BP remains above the recommended targets with the use of three or more antihypertensive drugs of different classes, at maximum recommended and tolerated doses, administered frequently, appropriate dosage and proven adherence or BP controlled by using four or more antihypertensive drugs
Stage 3 hypertension	Systolic BP ≥180 mm Hg and / or diastolic BP ≥110 mm Hg regardless of the presence of TOD or comorbidity
Stage 1 and 2 hypertension with TOD and / or comorbidity	Systolic BP between 140 and 179 mm Hg and / or diastolic BP between 90 and 109 mm Hg in the presence of TOD and / or comorbidity
Hypertensive heart disease	Hypertensive heart disease (left ventricular hypertrophy or dilation, atrial and ventricular overload, diastolic and / or systolic dysfunction, injuries to other target organs)
Coronary syndromes	Chronic coronary syndromes (angina pectoris, ischemic heart disease, post-acute myocardial infarction, others)
Valvopathies	Valve lesions with hemodynamic or symptomatic repercussions or with myocardial impairment (aortic stenosis or insufficiency, mitral stenosis or insufficiency, pulmonary stenosis or insufficiency, tricuspid stenosis or insufficiency, and others)
Cardiomyopathies and pericardiopathies	Myocardiopathies of any etiology or phenotype Chronic pericarditis Rheumatic heart disease
Diseases of the aorta, large vessels, and arteriovenous fistulas	Aneurysms, dissections, hematomas of the aorta and other large vessels
Cardiac arrhythmias	Cardiac arrhythmias of clinical importance and / or associated heart disease (atrial fibrillation and flutter, and others)
Congenital heart disease in adults	Congenital heart disease with hemodynamic repercussions, hypoxemic crises, heart failure, arrhythmias, myocardial involvement
Valve prostheses and implanted cardiac devices	Individuals with biological or mechanical valve prostheses and implanted cardiac devices (pacemakers, cardioverter defibrillators, resynchronizers, medium and long-term circulatory assistance)
Cerebrovascular disease	Ischemic or hemorrhagic stroke, transient ischemic attack, vascular dementia

HF: heart failure; BP: blood pressure; TOD: target organ damage. Source: correspondence sent to the National Immunization Program of the Brazilian Ministry of Health, on January 2, 2021.

diabetics, severely obese individuals, Afro-descendants, and Latinos. And, despite their relatively small number, that inclusion allows us to infer safety and efficacy for cardiac patients. The adverse effects observed were local, but less common in the elderly. The cardiovascular effects observed, such as hypertension, bradycardia, tachycardia, atrial fibrillation, ACS, and pulmonary thromboembolism, had a frequency lower than 0.1% and were similar in those who received the vaccines and those who received placebo (Table 3).

It is worth mentioning that Brazil has entered into partnerships since May 2020 for the research and development of vaccines that include technology transfer through the Oswaldo Cruz Foundation and the Butantan Institute. The vaccine developed by AstraZeneca and the Oxford University has already had its preliminary results published, being in use in England. This vaccine will be produced on a large scale in Brazil. Concomitantly, the vaccine called CoronaVac, developed by the Sinovac laboratory, will be produced at the Butantan Institute, which has reported in the media that "*in a clinical study with 12 400 volunteers, the immunizing agent showed 78% effectiveness for mild cases and 100% for moderate and severe cases*".[22] Thus, the perspective of having vaccines is good.

It is necessary to emphasize that Brazil has one of the most advanced health legislations in the world. The Brazilian Federal Constitution enshrines access to health as a fundamental right: "*Health is a right for all and a duty of the State, guaranteed through social and economic policies…*". Thus, public health policies that are safe, effective, and cost-effective are part of the existential minimum of each Brazilian, and should be offered in a universal, comprehensive, and free manner. That includes the vaccination campaigns, a true consolidated patrimony of Brazilians and national pride. In view of this, creating all the conditions to offer vaccines in a comprehensive immunization program against COVID-19 is "*a right for all and a duty of the State*", under penalty of constitutional duty becoming an inconsequential promise, frustrating the fair expectations deposited in the Brazilian State.

Table 3 – Demographic and clinical characteristics of volunteers vaccinated against COVID-19 in clinical trials

Characteristics	BNT162b2 (Pfizer/BioNTech)[19]	mRNA-1273 (Moderna / NIAID / NIH)[20]	ChAdOx1 COV 003 (Oxford/ AstraZeneca)[21]
Number of volunteers (n)	44 820	30 420	23 848 (4088 Brazil)
Age range (years)	16 to 91	18 to 95	≥18
Median age (years)	52 (42.2% ≥55)	51 (24.8% ≥65)	-
Afrodescendants (%)	9	10.2	10.4**
Latin or Hispanic (%)	28	24.8	-
Adverse effects	Local pain was more common in vaccinated individuals More frequent in younger people	Local pain after injection more frequent in the vaccinated than placebo group Adverse effects are more common after the second dose Most common in younger people	not available
Cardiovascular effects	not available	Bradycardia, syncope, tachycardia, acute coronary syndrome, atrial fibrillation, hypertension, hypotension, all <0.1% and similar frequency for those receiving placebo and vaccines	not available
Efficiency (%)	95.0 [CI 90.3 – 97.6]	94.1 [CI 89.3 – 96.8]	64.2 [CI 30.7 – 81.5]
Subgroup effectiveness	Similar in subgroups, including hypertensive, elderly, obese and Brazilians	Similar in risk subgroup for severe COVID-19	not available
Obese (BMI> 30 kg/m^2) (%)	35.1	6.7	20.4
Diabetics (%)	38.4*	9.5	3.0**
Cardiovascular disease (%)	2.7*	4.5	12.0**

BMI: body mass index. (*) Approximate calculation based on data published in the trial appendices. (**) Data refer to the series of the trial carried out in Brazil (VOC 003). Note: data obtained and analyzed with different criteria, therefore with limited comparisons.

Why vaccinate?

Figure 2 summarizes ten reasons for recommending the vaccine to your patient. It is our view, based on the best evidence available, that we should engage in the dissemination of this knowledge and motivate our patients. However, it is necessary to maintain the effective and proven measures to prevent COVID-19 spread: hand hygiene, face mask wearing, and social distancing. Even though the vaccination program may contribute to minimize spread, the classic preventive measures must certainly be maintained until the vaccination program benefit is definitively proven.

The Brazilian Society of Cardiology and its commitment to science

The SBC will not escape the historical legacy, built on the example of Carlos Chagas, Dante Pazzanese, and our pioneers and transmitted for more than seven decades to more than 14 000 members, confirmed in its social purpose. The SBC's objective is "*to expand, disseminate and encourage, at all levels, the knowledge, diagnosis, prevention and treatment of CVD, developing educational campaigns jointly with the government and other entities and associations, and disseminating the epidemiological aspects of CVD to the civil society, which should be educated about the prevention and treatment possibilities*".[23]

Despite the high cost of lost lives, the search for an efficient solution to the pandemic has brought us rapid advances in research, based on good quality science, leaving a remarkable legacy and achievements. In one year, the clinical picture, the epidemiological profile and the etiological agent at the molecular level were described, care was improved, empirical and futile treatments were refuted, and vaccines tested in clinical trials were produced. This is science in its fascinating evolution for effectiveness in favor of quality and quantity of life. However, the great lesson has been the need to strengthen the health system, our SUS.

The uncompromising defense of SUS, in short, is the defense of the dignity of the human person, a fundamental commitment of the Brazilian State. The SBC and the other scientific societies must ally themselves in the fight for the progress and diffusion of science and for the achievement of public policies capable of improving the lives of each of the more than 220 million Brazilians. The principles that guided the creation of the SBC in 1943, in the middle of the Second World War, are still the same that motivate us in this unprecedented health crisis.

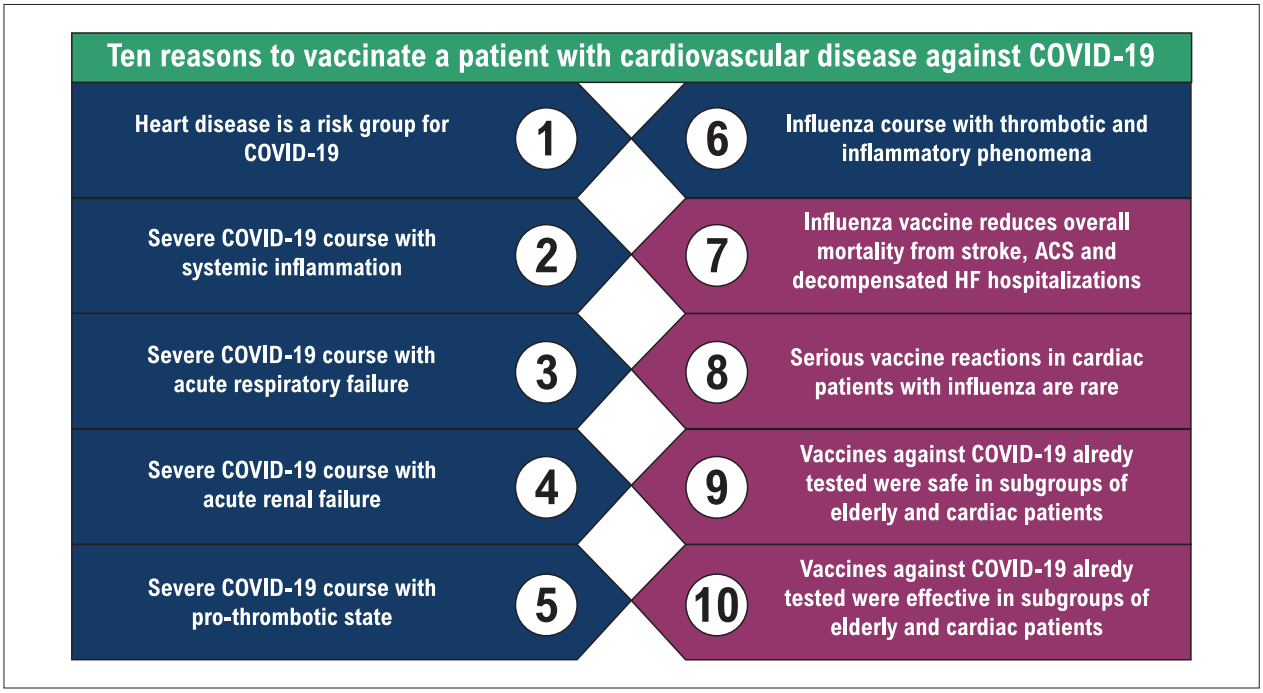

Figure 2 – *Ten reasons to vaccinate a patient with cardiovascular disease against COVID-19. ACS: acute coronary syndrome; HF: heart failure. Source: The authors.*

References

1. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU). Disponível em https://coronavirus.jhu.edu/map.html. Acesso em 09/01/2021.
2. New IHME Projection Sees COVID-19 Deaths in Brazil at More than 125,000. Disponível em http://www.healthdata.org/news-release/new-ihme-projection-sees-covid-19-deaths-brazil-more-125000. Acesso em 06/01/2021.
3. Brant LCC, Nascimento BR, Teixeira RA, Lopes MACQ, Malta DC, Oliveira GMM, et al. Excess of cardiovascular deaths during the COVID-19 pandemic in Brazilian capital cities. Heart. 2020. Heart. 2020;106:1898-905. doi:10.1136/heartjnl-2020-317663.
4. Pollard AJ, Bijker EM. A guide to vaccinology: from basic principles to new developments. Nature Rev Immunol. 2020. Disponível em: https://doi.org/10.1038/s41577-020-00479-7. Acesso em 2020 em 05/01/2021.
5. Martins WA. Vacinação no cardiopata. In: Manual de Prevenção Cardiovascular/ [Editores Ricardo Mourilhe Rocha. Wolney Andrade Martins] Rio de Janeiro: SOCERJ, 2017. cap.8, p:87-93.
6. Martins WA, Ribeiro MD, Oliveira LB, Barros LS, Jorge AC, Santos CM, et al. Influenza and pneumococcal vaccination in heart failure: a little applied recommendation. Arq Bras Cardiol. 2011:96(3):240-5.
7. Nichol KL, Nordin J, Mullooly J, Lask R, Fillbrandt K, Iwane M. Influenza vaccination and reduction in hospitalizations for cardiac disease and stroke among the elderly. N Engl J Med.2003;348(14):1322-32.
8. Yap FHY, Ho PL, Lam KF, Chan PKS, Cheng YH, Peiris JSM. Excess hospital admissions for pneumonia, chronic obstructive pulmonary disease, and heart failure during influenza seasons in Hong Kong. J Med Virol. 2004;73(4):617-23.
9. Sandoval C, Walter SD, Krueger P, Loeb MB. Comparing estimates of influenza-associated hospitalization and death among adults with congestive heart failure based on how influenza season is defined. BMJ Public Health. 2008;59(8). https://doi.org/10.1186/1471-2458-8-59
10. Jorge JEL, CagyII M, Mesquita ET, Costa TLM, Moscavitch SD, Rosa MLG. Seasonal variation in hospitalizations due to heart failure in Niterói city, Southeastern Brazil. Rev Saúde Pública 2009;43(3):555-7.
11. Estabragh ZR, Mamas MA. The cardiovascular manifestations of influenza:a systematic review. Intern J Cardiol. 2013;167(6):2397-403.
12. Wu WC, Jiang L, Friedmann PD, Trivedi A. Association between process quality measures for heart failure and mortality among US veterans. Am Heart J 2014;168(5):713-20.
13. Caldeira D, Costa J, Vaz-Carneiro A. Vacina contra influenza para prevenção de doença cardiovascular. Acta Med Port. 2015;28(4):424-6.
14. Blaya-Nováková V, Prado-Galbarro FJ, Sarría-Santamera A. Effects of annual influenza vaccination on mortality in patients with heart failure. Eur J Public Health. 2016;26(5):890-2.
15. Fang YA, Chen CI, Liu JC, Sung LC. Influenza vaccination reduces hospitalization for heart failure in elderly patients with chronic kidney disease:a population-based cohort study. Acta Cardiol Sin. 2016;32(3):290-8.
16. Bhatt AS, DeVore AD, Hernandez AF, Mentz RJ. Can vaccinations improve heart failure outcomes? JACC Heart Fail. 2017;5(3):194-203.
17. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA. 2020;323;(11):1061-9.
18. Sociedade Brasileira de Cardiologia. Departamento de Insuficiência Cardíaca. A IC e a vacina no contexto da sindemia coronavírus 2020-21. Disponível em http://departamentos.cardiol.br/sbc-deic/profissional/noticias/20201228-a-ic-e-a-vacina-no-contexto-da-sindemia-coronavirus-2020-21.asp. Acesso em 09/01/2021.
19. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020.383(27):2603-15. doi: 10.1056/NEJMoa2034577.
20. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 2020 Dec 30. doi:10.1056/NEJMoa2035389.
21. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet. 2020. Jan 09;397(10269):99-111.https://doi.org/10.1016/S0140-6736(20)32661-1.
22. Barifouse R. BBC News Brasil. CoronaVac: Butantan afirma que vacina evitou 78% de casos leves e 100% de graves em testes. Disponível em https://www.bbc.com/portuguese/brasil-55262727. Acesso em 08/01/2021.
23. Sociedade Brasileira de Cardiologia. Estatuto Social. Disponível em http://socios.cardiol.br/estatuto/EstatutoSBC_set2019.pdf. Acesso em 02/01/2021.

Long-Term Clinical and Hemodynamic Outcomes after Heart Transplantation in Patients Pre-Treated with Sildenafil

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Abstract

Background: Elevated pulmonary vascular resistance remains a major problem for heart transplant (HT) candidate selection.

Objective: This study sought at assess the effect of pre-HT sildenafil administration in patients with fixed pulmonary hypertension.

Methods: This retrospective, single-center study included 300 consecutive, HT candidates treated between 2003 and 2013, in which 95 patients had fixed PH, and of these, 30 patients were treated with sildenafil and eventually received a transplant, forming Group A. Group B included 205 patients without PH who underwent HT. Pulmonary hemodynamics were evaluated before HT, as well as 1 week after and 1 year after HT. Survival was compared between the groups. In this study, a p value < 0.05 was considered statistically significant.

Results: After treatment with sildenafil but before HT, PVR (-39%) and sPAP (-10%) decreased significantly. sPAP decreased after HT in both groups, but it remained significantly higher in group A vs. group B (40.3 ± 8.0 mmHg vs 36.5 ± 11.5 mmHg, p=0.022). One year after HT, sPAP was 32.4 ± 6.3 mmHg in group A vs 30.5 ± 8.2 mmHg in group B (p=0.274). The survival rate after HT at 30 days (97% in group A versus 96% in group B), at 6 months (87% versus 93%) and at one year (80% vs 91%) were not statistically significant (Log-rank p=0.063). After this first year, the attrition rate was similar among both groups (conditional survival after 1 year, Log-rank p=0.321).

Conclusion: In patients with severe PH pre-treated with sildenafil, early post-operative hemodynamics and prognosis are numerically worse than in patients without PH, but after 1 year, the medium to long-term mortality proved to be similar. (Arq Bras Cardiol. 2021; 116(2):219-226)

Keywords: Vascular Resistance; Heart Transplantation; Hypertension Pulmonary; Sildenafil Citrate; Phosphodiesterase 5 Inhibitors; Ventricular Dysfunction, Right.

Introduction

Heart transplant (HT) is the gold-standard of care for end-stage heart failure.[1] Epidemic studies have shown that 60-70% of heart failure (HF) patients develop pulmonary hypertension (PH).[2,3] In a Mayo Clinic study,[4] there was a strong positive graded association between systolic pulmonary artery pressure (sPAP) and mortality, and for this reason, the presence of severe PH is one of the major contraindications to HT because of post-operative right heart dysfunction.[5]

Elevated right-sided pressures in HF usually result from elevated left ventricle (LV) filling pressures. Therefore, diastolic pulmonary artery pressure (dPAP) correlates closely with pulmonary capillary wedge pressure (PCWP).[6,7] On the other hand, the vasoreactive component of PH develops with long-standing PH. It is characterized by vasospasm, vasoconstriction, and morphologic changes of the pulmonary vasculature.[8,9] In this case, PH persists even if the PCWP is lower after HT. Reflecting the "fixed" component of PH, the pulmonary vascular resistance (PVR) and the transpulmonary gradient (TPG) are elevated.[6]

At first, PH is reversible by systemic vasodilators, but later it becomes relatively stationary or "fixed".[6,9,10] Elevated PVR increases mortality in the early post-HT period and remains a major problem for candidate selection.[11,12] The inability of the transplanted heart to adapt to pre-existing significant PH usually results in right ventricle (RV) failure, which accounts for nearly 50% of all cardiac complications and up to 19% of all early postoperative deaths.[12,13] For this reason, the correct assessment that the reactivity of the pulmonary vasculature has in vasodilator therapy plays a crucial role in candidate selection. The American Heart Association guidelines define fixed PH as mean pulmonary artery pressure (mPAP) ≥ 25 mmHg and PVR ≥ 2.5 Wood units (WU) and/or TPG ≥ 12 mmHg, even after pharmacologic vasodilator testing.[14]

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Sildenafil is a selective and potent inhibitor of phosphodiesterase type 5 (PDE5), which specifically degrades cyclic guanosine monophosphate, the second messenger of nitric oxide in vascular smooth muscle cells.[8,15] Sildenafil has a favorable safety profile without oxygen desaturation or significant changes in heart rate or blood pressure.[16] Several single-center studies have demonstrated a positive favorable hemodynamic effect of pre-HT sildenafil administration in HT candidates with PH.[12,17] However, there is a paucity of data on the early and long-term outcomes of these high-risk patients.

The objective of this study was to compare the effect on early RV hemodynamics and mortality after HT of pre-HT sildenafil administration among patients with fixed PH who achieved HT eligibility and patients without PH. Our hypothesis is that patients with PH who received a transplant while taking sildenafil had a comparable prognosis to that of patients without PH.

Methods

Study Population

This retrospective, single-center, observational study included 300 consecutive patients, candidates to HT observed between November 2003 and December 2013. This population included 95 patients with fixed PH; of these, 30 patients were treated with sildenafil and eventually received transplants, forming Group A. Group B was formed by 205 patients without fixed PH who underwent HT.

In group A, sildenafil was administered orally at 20 mg tid, during a mean of 65 days (range 4 – 181 days) prior to HT. Sildenafil was well tolerated in all patients enrolled, with no serious adverse events observed.

Data Collection

Clinical, laboratorial, and hemodynamic data were extracted using a dedicated software. All patients underwent a candidacy right heart catheterization (RHC) with a Swan-Ganz catheter via the femoral vein before sildenafil initiation; the group of patients that were exposed to sildenafil underwent a second RHC to assess the hemodynamic effect of the drug. After HT, right ventricular systolic and end-diastolic pressures were registered during the first endomyocardial biopsy, which was performed at 1 week after HT. A late hemodynamic follow-up was collected during the predefined RHC at 1 year after HT in both groups.

Cardiac output (CO) was measured by the Fick method, and cardiac index (CI) was calculated by dividing the CO by the body surface area. PCWP, sPAP, dPAP, and mPAP were measured automatically. PVR and TGP were calculated using the following formulas: TPG (mmHg) = mPAP - PCWP; PVR (WU) = TGP/CO.[18] A follow-up was conducted for a median of 6.9 years (range 4.2 – 6.9 years) by personal interview in the outpatient ward, through a review of hospital registries, and by telephone contact, and was obtained for every patient included in this study. Confidentiality was always respected.

Endpoints

The co-primary outcome measures were (1) RV systolic pressure and end-diastolic pressure (the latter used as a surrogate of RV function) at 7 days after HT and (2) the sPAP and PVR 1 year after HT; the secondary outcome was the all-cause mortality after HT. The endpoints were compared between the pre-defined groups.

Statistical Analysis

Continuous variables were normally distributed and assessed using the Shapiro-Wilk test, and expressed as means±standard deviations, while those with non-normal distribution were expressed as median (interquartile range). Dichotomous variables were expressed as frequencies (percentages). To compare data between the groups, the Student`s T-test (Unpaired T-test) for continuous variables, the Mann-Whitney test for non-continuous data, and the Chi-Square test (Fisher, as appropriate) for dichotomous data were used. The McNemar test was used for paired categorical analysis. Kaplan-Meyer survival curves were constructed and compared using the Log-rank test. Conditional survival was assessed by limiting the group of patients analyzed to those who have survived to at least 1 year. The entire analysis was performed using STATA 12.0 (College Station, Texas, USA). Graphs were constructed with GraphPad 5.0 (La Jolla, California, USA). In this study, a p value < 0.05 was considered statistically significant.

Results

All 235 patients underwent successful HT. Baseline characteristics are presented in Table 1. Most patients were male, and the mean age of group A was 53.6 ± 10.9 years and of group B 52.9 ± 13.4 years (p = 0.545). Pre-HT hemodynamics are presented in Table 2 and were significantly different among groups. Group A patients displayed more severe pulmonary hemodynamics that Group B patients. After treatment with sildenafil but before HT, PVR (-39%) and sPAP (-10%) decreased significantly (Table 3).

Peri-HT Data and Post-HT Outcomes

The co-primary endpoint measures, assessed 1 week after HT, are presented in Table 3. The evolution of sPAP during the follow-up time in both groups is shown in Figure 1. sPAP decreased after HT in both groups, but remained significantly higher in patients pre-treated with sildenafil vs. patients that were not pretreated (40.3 ± 8.0 mmHg vs 36.5 ± 11.5 mmHg, p = 0.022). No differences were found regarding RVEDP at one week after HT, used as a surrogate of early RV dysfunction (Table 3). One year after HT, sPAP was 32.4 ± 6.3 mmHg in group A vs 30.5 ± 8.2 mmHg in group B (p = 0.274) (Table 3). PVR was also similar in the two groups (1.8 ± 0.8 mmHg versus 1.8 ± 1.0 WU, p = 0.789).

Survival Analysis

Post-HT all-cause mortality is shown in Figure 2 (Log-rank *P* = 0.055). The survival rate after HT in group A was 97% at 30 days, 87% at 6 months, and 80% at one year. In group

Table 1 – Characteristics of Patients with (Group A) and without (Group B) Sildenafil Pre-Treatment Before Heart Transplant

Characteristic[a]	Group A (n=30)	Group B (n = 205)	p-value[b]
Mean Age, years	53.6 ± 10.9	52.9 ± 13.4	0.545
Gender Male, %	86.7	76.2	0.247
Etiology			
Ischemic, %	50.0	34.0	0.346
Idiopathic, %	36.7	56.3	
Hypertrophic, %	3.3	4.4	
Restrictive, %	10.0	2.9	
Congenital, %	0.0	2.4	
NYHA Class			
III, %	33.3	36.4	0.968
IV, %	66.7	63.6	
Laboratorial Parameters			
Hemoglobin, g/dl	12.3 ± 1.8	12.7 ± 1.7	0.815
Creatinine, mg/dl	1.4 ± 1.0	1.3 ± 0.5	0.060
BNP, pg/ml	524 [396 - 912]	625 [306 - 1039]	0.906
Cardiac Parameters			
LVEF, %	19.6 ± 4.5	21.2 ± 8.4	0.021
Mitral Regurgitation			
Mild, %	16.0	12.5	0.703
Moderate, %	32.0	34.0	
Moderate-Severe, %	24.0	14.6	
Severe, %	24.0	31.2	
Cardiac Devices			
ICD, %	40.0	21.8	0.128
CRT, %	10.0	22.4	
Sildenafil, pre-HTx			
Duration, days	65 [4 – 181]		

BNP: blood natriuretic peptide; CRT: cardiac resynchronization therapy; HT: heart transplant; ICD: implantable cardioverter defibrillator; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association. [a]Data are expressed as percentages, mean ± standard deviation or median (interquartile range). [b]Student`s T-test for continuous variables with normal distribution, Mann-Whitney test for continuous variables without normal distribution and Chi-Square test for categorical variables.

B, survival in the same time frames was 96%, 93%, and 91%, respectively. The difference at the one-year time-point was not statistically significant (Log-rank p = 0.063). After this first year, the attrition rate was similar between both groups, as shown in Figure 3 (conditional survival after 1 year, Log-rank p = 0.321).

Discussion

Treatment of HT candidates with fixed PH with sildenafil enabled a successful post-operative period for most of the patients that were initially contraindicated for HT. Although displaying poorer hemodynamics shortly after the HT, and a numerically higher mortality during the first year, the prognosis during medium to long term follow-up was similar to that of HT patients without PH.

The limit between fixed and reversible PH is unclear, and there is no agreement on the time needed to reach the level of theoretical irreversibility and the best parameters to define this status.[12] At our center, RHC is routinely used with a vasodilator test, as this may be useful to establish the risk of death after HT.[5] One of the most useful variables to asses this risk is the PVR.[13] As shown by Taylor et al.[19] PVR is an independent predictor of early death after HT. This group reported that the survival in HT patients was significantly better if PVR was between 1 to 3 WU, compared with recipients with a PVR 3 to 5 WU, while patients with PVR > 5 WU had the worst outcomes. The present study used sildenafil to decrease PVR (3.3 ± 2.3 WU), thus making the patients eligible for HT. In fact, among the patients that were treated with sildenafil, the average PVR was significantly elevated and would preclude HT (5.4 ± 2.3 WU) if no intervention had been done. Moreover, if these

Table 2 – Hemodynamic Variables before Heart Transplant in Patients with (Group A) and without (Group B) Severe Hypertension

Variable	Group A Means ± SD	Group B Means ± SD	p-value [a]
PVR, WU	5.4 ± 2.3	2.7 ± 1.8	< 0.001
PAP, mmHg			
Systolic	58.9 ± 16.4	44.5 ± 15.2	< 0.001
Diastolic	23.1 ± 8.2	19.4 ± 8.0	0.025
Mean	36.4 ± 10.7	29.0 ± 10.3	0.001
CO, liters/min	3.7 ± 1.2	3.6 ± 1.0	0.645
BP, mmHg			
Systolic	75.0 ± 12.2	74.9 ± 10.8	0.980
HR, ppm	76 ± 18	76 ±16	0.873

BP: blood pressure; HR: heart rate; CO: cardiac output; PAP: pulmonary artery pressure; PVR: pulmonary vascular resistance; SD: standard deviation. [a]Student`s T test was used.

Table 3 – Hemodynamic Variables before and after Heart Transplant in Patients with (Group A) and without (Group B) Sildenafil Pre-Treatment

	Eligibility RHC		3-month post-sildenafil RHC		7th-day post-HTx EMB		1-year RHC	
	sPAP (mmHg)	PVR (WU)	sPAP (mmHg)	PVR (WU)	RV systolic pressure (mmHg)	RV end-diastolic pressure (mmHg)	sPAP (mmHg)	PVR (WU)
No sildenafil	44.5 (15.2)	2.7 (1.8)	--	--	36.5 (11.5)	7.0 (7.1)	30.48 (8.23)	1.8 (1.0)
Sildenafil	58.9 (16.4)	5.4 (2.3)	52.8 (17.1)[c]	3.3 (2.3)[d]	40.3 (8.0)	7.9 (5.8)	32.43 (6.39)	1.8 (0.8)
p - value[a]	< 0.001	< 0.001	--	--	0.022[b]	0.374[b]	0.274	0.789

EMB: endomyocardial biopsy; PVR: pulmonary vascular resistance; RHC: right heart catheterization; WU: wood units. [a] Student's t-test comparing no sildenafil patients vs. sildenafil-treated patients. [b]McNemmar test. [c]P = 0.845 vs. no sildenafil patients. [d]P = 0.806 vs. no sildenafil patients.

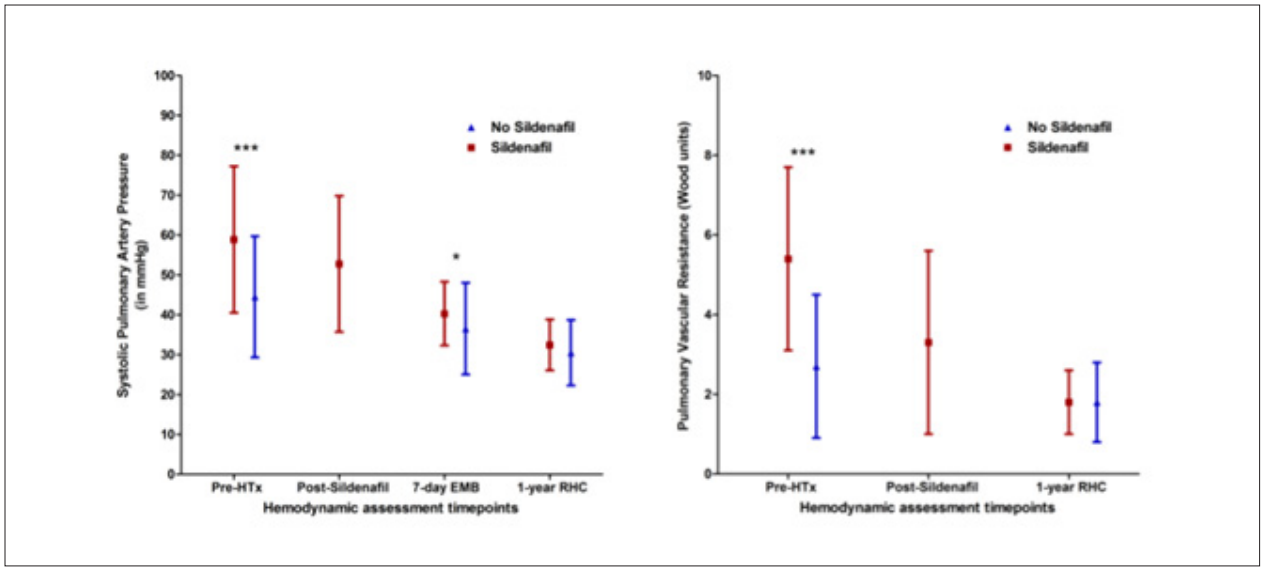

Figure 1 – *(Left panel) Systolic pulmonary artery pressure (sPAP, in mmHg) at four different time-points: baseline before HT without sildenafil treatment, before HT with sildenafil treatment, early after HT (7 days) and late after HT (one year). ***p < 0.001, * p = 0.022. (Right panel) Pulmonary vascular resistance (PVR, in Wood units) at three different time-points: baseline before HT without sildenafil treatment, before HT with sildenafil treatment and late after HT (one year). *** p < 0.001, * p = 0.789. EMB: endomyocardial biopsy; HT: heart transplant; RHC: right heart catheterization.*

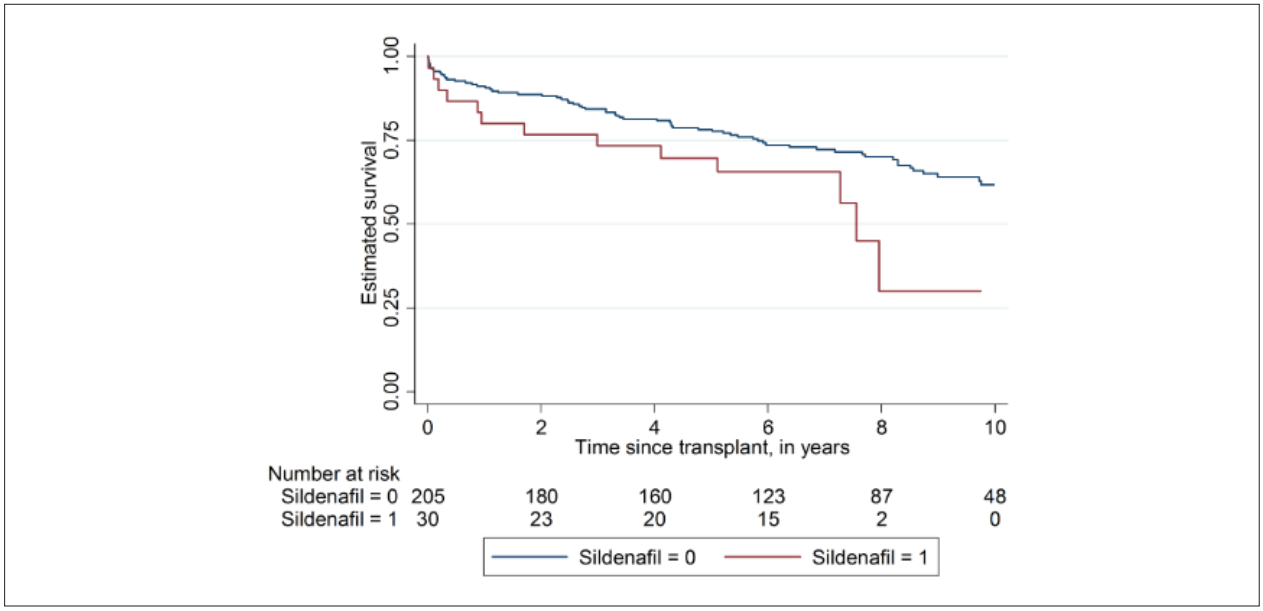

Figure 2 – *Kaplan-Meier analysis of all-cause mortality after transplant according to sildenafil treatment group. Log-rank p = 0.063.*

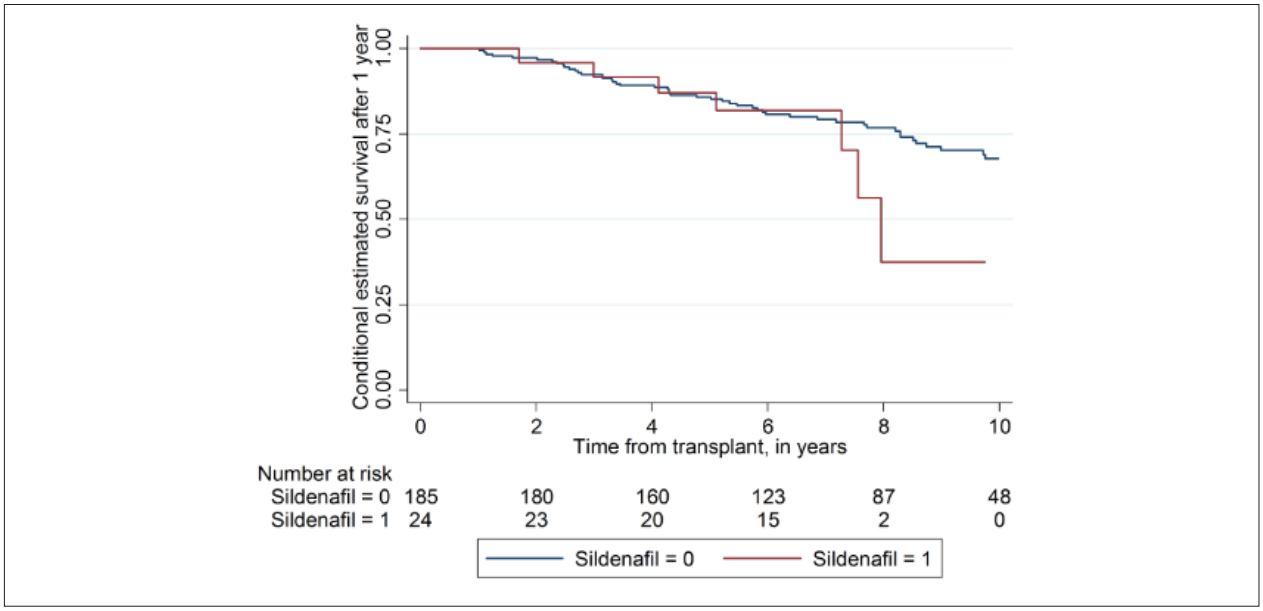

Figure 3 – *Kaplan-Meier analysis one-year conditional survival analysis. Log-rank p = 0.321.*

patients were not transplanted, their prognosis under medical therapy would have been poor unless a left ventricular assist device (LVAD) were implanted.

Interestingly, two recent studies suggest that LVAD support and continuous nonpulsatile mechanical unloading of the LV can reverse a previously medically unresponsive pulmonary hypertension and render patients eligible for HT.[20,21] Of interest, pre-LVAD PVR in these studies (4.3 ± 1.7 WU and 4.8 ± 1.8 WU) was similar to that of our cohort (5.4 ± 2.3 WU). According to Perez-Villa et al.[22] a strategy of reducing elevated PVR using oral therapy (sildenafil or bosentan) in patients considered ineligible for HT because of elevated PVR is feasible and may reduce the risk of post-operative RV dysfunction, as we have also shown in our study.

PDE5 inhibitors are receiving increasing interest in the field of left heart disase.[6,12] In addition to standard HF therapy, sildenafil intervention might improve the pulmonary hemodynamic parameters.[6,12] These favorable effects arise from its selective inhibition of the hydrolysis of cyclic guanosine monophosphate (cGMP) in the pulmonary

vasculature, which promotes vasodilation and less remodeling, as well as a milrinone-like effect in the RV due to a process of molecular crosstalk that can inhibit PDE3 and increase RV contractility.[15,18] In a recent meta-analysis,[2] sildenafil treatment was found to reduce PVR compared with placebo (weighted mean difference -1.0 WU, $p < 0.01$).[2] Our study also demonstrated that pre-HT sildenafil administration in HT candidates with PH had a positive hemodynamic effect by reducing PVR by about 2 WU.

Right-sided circulatory failure and its associated morbidity remains an important source of peri-operative death for HT patients. Pons et al.[12] also evaluated the effects of chronic sildenafil use on clinical outcomes in HT (mean follow-up, 3.4 ± 2.1 years). In this study, the survival rate after HT in the group of patients pre-treated with sildenafil (including only 15 patients) was 87% at 30 days. Importantly, no other patient died during the 5-year follow-up period after HT. By comparison, the survival rate after HT in group A was 97% at 30 days and 70% at five years. Accordingly, in the ISHLT International Registry for Heart Transplantation, the survival rate at five years was 72%, similar to our group of patients with fixed PH pre-treated with sildenafil.[23]

For all these reasons, a strategy of using sildenafil to reduce PVR can be considered to be a valuable "rescue therapy" in a group of patients with end-stage HF, who would otherwise not be eligible for HT. Our data show that it is associated with similar perioperative and long-term mortality similar to that observed in patients without fixed PH.

Limitations

The limitations of this study include its retrospective and uncontrolled nature, potentially conditioning selection bias. However, we included all patients that were consecutively transplanted in our center and no patient was lost to follow-up. In addition, the size of our sample is relatively small, limiting the statistical power. However, to the best of our knowledge, to date, this is the largest case series on HT patients pre-treated with sildenafil. Another limitation is the absence of direct RV function measurements immediately after HT; we tried to compensate for this fact using a hemodynamic measurement of RV function collected 7 days after the procedure. Despite all these shortcomings, we believe that the results can have external validity for other advanced HF populations, as the demographic, clinical, hemodynamic, and prognostic data are in line with those reported in other trials.

Conclusion

The use of sildenafil in HT candidates with fixed PH improved pulmonary hemodynamics to a threshold where transplant was possible. In this high-risk group of patients, early post-operative hemodynamics and results were slightly compromised when compared with patients without PH. However, after 1 year, the medium to long-term outcomes were similar between the groups. Our findings support the concept that sildenafil can rescue previously ineligible patients for HT.

Author Contributions

Conception and design of the research: Mendes SL, Moreira N; Acquisition of data: Mendes SL, Moreira N, Batista M, Ferreira AR, Marinho AV, Prieto D; Analysis and interpretation of the data: Mendes SL, Moreira N, Batista M, Ferreira AR, Marinho AV, Prieto D, Baptista R, Costa S; Statistical analysis: Mendes SL, Baptista R; Writing of the manuscript: Mendes SL, Ferreira AR, Baptista R; Critical revision of the manuscript for intellectual content: Costa S, Franco F, Pego M, Antunes MJ.

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

References

1. Ferreira AR, Mendes S, Leite L, Monteiro S, Pego M. Pulse pressure can predict mortality in advanced heart failure. Rev Port Cardiol. 2016;35(4):225-8.
2. Wu X, Yang T, Zhou Q, Li S, Huang L. Additional use of a phosphodiesterase 5 inhibitor in patients with pulmonary hypertension secondary to chronic systolic heart failure: a meta-analysis. Eur J Heart Fail. 2014;16(4):444-53.
3. Lam CSP, Roger VL, Rodeheffer RJ, Borlaug BA, Enders FT, Redfield MM. Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. J Am Coll Cardiol. 2009;53(13):1119-26.
4. Bursi F, McNallan SM, Redfield MM, Nkomo VT, Lam CSP, Weston SA, et al. Pulmonary pressures and death in heart failure: a community study. J Am Coll Cardiol. 2012;59(3):222-31.
5. Reichenbach A, Al-Hiti H, Malek I, Pirk J, Goncalvesova E, Kautzner J, et al. The effects of phosphodiesterase 5 inhibition on hemodynamics, functional status and survival in advanced heart failure and pulmonary hypertension: a case-control study. Int J Cardiol. 2013;168(1):60-5.
6. Guglin M, Rajagopalan N, Anaya P, Charnigo R. Sildenafil in heart failure with reactive pulmonary hypertension (Sildenafil HF) clinical trial (rationale and design). Pulm Circ. 2016;6(2):161-7.
7. Moreira N, Baptista R, Costa S, Franco F, Pêgo M, Antunes M. Lowering pulmonary wedge pressure after heart transplant: pulmonary compliance and resistance effect. Arq Bras Cardiol. 2015;105(3):292-300.
8. Guglin M, Khan H. Pulmonary hypertension in heart failure. J Card Fail. 2010;16(6):461-74.

9. Guazzi M. Pulmonary hypertension in heart failure preserved ejection fraction: prevalence, pathophysiology, and clinical perspectives. Circ Heart Fail. 2014;7(2):367-77.

10. Hefke T, Zittermann A, Fuchs U, Schulte-Eistrup S, Gummert JF, Schulz U. Bosentan effects on hemodynamics and clinical outcome in heart failure patients with pulmonary hypertension awaiting cardiac transplantation. Thorac Cardiovasc Surg. 2012;60(1):26-34.

11. Costard-Jäckle A, Fowler MB. Influence of preoperative pulmonary artery pressure on mortality after heart transplantation: testing of potential reversibility of pulmonary hypertension with nitroprusside is useful in defining a high risk group. J Am Coll Cardiol. 1992;19(1):48-54.

12. Pons J, Leblanc MH, Bernier M, Cantin B, Bourgault C, Bergeron S, et al. Effects of chronic sildenafil use on pulmonary hemodynamics and clinical outcomes in heart transplantation. J Heart Lung Transplant. 2012;31(12):1281-7.

13. Taylor DO, Stehlik J, Edwards LB, Aurora P, Christie JD, Dobbels F, et al. Registry of the International Society for Heart and lung transplantation: Twenty-sixth Official Adult Heart Transplant Report-2009. J Heart Lung Transplant. 2009;28(10):1007-22.

14. Costanzo MR, Augustine S, Bourge R, Bristow M, O'Connell JB, Driscoll D, et al. Selection and treatment of candidates for heart transplantation. A statement for health professionals from the Committee on Heart Failure and Cardiac Transplantation of the Council on Clinical Cardiology, American Heart Association. Circulation. 1995;92(12):3593-612.

15. Schwartz BG, Levine LA, Comstock G, Stecher VJ, Kloner RA. Cardiac uses of phosphodiesterase-5 inhibitors. J Am Coll Cardiol. 2012;59(1):9-15.

16. Lewis GD, Lachmann J, Camuso J, Lepore JJ, Shin J, Martinovic ME, et al. Sildenafil improves exercise hemodynamics and oxygen uptake in patients with systolic heart failure. Circulation. 2007;115(1):59-66.

17. Groote P, El Asri C, Fertin M, Goéminne C, Vincentelli A, Robin E, et al. Sildenafil in heart transplant candidates with pulmonary hypertension. Arch Cardiovasc Dis. 2015;108(6-7):375-84.

18. Galie N, Humbert M, Vachieryc JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2015;37(1):67-119.

19. Trulock EP, Edwards LB, Taylor DO, Boucek MM, Keck BM, Hertz MI. The Registry of the International Society for Heart and Lung Transplantation: twenty-first official adult lung and heart-lung transplant report--2004. J Heart Lung Transplant. 2004;23(7):804-15.

20. Alba AC, Rao V, Ross HJ, Jensen AS, Sander K, Gustafsson F, et al. Impact of fixed pulmonary hypertension on post–heart transplant outcomes in bridge-to-transplant patients. J Heart Lung Transplant. 2010;29(11):1253-8.

21. Etz CD, Welp HA, Tjan TDT, Hoffmeier A, Weigang E, Scheld HH, et al. Medically refractory pulmonary hypertension: treatment with nonpulsatile left ventricular assist devices. Ann Thorac Surg. 2007;83(5):1697-705.

22. Perez-Villa F, Farrero M, Sionis A, Castel A, Roig E. Therapy with sildenafil or bosentan decreases pulmonary vascular resistance in patients ineligible for heart transplantation because of severe pulmonary hypertension. J Heart Lung Transplant. 2010;29(7):817-8.

23. Yusen RD, Edwards LB, Dipchand AI, Goldfarb SB, Kucheryavaya AY, Levvey BJ, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-third Adult Lung and Heart–Lung Transplant Report-2016; Focus Theme: Primary Diagnostic Indications for Transplant. J Heart Lung Transplant. 2016;35(10):1170-84.

Sildenafil as an Eligible Heart Transplantation Therapy for Advanced Heart Failure Associated with Fixed Pulmonary Hypertension

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Short Editorial related to the article: Long-Term Clinical and Hemodynamic Outcomes after Heart Transplantation in Patients Pre-Treated with Sildenafil

Heart transplantation (HTx) has been associated to significant improvements in survival and quality of life in patients with advanced heart failure (HF). Despite a considerable increase in the indication of left ventricular assistant devices, HTx still remains the gold-standard approach in this clinical context.[1] Even though it is considered the gold-standard treatment for advanced HF, several reasons have impaired the widespread utilization of the HTx. There is limited availability of donors compared with the growing potential recipients. Moreover, the longer life expectancy of the patients due to better HF pharmacotherapy has been challenging the age-related contraindication for the procedure, as well as the presence of more comorbidities linked to aging.[2]

Another point to be observed related to HTx candidacy is pulmonary hypertension (PH), which is present in more than 60% of HF patients with reduced ejection fraction (HFrEF) and over 54% of patients with HF and preserved ejection fraction (HFpEF) and also might account for up to 50% of post-HTx complications.[1] An elevated pulmonary vascular resistance (PVR) > 2.5 Wood units is linked to a nearly 30% increase in mortality within the first-month post-transplant.[2] This HF-associated PH is considered to be the result of the passive effect of increased left ventricular end-diastolic pressure along with vasoreactivity secondary to vasoconstriction and arterial pulmonary remodeling.[3,4] When not reversible with a vasodilator challenge, it has been strongly associated with right ventricular dysfunction, HF hospitalizations, worsening in quality of life, and reduced survival.[5] The International Society for Heart and Lung Transplantation guidelines consider the presence of severe pre-transplant PH as a relative contraindication to heart transplantation.[6]

Likewise, the disproportionality between the need for cardiac transplantation and the reduced availability of donors should lead to an even more judicious selection of those potential candidates for HTx and further attempts in reducing the pre-HTx pulmonary hypertension are necessary.

Keywords

Heart Failure, Pulmonary Hypertension; Sildenafil Citrate/therapeutic use; Heart Transplantaion.

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One of the possible approaches for lowering fixed PH in HFrEF patients, the phosphodiesterase-5 inhibitors, mainly sildenafil, are well established and effective therapies for patients with group 1 PH, either alone or in combination with other vasodilator therapies.[5] For HFrEF-associated PH (group 2), smaller studies have shown that sildenafil therapy improved exercise capacity and hemodynamics, but larger trials on HFrEF outcomes are lacking.[7,8] One of those small studies randomized 19 HFrEF patients to sildenafil 50 mg TID *versus* placebo and also showed hemodynamic benefits (decreased pulmonary artery systolic pressure levels at 4 weeks) in the sildenafil-treated group.[9] The reduction in PVR has also been demonstrated in a single-center study by Pons et al.[10] Fifteen patients with a PVR > 2.5 Wood units were treated with pre-HTx sildenafil with a high target dose (109 ± 42 mg/day) for 163 ± 116 days. Important benefits in pulmonary pressures and the post-HTx mortality were comparable between the PH-treated group and the non-severe, non-treated group.[10] In contrast, a multicenter trial of sildenafil in HFpEF patients failed to determine benefits regarding clinical status or exercise capacity.[11] Based on these positive preliminary findings in HFrEF patients, some HTx centers have already adopted the off-label use of sildenafil as a rescue therapy in selected heart transplantation candidates with fixed severe PH, aiming to achieve a transplant-favorable status.[7]

The study[12] adds important knowledge to this field. Mendes et al.[12] have compared the effect of pre-HTx sildenafil treatment in 30 patients to 205 non-sildenafil treated HFrEF patients. It was a retrospective, single-center, observational study that compared the pulmonary hemodynamics and clinical outcomes at 1-week and at 1-year after the HTx in patients with fixed PH treated with 20 mg TID of sildenafil therapy to a non-PH group that did not receive any PH-directed treatment. Despite the non-randomized design, the baseline patients' characteristics were similar, but for the severity of the systolic dysfunction and the pulmonary hypertension hemodynamics in the sildenafil-treated group. The study showed an important decrease in the systolic pulmonary artery pressure and the pulmonary vascular resistance after a 3-month sildenafil prescription (58.9 to 52.8 mmHg and 5.4 to 3.3 Woods units, respectively, $p<0.001$ for both analyses). The pulmonary hemodynamics improvement led to a significant clinical benefit, which enabled the eligibility of HTx candidacy for those 30 who were, at first, considered to be ineligible patients.

In spite of having small differences in the systolic pulmonary artery pressure shortly after the HTx (7 days), there were no significant differences in the pulmonary pressures between the groups 1 year after the heart transplantation, which might have a practice impact regarding further assessments for

other HF-associated PH patients on the initial evaluation for advanced therapies. Similar results were shown in a small cohort of 18 patients that were treated with sildenafil to reduce the HF-associated PH and try to become eligible for HTx. Groote et al.[13] reported significant improvements in functional class, mean left ventricular ejection fraction and cardiopulmonary exercise testing parameters, as well as a considerable reduction in pulmonary vascular resistance (from 5.3 ± 1.9 to 3.3 ± 1.8 Woods units, p=0.01).[13] Other studies have also shown a decrease in pulmonary pressures in patients with persistent PH and left ventricular assistant devices.[14] Moreover, sildenafil seems to be useful for acute right ventricular failure and PH within the first 72 hours after HTx in a small case series of 13 patients.[15]

Although there were substantial benefits regarding the pulmonary hemodynamics parameters, the evidenced numerically higher mortality during the first year was linked to the initially PH severity and should be taken into consideration in the heart transplantation candidacy process decision-making during the initial evaluation.

Limitations of this study are linked to the retrospective, single-center, observational methodological design and the limited number of PH patients included. Also, right ventricular function was not measured during the study, which might have impaired the hemodynamics interpretation before and after sildenafil treatment. Although this study is unlikely powered for definitive conclusions and external validity, it might represent the largest cohort to date of severe HFrEF patients treated with sildenafil to enter a HTx process.

In conclusion, treatment with sildenafil in HFrEF patients with severe PH enabled a successful postoperative period for patients initially considered to be ineligible for HTx, with improvements in pulmonary vascular resistance but slightly lower survival 1 year after the HTx. This is an important finding for clinical practice as it might provide advanced therapies that are initially contraindicated for HTx candidates with severe HFrEF-associated PH, as well as promoting benefits on clinical status during the HTx waiting list period.

References

1. Gerges M, Gerges C, Pistritto A, Lang MB, Trip P, Jakowitsch, et al. Pulmonary Hypertension in Heart Failure. Epidemiology, Right Ventricular Function, and Survival. Am J Respir Crit Care Med . 2015 Nov 15;192(10):1234-46.
2. Vakil K, Duval S, Sharma A, Adabag S, Abidi KS, Taimeh, et al. Impact of pre-transplant pulmonary hypertension on survival after heart transplantation: a UNOS registry analysis. Int J Cardiol. 2014 Oct 20;176(3):595-9.
3. Lam CS, Roger VL, Rodeheffer RJ, Borlaug BA, Enders FT, Redfield MM. Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. J Am Coll Cardiol. 2009 Mar 31;53(13):1119-26.
4. Bursi F, McNallan SM, Redfield MM, Nkomo VT, Lam CS, Weston SA, et al. Pulmonary pressures and death in heart failure: a community study. J Am Coll Cardiol. 2012 Jan 17;59(3):222-31.
5. Konstam MA, Kiernan MS, Bernstein D, Bozkurt B, Jacob M, Kapur NK, et al. Evaluation and Management of Right-Sided Heart Failure: A Scientific Statement From the American Heart Association. Circulation. 2018 May 15;137(20):e578-e622.
6. Mehra MR, Kobashigawa J, Starling R, Russell S, Uber PA, Parameshwar J, et al. Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates--2006. J Heart Lung Transplant. 2006 Sep;25(9):1024-42.
7. Reichenbach A, Al-Hiti H, Malek I, Pirk J, Goncalvesova E, Kautzner J, et al. The effects of phosphodiesterase 5 inhibition on hemodynamics, functional status and survival in advanced heart failure and pulmonary hypertension: a case-control study. Int J Cardiol. 2013 Sep 20;168(1):60-5.
8. Guazzi M, Vicenzi M, Arena R. Phosphodiesterase 5 inhibition with sildenafil reverses exercise oscillatory breathing in chronic heart failure: a long-term cardiopulmonary exercise testing placebo-controlled study. Eur J Heart Fail. 2012 Jan;14(1):82-90
9. Behling A, Rohde LE, Colombo FC, Goldraich LA, Stein R, Clausell N, et al. Effects of 5'-phosphodiesterase four-week long inhibition with sildenafil in patients with chronic heart failure: a double-blind, placebo-controlled clinical trial. J Card Fail. 2008 Apr;14(3):189-97.
10. Pons J, Leblanc MH, Bernier M, Cantin B, Bourgault C, Bergeron S, et al. Effects of chronic sildenafil use on pulmonary hemodynamics and clinical outcomes in heart transplantation. J Heart Lung Transplant. 2012 Dec;31(12):1281-7
11. Redfield MM, Chen HH, Borlaug BA, Semigran MJ, Lee KL, Lewis G, et al. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. JAMA. 2013 Mar 27;309(12):1268-77.
12. Mendes SL, Moreira N, Batista M, Ferreira AR, Marinho AV, Prieto D, Baptista R, Costa S, et al. Resultados Clínicos e Hemodinâmicos de Longo Prazo após o Transplante de Coração em Pacientes Pré-Tratados com Sildenafil. Arq Bras Cardiol. 2021; 116(2):219-226.
13. Groote P, Asri CE, Fertin M, Goéminne C, Vincentelli A, Robin E, et al. Sildenafil in heart transplant candidates with pulmonary hypertension. Arch Cardiovasc Dis. Jun-Jul 2015;108(6-7):375-84.
14. Tedford RJ, Hemnes AR, Russell SD, Wittstein IS, Mahmud M, Zaiman AL, et al. PDE5A inhibitor treatment of persistent pulmonary hypertension after mechanical circulatory support. Circ Heart Fail. 2008 Nov;1(4):213-9.
15. Santo LS, Mastroianni C, Romano G, Amarelli C, Marra C, Maiello C, et al., Role of sildenafil in acute posttransplant right ventricular dysfunction: successful experience in 13 consecutive patients. Transplant Proc. Jul-Aug 2008;40(6):2015-8

Therapeutic Effects of Triple Antiplatelet Therapy in Elderly Female Patients with Diabetes and Acute Myocardial Infarction

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Abstract

Background: **Dual antiplatelet therapy (DAPT) is the cornerstone treatment of acute myocardial infarction (AMI).**

Objective: **The present study aimed to investigate the efficacy and safety of triple antiplatelet therapy (TAPT) in elderly female patients with diabetes and ST segment elevation myocardial infarction (STEMI), who had undergone percutaneous coronary intervention (PCI).**

Methods: **We designed a randomized, single-blind study. Control group A (97 elderly male patients with diabetes and STEMI, whose CRUSADE scores were < 30) received aspirin, ticagrelor, and tirofiban. A total of 162 elderly female patients with diabetes and STEMI were randomly divided into two groups according to CRUSADE score. Group B (69 patients with CRUSADE score > 31) received aspirin and ticagrelor. Group C (93 patients with CRUSADE score < 30) received aspirin, ticagrelor and tirofiban. P values < 0.05 were considered statistically significant.**

Results: **Compared to the findings in group A, post-PCI Thrombolysis in Myocardial Infarction (TIMI) grade 3 blood flow and TIMI myocardial perfusion grade 3 were significantly less prevalent in group B ($p < 0.05$). When compared to groups A and C, the incidence of major adverse complications was significantly higher in group B ($p < 0.05$).**

Conclusion: **TAPT could effectively reduce the incidence of major complications in elderly female patients with diabetes and STEMI. However, close attention should be paid to hemorrhage in patients receiving TAPT. (Arq Bras Cardiol. 2021; 116(2):229-235)**

Keywords: **Platelet Aggregation; Stroke; Woman; Aging; Diabetes Mellitus; Myocardial Infarction; Percutaneous Coronary Intervention/methods.**

Introduction

Dual antiplatelet therapy (DAPT) is a cornerstone in the treatment of acute myocardial infarction (AMI). Compared with clopidogrel, the inhibitory effect of ticagrelor on platelets in DAPT is rapid and potent, with dual-inhibition and reversible combination. Furthermore, it can dilate coronary arteries, and it is recommended by guidelines.[1] However, studies have shown that ticagrelor and clopidogrel might significantly increase the risk of hemorrhage, compared with clopidogrel.[2]

The incidence of slow blood flow, no-reflow, and thrombotic complications in female patients with diabetes and AMI is higher than in patients without diabetes or in male patients with diabetes and AMI who are receiving DAPT.[3-5] Glycoprotein IIb/IIIa receptor inhibitors, in addition to DAPT, can effectively reduce the onset of complications, such as slow blood flow, no reflow, acute and subacute thrombosis, and major adverse cardiac events (MACE).[6-9] However, it remains unknown whether the combination of triple antiplatelet therapy (TAPT) drugs, especially ticagrelor, would increase the risk of hemorrhage. The urgent issue in the treatment of AMI is how to balance the risk of ischemic events and hemorrhagic complications. In relation to DAPT (aspirin and ticagrelor), the present study aimed to investigate the short-term efficacy and safety of TAPT (aspirin, ticagrelor, and tirofiban) in elderly female patients with diabetes and AMI.

Materials and Methods

Subjects and Grouping

This study was conducted in two centers, Zhengzhou People's Hospital of Southern Medical University and Shenqiu County Hospital of Traditional Chinese Medicine, both in the Henan province. Elderly female patients with diabetes and STEMI, who were admitted to the coronary care unit and who received emergency percutaneous coronary intervention (PCI) treatment from January 2013 to December 2018, were included into this study. This study was randomized and single-blinded. Blood was drawn immediately after admission. The Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines (CRUSADE) score[10] was calculated

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according to patients' hematocrit, creatinine clearance rate, heart rate, blood pressure, existence of heart failure, diabetes mellitus, and previous vascular diseases. This was a prospective study. According to CRUSADE score, patients were randomly divided into the following two groups: group B (score higher than 30) and group C (score lower than 30). DAPT (aspirin and ticagrelor) was given to the patients in group B, and TAPT (aspirin, ticagrelor, and tirofiban) was given to the patients in group C. Elderly male patients with diabetes and STEMI, who received emergency PCI during the same period of hospitalization, were assigned to group A (control group), and they received the same drug therapy as the patients in group C. Diagnosis of STEMI was in accordance with the European Society of Cardiology guidelines,[11] and diagnosis of diabetes mellitus was in accordance with the World Health Organization criteria.[12] The inclusion criteria were as follows: (1) patients with the onset of STEMI at ≤ 12 hours, (2) patients with known diagnosis of diabetes mellitus, (3) patients who agreed to receive emergency PCI and DAPT or TAPT, and (4) patients between the ages of 60 and 79 years old. The exclusion criteria were as follows: (1) patients with the onset of STEMI at > 12 hours, (2) patients with blood pressure ≥ 180/110 mmHg, (3) patients with suspected aortic dissection, (4) patients with retrieved PCI after thrombolysis for STEMI, (5) patients with a history of cerebral hemorrhage and ischemic stroke within one year, (6) patients with severe hepatic and/or renal insufficiency, and (7) patients with a history of hemorrhagic diseases.[9] The present study conforms to the standards of medical ethics. With the approval of the Ethics Committee of Zhengzhou People's Hospital, all treatments were performed with the informed consent of patients or their families.[9]

Emergency Percutaneous Coronary Intervention

Eighteen-lead electrocardiogram was recorded immediately after admission, and vital signs were checked. Blood was drawn immediately after admission for assay of cardiac enzymes, troponin, and other related biochemical and routine testing items. In addition, 100 mg of aspirin (Bayer, Germany; 100 mg/tablet) and 180 mg of ticagrelor (Belinda Tablets, Astra Zeneca; 90 mg/tablet) were orally administered to patients in these three groups. Emergency coronary angiography and PCI were performed. If thrombi were found, a thrombus aspiration catheter was used to aspirate them (10 patients, 6 patients and 9 patients in groups A, B, and C, respectively). Tirofiban hydrochloride (10 μg/kg) was injected into the coronary artery in patients in groups A and C. After PCI, 0.075 μg/kg·min of tirofiban hydrochloride was continuously pumped into the vein for 24 hours [7]. Drug-eluting stents were used for all patients. Merely the culprit vessel was treated during the emergency. If a non-culprit vessel needed to be treated, selected PCI was performed 10 to 14 days later. In addition, 100 mg/d of aspirin and 90 mg/d of ticagrelor were given twice orally and continuously in patients in all three groups. Subsequently, DAPT was applied for at least 12 months. Furthermore, -receptor blockers, statins, hypoglycemic agents, and angiotensin converting enzyme inhibitors were continuously administered.[9]

Observation Criteria

The data for first-medical-contact-to-balloon time, door-to-balloon time, age, sex, heart rate, systolic pressure, serum creatinine, Killip classification of cardiac function, myocardial enzymes, troponin, hematocrit, past history of vascular disease and diabetes mellitus, and the existence of cardiac arrest were collected and counted. The GRACE scores[13] and CRUSADE integral[10] were calculated based on the above data. The SYNTAX integral[14] was calculated according to the pathological characteristics of coronary angiography. Subsequently, the characteristics of the culprit vessel were determined. Data for diameter and length of stents were recorded. For instance, if more than two stents were needed for more than two culprit vessels, the length of the separate stents was added to obtain the length of stent. If the target lesion was longer and more than two stents were placed in series, the total length of the stent was subtracted by 4 mm. The diameter and length of stents for selective secondary surgery of non-culprit vessels were not included. Data were also recorded for length of stay and adverse events, including selective PCI during hospitalization, post-infarction angina pectoris, re-infarction during hospitalization, acute and sub-acute thrombosis in the stent, severe arrhythmia (persistent ventricular tachycardia, ventricular fibrillation, newly emerged hemodynamically unstable atrial fibrillation or atrial flutter, and high grade atrioventricular block, excluding reperfusion arrhythmia during PCI), cardiac function above Killip grade III, cardiogenic shock, and 30-day mortality[7-9] of patients in these three groups. The Thrombolysis in Myocardial Infarction (TIMI) bleeding classification was recorded as follows: (1) severe hemorrhage: intracranial hemorrhage or clinically visible bleeding (including imaging diagnosis), decreased hemoglobin of ≥ 5 g/dl and decreased hematocrit by ≥ 15%); (2) moderate hemorrhage: clinically visible bleeding (including imaging diagnosis), decreased hemoglobin between 3 and 5 g/dl, slight bleeding; (3): mild hemorrhage: clinically visible bleeding (including imaging diagnosis), with decreased hemoglobin < 3 g/dl.[7-9,15] TIMI blood flow grading and TIMI myocardial perfusion grade (TMPG) of the infarction-related vessels after PCI were also recorded.[7-9,15]

Statistical Methods

SPSS 17.0 software was used for statistical analysis of all data. The measurement data were expressed as mean ± standard deviation. They presented a normal distribution according to Kolmogorov-Smirnov test, and the comparison between the two groups was conducted by unpaired Student's t test. The count data was expressed as the number of cases (constituent ratio), and the comparison between the two groups was performed by chi-squared test. One-way ANOVA was employed to compare these three groups, and $p < 0.05$ was considered statistically significant.[9]

Results

Clinical Characteristics

Group A (97 male patients with diabetes and STEMI; mean age: 65.9 ± 9.2 years), which was the control group,

had low risk CRUSADE scores (less than 30). Group B (69 female patients; mean age: 65.27 ± 9.8 years) had moderate and above moderate risk CRUSADE scores (higher than 31). Group C (93 female patients; mean age: 64.8 ± 7.2 years) had low risk CRUSADE scores (lower than 30). There were no statistically significant differences in age, first-medical-contact-to-balloon time, door-to-balloon time, hypertension, hyperlipidemia, body mass index, previous history of PCI, family history of coronary heart disease, and GRACE score among the three groups ($p > 0.05$, Table 1).

Characteristics of Coronary Artery Lesions

No significant differences were observed when comparing the number of lesions in three coronary arteries among the three groups. However, compared to group A, the diameter of the implanted stent in groups B and C was significantly smaller ($p < 0.05$). In addition, TIMI grade 3 blood flow and TMPG grade 3 after PCI were significantly less prevalent in group B than in groups A and C ($p < 0.05$, Table 2).

Length of Hospital Stay, Characteristics of PCI, and Incidence of Complications

The average length of hospital stay was significantly higher in group B than in group A and C ($p < 0.05$). In addition, group B had 14 cases of post-infarction angina pectoris, whereas the other two groups had 5 cases each Nine cases of severe arrhythmia occurred in group B, which was higher than that in other two groups (2 cases in group A and 3 cases in group C). There were 14 cases of heart failure, cardiogenic shock, and 30-day mortality in group B, which was higher than in groups A and C (5 cases and 4 cases, respectively). Furthermore, the incidence of selective PCI, re-infarction, and stent thrombosis during hospitalization was significantly higher in group B, when compared to group A ($p < 0.05$). In group B, there were 14 cases of post-infarction angina pectoris, 7 cases of re-infarction and 3 cases of stent thrombosis. Moreover, the total incidence of hemorrhage and the incidence of moderate hemorrhage were significantly higher in group C, when compared to groups A and B ($p < 0.05$, Table 3). There were 8 cases of moderate hemorrhage in group C, whereas groups A and group B had 1 case each.

Discussion

More than 50% of cardiovascular deaths occur in females. Regardless of the positive results of the pathophysiology, complaints, symptoms, signs and results of auxiliary examinations, or the short-term and long-term therapeutic effects, female patients have their own particularities.[16,17] Timely PCI in female patients with acute coronary syndrome can effectively reduce the incidence of MACE.[9,15,17,18] However, women, especially elderly women, often have no typical chest pain during ischemic attack, which may delay diagnosis and treatment. In the present study, the incidence of angina pectoris before infarction was significantly lower in women, when compared to men. Furthermore, non-specific symptoms, such as post-sternal discomfort, chest tightness, shortness of breath, nausea, vomiting, and fatigue, were more common in females with AMI. In addition, the sensitivity and specificity of electrocardiogram and exercise electrocardiogram in the diagnosis of coronary heart disease are lower in women. The lack of specific symptoms and the corresponding electrocardiogram changes in the pathophysiological condition of ischemia and the lack of timely and necessary medicines and lifestyle intervention, even in critical conditions, such as complete or subtotal vascular occlusion, often lead to late consultation, missing the most treatable stage and resulting in a lack of early intervention, such as emergency PCI, which is one of the main causes of the higher incidence of complications and mortality in female patients with AMI.[17,18]

Diabetes mellitus is an isocritical condition of coronary heart disease. The therapeutic effects of antiplatelet drugs in patients with diabetes are worse than in patients without diabetes. Furthermore, the incidence of slow blood flow and no reflow after emergency PCI and MACE are significantly higher than in patients without diabetes.[7-9,15] This suggests that enhanced antiplatelet therapy is needed for patients with diabetes. Diabetes mellitus is one of the most important risk factors for patients with acute coronary syndrome, regardless of whether the GRACE score is used for evaluating ischemic events or the CRUSADE score is used for predicting the risk of bleeding. DAPT is the cornerstone for preventing ischemia and thrombosis after PCI.[19] After receiving DAPT, some patients still have serious complications of thrombosis, especially in female patients with diabetes and elderly patients with diabetes. IIb/IIIa receptor inhibitors in addition to DAPT can effectively reduce the occurrence of slow blood flow and no reflow, the incidence of acute and subacute thrombosis, and the occurrence of MACE.[7-9-15] However, there were no significant differences in general characteristics, coronary lesion characteristics and GRACE scores among the three groups in the present study. These results revealed that TAPT was significantly superior to DAPT in reducing related ischemia-driven events, such as the incidence of post-infarction angina pectoris, severe arrhythmia, heart failure, cardiogenic shock, and 30-day mortality, in both elderly male and female patients with diabetes and STEMI, when compared to women with diabetes and STEMI who received DAPT. Furthermore, compared to patients receiving DAPT, the average hospital stay was shorter in those receiving TAPT. Moreover, the incidence of selective PCI, re-infarction, and stent thrombosis in elderly male patients with diabetes and STEMI who received TAPT was significantly lower, when compared to elderly female patients with diabetes and STEMI who received DAPT. This suggested that TAPT could effectively reduce the onset of ischemic events in elderly patients with diabetes and STEMI. Furthermore, male patients benefit more than female patients.

The CRUSADE score is an important index for evaluating the risk of hemorrhage.[10] Older age, the existence of diabetes mellitus, and female sex are all important risk factors for hemorrhage. Due to the strong antiplatelet effect of tirofiban and the combined application of ticagrelor, hemorrhagic complications have always been a matter of concern for cardiovascular physicians.[3,7-9,15] Close attention should be given to the application of DAPT and TAPT in order to minimize the occurrence of hemorrhagic complications. DAPT has been applied only for elderly female patients with STEMI, whose CRUSADE score was above middle-risk, while TAPT

Table 1 – Comparison of the general clinical characteristics among the three groups

Group	Male (aspirin + ticagrelor + tirofiban) (Group A, 97 cases)	Female (aspirin + ticagrelor) (Group B, 69 cases)	Female (aspirin + ticagrelor + tirofiban) (Group C, 93 cases)	p
Age (years)	65.9±9.2	65.27±9.8	64.8±7.2	0.824
Sex (male/female)	97/0	0/69	0/93	0.000
History of digestive tract disease [n(%)]	5(5.15)	3(4.35)	4(4.3)	0.953
Smoking [n(%)]	22(22.68)	2(2.9)[a]	3(3.23)[a]	0.000
Alcohol consumption [n(%)]	37(38.14)	7(10.14)	13(13.98)	0.000
LVEF < 40%[n(%)]	9(9.28)	6(8.7)	8(8.6)	0.985
Warfarin use [n(%)]	2(2.06)	1(1.45)	2(2.15)	0.943
Combined PPI [n(%)]	6(6.19)	3(4.35)	7(7.53)	0.257
FMC-to-B time	124.3±67.2	132.5±71.3	128.5±82.6	0.797
D-to-B time	65.6±21.4	71.3±26.9	62.6±27.2	0.892
Hypertension [n(%)]	57(58.77)	37(53,62)	55(59.14)	0.745
Hyperlipidemia [n(%)]	49(50.52)	36(52.17)	48(51.62)	0.976
BMI (kg/m^2)	32.46±4.65	30.13±5.26	29.99±6.31	0.823
Serum creatinine (mmol/L)	83.29±9.7	96..32±10.07[a]	83.46±12.35[b]	0.012
History of PCI [n(%)]	4(4.12)	2(2.90)	6(6.46)	0.543
Pre-infarction angina [n(%)]	19(19.59)	2(2.90)[a]	4(4.30)a	0.000
Family history of coronary heart disease [n(%)]	5(5.15)	3(4.35)	5(5.38)	0.954
GRACE score				
Low risk (< 85)[n(%)]	9(9.28)	8(11.59)	9(9.68)	0.526
Middle risk (85 to 133)[n(%)]	17(17.53)	12(17.39)	15(16.13)	0.963
High risk (>133)[n(%)]	71(73.20)	49(71.01)	69(74.19)	0.902
CRUSADE score				
Extremely low risk (1-20)[n(%)]	37(38.14)	0(0)a	42(45.16)[b]	0.000
Low risk (21-30)[n(%)]	60(61.86)	0(0)a	51(54.84)[b]	0.000
Middle risk (31-40)[n(%)]	0(0)	32(46.38)[a]	0(0)[b]	0.000
High risk (41-50)[n(%)]	0(0)	24(34.78)[a]	0(0)[b]	0.016
Extremely high risk (>51)[n(%)]	0(0)	13(18.84)[a]	0(0)[b]	0.000

BMI: body mass index; D-to-B: door-to-balloon; FMC-to-B: first-medical-contact-to-balloon; LVEF: left ventricular ejection fraction; PCI: percutaneous coronary intervention; PPI: proton pump inhibitors. Note: [a]: p < 0.05 compared with group A; [b]: p < 0.05 compared with group B.

has been applied for patients with low-risk CRUSADE scores. These results revealed that the total incidence of hemorrhage and the incidence of moderate hemorrhage in elderly female patients with diabetes after TAPT was significantly higher, when compared to that of female patients with relatively high risk of hemorrhage and elderly male patients with diabetes receiving TAPT. However, there was no significant difference in the risk of hemorrhage between male and female patients receiving TAPT. This indicated that the risk of hemorrhage is higher for elderly female patients with diabetes and STEMI. It is noteworthy that there are special pathophysiological conditions in antiplatelet therapy for elderly female patients with diabetes and STEMI, which are different from those of males. While preventing ischemia-driven events, close attention must be given to the increased risk of hemorrhage.

Study Limitations

The study only compared elderly female patients with diabetes who received TAPT and DAPT, and it did not include male patients receiving DAPT as a control. Furthermore, the sample size was small, and there was a lack of long-term follow-up. The team of authors is conducting further research to address these limitations.

Conclusion

The present study showed that the incidence of complications in elderly female patients with diabetes and STEMI receiving TAPT after PCI was significantly lower than in patients receiving DAPT. However, the incidence of hemorrhage in female patients receiving TAPT was significantly

Table 2 – Comparison of the characteristics of coronary artery lesions among the three groups (number of cases, %)

Lesion characteristics	Male (aspirin + ticagrelor + tirofiban) (Group A, 97 cases)	Female (aspirin + ticagrelor) (Group B, 69 cases)	Female (aspirin + ticagrelor + tirofiban) (Group C, 93 cases)	p
Single branch lesion	9(9.28)	6(8.70)	8(8.60)	0.992
Double branch lesion	11(11.34)	7(10.14)	9(9.68)	0.946
Three branch lesion	77(79.38)	56(81.16)	75(80.65)	0.956
Complicated with left main lesion	6(6.19)	3(4.35)	6(6.45)	0.867
SYNTAX score	22.21±6.18	21.75±8.57	22.31±7.27	0.863
PCI Target vessel Left anterior descending branch	51(52.58)	36(52.17)	49(52.69)	0.998
Right circumflex branch	14(14.43)	11(15.94)	8(8.60)	0.314
Right coronary artery	32(32.99)	22(31.88)	36(38.71)	0.564
Diameter of stents (mm, x±s)	3.01±0.33	2.69±0.27[a]	2.70±0.39[a]	0.046
Length of stents (mm, x±s)	28.29±3.74	27.36±5.13	28.12±5.07	0.783
Preoperative TIMI classification				
Grade 0	95(97.94)	68(98.55)	92(98.92)	0.857
Grade 1 or 2	2(2.06)	1(1.45)	1(1.08)	0.957
Grade 3	0	0	0	
Postoperative TIMI grading				
Grade 0 to 2	2(2.06)[c]	10(14.49)[ac]	4(4.30)[bc]	0.003
Grade 3	95(97.94)[c]	59(85.51)[ac]	89(95.70)[bc]	0.003
Preoperative TMPG classification				
Grade 0 to 2	97(100)	69(100)	93(100)	
Grade 3	0	0	0	
Postoperative TMPG grading				
Grade 0 to 2	6(6.19)	20(28.99)[ad]	14(15.05)[abd]	0.0003
Grade 3	91(93.81)[d]	49(71.01)[ad]	79(84.95)[abd]	0.0001

PCI: percutaneous coronary intervention. Note: [a]: p < 0.05 compared with group A; [b]: p < 0.05 compared with group B; [c]: comparisons with intra-group preoperative TIMI of the same grade, p < 0.05; [d]: comparisons with intra-group preoperative TMPG of the same grade, p < 0.05.

higher, when compared to male patients receiving TAPT and female patients receiving DAPT.

Author Contributions

Conception and design of the research: Liu Y, Chen Q, Ji J, Jia K; Acquisition of data: Liu Y, Gao Y, Liu H, Chen Q, Ji J, Jia K; Analysis and interpretation of the data: Liu H, Ji J, Jia K; Statistical analysis: Liu Y, Gao Y, Chen Q; Obtaining financing: Gao Y, Liu H; Writing of the manuscript: Liu Y, Liu H; Critical revision of the manuscript for intellectual content: Liu H.

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.

Table 3 – Comparison of length of hospital stay, characteristics of PCI, and incidence of complications in the three groups

Item	Male (aspirin + ticagrelor + tirofiban) (Group A, 97 cases)	Female (aspirin + ticagrelor) (Group B, 69 cases)	Female (aspirin + ticagrelor + tirofiban) (Group C,93 cases)	p
Average length of hospital stay (days)	7.8±1.5	11.2±3.3[a]	8.3±1.9[ab]	0.042
Selective secondary surgery [n(%)]	12(12.37)	19(27.54)[a]	9(20.93)	0.047
Post-infarction angina pectoris [n(%)]	5(5.05)	14(19.72)[a]	5(5.38)[b]	0.001
Re-infarction [n(%)]	0(0)	7(10.14)[a]	6(6.45)	0.009
Stent thrombosis [n(%)]	0(0)	3(4.35)[a]	1(1.08)	0.073
Severe arrhythmia [n(%)]	2(2.06)	9(13.04)[a]	3(3.23)[b]	0.004
Cardiac function above Killip grade III [n(%)]	2(2.60)	14(20.29)[a]	8(8.60)[ab]	0.0001
Postoperative cardiogenic shock [n(%)]	0(0)	5(7.25)[a]	1(1.08)[b]	0.006
30-day mortality [n(%)]	0(0)	4(5.80)[a]	1(1.08)	0.004
Total hemorrhage [n(%)]	7(7.22)	6(8.70)	20(21.98)[ab]	0.005
Severe hemorrhage	0(0)	0(0)	1(1.08)	0.408
Moderate hemorrhage	1(1.03)	1(1.45)	8(8.60)[ab]	0.012
Mild hemorrhage	6(6.19)	5(7.25)	11(11.83)	0.344

a: $p < 0.05$ compared with group A; b: $p < 0.05$ compared with group B.

References

1. Yoshikawa Y, Shiomi H, Watanabe H, Natsuaki M, Kondo H, Tamura T, et al. Application of DAPT score to predict ischaemic and bleeding events in patients who underwent drug-eluting stent implantation: a landmark analysis of large pooled cohort. EHJ. 2017;38(suppl_1):611-2.
2. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009 Sep 10;361(11):1045-57.
3. Brener SJ, Mehran R, Dressler O, Cristea E, Stone GW. Diabetes mellitus, myocardial reperfusion, and outcome in patients with acute ST-elevation myocardial infarction treated with primary angioplasty (from HORIZONS AMI).Am J Cardiol. 2012;109(8):1111-6.
4. Farhan S, Höchtl T, Kautzky-Willer A, Wojta J, Huber K. Antithrombotic therapy in patients with coronary artery disease and with type 2 diabetes mellitus. Wien Med chenschr. 2010;160(1-2):30-8.
5. Liu HL, Liu Y, Hao ZX, Geng GY, Zhang ZF, Jing SB, et al. Comparison of primary coronary percutaneous coronary intervention between Diabetic Men and Women with acute myocardial infarction. Pak J Med Sci. 2015;31(2):420-5.
6. Park KH, Jeong MH, Ahn Y, Ahn TH, Seung KB, Oh DJ, et al. Comparison of short-term clinical outcomes between ticagrelor versus.clopidogrel in patients with acute myocardial infarction undergoing successful revascularization; from Korea acute myocardial infarction Registry-Nationgl,Institute of Health. Int J Cardiol.2016;215:193-200.
7. Liu Y, Liu H, Hao Z, Geng G, Chen Q, Han W, et al. Efficacy and safety of different doses of tirofiban combined with ticagrelor on diabetic patients with AMI receiving in emergency percutaneous coronary intervention (PCI). Int J Clin Exp Med. 2015;8(7):11360-9.
8. Liu Y, Liu HL, Hao Y, Hao Z, Geng G, Han W, et al. Short-term efficacy and safety of three different antiplatelet regimens in diabetic patients treated with primary percutaneous coronary intervention: a randomised study. Kardiol Pol. 2017;75(9):850-8.
9. Liu Y, Liu HL, Geng YG, Ba N, Jing SB, Guo W, et al. Effect of intracoronary injection of tirofiban on acute myocardial infarction in elderly patients with diabetes mellitus. Chinese Journal of Geriatric Heart Brain and Vessel Diseases. 2013;15:799-802.
10. Subherwal S, Bach RG, Chen AY, Gage BF, Rao SV, Newby LK, et al. Baseline risk of major leeding in non·-ST·-segment··elevation myocardial infarction:the CRUSADE (Can rapid risk stratification of unstable angina patients suppress adverse outcomes with early implementation of the ACC/AHA Guidelines)Bleeding Score. Circulation. 2009;119(14):1873-82.
11. Wessler JD, Stant J, Duru S, Rabbani L, Kirtane AJ. Updates to the ACCF/AHA and ESC STEMI and NSTEMI Guidelines: Putting Guidelines Into Clinical Practice. Am J Cardiol. 2015;115(5 Suppl):23A-8A.
12. America Disbetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2010;33:204-9.
13. Bekler A, Altun B, Gazi E, Temiz A, Barutçu A, Güngör Ö, et al. Comparison of the GRACE risk score and the TIMI risk index in predicting the extent and severity of coronary artery disease in patients with acute coronary syndrome. Anatol J Cardiol. 2014;15(10):801-6.
14. Schwietz T, Spyridopoulos I, Pfeiffer S, Laskowski R, Palm S, DE Rosa S, et al. Risk stratification following complex PCI: clinical versus anatomical risk stratification including 'post PCI residual SYNTAX-score' as quantification of incomplete revascularization. J Interv Cardiol. 2013; 26(1):29-37.
15. Chen Q, Liu Y, Liu HL. Effects of intracoronary tirofiban administration on diabetes mellitus complicated by acute myocardial infarction in female patients undergoing emergency percutaneous coronary intervention. Int J Clin Exp Med. 2016;9:11966-73.
16. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2012 update: a report from the American Heart Association. Circulation. 2012;125(1): e2-e220.

17. D'Ascenzo F , Gonella A , Quadri G , Longo G, Biondi-Zoccai G, Moretti C, et al. Comparison of mortality rates in women versus men presenting with ST-segment elevation myocardial infarction. Am J Cardiol. 2011;107(5):651-4.

18. Fath-Ordoubadi F, Barac Y, Danzi GB, Kerner A, Nikolsky E, Halabi M, et al. Gender impact on prognosis of acute coronary syndrome patients treated with drug-eluting stents. Am J Cardiol. 2012;110(5):636-42.

19. Sathyamurthy I, Jayanthi K. Dual antiplatelet therapy in acute coronary syndromes and coronary artery interventions. J Assoc Physicians India. 2014, 62(7):596-601.

Is There a Second Wind for Glycoprotein IIb/IIIa Inhibitors in Elderly Diabetic Females with ST-Elevation Myocardial Infarction, or are We on Thin Ice?

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Short Editorial related to the article: Therapeutic Effects of Triple Antiplatelet Therapy in Elderly Female Patients with Diabetes and Acute Myocardial Infarction

The standard of care in patients undergoing primary percutaneous coronary intervention (PCI) is double antiplatelet therapy (DAPT), with a combination of aspirin and a P2Y12 inhibitor.[1] Prasugrel and ticagrelor are the preferred P2Y12 inhibitors because they have a more rapid onset of action, greater potency, and are superior to clopidogrel in terms of clinical outcomes.[1] They should be maintained over 12 months unless there are contraindications, such as excessive risk of bleeding.[1] The choice of treatment should be a balanced decision, considering the ischemic and bleeding risks. Most of the trials evaluating glycoprotein (Gp) IIb/IIIa inhibitors in ST-elevation myocardial infarction (STEMI) patients treated with primary PCI pre-date the era of routine oral DAPT pre-treatment, particularly in the setting of potent oral platelet inhibitors. At that time, they demonstrated a reduction in the incidence of ischemic events, but at the expense of a consistent increase in major bleeding.[2] Presently, there is no compelling evidence for an additional benefit of the routine use of a Gp IIb/IIIa strategy in primary PCI patients that receive DAPT treatment, particularly with ticagrelor.[2] The use of Gp IIb/IIIa inhibitors should be considered for bailout therapy in the event of angiographic evidence of a large thrombus, slow- or no-reflow, and other thrombotic complications, although this strategy has not been addressed in randomized controlled trials.[2] Also, intracoronary administration is not superior to its intravenous use.[3]

Elderly patients are at high-risk of bleeding and other complications from acute therapies, not only because of their age, but because they have more often renal dysfunction and more co-morbidities.[2] Diabetes is also a frequent comorbidity in STEMI patients. Diabetic patients have more diffuse atherosclerotic disease and are at higher risk of death and complications, including repeated revascularization after PCI.[2] In fact, diabetic patients who have suffered a myocardial infarction have a worse prognosis, and the presence of diabetes amplifies the risk of any cardiovascular event, as shown in many previous studies of acute coronary syndrome treatment.[1,2,4] However, in the current context of the use of oral P2Y12 inhibitors, there is no indication that antithrombotic pharmacotherapy should differ between diabetics and patients without diabetes undergoing revascularization.[1,2]

In the present number of this journal, a Chinese group investigated the possible benefit of triple anti-platelet therapy (TAPT) with aspirin, ticagrelor and tirofiban, in elderly female diabetic patients compared to DAPT.[5] They studied 162 elderly and diabetic female patients separately in two groups according to the CRUSADE score. The group with a lower CRUSADE score (< 30) received TAPT, as well as a control group of 97 elderly and diabetic males, also with low CRUSADE score. The female group with high CRUSADE score received only DAPT. In general, women had more ischemic and hemorrhagic complications. When comparing males and females with low CRUSADE score and receiving TAPT, despite similar treatment, women had more re-infarction, stent thrombosis, cardiogenic shock and 30-day mortality, but also more moderate and severe bleeding. Comparing only the female groups, the group that received DAPT had less recovery in terms of TIMI grading and TIMI myocardial perfusion grading after PCI, more stent thrombosis, cardiogenic shock and 30-day mortality, but less moderate / severe bleeding. The authors concluded that a TAPT strategy in elderly diabetic women with STEMI showed less cardiovascular events at 30-day follow-up but more hemorrhagic complications.

However, some remarks and limitations should be highlighted. Firstly, the mean age of the patients in each group is in fact not "elderly" as we might define it. Mean age is around 65 years in all groups and "elderly" was defined as above 60 years. For that reason, TAPT was tested in relatively young patients. Thus, the conclusions cannot be drawn for truly elderly patients, who might be considered as those above 75 years of age. Secondly, inclusion was performed for six years and an average of 43 patients/ year were included. We can suspect that the centre has a moderate volume, or inclusion was not consecutive, and a significant number of patients were not included. For that reason, the sample is relatively small and statistical power is not adequate. Thirdly, in studies with anti-thrombotic therapies, it is important to provide additional results, particularly in the form of composite outcomes encompassing ischemic and bleeding events, such as Net Clinical Benefit or Net Adverse Clinical Events. This is a better way to clearly define if the benefits

Keywords

Platelet Agregation; Glycoprotein IIb/IIIa inhibitors; Elderly; Women; Diabetes Mellitus; Myocardial Infarction; Hemorrhage.

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outweigh the risks and safety problems. Fourthly, mean body mass index (BMI) is high, with a mean BMI of around 30 in all groups. We can assume that patients with normal or low body weight, an important risk factor for bleeding, were not included. Finally, multivariable analysis should have been performed to confirm the benefit of TAPT over DAPT in elderly and diabetic female patients. There are some differences in baseline characteristics that might have a significant impact on the outcome that should have been adjusted. Despite all the highlighted limitations, there are, however, two important points that we can observe based on the presented results. Contrary to general belief, we did not observe any difference in time delays in elderly diabetic women, when compared to men and coronary anatomy was also similar.

In conclusion, the present study does not give enough evidence to change the usual clinical practice in STEMI elderly diabetic female patients. Many questions were not properly addressed and the additional benefit of routine use of Gp IIb/IIIa together with potent DAPT in primary PCI in this sub-group of patients was not undoubtedly demonstrated.

References

1. Neumann FJ, Sousa-Uva M, Ahlsson A, Allonso F, Banning A, Benedetto U, et al. 2018 ESC /EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019; 40(2): 87-165.
2. Ibanez B, James S, Agewal S, Antunes M, Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2018;39(2):119-77.
3. Friedlands S, Eisenberg MJ, Shimony A. Meta-analysis of randomized controlled trials of intracoronary versus intravenous administration of glycoprotein IIb/IIIa inhibitors during percutaneous coronary interventions for acute coronary syndromes. Am J Cardiol. 2011;108(9):1244-51.
4. Haffner SM, Lehto S, Ronnemaa A, Pyorala K, Laakso M, et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in non-diabetic subjects with and without prior myocardial infarction. N Engl J Med. 1998;339(4):229-34.
5. Liu Y, Gao Y, Liu H, Chen Qi, Ji J, Jia K, et al,. Efeitos terapêuticos da tripla antiagregação plaquetária em pacientes femininas idosas com diabetes e infarto agudo do miocárdio. Arq Bras Cardiol. 2021; 116(2):229-235.

Outcomes in Coronary No-Reflow Phenomenon Patients and the Relationship between Kidney Injury Molecule-1 and Coronary No-Reflow Phenomenon

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Abstract

Background: Coronary no-reflow phenomenon (CNP) is associated with an increased risk of major cardiovascular adverse events (MACE).

Objective: This study aimed to evaluate the relationship between serum Kidney Injury Molecule-1 (KIM-1) levels and CNP in patients with acute ST-segment elevation myocardial infarction (STEMI).

Methods: This study included a total of 160 patients (113 males and 47 females; mean age: 61.65±12.14 years) who were diagnosed with STEMI. The patients were divided into two groups, the reflow group (RG) (n=140) and the no-reflow group (NRG) (n=20). Patients were followed during one year. A p-value of <0.05 was considered significant.

Results: CNP was observed in 12.50% of the patients. Serum KIM-1 was significantly higher in the NRG than in the RG (20.26±7,32 vs. 13.45±6.40, p<0.001). Body mass index (BMI) was significantly higher in the NRG than in the RG (29.41 (28.48-31.23) vs. 27.56 (25.44-31.03), p=0.047). Heart rate (HR) was significantly lower in the NRG than in the RG (61.6±8.04 vs. 80.37±14.61, p<0.001). The European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) was significantly higher in the NRG than in the RG (3.06±2.22 vs. 2.36±2.85, p=0.016). The incidence of stroke was significantly higher in the NRG than in the RG (15% vs. 2.90%, p=0.013). The baseline KIM-1 level (OR=1.19, 95% CI:1.07 to 1.34, p=0.002) and HR (OR=0.784, 95% CI:0.69 to 0.88, p<0.001) were the independent predictors of CNP.

Conclusion: In conclusion, baseline serum KIM-1 concentrations and lower HR are independently associated with CNP in STEMI patients and the incidence of stroke was significantly higher in the NRG in the one-year follow-up. (Arq Bras Cardiol. 2021; 116(2):238-247)

Keywords: Cardiovascular Diseassses; Myocardial Infarction Stroke; Percutaneous Coronary Intervention; Coronary Thrombosis; Heart Rate.

Introduction

The coronary no-reflow phenomenon (CNP) was defined as the lack of myocardial perfusion despite the opening of the coronary vessel in the setting of primary percutaneous coronary intervention (PCI).[1] Overall, angiographic CNP is defined as the presence of Thrombolysis In Myocardial Infarction (TIMI) score of 0-I, which refers to the sudden loss of epicardial flow, after balloon dilatation or stent placement without the presence of dissection, mechanical obstruction, significant residual stenosis, spasm or thrombus of the coronary vessel.[2] The underlying mechanisms of CNP are inflammation, atherothrombotic microembolization, and activation of neutrophils and platelets, which cause the release of oxygen-free radicals, proteolytic enzymes, and proinflammatory mediators that can cause tissue and endothelial damage, particularly in critically-injured myocytes.[3] Biomarkers of kidney tubular injury, such as KIM-1, have been associated with both the incidence and progression of acute kidney injury (AKI) and chronic kidney disease (CKD).[4] KIM-1 is a type-1 transmembrane protein, which is expressed in the proximal tubule apical membrane according to the injury.[5] AKI and CKD are strongly associated with cardiovascular disease (CVD), and AKI has been reported as being associated with cardiovascular events.[6] KIM-1 acts as a pro-inflammatory molecule and has both chemo-attractant and cell-adhesion functions.[4] The structure of KIM-1 suggests that it may be involved in surface adhesion interactions.[4-6] The pro-inflammatory cytokines contribute to the inflammation by enhancing and stimulating the inflammatory cells and inflammatory response.[4] KIM-1 also has a spatial relation with inflammatory T-cells.[4] KIM-1 has been shown to interact with T-cell proliferation, and KIM-1 also interacts with other pro-inflammatory proteins.[4] Moreover, T-cells have been implicated in the pathophysiology

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of the post-ischemic injury of the endothelium.[4] It is possible that KIM-1 plays an important role for the surviving epithelial cells to undergo differentiation, migration, proliferation, and the restoration of morphological and functional epithelial integrity. Nevertheless, KIM-1 is associated with fibrosis and inflammation.[4] We hypothesized that KIM-1 expression is induced in STEMI and is related to CNP and endothelial damage due to the pro-inflammatory response. The association between KIM-1 protein levels and CNP has not been addressed in the literature yet. Understanding which biologic pathways and markers are associated with CNP may allow for the design of future studies to explore the mechanistic link between these pathways and to evaluate the efficacy of interventions designed to reduce the burden of CVD in these patients. Furthermore, the aim of this study was to evaluate the relationship between baseline serum KIM-1 protein levels and CNP in patients with acute STEMI.

Methods

This study was prospectively conducted between May 2016 and May 2018 at Bezmialem Vakif University Hospital. For this single-center study, we enrolled 346 patients between 18 and 90 years who were diagnosed with STEMI and underwent primary PCI within 6 hours of symptom onset. All STEMI patients referred to the cath lab to undergo primary PCI were included (n=346). Patients with coronary artery bypass graft (CABG), cardiogenic shock, pulmonary edema, Killip class ≥2, stent thrombosis, who underwent thrombus aspiration in the index event, had acute or chronic infective or neoplastic disease, moderate-to-severe chronic kidney disease, and chronic liver disease were excluded from this study (n=186). Accordng to the final results of the angiographic features of TIMI flow of the treated artery, a total of 20 patients with angiographically proven CNP were enrolled in the NRG and we included 140 patients in the RG. All patients were given a therapy consisting of 300 mg acetylsalicylic acid and a loading dose of clopidogrel (600mg) and UF heparin (100mg/kg) prior to PCI. All participants gave written informed consent prior to participation and the study was approved by the local ethics committee. Furthermore, the study was conducted under the provisions of the Declaration of Helsinki.

Biochemical analyses

Venous blood samples were taken immediately after hospital admission before PCI from the antecubital vein. The 12-lead electrocardiograms were obtained at baseline and HR was noted. BMI was calculated using the formula weight (kg)/height^2 (m^2). The estimated glomerular filtration rate (eGFR) of each patient was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. Routine blood chemistry, lipid parameters, and troponin-I were measured using standard auto-analyzer equipment. Blood counts were measured using a Sysmex K-1000 (Block Scientific, Bohemia, NY, USA) auto-analyzer. Samples were centrifuged at 3000 rpm for 10 min, and the supernatant and serum separated from the samples. Then they were frozen at -80° C until further analysis. Serum KIM-1 levels (ng/mL) were measured using a commercially available enzyme-linked immunosorbent assay ELISA kit (Human KIM-1 ELISA kit, Elabscience Biotech Co., Ltd, Catalog no: E-EL-H0186, Wuhan, China).[4] The KIM-1 kit analysis inter and intra-assay coefficients of variation for the assay was less than 10%, and sensitivity was 0.10 ng/mL.

Diagnosis of acute ST-segment elevation myocardial infarction

The STEMI diagnosis was attained in the presence of the following characteristics based on definitions from clinical practice guidelines: typical chest pain lasting more than 30 minutes, new-onset or presumably new ST-segment elevation in two or more contiguous leads with ST-segment elevation ≥ 2.5 mm in men < 40 years, ≥2 mm in men ≥ 40 years, or ≥ 1.5 mm in women in leads V2–V3 and/or ≥ 1 mm in the other leads (in the absence of left ventricular hypertrophy or left bundle-branch block). In patients with inferior MI recorded with right precordial leads (V3R and V4R ST-segment elevation), it was considered a case of concomitant right ventricular infarction. Likewise, ST-segment depression in leads V1–V3 and positive T-wave (ST-segment elevation equivalent), additionally concomitant ST-segment elevation ≥ 0.5 mm recorded in leads V7–V9 was considered as a posterior MI.[7]

Cardiovascular risk factors

After detailed examinations, the medical history of each patient was collected by the same investigator. Risk factors for coronary artery disease (CAD), including age, gender, hypertension (HT), diabetes mellitus (DM), hyperlipidemia (HPL), and smoking status, were noted. Patients who were previously receiving antihypertensive therapy or whose blood pressure levels, measured at least twice, were ≥140/90 mmHg were considered to be hypertensive.[8] Patients who were previously receiving an oral antidiabetic and/or using insulin therapy or whose fasting blood glucose, measured at least twice, was ≥125 mg/dL were considered to be diabetic.[9] The presence of HPL was considered when total cholesterol level was >200 mg/dL or low-density lipoprotein cholesterol (LDL-C) was >100 mg/dL or when the patient was previously receiving a lipid-lowering medication in accordance with the "Adult Treatment Panel III" guideline.[10] Patients who were still using tobacco products on admission to the emergency service and those who had ceased smoking within the past month were considered smokers.

Coronary angiography

Coronary angiography procedures were performed using a Philips (Optimus 200 DCA and Integris Allura 9, Philips Medical Systems, Eindhoven, Netherlands) angiography device using the femoral approach. Coronary angiography and PCI were performed according to the standard clinical practice with nonionic, iso-osmolar contrast medium (iodixanol, Visipaque 320mg/100mL; GE Healthcare, Cork, Ireland). Primary PCI of the infarct-related artery was performed. Angiographic images were shot at a rate of at least 80 image frames and were recorded at a rate of 25 frames per second. At least two cardiologists assessed the coronary anatomic examination records offline. Coronary blood flow velocity

was determined by the quantitative number of frame count as described by Gibson et al.[11] The CNP was defined angiographically as post-PCI TIMI flow grades ≤1, without the presence of dissection, mechanical obstruction, or significant stenosis.[1] CNP patients received intracoronary (IC) glycoprotein IIb/IIIa inhibitors (Gp-IIb/IIIa inh.) or IC adenosine or epinephrine for the treatment of CNP, respectively. After the procedure, all patients received intravenous (IV) hydration with isotonic saline for at least 12 hours.

Transthoracic echocardiography

Each patient underwent a transthoracic echocardiographic examination with a 3.5-MHz transducer (Vivid 7 GE Medical System, Horten, Norway) by the same investigators before hospital discharge. Examinations and measurements were performed according to the recommendations of the American Echocardiography Unit. Simpson's method was used to calculate left ventricular ejection fraction (LVEF).

Follow-up

The follow-up information was obtained through hospital records and at the patients' consultations carried out at the hospital at 1, 3, 6 and 12 months by the same investigators. The endpoints of this study, MACE including all-cause mortality, cardiovascular death, stroke, and myocardial re-infarction were obtained from hospital records and death certificates, or by telephone contact with the patients' relatives.

Statistical analysis

Data analyses were performed using SPSS version 24.0 statistical software package (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to control the variable distributions. Student's *t* test for two independent samples, was used for normally distributed data and reported as mean and standard deviation, and Mann–Whitney U test was used to compare non-normally distributed data and reported as median and 25th and 75th percentiles. Categorical data were compared using the Chi-square test. The correlations between variables were performed using Spearman's rank-order correlation analysis. The Kaplan-Meier method was used to estimate event-free survival rates. Receiver operating characteristic (ROC) curve analysis was performed to determine KIM-1 predictive value for CNP. Logistic regression analysis was performed to assess the predictors of CNP. Univariate logistic regression analysis was performed, and the variables that were found to be statistically significant ($p<0.1$) were analyzed with multivariate logistic regression analysis. A two-tailed p value of <0.05 was considered significant.

Results

This study included a total of 160 patients (113 males and 47 females; mean age: 61.65±12.14 years) who were diagnosed with CNP. CNP was observed in 12.50% of the study population. Demographic findings and medications in the groups were described in Table 1. Regarding the cardiovascular risk factors, BMI (kg/m^2) was significantly higher in the NRG than in the RG (29.41 (28.48-31.23) vs. 27.56 (25.44-31.03), p=0.047). The baseline laboratory characteristics of the patients are described in Table 2. KIM-1 was significantly higher in the NRG than in the RG (20.26±7.32 vs 13.45±6.40, p<0.001), HR was significantly lower in the NRG than in the RG (61.60±8.04 vs 80.37±14.61, p<0.001) and EuroSCORE II was significantly higher in the NRG than in the RG (3.06±2.22 vs 2.36±2.85, p=0.016). In 4 patients, CNP was resolved with IC Gp-IIb/IIIa inh., in 8 patients CNP was resolved with intracoronary (IC) Gp-IIb/IIIa inh. plus IC adenosine and in 5 patients CNP was resolved with IC Gp-IIb/IIIainhibitor plus IC adenosine and IC epinephrine (Table 1). In 17 patients CNP was resolved and they were added to the RG. CNP persisted in 20 patients and they were added to the NRG.

Clinical follow-up findings, including all-cause mortality, cardiovascular death, stroke, myocardial infarction, and MACE are described in Table 3. Stroke was significantly higher in the NRG than in the RG (15% vs. 2.9%, p=0.013). There were no differences between the two groups regarding other demographic or clinical findings. Kaplan-Meier curves for stroke and MACE rates are described in Figures 1 and 2. Age, eGFR, Mehran score, LVEF, and hs-CRP were significantly associated with EuroSCORE II (p<0.05) (Table 4). Forward conditional logistic regression analysis demonstrated that KIM-1 (OR=1.199, 95%CI: 1.07-1.343, p=0.002) and HR (OR=0.784, 95%CI: 0.696-0.883, p<0.001) were the independent predictors of CNP in STEMI patients (Table 5). In the ROC analysis, the values of serum KIM-1 above 21,53 ng/mL predicted the presence of CNP with 85% of sensitivity and 93,6% of specificity. The area under the curve was 0.80 (95% CI: 0.653–0.946, p<0.001) (Figure3).

Discussion

The main finding of this study was that increased KIM-1 levels and lower HR were the two determinants of CNP. We have shown that the values of serum KIM-1 above 21.53 ng/mL suggest the presence of CNP;thus, elevated serum KIM-1 levels can be used as a promising biomarker of CNP. In our study, we found that CNP was independently associated with baseline serum KIM-1 concentrations and lower HR in STEMI patients. To the best of our knowledge, this is the first report in the literature demonstrating the relationship between KIM-1 concentrations and lower HR with CNP. Additionally, in patients with STEMI, CNP was significantly associated with poor outcomes. In the one-year clinical follow-up, findings demonstrated that stroke was significantly higher in the NRG.

Although the exact mechanism of CNP is not consistently determined in the literature, there are several suggested CNP mechanisms. These reported mechanisms are such as pre-existing microvascular dysfunction, microvascular arteriolar spasm, distal thrombo-embolization due to high platelet activity and thrombus burden, ischemic-reperfusion injury, and swelling of myocardial cells compressing microvascular vessels.[1-3] Therefore, the pathogenesis and mechanisms of CNP remain controversial.

CNP is a significant prognostic marker related to short-term poor cardiac outcomes in STEMI. Regarding the published data, the estimated frequency of CNP ranged from 5% to 60%.[12] In our study, CNP was observed in 12.50% of

the study population. Consistent with the published data, patients with CNP had worse outcomes.[13] In our study, one-year clinical follow-up findings demonstrated that stroke incidence was significantly higher in the NRG. Stroke was associated with thrombus burden. According to our study, the associated mechanism underlying this adverse event is continuing thrombus activation still ongoing after the index event, and this may be the main reason for stroke. Despite the fact that all STEMI patients were taking antithrombotic medications regularly, stoke incidence was significantly higher in the NRG. Thus, such patients should be monitored and followed carefully. BMI is the most widely used tool for the assessment of obesity.[14] Bakirci et al.[15] found that increased epicardial fat in obese patients was associated with impaired coronary flow in patients with non-STEMI.[15] Recent studies suggested that CNP is more frequently seen in association with hyperglycemia, hypercholesterolemia, and mild-to-moderate renal insufficiency.[16] However, the understanding of these risk factors for the pathogenesis of CNP is limited and controversial. In our study, we found that BMI was significantly higher in the NRG. This may be proven to be associated with the risk of stroke as well. Thus, calculating the BMI may be a useful method for estimating cardiac outcomes in CNP. In addition, decreasing BMI may protect patients against stroke. Randomized studies that have utilized manual thrombus aspiration have shown better microvascular perfusion and long-term outcomes compared to control patients undergoing PCI during STEMI.[17] However, using thrombus aspiration can cause stroke due to device complications, and for that reason in our study we excluded the patients (n=12) from the studies that used thrombus aspiration catheter. The routine use of platelet inhibitors (Gp-IIb/IIIa inh., abciximab, tirofiban), nicorandil, nitroprusside, and adenosine have shown beneficial effects on myocardial perfusion in STEMI.[18-20] Aksu et al. found that epinephrine has a beneficial effect on CNP too.[21] Epinephrine causes a potent coronary vasodilator effect via beta-2 receptor activation, which then mediate vasodilatation of the arteriolar circulation. Also, it has chronotropic and inotropic effects on the heart.[22] IC epinephrine may restore normotensive blood pressure in these patients, since this agent stimulates alpha vasoconstrictor receptors.[21] Skelding et al.[24] found that the increase in coronary flow due to correction of hypotension may be the other potential beneficial effect of epinephrine.[22] In our study, we found that lower HR was independently

Table 1 – Baseline characteristics and medications of the patients

Variable, n(%)	NRG n=20 (12.5)	RG n=140 (87.5)	p-value
Age, y	64.35±14.03	61±11.86	0.291
Male gender, n(%)	11 (55.00)	102 (72.90)	0.101
BMI (kg/m²)	29.41 (28.48-31.23)	27.56 (25.44-31.03)	0.047
HT, n(%)	15 (75)	79 (56.40)	0.115
DM, n(%)	7 (35)	50 (35.70)	0.950
HL, n(%)	6 (30)	62 (44.30)	0.227
Smoker, n(%)	11 (55)	90 (64.30)	0.421
Family History, n(%)	6 (30)	54 (38.60)	0.459
PAD, n(%)	3 (15)	11 (7.90)	0.290
COPD, n(%)	3 (15)	26 (18.60)	0.698
LVEF (%)	51.25±6.72	52.01±7.49	0.561
Medications n(%)			
Ace inh	14 (70)	75 (53.60)	0.167
ARB	5 (25)	44 (31.40)	0.560
B blocker	19 (95)	133 (95)	1
CCB	6 (30)	34 (24.30)	0.581
Statin	20 (100)	124 (88.60)	0.111
Nitrat	9 (45)	49 (35)	0.384
OAD	7 (35)	48 (34.30)	0.950
IC Gp-IIb/IIIa inh.	20 (100)	17 (12.10)	<0.001
IC adenosine	20 (100)	13 (9.3)	<0.001
IC epinephrine	20 (100)	5 (3.6)	<0.001

Data were reported as n(%) for categorical variables; median and 25th-75th percentile for non-parametric measurements; mean and standard deviation for parametric measurements. Y: year; BMI: Body Mass Index; HT: hypertension; DM: diabetes mellitus type II; HL: hyperlipidemia; PAD: peripheral arterial disease; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; ACE inh: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers; B blocker: beta-blocker; CCB: calcium channel blockers; OAD: oral antihyperglycemic drugs; IC: intracoronary; Gp-IIb/IIIa inh: glycoprotein-IIb/IIIa inhibitors.

Table 2 – Baseline laboratory characteristics of the patients

Variable, n(%)	NRG n=20 (12.5)	RG n=140 (87.5)	p-value
KIM-1 ng/mL	20.26±7.32	13.45±6.40	<0.001
Glucose, mg/dl	134.25±65.06	136.73±61.27	0.689
Uric acid, mg/dl	5.63±1.51	5.73±1.73	0.883
eGFR (mL/min per 1.73 m2)	75.54±22.63	82.3±21.47	0.154
Mehran Score	5 (2-8)	3.5 (2-6.75)	0.145
CIN development, n(%)	1(5)	14(10)	0.473
WBC, 10^3/uL	9.86±4.32	9.45±3.30	0.796
HTC, %	40.07±3.44	40.36±4.66	0.678
Platelet, 10^3/uL	231.60±62.13	238.83±73.29	0.520
In-hospital stay, day	3.15±0.48	3±1.12	0.408
Trigliseride, (mg/dL)	160.50±37.62	155.37±57.52	0.323
HDL, (mg/dL)	39.70±5.01	41.05±7.83	0.938
LDL, (mg/dL)	138.15±31.86	123.77±33.91	0.076
Total Cholesterol, (mg/dL)	214.15±33.47	200.75±38.1	0.188
hs-CRP, (mg/dL)	0.10 (0.01-0.43)	0.20 (0.05-0.50)	0.532
Peak Troponin-I (pg/ml)	2293 (432.75-13501.25)	808.50 (68.25-3770.50)	0.220
Heart Rate, (bpm)	61.6±8.04	80.37±14.61	<0.001
TSH, uIU/mL	1.05 (0.70-1.30)	1.10 (0.90-1.40)	0.245
NYHA class	2.45±0.51	2.30±0.53	0.278
EuroSCORE II, (%)	3.06±2.22	2.36±2.85	0.016

Data were reported as n(%) for categorical variables; median and 25th-75th percentile for non-parametric measurements; mean and standard deviation for parametric measurements. KIM-1: Kidney injury molecule-1; eGFR: estimated glomerular filtration rate; CIN: Contrast-induced nephropathy; HTC: hematocrit; HDL: high-density lipoprotein; LDL: low-density lipoprotein; hs-CRP: high-sensitivity C-reactive protein; TSH: thyroid-stimulating hormone; NYHA: the New York Heart Association Functional Classification; EuroSCORE II: European System for Cardiac Operative Risk Evaluation II.

Table 3 – Clinical follow-up findings

Variable, n(%)	NRG n=20 (12.5)	RG n=140 (87.5)	p-value
All-Cause Mortality	2 (10)	21 (15)	0.551
Cardiovascular Death	2 (10)	16 (11.4)	0.850
Stroke	3 (15)	4 (2.9)	0.013
Myocardial infarction	2 (10)	17 (12.1)	0.782
MACE	6 (30)	35 (25)	0.682

Data were reported as n(%). MACE: Major Adverse cardiovascular events.

associated with CNP. If the microcirculation is slow, CNP will occurr and we have suggested that a lower HR can be used as an indicator of CNP. Moreover, operators have to be aware of the patient's HR, and a lower HR should be considered as a candidate for CNP before starting PCI. Despite the encouraging results of our study, lower HR findings should be explained by large randomized studies.

EuroSCORE II shows us the patient's fragility and frailty.[23] Gül et al.[24] found that STEMI patients with higher EuroSCORE II had significantly higher CNP.[24] In this study, in the NRG, we calculated a significantly higher EuroSCORE II, consistent with the literature. Additionally, we found that age, eGFR, Mehran score, LVEF, and hs-CRP, were significantly associated with EuroSCORE II.

KIM-1 is released in the blood and urine and can be used as a sensitive and early diagnostic indicator of proximal tubular injury in humans when compared to any of the conventional diagnostic markers, e.g., serum creatinine and cystatin C or proteinuria.[4] Under normal conditions, very low KIM-1 levels are expressed in kidney proximal tubulesa. However, in the ischemic kidney, KIM-1 expression is significantly increased.[25] KIM-1 has been shown to interact

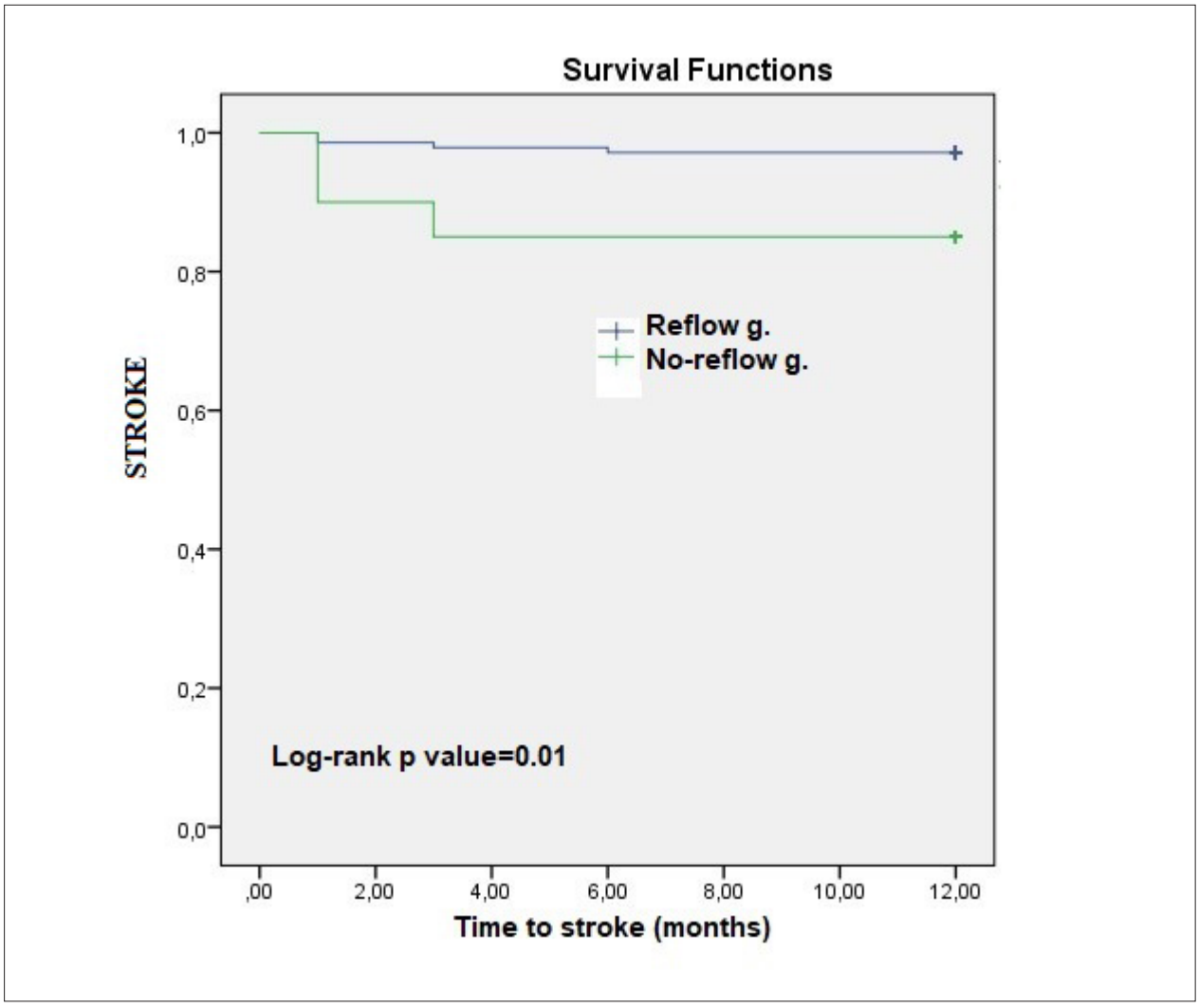

Figure 1 – *Kaplan-Meier curve for Stroke.*

with T-cell proliferation. Published studies have suggested that KIM-1 also interact with other pro-inflammatory proteins.[4-25] Moreover, T-cells have been implicated in the pathophysiology of the post-ischemic injury of the endothelium.[4] The protein structure of KIM-1 acts as an adhesion molecule for the cell surface.[25] Therefore, we speculate that KIM-1 might alter cell adhesion and modulate interactions between the injured epithelial cells and the luminal contents that include casts, debris, and viable epithelial cells that have become dislodged from the intimal endothelium and might cause the CNP. KIM-1 may enhance mobility and proliferation of the surviving epithelial cells.[25] Macrophages and T-lymphocytes are the main source of various cytokines and molecules that interact with endothelial cells, which leads to an aggravation of inflammatory pathways. Endothelial dysfunction, inflammation and unknown increased expression of vasoactive agents, such as endothelin-1 and angiotensin molecules are the main agents responsible for the pathophysiological mechanisms.[4-25] Inflammation plays a major role in CNP development and progression. Therefore, it seems logical to combine these pro-inflammatory pathways to explain the underlying mechanisms of CNP. KIM-1 not only leads to macrophage and T-lymphocyte aggregation but also increases the oxidative cytokine secretion. Increased KIM-1 was associated with systemic inflammation and endothelial dysfunction, and it was defined as a novel inflammation-based prognostic marker in CVD.[6] The main pathophysiological links between KIM-1 and CNP might be cell adhesion, endothelial dysfunction, and pro-inflammation.

The results of this study show that serum KIM-1 concentrations are positively associated with CNP. We propose that inflammation, atherothrombotic microembolization, activation of neutrophils and platelets, which cause the release of oxygen-free radicals, proteolytic enzymes, and proinflammatory mediators that can cause tissue and endothelial damage, particularly in critically injured myocytes during STEMI, are the initial mechanisms of CNP. These common mechanisms also work on every ischemia-sensitive organ, especially on the kidney and heart. KIM-1 can be used

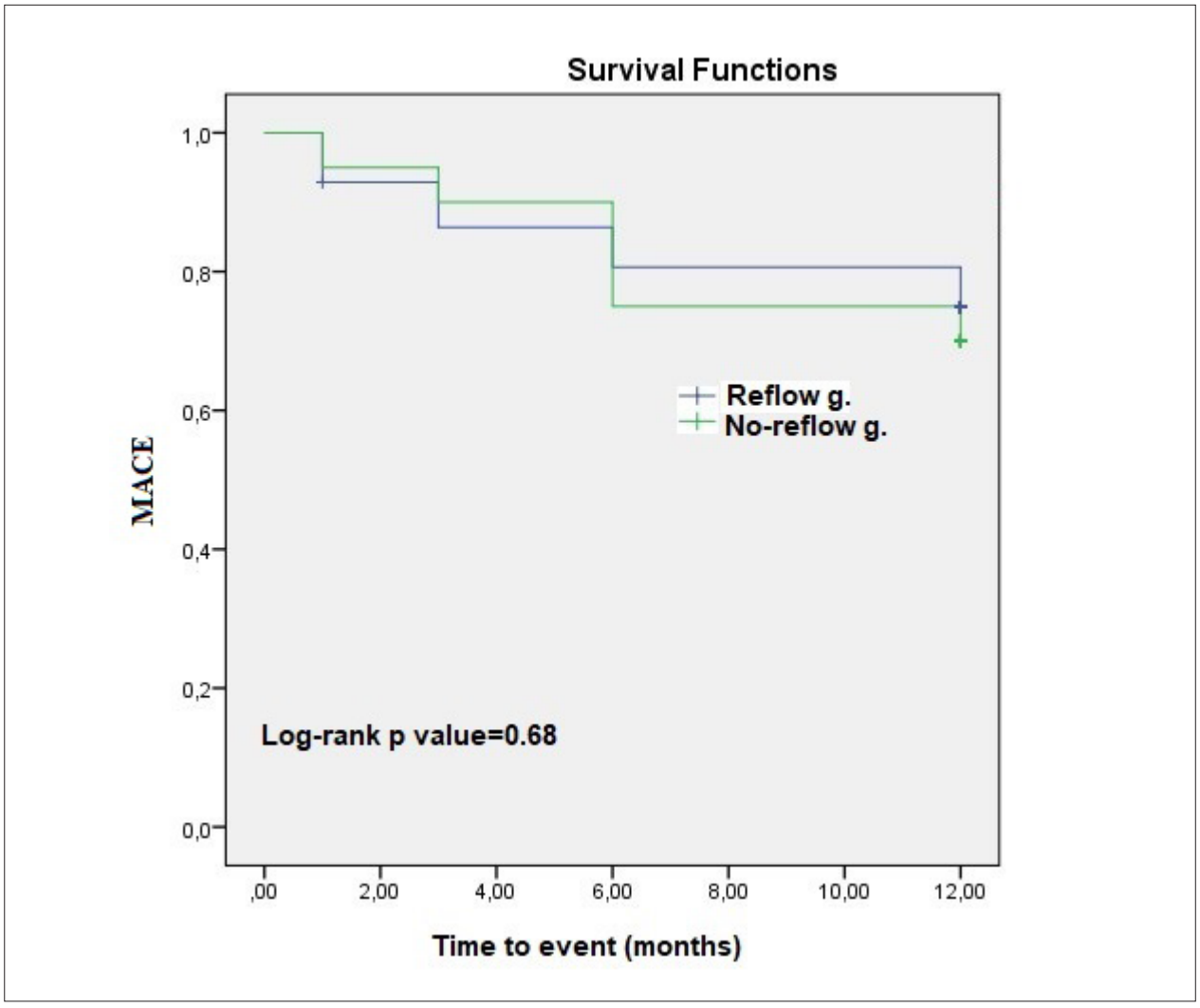

Figure 2 – *Kaplan-Meier curve for MACE.*

Table 4 – Correlations between EuroSCORE II with clinical parameters

Variable	r-value	p-value
Age	0.64	<0.001
eGFR	-0.64	<0.001
Mehran Score	0.77	<0.001
LVEF, (%)	-0.70	<0.001
hs-CRP (mg/dL)	0.24	0.002

r: Spearman's rank correlation coefficient; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; hs-CRP: high-sensitivity C-reactive protein.

Table 5 – Independent predictors of CNP in STEMI

Variable	OR	95% CI	p-value
KIM-1	1.199	1.07-1.343	0.002
HR	0.784	0.696-0.883	<0.001

KIM-1: kidney injury molecule-1; HR: heart rate; bpm: beat per minute; OR: Odds ratio; CI: Confidence interval.

as an early prognostic marker of CNP. However, we did not determine the exact mechanism of KIM-1 in the pathogenesis of this phenomenon. To the best of our knowledge, this is the first report in the literature demonstrating the relationship between KIM-1 and CNP.

Limitations

First: Although we performed a multivariate Cox model to adjust for confounding factors, a bias was unavoidable, because this was a single-center study that included a relatively small sample size. A multicenter study involving more patients could yield more significant results and data. Second: We used only angiographic parameters in determining CNP, the microcirculation was not directly evaluated by contrast echocardiography or by magnetic

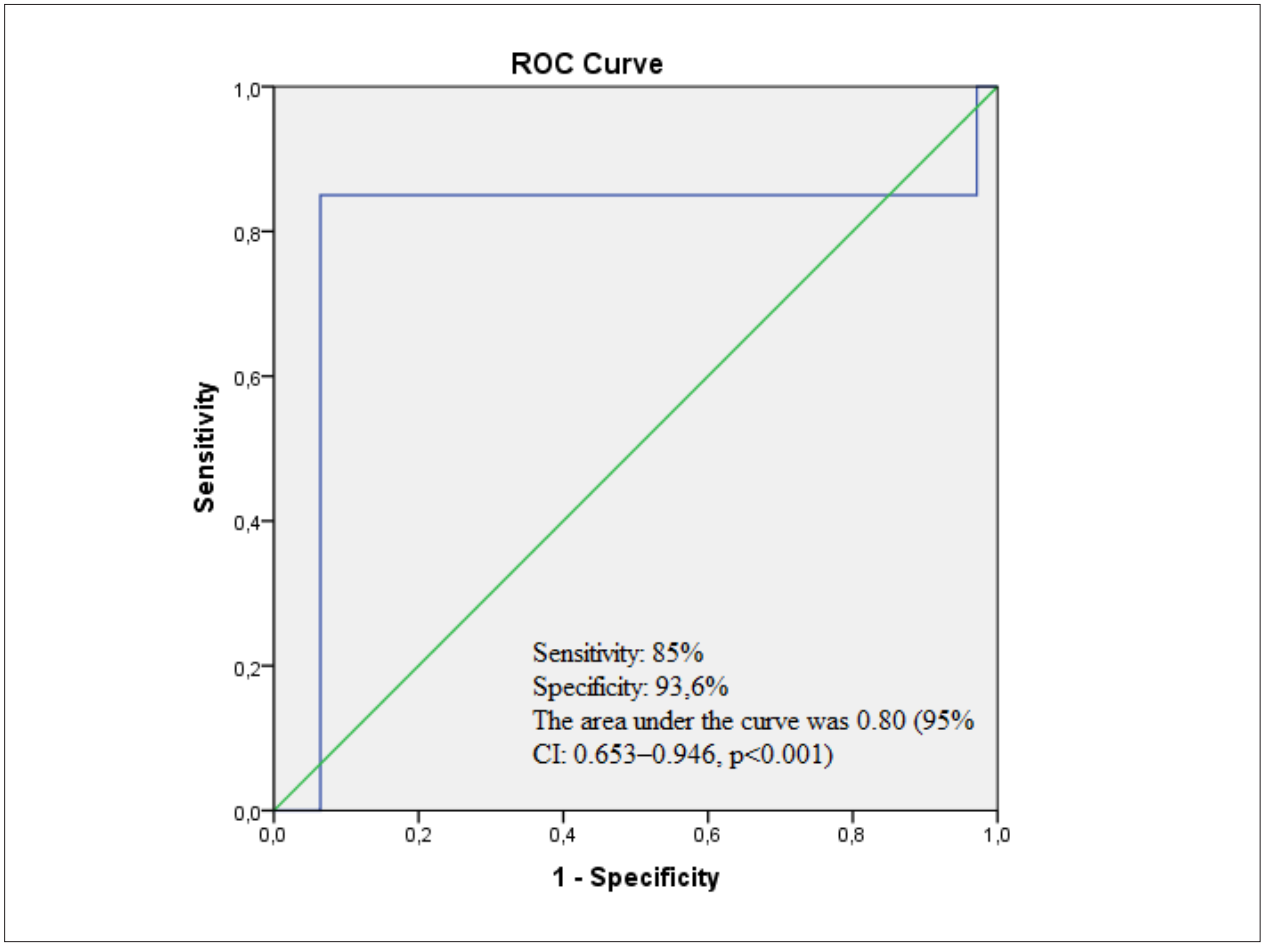

Figure 3 – *ROC analysis curve for the specificity and sensitivity of serum KIM-1.*

resonance imaging to confirm the adequate reperfusion at the microvascular level. These factors are limitations of our study.

Conclusion

In conclusion, inflammation plays a major role in CNP development and progression. Therefore, high concentrations of KIM-1, which is defined as a pro-inflammatory marker, can reflect and lead the underlying mechanisms of CNP. Moreover, baseline serum KIM-1 concentrations and lower HR are the independent predictors of CNP in STEMI patients, and stroke was significantly higher in those patients in one-year follow-up.

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Author contributions

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

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.

References

1. Rezkalla SH, Kloner RA. No-reflow phenomenon. Circulation. 2002 Feb 5;105(5):656-62.
2. Tasar O, Karabay AK, Oduncu V, Kirma C. Predictors and outcomes of no-reflow phenomenon in patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. Coron Artery Dis. 2019 Jun;30(4):270-6.
3. Yarlioglues M, Yalcinkaya D, Celik IE, Duran M. CHA2DS2VASc Score and Coronary No-Reflow Phenomenon. Angiology. 2019 May 23:3319719851698. doi: 10.1177/0003319719851698.
4. van Timmeren MM, van den Heuvel MC, Bailly V, Bakker SJ, van Goor H, Stegeman CA. Tubular kidney injury molecule-1 (KIM-1) in human renal disease. J Pathol. 2007 Jun;212(2):209-17.
5. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004 Sep 23;351(13):1296-305. Erratum in: N Engl J Med. 2008;18(4):4.
6. Gammelager H, Christiansen CF, Johansen MB, Tønnesen E, Jespersen B, Sørensen HT. Three-year risk of cardiovascular disease among intensive care patients with acute kidney injury: A population-based cohort study. Crit Care. 2014 Oct 14;18(5):492.
7. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018;39(2):119–77.
8. Armstrong C, Joint National Committee. JNC 8 Guidelines for the Management of Hypertension in Adults, Am Fam Physician 2014 Oct 1;90(7):503-4.
9. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care. 2003;26(Suppl 1): S5-20.
10. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment Panel III) final report. Circulation. 2002;106:3143-421.
11. Gibson CM, Cannon CP, Daley WL, Dodge JT Jr, Alexander B Jr, Marble SJ, et al. TIMI frame count: a quantitative method of assessing coronary artery flow. Circulation 1996 Mar 1;93(5):879-88.
12. Durante A, Camici PG. Novel insights into an "old" phenomenon: the no reflow. Int J Cardiol. 2015;187:273-80.
13. Ndrepepa G, Tiroch K, Fusaro M, Keta D, Seyfarth M, Byrne RA, et al. 5-year prognostic value of no-reflow phenomenon after percutaneous coronary intervention in patients with acute myocardial infarction. J Am Coll Cardiol. 2010 May 25;55(21):2383-9.
14. Bergman RN, Kim SP, Catalano KJ, Hsu IR, Chiu JD, Kabir M, et al. Why visceral fat is bad: mechanisms of the metabolic syndrome. Obesity (Silver Spring). 2006 Feb;14(suppl 1):16-19.
15. Bakirci EM, Degirmenci H, Duman H, Inci S, Hamur H, Buyuklu M, et al. Increased epicardial adipose tissue thickness is associated with angiographic thrombus burden in the patients with non-st-segment elevation myocardial infarction. Clin Appl Thromb Hemost. 2015 Oct;21(7):612-8.
16. Ipek G, Onuk T, Karatas MB, Gungor B, Osken A, Keskin M, et al. CHA2DS2-VASc score is a predictor of no-reflow in patients with ST-segment elevation myocardial infarction who underwent primary percutaneous intervention. Angiology. 2016 Oct;67(9):840-5.
17. Vlaar PJ, Svilaas T, van der Horst IWC, Diercks GFH, Fokkema ML, de Smet BJGL, et al. Cardiac death and reinfarction after 1 year in the thrombus aspiration during percutaneous coronary intervention in acute myocardial infarction Study (TAPAS): a 1-year follow-up study. Lancet. 2008 Jun 7;371(9628):1915-20.
18. Danzi G, Sesana M, Capuano C, Mauri L, Centurini PB, Baglini R. Comparison in patients having primary coronary angioplasty of abciximab versus tirofiban on recovery of left ventricular function. Am J Cardiol. 2004 Jul 1;94(1):35-9.
19. Hillegass WB, Dean NA, Liao L, Rhinehart RG, Myers PR. Treatment of no-reflow and impaired flow with the nitric oxide donor nitroprusside following percutaneous coronary interventions: initial human clinical experience. J Am Coll Cardiol. 2001 Apr;37(5):1335-43.
20. Amit G, Cafri C, Yaroslavtsev S, Fuchs S, Paltiel O, Abu-Ful A, et al. Intracoronary nitroprusside for the prevention of the no-reflow phenomenon after primary percutaneous coronary intervention in acute myocardial infarction. A randomized, double-blind, placebo-controlled clinical trial. Am Heart J. 2006 Nov;152(5):887. e9-14.
21. Aksu T, Guler TE, Colak A, Baysal E, Durukan M, Sen T, et al. Intracoronary epinephrine in the treatment of refractory no-reflow after primary percutaneous coronary intervention: a retrospective study. BMC Cardiovasc Disord. 2015 Feb 19;15:10.
22. Skelding KA, Goldstein JA, Mehta L, Pica MC, O'Neill WW. Resolution of refractory no-reflow with intracoronary epinephrine. Catheter Cardiovasc Interv. 2002 Nov;57(3):305-9.
23. Capodanno D, Dipasqua F, Marcantoni C, Ministeri M, Zanoli L, Rastelli S, et al. EuroSCORE II versus additive and logistic EuroSCORE in patients undergoing percutaneous coronary intervention. Am J Cardiol. 2013 Aug 1;112(3):323-9.
24. Gul I, Zungur M, Aykan A, Islamli A , Yildiz B , Bilgin M. Importance of EuroSCORE-II in the Development of Acute Ischemic Heart Failure After Acute Anterior ST Elevation Myocardial Infarction. Koşuyolu Heart Journal. 2016; 19(2): 71-65.
25. Ichimura T, Hung CC, Yang SA, Stevens JL, Bonventre JV. Kidney injury molecule-1: a tissue and urinary biomarker for nephrotoxicant-induced renal injury. Am J Physiol Renal Physiol. 2004 Mar;286(3):F552-63.

Galectin-3 Associated with Severe Forms and Long-term Mortality in Patients with Chagas Disease

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Abstract

Background: The histopathological characteristics of Chagas disease (ChD) are: presence of myocarditis, destruction of heart fibers, and myocardial fibrosis. Galectin-3 (Gal-3) is a biomarker involved in the mechanism of fibrosis and inflammation that may be useful for risk stratification of individuals with ChD.

Objectives: We sought to evaluate whether high Gal-3 levels are associated with severe forms of Chagas cardiomyopathy (CC) and whether they are predictive of mortality.

Methods: We studied anti-T. cruzi positive blood donors (BD): Non-CC-BD (187 BD without CC with normal electrocardiogram [ECG] and left ventricular ejection fraction [LVEF]); CC-Non-Dys-BD (46 BD with CC with abnormal ECG but normal LVEF); and 153 matched serum-negative controls. This cohort was composed of 97 patients with severe CC (CC-Dys). We used Kruskall-Wallis and Spearman's correlation to test hypothesis of associations, assuming a two-tailed $p<0.05$ as significant.

Results: The Gal-3 level was 12.3 ng/mL for Non-CC-BD, 12.0 ng/mL for CC-Non-Dys-BD, 13.8 ng/mL for controls, and 15.4 ng/mL for CC-Dys. LVEF<50 was associated with higher Gal-3 levels ($p=0.0001$). In our linear regression adjusted model, we found association between Gal-3 levels and echocardiogram parameters in T. cruzi-seropositive subjects. In CC-Dys patients, we found a significant association of higher Gal-3 levels (≥15.3 ng/mL) and subsequent death or heart transplantation in a 5-year follow-up (Hazard ratio – HR 3.11; 95%CI 1.21–8.04; $p=0.019$).

Conclusions: In ChD patients, higher Gal-3 levels were significantly associated with severe forms of the disease and more long-term mortality, which means it may be a useful means to identify high-risk patients. (Arq Bras Cardiol. 2021; 116(2):248-256)

Keywords: Chagas Disease; Chagas, Cardiomyopathy; Mortality; Galectin-3; Biomarkers; Electrocardiography/methods; Heart Failure.

Introduction

Chagas cardiomyopathy (CC), one of the leading causes of heart disease and death in Latin America, has a poor prognosis compared to noninflammatory cardiomyopathies.[1]

The natural history of Chagas disease (ChD) involves an acute phase, followed by the chronic phase. It is still unknown, however, which patients are more likely to progress to severe forms. Direct parasite injury, inflammation triggered by the immune system, and autonomic dysfunction are role-players in the pathogenesis of CC. When the cardiac tissue is injured, replacement fibrosis appears to be a cause of structural disorganization, geometry, and functional heart impairment.[2]

Galectin-3 (Gal-3) is secreted by activated macrophages and is involved in the fibrogenesis of heart failure (HF). This biomarker has recently been linked to development of HF and mortality. In an experimental model of ChD, Gal-3 promoted cell infiltration in the heart and fibrosis.[3,4]

The lack of a good marker of active infection or incipient CC makes the development of new treatments in this population a challenge. The use of biomarkers that can accurately predict clinical outcomes in CC would have the potential to guide therapy, by identifying patients at higher risk and who would need an earlier, more intensive, and personalized strategy.[5]

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The aim of our study was to evaluate whether high Gal-3 levels are associated with severe forms of CC and whether it is a predictive factor for subsequent mortality or the need for heart transplantation.

Methods

Study Design

Samples were collected during the Retrovirus Epidemiology Donor Study-II (REDS-II),[6] a retrospective cohort study in which *T. cruzi*-seropositive blood donors (BD) were identified by screening blood banks in 1996-2002 (233 from the city of Sao Paulo), in addition to 153 serum-negative control BDs (matched by year of donation, age and gender). This cohort of BD was composed of 97 previously diagnosed cases of CC from the Heart Institute (INCOR) of the Medical School of Universidade de São Paulo. From July 2008 to October 2010, recruited individuals (BD and CC patients) filled in health questionnaires and went through medical evaluations, including electrocardiogram (ECG), echocardiogram (ECHO), and phlebotomy with processing and cryopreservation of samples for subsequent batched blinded analyses of cardiac markers, polymerase chain reaction (PCR) for detection of *T. cruzi*, and other biomarkers (see below).

First, we performed a cross-sectional study in which *T. cruzi*-seropositive participants filled in a questionnaire and received a medical evaluation (laboratory, ECG, and ECHO parameters), resulting in groups stratified by CC status. Then, a longitudinal cohort study was carried out, in which 97 *T. cruzi*-seropositive patients suffering from chronic and more severe CC forms were followed up in an outpatient service from INCOR, in which time-to-event data was available.

All blood samples were collected in EDTA and serum tubes, processed for parasite detection, or submitted to spinning and divided in aliquots. All specimens were frozen in Brazil at -20°C until shipped to the REDS-II Central Laboratory (*Blood Systems Research Institute, San Francisco, CA*) on dry ice and maintained at -70°C.

Four groups were created: a control serum-negative group and three *T. cruzi* seropositive groups: BD without cardiomyopathy, presenting with normal ECG and left ventricular ejection fraction (LVEF) (Non-CC-BD); BD with CC, presenting with ECG abnormalities but normal systolic function (CC-Non-Dys-BD); and participants with CC and left ventricular dysfunction (CC-Dys). The dysfunction was defined as LVEF <50% upon ECHO.

Data regarding time-to-event analysis were available only for CC-Dys subjects. From July to September 2015, we proceeded with CC-Dys patients' chart analysis and phone calls to monitor events and get respective dates.

The local ethics committees approved the study protocol, and all participants signed an informed consent form.

PCR Procedures

From each participant, we collected 20 mL of EDTA-anti-coagulated blood that were immediately mixed with an equal volume of 6 M guanidine hydrochloride -0.2M EDTA solution. The target-capture real-time PCR assay used in this study was developed based on the PCR method described by Virreira et al.,[7] targeting the kinetoplast *T. cruzi* mitochondrial minicircle DNA. The DNA extraction was improved with a target-capture step using magnetic beads coated with a *T. cruzi*-specific 20-mer capture oligonucleotide.

Cardiac Measurements

Resting 12-lead ECGs were recorded (*General Electric MAC 1200 electrocardiograph; GE Healthcare, Waukesha, WI*).[8,9]

Echocardiograms were performed using a Sequoia™ 512 ultrasound machine (*Acuson, Mountain View, CA*), per guidelines by the American Society of Echocardiography.[10,11] Studies were recorded in digital format, and all measurements were made on digital loops using a *Digisonics* offline analysis station (*version 3.2 software; Digisonics, Houston, TX*) at the Cardiovascular Branch, Echocardiography Laboratory, of the National Heart, Lung, and Blood Institute (*Bethesda, MD*).[12]

Soluble Biomarkers

Biomarkers associated with *T. cruzi* infection have been previously described.[12] Blinded plasma samples were tested using Milliplex kits (*Millipore*) with antibody-coated beads for detection of tumor necrosis factor alpha (TNF-α), interleukin (IL) 6 (IL-6), IL-8, IL-10, and interferon gamma (IFNγ). Standard curves and samples were tested in duplicate. Results were acquired on a Labscan 200 analyzer (Luminex) using the Bio-Plex manager software v6.1 (Bio-Rad). IFNγ was predominantly below the threshold of detection (57%).

Concentrations of N-terminal pro B-type natriuretic peptides (NT-proBNPs) and troponin were measured using U.S. Food and Drug Administration-cleared assays on the VITROS System (*Ortho Clinical Diagnostics, Raritan, NJ*).

Plasma Gal-3 levels were determined by an enzyme-linked fluorescence assay and measured on a BioMerieux Vidas 30 system (*BioMerieux, Marcy l'Etoile, Lyon, France*), following the manufacturer's recommendations.

Statistical Analyses

Normality was tested with the Shapiro-Wilk test. Continuous non-normally distributed variables were: age, Gal-3 levels, ejection fraction, and other cardiac and inflammatory biomarkers, being expressed as median and interquartile range. Differences between groups as to variables were compared using the Kruskal-Wallis test, while chi-squared or Fisher's test and logistic regression were used to assess variable type and distribution. Use of ranks in one-criterion variance analysis and post-hoc analysis was made with Dunn's test to evaluate median-value differences between the groups with Bonferroni adjustment for multiple comparisons. For analysis of correlations, the Spearman's correlation was used, reporting p values.

Receiver operating characteristic (ROC) curves were performed for Gal-3 and NT-proBNP to optimize the definition of the cutoff points that would best discriminates the event at follow-up, and an area under the curve (AUC) were identified. Both curves were compared with DeLong and chi-squared tests.

For a time-to-event analysis, the CC-Dys group was divided in two profiles regarding Gal-3 and NT-proBNP cutoff values: low Gal-3 or NT-proBNP (≤ cutoff) and high Gal-3 or NT-proBNP (≥ cutoff). Analysis of incidence of cumulative events across Gal-3 and NT-proBNP strata and the additive value of Gal-3 relative to NT-proBNP was made by a Kaplan-Meier-like method followed by log-rank test.

Bivariate and multivariate Cox proportional-hazards regression models were constructed to evaluate the association of Gal-3 and NT-proBNP values (below *versus* above or equal to the cutoff value) with incident events. Models were adjusted for sex, age, serum creatinine, New York Heart Association (NYHA) classification and LVEF; 95% confidence intervals (CI) were used to depict the association of each marker and the events in the final fitted Cox proportional-hazards model. Sensitivity was analyzed using Gal-3 and NT-proBNP as continuous variables. A two-tailed $p<0.05$ was considered as significant.

All graphs and statistical analyses were made in the software Stata (*version 13.0, Stata Corp., College Station, TX*).

Results

Of the original 570 participants in REDS-II, 483 had samples available for Gal-3 testing; 153 were anti-*T. cruzi* serum-negative BD, and the remainder were sorted into three groups: 187 Non-CC-BD presenting with normal ECG and LVEF; 46 CC-non-Dys; and 97 CC-Dys (Figure 1).

Patient Clinical and Biomarker Characteristics

Demographic and clinical characteristics are described in Table 1. Gal-3 levels were greater in patients from the CC-Dys group, than other clinical groups. Higher Gal-3 levels were also seen in controls when compared with Non-CC-BD. We did not observe significant differences in Gal-3 levels between Non-CC-BD and CC-non-Dys-BD, or between CC-non-Dys-BD and controls. Inflammatory markers (TNF-α, IL-6, IL-8, IL-10), as well as biomarkers associated with, cardiac dysfunction or damage (NT-proBNP and troponin) were elevated in CC-Dys patients compared to other groups (Table 1).

Positive *T. cruzi* PCR indicated a statistically significant difference between Non-CC-BD and CC groups: CC-Non-Dys-BD ($p=0.010$) and CC-Dys. By contrast, no difference in parasitemia was observed when comparing CC-Non-Dys-BD and CC-Dys (Table 1). However, we did not find a significant difference in CC-Dys patients between *T. cruzi* PCR and event occurrence. No significant association between *T. cruzi* PCR and Gal-3 was found.

Among the T. cruzi infected subjects, Spearman's correlation was applied to assess the relationship between Gal-3 and cardiac biomarkers, inflammatory mediators, and parasite load. There was a weak correlation for TNF- ($r_s=0.25$, $p<0.001$) and IL-8 ($r_s=0.22$, $p<0.001$). By contrast, no association between Gal-3 and Troponin, NT-proBNP, IL-6, IL-10, IFN-, or with parasite load was found.

Echocardiography was carried out, and we used Spearman's correlation, to verify any relationship between Gal-3 levels and echocardiographic parameters among T. cruzi infected patients. No moderate or strong statistically significant correlation was found between Gal-3 levels and left ventricular end-diastolic diameter (LVEDD) ($rs=0.09$, $p=0.07$), left ventricular end-systolic dimension (LVESD) ($rs=0.11$, $p=0.03$), LVEF ($r_s=-0.16$, $p=0.001$), left atrial diameter ($r_s=0.11$, $p=0.02$), left atrial volume indexed to body surface area ($r_s=0.09$, $p=0.18$), right atrial area ($r_s=0.032$, $p=0.53$) and septal E/e' ratio ($r_s=0.135$, $p=0.009$).

Survival and Risk Analysis

Time-to-event data were available for 97 patients, with mean follow-up of 51.2 ± 10.8 months and median of 58

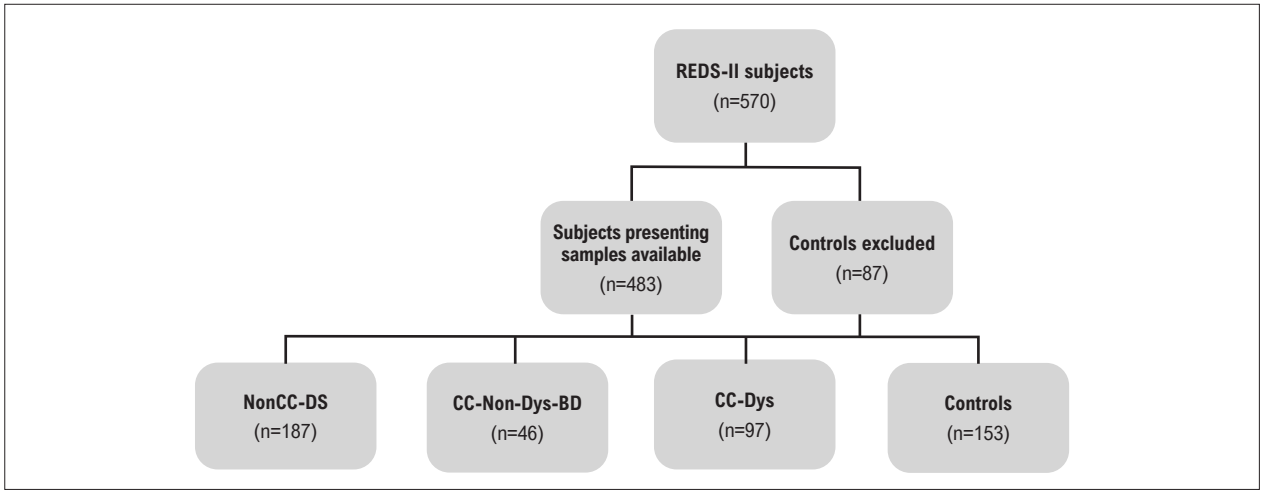

Figure 1 – *Flowchart of inclusion.*
CC: Chagas cardiomyopathy; Non-CC-BD: blood donors with positive T. cruzi serology and without cardiomyopathy, presenting normal electrocardiogram (ECG) and left ventricular ejection fraction (LVEF); CC-Non-Dys-BD: blood donors with positive T. cruzi serology and presenting ECG abnormalities and normal LVEF at rest; CC-Dys: patients with positive T. cruzi serology and CC, with left ventricular dysfunction.

Table 1 – Clinical, laboratory, and echocardiographic findings

	Non-CC-BD	CC-Non-Dys-BD	CC-Dys	Controls	
	n=187 (38.6%)	n=46 (9.5%)	n=97 (20.2%)	n=153 (31.6%)	p-value
Age (y)	49 [41-58]	50 [44-59]	48.5 [43-54]	48 [42-55]	0.20
Male, n (%)	110 (58.8)	29 (63)	59 (60.2)	89 (58.2)	0.39
Ejection fraction (%)	63 [60-65]	60 [55-65]	30 [20-40]	64 [60-65]	<0.001*
Cardiac biomarkers					
Galectin-3 (ng/mL)	12.3 [10-15.4]	12.0 [9.5-14.9]	15.4 [11.8-19.8]	13.8 [11.2-16.2]	<0.001†
NT-proBNP (pg/mL)	40.6 [23.6-66.8]	59 [35.0-109.1]	748 [379.20-2223.41]	27.5 [19.3-48.1]	<0.001‡
Troponin	0.012 [0.01-0.012]	0.012 [0.012-0.015]	0.021 [0.12-0.03]	0.012 [0.012-0.012]	<0.001§
Inflammatory markers					
TNF-α	2.94 [1.64-4.59]	3.02 [1.25-4.69]	3.65 [2.57-5.52]	2.84 [1.62-3.91]	0.002#
IL-6	0.69 [0.32-1.63]	0.77 [0.32-1.8]	1.60 [0.64-3.13]	1.14 [0.32-1.7]	<0.001 **
IL-8	1.61 [0.95-2.79]	1.53 [0.99-2.5]	2.23 [1.38-3.2]	1.44 [0.95-2.54]	0.003††
IL-10	1.28 [0.32-4]	2.02 [0.32-4.11]	4.37 [1.62-8.06]	1.22 [0.32-3.35]	<0.001‡‡
IFN-γ	0.32 [0.32-0.64]	0.32 [0.32-0.84]	0.32 [0.32-1.07]	0.32 [0.32-0.39]	0.06
Parasite load					
Parasite estimate per 20mL	0.05 [0-2.5]	0.68 [0.03-5.47]	1.77 [0.16-5]	-	<0.001§§

p-values were reported for Kruskal-Wallis and Dunn post-hoc hypothesis testing.
Median [interquartile range] reported for all biomarkers tested. Non-CC-BD, blood donors without Chagas cardiomyopathy; CC-Non-Dys-BD, blood donors with Chagas cardiomyopathy; CC-Dys, Chagas cardiomyopathy patients with cardiac dysfunction; NT-proBNP, N-terminal pro B-type natriuretic peptide; TNF, tumor necrosis factor; IL, interleukin; IFN, interferon.
**Statistically significant difference in ejection fraction levels between Non-CC BD/CC-Dys (p<0.001); CC-Non-Dys-BD/CC-Dys (p<0.001); CC-Non-Dys-BD/controls (p=0.042); CC-Dys/controls (p<0.001).*
†Statistically significant difference in Gal-3 levels between Non-CC-BD/CC-Dys (p<0.001); Non-CC-BD/controls (p=0.010); CC-Non-Dys-BD/CC-Dys (p<0.001); CC-Dys/controls (p=0.028).
‡Statistically significant difference in NT-proBNP levels between Non-CC-BD/CC-Dys (p<0.001); Non-CC-BD/controls (p=0.004); CC-Non-Dys-BD/CC-Dys (p<0.001); CC-Non-Dys-BD/controls (p<0.001); CC-Dys/controls (p<0.001).
§Statistically significant difference in troponin levels between Non-CC-BD/CC-Dys (p=0.024); Non-CC-BD/CC-controls (p<0.001); CC-Non-Dys-BD/CC-Dys (p<0.001); CC-Non-Dys-BD/controls (<0.001); CC-Dys/controls (p<0.001).
#Statistically significant difference in TNF-α levels between Non-CC-BD/CC-Dys (p=0.019); CC-Dys/controls (p<0.001).
***Statistically significant difference in IL-6 levels between Non-CC-BD/CC-Dys (p<0.001); CC-Non-Dys-BD/CC-Dys (p=0.032); CC-Dys/controls (p=0.004).*
††Statistically significant difference in IL-8 levels between Non-CC-BD/CC-Dys (p=0.016); CC-Non-Dys-BD/CC-Dys (p=0.039); CC-Dys/controls (p=0.001).
‡‡Statistically significant difference in IL-10 levels between Non-CC-BD/CC-Dys (p<0.001); CC-Non-Dys-BD/CC-Dys (p=0.001); CC-Dys/controls (p<0.001).
§§Statistically significant difference in parasite estimate per 20mL between Non-CC-BD/CC-Dys (p=0.011); Non-CC-BD/controls (p<0.001).

months (range: 8 to 60 months). Events were observed in 28 patients (29%), and were due to three (10.8%) heart transplantations and 25 (89.2%) deaths by all causes. Among event-experienced patients, median concentrations of Gal-3 and NT-pro-BNP were significantly higher, while the ejection fraction was significantly lower. Age, sex, NYHA class >I, ejection fraction on echocardiography, and laboratory data of event-experienced patients are compared in Table 2.

Gal-3 cutoff point (<15.3 ng/mL) by ROC curve was used to divide CC-Dys subjects into two strata (low and high levels), as was the NT-proBNP cutoff point (<1278 pg/mL). ROC identified the potential to reach an event. Although the AUC of NT-proBNP was larger than the Gal-3 AUC, there were no differences (p=0.22).

After adjusting for sex, age, renal function, NYHA functional class >I, and LVEF, we found a significant association of higher levels of Gal-3 with subsequent events in a 5-year follow-up (Table 3 and Figure 2). Complementarily, the risk of events also increased as the levels of NT-proBNP climbed (Table 3). Similar results were seen when Gal-3 and NT-proBNP (by 100-unit increase) were analyzed as continuous variables (Appendix).

Among patients presenting higher Gal-3 levels, we found differences in events when dichotomized with both NT-proBNP strata: patients with additionally high NT-proBNP levels were more likely to experience any event than patients with low NT-proBNP. Moreover, patients in the lower Gal-3 strata, when dichotomized with NT-proBNP levels, were more likely to present any event when NT-proBNP was higher (Figure 3).

Patients in the higher strata of both Gal-3 and NT-proBNP levels had 11 to 16-fold increased risk of event compared with those with the lowest biomarker levels (unadjusted HR, 16.22; 95%CI: 3.71–70.83; p<0.001; adjusted HR, 11.39; 95%CI: 1.97–65.76; p=0.007). Subjects with low Gal-3 and low NT-proBNP had the lowest event rates.

Table 2 – Demographic and laboratory information of CC-Dys patients according to death or heart transplantation

	No events (n=69)	Events (n=28)	p-value
Age (y)	49 [42-54]	47.5 [44.5-52]	0.96
Male, n (%)	42 (61%)	16 (57%)	0.73
Creatinine (mg/dL)	1.01 [0.85-1.14]	1.14 [0.87-1.23]	0.06
Ejection fraction (%)	35 [25-40]	20 [20-30]	0.001
NYHA >1	29	20	0.009
Galectin-3 (ng/mL)	14.4 [10.9-19.1]	18.5 [14.7-23.4]	0.005
Low	39	7	
High	30	21	
NT-proBNP (pg/mL)	542 [281-1337]	2643 [1047-4771]	
Low	50	7	<0.001
High	19	21	
Parasite estimate*	1.77 [0.19-4.2]	1.25 [0.16-12.61]	0.08

*Median [25th, 75th percentile) by death or heart transplantation as an outcome. CC-Dys: patients with positive T. cruzi serology and CC with left ventricular dysfunction; NT-proBNP: N-terminal pro B-type natriuretic peptide; NYHA: New York Heart Association. Low Galectin-3 = <15.3 ng/mL; Low NT-proBNP = <1278 pg/mL. *Parasite load per 20mL.*

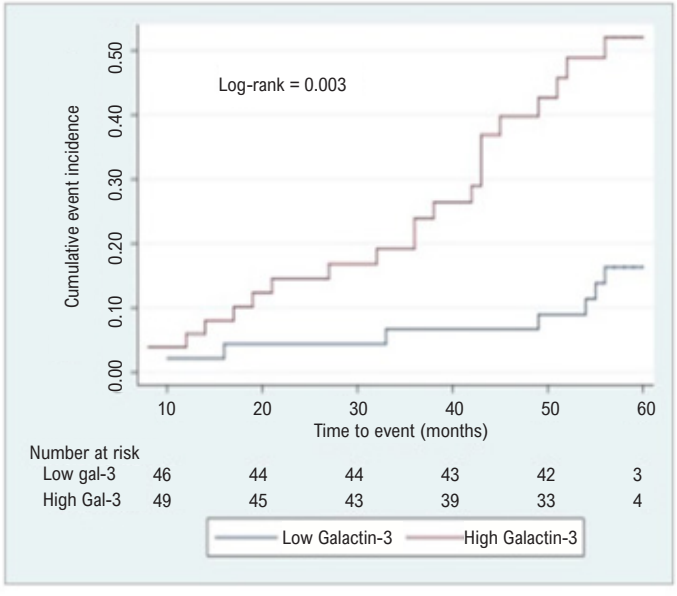

Figure 2 – *Time-to-event curves between Gal-3 levels. Time-to-event curves between stratified Gal-3 levels results in CC-Dys. Cutoff level: Gal-3 <15.3 ng/mL.*

Discussion

Increased Gal-3 was significantly associated with severe forms of ChD and predictive of subsequent morbidity/mortality.

Gal-3 is an emerging biomarker and modulates several physiological processes that contribute to HF, inflammation, and fibrosis.[13-15] Inflammation is a prerequisite for tissue healing and scar formation,[16] and Gal-3 has been shown to play a major role as a mediator in parasitic, viral,[14,17] and bacterial infection.[18] In ChD, experimental studies have shown that Gal-3 has upregulated expression following *T. cruzi* infection in dendritic cells, B cells,[19,20] and CD68+ macrophages. Significantly, CD68+ macrophages represent 50% of the mononuclear cell infiltrate in hearts with CC.[21]

T. cruzi and several immune-mediated mechanisms have a direct involvement in CC. Previous studies have reported

Table 3 – Association between galectin-3 and death or heart transplantation in the CC-Dys subgroup using ROC and Cox regression models, both crude and adjusted for age, sex, serum creatinine level, NYHA functional class >I and LVEF, and using Galectin-3 and NT-proBNP as categorical variables

				Crude Model		Adjusted Model	
	AUC	Cutoff	Cutoff Level	p	HR (95%CI)	p	HR (95%CI)
Galectin-3 (ng/mL)	0.71	15.3	Low				
			High	0.007	3.27 (1.39-7.71)	0.04	2.63 (1.00-6.90)
NT-proBNP (pg/mL)	0.80	1278	Low				
			High	<0.001	5.69 (2.41-13.42)	0.02	3.44 (1.21-9.78)

AUC: area under the curve; CI: confidence interval; HR: hazard ratio; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro B-type natriuretic peptide; NYHA: New York Heart Association; ROC: receiver operating characteristic

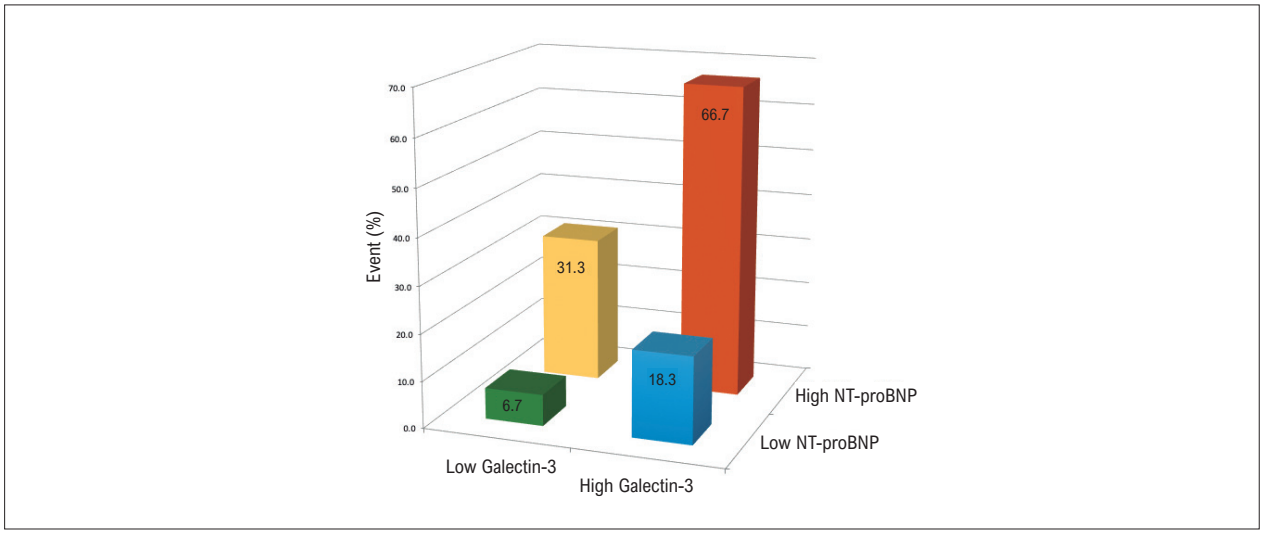

Figure 3 – *Event frequency at 5-year as a function of Gal-3 and NT-proBNP concentrations among CC patients. The percentage of patients who experienced any event is shown for each group. Low Gal-3: values <15.3 ng/mL; high Gal-3: values ≥15.3 ng/mL; low NT-proBNP: values <1,278 pg/mL; high NT-proBNP: values ≥1,278 pg/mL.*

that Gal-3 binds to 45KD, enhancing its adhesion to the extracellular matrix and even its entry into cells. Other studies have shown the importance of Gal-3 in the early process of *T. cruzi* infection, as it allows parasites to accumulate in the extracellular matrix before invading host cells.[22,23]

An experimental model of acute *T. cruzi* infection showed that induction of myocarditis was associated with the upregulation of Col I, Gal-3, IFN-, and IL-13.[21] Gal-3 was primarily detected in interstitial cells and was higher in fibrotic areas. In myocardial areas of fibrosis, the intensity of myocarditis and significant matrix extracellular remodeling was correlated with the presence of Col I and Gal-3. In addition, myofibroblasts can induce fibrosis, which results in myocardial stiffness and cardiac dysfunction. Importantly, myofibroblasts are also a significant source of proinflammatory cytokines, including TNF-α and IL-1, which have a known deleterious effect on the myocardium. However, we did not find any significant association between Gal-3 and inflammatory markers.

Sabino et al.[24] compared the detection of *T. cruzi* DNA with known clinical and laboratory markers of CC severity and observed that the presence of parasitemia was associated with markers of disease progression, such as QRS and QT interval duration, lower LVEF, and elevated troponin and NT-proBNP levels. It was also observed that detection of *T. cruzi* DNA was significantly higher in patients with cardiomyopathy as compared to Non-CC-BD group; however, *T. cruzi* PCR did not correlate with Gal-3. Moreover, there was no significant difference in the detection of *T. cruzi* DNA between CC patients with and without dysfunction, nor between CC patients who did or did not experience events. Thus, in our study, parasitism was a marker of typical ECG changes in cardiomyopathy, but not of disease severity or clinical prognosis.

De Boer et al.[25] suggested that Gal-3 likely represents a unique phenotype at high risk for the development and progression of HF or other cardiovascular diseases. Chronic elevations in Gal-3 induce active fibrogenesis and may provoke pathological cardiac remodeling. De Boer et al.[25] also hypothesized that patients with this phenotype of Gal-3 overexpression are more likely to have a "fibrogenic" pathway for cardiac remodeling. In our study, high levels of Gal-3 were associated with the most severe form of cardiomyopathy, but without a strong association with echocardiographic

parameters. So, Gal-3 levels defined a population with more severe disease, characterized by left systolic and diastolic ventricular dysfunction, higher left and right diastolic diameter, and elevated of NT-proBNP and troponin levels.

Echeverria et al.[26] examined the diagnostic value of a panel of biomarkers to distinguish the severity of CC and found no associations between sST2 and Gal-3 levels. However, the sample size was small and did not include patients with stage A (positive *T. cruzi*, but normal ECG and echocardiography), which could have allowed the examination of the role played by the biomarkers in asymptomatic patients. They also do not provide any prognostic information of Gal-3.

We found higher Gal-3 levels in the control group compared to the Non-CC-BD group. However, the values were lower compared to the CC-Dys group. It is known, since Carlos Chagas' pioneering studies,[27] that up to 60% of infected patients have no evidence suggesting cardiovascular or gastrointestinal involvement. These individuals are thought to have the so-called indeterminate form, defined as Non-CC-BD in our study. As a result, survival in this group of patients appears to be comparable to the general population. Our results showed low Gal-3 levels in this group, which supports this concept.

Galectin-3 phenotype is an important factor in the onset and progression of HF. It is known that HF patients with low Gal-3 levels have slow progression and better outcomes than patients with HF and high Gal-3 levels.[25,28] Gal-3 was shown to predict the development of all-cause mortality and HF in the general population[28] and can be used to define and identify patients with HF at very low risk for 30-day and 180-day mortality, and HF rehospitalizations after an episode of acute HF.[29] A meta-analysis by Chen et al.[30] reported the value of serum Gal-3 as a predictor factor of all-cause mortality and cardiovascular mortality in HF patients.[30]

Our study's most striking finding was the relationship between Gal-3 and the risk of events among patients with CC. Because both Gal-3 and NT-proBNP were independent predictors of adverse events, we also showed that the increase of both markers was associated with the highest rates of death or heart transplantation in patients with CC.

Study Limitations

This was a single-center study with a relatively small sample. In addition, we had only a single-time point measure of Gal-3 and NT-proBNP and, therefore, did not assess dynamic changes in these biomarkers over time. Another limitation was the use of non-parametric tests to analyze associations between continuous variables, resulting in loss of efficiency.

Conclusions

High plasma Gal-3 levels were significantly associated with cardiac dysfunction and CC severity. Our findings suggest that a biomarker-based approach for risk stratification in ChD patients might help physicians identify patients who are more likely to have worse outcomes and potentially guide the development of treatment strategies for this high-risk group.

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Author contributions

Conception and design of the research: Fernandes F, Moreira CHV, Ianni BM, Ramires FJA, Nastari L, Cunha-Neto E, Ribeiro AL, Sabino EC, Mady C; Acquisition of data: Fernandes F, Moreira CHV, Souza-Basqueira M, di Lorenzo C, Nastari L, Ribeiro AL, Keating SM, Sabino EC; Analysis and interpretation of the data: Fernandes F, Moreira CHV, Souza-Basqueira M, Ianni BM, di Lorenzo C, Ramires FJA, Lopes RD, Keating SM, Sabino EC, Mady C; Statistical analysis: Moreira CHV, Ianni BM; Obtaining financing: Fernandes F, Ramires FJA, Nastari L, Sabino EC, Mady C; Writing of the manuscript: Fernandes F, Moreira CHV, Ianni BM, Ramires FJA, Lopes RD, Sabino EC, Mady C; Critical revision of the manuscript for intellectual content: Fernandes F, Moreira CHV, di Lorenzo C, Cunha-Neto E, Lopes RD, Sabino EC, Mady C.

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.

References

1. Nadruz W, Gioli-Pereira L, Bernardez-Pereira S, Marcondes-Braga FG, Fernandes-Silva MM, Silvestre OM, et al. Temporal trends in the contribution of Chagas cardiomyopathy to mortality among patients with heart failure. Heart. 2018;104(18):1522-8.
2. Cunha-Neto E, Coelho V, Guilherme L, Fiorelli A, Stolf N, Kalil J. Autoimmunity in Chagas' disease. Identification of cardiac myosin-B13 Trypanosoma cruzi protein crossreactive T cell clones in heart lesions of a chronic Chagas' cardiomyopathy patient. J Clin Invest. 1996;98(8):1709-12.
3. Filipe MD, Meijers WC, Rogier van der Velde A, de Boer RA. Galectin-3 and heart failure: prognosis, prediction & clinical utility. Clin Chim Acta. 2015;443:48-56.
4. Pineda MA, Cuervo H, Fresno M, Soto M, Bonay P. Lack of galectin-3 prevents cardiac fibrosis and effective immune responses in a murine model of Trypanosoma cruzi infection. J Infect Dis. 2015;212(7):1160-71.
5. Pecoul B, Batista C, Stobbaerts E, Ribeiro I, Vilasanjuan R, Gascon J, et al. The BENEFIT Trial: Where Do We Go from Here? PLoS Negl Trop Dis. 2016;10(2):e0004343.

6. Sabino EC, Ribeiro AL, Salemi VM, Di Lorenzo Oliveira C, Antunes AP, Menezes MM, et al. National Heart, Lung, and Blood Institute Retrovirus Epidemiology Donor Study-II (REDS-II), International Component. Ten-year incidence of Chagas cardiomyopathy among asymptomatic Trypanosoma cruzi-seropositive former blood donors. Circulation. 2013;127:1105-15.

7. Virreira M, Torrico F, Truyens C, Alonso-Vega C, Solano M, Carlier Y, et al. Comparison of polymerase chain reaction methods for reliable and easy detection of congenital Trypanosoma cruzi infection. Am J Trop Med Hyg. 2003;68(5):574-82.

8. Prineas RJ CR, Blackburn H. The Minnesota Code Manual of Electrocardiographic Findings. Littleton, MA: John Wright-PSG; 1982.

9. Ribeiro AL, Sabino EC, Marcolino MS, Salemi VM, Ianni BM, Fernandes F, et al. Electrocardiographic abnormalities in Trypanosoma cruzi seropositive and seronegative former blood donors. PLoS Negl Trop Dis. 2013;7(2):e2078.

10. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005;18(12):1440-63.

11. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. Eur J Echocardiogr. 2009;10(2):165-93.

12. Keating SM, Deng X, Fernandes F, Cunha-Neto E, Ribeiro AL, Adesina B, et al. Inflammatory and cardiac biomarkers are differentially expressed in clinical stages of Chagas disease. Int J Cardiol. 2015;199:451-9.

13. Liu FT, Rabinovich GA. Galectins: regulators of acute and chronic inflammation. Ann N Y Acad Sci. 2010;1183:158-82.

14. Jaquenod De Giusti C, Ure AE, Rivadeneyra L, Schattner M, Gomez RM. Macrophages and galectin 3 play critical roles in CVB3-induced murine acute myocarditis and chronic fibrosis. J Mol Cell Cardiol. 2015;85:58-70.

15. Ma F, Li Y, Jia L, Han Y, Cheng J, Li H, et al. Macrophage-stimulated cardiac fibroblast production of IL-6 is essential for TGF/Smad activation and cardiac fibrosis induced by angiotensin II. PLoS One. 2012;7(5):e35144.

16. de Boer RA, Daniels LB, Maisel AS, Januzzi JL Jr. State of the art: Newer biomarkers in heart failure. Eur J Heart Fail. 2015;17(6):559-69.

17. Sato S, Ouellet M, St-Pierre C, Tremblay MJ. Glycans, galectins, and HIV-1 infection. Ann N Y Acad Sci. 2012;1253:133-48.

18. Mishra BB, Li Q, Steichen AL, Binstock BJ, Metzger DW, Teale JM, et al. Galectin-3 functions as an alarmin: pathogenic role for sepsis development in murine respiratory tularemia. PLoS One. 2013;8(3):e59616.

19. Acosta-Rodríguez EV, Montes CL, Motrán CC, Zuniga EI, Liu FT, Rabinovich GA, et al. Galectin-3 mediates IL-4-induced survival and differentiation of B cells: functional cross-talk and implications during Trypanosoma cruzi infection. J Immunol. 2004;172(1):493-502.

20. Vray B, Camby I, Vercruysse V, Mijatovic T, Bovin NV, Ricciardi-Castagnoli P, et al. Up-regulation of galectin-3 and its ligands by Trypanosoma cruzi infection with modulation of adhesion and migration of murine dendritic cells. Glycobiology. 2004;14(7):647-57.

21. Ferrer MF, Pascuale CA, Gomez RM, Leguizamón MS. DTU I isolates of Trypanosoma cruzi induce upregulation of Galectin-3 in murine myocarditis and fibrosis. Parasitology. 2014;141(6):849-58.

22. Nde PN, Lima MF, Johnson CA, Pratap S, Villalta F. Regulation and use of the extracellular matrix by Trypanosoma cruzi during early infection. Front Immunol. 2012;3:337.

23. Reignault LC, Barrias ES, Soares Medeiros LC, de Souza W, de Carvalho TM. Structures containing galectin-3 are recruited to the parasitophorous vacuole containing Trypanosoma cruzi in mouse peritoneal macrophages. Parasitol Res. 2014;113(6):2323-33.

24. Sabino EC, Ribeiro AL, Lee TH, Oliveira CL, Carneiro-Proietti AB, Antunes AP, et al. Detection of Trypanosoma cruzi DNA in blood by PCR is associated with Chagas cardiomyopathy and disease severity. Eur J Heart Fail. 2015;17(4):416-23.

25. de Boer RA, van der Velde AR, Mueller C, van Veldhuisen DJ, Anker SD, Peacock WF, et al. Galectin-3: a modifiable risk factor in heart failure. Cardiovasc Drugs Ther. 2014;28(3):237-46.

26. Echeverría LE, Rojas LZ, Calvo LS, Roa ZM, Rueda-Ochoa OL, Morillo CA, et al. Profiles of cardiovascular biomarkers according to severity stages of Chagas cardiomyopathy. Int J Cardiol. 2017;227:577-82.

27. Lewinsohn R. Carlos Chagas (1879-1934): the discovery of Trypanosoma cruzi and of American trypanosomiasis (foot-notes to the history of Chagas's disease). Trans R Soc Trop Med Hyg. 1979;73(5):513-23.

28. de Boer RA, van Veldhuisen DJ, Gansevoort RT, Muller Kobold AC, van Gilst WH, Hillege HL, et al. The fibrosis marker galectin-3 and outcome in the general population. J Intern Med. 2012;272(1):55-64.

29. Meijers WC, de Boer RA, van Veldhuisen DJ, Jaarsma T, Hillege HL, Maisel AS, et al., Biomarkers and low risk in heart failure. Data from COACH and TRIUMPH. Eur J Heart Fail. 2015;17(12):1271-82.

30. Chen A, Hou W, Zhang Y, Chen Y, He B. Prognostic value of serum galectin-3 in patients with heart failure: a meta-analysis. Int J Cardiol. 2015;182:168-70.

*Supplemental Materials

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Does Galectin-3 (Myocardial Fibrosis Biomarker) Predict Progression in Chagas Disease?

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Short Editorial related to the article: Galectin-3 Associated with Severe Forms and Long-term Mortality in Patients with Chagas Disease

In recent decades, the epidemiology of Chagas disease (Chd) has changed significantly as a consequence of urbanization and migration.[1] In Brazil, to date, it is the neglected disease with the highest burden, of which ~30% of individuals will progress to the symptomatic tissue disruptive stage within 20 – 30 years after being infected[2] (around 2% per year progress from the indeterminate to the cardiac form, according to a contemporary study).[3]

Persistent myocardial inflammation and fibrosis represent the main pathological characteristics of Chd that would be correlated with its progression.[4,5] The use of myocardial fibrosis biomarkers to predict progression in patients with normal or near normal LV function is certainly important in Chd, where traditional risk factors, such as LVEF, may not be as useful. Nevertheless, studies have shown the value of myocardial fibrosis biomarkers in the progression of Chd pathogenesis.[6]

In this edition, Fernandes et al.[7] present data that contributes to our understanding related to the burden of myocardial fibrosis in different stages of Chd. To this end, the authors assessed the presence (or not) of Galectin-3 (Gal-3), a myocardial fibrosis biomarker, in different stages of the disease compared to a control group and whether it is associated with mortality or need for a heart transplant in the most advanced stage of the disease. For this purpose, 2 studies with different designs were carried out. Initially, in order to stratify the groups by the Chagas cardiomyopathy (CC) status using a cross-sectional study design, 330 patients seropositive for *T. cruzi* (187 without cardiomyopathy; 46 CC-abnormal ECG and LVEF>50%; and 97 CC-abnormal ECG with LVEF<50%) were included, in addition to 153 seronegative controls (matched by age and gender). Of these seropositive patients, 97 with more severe cardiac forms of CC were part of the prospective longitudinal study censored until the event (mortality or need for a heart transplant).

The results were summarized and analysed in the different groups. The median age was 49 ± 9.2 years, with a median follow-up of 58 months. Chagas disease patients without cardiomyopathy (n = 187) and those with cardiomyopathy and LVEF >50% (n = 46) had Gal-3 levels similar to those of healthy controls (n = 153), but those with cardiomyopathy and LVEF <50% (n = 97) had significantly higher Gal-3 levels than the healthy controls (p = 0.0001). A significant correlation was observed between Gal-3 levels and LVEF (r_s=-0.16, p=0.001). Events were observed in 28 patients (29%). In patients with cardiopathy and LVEF< 50%, the adjusted linear regression model showed a significantly association between Gal-3 levels and death or heart transplantation during a five-year follow-up (Hazard ratio - HR 3.11; 95% CI = 1.21–8.04; p = 0.019). The authors concluded that in patients with the cardiac form, higher Gal-3 levels were significantly associated with severe forms of the disease and a higher long-term mortality rate, which means that they can be effectively used to identify high-risk patients.

Nevertheless, the major findings of Fernandes et al.[7] were as follows: First, Gal-3 levels did not show any difference between normal individuals and Chd patients without cardiomyopathy and with cardiomyopathy / LVEF >50%. This observation suggests that Gal-3 levels in this patient sample could be not used as a marker of myocardial disease progression . The second important finding of this study was that the higher Gal-3 levels were significantly associated with the severe forms of the disease and a higher long-term mortality rate. This result is not unique to Chd, as similar findings were seen in the studies by Nagase et al.[8] and Spinale.[9]

The interpretation of these results should consider the small number of patients who had a five-year follow-up and single center experience already quoted by the authors. In the group of patients with cardiomyopathy and LVEF <50%, different degrees of myocardial involvement were possibly used, since there was a wide spectrum of LVEF (ranging from 20% to 40%) leading to different patient profiles included in the groups.[7] It is noticeable that the rate of events was low and significantly inferior to that of the Rassi high risk cohort (annual mortality rate of 5.8% vs. 12.6%); thus, the results from the multivariate analyses, which included 5 independent variables, should be taken with caution due to likely model oversaturation.

One of the mayor challenges in Chd is the difficulty in identifying at an early stage the infected subjects who will be part of those 20% to 30% who might develop cardiomyopathy. Unfortunately, at present there is no way to predict this possible progression. Thus, finding reliable biomarkers of disease progression would mean the greatest leap forward in the history of Chd since its discovery in 1909 by Dr. Carlos Chagas. For this reason, there are numerous research groups devoted to the search of both host-derived and T. cruzi-derived biomarkers.[10] This would mean a breakthrough in the management of Chd

Keywords

Galectin 3; Apoptosis; Endomyocardial Fibrosis;Chagas Disease Biomarkers.

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References

1. Martins-Melo FR, Carneiro M, Ramos Jr AN, Heukelbach J, RibeiroALP, Werneck GL. The burden of Neglected Tropical Diseases in Brazil, 1990-2016: A subnational analysis from the Global Burdenof Disease Study 2016. PLoS Negl Trop Dis. 2018; 12(6):e0006559.
2. Nunes MCP, Beaton A, Acquatella H, Bern C, Bolger AF, Echeverría LE et al. Chagas Cardiomyopathy: An Update of Current Clinical Knowledge and Management A Scientific Statement From the American Heart Association. Circulation. 2018 Sep 18;138(12):e169-e209.
3. Sabino EC, Ribeiro AL, Salemi VM, Di Lorenzo OC, Antunes AP, Menezes MM, et al. Ten-year incidence of Chagas cardiomyopathy among asymptomatic Trypanosoma cruzi-seropositive former blood donors. Circulation 2013; 127(10):1105-15.
4. Chaves AT, Menezes CAS, Costa HS, Nunes MCP, Rocha MOC. Myocardial fibrosis in chagas disease and molecules related to fibrosis. Parasite Immunol 2019; 41(10): e12663.
5. Bonney KM, Luthringer DJ, Kim SA, Garg NJ, Engman DM. Pathology and Pathogenesis of Chagas Heart Disease. Annu Rev Pathol 2019; 14: 421-47.
6. L. Giordanengo L, Gea S, Barbieri G, Rabinovich GA. Anti-galectin-1 autoantibodies in human Trypanosoma cruzi infection: differential expression of this β- galactoside-binding protein in cardiac Chagas' disease. Clin. Exp. Immunol 2001; 124(2):266–73.
7. Fernandes F, Moreira CHV, Oliveira LC, Souza-Basqueira M, Ianni BM, di Lorenzo C, et al. Galectina-3 Associada a Formas Graves e Mortalidade em Longo Prazo em Pacientes com Doença de Chagas. Arq Bras Cardiol. 2021; 116(2):248-256.
8. Nagase H, Visse R, Murphy G. Structure and function of matrix metalloproteinases and TIMPs. Cardiovasc Res 2006; 69(3):562-73.
9. Spinale FG. Myocardial matrix remodeling and the matrix metalloproteinases: influence on cardiac form and function. Physiol Rev 2007; 87(4):1285-342.
10. Linhares-Lacerda L, Granato A, Gomes-Neto JF, Conde L, Freire-de-Lima L, de Freitas EO, et al. Circulating Plasma MicroRNA-208a as Potential Biomarker of Chronic Indeterminate Phase of Chagas Disease Front Microbiol. 2018 Mar 6;9:269. Referências

The Role of Stress Echocardiography in the Early Detection of Diastolic Dysfunction in Non-Severe Chronic Obstructive Pulmonary Disease Patients

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Abstract

Background: Exertional dyspnea is a common complaint of patients with heart failure with preserved ejection fraction (HFpEF) and chronic obstructive pulmonary disease (COPD). HFpEF is common in COPD and is an independent risk factor for disease progression and exacerbation. Early detection, therefore, has great clinical relevance.

Objectives: The aim of the study is to detect the frequency of masked HFpEF in non-severe COPD patients with exertional dyspnea, free of overt cardiovascular disease, and to analyze the correlation between masked HFpEF and the cardiopulmonary exercise testing (CPET) parameters.

Methods: We applied the CPET in 104 non-severe COPD patients with exertional dyspnea, free of overt cardiovascular disease. Echocardiography was performed before and at peak CPET. Cut-off values for stress-induced left and right ventricular diastolic dysfunction (LVDD/ RVDD) were E/e'>15; E/e'>6, respectively. Correlation analysis was done between CPET parameters and stress E/e'. A p-value <0.05 was considered significant.

Results: 64% of the patients had stress-induced LVDD; 78% had stress-induced RVDD. Both groups with stress LVDD and RVDD achieved lower load, lower V'O_2 and O_2-pulse, besides showing reduced ventilatory efficiency (higher VE/ VCO_2 slopes). None of the CPET parameters were correlated to stress-induced left or right E/e'.

Conclusion: There is a high prevalence of stress-induced diastolic dysfunction in non-severe COPD patients with exertional dyspnea, free of overt cardiovascular disease. None of the CPET parameters correlates to stress-induced E/e'. This demands the performance of Exercise stress echocardiography (ESE) and CPET for the early detection and proper management of masked HFpEF in this population. (Arq Bras Cardiol. 2021; 116(2):259-265)

Keywords: Echocardiography,Stress/methods; Heart Failure,Diastolic; Stroke Volume; Pulmonary Disease,Chronic Obstructive; Respiratory Funstion Tests

Introduction

Cardiovascular abnormalities are common in chronic obstructive pulmonary disease (COPD).[1,2] Arterial stiffness is present even in mild COPD patients free of cardiovascular diseases. It is an independent cardiovascular risk factor that contributes for the development of diastolic dysfunction.[3] Dyspnea and exercise intolerance are common symptoms for both COPD and diastolic dysfunction.[4] Recent studies with large patient cohorts have identified a cardiovascular phenotype in COPD patients who present with a different clinical course and prognosis.[5] Early diagnosis and management is, therefore, very important from the clinical point of view.

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Cardiopulmonary exercise testing (CPET) may distinguish cardiac and respiratory dyspnea or diminished physical activity.[6-9] The combination of exercise stress-echocardiography (ESE) and CPET is a reliable approach to identify patients with masked heart failure with preserved ejection fraction (HFpEF). Moreover, the results from invasive measurements are comparable to data obtained with non-invasive studies during ESE.[10]

The aims of our study were: 1) to detect the frequency of subclinical left ventricular (LV) and right ventricular (RV) diastolic dysfunction in non-severe COPD patients free of cardiovascular disease; 2) to establish a correlation between cardiopulmonary exercise and echocardiographic parameters for diastolic dysfunction (E/e').

Materials and Methods

Patients and Study Protocol

This was a retrospective study conducted with 224 clinically stable outpatients diagnosed with COPD at the University

Hospital for Respiratory Diseases "St. Sophia", Sofia. Only 163 of them met the inclusion criteria for non-severe COPD – forced expiratory volume in the first second higher than 50% (FEV_1>50%). All subjects had exertional dyspnea, but a total of 104 patients (64 men, 40 women; mean age of 62.9±7.5 years) were considered eligible, assuming the exclusion criteria. The recruitment period was between May 2017 and April 2018, and was approved by the local Ethics Committee (protocol 5/12.03.2018). All participants signed the informed consent form before the study initiation.

The following exclusion criteria were considered: 1) left ventricular ejection fraction (LVEF) <50%; 2) left ventricular diastolic dysfunction at rest higher than first grade; 3) echocardiographic findings suggesting pulmonary hypertension (systolic pulmonary arterial pressure >36 mmHg, tricuspid regurgitation (TR) jet maximum velocity >2.8 m/s; 4) valvular heart disease; 5) documented cardiomyopathy; 6) severe uncontrolled hypertension (systolic blood pressure >180 mmHg and diastolic blood pressure >90 mmHg); 7) atrial fibrillation or malignant ventricular arrhythmia; 8) ischemic heart disease; 9) anemia; 10) diabetes mellitus; 11) cancer; 12) chronic kidney disease (CKD); 13) recent chest or abdominal surgery; 14) recent exacerbation (over the last three months); 15) recent change (over the last three months) in medical therapy.

Procedures

Pulmonary Function Testing

All subjects underwent preliminary clinical examination including chest X-ray, spirometry, electrocardiography, echocardiography. Patients eligible for the study performed spirometry and an exercise stress test. They were performed on Vyntus, Cardiopulmonary exercise testing (Carefusion, Germany), in accordance with the European Respiratory Society (ERS) guidelines.[11] Only patients with mild to moderate airway obstruction (FEV1 >50%) were selected.

Stress Test Protocol – Cardiopulmonary exercise testing (CPET)

A continuous ramp protocol was applied according to guidelines.[6] After two minutes of unloaded pedaling (rest phase 0W), a three-minute warm-up phase (20W) followed. The test phase included 20W/2min load increments. Patients were instructed to pedal with 60 rotations per minute.

Expiratory gases were collected on a breath-by-breath basis. Peak VO_2 was expressed as the highest 30-second average value, obtained during the last stage of the exercise test. The peak values of VO_2 are expressed as -O_2 ml/kg/min. Ventilatory efficiency (VE/VCO_2) was measured by the V-slope method. Peak respiratory exchange ratio (pRER) was the highest 30-second value averaged in the last stage of the test. RER >1.10 at the end of the ESE-CPET test was considered as achievement of maximal effort.

Echocardiographic Methods

M-mode, two-dimensional and Doppler echocardiography were performed.[12,13] Apical four-chamber views were used to measure chamber volumes based on Simpson's modified rule and LV ejection fraction was considered preserved if >50%. Doppler tissue echocardiography (DTE) analysis was performed in the septal-lateral dimension of mitral annulus, and lateral dimension of tricuspid annulus to assess myocardial systolic (S) and diastolic (E', A') waves of LV and RV. The E' value was used as average of medial and lateral measurements. Peak E/e' ratio >15 was considered a marker for stress-induced left ventricular diastolic dysfunction.

Right ventricular systolic function was assessed using tricuspid annular plane systolic excursion (TAPSE) and tissue Doppler S peak velocity. Right ventricular wall thickness (RVWT) was measured from the subcostal long-axis view at the tip of the anterior tricuspid leaflet in end-diastole. Pulmonary pressure was calculated directly by sampling the tricuspid insufficiency and indirectly by the acceleration time (AT) on pulmonary flow. Right atrium volume index (RAVI) was measured with the right ventricular end-systolic volume by the Simpson's modified rule. Stress-induced RV diastolic dysfunction was considered if stress-induced E/e' ratio >6. All parameters were measured at end-expiration and in triplicate during different heart cycles.[14]

Statistical Analysis

Demographic and clinical data were presented with descriptive statistics. The Kolmogorov-Smirnov test was used to explore the normality of distribution. Continuous variables in each group of subjects were expressed as median and interquartile range when data was not normally distributed and as mean ± standard deviation (SD) if normal distribution was observed. Categorical variables were presented as proportions. Data were compared between patients with and without LVDD, as well as between patients with and without RVDD. The unpaired Student's t test was used to analyze normally distributed continuous variables. The Mann-Whitney-U test was used in other cases. Categorical variables were compared by the χ^2 test or the Fisher's exact test. The Spearman's rank correlation was used to assess the association between CPET parameters and stress-induced E/e' ratio for the left and right ventricles.

In all cases, a p value of less than 0.05 was considered significant, as determined with SPSS® 13.0 Software (SPSS, Inc, Chicago, Ill) statistics.

Results

In the COPD group, 30% (32/104) of patients had grade I LVDD at rest; 14% (15/104) had grade I RVDD at rest and only 3% (4/104) had both RV and LVDD at rest. After CPET, the stress-echocardiography established that 64% (67/104) of the subjects had stress-induced LVDD, and 78% (82/104) had stress-induced RVDD. All patients with stress-induced LVDD also had stress-induced RVDD. The demographic and clinical data of patients are listed in Table 1. The echocardiographic parameters of patients are shown in Table 2. Except for RAVI, RVWT, acceleration time and systolic pulmonary arterial pressure after load, no other significant differences were found between patients with and without LVDD (Tables 1 and 2). The results for patients with and without RVDD were similar (Tables 1 and 2).

Table 1 – Anthropometric and cardiopulmonary characteristics of patients with and without LVDD and RVDD

	Patients w/o stress LVDD (37)	Patients with stress LVDD (67)	Patients w/o stress RVDD (22)	Patients with stress RVDD (82)
Demographic data				
Age, year	60.44 ± 7.72	64.16 ± 6.97*	6.95±7.36	63.74±7.60*
Male:Female gender, n	21:16	44:23‡	14:8	50:32‡
Packet, years	27.21 (23.87-31.76)	33.79 (30.51± 37.87)†	26.52 (23.46-30.43)	32.11(28.82-36.13)‡
Body mass index, kg/m^2	27.00 (24.75-31.00)	27.96 (22.75-30.75)†	28.00 (25.25-30.5)	26.52 (22.72-30.61)†
Respiratory function				
FVC, l/min	2.06 (1.76-3.09)	2.34 (1.77-3.09)†	2.05 (2.11-3.73)	2.21 (1.71-2.93)†
FEV_1, l/min	1.31 (0.94-1.53)	1.36 (1.14-1.75)†	1.60 (1.15-2.42)	1.52 (1.14-1.75)†
FEV_1/FVC %	60.5 (46.91-67.47)	53.30 (45.76-66.55)†	65.50 (54.81-68.82)	62.59 (46.57-66.79)†
Acid-base balance				
pO_2, mmHg	68.60(63.4-71.8)	71.35 (64.7-74)†	67.20 (63.56-71.68)	70.6 (63.2-74)†
pCO_2, mmHg	32.30 (30.1-35.37)	37.65 (32.5-40)†	34.73 (31.27-39.21)	35.7 (32.5-40)†
Sat, %	94.9 (94.4-95.25)	95.00 (94.02-95.67)†	94.75 (92.67-95.0)	95.00 (93.9-95.5)†
CPET parameters				
Peak Load, W	82.75 (69.8-89.1)	▪ 76.05 (68.4-92.1)†	86.66 (78.65-94.76)	▪▪73.08 (68.93-83.16)†
Peak VE, l/min	40 (34-52.5)	38.50 (32-48)†	41.1 (32.12-48.17)	39.07 (31.89-48.32)†
Peak V'O_2, ml/min/kg	14.30(12.6-16.15)	13.90 (12.67-15.7)†	14.30 (12.6-16.15)	13.40(15.77-12.55)†
RER	1.06 (0.98-1.19)	1.09 (1.00-1.28)†	1.05 (0.98-1.18)	1.08 (1.01-1.19)†
Peak O_2 pulse ml/min/kg	9.80 (9.5-12.2)	▪7.90 (6.15-9.32)†	9.51 (9.02-13.1)	▪▪7.92(6.27-9.84)†
Peak VE/VCO_2 slope	34.08 (33.98-36.72)	▪36.93 (34.19-38.74)†	34.11 (33.78-36.89)	▪▪36.98 (34.26-38.91)†

**Unpaired t test; †Mann-Whitney U test; ‡chi-square test; §Abbreviations: LVDD: left ventricular diastolic dysfunction; RVDD: right ventricular diastolic dysfunction; O_2 pulse: oxygen pulse; FVC: forced vital capacity; VE: minute ventilation; RER: respiratory exchange ratio; V'O_2: oxygen consumption; VE/VCO_2 slope: ventilatory efficiency; ▪p<0.05 between patients with and without LVDD; ▪▪p<0.05 between patients with and without RVDD.*

Exercise capacity was reduced in COPD patients with stress-induced right and left diastolic dysfunction, compared to those without it (Table 1). The COPD-RVDD/LVDD patients achieved lower load, lower VO_2 and O_2-pulse. They performed with significantly higher VE/VCO_2 slopes (Table 1). None of the CPET parameters was associated with stress-induced left or right E/e' ratio (Table 3.)

Discussion

Our main findings were: 1) 64% of the patients with non-severe COPD and exertional dyspnea who are free of clinically evident cardiovascular disease have stress-induced LVDD; 1) 78% of the same group of patients have stress-induced RVDD; 3) none of the CPET parameters was correlated with stress-induced E/e' ratio either in the left or the right ventricle. To our knowledge, this is the first study using combined ESE-CPET in non-severe COPD patients with exertional dyspnea and free of overt cardiovascular diseases. Stress-induced increase of E/e' ratio >15 of the left ventricle was detected in 64% of them; stress-induced elevation of E/e' ratio >6 of the right ventricle was met in 78% of cases. We cannot compare our data to other studies of non-severe COPD patient populations because most of them report on the incidence of diastolic dysfunction at rest+[15-17]

Nedeljkovic et al. performed ESE in a population of 87 hypertensive patients with exertional dyspnea and normal left ventricular function. They found in 9.2% of the patients a stress ratio E/e' >15.[18] Kaiser et al. also investigated a general population of 87 patients with exertional dyspnea and reported diastolic dysfunction in 9% of them.[19]

The higher prevalence of stress diastolic dysfunction that we describe in COPD patients confirms that COPD itself is a cardiovascular risk factor.[20,21] Arterial stiffness is a feature of COPD, regardless of the smoking burden. The ventricular wall stress seen during respiration is also reported as an independent pathophysiological mechanism for LV remodeling in mild COPD patients without overt cardiovascular pathology.[22] Both arterial stiffness and ventricular wall stress cause diffuse LV fibrosis in COPD patients free of cardiovascular diseases.[23,24]

In our study, patients with stress-induced diastolic dysfunction (both LVDD and RVDD) achieve lower load, VO_2 and O_2-pulse and perform with significantly higher VE/VCO_2 slopes. None of the CPET parameters, however, correlates with stress E/e' ratio (neither in LV nor RV). These findings are similar to what have been reported in the general population. Nedeljkovic et al. detected lower load, lower oxygen consumption and lower ventilatory efficiency in hypertensive patients with exertional dyspnea and stress-induced LVDD.[18] Kaiser et al. described increased heart rate reserve and reduced oxygen pulse in a general population of patients with exertional dyspnea.[19] Guazzi et al. also

Table 2 – Echocardiographic parameters of patients with and without LVDD and RVDD

	Patients w/o stress LVDD (37)	Patients with stress LVDD (67)	Patients w/o stress RVDD (22)	Patients with stress RVDD (82)
LV structural parameters				
LVEF, %, Simpson	63.50(60-66)	60.00(57-65)*	65.00(60-66)	61.00 (67-65)*
Septum, mm	12.00(11-13)	12.00(11-13) *	12.00 (11-12.75)	12.00 (11-13)*
PW, mm	12.00(11.75-12)	12.00(11-13) *	12.00 (11.25-12.75)	12.00 (11-13)*
LV functional parameters at rest				
E/A ratio	0.79(0.75-0.85)	0.85 (0.76-1.20)*	0.78 (0.76-0.83)	0.84 (0.75-1.21.)*
E/e' aver ratio	6.66 (6.25-8.33)	6.97 (5.76-8.15)*	6.96 (6.27-8.33)	6.66 (5.63-8.1)*
LV functional parameters after exercise stress test				
E/A ratio	1.25(0.8-1.5)	ǂ1.73 (1.55-2.00)*	1.22 (0.88-1.37)	ǂǂ1.71 (1.5-2.00)*
E/e' aver	8.07 (6.7-9.6)	ǂ17.33 (15.71-8.46)*	8.12 (7.25-10)	ǂǂ17.14 (14.66-18.39)*
RV structural parameters				
RAVI, ml/m^2	17.57 (16.07-19.97)	ǂ22.66 (21.31-24.13)*	16.55 (15.81-17.54)	ǂǂ22.27 (20.65-23.85)*
RWT, mm	5.00 (4.5-6.5)	ǂ6.50 (6-7)*	5.00 (4.12-5.00)	ǂǂ6.50 (6.00-7.00)*
TAPSE,mm	23.00 (22.00-26.00)	22.00 (21.00-23.00)*	23.00 (21.25-26.00)	22.00 (21-23.5)*
RV functional parameters at rest				
E/A ratio	0.83 (0.75-0.95)	0.69 (0.62-0.75)*	0.83 (0.76-1.16)	0.71 (0.66-0.83)*
E/e' aver	5.47 (4.56-5.69)	4.16(3.33-5.00)*	5.47 (4.56-5.69)	4.54(3.33-5.22)*
AT, msec	170 (163.75-180)	170(160-180)*	170 (165-180)	170(160-180)*
sPAP, mmHg	26.00 (25-28)	28.00 (25-30)*	25.00 (23-27)	28.00 (25-30)*
RV functional parameters after exercise stress test				
E/A ratio	1.26 (1.09-1.48)	1.31(1.18-1.49)*	1.28 (1.14-1.5)	1.37 (1.22-1.52)*
E/e' aver	6.21 (5.38-7.89)	10.83 (9.04-13.23)*	6.92 (5.46-8.00)	ǂǂ11.25 (9.00-13.33)*
AT, msec	165(155-175)	ǂ105(95-110)*	162.5(155-170)	ǂǂ110(95-115)*
sPAP, mmHg	32.00(30-33.25)	ǂ38.00 (36-42)*	32.00 (30-33.75)	ǂǂ 38.00 (35-40)*

**Mann-Whitney U test; LVDD: left ventricular diastolic dysfunction; RVDD: right ventricular diastolic dysfunction; LVEF: left ventricular ejection fraction; RAVI: Right atrium volume index; TAPSE: tricuspid annular plane systolic excursion; PW: posterior wall; SPAP: systolic pulmonary arterial pressure; RWT: right ventricular wall thickness; AT: accelaration time. ǂp<0.05 between patients with and without LVDD; ǂǂp<0.05 between patients with and without RVDD.*

Table 3 – Correlation analysis between respiratory and cardiopulmonary exercise testing parameters with stress-induced E/e' ratio for the left ventricle/right ventricle, respectively

Parameters	LVDD		RVDD	
	Spearman rho	p-value	Spearman rho	p-value
Peak Load , W	0.02	0.84	0.03	0.78
Peak VE, l/min	0.02	0.85	0.12	0.28
PeakVO_2, ml/min/kg	0.12	0.56	0.03	0.73
RER	0.06	0.74	0.12	0.27
PeakO_2 pulse ml/min/kg	0.10	0.60	0.11	0.32
Peak VE/VCO_2 slope	0.35	0.07	0.02	0.80
FVC, l/min	0.28	0.11	0.10	0.34
FEV_1, l/min	0.01	0.95	0.04	0.71

LVDD: left ventricular diastolic dysfunction; RVDD: right ventricular diastolic dysfunction; RER: respiratory exchange ratio; VO_2: oxygen consumption; VE/VCO_2 slope: ventilatory efficiency; FVC: forced vital capacity; VE: minute ventilation.

established an association between diastolic dysfunction (E/e' ratio) and peak oxygen consumption, ventilatory efficiency and heart rate recovery.[25] In Guazzi's group of patients with overt cardiovascular pathology and normal echocardiography at rest, ventilatory efficiency correlated best to peak E/e' ratio>15. The clinical advantage of VE/VCO_2 ratio as the best predictor of stress E/e' ratio was also confirmed in the diastolic heart failure patients analyzed by Nedeljkovic et al.[18] Kaiser et al. do not support such conclusions, emphasizing the importance of the increased heart rate reserve and diminished oxygen pulse as predictors of stress E/e' ratio in the general population of patients with exertional dyspnea and free of overt cardiovascular disease.[19]

It seems that the CPET parameters may help in the differential diagnosis of dyspnea in the general population, as well as in patients with diagnosed cardiovascular pathology.[6-9] According to our results, in COPD patients, these are not reliable clinical parameters that may serve as independent predictors for cardiovascular abnormality and, thus, are not applicable in the diagnostic algorithm of masked diastolic dysfunction.

Our findings support the presence of functional impairment in non-severe COPD patients with exertional dyspnea and free of overt cardiovascular disease. The performance of tissue Doppler imaging during exercise demonstrates the complex heart-lung interaction and the effort-induced changes, which increase cardiac functional impairments that may not be evident at rest. Our findings support the current recommendations for ESE-CPET as a tool for early detection of HFpEF.[6] As none of the cardiopulmonary exercise testing parameters proved to be predictive of stress-induced LVDD/RVDD, stress echocardiography has great clinical relevance for an accurate diagnosis of cardiac and respiratory pathology in non-severe COPD patients with exertional dyspnea.

Study limitations

The study had the following limitations: 1) relatively small sample size; 2) lack of body plethysmography and diffusion capacity measurement, which are informative for the proper assessment of dyspnea; 3) COPD patients experience enhanced pressure swings during the respiratory cycle, and the measurement was performed at the end of expiration, which may influence results; 4) measurements were made in early recovery period (approximately 2 min) after symptom-limited exercise. The timeline of changes of pulmonary and intrathoracic pressures during the brief interval between peak exercise and their measurement in early recovery is not well known and it could, therefore, be underestimated.

Conclusion

There is a high prevalence of stress-induced diastolic dysfunction in non-severe COPD patients with exertional dyspnea, free of overt cardiovascular disease. None of the CPET parameters correlates with the stress-induced E/e' ratio. Therefore, the performance of ESE-CPET is needed for the early detection and proper management of masked HFpEF in this population.

Author contributions

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

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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References

1. Papaioannou A, Bartziokas K, Loukides S, Tsikrika S, Karakontaki F, Haniotou A, et al. Cardiovascular comorbidities in hospitalised DPOC patients: a determinant of future risk? Eur Respir J. 2015;46(3):846-9.
2. Müllerova H, Agusti A, Erqou S, Mapel D. Cardiovascular comorbidity in COPD: systematic literature review. Chest. 2013;144(4):1163-78.
3. Barr RG, Bluemke DA, Ahmed FS, Carr J, Enright L, Hoffman A, et al. Percent emphysema, airflow obstruction, and impaired left ventricular filling. N Engl J Med. 2010;362(3):217-27.
4. Fu M, Zhou J, Thunström E, Almgren T, Grote L, Bollano E, et al. Optimizing the management of heart failure with preserved ejection fraction in the elderly by targeting comorbidities (OPTIMIZE-HFPEF). J Card Fail. 2016;22(7):539-44.
5. Vanfleteren LE, Spruit MA, Groenen M, Gaffron S, Empel V, Bruijnzeel P, et al. Clusters of comorbidities based on validated objective measurements andsystemic inflammation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2013;187(7):728-35.
6. Guazzi M, Arena R, Halle M, Piepoli MF, Myers J, Lavie CJ. Focused update: clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. Circulation. 2016;133(24):694-711.
7. Arena R, Sietsema KE. Cardiopulmonary exercise testing in the clinical evaluation of patients with heart and lung disease. Circulation. 2011;123(6):668-80.
8. Arena R, Myers J, Guazzi M. Cardiopulmonary exercise testing is a core assessment for patients with heart failure. Congest Heart Fail. 2011;17(3):115-9.
9. Herdy AH, Ritt LE, Stein R, Araújo C, Milani M, Meneghelo RS, et al. Cardiopulmonary exercise test: background, applicability and interpretation. Arq Bras Cardiol. 2016;107(5):467-81.
10. Little WC, Zile MR, Klein A, Appleton CP, Kitzman DW, Wesley-Farrington DJ, et al. Effect of losartan and hydrochlorothiazide on exercise tolerance in the exertional hypertension and left ventricular diastolic dysfunction. Am J Cardiol. 2006;98(3):383-5.

11. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-38.

12. Mitchell C, Rahko P, Blauwet L, Canaday B, Finstuen JA, Foster MC, et al. Guidelines for performing a comprehensive transthoracic echocardiographic examination in adults: recommendations from the American Society of Echocardiography. J Am Soc Echocardiogr. 2019;32(1):1-64.

13. Nagueh SF, Smiseth OA, Appleton CP, Byrd 3rd BF, Dokainish H, Edvardsen T, et al. Recommendations for the Evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2016;29(4):277-314.

14. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr. 2010;23(7):685-713.

15. Huang YS, Feng YC, Zhang J, Bai L, Huang W, Li M, et al. Impact of chronic obstructive pulmonary diseases on left ventricular diastolic function in hospitalized elderly patients. Clin Interv Aging. 2014 Dec 19;10:81-7.

16. Kubota Y, Asai K, Murai K, Tsukada YT, Hayashi H, Saito Y, et al. COPD advances in left ventricular diastolic dysfunction. Int J Chron Obstruct Pulmon Dis. 2016 Mar 29;11:649-55.

17. Caram LM, Ferrari R, Naves CR, Tanni SE, Coelho LS, Zanati SG, et al. Association between left ventricular diastolic dysfunction and severity of chronic obstructive pulmonary disease. Clinics. 2013;68(6):772-77.

18. Nedeljkovic I, Banovic M, Stepanovic J, Giga V, Djordjevic-Dikic A, Trifunovic D, et al. The combined exercise stress echocardiography and cardiopulmonary exercise test for identification of masked heart failure with preserved ejection fraction in patients with hypertension. Eur J Prev Cardiol. 2016;23(1):71-7.

19. Kaiser T, Datta D. Can Diastolic dysfunction be identified on cardiopulmonary exercise testing. Chest. 2017;152(4):A976.

20. Lucas-Ramos P, Izquierdo-Alonso JL, Rodriguez-Gonzalez Moro JM, Frances JF, Lozano PV, Bellón-Cano JM, et al. Chronic obstructive pulmonary disease as a cardiovascular risk factor. Results of a case-control study (CONSISTE study). Int J Chron Obstruct Pulmon Dis. 2012;7:679-86.

21. Fisk M, McEniery CM, Gale N, Mäki-Petäjä K, Forman JR, Munnery M, et al. Surrogate markers of cardiovascular risk and chronic obstructive pulmonary disease: a large case-controlled study. Hypertension. 2018;71(3):499-506.

22. Pelà G, Calzi M, Pinelli S, Roberta Andreoli, Nicola Sverzellati, Giuseppina Bertorelli, et al. Left ventricular structure and remodeling in patients with COPD. Int J Chron Obstruct Pulmon Dis. 2016 May 13;11:1015-22.

23. Neilan TG, Bakker JP, Sharma B, Owens R, Farhad H, Shah R, et al. T1 measurements for detection of expansion of the myocardial extracellular volume in chronic obstructive pulmonary disease. Can J Cardiol. 2014;30(12):1668-75.

24. Sabit R, Bolton CE, Fraser AG, Edwards JM, Edwards PH, Ionescu AA, et al. Sub-clinical left and right ventricular dysfunction in patients with COPD. Respir Med. 2010;104(8):1171-78.

25. Guazzi M, Myers J, Arena R. Cardiopulmonary exercise testing in the clinical and prognostic assessment of diastolic heart failure. J Am Coll Cardiol. 2005;46(10):1883-90.

Increased Home Death Due to Cardiopulmonary Arrest in Times of COVID-19 Pandemic

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Abstract

Background: **Cardiovascular diseases constitute an important group of causes of death in the country. Ischemic heart diseases that are the main causes of cardiopulmonary arrest, leading to an impact on the mortality of the cardiovascular diseases in the health system.**

Objective: **Assess the number of home deaths by cardiopulmonary arrest notified by the Mobile Emergency Medical Service (SAMU) in March 2018, 2019 and 2020.**

Methods: **Observational study carried out from the analysis of cardiopulmonary arrest mortality data of citizens assisted by SAMU in Belo Horizonte, Minas Gerais, Brazil. Social and clinical characteristics and occurrence information of the patients were analyzed. The mortality rate due to cardiopulmonary arrest in relation to the total number of attendances was assessed. A significance level of 95% was considered.**

Results: **There was increase of home deaths due to cardiopulmonary arrest in March 2020 compared to March 2018 ($p<0.001$) and March 2019 ($p=0.050$). Of the deaths reported in 2020, 63.8% of the patients were aged 60 years or older, 63.7% of the occurrences were performed in the afternoon and approximately 87% of the cardiopulmonary arrest notified had associated clinical comorbidities, with systemic arterial hypertension and heart failure represented by 22.87% and 13.03% of the reported cases, respectively. The majority of the evaluated sample of this study did not have any medical care follow-up (88.7%).**

Conclusion: **Considering the increase in the number of the deaths, we suggest reflections and readjustments regarding the monitoring of chronic non-transmissible diseases during a pandemic, as well as improvements in death surveillance. (Arq Bras Cardiol. 2021; 116(2):266-271)**

Keywords: **COVID-19; Betacoronavirus; Pandemics; Heart Arrest; Deaths; Emergency Medical Services.**

Introduction

Mobile Emergency Care Service (SAMU) represents the mobile emergency component that is normatively instituted by the Brazilian Public Health System (SUS). A component of the Urgency and Emergency Network since 2003, SAMU is currently a public assistance service working with the objective of mobile pre-hospital assistance in SUS. In addition, this service brings patients to private hospitals, and it is an important component of admissibility of patients from the private healthcare network.[1,2]

SAMU comprises central regulation and ambulance teams, composed of doctors and nurses. According to the guidelines recommended by SUS, any citizen can request pre-hospital mobile assistance through free telephone access by calling the number 192. At central regulation, a telephone operator identifies the patient and the location of the call and transfers the service to the medical regulator, who can guide the patient by phone or call the assistance team to answers the user's request. All stages of care are recorded with the consent of both parties, professionals and users.[1]

The ambulance teams consist of basic support units, in which a nursing technician, drivers and nurses are present, and advanced support units, an ambulance with more technological resources and the presence of a doctor and a nurse. Depending on regional needs, the ambulances are motorcycles, boats, or an aeromedical system consisting of a helicopter or airplane.[3]

Cardiovascular diseases (CVD) are currently an important group of causes of death in Brazil and worldwide. According to the Brazilian Society of Cardiology, as of the first day of July, CVD caused more than 198,000 deaths among

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Brazilians in 2020.[4] These diseases include ischemic heart diseases, which are the main causes of cardiopulmonary arrest (CPA).

According to the *Cardiomêtro*, an indicator of the number of deaths from CVD, created by the Brazilian Society of Cardiology, between 2004 and 2014, ischemic diseases constituted the group of cardiovascular causes with the highest prevalence of death events due to CVD.[4] The data in the literature regarding the incidence of CPA in Brazil are scarce, and the impact of this event on the mortality of individuals is observed.[5-7]

In this context, this study aims to describe the number of home deaths due to CPA notified by SAMU in the city of Belo Horizonte in 2020 and to compare the home deaths due to CRA in March 2020 in relation to March 2018 and March 2019.

Methodology

This study is part of the SAMU notification service in Belo Horizonte, Minas Gerais, Brazil, and it refers to data collected in March 2018, March 2019, and March 2020. The notifications were selected based on the manual handling of files regarding the total attendance of the teams in the previously determined period. Exclusion criteria were not established for evaluating users/deaths. Thus, sampling was performed for convenience, covering all notifications registered with the service during the periods described.

This is a retrospective observational study carried out based on the analysis of primary data on mortality due to CPA in citizens assisted by SAMU in Belo Horizonte.

Statistical Analysis

Age, occurrence characteristics (day of the month and time of day) and clinical characteristics (cause of CPA, medical follow-up, and associated comorbidities) were collected. The mortality rate was calculated according to the SAMU notification system.

The data were collected by the researchers of the service and subsequently submitted to descriptive analysis. The descriptive analysis of the variables was performed using the distribution of frequencies and absolute numbers of the categorical variables. The prevalence of outcomes and 95% confidence intervals were estimated for the population.

For data analysis, the public and free OpenEpi® statistical program was used. Categorical variables were analyzed using frequency distribution and compared using the chi-square test. The significance level was set at 95% ($p < 0.05$).

Results

A total of 1,662 deaths were recorded by SAMU in the month of March in 2018 (n = 563), 2019 (n = 494), and 2020 (n = 605). During this period (March), SAMU reported 919 home deaths due to CPA in the years 2018, 2019, and 2020, distributed in 260 deaths in March 2018 (28.3%), 283 deaths in March 2019 (30.8%), and 376 deaths in March 2020 (40.9%). It was observed that the death rates for the total number of attendances at SAMU during these periods were 0.51, 0.57 and 0.62, respectively.

Figure 1 shows a 33% increase in cases of home deaths between March 2018 and March 2020. Table 1 compares the gross number of deaths by CPA and other causes, showing that 2020 had more notifications of home deaths due to CPA, with statistical difference in relation to 2018 and 2019.

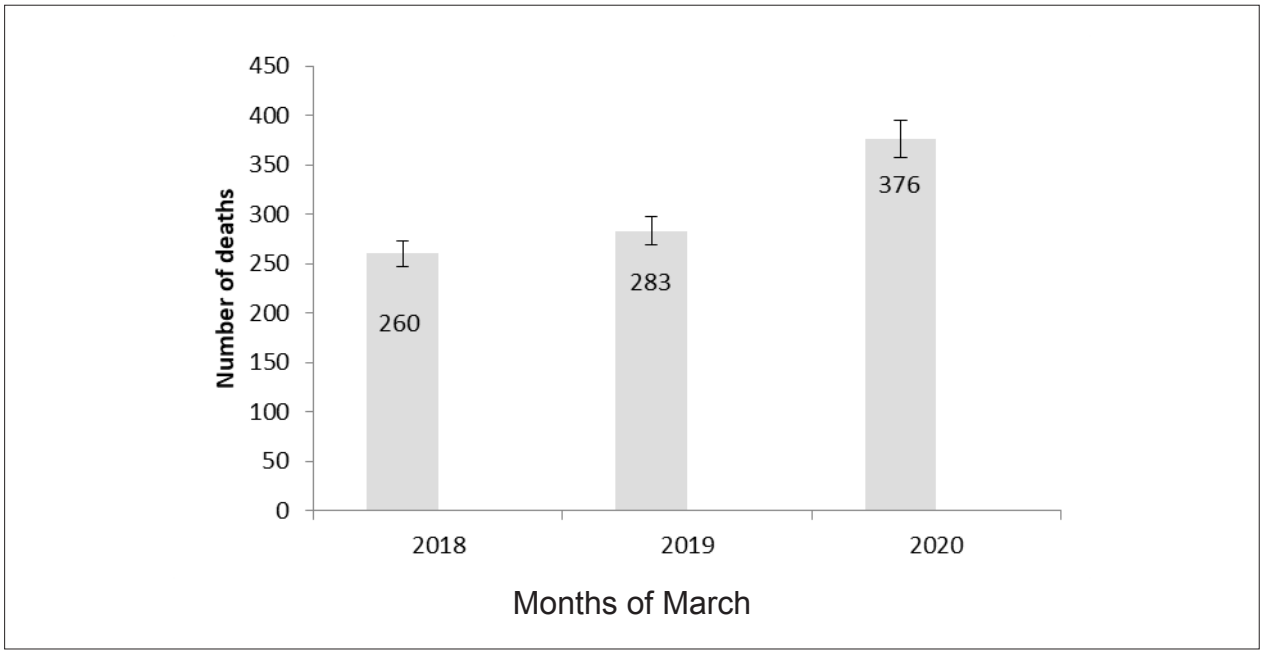

Figure 1 – *Prevalence of death outcome in patients assisted by the Mobile Emergency Care Service of Belo Horizonte, Minas Gerais, Brazil, March 2018-2020.*

Table 1 – Comparison of home deaths due to cardiopulmonary arrest and other causes in March 2018 and 2019 compared to March 2020, notified by the Mobile Emergency Care Service of Belo Horizonte, Minas Gerais, Brazil

Deaths	Years		p value*	Years		p value *
	2018	2020		2019	2020	
CPA	260	376	<0.01	283	376	0.05
Other causes	303	229		211	229	

CPA: cardiopulmonary arrest; p value - chi-square Test.*

Table 2 – Descriptive analysis of deaths by cardiopulmonary arrest in March 2020, notified by the Mobile Emergency Care Service of Belo Horizonte, Minas Gerais, Brazil

Variables	n	%
Social characteristics		
Age (years)		
≤ 19	10	2.70
20-59	126	33.50
≥ 60	240	63.80
SAMU occurrence characteristics		
Attendance		
First half of March	190	50.50
Second half of March	186	49.50
SAMU occurrence time		
6:00 am to 11:59 am	142	37.70
12:00 pm to 5:59 am	98	26.00
6:00 pm to 11:59 pm	89	23.60
12:00 am to 05:59 am	47	12.70
Clinical characteristics		
Cause of CPA		
Clinical	326	86.70
Trauma	50	13.30
Medical follow-up		
Yes	45	12.00
No	331	88.00

CPA: cardiopulmonary arrest; SAMU: Mobile Emergency Care Service; am: ante meridiem; pm: post meridiem. Sample size = 376.

Table 2 describes social, clinical, and notification characteristics. Of the deaths reported in March 2020, 63.8% of the patients were aged 60 years or over. According to the notification time, 63.7% occurred during the daytime with 37.7% in the morning and 26.0% in the afternoon, with no difference between the proportions of the 31 consecutive days of that period (Table 2).

Regarding clinical characteristics, it was observed that approximately 87.0% of patients with CPA had other clinical comorbidities and that the majority of the evaluated sample did not have any medical follow-up according to the data collected (88.7%) (Table 2). However, many of the patients' companions and family were unaware of the patients' history.

Table 3 describes clinical comorbidities notified by the service, which represents 87.0% (n = 331) of the patients evaluated, according to the course of the disease observed. Among the chronic diseases observed, hypertension was associated with CPA in 22.87% of the reported cases; heart failure and diabetes mellitus were present in 13.03% and 11.0% of cases, respectively. Among other comorbidities, it is interesting to note that in 38.4% of the reported cases, although the family or friends reported the presence of associated comorbidity, they were unable to specify the patient's associated comorbidities.

Discussion

As a main result of this study, a gradual numerical increase was observed in the rate of home deaths due to CPA for the total number of attendances by SAMU and a proportional increase of 33% of home deaths in March 2020, which is the month when the World Health Organization declared the COVID-19 pandemic.[8]

Since the confirmation of the first case in Brazil, on February 26, 2020, the press, as well as health authorities, in the absence of vaccines or antiviral medications, has warned of the need for social distance, the use of masks, hand washing, and reinforcement for care regarding respiratory etiquette. In the city of Belo Horizonte, the first notification of COVID-19 occurred on March 16, 2020; however, since the world declaration of the pandemic, the city government instituted social isolation early, preventing residents from non-essential contact.

Approximately 80% of COVID-19 cases are mild or oligosymptomatic.[9] A recent study shows that 20% required hospital care, with 5% to 15% of these being treated in intensive care units requiring ventilatory support. Mortality for these patients can reach up to 80%.[9] SARS-CoV-2 can be transmitted from person to person (contact with hands, cough, or saliva droplets) or through surfaces and objects contaminated by the virus.[10] On May 16, 2020, more than 4,605,673 people had been diagnosed with COVID-19, and there were 310,180 deaths worldwide. In Brazil, by May 16, 2020, 222,877 cases had been recorded, with 15,046 deaths.[11] Among the measures to prevent COVID-19 infection, individuals are recommended to clean their hands, surfaces, and objects with water and soap or hand sanitizer. Other

Table 3 – Comorbidities related to deaths by cardiopulmonary arrest in March 2020, notified by the Mobile Emergency Care Service of Belo Horizonte, Minas Gerais, Brazil

Clinical comorbidities	n	%
Not reported	145	38.56
Arterial hypertension	86	22.87
Heart failure	49	13.03
Diabetes mellitus	42	11.17
Cancer	40	10.64
Dementia	26	6.91
Respiratory infections	23	6.12
Stroke	19	5.05
Arrhythmia	12	3.19
Urinary tract infection	3	0.80

Sample size = 376.

indications include avoiding contact with eyes, nose, and mouth; permanent use of a facemask; maintaining healthy eating and sleep habits; and social isolation and distancing.[12]

The increase in the number of deaths, in the context of the pandemic, can aggravate users' fear of leaving social isolation and seeking medical assistance and essential services. This could delay the demand for health services affecting the underlying disease. It is interesting to note that almost 89% of our sample did not have medical follow-up, and in a similar frequency (87%) the nature of the CPA was the clinical cause.

Gonzales-Olmo et al.,[13] in a recent study, with data from the population of Madrid, demonstrated high levels of individual self-perception of greater vulnerability in relation to COVID-19 infection when seeking dental care, which is considered an essential health service. Thus, the researchers observed that the sample of individuals over 60 years of age with systemic diseases avoided dental care most of the time.[13]

In accordance with our results, Holmes et al. (2020) indicated that there was a structural break in the time series of weekly admissions deferred annually according to emergency services in the United Kingdom between September 2019 and April 2020.[14] These researchers observed the period of time corresponding to September 2019 and April 2020.

Scales for assessing individuals' fear have been developed and are in the validation phase (such as the "Fear of COVID-19 Scale") in order to assess this emotion. New studies are expected to assess the context of the pandemic in this regard, monitoring fear at the expense of not seeking essential health services, improving quality of life, and delaying mortality due to causes that do not involve COVID-19.[15-17]

Julia et al.[18] report on the reorganization of the health service in France during the pandemic. Important investments have been made in terms of teleconsultations for the follow-up of patients with COVID-19, but the most vulnerable population with difficulties in accessing the internet and digital technologies or those with language barriers were left without adequate assistance. In addition, the available hospital beds have been drastically reduced, and primary health care professionals have thus had to deal with emergencies due to chronic diseases.[18] Home visits have been divided according to patients with and without COVID-19, leading to service overload. A flow for primary care has now been adopted for patients with chronic diseases, in order to avoid delays for outpatient control.[17]

In Belo Horizonte, there has been a reduction in demand from the population for care in the Basic Health Units and the Emergency Care Units. During the first four months of 2019, 1,478,905 people were attended; during the same period of 2020, this number was 1,215,543, which represents an 18% reduction.[19] Thus, it is important to monitor the management of chronic diseases and promote educational actions so that the population understands the importance of health care follow-up and the regular use of necessary medicines. Accordingly, the Municipal Health Department of Belo Horizonte has updated the flow of care in primary health care.[19,20]

Souza et al.[21] report on the primary health care provided by SUS in Brazil and on the investments that have been destined for acquisition of equipment and expansion of hospital beds for patients with COVID-19. They reinforce the need to strengthen primary care as an instrument to prevent collapse in the health system, avoiding deaths due to COVID-19 and chronic diseases.[21] It is necessary to reflect on how to find the balance so that health actions are not paralyzed during the pandemic.

The Municipal Health Department of Belo Horizonte has carried out initiatives such as training through web conferences, web classes, and discussion of clinical cases and technical notes for care and flow of patients with COVID-19, establishing partnerships for online care and assisting patients risk groups. At the same time, it has been taking measures to adapt emergency services and primary health care, seeking to avoid overloading services and promoting better care for patients with and without COVID-19.[20]

The increased numbers of home deaths have aroused the attention of health managers, and the idea is to reinforce the importance of outpatient control of chronic diseases and to clarify adopted safety measures to the population regarding clinical complications not related to COVID-19 during the pandemic.

It is a favorable moment to reinvent the relationship between users and primary health care professionals, seeking greater closeness to establish bonds, strengthen the importance of controlling chronic diseases and avoiding unnecessary deaths. It is also necessary to implement measures to improve death surveillance. Primary health care services should organize assistance and patient flows in order to ensure adequate care for patients with and without COVID-19.

As a study limitation, we point out the high percentage of individuals for whom it was not possible to collect information about the existence of comorbidities (38.5% of the sample) due to the lack of information from the interviewed relatives or friends, which may have underestimated the values presented.

Conclusion

The results point to an increase in the number of home deaths due to CPA notified by SAMU in March 2020 in relation to March 2018 and March 2019 in Belo Horizonte, Minas Gerais. It is necessary to carry out new studies with a longitudinal design in order to monitor the increase in mortality of health system users and analyze its causal relationships in order to avoid deaths due to other diseases that do not involve COVID-19.

Author Contributions

Conception and design of the research: Guimarães NS, Carvalho TML, Pinto JM, Lage R, Bernardes RM, Peres ASS, Raposo MA, Rodrigues VM, Melo MCB, Tupinambás U; Acquisition of data: Carvalho TML, Pinto JM, Lage R, Bernardes RM, Peres ASS, Raposo MA, Carvalhais RM, Oliveira BC, Melo MCB, Tupinambás U; Marcini RA; Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Guimarães NS, Carvalho TML, Pinto JM, Lage R, Bernardes RM, Peres ASS, Raposo MA, Carvalhais RM, Oliveira BC, Rodrigues VM, Melo MCB, Tupinambás U; Statistical analysis: Guimarães NS, Raposo MA, Tupinambás U; Writing of the manuscript: Guimarães NS, Carvalho TML, Pinto JM, Lage R, Bernardes RM, Peres ASS, Carvalhais RM, Oliveira BC, Rodrigues VM, Melo MCB, Tupinambás U, Marcini RA.

Potential Conflict of Interest

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

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

References

1. Brasil. Ministério da Saúde. Portaria 1.600 de 7 de julho de 2011. Diário Oficial da União. Brasília, 2011.
2. O'Dwyer G, Konder MT, Reciputti LP, Macedo C, Lopes MGM. O processo de implantação do Serviço de Atendimento Móvel de Urgência no Brasil: estratégias de ação e dimensões estruturais. Cad Saúde Pública. 2017; 33 (7):1-14.
3. Brasil. Ministério da Saúde. Política Nacional de Atenção às Urgências e Rede de Atenção às Urgências. Portaria de Consolidação nº 3, de 28 de setembro de 2017; consolida as normas sobre as redes do Sistema Único de Saúde. Brasília, 2017.
4. Sociedade Brasileira de Cardiologia. Cardiomêtro: Mortes por Doenças Cardiovasculares no Brasil. Rio de Janeiro, 2020. Disponível em: http://www.cardiometro.com.br/
5. Sociedade Brasileira de Cardiologia. Atualização da Diretriz de Ressuscitação Cardiopulmonar e Cuidados Cardiovasculares de Emergência da Sociedade Brasileira de Cardiologia – 2019. Arq Bras Cardiol .2019; 113(3):449-663.
6. Malta DC, França E, Abreu DMX, Perillo RD, Salmen MC, Teixeira RA et al. Mortalidade por doenças não transmissíveis no Brasil, 1990 a 2015, segundo estimativas do estudo de Carga Global de Doenças. São Paulo Med J. 2017; 135(3): 213-21.
7. Saltarelli RMF, Prado RR, Monteiro RA, Machado IE, Teixeira BSM, Malta DC. Mortes evitáveis por ações do Sistema Único de Saúde na população da Região Sudeste do Brasil. Ciênc Saúde Coletiva. 2019, 24(3):887-98.
8. World Health Organization. (WH))Naming the coronavirus disease (COVID-2019) and the virus that causes it. Geneva; 2020.
9. Wu Z, JenMcGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020;323(13):1239-42.
10. Garg S, Kim L, Whitaker M et al. Hospitalization Rates and Characteristics of Patients Hospitalized with Laboratory-Confirmed Coronavirus Disease 2019 - COVID-NET, 14 States, March 1-30, 2020. MMWR Morb Mortal Wkly Rep. 2020 Abril 69(15):458-64.
11. Johns Hopkins University. Coronavirus Resourde Center. COVID-19 Global Cases by the Center for Systems Science and Engineering at John Hopkins University (JHCHSU). United States;2020New York; 2020.
12. Center for Disease Control and Prevention (CDC). How coronavirus spreads. Acessed in 2020 Apr 23] Available from: https://www.cdc.gov/coronavirus/2019-ncov/prepare/transmission.html.
13. González-Olmo MJ, Ortega-Martínez AR, Delgado-Ramos B, Romero-Maroto M, Carrillo-Diaz M. Perceived vulnerability to coronavirus infection: impact on dental practice. Braz Oral Res. 2020;34:e044.
14. Holmes JL, Brake S, Docherty M, Lilford R, Watson S. Emergency ambulance services for heart attack and stroke during UK's COVID-19 lockdown. Lancet, 2020;395;May23.
15. Ahorsu DK, Lin CY, Imani V, Saffari M, Griffiths MD, Pakpour AH. The Fear of COVID-19 Scale: Development and Initial Validation. Int J Ment Health Addict. 2020; Mar 27:1-9.
16. oraci P, Ferrari A, Abbiati FA, Del Fante E, De Pace R, Urso A, et al. Validation and Psychometric Evaluation of the Italian Version of the Fear of COVID-19 Scale. Int J Ment Health Addict . 2020 May 4:1-10.
17. Bitan TH, Giron AG, Bloch Y, Mayer Y, Shiffman N, Mendlovic S. Fear of COVID-19 scale: Psychometric characteristics, reliability and validity in the Israeli population. Psychiatry Res. 2020;Jul;289:113100.
18. Julia C, Saynac Y, Le Joubioux C, Cailhol J, Lombrail P, Bouchaud O. Organising community primary care in the age of COVID-19: chanllenges in disadvantaged areas. Correspondence. Lancet Public Health. 2020;5(6):e313.
19. Prefeitura Municipal de Belo Horizonte. Secretaria Municipal de Saúde. Belo Horizonte. 2020. Nota técnica COVID-19. no 007/2020. CIEVS/GVIGE/DPSV/GEAPS/GEURE/GERRE/GEASF/DIAS/GCINT/DMAC/SMSA/PBH. Belo Horizonte;2020.
20. Prefeitura Municipal Belo Horizonte. Secretaria Municipal de Saúde. CORONAVIRUS=19. Belo Horizonte;2020.
21. Souza CDF, Gois-Santos VT, Correia DS, Martins-Filho PR, Santos VS. The need to strengthen Primary Health Care in Brazil in the context of the COVID-19 pandemic. Braz Oral Res. 2020;34:e047.

Out-Of-Hospital Cardiac Arrest during the Coronavirus Disease 2019 (COVID-19) Pandemic in Brazil: The Hidden Mortality

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Short Editorial related to the article: Increased Home Death Due to Cardiopulmonary Arrest in Times of COVID-19 Pandemic

"Somewhere, something incredible is waiting to be known."

Carl Sagan

Abstract

The world changed in just a few months after the emergence of the novel coronavirus disease 2019 (COVID-19), caused by a beta coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 was declared a pandemic by the World Health Organization (WHO) on March 11, 2020. Brazil currently has the world's second-highest COVID-19 death toll, second only to the USA. The COVID-19 pandemic is spreading fast in the world with more than 181 countries affected. This editorial refers to the article published in Arquivos Brasileiros de Cardiologia: "Increase in home deaths due to cardiorespiratory arrest in times of COVID-19 pandemic."[1] Their main results show a gradual increase in the rate of out-of-hospital cardiac arrest during the Coronavirus disease 2019 (COVID-19) pandemic in the city of Belo Horizonte, Minas Gerais, Brazil. Their data demonstrate a proportional increase of 33% of home deaths in March 2020 compared to previous periods. Their study is the first Brazilian paper to demonstrate the same trend observed in other countries.

My personal interest in Science must be credited to Carl Sagan. During my youth, I saw his TV program "Cosmos" and this changed everything. Today, Science is one of the top priorities of humankind. The world changed in just a few months after the emergence of the novel coronavirus disease 2019 (COVID-19), caused by a beta coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 was declared a pandemic by the World Health Organization (WHO) on March 11, 2020.[2] Brazil currently has the world's second highest Covid-19 death toll, second only to the USA. The COVID-19 pandemic is spreading fast in world with more than 181 countries affected.

In the majority of patients, COVID-19 is a mild disease with some respiratory symptoms. COVID-19 is more severe and fatal among patients with pre-existing cardiovascular risk factors or diseases.[3] The Chinese Center for Disease Control and Prevention published a survey demonstrating that among patients diagnosed with COVID-19, 13% had hypertension, 5% had diabetes mellitus and 4% had a history of cardiovascular disease. However, in the same cohort, among patients who had not survived, 40% had hypertension, 20% had diabetes and 22% had pre-existing cardiovascular diseases.[4] Patients with cardiovascular diseases had the highest case fatality rate (10.5%). Risk factors of cardiac events after COVID-19 pandemic include older age, pre-existing cardiovascular diseases and greater severity of pneumonia at presentation.[2] Coronary heart disease has also been found to be associated with acute cardiac events and poor outcomes in influenza and other respiratory viral infections.[5,6] COVID-19 has also demonstrated damage to the cardiovascular system with several manifestations, such as myocardial injury, acute myocardial infarction, heart failure, Takotsubo syndrome (TS), arrhythmias, myocarditis and shock.[7] Not only chronic cardiovascular conditions, such as hypertension or heart failure, are relevant to the COVID-19 outcomes, but also age, immunological status of the host and the effect of cardiovascular drugs like antithrombotic drugs or antihypertensives.[8] Figure 1 demonstrates the interaction between cardiovascular diseases/risk factors and COVID-19.

The damage that COVID-19 causes in the cardiovascular system is probably multifactorial and can result from an imbalance between high metabolic demand and low cardiac reserve, systemic inflammation and thrombogenesis, in addition to direct cardiac damage from the virus.[7] Cardiovascular system complications occur mainly in patients with cardiovascular risk factors (advanced age, hypertension and diabetes) or preexisting cardiovascular diseases. There are few reports of COVID-19 patients who presented with acute ST-segment elevations and, for those patients, the ECG changes were present in the inferior leads. In each case, a diagnosis of myocarditis was supported by elevated cardiac troponins, a moderate decrease of left ventricular ejection fraction and the absence of flow-limiting coronary artery disease by invasive coronary angiography.[9] Autopsy findings support the concept that the pathogenesis of severe COVID-19 disease involves direct viral-induced injury of

Keywords

COVID-19/complications; Betacoronavirus; Mortality; Pandemics; Heart Arrest; Risk Factors, Elderly; Cardiovascular Diseases, Pneumopathies

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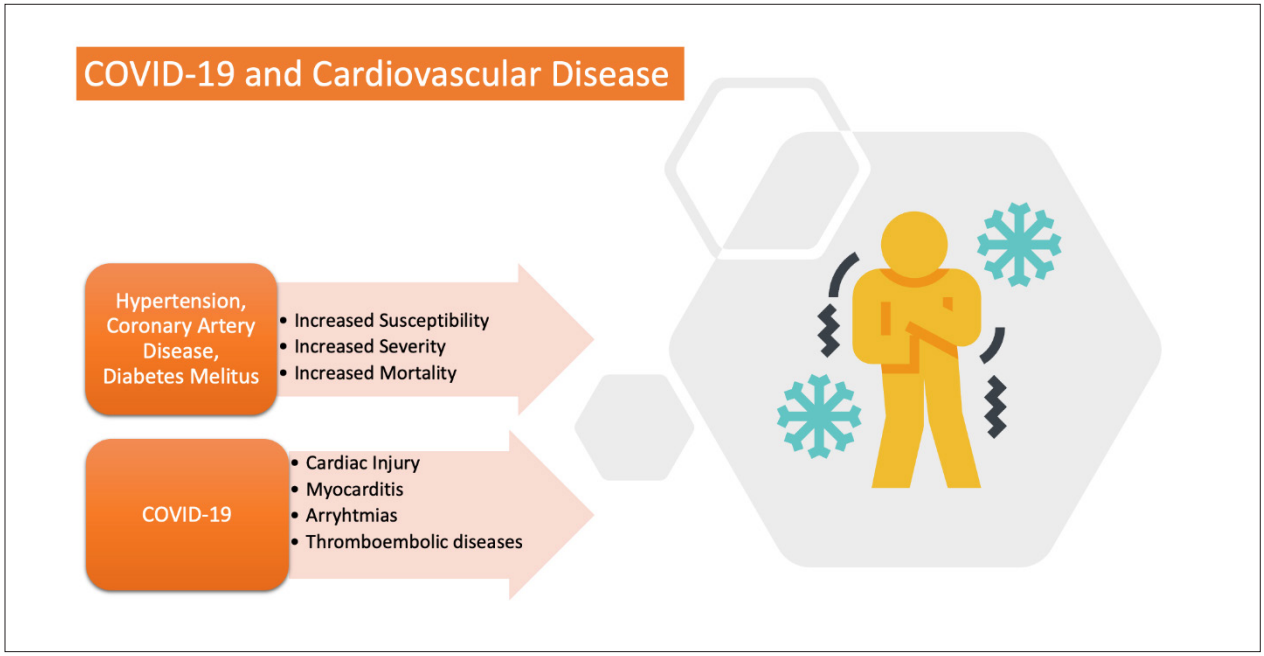

Figure 1 – *Interaction between cardiovascular diseases/risk factors and COVID-19. Cardiovascular comorbidities such as hypertension and coronary artery disease are associated with increased susceptibility and higher mortality in patients with COVID-19. COVID-19 is also associated with cardiovascular manifestations including myocardial injury, myocarditis, arrhythmias, acute coronary syndrome and thromboembolism.*

multiple organs, including heart and lungs, coupled with the consequences of a procoagulant state with coagulopathy.[10] Table 1 lists the most frequent cardiovascular consequences of COVID-19 described in the literature.

Concerning coronary artery disease epidemiology, some studies showed a decreased incidence of hospitalization for acute myocardial infarction during the COVID-19 pandemic. Solomon et al.[13] noted that the weekly rates of hospitalization for acute myocardial infarction decreased by up to 48% during the COVID-19 period. De Filippo et al.[14] found a similar decrease in hospitalization for acute coronary syndrome in 15 hospitals in northern Italy.[14] This decrease is partially related to the anxiety and fear of catching COVID-19 in the emergency department that many patients demonstrated during the initial months of the pandemic. Due to this decrease in myocardial infarction hospitalizations, a transient increase in out-of-hospital cardiac arrest (AOHCA) was observed, compared to the equivalent time period in the years before the pandemic.[15] This increase of AOHCA is directly attributable to COVID-19 infections and to the potential increase of patients with acute coronary syndrome that did not go immediately to emergency settings.

We must congratulate the authors of the article published in Arquivos Brasileiros de Cardiologia.[1] Their main findings show a gradual increase in the rate of out-of-hospital cardiac arrest during the coronavirus disease 2019 (COVID-19) pandemic in the city of Belo Horizonte, Minas Gerais, Brazil. Their data demonstrates a proportional increase of 33% of home deaths in March 2020 compared to previous periods. Their study is the first Brazilian paper to demonstrate the same trend observed in other countries.[14,15] The main limitations of the study are: short observation period, sample from a single Brazilian metropolitan region and lack of complete information on comorbidities in about 40% of cases. However, these data do not invalidate the main messages of the study, which are: (1) the need to organize the health system to deal with cases of acute diseases during the COVID-19 pandemic, (2) educating the population about the need to seek continued health care, and (3) the search for better treatments and prevention.

The approval of effective vaccines for the prevention of COVID-19 and the beginning of the Brazilian national immunization program against COVID-19 in January 2021 fill us with hope and optimism.[16,17] However, as long as vaccination is not widely available to the population, it is necessary to continue with effective and scientifically proven measures of social distancing, the use of masks and hand hygiene. Only then will the COVID-19 pandemic be a page in history and no longer a harsh reality.

Table 1 – Cardiovascular consequences of COVID-19

Cardiovascular Complication	Frequency	Implications
Myocardial injury and myocarditis	7–20% of patients with COVID-19	Myocardial injury is associated with a 5-fold increase in the need for invasive mechanical ventilation and an 11-fold increase in mortality
Acute coronary syndrome (ACS)	Less than 5% of patients with COVID-19	Reduction in hospitalizations for ACS and a 40% reduction in ST-segment elevation myocardial infarction during the pandemic. This decrease in ACS cases is associated with a similar increase in out-of-hospital cardiac arrest.
Heart failure	Incidence of 24% in all patients with COVID-19 and 49% in patients who died	Heart failure can contribute to respiratory failure in patients with ARDS. Adequate management of HF is mandatory to reduce mortality.
Arrhythmias and sudden cardiac arrest	Malignant arrhythmias, such as ventricular tachycardia and fibrillation, can occur in patients with elevated levels of troponin T	Atrial and ventricular tachycardia and fibrillation can be triggered by myocardial injury, systemic causes or drug interactions. Special attention is needed with drug-induced QT prolongation
Coagulation abnormalities and thrombosis	Elevated levels of d-dimer (>0.5 mg/l) can be found in 60% of those with severe illnesses	Optimal anticoagulation regimen to prevent thromboembolic events is not known but anticoagulation is often empirically prescribed. Recommendations on antithrombotic treatment and PCI for acute coronary syndromes should be maintained during COVID-19 treatment

ARDS: acute respiratory distress syndrome; PCI: percutaneous coronary intervention (adapted from Nishiga et al.[11] and Prieto-Lobato et al.[12])

References

1. Guimarães NS, Carvalho TML, Machado-Pinto J, Lage R, Bernardes RM, Peres, ASS. Aumento de Óbitos Domiciliares devido a Parada Cardiorrespiratória em Tempos de Pandemia de COVID-19. Arq Bras Cardiol. 2021; 116(2):266-271.
2. Oliveira GMM de, Pinto FJ. COVID-19: A Matter Close to the Heart. Int J Cardiovasc Sci. 2020;33(3):199–202.
3. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet [Internet]. 2020;395(10229):1054–62. Available from: http://dx.doi.org/10.1016/S0140-6736(20)30566-3
4. Lang JP, Wang X, Moura FA, Siddiqi HK, Morrow DA, Bohula EA. A current review of COVID-19 for the cardiovascular specialist. Am Heart J [Internet]. 2020;226:29–44. Available from: https://doi.org/10.1016/j.ahj.2020.04.025
5. Corrales-Medina VF, Musher DM, Shachkina S, Chirinos JA. Acute pneumonia and the cardiovascular system. Lancet [Internet]. 2013;381(9865):496–505. Available from: http://dx.doi.org/10.1016/S0140-6736(12)61266-5
6. Musher DM, Abers MS, Corrales-Medina VF. Acute Infection and Myocardial Infarction. N Engl J Med [Internet]. 2019;380(2):171–6. Available from: http://www.nejm.org/doi/10.1056/NEJMra1808137
7. Costa IBS da S, Bittar CS, Rizk SI, Filho AE de A, Santos KAQ, Machado TIV, et al. The heart and COVID-19: What cardiologists need to know. Arq Bras Cardiol. 2020;114(5):805–16.
8. Pedro SDS, Carla F, Brito F De, Bretas C, Scaramello V. Challenges in Pharmacological Management of Cardiovascular Diseases in Covid-19 : do Benefits Outweigh Risks ? Int J Cardiovasc Sci. 2020;33(4):404–11.
9. Loghin C, Chauhan S, Lawless SM. Pseudo-Acute Myocardial Infarction in a Young COVID-19 Patient. JACC Case Reports [Internet]. 2020;2(9):1284–8. Available from: https://doi.org/10.1016/j.jaccas.2020.04.015
10. Buja LM, Wolf D, Zhao B, Akkanti B, McDonald M, Lelenwa L, et al. The emerging spectrum of cardiopulmonary pathology of the coronavirus disease 2019 (COVID-19): Report of 3 autopsies from Houston, Texas, and review of autopsy findings from other United States cities. Cardiovasc Pathol [Internet]. 2020;48:107233. Available from: https://doi.org/10.1016/j.carpath.2020.107233
11. Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. Nat Rev Cardiol [Internet]. 2020;1–16. Available from: http://www.nature.com/articles/s41569-020-0413-9
12. Prieto-Lobato A, Ramos-Martínez R, Vallejo-Calcerrada N, Corbí-Pascual M, Córdoba-Soriano JG. A Case Series of Stent Thrombosis During the COVID-19 Pandemic. JACC Case Reports [Internet]. 2020;2(9):1291–6. Available from: https://doi.org/10.1016/j.jaccas.2020.05.024
13. Solomon MD, McNulty EJ, Rana JS, Leong TK, Lee C, Sung S-H, et al. The Covid-19 Pandemic and the Incidence of Acute Myocardial Infarction. N Engl J Med [Internet]. 2020 May 19;NEJMc2015630. Available from: http://www.nejm.org/doi/10.1056/NEJMc2015630
14. De Filippo O, D'Ascenzo F, Angelini F, Bocchino PP, Conrotto F, Saglietto A, et al. Reduced Rate of Hospital Admissions for ACS during Covid-19 Outbreak in Northern Italy. N Engl J Med [Internet]. 2020 Jul 2;383(1):88–9. Available from: http://www.nejm.org/doi/10.1056/NEJMc2015630
15. Marijon E, Karam N, Jost D, Perrot D, Frattini B, Derkenne C, et al. Out-of-hospital cardiac arrest during the COVID-19 pandemic in Paris, France: a population-based, observational study. Lancet Public Heal. 2020;2667(20):1–7.
16. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med [Internet]. 2020;1–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/33301246
17. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet . [Internet]. 2020;1–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/33306989

COVID-19 and Myocardial Injury in a Brazilian ICU: High Incidence and Higher Risk of In-Hospital Mortality

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Abstract

Background: **The incidence of myocardial injury (MI) in patients with COVID-19 in Brazil and the prognostic impact of MI have not been elucidated.**

Objectives: **To describe the incidence of MI in patients with COVID-19 in the intensive care unit (ICU) and to identify variables associated with its occurrence. The secondary objective was to assess high-sensitivity troponin I as a predictor of in-hospital mortality.**

Methods: **Retrospective, observational study conducted between March and April 2020 with cases of confirmed COVID-19 admitted to the ICU. Numerical variables were compared by using Student t test or Mann-Whitney U test. The chi-square test was used for categorical variables. Multivariate analysis was performed with variables associated with MI and $p<0.2$ to determine predictors of MI. The ROC curve was used to determine the troponin value capable of predicting higher in-hospital mortality. Survival functions were estimated by use of the Kaplan-Meier method from the cut-off point indicated in the ROC curve.**

Results: **This study assessed 61 patients (63.9% of the male sex, mean age of 66.1±15.5 years). Myocardial injury was present in 36% of the patients. Systemic arterial hypertension (HAS) [OR 1.198; 95%CI: 2.246-37.665] and body mass index (BMI) [OR 1.143; 95%CI: 1.013-1.289] were independent risk predictors. High-sensitivity troponin I >48.3 ng/mL, which was determined in the ROC curve, predicts higher in-hospital mortality [AUC 0.786; $p<0.05$]. Survival in the group with high-sensitivity troponin I >48.3 ng/mL was lower than that in the group with values ≤48.3 ng/dL [20.3 x 43.5 days, respectively; $p<0.05$].**

Conclusion: **There was a high incidence of MI in severe COVID-19 with impact on higher in-hospital mortality. The independent risk predictors of MI were SAH and BMI. (Arq Bras Cardiol. 2021; 116(2):275-282)**

Keywords: **COVID-19; SARS-CoV-2; Coronavirus; Betacoronavirus; Infection; Myocarditis; Myocardial Infarction; Hospitalization; Morbidity.**

Introduction

The disease caused by the novel coronavirus (SARS-CoV-2, severe acute respiratory syndrome coronavirus 2) was named COVID-19 according to guidance issued by the World Health Organization (WHO). Its outbreak was first described in the city of Wuhan, China, at the end of 2019. COVID-19 was declared a public health emergency of international concern on January 30th, 2020, and at the time this paper was written 12 964 809 confirmed cases and 570 288 deaths had been counted worldwide.[1] By July 14th, 2020, Brazil had 1 926 824 confirmed cases and 74 133 deaths.[2]

Most cases of SARS-CoV-2 infection are not severe and include asymptomatic and oligosymptomatic presentations. Nevertheless, reports have suggested that up to 20% of infected individuals require hospitalization, of whom as much as 25% need admission to the intensive care unit (ICU).[3,4] Those rates vary according to cultural differences regarding ICU admission criteria and regional characteristics, such as population age and prevalence of other comorbidities. Development of dyspnea and severe acute respiratory syndrome are the most common indications for ICU adimission.[3-5]

Cardiac impairment in critically-ill patients with COVID-19 is not uncommon and comprises a wide range of presentations, such as arrhythmias, cardiomyopathies, and myocardial injury.[5-7] The incidence of myocardial injury in hospitalized patients varies from 7% to 28%, and correlation of myocardial injury with worse clinical outcomes has been

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suggested.[7-9] However, the causes of myocardial injury and its contribution to the prognosis are yet to be elucidated.

This study's primary objective was to describe the incidence of myocardial injury in patients with COVID-19 admitted to the ICU and to identify possible risk factors related to its occurrence. This study's secondary objective was to assess high-sensitivity troponin I as a predictor of in-hospital mortality.

Methods

This is a retrospective observational study conducted in the ICU of a private hospital in the city of Rio de Janeiro, Brazil, with patients admitted with the diagnosis of confirmed COVID-19 between March and April 2020. Data were collected from the electronic medical records system. The cases without high-sensitivity troponin I measures and those with chronic renal disease and glomerular filtration rate (GFR) lower than 30 mL/min/1.73m^2 were excluded from the study. All participants were older than 18 years. This study was approved by the Ethics Committee in Research of the Rio de Janeiro State University. Written informed consent was waived because of the retrospective nature of this study. All patients received antimicrobial therapy for community-acquired bacterial pneumonia on hospital admission, and the therapeutic plan was adjusted according to clinical course, allowing medication reconciliation whenever possible.

The diagnosis of COVID-19 was in accordance with the guidance from the WHO.[10] The cases were confirmed by use of the polymerase chain reaction (PCR) to identify SARS-CoV-2 in the nasopharyngeal swab from patients admitted to the ICU. Myocardial injury was defined as the detection of at least one cardiac troponin I value above the 99th percentile upper reference limit (URL), in accordance with the Fourth Universal Definition of Myocardial Infarction.[11] High-sensitivity troponin I assays, whose reference value is lower than 19 ng/mL, were used. Troponin I was measured according to the ICU protocol on patient's admission or under the following conditions: global or regional left ventricular wall motion abnormalities, inexplicable cardiac arrhythmias, dynamic electrocardiographic changes, acute coronary syndrome, or heart failure syndrome.

The following variables were analyzed: age, sex, body mass index (BMI, kg/m^2) and the most prevalent comorbidities, time from COVID-19 symptom onset to hospitalization, length of ICU stay, length of hospital stay, myocardial injury detection, need for hemodynamic support with vasopressors, need for invasive ventilatory support, acute respiratory distress syndrome according to the Berlin definition,[12] and the Simplified Acute Physiology Score III (SAPS 3).[13]

Statistical Analysis

The normally distributed continuous variables were expressed as mean and standard deviation, and the nonnormally distributed continuous variables were expressed as median and interquartile interval. The categorical variables were expressed as absolute and relative frequencies. The Kolmogorov-Smirnov test was used to test for normality. The continuous variables were compared by using unpaired Student *t* test or Mann-Whitney U test. The categorical variables were compared by using the chi-square test or Fisher exact test. Logistic regression was used to determine the predictors of myocardial injury. The variables that associated with myocardial injury at the significance level of $p< 0.20$ were included in the multivariate regression model. The forward stepwise method was used. The magnitude of the effect of each variable was estimated by calculating the odds ratio (OR) and the respective 95% confidence interval (CI). The Receiver Operating Characteristic (ROC) curve was analyzed to determine the high-sensitivity troponin I value capable of predicting in-hospital mortality. The survival functions were calculated by using the nonparametric Kaplan-Meier estimator. The patients were divided according to covariables selected by their probable prognostic role based on literature review. The log-rank test was used to compare the survival functions for each covariable. Relative risks (RR) were calculated for the prognosis of the variables associated with the outcomes, with 95% CI, according to the Cox proportional hazards model. Initially, Cox bivariate analysis was performed, and then multivariate analysis was performed for the factors possibly playing a role in the outcome ($p<0.10$). Schoenfeld residuals were used to check the proportional hazards of the Cox models. The tests were two-tailed, and the level of statistical significance adopted was $p<0.05$. Data were analyzed by use of the SPSS 22.0 (IBM, Chicago, IL). The statistical graphs were generated by using MedCalc 19.3.

Results

This study identified 105 cases of confirmed COVID-19 in the ICU of a private hospital, in the city of Rio de Janeiro, between March and April 2020. After excluding 35 patients who had no troponin I value and 9 patients with GFR < 30 mL/min/1.73m^2, 61 cases of confirmed COVID-19 were included in this study, 36% of which had myocardial injury (Figure 1).

Of the 61 patients, 63.9% were of the male sex and the mean age was 66.1±5.5 years. The mean time from COVID-19 symptom onset to hospital admission was 7±6 days, and the mean lengths of hospital and ICU stay were 19 and 15 days, respectively. The most prevalent comorbidities were arterial hypertension (55.7%) and diabetes mellitus (27.8%), as shown in Table 1. Fifteen patients died, resulting in a mortality rate of 24.6%. Invasive intensive support was used in a significant part of the sample, 59% of which required invasive ventilatory support, 57.4% required hemodynamic support with vasopressors at some point during hospitalization, and 36% underwent renal replacement therapy by use of hemodialysis.

The patients with myocardial injury had slightly longer lengths of hospital and ICU stay than those without troponin I elevation, but the difference was not statistically significant between the groups. Similarly, their prognostic assessment by use of the SAPS 3 score did not significantly differ, with an expected mortality of 55.7±27.1% among patients with myocardial injury and of 46.2±32.8% among those without myocardial injury ($p=0.2$), as shown in Table 1. On multivariate regression, the predictors of myocardial injury were systemic arterial hypertension (OR 9.198; 95%CI:

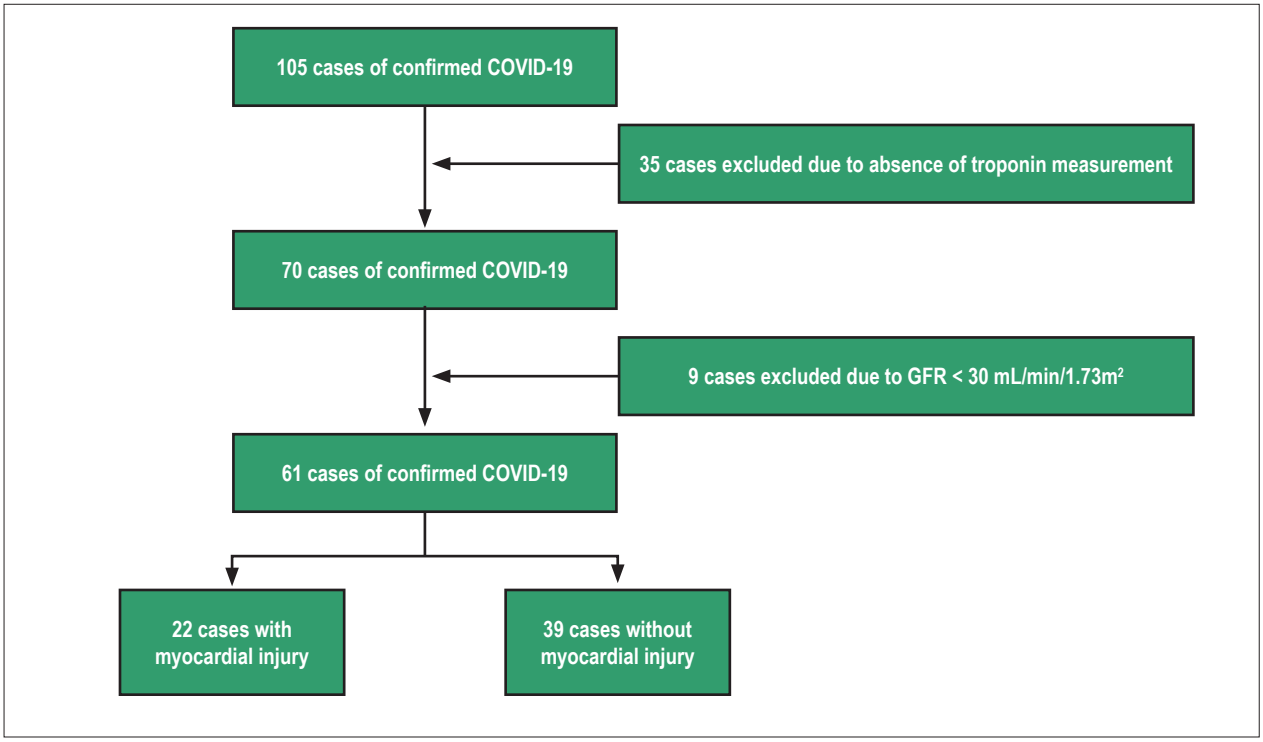

Figure 1 – *Flowchart for recruiting patients.*

2.246-37.665) and BMI (OR 1.143; 95%CI: 1.013-1.289), as shown in Table 2.

The ROC curve was analyzed to determine the high-sensitivity troponin I value capable of predicting in-hospital mortality. In Figure 2, the area under the ROC curve for the outcome was 0.786 (95%CI: 0.662-0.880; p = 0.001). The cut-off point for high-sensitivity troponin I was 48.3 ng/mL. In Kaplan-Meier analysis (Figure 3), the survival in the group with high-sensitivity troponin I over 48.3 ng/mL was 20.3 days (95%CI: 11.4-29.2), while the survival in the group with high-sensitivity troponin I below that value was 43.5 days (95%CI: 37.8-49.2), p = 0.0003. On Cox bivariate survival analysis stratified according to high-sensitivity troponin I, only age related to the outcome (RR=1.046; 95%CI: 1.006-1.087). On multivariate analysis, no variable was an independent predictor of survival.

Discussion

The term 'myocardial injury' is widely used to designate different pathophysiological processes that involve the death of cardiomyocytes and can include myocardial ischemia as a contributing cause. Different reports have shown association between that condition and the SARS-CoV-2 infection. However, the exact mechanism of myocardial injury in such cases and its prognostic importance are yet to be known.[3,5,7-9]

The most plausible causes of myocardial injury in patients with COVID-19 include myocarditis, hypoxemia, stress cardiomyopathy, acute *cor pulmonale*, and myocardial ischemia caused by microvascular dysfunction or epicardial coronary artery disease.[7-9,14] However, the isolated contribution of each cause to myocardial injury is yet to be determined. The current body of evidence about myocarditis caused by SARS-CoV-2 is scarce and sometimes lacks cardiac histological assessment and viral genome analysis, resulting in differential diagnosis based on clinical suspicion. In addition, the contribution of the angiotensin-converting-enzyme II signaling pathways to myocardial damage in this scenario has not been thoroughly investigated.

It has been postulated that SARS-CoV-2 infection involves an intense inflammatory response with a hypercoagulable state and ischemia aggravated by hypoxemia. In addition, the systemic inflammatory response can result in endothelial injury with consequent increase in thrombin generation and reduction in endogenous fibrinolysis.[15] Furthermore, intrinsic aspects of the novel coronavirus can contribute directly to myocardial injury, such as the cases with suspected myocarditis.[16-18] Several pathophysiological mechanisms have been proposed and can be summarized in the following 6 conditions: endothelial dysfunction, increased oxidative stress, hypoxemia, imbalance between myocardial oxygen supply and demand, immune-mediated myocardial injury, and possible direct myocardial injury by SARS-CoV-2.[18-20]

Although the rates may vary, up to 25% of the individuals hospitalized from COVID-19 are estimated to require intensive care.[3,4] Those rates vary according to cultural differences regarding the ICU admission criteria and regional

Table 1 – Characteristics of 61 patients admitted to the intensive care unit with and without myocardial injury

Characteristics	General population (n=61)	With myocardial injury (n=22)	Without myocardial injury (n=39)	p-value
General				
Age	66.1±15.5	67.8±15.8	65.2±16.3	0.6010
Male sex	39 (63.9%)	14 (63.6%)	25 (64.1%)	0.9710
From symptom to admission (days)	7±6	6±5	7±3	0.1410
Length of ICU stay (days)	14.5 [5.2-28.7]	18.0 [8.7-33.2]	10.0 [5-28]	0.6940
Length of hospital stay (days)	17.0 [9.0-36]	21.5 [9.7-36.2]	13.0 [9.0-37.7]	0.5720
SAPS 3	49.7±28	55.7±27.1	46.2±32.8	0.2120
Comorbidities				
Systemic arterial hypertension	34 (5.7%)	19 (86.4%)	15 (38.5%)	0.0001
Diabetes mellitus	17 (27.8%)	6 (27.3%)	11 (28.2%)	0.9380
CAD	4 (6.5%)	3 (13.6%)	1 (2.6%)	0.930
COPD	2 (3.2%)	2 (9.1%)	0 (0%)	0.0560
Neoplasm	4 (6.5%)	1 (4.5%)	3 (7.7%)	0.6340
Asthma	2 (3.2%)	0 (0%)	2 (3.3%)	0.2800
BMI (kg/m^2)	29.46±6.3	32±7.6	28±5.4	0.0220
Complications				
Mild ARDS	2 (3.2%)	0 (0%)	2 (5.1%)	0.2800
Moderate ARDS	18 (29.5%)	8 (36.4%)	10 (25.6%)	0.3780
Severe ARDS	17 (27.8%)	10 (45.5%)	7 (17.9%)	0.0210
Mechanical ventilation	36 (59%)	18 (81.8%)	18 (46.2%)	0.0070
Vasopressor use	35 (57.4%)	18 (81.8%)	17 (43.6.%)	0.0040
Venous thromboembolism	11 (18%)	6 (27.3%)	5 (12.8%)	0.1590
ARF with dialysis	22 (36%)	12 (54.5%)	10 (25.6%)	0.0240
Death	15 (24.6%)	9 (40.9%)	6 (15.4%)	0.0260

ICU: intensive care unit; SAPS 3: Simplified Acute Physiology Score III; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; BMI: body mass index; ARDS: acute respiratory distress syndrome; ARF: acute renal failure.

Table 2 – Multivariate analysis of myocardial injury predictors in patients admitted to the intensive care unit

Characteristics	OR	95%CI	p-value
Age	1.010	0.977-1.045	0.543
Male sex	0.980	0.330-2.907	0.971
Arterial hypertension	10.13	2.544-40.198	0.001
Coronary artery disease	6.0	0.584-61.619	0.132
Body mass index	1.108	1.009-1.218	0.033
SAPS 3	1.010	0.989-1.032	0.341

OR: odds ratio; 95%CI: 95% confidence interval; SAPS 3: Simplified Acute Physiology Score III.

characteristics, such as population age and prevalence of other comorbidities. Likewise, the fatality rates in the ICU range from 22% to 67%.[21-24] In an Italian study with 1591 patients, the ICU mortality was 26%; however, a significant part of the cohort remained at the ICU at the time of the study publication, which might have underestimated that indicator.[24] In our ICU, the mortality rate was 24.6%, which is below the expected mean according to the prognosis indicator SAPS 3 (49.7±28%).

The incidence of myocardial injury in patients hospitalized varies from 7% to 28%.[7-9] Recent Chinese studies have shown that patients with COVID-19 requiring intensive care are more likely to progress with myocardial injury, which is associated

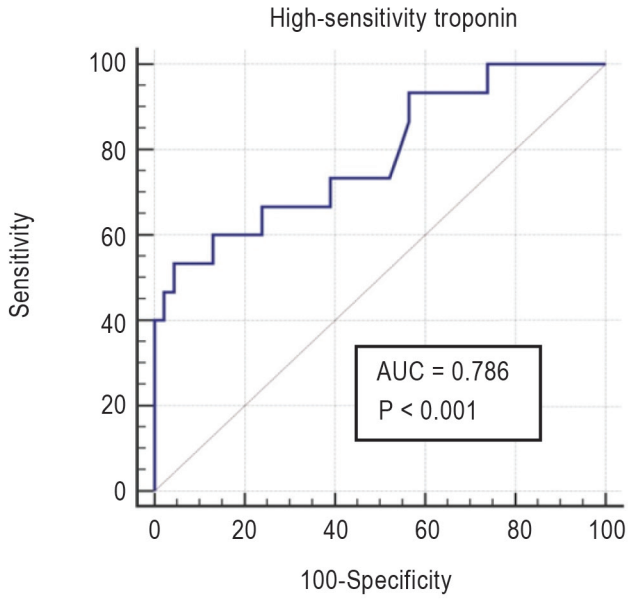

Figure 2 – *Prediction of in-hospital mortality based on troponin values. AUC: area under the ROC curve.*

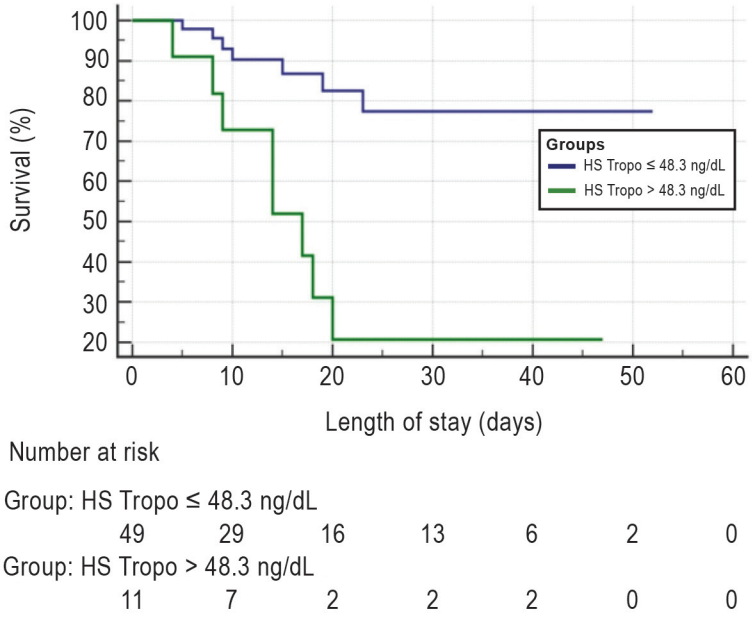

Figure 3 – *Survival of patients with COVID-19 admitted to the intensive care unit with and without myocardial injury, Kaplan-Meier method. HS-Tropo: high-sensitivity troponin.*

with a higher mortality risk.[5,25] Our study evidenced a high incidence of myocardial injury (36%) in a sample of patients admitted to a Brazilian ICU with the diagnosis of confirmed COVID-19, and systemic arterial hypertension was an independent risk factor for that complication. This pandemic and the need for strict control of hospital infection, including that by the novel coronavirus, have limited the use of complementary diagnostic methods, therefore hindering the ability to determine the mechanisms of myocardial injury.

An international prospective study, conducted between April, 3, and April, 20, 2020, with 1216 patients hospitalized from COVID-19, mostly in the ICU, aimed at assessing the major indications for echocardiography and the echocardiographic changes of the SARS-CoV-2-related cardiac impairment. The most common indications for echocardiography were: left ventricular failure (40%), elevated levels of cardiac biomarkers (26%), and right ventricular failure (20%). Left ventricular abnormalities were reported in 479 patients (39%), and the left ventricular impairment was classified as mild (17%), moderate (12%) or severe (9%). That study shows the cardiac impairment attributed to COVID-19, revealing a significant incidence of elevation in cardiac biomarkers and damage to the ventricular function in that population. However, the exact mechanism of myocardial injury cannot always be determined.[26]

In a recently published study, Giuseppe Lippi and Mario Plebani have reviewed 217 articles searching for laboratory tests that might have prognostic importance for the novel coronavirus infection. However, 206 articles were excluded because of lack of technical information on the data presented. In the remaining 11 articles, the following major laboratory abnormalities in patients with unfavorable progression of COVID-19 could be established: increased white blood cell count, increased neutrophil count, reduced lymphocyte count, decrease in albumin levels, increase in lactic dehydrogenase levels, increase in alanine aminotransferase levels, increase in aspartate aminotransferase levels, increase in total bilirubin levels, increase in creatinine levels, increase in cardiac troponin levels, increase in D-dimer levels, longer prothrombin time, and increase in procalcitonin and in C-reactive protein levels. Regarding troponin I, a retrospective analysis has shown that increases greater than 2.2 times the URL correlated with adverse clinical results.[27]

A study carried out with 2736 patients with COVID-19 admitted to the Mount Sinai Health System hospitals in New York city between February 27, 2020, and April 12, 2020, has reported that even small amounts of myocardial injury, quantified by troponin elevation, mainly in patients with history of cardiovascular disease were associated with high risk of death.[28] Despite its small sample size, our study could show the statistical significance of the association between troponin I levels greater than 2.5 times the URL and in-hospital mortality, and the cut-off point was determined by use of the ROC curve. This shows that even modest elevations in that cardiac biomarker can help identify individuals at risk for adverse events. However, the use of different laboratory methods is the major limiting factor of the analysis of a cut-off point for large population clusters, with studies being conducted at single centers. The higher diversity of the methodologies of the articles on that subject might require assessment by use of meta-analysis to better determine the cut-off point related to worse clinical outcomes.

The small number of patients included in this study and the lack of data on the frequency of myocardial injury in asymptomatic or mildly symptomatic SARS-CoV-2-infected patients are important limitations. The ICU protocol may have influenced the sampling, because, after admission, the biomarker was measured again if a change in the clinical status or in complementary tests occurred. Another important aspect was the sample loss greater than 10% caused by the absence of troponin measurement. However, that could not prevent the association of death with troponin elevation, but might have selected the most severe cases, whose troponin levels were measured, and the data obtained served as part of an exploratory research in a retrospective cohort about the theme. To prevent statistical bias, data from multiple centers and larger samples are necessary to confirm the results presented.

Conclusion

In the sample studied, the incidence of myocardial injury among patients admitted to the ICU with the diagnosis of confirmed COVID-19 was 36%, and systemic arterial hypertension and BMI were independent risk predictors. This study showed the impact of myocardial injury on mortality. In addition, survival in the group with high-sensitivity troponin I levels higher than 43.8 ng/dL was lower than that in the group with high-sensitivity troponin I levels lower than that value.

Author contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Statistical analysis, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Nascimento JHP, Costa RL, Simvoulidis LFN, Pinho JC, Pereira RS, Porto AD, Silva ECF, Oliveira LP, Ramos MRF, Oliveira GMM

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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References

1. Organização Mundial da Saúde. OMS.Relatórios de situação da doença coronavírus 2019 (COVID-2019). Organização Mundial de Saúde. [Citado em 2010 jul 15]Disponível em: <https://who.sprinklr.com/>.
2. Brasil.Ministério da Saúde. Situação epidemiológica da COVID-19 no Brasil. [Acesso em 2020 jul 14].Disponível em: <https://covid.saude.gov.br/>.
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497.
4. Wu Z, McGoogan JM. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;10.1001/jama.2020.2648.
5. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020 Feb 7;323(11):1061-9.
6. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020;368:m1091.
7. Arentz M, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, et al. Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. JAMA. 2020 Mar 19;323(16):1612-4.
8. Lippi G, Lavie CJ, Sanchis-Gomar F. Cardiac troponin I in patients with coronavirus disease 2019 (COVID-19): Evidence from a meta-analysis. Prog Cardiovasc Dis. 2020 Mar 10.ahead print
9. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. JAMA Cardiol. 2020 Mar 25:e200950.
10. World Health Organization. (WHO) Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected: interim guidance.[Cited in 2020 mar 12] Disponível em: <https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected>.
11. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth Universal Definition of Myocardial Infarction (2018). J Am Coll Cardiol. 2018;72(18):2231.
12. The ARDS Definition Task Force. Acute Respiratory Distress Syndrome: The Berlin Definition. JAMA. 2012; May 21, 2012: ahead print
13. RP. Moreno, RA Campos, et al. SAPS 3: from evaluation of the patient to evaluation of the intensive care unit. Intensive Care Med (2005) 31:1345-55.
14. Creel-Bulos C, Hockstein M, Amin N, Melhem S, Truong A, Sharifpour M. Acute Cor Pulmonale in Critically Ill Patients with Covid-19. N Engl J Med. 2020;382(21):e70.
15. Nascimento JHP, Gomes BFO, Petriz JLF, Carmo Junior PR, Rizk SI, Costa IBSS, et al. COVID-19 e estado de hipercoagulabilidade: uma nova perspectiva terapêutica Arq Bras Cardiol. 2020;114(5):829-33.
16. Zeng JH, Liu YX, Yuan J, Wang FX, Wu WB, Li JX, et al. First case of COVID-19 infection with fulminant myocarditis complication: case report and insights. *Life Sci.* 2020 March 11.ahead print
17. Hu H, Ma F, Wei X, Fang Y. Coronavirus fulminant myocarditis treated with glucocorticoid and human immunoglobulin. *Eur Heart J.* 2020 Mar 16.ahead print
18. Inciardi RM, Lupi L, Zaccone G, Italia L, Raffo M, Tomasoni D, et al. Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 2020; March 27,ahead print
19. Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardiol 2020; 17:259.
20. Tersalvi G, Vicenzi M, Calabretta D. Elevated Troponin in Patients With Coronavirus Disease 2019: Possible Mechanisms. J Card Fail 2020.ahead print.
21. Murthy S, Gomersall CD, Fowler RA. Care for Critically Ill Patients With COVID-19. JAMA. 2020, ahead print
22. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet. 2020.ahead print.
23. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020.ahaed print.
24. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA. 2020 ahead print.
25. Shaobo Shi MD, Mu Qin MD, Bo Shen MD, Yuli Cai MD, Tao Liu MD, Fan Yang, MD. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. *JAMA Cardiol*. Published online March 25, 2020.ahead print.
26. Dweck MR, Bularga A, Hahn RT, Bing R, Lee KK, Chapman AR, et al. Global evaluation of echocardiography in patients with COVID-19. Eur Heart J – Cardiovasc Imaging (2020) 0, 1-10.
27. Lippi G, Plebani M. (2020). Laboratory abnormalities in patients with COVID-2019 infection, Clin Chem Lab Med. (CCLM), 58(7), 1131-4.
28. Lala A Kipp Johnson KW, Januzzi JL, Russak AJ, Paranjpe I, Richter F, et al. Prevalence and Impact of Myocardial Injury in Patients Hospitalized With COVID-19 Infection. J Am Coll Cardiol. 2020;76:533–46.

Association of Cardiac Injury with Mortality in Hospitalized Patients with COVID-19

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Short Editorial related to the article: COVID-19 and Myocardial Injury in a Brazilian ICU: High Incidence and Higher Risk of In-Hospital Mortality

Covid-19 disease emerged in December 2019 in Wuhan City, Hubei Province, China. It is caused by the new coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the seventh coronavirus identified to date, which is different from other coronaviruses that cause pneumonia and common cold.[1] Due to the greater and faster transmissibility, a pandemic was declared by the World Health Organization on 11 March 2020.[2]

Since then, several studies worldwide have been conducted and published with the aim of determining the risk factors for developing the disease, as well as its complications, degrees of severity, treatment, morbidity, and mortality.

One of the initial studies was conducted by the Chinese Center for Disease Control and Prevention, which evaluated the degree of severity of 72,314 patients with Covid-19 in this population. In 81.4% of the cases, the disease was classified as mild, severe in 13.9%, and critical in 4.7%.[3]

Regarding cardiac involvement, the manifestation occurs with myocardial injury, which is defined by high levels of troponin, and it occurs especially due to non-ischemic myocardial processes, including respiratory infection with severe hypoxia, sepsis, systemic inflammation, pulmonary thromboembolism, cardiac adrenergic hyperstimulation during cytokine storm syndrome, and possibly myocarditis due to direct action of the virus. Ischemic etiology is also present due to rupture of coronary atherosclerotic plaque, coronary spasm, microthrombi, or direct endothelial lesion.[4]

A significant aspect that has been described is that patients with myocardial injury are associated with a greater need for ventilatory support and in-hospital mortality. They are generally older patients with a higher prevalence of systemic arterial hypertension, diabetes mellitus, coronary artery disease, and heart failure.[5]

In a systematic review of 4 studies with 374 patients, troponin I levels were significantly higher in patients with severe Covid-19 compared to those with non-severe forms of the disease.[6]

Keywords

COVID-19; Coronavirus, Betacoronavirus, SARS CoV-2, Infection; Myocarditis; Myocardial Infarction; Hospitalization; Morbidity.

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Regarding prevalence, studies developed in China have reported myocardial injury with elevated troponin levels ranging from 7% to 17% in hospitalized patients, from 22% to 31% among patients admitted to intensive care units (ICU), and up to 59% of patients who died.[7,8] This variation in the incidence of myocardial injury has been replicated in various publications in different centers, and it has also been demonstrated in a meta-analysis of 10 studies involving 3,118 patients in Wuhan, China, with a prevalence of myocardial injury ranging from 15% to 44%; the combined effect of these studies showed that, in patients with high troponin, the mortality risk was 21 times higher (OR = 21.15).[9] This variation reflects the heterogeneity of the definitions of myocardial injury and of the population studied and regional characteristics, which will in some way also reflect the lethality rates, with data showing an incidence of 13% to 67% of patients with elevated troponin hospitalized in the ICU.[9]

Therefore, a Brazilian study is necessary to evaluate the presence of myocardial injury in our population, with regard to the mortality of this group of patients, as well as the presence of comorbidities as a predictor of death.

In this edition, Brazilian[10] authors present the results of an observational, retrospective study conducted in the ICU of a private hospital in Rio de Janeiro, between March and April 2020. Initially, 105 confirmed cases of Covid-19 were included. After excluding 35 patients due to the absence of troponin I and 9 due to severe renal failure, 61 patients remained, and 36% of them presented myocardial injury with elevated troponin I. The primary objective was to describe the incidence of myocardial injury and to identify variables associated with its occurrence. The secondary objective was to evaluate ultrasensitive troponin I as a predictor of hospital mortality.

After univariate analysis and multivariate logistic regression of a series of general variables and comorbidities, the predictors of myocardial injury with statistical significance were systemic arterial hypertension and body mass index. The mortality rate of this group was 24.6%, and the troponin I value was related to hospital mortality.

Although this study has important limitations, such as a small number of patients and loss of cases due to the absence of troponin I dosage, the impact of myocardial injury on in-hospital mortality and the identification of risk predictors such as systemic arterial hypertension and body mass index were demonstrated.

More robust, multicenter national studies may confirm the findings revealed in this study and draw a profile of the Brazilian population.

References

1. Wei-jie G, N Z-y, Hu Y, Liang W-h, Ou Cq, et al."Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708-20.
2. WHO Director-General's opening remarks at the media briefing on COVID19 - March 2020. [Cited in 2021 Jan 12] Available from: who.int/diretor-general/speeches/details/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19-11-march-2020
3. Wu Z, McGoogan JW. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA.2020;323(13):1239-42.
4. Massimo I,Croft LB, Oates CP, Takotsubo T. "COVID-19 pandemic and troponin: indirect myocardial injury, myocardial inflammation or myocarditis?. Heart.2020 [Epub ahead print]2020-317186. Doi 10.1136/heartjnl
5. Giustino G. "Coronavirus and Cardiovascular Disease, Myocardial Injury, and Arrhythmia: JACC Focus Seminar. J Am Coll Cardiol.2020;76(17):2111-23.
6. Lippi G, Lavie CJ, Sanchis Gomar F.Cardiac troponin I in patients with coronavirus disease 2019 (COVID-19): Evidence from a meta-analysis.Progr Cardiovasc Dis. 2020;63(3):390-1.
7. Zhou F, Yu T, D R, Fan G, Liu Y, Liu Z.Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet.2020;395(10229):1038.
8. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA.2020;323(11):1061-9.
9. Xintao J,Guan Bo, Su T, Liu W, Chen M, Waleed KB, et al. Impact of cardiovascular disease and cardiac injury on in-hospital mortality in patients with COVID-19: a systematic review and meta-analysis. Heart.2020;106(25):11754-74.
10. Nascimento JH, Costa RL, Simvoulidis LFN, PinhoJC, Pereira RS, Porto AD, et al. COVID-19 e injúria miocárdica em UTI brasileira: alta incidência e maior risco de mortalidade intra-hospitalar. Arq Bras Cardiol. 2021; 116(2):275-282.

Association between Statin Therapy and Lower Incidence of Hyperglycemia in Patients Hospitalized with Acute Coronary Syndromes

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Abstract

Background: Increased risk of new-onset diabetes with statins challenges the long-term safety of this drug class. However, few reports have analyzed this issue during acute coronary syndromes (ACS).

Objective: To explore the association between early initiation of statin therapy and blood glucose levels in patients admitted with ACS.

Methods: This was a retrospective analysis of patients hospitalized with ACS. Statin-naïve patients were included and divided according to their use or not of statins within the first 24 hours of hospitalization. The primary endpoint was incidence of in-hospital hyperglycemia (defined as peak blood glucose > 200 mg/dL). Multivariable linear and logistic regression models were used to adjust for confounders, and a propensity-score matching model was developed to further compare both groups of interest. A p-value of less than 0.05 was considered statistically significant.

Results: A total of 2,357 patients were included, 1,704 of them allocated in the statin group and 653 in the non-statin group. After adjustments, statin use in the first 24 hours was associated with a lower incidence of in-hospital hyperglycemia (adjusted OR=0.61, 95% CI 0.46-0.80; p < 0.001) and lower need for insulin therapy (adjusted OR = 0.56, 95% CI 0.41-0.76; p < 0.001). These associations remained similar in the propensity-score matching models, as well as after several sensitivity analyses, such as after excluding patients who developed cardiogenic shock, severe infection or who died during index-hospitalization.

Conclusions: Among statin-naïve patients admitted with ACS, early statin therapy was independently associated with lower incidence of in-hospital hyperglycemia. (Arq Bras Cardiol. 2021; 116(2):285-294)

Keywords: Statins; Acute Coronary Syndrome; Myocardial Infarction; Blood Glucose; Hidroxymethylglutaryl-CoA-Reductase Inhibition.

Introduction

There is established evidence that statins improve cardiovascular outcomes among patients with stable coronary artery disease (CAD).[1,2] At the same time, patients with increased risk of CAD but without overt atherosclerosis may also derive benefit,[3,4] making guidelines to recommend statins for those two groups.[5] Also, statins play an important role in acute coronary syndromes (ACS)[6,7] and, in patients submitted to percutaneous revascularization, early therapy can confer additional benefit.[8,9] Despite these benefits, concerns have been raised about increased risk of new onset diabetes mellitus (DM) with long-term statin therapy.[10-12] Furthermore, statins can worsen glucose control in patients with known diagnosis of DM, or anticipate progression to overt DM in those with metabolic syndrome, impaired fasting blood glucose and glucose intolerance.[13,14] Many possible mechanisms have been proposed to explain the influence of statins over glycemia.[15] Statins could impair beta-cell function and decrease insulin secretion, a pathway directly related to inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase or to other potential intracellular mechanisms.[16,17] On the other hand, there is also some evidence that statins could decrease insulin resistance, thus compensating for the harmful mechanism mentioned before.[18]

While there is a huge body of data about long-term influence of statins over glycemia in stable CAD patients, there are scarce data in individuals with ACS. Despite the

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aforementioned concerns with impaired glucose tolerance in the long-term, due to their anti-inflammatory effects,[19,20] statins could potentially decrease inflammation in the acute phase of ACS and thus indirectly reduce blood glucose levels related to the acute phase stress. Therefore, we hypothesized that, in patients hospitalized with ACS, early statin therapy would be associated with lower incidence of hyperglycemia during hospitalization in the coronary care unit (CCU).

Methods

Population and variables selection

We performed a retrospective data analysis of patients admitted with a diagnosis of ACS at the CCU of the Heart Institute of Sao Paulo University Medical School (*Instituto do Coração da Faculdade de Medicina da Universidade de São Paulo*). All consecutive patients admitted to our CCU with a diagnosis of ACS were prospectively registered in a dedicated database from January 1st, 1998 through May 1st, 2019. We identified statin-naïve patients at hospital admission and compared patients who received statins in the first 24 hours of admission (and continued during the whole hospitalization) versus those who did not.

Variables concerning ACS type – ST-elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), or unstable angina (UA) – baseline demographic characteristics, risk factors, past CAD history or procedures, concomitant medications and baseline laboratory results were also collected. Blood glucose was obtained by blood sample daily; the first blood glucose level (admission glucose level) and the highest blood glucose level during hospitalization (i.e., peak glucose level) were registered in the database for further analysis.

We defined an ACS case as any patient presenting with new-onset ischemic symptoms at rest or worsening exertional ischemic symptoms requiring urgent hospital admission within the first seven days of symptoms onset. Myocardial infarction (MI) was defined according to the current Universal Definition of MI during data collection. STEMI was defined as persistent ST elevation of at least 1 mm in two or more contiguous leads (except V2-V3, where at least 1.5 mm was required in women and men older than 40 years and at least 2 mm in men younger than 40 years) or new/presumably new left bundle branch block at admission electrocardiogram (ECG). Cases not fulfilling criteria for MI were classified as UA. Patients were excluded if they were taking any statin immediately prior to index-hospitalization or if they did not have information regarding blood glucose levels or statin therapy at index hospitalization.

The primary outcome of interest in our analysis was the occurrence of in-hospital hyperglycemia, defined as peak blood glucose level > 200 mg/dL at any time during hospitalization, and secondary outcomes were peak blood glucose > median value of the peak blood glucose in our sample, and hyperglycemia requiring intravenous insulin therapy. This cut-off of 200 mg/dL was based on the most recent guidelines considering the suggested target level for glucose control in patients with ACS.[21] We also explored the associations between hyperglycemia and in-hospital mortality.

Laboratory routine

Every patient admitted with ACS had blood drawn from a forearm vein by venipuncture during admission. Blood was then centrifugated and sent to the laboratory, where glucose was determined by a standard procedure. For this first sample, fasting was not required, since we were interested in the first random blood glucose after ACS presentation. For further measures, fasting blood glucose was obtained, together with other routine laboratory samples.

Statistical analysis

Categorical variables were compared with $\chi 2$ or Fisher's exact tests as appropriate and were described as absolute numbers and percentages. Continuous variables are described as means ± standard deviations or median with interquartile ranges (IQR) and were compared with two-sample Student's t-test (normal distribution) or the Mann-Whitney test (non-Gaussian distribution), as appropriate. Shapiro-Wilk test and visual analysis of histograms were used for normality testing.

Specifically, the Mann-Whitney test was used in the unadjusted analyses to compare the continuous outcomes of blood glucose between the two groups of interest. For the unadjusted analyses regarding the binary outcomes (incidence of hyperglycemia and in-hospital death), univariate logistic regression models were used.

In order to adjust for confounders, multivariable regression models were used in the adjusted analyses. Log-transformed blood glucose levels for the admission and peak glycemia were included in a multiple linear regression model. Transformation was done to meet normality of residuals assumption in the model. The model included as independent variables the baseline demographic data and comorbidity-related variables. A stepwise selection procedure was used to fit the model, with a threshold p-value of 0.2 to remove covariates and 0.05 for to add covariates in the model. A logistic regression model was also built following the same steps to assess hyperglycemia as a categorical variable (considering the three aforementioned definitions) and in-hospital death. Those models were adjusted for the following covariates: age, race, sex, DM, hypertension, hypercholesterolemia, smoking, heart failure (HF), prior MI, prior percutaneous coronary intervention (PCI), prior coronary artery bypass graft (CABG), prior stroke, creatinine clearance (CrCl) < 60 mL/min, ACS phenotype (STEMI versus NSTEMI or UA), Killip class 2 or more, year of admission (before or after 2010, which was the midpoint of the time span of the database), type of health insurance coverage (private versus government-funded), and GRACE (Global Registry of Acute Coronary Events) score.[22] Values of glycated hemoglobin (HbA1c) and body mass index (BMI) were not available for all patients and were not included in the main model, but were included in sensitivity analyses (see below).

Additionally, a propensity score matching model was developed, considering the probability of receiving statin in the first 24 hours after admission. The model was built from a logistic regression and used a nearest neighbor of 1 and a caliper of 0.001, using the same variables used in the regression models. After matching, baseline variables were checked between the two groups to verify whether there remained imbalances, with both a p-value above 0.10 and a

standardized mean difference less than 10% considered as appropriate, according to previous literature on the topic.[23]

For sensitivity analysis, we also ran additional models adjusting for all baseline variables, and for the use of aspirin, angiotensin converting-enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), oral betablockers, $P2Y_{12}$ inhibitor, unfractionated heparin, low-molecular-weight heparin, intravenous betablockers, nitrates, and intravenous glycoprotein IIbIIIa inhibitors in the first 24 hours of admission. Besides that, we also ran a model including BMI in kg/m^2 and another one including HbA1c at hospital admission as covariates. Finally, we also ran models excluding patients who developed cardiogenic shock, severe infection or who have died during the index hospitalization.

No imputation was used for missing data. Only individuals with valid information regarding statin use and blood glucose levels were included. All tests are two-tailed. A p-value of less than 0.05 was considered statistically significant. The software Stata™ version 15.1 (Statacorp, College Station, TX, USA) was used for statistical calculations.

Results

Descriptive analyses

Out of 7,099 patients included in the database between January 1st 1998 through May 1st 2019, a total of 2,357 statin-naïve patients were included in this analysis – 1,704 were administered statin in the first 24 hours of hospital admission and 653 not (Figure 1). In the overall study population, the mean age was 62.9 ± 12.6 years, 713 patients (30.3%) were female, 789 (33.5%) had a history of known DM at admission, and 1,073 (45.5%) had STEMI as the clinical ACS presentation (Table 1).

As expected, there were several differences between patients taking statins compared with those not taking statins in the first 24 hours of hospitalization. Patients taking statins were younger, and more likely to have a history of hypertension, DM and CrCl < 60 mL/min at admission, among other differences. Also, they were more likely to have been included in the database after January 2010. Conversely, they were less likely to be white and to have private health insurance (Table 1). Patients taking statins in the first 24 hours were also more likely to be treated with aspirin, $P2Y_{12}$ inhibitor and ACEI or ARB in the first 24 hours (Table 1). In terms of baseline laboratory values, patients taking statins in the first 24 hours had higher levels of triglycerides and a trend for higher levels of HbA1c, but similar levels of total cholesterol, LDL-cholesterol, and HDL-cholesterol (Table 1).

Association between statin use in the first 24 hours and blood glucose levels

In the unadjusted analysis, blood glucose levels at admission were not different between patients taking statins and those not taking statins in the first 24 hours. However, patients taking statins in the first 24 hours, as compared to those not taking, had lower peak blood glucose (Table 2A).

In the adjusted multivariable analysis, statin therapy in the first 24 hours remained independently associated with lower peak blood glucose during index hospitalization (adjusted geometric means 139.0 versus 150.3 mg/dL, respectively; 95% CI of the difference of -15.9 to -6.5 mg/dL, adjusted p < 0.001). After adjustments, there remained no significant differences in admission blood glucose (Table 2B).

In a propensity score matched analysis, 500 patients from the statin group were matched with a similar number of patients from the group without statin therapy. After matching, baseline characteristics used to build the model were well balanced between the two groups, without any p-value < 0.10 nor any standardized mean difference > 10 % (Supplementary Table 1 and Supplementary Figure 1). Considering the propensity score matched analysis, statin therapy remained significantly associated with lower levels of peak blood glucose (Supplementary Table 2).

Association between statin and occurrence of in-hospital hyperglycemia

In the unadjusted analysis, statin therapy in the first 24 hours was associated with lower incidence of hyperglycemia, including peak blood glucose above 200 mg/dL, peak blood glucose above the median, and hyperglycemia with the need for insulin therapy (Supplementary Table 3).

After adjusted multivariable analysis, statin therapy remained independently associated with lower incidence of peak blood glucose above 200 mg/dL (adjusted OR = 0.61, 95% CI 0.46-0.80; p < 0.001), as well as peak blood glucose above the median and hyperglycemia requiring insulin therapy (See Supplementary Table 3 and Figure 2A for more details).

In the propensity score matching analysis, results were similar to those obtained in the multivariable regression approach, with significant associations between statin use and lower risk of hyperglycemia according to all three definitions (Supplementary Table 3 and Figure 2B).

Sensitivity analyses

Associations between statin therapy and lower incidence of hyperglycemia (peak blood glucose > 200 mg/dL) remained consistent after several sensitivity analyses were conducted, such as including other concomitant medications in the model. Results for the primary endpoint also remained consistent in a model that considered the date of inclusion in the database as a continuous variable. In another analysis, where patients were stratified according to period of inclusion (before versus after January 2010), there was no significant effect modification for the primary endpoint Additionally, when patients who developed cardiogenic shock or severe infection, or who did not survive up to hospital discharge were excluded from the analysis, there remained significant associations between use of statin in the first 24 hours and lower occurrence of hyperglycemia. Finally, in models that included HbA1c (%) or BMI as covariates, although the point estimates for the OR´s remained similar, no significant association remained, probably due to the small number of patients with those two variables available. These results are described in Supplementary Tables 4 to 11.

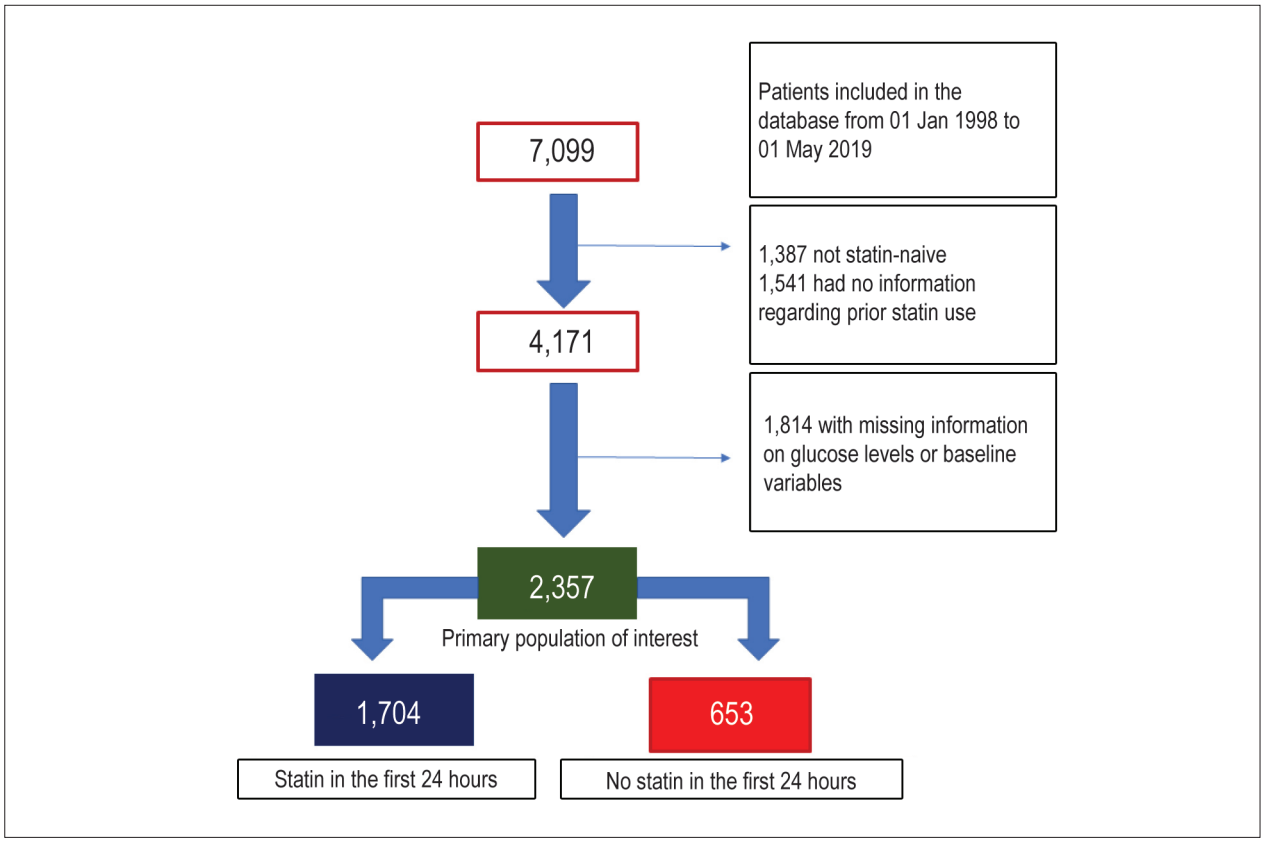

Figure 1 – *Flowchart of patients' selection and allocation process.*

Association between blood glucose levels and in-hospital mortality

In the overall study population, higher peak blood glucose levels were independently associated with higher in-hospital mortality (OR 1.05; 95%CI 1.03-1.07 for every 10 mg/dL; $p < 0.001$). On the other hand, admission blood glucose was not independently associated with in-hospital mortality (Table 3).

Discussion

Study main findings

There are several important results of this study. First, that statin use in the first 24 hours of hospitalization in ACS was highly associated with comorbidities and, more importantly, there was an important temporal association, such that, in our data, a large difference existed between patients included before versus patients included after 2010. This is likely related to the body of evidence accumulated regarding the use of statins in ACS,[6,7] although there is no guideline recommendation supporting initiation of statin therapy within the first 24 hours of hospital admission.[5,21] Second, there was an independent association between early statin therapy and lower incidence of in-hospital hyperglycemia. This association was observed in two different adjusted models (logistic regression and propensity score matching) and after several sensitivity analyses performed to verify the consistency of the findings. Therefore, despite the established risk of new-onset DM in the chronic phase, our results probably exclude any apparent harm, or impairment in glucose tolerance with statins during the acute phase of ACS, a period where the surge of catecholamines and inflammatory mediators may increase susceptibility to stress hyperglycemia and its potential clinical consequences.[24]

Comparison with previous studies

Despite the vast literature investigating the effects of statins over impaired glucose tolerance chronically, few reports have investigated any possible effect in the acute scenario. Yan et al.[25] have reported a higher risk of stress hyperglycemia in patients with acute MI receiving statins, but the lack of adjusted analysis and the arbitrary cut-off for stress hyperglycemia weaken the conclusions of that study. Sposito et al.[26] studied this issue in patients hospitalized with STEMI, showing that simvastatin 80 mg decreased insulin sensitivity compared to simvastatin 10 mg assessed by euglycemic hyperinsulinemic clamp.[26] Although these results appear to contrast to ours, the inclusion of only patients without DM and the use of euglycemic hyperinsulinemic clamp limit the generalization of their finds to a real-world scenario such as our study. Nevertheless, it is possible that, despite an adverse effect over insulin resistance early in the acute phase of ACS, statins could compensate for that by reduction in inflammatory response, leading to a decrease in glucose blood levels.

Table 1 – Baseline characteristics, laboratory values, medications in the first 24 hours and revascularization strategies for the index-event according to study groups

Variables	Total (N = 2357)	Statin group (N=1704)	No statin group (N=653)	p-value
White race	2102 (89.2)	1500 (88.0)	602 (92.2)	0.004
Female sex	713 (30.3)	522 (30.6)	191 (29.3)	0.51
Age in yrs; mean ± SD	62.9 ± 12.6	62.6 ± 12.5	63.8 ± 12.9	0.038
Diabetes	789 (33.5)	591 (34.7)	198 (30.3)	0.045
Hypertension	1688 (71.6)	1246 (73.1)	442 (67.7)	0.009
Dyslipidemia	1241 (52.7)	912 (53.5)	329 (50.4)	0.17
Smoking	611 (25.9)	450 (26.4)	161 (24.7)	0.39
Prior MI	653 (27.7)	461 (27.1)	192 (29.4)	0.25
Prior CABG	327 (13.9)	234 (13.7)	93 (14.2)	0.75
Prior PCI	413 (17.5)	304 (17.8)	109 (16.7)	0.51
Prior stroke	113 (4.8)	87 (5.1)	26 (4.0)	0.25
Prior HF	212 (9.0)	162 (9.5)	50 (7.7)	0.16
CrCl ≤ 60 mL/min	1316 (55.8)	1053 (61.8)	263 (40.3)	< 0.001
STEMI as index-event	1073 (45.5)	781 (45.8)	292 (44.7)	0.63
Killip class 2 or more	447 (19.0)	308 (18.1)	139 (21.3)	0.075
GRACE score, mean ± SD	141.6 ± 47.5	140.5 ± 46.7	144.3 ± 49.4	0.14
Public health insurance	1736 (73.7)	1334 (78.3)	402 (61.6)	< 0.001
Included after jan-2010	950 (40.3)	870 (51.0)	80 (12.2)	< 0.001
BMI in kg/m^2, median (IQR)[1]	25.7 (23.4 – 28.7)	25.7 (23.3 – 28.6)	25.9 (25.0 – 29.1)	0.19
Total cholesterol in mg/dL, median (IQR)[2]	182 (151-215)	182 (150-217)	178 (152-213)	0.51
LDL cholesterol in mg/dL; median (IQR)[2]	113 (87 – 143)	114 (86 – 144)	113 (90- 141)	0.96
Triglycerides in mg/dL; median (IQR)[2]	128 (91-180)	129 (92-184)	122 (89-171)	0.042
HDL cholesterol in mg/dL; median (IQR)[2]	37 (31-44)	37 (31-44)	38 (31-45)	0.36
HbA1c in %; median (IQR)[3]	5.9 (5.6 – 6.8)	5.9 (5.6 – 6.8)	5.9 (5.3 – 6.5)	0.054
Aspirin	2247 (95.4)	1646 (96.7)	601 (92.0)	< 0.001
P2Y12 inhibitor[4]	1199 (50.9)	1024 (60.1)	175 (26.8)	< 0.001
Oral beta-blocker	1424 (60.4)	1048 (61.5)	376 (57.6)	0.081
Intravenous beta-blocker	189 (8.0)	95 (5.6)	94 (14.4)	< 0.001
Nitrate	1461 (62.0)	1002 (58.8)	459 (70.3)	< 0.001
LMWH	1326 (56.3)	1099 (64.5)	227 (34.8)	< 0.001
UFH	772 (32.8)	463 (27.2)	309 (47.3)	< 0.001
ACEI/ARB	1651 (70.1)	1227 (72.0)	424 (64.9)	0.001
GpIIbIIIa inhibitor	867 (36.8)	632 (37.1)	235 (36.0)	0.62
Primary PCI	544 (23.1)	409 (24.0)	135 (20.7)	0.086
Fibrinolytic	264 (11.2)	195 (11.4)	69 (10.6)	0.55
Revascularization for the index event[5]				
PCI	1341 (56.9)	986 (57.9)	355 (54.5)	0.13
CABG	423 (18.0)	285 (16.7)	138 (21.1)	0.013
Medical management	637 (27.0)	460 (27.0)	177 (27.1)	0.96

Data are for n and % unless otherwise specified; 1- information about BMI was available for 287 patients; 2- information about cholesterol panel was available for 2062 patients; 3- information about HbA1c was available for 540 patients; 4- Seven patients, all in the statin group, were taking ticagrelor within the first 24 hours of admission, and all remaining patients on a $P2Y_{12}$ inhibitor were taking clopidogrel; 5- CABG and PCI are not necessarily mutually exclusive since some patients may have been submitted to both. ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; CABG: coronary artery bypass grafting; CrCl: creatinine clearance; GpIIbIIIa: glycoprotein IIbIIIa; GRACE: Global Registry of Acute Coronary Events; HF: heart failure; IQR: inter-quartile range; LMWH: low molecular weight heparin; MI: myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction; UFH: unfractionated heparin.

Table 2A – Unadjusted analysis[1]: median values of the first blood glucose level and peak blood glucose according to statin treatment groups

	Statin group (N=1704)	No statin group (N=653)	P-value
First blood glucose level (mg/dL); median (IQR)	116 (97 – 159)	113 (95 – 153)	0.22
Peak blood glucose (mg/dL); median (IQR)	124 (101 – 175)	134 (106 – 196)	< 0.001

Table 2B – Multivariable analysis[2]: adjusted geometric means of the blood glucose level according to statin treatment group

	Statin group (N=1704)	No statin group (N=653)	95% CI of the difference	Adjusted p-value
1st blood glucose in mg/dL	124.4	125.2	- 5.2 to 3.3	0.64
Peak blood glucose in mg/dL	139.0	150.3	-15.9 to -6.5	< 0.001

Adjusted for age, race, sex, diabetes, hypertension, hypercholesterolemia, smoking, heart failure, prior myocardial infarction, prior percutaneous coronary intervention, prior coronary artery bypass graft, prior stroke, creatinine clearance < 60 ml/min, ACS phenotype (STEMI versus NSTEMI), Killip class 2 or more, GRACE score, health insurance coverage status and period of inclusion (before versus after January 2010) 1- Unadjusted analysis made by Mann Whitney test. 2- Multivariable analysis performed by multivariate linear regression

Table 3 – Associations between blood glucose levels and in-hospital death

	Unadjusted OR (95% CI); p-value	Adjusted OR (95% CI); p-value
Admission blood glucose (for every 10 mg/dL)	1.03 (1.01 – 1.06); < 0.001	1.02 (0.99 – 1.04); 0.12
Peak blood glucose (for every 10 mg/dL)	1.06 (1.04 – 1.08); < 0.001	1.05 (1.03 – 1.07); < 0.001
Admission blood glucose > 200 mg/dL	1.72 (1.15 – 2.56); 0.008	1.42 (0.90-2.24); 0.14
Peak blood glucose > 200 mg/dL	3.06 (2.20-4.28); <0.001	2.70 (1.76-4.16); <0.001

Adjusted for: age, race, sex, diabetes, hypertension, hypercholesterolemia, smoking, heart failure, prior myocardial infarction, prior percutaneous coronary intervention, prior coronary artery bypass graft, prior stroke, creatinine clearance < 60 ml/min, ACS phenotype (STEMI versus NSTEMI), Killip class 2 or more, GRACE score, type of health insurance and period of inclusion (before versus after January 2010). Models were performed using univariate logistic regression for unadjusted analyses and multivariate logistic regression for adjusted analyses

The association between statins and lower blood glucose in stress situations could be at least partially explained by the direct effects of statins on inflammation, which is well-established in the literature.[19] Other reports have suggested that those pleiotropic effects from statins may occur early in the course of ACS. Two randomized studies have demonstrated that short-duration (less than 5 days) treatment with rosuvastatin, compared to placebo, decreased the incidence of post-contrast acute kidney injury.[27,28] This effect seemed to be mediated by an anti-inflammatory action, since no lipid-lowering effect would be expected in such a short timeframe.[29] Additionally, an early statin loading has been found to decrease the incidence of peri-procedural MI in one meta-analysis.[8] However, a larger randomized study, the SECURE-PCI trial, did not find a decrease in ischemic events after ACS with an 80 mg loading dose of atorvastatin,[9] despite a potential benefit in the subgroup of patients who were submitted to PCI after randomization.[30]

Hyperglycemia and mortality after ACS

The impact of hyperglycemia on survival after ACS is well-established both in patients with and without DM.[24] In a sub-analysis in the CARDINAL trial, Goyal et al.[31] have suggested that persistence of elevated blood glucose through 24 hours after admission was even more associated with lower survival than admission high blood glucose.[31] While there is an association between glycemia and mortality, it is not completely understood whether high blood glucose is a direct mediator of increased cell death and injury during MI, or just a marker of increased baseline risk. From a biological perspective, hyperglycemia may be associated with direct impairment of microcirculation and adverse left ventricular remodeling.[32] On the other hand, findings from randomized studies that failed to demonstrate better prognosis with stricter glycemic control support the latter hypothesis.[33,34] Nevertheless, if high blood glucose could be partially implicated in myocardial damage during MI, our results are reassuring, since they likely exclude a harmful effect of statins on glucose metabolism in the acute phase of ACS.

Study limitations

Our study has several limitations. First, we did not collect detailed information on dosages and types of statins that were used. Although some studies have found differential effects among different statins on glucose metabolism, other studies have suggested that the risk of DM with statins might be a class effect.[35,36] Second, our database spans over a long timeline, including patients since 1998, when the use of statins during acute phase of MI was less widespread. However, we considered this covariate in the adjusted models and in additional sensitivity analyses, thus supporting the findings that the association was not spuriously driven by this confounding factor. Third, we did not collect detailed information about indications and contraindications for starting or not early statin

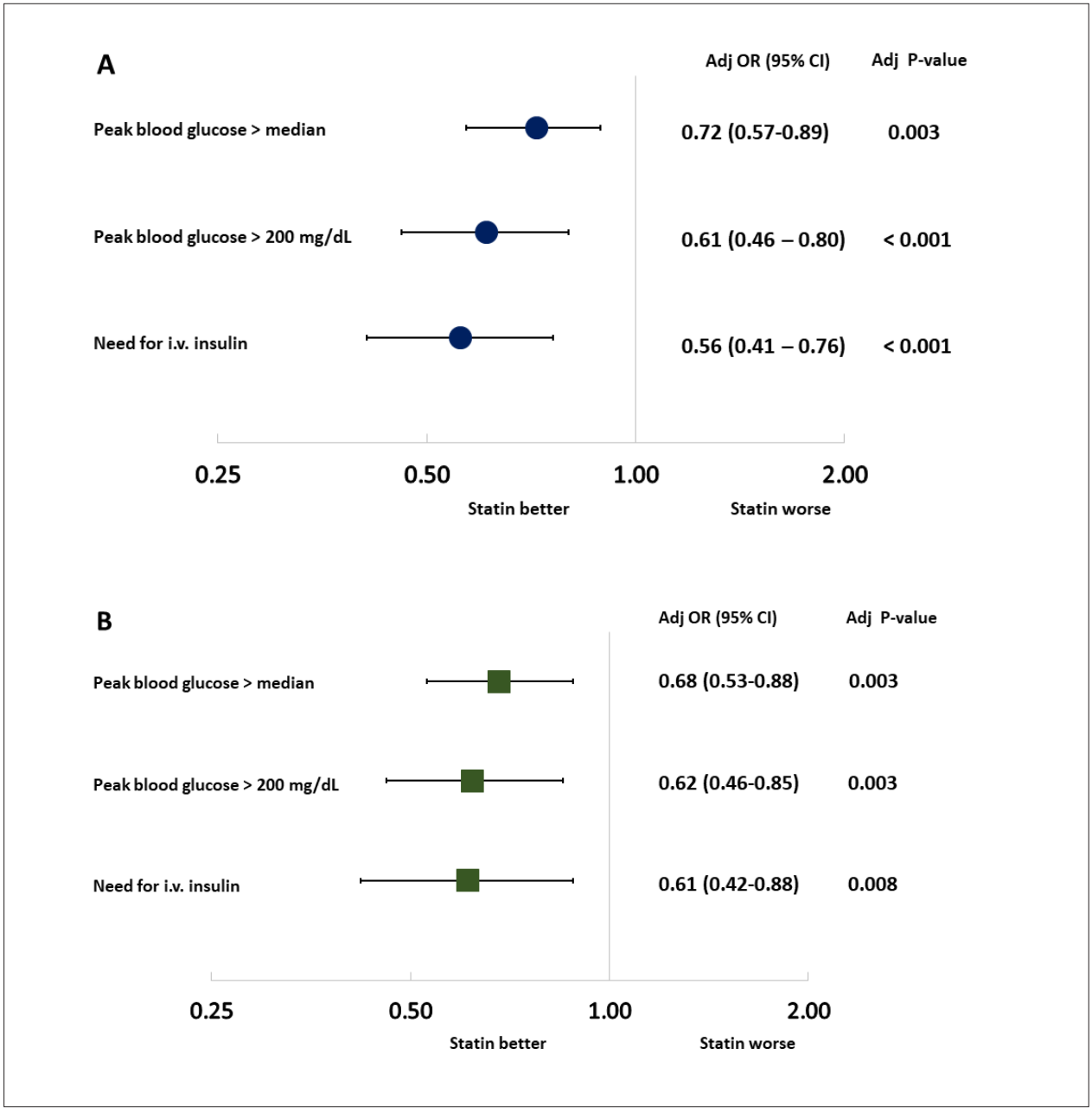

Figure 2 - *Adjusted risk of in-hospital hyperglycemia according to different definitions. A Adjusted by multivariable logistic regression. B: adjustment by propensity score matching. Adjusted for: age, race, sex, diabetes, hypertension, hypercholesterolemia, smoking, heart failure, prior myocardial infarction, prior percutaneous coronary intervention, prior coronary artery bypass graft, prior stroke, creatinine clearance < 60 ml/min, ACS phenotype (STEMI versus NSTEMI), Killip class 2 or more, GRACE score, type of health insurance and period of inclusion (before versus after Jan-2010).*

therapy in ACS. Accordingly, it might be possible that patients at a higher risk of death or in critical clinical condition were less likely to be administered statins in the first 24 hours by the treating physician. Several factors, in addition to the drug effect on glucose metabolism, may have influenced the decision to initiate statins in the first 24 hours. Also, although adjustments were made for several comorbidities and other demographic and socioeconomic factors, unknown residual confounders may remain. However, the GRACE score, a well-established predictor of in-hospital death among patients with ACS[22] was included as covariate, and we also performed several sensitivity analyses excluding patients who developed cardiogenic shock or severe infection, and those who died during index hospitalization. Fourth, due to the retrospective nature of our analysis, it could not be determined whether our findings were subject to reporting bias. Fifth, our data come from a single-center database, so it is uncertain whether our findings could be extrapolated to other countries or to different standards of practice in other hospitals.

Finally, due to the observational nature of our study, we cannot make any causal inference but only conclude about associations, so that our findings are only hypothesis-generating and should be confirmed in dedicated randomized trials.

Conclusion

In patients admitted with ACS, statin therapy in the first 24 hours was associated with lower incidence of in-hospital hyperglycemia. This finding suggests that, while statins can increase the risk of new-onset DM in the long-term, they could be associated with salutary effects over glucose metabolism in the short-term in ACS.

Compliance with Ethical Standards

This study is in accordance with the recommendations of Helsinki Declaration and Good Clinical Practice norms on medical research in humans. Since this study was a retrospective analysis based on a de-identified administrative database of routine care of patients admitted to our hospital, Informed Consent Form was waived according to local regulations.

Author contributions

Conception and design of the research: Furtado RHM, Nicolau JC; Acquisition of data: Furtado RHM, Dalçóquio TF, Baracioli LM, Lima FG, Franci A, Giraldez RRCV, Menezes FR; Analysis and interpretation of the data: Furtado RHM, Genestreti PR, Dalçóquio TF, Nicolau JC; Statistical analysis: Furtado RHM; Writing of the manuscript: Furtado RHM; Critical revision of the manuscript for intellectual content: Genestreti PR, Dalçóquio TF, Baracioli LM, Lima FG, Franci A, Giraldez RRCV, Menezes FR, Ferrari AG, Lima VM, Pereira CAC, Nakashima CAK, Salsoso R, Godoy LC, Nicolau JC.

Potential Conflict of Interest

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Dr. Paulo Rizzo Genestreti - Advisory board: Novo Nordisk, Sanofi, Astrazeneca. Eli-Lilly, Boehinger.

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Study Association

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

References

1. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994; 344(8934):1383-9.
2. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, et al. Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med. 2005; 352(14):1425–35.
3. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008; 359(21):2195=-207.
4. Yusuf S, Bosch J, Dagenais G, Zhu J, Xavier D, Liu L, et al. HOPE-3 Investigators. Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease. N Engl J Med. 2016 May 26; 374(21):2021-31.
5. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol. Circulation. 2019; 139(25):e1082-e1143.
6. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, et al. Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004;350(15):1495-504.
7. Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, et al. Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study Investigators. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. JAMA. 2001;285(13):1711-8.
8. Winchester DE, Wen X, Xie L, Bavry AA. Evidence of pre-procedural statin therapy a meta-analysis of randomized trials. J Am Coll Cardiol.2010;56(14):1099-109.
9. Berwanger O, Santucci EV, Silva PG, Jesuíno IA, Damiani LP, Barbosa LM, et al. Effect of Loading Dose of Atorvastatin Prior to Planned Percutaneous Coronary Intervention on Major Adverse Cardiovascular Events in Acute Coronary Syndrome: The SECURE-PCI Randomized Clinical Trial. JAMA. 2018; 319(13):1331-40.
10. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, Craen AJ, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet 2010; 375(9716): 735–42.
11. Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. Lancet. 2012; 380(9841):565–71.
12. Carter AA, Gomes T, Camacho X, Juurlink DN, Shah BR, Mamdani MM. Risk of incident diabetes among patients treated with statins: population based study. BMJ. 2013; 346: f2610.
13. Livingstone SJ, Looker HC, Akbar T, Betteridge DJ, Durrington PN, Hitman GA, et al. Effect of atorvastatin on glycaemia progression in patients with diabetes: an analysis from the Collaborative Atorvastatin in Diabetes Trial (CARDS). Diabetologia .2016; 59(2):299-306.
14. Erqou S, Lee CC, Adler AI. Statins and glycaemic control in individuals with diabetes: a systematic review and meta-analysis. Diabetologia. 2014; 57(12):2444-52.
15. Brault M, Ray J, Gomez YH, Mantzoros CS, Daskalopoulou SS. Statin treatment and new-onset diabetes: a review of proposed mechanisms. Metabolism. 2014; 63(6):735-45.

16. Yaluri N, Modi S, López Rodríguez M, Stančáková A, Kuusisto J, Kokkola T, et al. Simvastatin Impairs Insulin Secretion by Multiple Mechanisms in MIN6 Cells. PLoS One. 2015; 10(11):e0142902.

17. Shen L, Gu Y, Qiu Y, Cheng T, Nie A, Cui C, et al. Atorvastatin Targets the Islet Mevalonate Pathway to Dysregulate mTOR Signaling and Reduce β-Cell Functional Mass. Diabetes. 2020; 69(1):48-59.

18. Gruzdeva O, Uchasova E, Dyleva Y, Akbasheva O, Karetnikova V, Barbarash O. Early Effects of Treatment Low-Dose Atorvastatin on Markers of Insulin Resistance and Inflammation in Patients with Myocardial Infarction. Front Pharmacol. 2016; 7:324.

19. Albert MA, Danielson E, Rifai N, Ridker PM; PRINCE Investigators. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. JAMA 2001; 286(1):64-70.

20. Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, McCabe CH, et al. Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) Investigators. C-reactive protein levels and outcomes after statin therapy. N Engl J Med 2005; 352(1):20-8.

21. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018; 39(2):119-77.

22. Fox KA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Werf FV, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). BMJ. 2006; 333(7578):1091.

23. Elze MC, Gregson J, Baber U, Williamsom E, Sartori S, Mehran R, et al. Comparison of Propensity Score Methods and Covariate Adjustment: Evaluation in 4 Cardiovascular Studies. J Am Coll Cardiol. 2017; 69(3):345-57.

24. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. Lancet 2000; 355(9206):773–8.

25. Yan C, Qin M, Juan YS, Tao LY, Dong GM, Zechun Z, et al. Association of statin use and stress-induced hyperglycemia in patients with acute ST-elevation myocardial infarction. JRSM Cardiovasc Dis. 2016; 5:2048004016639442.

26. Sposito AC, Carvalho LSF, Moura FA, Staffico AM, Cintra RM, Nadruz W, et al. Statin Short-term Inhibition of Insulin Sensitivity and Secretion During Acute Phase of ST-Elevation Myocardial Infarction. Sci Rep. 2019; 9(1):16401.

27. Leoncini M, Toso A, Maioli M, Tropeano F, Villani S, Bellandi F. Early high-dose rosuvastatin for contrast-induced nephropathy prevention in acute coronary syndrome: Results from the PRATO-ACS Study (Protective Effect of Rosuvastatin and Antiplatelet Therapy On contrast-induced acute kidney injury and myocardial damage in patients with Acute Coronary Syndrome). J Am Coll Cardiol. 2014; 63(1):71-9.

28. Han Y, Zhu G, Han L, Hou F, Huang W, Liu H, et al. Short-term rosuvastatin therapy for prevention of contrast-induced acute kidney injury in patients with diabetes and chronic kidney disease. J Am Coll Cardiol. 2014; 63(1):62-70.

29. Toso A, Leoncini M, Maioli M, Tropeano F, Vicenzo E, Villani S, et al. Relationship Between Inflammation and Benefits of Early High-Dose Rosuvastatin on Contrast-Induced Nephropathy inPatients With Acute Coronary Syndrome: The Pathophysiological Link in the PRATO-ACS Study (Protective Effect of Rosuvastatin and Antiplatelet Therapy on Contrast-Induced Nephropathy and Myocardial Damage in Patients With Acute Coronary Syndrome Undergoing Coronary Intervention). JACC Cardiovasc Interv. 2014; 7(12):1421-9.

30. Lopes RD, Silva PG, Jesuíno IA, Santucci EV, Barbosa LM, Damiani LP, et al. Timing of Loading Dose of Atorvastatin in Patients Undergoing Percutaneous Coronary Intervention for Acute Coronary Syndromes: Insights From the SECURE-PCI Randomized Clinical Trial. JAMA Cardiol. 2018; 3(11):1113-8.

31. Goyal A, Mahaffey KW, Garg J, Nicolau JC, Hochman JS, Weaver WD, et al. Prognostic significance of the change in glucose level in the first 24 h after acute myocardial infarction: results from the CARDINAL study. Eur Heart J 2006; 279(11):1289–97.

32. Yana M, Chena K, Suna R, Lin K, Qian X, Yuan M, et al. Glucose impairs angiogenesis and promotes ventricular remodeling following myocardial infarction via upregulation of microRNA-17. Exp Cell Res. 2019; 381(2):191–200.

33. Malmberg K, Rydén L, Wedel H, Birkeland K, Bootsma A, Dickstein K, et al. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. Eur Heart J. 2005; 26(7):650-61.

34. NICE-SUGAR Study Investigators, Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009;360(13):1283–97.

35. Baker WL, Talati R, White CM, Coleman CI. Differing effect of statins on insulin sensitivity in non-diabetics: a systematic review and meta-analysis. Diabetes Res Clin Pract. 2010; 87(1):98-107.

36. Kim J, Lee HS, Lee KY. Effect of statins on fasting glucose in non diabetic individuals: nationwide population based health examination in Korea. Cardiovasc Diabetol. 2018; 17(1):155.

*Supplemental Materials

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Evaluation of Dipper and Non-dipper Blood Pressure Patterns and Quality of Life Among Patients with Chronic Obstructive Pulmonary Disease

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Abstract

Background: **Non-dipper blood pressure is defined by less than a 10% reduction in nighttime blood pressure, and it is associated with cardiovascular disease. Inflammation is thought to play a role in the pathogenesis of both chronic obstructive pulmonary disease (COPD) and non-dipper blood pressure pattern, and both diseases are associated with lower quality of life.**

Objective: **The aim of this study was to investigate the effects of non-dipper blood pressure pattern in patients with COPD.**

Methods: **A cross-sectional study was carried out with 142 patients with COPD. The Saint George Respiratory Questionnaire and the Euro Quality of Life Scale were used to collect data. To understand arterial stiffness, the augmentation index and pulse wave velocity were measured, and 24-hour ambulatory blood pressure monitoring was subsequently performed. A multivariable logistic regression model was used to understand the relationship between different independent variables and blood pressure pattern. P values lower than 0.05 were considered statistically significant.**

Results: **As a result, 76.1% (n = 108) of the patients had non-dipper blood pressure pattern. Non-dipper patients had higher C-reactive protein (OR:1.123; 95% CI:1.016;1.242), augmentation index (OR: 1.057; 95% CI: 1.011;1.105) and Saint George Respiratory Questionnaire total score (OR: 1.021; 95% CI: 1.001;1.042) than dipper patients. Also, as the number of people living at home increased, non-dipper blood pressure pattern was found to be more frequent (OR: 1.339; 95% CI: 1.009;1.777).**

Conclusion: **Non-dipper blood pressure pattern may increase cardiovascular risk by triggering inflammation and may adversely affect the prognosis of COPD by lowering the disease-related quality of life. (Arq Bras Cardiol. 2021; 116(2):295-302)**

Keywords: **Pulmonary Disease Chronic Obstructive; Monitoring; Dipper, No-Dipper; Prognosis; Quality of Life.**

Introduction

Chronic obstructive pulmonary disease (COPD) is highly prevalent worldwide; it is characterized by the limitation of airway flow and, according to the World Health Organization, it will be the third leading cause of death in 2030.[1]

A reduction in blood pressure by more than 10% at night is a physiological process[2]. If the reduction in blood pressure at night is less than 10%, it is called the non-dipper blood pressure pattern, which is known to be associated with cardiovascular disease and end-organ damage.[2] The augmentation index (Aix) and pulse wave velocity (PWV) are indicators of arterial stiffness that can predict future cardiovascular events, and Aix and PWV values are higher in the non-dipper blood pressure pattern.[3,4] It is controversial how non-dipper blood pressure pattern causes these effects, but it is thought that this pattern induces cytokine expression from the endothelium and triggers an inflammatory process.[5] Inflammation markers such as C-reactive protein (CRP), the neutrophil-lymphocyte ratio (NLR), and the platelet-lymphocyte ratio (PLR) are higher among individuals with non-dipper blood pressure compared to their counterparts.[5]

Systemic inflammation plays a major role in the pathogenesis of COPD, and it is believed that CRP and NLR can be used as markers for diagnosis and prognosis of COPD.[6,7] The presence of an inflammatory process in the pathogenesis of both COPD and non-dipper blood pressure suggests that the incidence of non-dipper blood pressure pattern may be high in patients with COPD.[8] Another common point of both diseases is their negative effects on quality of life.[9,10] Quality of life is the health perception of the individual, and it has a direct impact on

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physical and mental health; it is also related to the number of acute exacerbations and hospitalizations in COPD.[9]

Studies that have investigated the effects of blood pressure patterns on COPD are quite limited, and elucidation of this subject might be a guide for COPD management. The aim of this study is to investigate the effect of non-dipper blood pressure pattern on laboratory values and quality of life in COPD.

Methods

The diagnosis of COPD should be confirmed via spirometry in patients with dyspnea, chronic cough, chronic sputum production, and exposure to risk factors of COPD. In our study, patients diagnosed with COPD by chest disease specialists, who were therefore taking medication, were accepted as COPD. In addition, spirometry examinations of patients were checked by the computer system.

Participants

This cross-sectional study was conducted with patients with COPD, between the ages of 18 and 80 years, who were admitted to Izmir Katip Celebi University Atatürk Training and Research Hospital's inpatient or outpatient clinic for pulmonary diseases. The study excluded patients who, in addition to COPD, had known active infection, malignancy, congestive heart failure, diabetes mellitus, or renal failure. The study was conducted between January and June 2018.

Sample size

The sample size was calculated using the GPOWER 3.1 program. By using a previous research finding, we assumed the mean CRP levels would be 4.9 ± 1.7 mg/lt in the non-dipper group and 3.8 ± 1.5 mg/lt in the dipper group. In order to show the differences between the two groups, the required sample size was calculated at 128, with 95% power and a two-sided type-1 error rate of 5%. We increased the sample size by 10% and aimed to reach 140 patients.[11]

Data collection tools

Sociodemographic characteristics

In order to examine sociodemographic data, education level was categorized into two groups (middle school or lower and high school or higher). Income level was categorized into three groups (≥ 1500 Turkish Liras (TL), 1501 to 3499 TL, and ≤ 3500 TL). Body mass index values were divided into three categories (normal [≤ 24.99 kg/m^2], overweight [25 to 29.99 kg/m^2], and obese [≥ 30 kg/m^2]). Marital status was divided into two groups (single and married). Alcohol intake was also divided into two groups (yes and no). Places where patients were included in the study were divided into two groups (inpatient service and outpatient clinic), and COPD history in their families was categorized into two groups (yes and no). Patients diagnosed with hypertension by a physician and receiving prescription medication were considered as having hypertension. Patients who smoked regularly, at least once a day, were considered as active smokers. Regarding continuous variables, patients were asked to respond to questions such as age, number of people living at home, years of smoking and package numbers, number of admissions to the emergency unit due to COPD during the last year, and number of hospital admissions for COPD.

Saint George's Respiratory Questionnaire

Saint George's Respiratory Questionnaire (SGRQ) is a quality of life scale especially developed for the respiratory system that can be used in patients with asthma and COPD, as well as in patients with bronchiectasis and sarcoidosis.[12] The scale includes the components of symptoms, activity, and effect, and, after scoring, all three components and total quality of life scores are obtained.[12] The scale is scored from 0 to 100. For each component and for the produced total score, '0' indicates 'perfect' and '100' indicates 'worst' quality of life.[12] The validity and reliability of the Turkish version of the scale have been confirmed.[12]

Euro Quality of Life Scale

The Euro Quality of Life Scale (EQ-5D) is a 5-question overall quality of life scale, each consisting of 3 levels.[13] The scale is composed of 5 dimensions, including mobility, self-care, daily activities, pain, and mood. Higher scores indicate higher quality of life.[13] The utility of the EQ-5D score was computed using the MVH-A1 algorithm by Dolan.[14] This algorithm provides a range from −0.594 to +1, where higher values indicate better quality of life. The scale's validity and reliability have been confirmed in Turkish settings.[13]

Augmentation index and pulse wave velocity

After the administration of the questionnaire and blood sampling, patients were examined in terms of Aix and PWV. A Mobil-O-Graph® (IEM; Stolberg, Germany) device calculated the Aix and PWV by recording oscillometric brachial blood pressure; the cuff subsequently reinflated at the diastolic phase for approximately 10 seconds, recording brachial pulse waves with a high-fidelity pressure sensor.

24-hour ambulatory blood pressure monitoring and blood sampling

For 24-hour blood pressure measurement, patients were monitored with a Mobil-O-Graph NG® (IEM; Stolberg, Germany) device. The device was adjusted to perform a 24-hour measurement, once every 15 minutes during the day and once every 30 minutes at night. The next day, at the same time, patient returned the devices. The non-dominant arm was used for measurement, and day and night measurements were adjusted according to the patients' sleeping and waking hours. Patients were instructed to continue their usual activities and to avoid exhausting exercise. Blood tests were obtained from patients before treatment was administered. Among patients who were hospitalized in the pulmonary diseases service, the questionnaire was applied on the same day. The 24-hour ambulatory blood pressure monitoring (24-h ABPM) measuring device was applied in similar conditions for outpatients.

The results of 24-h ABPM measurement were examined, and, if nighttime average values of systolic and diastolic blood pressures were decreased by 10% or more with respect to day-time average values, this was considered as dipper blood pressure[2]. When the decrease in blood pressure was less than 10%, it was considered as non-dipper blood pressure pattern.[2] CRP blood tests were carried out in a Architect C16000 autoanalyzer (Abbott Diag., USA), and the hemogram was analysed in a Mindray BC-6800 whole blood device (Mindray, China).

Ethical approval

The ethical approval for the study was obtained from the Izmir Katip Celebi University Interventional Clinical Research Ethics Committee under decision number 164 (date of approval: December 22, 2016). 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.

Statistical analysis

Statistical analysis was performed using SPSS version 16. In this study, the distribution of the continuous variables were assessed with Kolmogorov-Smirnov test, and the data were not distributed normally. Continuous variables were presented as medians and inter quartile ranges (IQR). Statistical comparison of two independent groups was performed using the Mann Whitney U test. The between-group comparisons of categorical variables were performed using the chi-square test. The strength of association between two continuous variables was assessed using Spearman correlation tests.

Independent effects with respect to the presence of non-dipper blood pressure of the different identifying factors were examined using logistic regression models. The Hosmer-Lemeshow test was used for assesing the model fit. Independent variables with $p \leq 0.10$ on bivariate analysis were included in the multivariate logistic regression model with a "backward" elimination method. Due to high correlation between nighttime systolic blood pressure and nighttime mean arterial pressure, only nighttime mean arterial pressure was added to the model. Adjusted coefficients are presented with their 95% confidence intervals. All p values were two-tailed, and p values lower than 0.05 were considered statistically significant.

Results

One hundred and sixty-seven patients were invited to the study. Twelve patients did not want to wear the 24-h ABPM device or did not want to participate in the study due to lack of time. Thirteen patients were excluded from the study due to inappropriate 24-h ABPM measurements, and the study was completed with 142 patients. In total, 23.9% (n = 34) of the patients had dipper and 76.1% (n = 108) had non-dipper blood pressure pattern. Among these patients, 43% (n = 61) participated from the inpatient clinic, and 57% (n = 81) were outpatients.

According to univariate analysis, sociodemographic variables such as age, sex, and marital status did not significantly affect the blood pressure pattern. On the other hand, the median number of people living in the household were higher in those who had non-dipper blood pressure pattern compared to those with dipper blood pressure pattern. The relationship between sociodemographic variables and blood pressure pattern is presented in Table 1.

Mean nighttime systolic blood pressure, mean nighttime arterial pressure, Aix, and CRP values were significantly higher among participants with non-dipper blood pressure pattern compared to thier counterparts. The association between 24-hour blood pressure and laboratory results are shown in Table 2. When patient quality of life was examined according to blood pressure pattern, SGRQ symptoms, effects, and total scores were higher among the patients with non-dipper blood pressure, and the EQ-5D score was lower; the differences were statistically significant. (Table 3).

According to multivariate logistic regression analysis, CRP (OR: 1.123; 95% CI: 1.016;1.242), Aix (OR: 1.057; 95% CI: 1.011;1.105), and SGRQ total score (OR: 1.021; 95% CI: 1.001;1.042) were higher in patients with non-dipper blood pressure pattern than in those with dipper blood pressure. In addition, individuals with non-dipper blood pressure pattern were living in more crowded houses, compared to individuals with dipper blood pressure pattern (OR: 1.339; 95% CI: 1.009;1.777) (Table 4).

Discussion

In this study, we investigated the effects of the dipper and non-dipper blood pressure patterns on laboratory results and quality of life of patients with COPD. According to our study findings, patients with COPD and non-dipper blood pressure pattern had higher CRP and Aix values and lower quality of life due to COPD. The increase in the prevalence of the non-dipper blood pressure pattern with the number of people living at home is another finding of the study.

The 24-h ABPM used for diagnosis and follow-up of hypertension provides information about the presence of dipper and non-dipper blood pressure.[2] In our study, 76.1% of patients with COPD had a non-dipper blood pressure pattern. Nersesyan et al. found that the rate of non-dipper blood pressure pattern in patients with COPD was 72.7%.[15] In the study performed by Aidar et al.,[8] the decrease in nighttime blood pressure was higher than 10%, with respect to daytime blood pressure, in the healthy control group, while the mean value of nighttime blood pressure in patients with COPD was below 10%, with respect to daytime blood pressure.[8] Although the frequency data were not shared in the study by Aidar et al.,[8] it was understood that the decrease in nighttime blood pressure of patients with COPD was insufficient. The presence of inflammatory processes based on both conditions might explain the association between non-dipper blood pressure and COPD. However, the effects of each factor on one another are still unclear.[8] In this study, CRP levels were higher among individuals with non-dipper blood pressure pattern. A previous study conducted by Kaya et al.[11] presented the same finding, where CRP values were higher in patients with non-dipper

Table 1 – Sociodemographic variables

Categorical variables	Dipper	Non-dipper	Total	P value
	(n = 34)	(n = 108)	(n = 142)	
Sex n (%)				
Female	7 (20.6)	25(23.1)	32 (22.5)	0.819
Male	27 (79.4)	83 (76.9)	110 (77.5)	
Body mass index n (%)				
Normal (18.5 to 24.5)	19 (55.9)	51 (47.2)	70 (49.3)	0.571
Overweight (25 to 29,9)	10 (29.4)	33 (30.6)	43 (30.3)	
Obese (30 to 40)	5 (14.7)	24 (22.2)	29 (20.4)	
Level of education n (%)				
Middle school and lower	11 (32.4)	43 (39.8)	54(38)	0.544
High school and higher	23(67.6)	65 (60.2)	88 (62)	
Income level n (%)				
1500 Turkish liras or below (low)	0 (0)	9 (8.3)	9 (6.3)	0.217
1501 to 3500 Turkish lira (medium)	20 (58.8)	60 (55.6)	80 (56.3)	
3501 Turkish liras or higher (high)	14 (41.2)	39 (36.1)	53 (37.3)	
Marital status n (%)				
Single	9 (26.5)	24 (22.2)	33 (23.2)	0.644
Married	25 (73.5)	84 (77.8)	109 (76.8)	
Place of attendance n (%)				
Inpatient services	11 (32.4)	50 (46.3)	61 (43)	0.169
Outpatient clinic	23 (67.6)	58 (53.7)	81 (57)	
Presence of hypertension n (%)				
Yes	18 (52.9)	49 (47.1)	67 (48.6)	0.693
No	16 (47.1)	55 (52.9)	71 (51.4)	
Family history of COPD n (%)				
Yes	9 (26.5)	43 (39.8)	52 (36.6)	0.221
No	25 (73.5)	65 (60.2)	90 (63.4)	
Smoking n (%)				
Yes	8 (23.5)	21 (29.4)	29 (20.4)	0.629
No	26 (76.5)	87 (80.6)	113 (79.6)	
Use of alcohol n (%)				
Yes	12 (35.3)	25 (23.1)	37 (26.1)	0.182
No	22 (64.7)	83 (76.9)	105 (73.9)	
Non-categorical variables				
Age, median (IQR)	65 (59.75-73)	66 (55-71.75)	66 (55.75-72)	0.739
Number of people living at home, median (IQR)	2 (1-2)	2 (2-3)	2 (2-3)	0.038*
Smoking, pack years, median (IQR)	42.5 (23.75-60)	50 (30-80)	50 (30-74.25)	0.317
Number of visits to emergency department in the last year, median (IQR)	3,5 (1-6)	3 (1.25-6)	3 (1-6)	0.929
Number of hospitalization in the last year, median (IQR)	2 (0-3)	1 (0-2)	1 (0-2)	0.296

*p: percentiles; IQR: interquartile range. * Statistical significance (p < 0.05)*

Table 2 – 24-Hour Ambulatory Blood Pressure Values and Laboratory

Blood pressure values and laboratory results	Dipper (n = 34)	Non-dipper (n = 108)	Total (n = 142)	P value
24-h mean SBP, mmHg, median (IQR)	122 (111-129)	122.5 (116-129.75)	122 (115.75-129.25)	0.985
24-h mean DBP, mmHg, median (IQR)	76 (71- 85.75)	73.5 (67.25-82)	74 (68-84)	0.236
24-h mean AP, mmHg, median (IQR)	97 (88-113)	97 (90-105)	97 (88.75-106)	0.305
24-h mean heart rate, median (IQR)	84 (69.75-88)	77 (70-84.75)	77.5 (70-88)	0.152
24-h pulse pressure, mmHg, median (IQR)	47 (37-51)	47 (42-52)	47 (42-51.25)	0.979
Daytime mean SBP, mmHg, median (IQR)	128 (110.75-145)	124 (116-131)	124.5 (116-133)	0.224
Daytime mean DBP, mmHg, median (IQR)	74 (71-83)	75 (67-82)	74 (69-82)	0.622
Daytime mean AP, mmHg, median (IQR)	99 (73.25-91.5)	97 (90-104)	98 (91-106)	0.098
Daytime mean heart rate, median (IQR)	84 (73.25-91.5)	78 (71-86.75)	80 (71-87)	0.127
Daytime pulse pressure, mmHg, median (IQR)	47 (38-52.25)	47 (42-52)	47 (42-52)	0.781
Nighttime mean SBP, mmHg, median (IQR)	118 (107.75-120)	120 (115-133)	118 (114-131.5)	0.012*
Nighttime mean DBP, mmHg, median (IQR)	71 (64.75-73)	72 (65-80)	72 (65-78)	0.099
Nighttime mean AP, mmHg, median (IQR)	94 (82.5-94)	94 (87-104.5)	94 (86-101)	0.045*
Nighttime mean heart rate, median (IQR)	74.5 (54-88)	73 (61-82)	73 (61-82)	0.698
Nighttime pulse pressure, mmHg, median (IQR)	44 (43.25-51.5)	47.5 (44-52)	47 (44-52)	0.105
Augmentation index, median (IQR)	20.40 (14.75-24.3)	27 (18-35)	23.05 (17-33)	0.020*
Pulse wave velocity, median (IQR)	9.65 (8.67-10.32)	9.2 (8-10.2)	9.45 (8.2-10.8)	0.794
WBC, median (IQR)	8.85 (7.71-10.63)	9.61 (8.64-11.18)	9.44 (8.32-11.14)	0.073
CRP, median (IQR)	0.97 (0.02-3)	4.34 (1.12-7.42)	2.86 (0.6-6.54)	<0.001*
NLR, median (IQR)	2.89 (2.29-5.47)	3.93 (2.28-6.19)	3.76 (2.31-5.88)	0.210
PLR, median (IQR)	130.5 (95.16-203.58)	160.37 (115.38-201.61)	152.06 (107.74-201)	0.110

*SBP: Systolic blood pressure; DBP: Diastolic blood pressure; AP: arterial pressure; WBC: White blood cells; CRP: C reactive protein; NLR: neutrophil lymphocyte ratio; PLR: platelet lymphocyte ratio; IQR: interquartile range. * Statistical significance (p <0.05)*

Table 3 – Saint George's Respiratory Questionnaire and Euro Quality of Life Scale scores

Scores	Dipper (n = 34)	Non-dipper (n =108)	Total (n = 142)	p value
SGRQ Symptoms, median (IQR)	74.13 (56.43-78.97)	78.08 (64.97-83.68)	76.08 (61.4-82.27)	0.021*
SGRQ Activity, median (IQR)	62.49 (48.38-86.72)	74.48 (60.67-87.53)	71.4 (53.83-87.53)	0.091
SGRQ Impact, median (IQR)	47.64 (25.15-67.32)	58.1 (46.33-74.77)	56.99 (38.33-74.3)	0.025*
SGRQ Total, median (IQR)	53.84 (35.64-73.64)	65.23 (53.84-79.85)	63.71 (52.01-78.63)	0.021*
EQ-5D, median (IQR)	0.51 (0.51-0.58)	0.51 (0.51-0.51)	0.51 (0.51-0.51)	0.034*

*p: percentiles; SGRQ : Saint George's Respiratory Questionnaire; EQ-5D: Euro Quality of Life Scale; IQR: interquartile range. * Statistical significance (p < 0.05)*

pattern, compared to patients with dipper blood pressure.[11] Previous studies have shown that non-dipper blood pressure decreases the number of endothelial progenitor cells, disrupts vascular repair mechanisms and endothelial homeostasis, and consequently induces inflammation by increasing the expression of endothelial cytokines.[5] In our study, we suggest that the higher CRP levels in individuals with the non-dipper blood pressure pattern were caused by similar mechanisms.

In our study, there was no significant difference between NLR and PLR values based on blood pressure patterns. Previous studies have shown that NLR and PLR values are higher in patients with non-dipper blood pressure.[5] Golpe et al. investigated the relationship between blood pressure pattern and inflammatory markers in patients with COPD, and they concluded that blood pressure pattern does not affect neutrophil and lymphocyte levels.[16] Given that the sample of

Table 4 – Logistic regression analysis of non-dipper blood pressure

Determining factors	Odds ratio (Univariate)			Odds ratio (Multivariate)		
	β	95% CI	p value	β	95% CI	p value
Age	0.997	0.961;1.034	0.879	0.995	0.950;1.042	0.817
Sex						
Female	1	1	1	1	1	1
Male	0.861	0.335;2.212	0.756	1.100	0.341;3.546	0.873
Number of people living at home	1.169	0.903;1.515	0.236	1.339	1.009;1.777	0.043*
Nighttime mean AP, mmHg	1.038	0.999;1.078	0.055	1.033	0.991;1.077	0.122
Augmentation index	1.049	1.008;1.092	0.018*	1.057	1.011;1.105	0.015**
CRP	1.141	1.025;1.270	0.016*	1.123	1.016;1.242	0.024*
SGRQ Total	1.023	1.003;1.043	0.025*	1.021	1.001;1.042	0.040*
EQ-5D	0.440	0.076;2.540	0.358	0.766	0.118;4.960	0.780

*β: regression coefficient; 95% CI: confidence interval; AP: arterial pressure; CRP: C reactive protein; SGRQ : Saint George's Respiratory Questionnaire; EQ-5D: Euro Quality of Life Scale. * Statistical significance (p < 0.05)*

our study only consisted of patients with COPD and that inflammatory pathways play a major role in COPD, the NLR and PLR values may not have been affected by the blood pressure pattern.

As a result of our study, we found higher Aix values among patients with non-dipper blood pressure; this finding is in concordance with the results of previous studies in the literature.[4] Aix is considered as one of the best indicators of arterial stiffness and atherosclerosis-related conditions, and it is thought to predict oncoming cardiovascular events.[3] Non-dipper blood pressure triggers the inflammatory process and causes atherosclerosis and arteriosclerosis, and it is thought to be associated with increased risk for both cardiovascular mortality and end-organ damage.[2,3] Considering the increased risk of inflammation and atherosclerosis caused by non-dipper blood pressure, Aix might be expected to be higher in individuals with non-dipper blood pressure pattern. As a result of this finding supported by our study, it might be useful to closely monitor patients with COPD and non-dipper blood pressure pattern, in order to improve management of cardiovascular diseases.

In our study, the general quality of life measured by EQ-5D was lower in patients with non-dipper blood pressure pattern according to univariate analyses; however, this relationship lost its significance in multivariate analyses. SGRQ quality of life scale scores, which were specific for COPD, were higher in patients with non-dipper blood pressure pattern, and this relationship remained significant in multivariate analyses. One reason for this could be due to the fact that the EQ-5D measures the overall quality of life, while the SGRQ is specific for COPD. Considering that the overall quality of life of individuals with COPD is lower than that of healthy individuals, the non-dipper blood pressure pattern in patients with COPD may further decrease the quality of life.[17] The study of Wacker et al. reported that, in association with disease burden, SGRQ score predicts acute COPD exacerbations, hospitalizations due to exacerbations, and deaths due to all causes.[9] In individuals with a non-dipper blood pressure pattern, our mean SGRQ score was higher, which may indicate the importance of blood pressure control during COPD management.

In our study, we found that the increase in the number of people living at home increased the prevalence of the non-dipper blood pressure pattern. Increased number of people living in the same house and the number of children are factors that increase the responsibility and hence lead to stress on individuals.[18] As stress physiologically triggers the release of epinephrine and norepinephrine, the non-dipper blood pressure pattern can be expected to be more frequent in people with high stress factors.[19] Moreover, the overcrowding rate describes the proportion of people living in overcrowded dwellings, as defined by the number of rooms available to the household, the household's size, its members' ages, and their family situation; 40% of the population of Turkey lives in overcrowded families.[20] This case may constitute a high risk for people of Turkey for the development of non-dipper blood pressure pattern.

It is necessary to mention that there are some limitations to our study. First, as our study is cross-sectional, there is a temporality problem where we cannot be sure whether the factor preceded the occurrence of the outcome or not. In our case, we do not know whether inflammation caused non-dipper blood pressure pattern or vice verse; hence, prospective studies are needed in order to assess causality. Failure to include a healthy control group may be a limitation. Comparisons of healthy individuals and patients with COPD might provide better information regarding the effects of blood pressure patterns. Also, in our study, the presence of sleep apnea syndrome was not investigated. Non-dipper blood pressure pattern was found to be high in patients with sleep apnea syndrome, and sleep apnea syndrome is common in patients with COPD.[21,22] Our participation rate was lower than expected; however, we determined differences in major indicators such as CRP and EQ-5D and SGRQ quality of life scores, which were related to the primary hypotheses, and we achieved more

than 90% power in post hoc power calculations for these parameters.

Conclusion

The non-dipper blood pressure pattern was more common in patients with COPD, and patients with COPD and non-dipper blood pressure had higher CRP levels and Aix values. This poses an increased risk of cardiovascular disease and end-organ damage. At the same time, the non-dipper blood pressure pattern adversely affects quality of life of patients with COPD, and this is thought to negatively affect exacerbations of the disease, hospitalizations, and mortality. For these reasons, close monitoring of blood pressure in patients with COPD may contribute to increased individual quality of life and decreased levels of mortality related to cardiovascular diseases.

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Author contributions

Conception and design of the research: Askın M, Koc EM, Sozmen K, Turan MO, Soypacacı Z, Aksun S; Data acquisition and Writing of the manuscript: Askın M, Turan MO, Soypacacı Z, Aksun S; Analysis and interpretation of the data and Statistical analysis: Askın M, Koc EM, Sozmen K; Critical revision of the manuscript for intellectual content: Koc EM, Sozmen K, Turan MO, Soypacacı Z, Aksun S.

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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References

1. WHO. World Health statistics 2008.[Accessed in 2018 06]. Available: http://www.who.int/whosis/whostat/EN_WHS08_Full. pdf?ua=1
2. Liu M, Takahashi H, Morita Y, Maruyama S, Mizuno M, Yuzawa Y, et al. Non-dipping is a potent predictor of cardiovascular mortality and is associated with autonomic dysfunction in haemodialysis patients. Nephrol Dial Transplant. 2003; 18 (3): 563–9.
3. Cecelja M, Chowienczyk P. Role of arterial stiffness in cardiovascular disease. J R Soc Med Cardiovasc Dis. 2012; 1(4): cvd.2012.012016.
4. Lekakis JP, Zakopoulos NA, Protogerou AD, Papaioannou TG, Kotsis VT, Pitiriga VCh, et al. Arterial stiffness assessed by pulse wave analysis in essential hypertension: relation to 24-h blood pressure profile. Int J Cardiol. 2005; 102 (3): 391-5.
5. Kılıçaslan B, Dursun H, Kaymak S, Aydın M, Ekmekçi C, Susam İ, et al. The relationship between neutrophil to lymphocyte ratio and blood pressure variability in hypertensive and normotensive subjects. Turk Kardiyol Dern Ars. 2015; 43 (1): 18-24.
6. Ding GZ, Li WS. The expressions and significance of APN, D-D, IL-17 and hs-PCR in patients with acute exacerbation of chronic obstructive pulmonary disease. Eur Rev Med Pharmacol Sci. 2018; 22 (19): 6463-8.
7. Teng F, Ye H, Xue T. Predictive value of neutrophil to lymphocyte ratio in patients with acute exacerbation of chronic obstructive pulmonary disease. PLoS One. 2018; 13 (9): e0204377.
8. Aidar NA, Silva MA, Melo e Silva CA, Ferreira Júnior PN, Tavares P. MAPA in DPOC patients with sleep desaturation. Arq Bras Cardiol. 2009; 93 (3): 275-82.
9. Wacker ME, Jörres RA, Karch A, Wilke S, Heinrich J, Karrasch S, et al. Assessing health-related quality of life in DPOC: comparing generic and disease-specific instruments with focus on comorbidities. BMC Pulm Med. 2016; 16 (1): 70.
10. Afsar B, Elsurer R, Sezer S, Ozdemir FN. Nondipping phenomenon and quality of life: are they related in essential hypertensive patients? Clin Exp Hypertens. 2010; 32 (2): 105-12.
11. Kaya MG, Yarlioglues M, Gunebakmaz O, Gunturk E, Inanc T, Dogan A, et al. Platelet activation and inflammatory response in patients with non-dipper hypertension. Atherosclerosis. 2010; 209 (1): 278-82.
12. Polatlı M, Yorgancıoglu A, Aydemir O, Yılmaz Demirci N, Kırkıl G, Atış Naycı S, et al. Validity and reliability of Turkish version of St. George's respiratory questionnaire. Tüberk Toraks 2013; 61 (2): 81-7.
13. Kahyaoğlu Sut H, Unsar S. Is EQ-5D a valid quality of life instrument in patients with acute coronary syndrome? Anadolu Kardiyol Derg. 2011; 11 (2): 156-62.
14. Dolan P. Modeling valuations for EuroQol health states. Med Care. 1997; 35 (11): 1095-108.
15. Nersesyan **Z**, Ovcharenko **S**, Morozova **T.** Characteristics of essential hypertension in DPOC patients**.** European Respiratory Journal. 2014; 44: P3628**.**
16. Golpe R, Mateos-Colino A, Testa-Fernández A, Pena-Seijo M. Blood Pressure Profile and Hypertensive Organ Damage in DPOC Patients and Matched Controls. The RETAPOC Study. PLoS One. 2016; 11 (6): e0157932.
17. Moayeri F, Hsueh YS, Clarke P, Hua X, Dunt D. Health State Utility Value in Chronic Obstructive Pulmonary Disease (DPOC); The Challenge of Heterogeneity: A Systematic Review and Meta-Analysis. DPOC. 2016; 13 (3): 380-98.
18. Falkson S, Knecht C, Hellmers C, Metzing S. The Perspective of Families With a Ventilator-Dependent Child at Home. A Literature Review. J Pediatr Nurs. 2017; 36: 213-224.
19. Lundberg U. Stress hormones in health and illness: the roles of work and gender. Psychoneuroendocrinology. 2005; 30 (10): 1017-21.
20. Housing statistics in the European Union (Eurostat) 2018. { Accessed in 2019 Jan 10].Available online: https://ec.europa.eu/eurostat/statistics-explained/pdfscache/1158.pdf.
21. Shawon MS, Perret JL, Senaratna CV, Lodge C, Hamilton GS, Dharmage SC. Current evidence on prevalence and clinical outcomes of co-morbid obstructive sleep apnea and chronic obstructive pulmonary disease: A systematic review. Sleep Med Rev. 2017;32:58-68.
22. Genta-Pereira DC, Furlan SF, Omote DQ, Giorgi DMA, Bortolotto LA, Lorenzi-Filho G, et al. Nondipping Blood Pressure Patterns Predict Obstructive Sleep Apnea in Patients Undergoing Ambulatory Blood Pressure Monitoring. Hypertension. 2018; 72 (4): 979-85.

To Dip or not to Dip Blood Pressure in Chronic Obstructive Pulmonary Disease: That is the Question!

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Short Editorial related to the article: Evaluation of Dipper and Non-dipper Blood Pressure Patterns and Quality of Life Among Patients with Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is a major health problem worldwide.[1] It is characterized as a chronic inflammatory lung disease that causes obstructed airflow from the lungs. It is typically caused by long-term exposure to cigarette smoke, but household air pollution, ambient particulate matter, ozone, and occupational particulates, including coal dust, also contribute to COPD.[2] According to the Global Burden of Disease, 544.9 million people worldwide had a chronic respiratory disease in 2017, which represents an increase of 39.8% compared with 1990.[1] Among the respiratory diseases, COPD remained the most prevalent disease-specific condition in 2017, accounting for 55.1% of chronic respiratory disease prevalence among men and 54.8% among women globally.[1] More importantly, most chronic respiratory disease-attributable deaths and disability-adjusted life years were due to COPD.[1]

Consistent evidence has indicated that COPD is associated with increased cardiovascular risk, which is an important cause of death in COPD patients.[3,4] Systemic inflammation, chronic hypoxia, sympathetic activation, lung hyperinflation, secondary erythrocytosis, and loss of pulmonary vascular surface are responsible for increasing the rate of conditions such as pulmonary hypertension, right ventricular dysfunction, arrhythmias, ischemic coronary disease, among others.[3] More recently, the association between COPD and hypertension has gained increasing attention. In a Danish cohort of more than 70,000 COPD patients, 47.6% of the patients had hypertension (the most common comorbidity in these patients).[5] Although it is not clear whether COPD increases the incidence of hypertension, uncontrolled blood pressure (BP) is associated with poor prognosis in patients with COPD.[6] These findings pave the way for additional characterization of the impact of COPD on BP variability.

In this issue of the *Arquivos Brasileiros de Cardiologia*,[7] the authors conducted an interesting cross-sectional study to investigate the associations between non-dipper BP patterns, which are markers of subclinical inflammation, arterial stiffness, and quality of life, in 142 adult patients with COPD. COPD was defined using spirometry and suggestive clinical features. As expected, all patients were classified as dippers or non-dippers by 24-hour ambulatory BP monitoring (ABPM). In addition, the authors assessed arterial stiffness parameters using a validated device calculating the augmentation index and pulse wave velocity. The quality of life was evaluated by two scales, the Saint George' Respiratory Questionnaire and the Euro Quality of Life Scale (EQ-5D). The first one is a standardized self-administered airways disease-specific questionnaire divided into three subscales: symptoms (eight items), activity (16 items), and impacts (26 items). For each subscale and for the overall questionnaire, scores range from zero (no impairment) to 100 (maximum impairment). The EQ-5D is a non-disease specific instrument to describe and evaluate the health-related quality of life. It is noteworthy that the initial intention of the authors for using these two scales was not clear. The authors found a very high percentage of non-dipper BP patterns (< 10% reduction in BP during sleep compared with the waking period) in patients with COPD, namely, 76.1% (n = 108). As previously described in other investigations, higher values of augmentation index were found in those with the non-dipper BP profile. Interestingly, the quality of life (measured by the EQ-5D) was lower in patients with COPD who presented a non-dipping BP pattern. Consistently, the Saint George Respiratory Questionnaire revealed higher values (less quality of life) when comparing non-dippers and dippers. In the multivariate logistic regression, participants with the non-dipper BP pattern presented higher values of C-reactive protein (12%), augmentation index (5.7%), and a higher total score of the Saint George Questionnaire (2.1%), compared to the reference group (dipper BP pattern). EQ-5D was not independently associated with non-dipping BP pattern. Moreover, the frequency of the non-dipper pressure BP pattern increased in parallel to the increased number of people living in the household (33%).

The study conducted by Askin et al.[7] has merit for addressing not only ABPM in COPD but also potential interfaces in this association. Three quarters of COPD patients presented non-dipping BP pattern, a rate comparable to other chronic conditions, such as diabetes and chronic kidney disease.[8,9] The independent association of non-dipping BP with subclinical inflammation may have the following two potential implications: 1) Inflammation may be one of the potential mechanisms of non-dipping BP pattern in patients with COPD, but the opposite may also be true; 2) This combination potentially denotes a sub-group of patients with COPD with higher cardiovascular risk. The independent association between the number of people living in the household and the non-dipper BP pattern is interesting, and

Keywords

Pulmonary Disease Chronic Obstructive; Cardiovascular Diseases; Monitoring; Dipper; Non-Dipper; Prognosis; Quality of Life.

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it is potentially not specific to COPD. As speculated by the authors, the higher the number of people living in a place, the higher the levels of anxiety (and possibly insomnia) that in turn may influence the circadian BP pattern. Despite the strengths, it is important to comment on some limitations to guide potential investigations in the future. First, this cross-sectional design prevents any inference about causality. Some associations (for instance, inflammation and non-dipping BP pattern) may be bidirectional. Second, around 50% of patients with COPD had a formal diagnosis of hypertension. Detailed inclusion of the effects of anti-hypertensive treatment would be necessary to improve the quality of the multivariate analysis. Third, patients with non-dipping BP may suffer from important and prevalent sleep-disordered breathing, such as obstructive sleep apnea (OSA).[10] Overlap syndrome, i.e. the co-existence of both COPD and OSA, is relatively common, and it has an additional impact on cardiovascular system, multiplying the risk of morbidity and mortality.[11,12] Therefore, it is conceivable that OSA is a major residual factor for explaining the main results. Despite the lack of detailed data on ABPM in overlap syndrome, previous evidence on OSA showed that diastolic attenuated and systolic/diastolic reverse dipping BP are independently associated with moderate to severe OSA.

In conclusion, COPD is potentially a "new kid in the block" in terms of impact on the 24-hour BP profile. Because non-dipping BP has prognostic significance, future studies aiming to evaluate whether the cardiovascular risk attributed to COPD is partially mediated by ABPM parameters are necessary.

References

1. GBD Chronic Respiratory Disease Collaborators. Collaborators. Prevalence and attributable health burden of chronic respiratory diseases, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Respir Med 2020 Jun;8(6):585-96
2. Hatipoğlu U. Chronic obstructive pulmonary disease: More than meets the eye. Ann Thorac Med. 2018 Jan-Mar;13(1):1-6.
3. André S, Conde B, Fragoso E, Boléo-Tomé JP, Areias V, Cardoso J. DPOC-Grupo de Interesse na Doença Pulmonar Obstrutiva Crónica. COPD and Cardiovascular Disease. Pulmonology. 2019 May-Jun;25(3):168-76.
4. Morgan AD, Zakeri R, Quint JK. Defining the relationship between COPD and CVD: what are the implications for clinical practice? Ther Adv Respir Dis. 2018 Jan-Dec;12:1753465817750524.
5. Hansen NS, Ängquist L, Lange P, Jacobsen R. Comorbidity Clusters and Healthcare Use in Individuals With COPD. Respir Care. 2020 Aug;65(8):1120-7.
6. Byrd JB, Newby DE, Anderson JA, Calverley PMA, Celli BR, Cowans NJ,et al. SUMMIT Investigators. Blood pressure, heart rate, and mortality in chronic obstructive pulmonary disease: the SUMMIT trial. Eur Heart J. 2018 Sep 1;39(33):3128-34.
7. Askin M, Koc EM, Sozmen K, Turan MO, Soypacaci Z, Aksun S, et al. Avaliação de padrões pressóricos Dipper e Não-Dipper e qualidade de vida entre pacientes com doença pulmonar obstrutiva crônica. Arq Bras Cardiol. 2021; 116(2):295-302
8. Pistrosch F, Reissmann E, Wildbrett J, Koehler C, Hanefeld M. Relationship between diurnal blood pressure variation and diurnal blood glucose levels in type 2 diabetic patients. Am J Hypertens. 2007 May;20(5):541-5.
9. Minutolo R, Agarwal R, Borrelli S, Chiodini P, Bellizzi V, Nappi F, et al. Prognostic role of ambulatory blood pressure measurement in patients with nondialysis chronic kidney disease. Arch Intern Med. 2011 Jun 27;171(12):1090-8.
10. Pio-Abreu, Moreno H Jr, Drager LF. Obstructive Sleep Apnoea and Ambulatory Blood Pressure Monitoring: Current evidence and research gaps. J Hum Hypert. Jan 07 2021 (in press).Doi: 10.1038/s41371-00-00470 [online] ahead print
11. Machado MC, Vollmer WM, Togeiro SM, Bilderback AL, Oliveira MV, Leitão FS, et al. CPAP and survival in moderate-to-severe obstructive sleep apnoea syndrome and hypoxaemic COPD. Eur Respir J. 2010 Jan;35(1):132-7.
12. Genta-Pereira DC, Furlan SF, Omote DQ, Giorgi DMA, Bortolotto LA, Lorenzi-Filho G, et al. Nondipping Blood Pressure Patterns Predict Obstructive Sleep Apnea in Patients Undergoing Ambulatory Blood Pressure Monitoring. Hypertension. 2018; 72 (4): 979-85.
13. Voulgaris A, Archontogeorgis K, Steiropoulos P, Papanas N. Cardiovascular disease in patients with chronic obstructive pulmonary disease, obstructive sleep apnoea syndrome and overlap syndrome. Curr Vasc Pharmacol. 2020 Mar 17 Pub Date: 2021-05-01. doi: 10.2174/1570161118666200318103553. [online] ahead print

Current Use of Pediatric Cardiac Magnetic Resonance Imaging in Brazil

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Abstract

Background: **Data on the use of cardiac magnetic resonance imaging (CMR) on children in Brazil is lacking.**

Objectives: **This study sought to provide information on current pediatric CMR practices in Brazil.**

Methods: **A questionnaire was sent out to referring physicians around the country. It covered information on the respondents, their CMR practices, the clinical context of the patients, and barriers to CMR use among children. For statistical analysis, two-sided $p < 0.05$ was considered significant.**

Results: **The survey received 142 replies. CMR was reported to be available to 79% of the respondents, of whom, 52% rarely or never use CMR. The most common indications were found to be cardiomyopathies (84%), status of post-tetralogy of Fallot repair (81%), and aortic arch malformations (53%). Exam complexity correlated with CMR-to-surgery ratio (Rho = 0.48, 95% CI = 0.32-0.62, $p < 0.0001$) and with the number of CMR exams (Rho = 0.52, 95% CI = 0.38-0.64, $p < 0.0001$). Further, a high CMR complexity score was associated with pediatric cardiologists conducting the exams (OR 2.14, 95% CI 1.2-3.89, $p < 0.01$). The main barriers to a more frequent use of CMR were its high cost (65%), the need for sedation (60%), and an insufficient number of qualified professionals (55%).**

Conclusion: **Pediatric CMR is not used frequently in Brazil. The presence of a pediatric cardiologist who can perform CMR exams is associated with CMR use on more complex patients. Training pediatric CMR specialists and educating referring providers are important steps toward a broader use of CMR in Brazil. (Arq Bras Cardiol. 2021; 116(2):305-312)**

Keywords: **Pediatrics; Heart Defects,Congenital/surgery; Diagnostic Techniques Procedures; Magnetic Resonance Imaging; Cardiac Catheterization.**

Introduction

Cardiac magnetic resonance imaging (CMR) is considered the gold standard for the assessment of ventricular volumes, systolic function, and *in vivo* flow quantification.[1-5] It can also diagnose edema and fibrosis with good agreement with histology.[6,7] In addition, CMR images may be used as a matrix source in order to produce three-dimensional cardiac models that can be used for teaching, training, and preoperative planning.[8,9] The combination of these advantages makes CMR a powerful tool in the management of patients with congenital heart disease (CHD).

Over the last decade, CMR has been routinely employed at leading pediatric cardiology centers worldwide. In some hospitals, the number of CMR exams exceeds the number of cardiac surgeries. At Boston Children's Hospital, for example, there were 1,270 CMR exams and 947 surgeries in 2016/2017 (http://www.childrenshospital.org); at Texas Children's Hospital, there were 941 CMR exams and 926 surgeries in 2018 (https://www.texaschildrens.org); and at the Hospital for Sick Children in Toronto, roughly 700 CMR exams and 600 surgeries are performed each year. These figures result in a CMR-to-surgery ratio between 1.02 and 1.34.

In Brazil, numbers on the use of CMR are not publicly available. It was hypothesized that CMR is not widely available for the pediatric population and that it is being underused. Information on CMR use, the most frequent indications for and barriers to its use, as well as the role of CMR in cardiac and surgical decision-making are not available. Unpublished data from the Heart Institute of Distrito Federal show that their average annual number of pediatric CMR exams is 55, while their average annual number of pediatric cardiac surgeries is 180, resulting in a CMR-to-surgery ratio of 0.31. At the Children's and Maternity Hospital of São Jose do Rio Preto, where approximately 300 surgeries are performed each year, only 21 CMR exams were performed in 2018 (personal communication), resulting in a CMR-to-surgery ratio of 0.07.

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Because these numbers are not necessarily representative, the present study sought to obtain information on the use of CMR on children in Brazil.

Methods

A survey was distributed to pediatric cardiologists and cardiac surgeons from across Brazil. These individuals were identified mainly from three WhatsApp groups related to the field of pediatric cardiology: "Grande INCOR" (a group consisting of current and prior pediatric cardiologists and pediatric cardiac surgeons from the Heart Institute of São Paulo [INCOR]), "DCC/CP" (a group created by the Department of Congenital Heart Disease and Pediatric Cardiology of the Brazilian Society of Cardiology, including pediatric cardiologists and pediatric cardiac surgeons from around the country), and "GBCO-Ped" (a Brazilian pediatric cardio-oncology group, which includes pediatric cardiologists with any interest in cardio-oncology). These groups include a total of more than 350 individuals. The first author's individual contacts were also asked to participate. A questionnaire with 10 questions (Supplementary Material) was converted into electronic format via SurveyMonkey (Palo Alto, CA, USA) and sent out to the aforementioned groups. Respondents who worked in more than one institution were asked to provide answers regarding only one of them. The identity of the respondents and their institutions remained anonymous, thus allowing for multiple respondents from a single institution.

Due to the large number of contacts from the city of São Paulo (SP) and because it is a city with half of the cardiac surgery centers in the state of São Paulo with a population that is larger than the regions North and Central-West (Figure 1), SP, for the purpose of this study, was thus treated as a separate geographic area, rather than part of the Southeast region.[10]

The questionnaire contained questions covering the respondents (workplace, expertise, and number of cardiac surgeries performed at his/her main reference institution), CMR practices (availability, specialist performing the exams, and frequency of CMR exams), clinical contexts of the patients (CMR indication, readiness to proceed with Fontan operation without a prior cardiac catheterization, among others), and barriers faced when using CMR in this population. Questionnaires containing only answers about the respondents were excluded from the analysis, since this information alone would have not added relevant data to the objectives of the study. The same questionnaire was sent out to a WhatsApp group of cardiac imagers with pediatric/congenital expertise in Brazil, in which the first author participates, with the objective of obtaining data on their numbers of CMR exams and their CMR practices.

Figure 1 – *CMR survey respondents' geographic distribution (adapted from https://suportegeografico77.blogspot.com/2019/04/mapa-regioes-do-brasil.html).*

This study used the answers to Questions 3 (the number of surgeries performed annually) and 6 (the number of CMR exams performed monthly) to estimate the CMR-to-surgery ratio for each respondent. Each individual categorical answer was transformed into a number, since the answer options were number based. With regard to the number of surgeries (Question 3), if fewer than 150 surgeries were performed annually, the answer was treated as 100; if between 150 and 249 surgeries were performed, the answer was treated as 200; if between 250 and 349 surgeries were performed, the answer was treated as 300; and if 350 or more surgeries were performed a year, the answer was treated as 500. With regard to the number of CMR exams performed monthly (Question 6), if no CMR exams were performed, the answer was treated as zero; if one or two CMR exams were performed, the answer was treated as 2; if three to five CMR exams were performed, the answer was treated as 5; if six to twelve CMR exams were performed, the answer was treated as 12; and if thirteen or more CMR exams were performed a month, the answer was treated as 20. These rates were multiplied by twelve in order to transform the monthly rate of CMR exams into an annual rate.

Using these numbers, it was possible to estimate the CMR-to-surgery ratio for each site by dividing the number of CMR exams by the number of cardiac surgeries.

The complexity of the CMR was stratified as follows. High complexity procedures involved "complex CHD with a diagnostic query," "status following Jatene, Senning, or Mustard operations", "Ebstein's anomaly," "hypoplastic right or left ventricles" (borderline ventricles), "status pre- or post- Glenn and Fontan operations," and "fetal CMR". Medium complexity procedures involved "status post-tetralogy of Fallot repair," "situs anomalies," and "pulmonary venous return anomalies". Low complexity procedures defined all of the remaining answers. These indications received a numerical score: High complexity = 3, medium complexity = 2, and low complexity = 1. The respondents' individual answers were multiplied by these scores added together. The maximum possible score was 32, which covered all possible clinical indications. For instance: if someone has used CMR only for Ebstein´s anomaly, hypoplastic left ventricle, status post-tetralogy of Fallor repair and cardiomyopathy, this respondent´s score is 9.

Statistical Analyses

Considering that the number of registered pediatric cardiologists in Brazil is 491 (portal.cfm.org.br), the sample size estimated to have a 95% confidence interval (CI) and a margin of error of ± 3%, which, according to Cochran´s formula, was 95. Continuous variables were expressed as means plus or minus standard deviation or median with interquartile range (25-75), as appropriate. For the assessment of data normality, a calculation tool was employed to calculate the area under a normal curve, assumed to be when approximately 95% of the area was within 1.96 standard deviations of the mean. Categorical variables were summarized as numbers and percentages. The chi-square test was used to assess associations between categorical variables and adjusted odds ratios (ORs) with their 95% CIs. Spearman's rank test was used to assess correlations between ordinal variables with skewed distributions. Two-sided $p < 0.05$ was considered statistically significant. Analyses were performed using StatsDirect, v. 2.7.2 2008 (Cheshire, UK).

Results

Our survey produced 142 responses for a response rate of 142/364 (40%). In summary, responses were received from the following regions: the North (1.4%), the Northeast (14.8%), the Central-West (13.4%), SP (24.65%), the Southeast (not including São Paulo) (24.65%), and the South (21.1%) (Figure 1). Due to the limited participation of respondents from the North, this region was not represented in further analyses that were stratified by region. Most of the respondents (75%) worked in state capitals and were most commonly pediatric cardiologists (91.5%), followed by cardiac surgeons (7%), and adult cardiologists who also treat children (1.4%). The size of the cardiac surgery programs where the referring physicians worked varied by region (Table 1).

CMR was reported as 'available' by 79% of the respondents. This rate varied widely by region (Table 1), with respondents from Goiânia, Belém, and Palmas reporting that CMR was not available to them. CMR was available to 68% of the physicians who work outside of capital cities.

In Brazil, CMR is performed by radiologists, followed by pediatric cardiologists. In some areas, pediatric cardiologists who perform CMR exams are rare or non-existent (Figure 2).

Most of the respondents (61%) reported that they rarely

Table 1 – Summary of the most important survey results stratified by region and the city of São Paulo

	NE (n = 21)	CW (n = 19)	SE (n = 35)	SP (n = 35)	S (n = 30)
Estimated number of cardiac surgeries per center/year	200 (200-300)	180 (180-180)	200 (100-307.5)	400 (200-500)	300 (200-480)
CMR available – yes	67%	95%	86%	94%	83%
Ped cardiologist performing CMR exams – yes	0	68.5%	28.2%	68.6%	30%
Estimated number of CMR exams per center/month (IQ)	2 (2-2)	4.58 (4.58-4.58)	2 (2-5)	5 (2-12)	2 (2-5)
CMR complexity score:0-32 (IQ)	7 (5-9)	25 (15-25)	8 (5.5-14)	11 (7-17.8)	9 (6-15)
CMR-to-surgery ratio (SD)	0.11 ± 0.08	0.35 ± 0.27	0.24 ± 0.35	0.36 ± 0.35	0.14 ± 0.1

CMR: cardiac magnetic resonance imaging; Regions: NE: Northeast; CW: Central-West; SE: Southeast; SP: São Paulo; S: South.

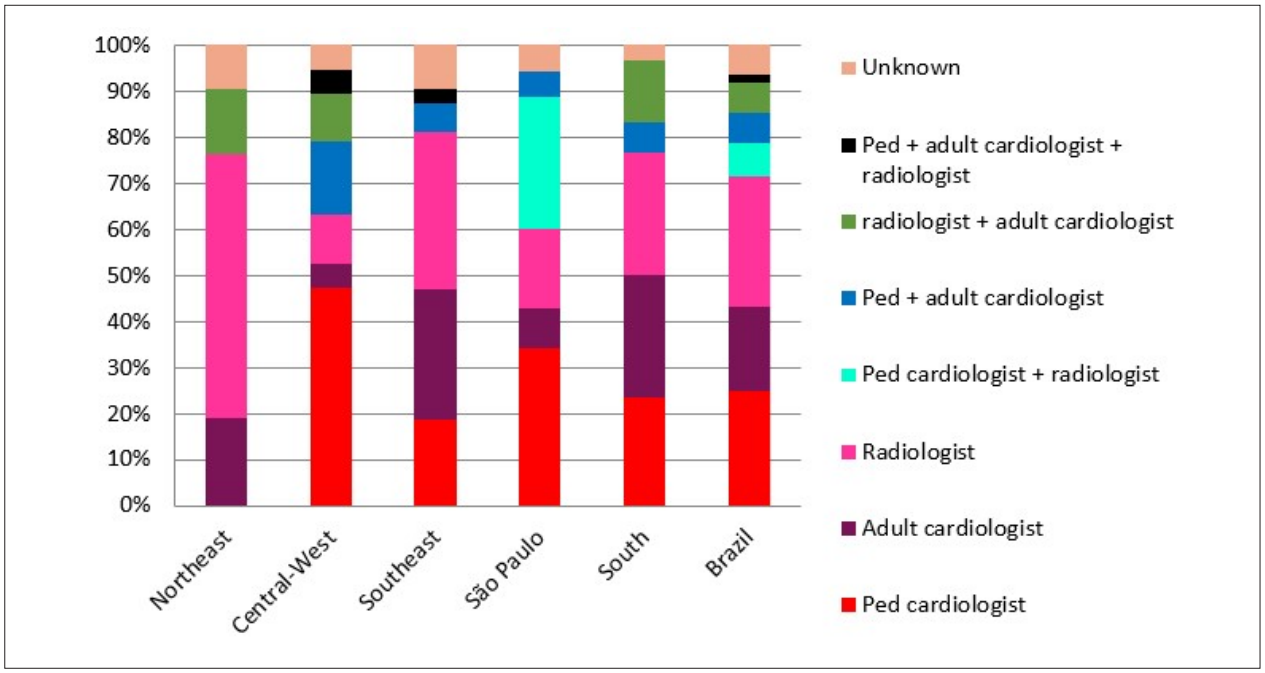

Figure 2 – *Types of specialists performing pediatric CMR in Brazil by region.*

or never use CMR, while 15% reported that they use it often. The frequency of CMR use varied by geographic region (Table 1). The overall Brazilian CMR-to-surgery ratio was estimated to be 0.22 ± 0.27, which also varied by region (Table 1).

Cardiac Magnetic Resonance Indications

Our survey showed that the three most common indications for CMR were cardiomyopathies (84%), status post-tetralogy of Fallot repair (81%), and aortic arch malformations (53%) (Table 2). Regional differences on CMR complexity were also found (Table 1).

Our findings showed correlations between exam complexity and CMR-to-surgery ratio (Rho = 0.48, 95% CI = 0.32-0.62, p < 0.0001), as well as between exam complexity and the number of CMR exams (Rho = 0.52, 95% CI = 0.38-0.64, p < 0.0001). No correlation was found between CMR complexity and number of surgeries (p = 0.73).

The results also pointed to a positive correlation between a high CMR complexity score (≥ 18) and whether the exam was performed by a pediatric cardiologist (OR 2.14, 95% CI 1.2-3.89, p 0.01), as well as an inverse correlation between high complexity and performance by an adult cardiologist (OR 0.42, 95% CI 0.19-0.89, p 0.03).

Need for Routine Catheterization prior to Fontan

A relatively high number of the respondents (43%) would consider ordering a Fontan operation without prior cardiac catheterization (cath) in selected patients, based on the combination of echocardiography (echo) and CMR assessments.

It was observed that the willingness to proceed with the Fontan completion without prior cath correlated inversely with the size of the cardiac surgery program (OR 0.6, 95% CI 0.38-0.93, p 0.02) and with a lack of confidence in CMR flow assessment (OR 0.42, 95% CI 0.31-0.56, p < 0.0001).

Confidence in Echocardiography and Cardiac Catheterization versus CMR for Flow Assessments

Of the respondents, 74% reported relying more on flow assessments by echo and/or cath than on the flow assessment by CMR.

No associations were found between confidence in echo/cath or CMR flow assessment and the number of CMR exams performed monthly, the use of CMR for pre- or post- Glenn and Fontan surgeries, or the type of specialist performing the CMR exams.

Barriers to CMR Use

According to the respondents, the main barriers to the more frequent use of CMR are its high cost (65%), the need for sedation or anesthesia (60%), and the insufficient number of qualified professionals (55%; Table 3). One of the respondents mentioned that CMR is available only for adults in the city where he/she is employed.

Discussion

To the best of our knowledge, this is the first survey to assess the use of CMR in children in Brazil. Regional differences were identified in many aspects of CMR practice: specialist performing CMR, CMR indications, CMR-to-surgery ratio, among others. This corroborates our

Table 2 – CMR indications for children in Brazil

CMR Indication	Affirmative Answers (%)
Cardiomyopathies	84
Status post-tetralogy of Fallot repair	81
Aortic arch disease	53
Complex CHD	46
Ebstein's anomaly	45
Cardiac tumors	44
Right or left ventricular hypoplasia	36
Pre- and or post-Glenn and Fontan	36
Status post-transposition of the great arteries repair	34
Coronary anomalies	32
Pulmonary venous return	31
Marfan	18
Status post-heart transplant	16
Cardiotoxicity	14
Situs anomalies	14
Takayasu arteritis	14
Fetal CMR	3

CMR: cardiac magnetic resonance imaging; CHD: congenital heart disease.

Table 3 – Barriers to CMR use

Barriers	%
Cost	65
Need for sedation	60
Insufficient number of qualified professionals	55
Waiting time	40
Limited education on and promotion of CMR	24
Inferiority to computed tomography angiography	21
Limited credibility	16
Other	5

CMR: cardiac magnetic resonance imaging.

impression that CMR use is diverse throughout the country. This study found that, in comparison to the leading centers in Europe and North America, CMR is very underused in Brazil as regards the number of surgeries. This study suggests that the reason for this finding may be multifactorial.

Cost was cited as the main barrier to more frequent CMR use. However, considering the relatively high availability of pediatric CMR reported in this survey, this answer might instead be reflecting a difficulty of access to CMR. In Brazil, most patients with CHD are treated at public facilities, which usually operate with very restricted budgets. In stark contrast to the needs of children and adolescents with CHD, according to 2012 data from the Brazilian Ministry of Health, 84 MRI scanners were available for the country's publicly funded health insurance, and 1,263 MRI scanners were available for private practice. The paucity of available scan time is further worsened by the need to share the magnet with other pediatric and/or adult specialties. At the first author's practice, for example, there is only one scanner, which is available for routine pediatric or congenital CMR exams only one morning per week. Therefore, the highest CMR-to-surgery ratio we can achieve is 0.6:1. For the sake of comparison, at the Hospital for Sick Children in Toronto, there are six scanners for clinical use, one of which is dedicated exclusively to pediatric CMR exams for 6 hours every day. Another possible explanation for the reported barrier of 'scanner availability' is the question of reimbursement. At our site, the public health care system reimburses CMR exams with BRL$403 (US$103), while BRL$322 (US$83) is reimbursed for a computed tomography (CT), and BRL$165 (US$42) is reimbursed for an echo. In relative terms, these differences are not dissimilar to those in the US. Therefore, it does not seem to be a suitable reason for the underuse of CMR as regards echo and CT. In absolute figures, however, the reimbursement for all types of imaging studies is insufficient (http://www2.ebserh.gov.br/documents).

The second most important barrier to a more frequent application of CMR was found to be the need for sedation or anesthesia, which is usually requested for children under 8 years of age. This is often a concern for both the referring physician and his or her parents. However, it is important to emphasize that the number of adverse events experienced by children as a result of sedation for CMR is very low.[11] Another point to consider is that CMR is a non-invasive technique that does not expose patients to ionizing radiation, as is the case with the use of cardiac cath or CT.[12] However, it is important to mention that measures are taken to avoid sedation and that there are many strategies that can be used to this end.[13-16]

The third most important barrier to a more frequent use of CMR was reported to be an insufficient number of qualified professionals. The Society for Cardiovascular Magnetic Resonance stratifies CMR training into three levels: 1. basic training, 2. specialized training, and 3. advanced training.[17] There is a requirement to perform at least 150 CMR cases a year to obtain the level 2 certificate which constitutes the minimum level required in Europe for pediatric cardiologists to perform a CMR.[17-19] In Brazil, there is no regulation on this matter, but it would not seem unreasonable to seek the implementation of European standards. It may be simply a matter of time before specialization in pediatric/congenital CMR evolves and more qualified professionals are available in the market. Interestingly, the COCATS 4 task force recognizes that skills to identify basic and complex CHD in adults, including quantification of shunts, are usually acquired after 36 months of exposure to CMR cases in a general CMR setting.[20] Therefore, it is advisable to "concentrate" the learning experience by training in specialized pediatric

facilities. In Europe and North America, for example, pediatric/congenital CMR fellowships are offered at sites that perform a high number of pediatric and congenital exams. These programs are usually located within pediatric hospitals with a high volume of cardiac surgeries. More often than not, these sites have a pediatric cardiologist as an integral member of their imaging teams. In Brazil, this setup exists only in the city of São Paulo, where the number of surgeries is high and where there are pediatric cardiologists routinely involved in the pediatric CMR practice. At the present time, training radiologists and cardiologists to become experts in pediatric CMR exams realistically involves physicians training at academic centers in Europe and North America.

Almost all of the respondents had previously requested CMR exams for patients with cardiomyopathy or after tetralogy of Fallot repair, indications of low and medium complexity. More complex CMR exams are performed in centers with the highest CMR-to-surgery ratios and especially when pediatric cardiologists are involved in scanning. On the other hand, the complexity of the exams was not necessarily found to be related to the number of surgeries performed. It seems possible that sites that offer CMR and that employ pediatric cardiologists attract more complicated cases, perhaps because they are more prepared to take on these cases or because these services tend to be more integrated into cardiology practice.

In the vast majority of centers worldwide, it is routine for a patient with a univentricular heart to receive a pre-Fontan cardiac cath for the assessment of the pulmonary arterial anatomy, measurement of the pressure of the pulmonary arterial bed, and estimation of pulmonary vascular resistance. Some experts have encouraged the routine sole use of CMR in pre-Fontan patients, with cath reserved for high-risk patients.[21-25] In this survey, 43% of respondents reported that they would be willing to order a Fontan operation only with information from echo and CMR, thus avoiding cath in patients who are deemed to be standard risk, although there is a large variation in practices between regions.

Study Limitations

The authors of this study recognize that, although the sample size estimated was sufficient to address our questions, the high number of non-respondents, something expected in these kinds of surveys, was a potential source of bias. The most important limitation of our survey, however, was the fact that the actual number of pediatric CMR exams per center remains unknown. We tried to obtain these numbers from radiologists and cardiologists who lead or are part of the imaging teams of the largest pediatric cardiac surgery programs in Brazil, but only one site agreed to share its CMR statistics. Therefore, the CMR-to-surgery ratios found and all associations between the number of CMR exams and the number of surgeries were mere estimates, and may not be, to some extent, representative of Brazil. To mitigate uncertainties and improve comparability between sites, our study offered answer options that included ranges rather than precise numbers. It is possible that we have received responses from several individuals from the same institution and that these responses may, to a certain extent, have expressed individual estimates rather than concrete institutional data and that some institutions may have been overrepresented in the pool of respondents. It was also impossible to evaluate the availability of CMR and other aspects of CMR in the North of Brazil due to the low participation of colleagues from this area.

Conclusions

Pediatric CMR is available to approximately 2/3 of practitioners, but it is rarely used in Brazil. Exams are most often performed by radiologists. CMR is most commonly obtained for cardiomyopathies and after tetralogy of Fallot repair. The presence of a pediatric cardiologist to perform the CMR exams is associated with CMR use in more complex patients. Obstacles to a more frequent use of CMR are cost, the need for sedation, and a lack of qualified professionals. Training pediatric CMR specialists and educating referring providers are important steps toward an increased use of CMR in Brazil. Collaboration between institutions is advisable and necessary in order to have a better picture of the use of CMR in the pediatric population in Brazil.

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Author contributions

Conception and design of the research, Acquisition of data and Statistical analysis: Kozak MF; Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Kozak MF, Afiune JY, Grosse-Wortmann L.

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

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

References

1. Hendel RC, Patel MR, Kramer CM, Poon M, Carr JC, Gerstad NA, et al. ACCF/ACR/SCCT/SCMR/ASNC/NASCI/SCAI/SIR 2006 Appropriateness Criteria for Cardiac Computed Tomography and Cardiac Magnetic Resonance Imaging: A Report of the American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group, American College of Radiology, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, American Society of Nuclear Cardiology, North American Society for Cardiac Imaging, Society for Cardiovascular Angiography and Interventions, and Society of Interventional Radiology. J Am Coll Cardiol. 2006;48(7):1475-97.
2. Clarke CJ, Gurka MJ, Norton PT, Kramer CM, Hoyer AW. Assessment of the accuracy and reproducibility of RV volume measurements by CMR in congenital heart disease. JACC Cardiovasc Imaging. 2012;5(1):28-37.
3. Hundley WG, Li HF, Hillis LD, Meshack BM, Lange RA, Willard JE, et al. Quantitation of cardiac output with velocity-encoded, phase-difference magnetic resonance imaging. Am J Cardiol. 1995;75(17):1250-5.
4. Hundley WG, Li HF, Lange RA, Pfeifer DP, Meshack BM, Willard JE, et al. Assessment of left-to-right intracardiac shunting by velocity-encoded, phase difference magnetic resonance imaging. A comparison with oximetric and indicator dilution techniques. Circulation. 1995;91(12):2955-60.
5. Powell AJ, Maier SE, Chung T, Geva T. Phase-velocity cine magnetic resonance imaging measurement of pulsatile blood flow in children and young adults: in vitro and in vivo validation. Pediatr Cardiol. 2000;21(2):104-10.
6. Mewton N, Liu CH, Croisille P, Bluemke D, Lima JAC. Assessment of myocardial fibrosis with cardiovascular magnetic resonance. J Am Coll Cardiol. 2011;57(8):891-903.
7. Jordan JH, Vasu S, Morgan TM, D'Agostino Jr RB, Melendez GC, Hamilton CA, et al. Anthracycline-associated T1 mapping characteristics are elevated independent of the presence of cardiovascular morbidities in cancer survivors. Circ Cardiovasc Imaging. 2016;9(8):e004325.
8. Costello JP, Olivieri LJ, Su L, Krieger A, Alfares F, Thabit O, et al. Incorporating three-dimensional printing into a simulation-based congenital heart disease and critical care training curriculum for resident physicians. Congenit Heart Dis. 2015;10(2):185-90.
9. Costello JP, Olivieri LJ, Krieger A, Thabit O, Marshall MB, Yoo SJ, et al. Utilizing three-dimensional printing technology to assess the feasibility of high-fidelity synthetic ventricular septal models for simulation in medical education. World J Pediatr Congenit Heart Surg. 2014;5(3):421-6.
10. Caneo LF, Jatene MB, Yatsuda N, Gomes WJ. A reflection on the performance of pediatric cardiac in the State of São Paulo. Rev Bras Cir Cardiovasc. 2012;27(3):457-62.
11. Rangamani S, Varghese J, Li L, Harvey L, Hammel JM, Fletcher SE, et al. Safety of cardiac magnetic resonance and contrast angiography for neonates and small infants: a 10-year single-institution experience. Pediatr Radiol. 2012;42(11):1339-46.
12. Callahan MJ, MacDougall RD, Bixby SD, Voss SD, Robertson RL, Cravero JP. Ionizing radiation from computed tomography versus anesthesia for magnetic resonance imaging in infants and children: patient safety considerations. Pediatr Radiol. 2018;48(1):21-30.
13. Kharabish A, Mkrtchyan N, Meierhofer C, Martinoff S, Ewert P, Stern H, et al. Cardiovascular magnetic resonance is successfully feasible in many patients aged 3 to 8 years without general anesthesia or sedation. J Clin Anesth. 2016 Nov;34:11-4.
14. Lu JC, Nielsen JC, Morowitz L, Musani M, Mahani MG, Agarwal PP, et al. Use of a 1.0 Tesla open scanner for evaluation of pediatric and congenital heart disease: a retrospective cohort study. J Cardiovasc Magn Reson. 2015;17(1):39.
15. Shariat M, Mertens L, Seed M, Grosse-Wortmann L, Golding F, Marcer-Rosa L, et al. Utility of feed-and-sleep cardiovascular magnetic resonance in young infants with complex cardiovascular disease. Pediatr Cardiol. 2015;36(4):809-12.
16. Windram J, Grosse-Wortmann L, Shariat M, Greer ML, Crawford CW, Yoo SJ. Cardiovascular MRI without sedation or general anesthesia using a feed-and-sleep technique in neonates and infants. Pediatr Radiol. 2012;42(2):183-7.
17. Kim RJ, Simonetti OP, Westwood M, Kramer CM, Narang A, Friedrich MG, et al. Guidelines for training in cardiovascular magnetic resonance (CMR). J Cardiovas Mag Reson. 2018;20:57.
18. Helbing WA, Mertens L, Sieverding L. Recommendations from the Association for European Paediatric Cardiology for training in congenital cardiovascular magnetic resonance imaging. Cardiol Young. 2006;16(4):410-2.
19. Plein S, Schulz-Menger J, Almeida A, Mahrholdt H, Rademakers F, Pennell D, et al. Training and accreditation in cardiovascular magnetic resonance in Europe: a position statement of the working group on cardiovascular magnetic resonance of the European Society of Cardiology. Eur Heart J. 2011;32(7):793-8.
20. Kramer CM, Hundley WG, Kwong RY, Martinez CW, Raman SV, Ward RP. COCATS 4 task force 8: training in cardiovascular magnetic resonance imaging. J Am Coll Cardiol. 2015;65(17):1822-31.
21. Downing TE, Whitehead KK, Dori Y, Gillespie MJ, Harris MA, Fogel MA, et al. Accuracy of conventional oximetry for flow estimation in patients with Superior cavopulmonary connection: a comparison with phase-contrast MIR. Circ Cardiovasc Imaging. 2013;6(6):943-9.
22. Fogel MA, Pawlowski TW, Whitehead KK, Harris MA, Keller MS, Glatz AC, et al. Cardiac magnetic resonance and the need for routine cardiac catheterization in single ventricle patients prior to fontan: a comparison of 3 groups. J Am Coll Cardiol. 2012;60(12):1094-1102.
23. Prakash A, Khan MA, Hardy R, Torres AJ, Chen JM, Gersony WM. A new diagnostic algorithm for assessment of patients with single ventricle before a Fontan operation. J Thorac Cardiovasc Surg. 2009;138(4):917-23.
24. Ven JPG, Bosch E, Bogers AJCC, Helbing WA. State of the art of the Fontan strategy for treatment of univentricular heart disease. F1000Res. 2018 Jun 27;7:F1000.
25. Brown DW, Gauvreau K, Powell AJ, Lang P, Nido PJ, Odegard KC, et al. Cardiac magnetic resonance versus routine cardiac catheterization before bidirectional Glenn anastomosis: long-term follow-up of a prospective randomized trial. J Thorac Cardiovasc Surg. 2013;146(5):1172-8.

Cardiovascular Imaging in Congenital Heart Diseases: Why not Leverage New Imaging Modalities?

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Short Editorial related to the article: Current Use of Pediatric Cardiac Magnetic Resonance Imaging in Brazil

"There can be no keener revelation of a society's soul than the way in which it treats its children."

Nelson Mandela (8 May 1995)

Worldwide, we are living in an era burdened by congenital heart diseases (CHD).[1] If we take a snapshot in 2018, there were 2,944,932 live births in Brazil (Tabnet, DATASUS). Considering the incidence of CHD, about 9 per 1000 live births, which has been stable across countries and populations, we would expect around 26,000 new patients with some form of CHD in our country. On the other hand, worldwide survival rate for CHD in the last 3 decades has been close to 98%.[2] Having said that, CHD continues to be a public health problem worldwide.

In the last four centuries, the specialty of pediatric cardiology has grown tremendously, achieving several milestones in clinical and surgical scenarios, mostly due the incredible advances in cardiovascular imaging diagnostic tools. This allows non-invasive diagnosis in all ages from fetal life until adulthood. The relatively new modality of cardiac magnetic resonance imaging (CMR) provides clinically useful information in various situations in patients with CHD. Current guidelines for diagnosis and management include echocardiogram, CMR and cardiac catheterization for the majority of CHD patients.[3]

Kozak et al.[4] took a snapshot of the Brazilian situation on the use of CMR in pediatric populations interviewing cardiologists from most states, including centers with different levels of care and surgical volumes. The big picture: *it is not being fully used*! About half of the cardiologists (52%) rarely use CMR for children. If we magnify this picture, two major layers are revealed. The first layer involves the process of changing practices and incorporating new technologies. The predominant use of CMR still relies on use for cardiomyopathies, tetralogy of Fallot post-repair, and aortic arch anomalies, according to this data. However, the current era of CMR in cardiology goes beyond anatomical assessment, allowing us to access hemodynamic and other functional data which impacts patient care, surgical decision making, and even prognostic risk factors. The second layer, not surprisingly, is the cost of CMR, which should be analysed in the context of healthcare costs for populations with CHD. As countries develop economically, the burden of poverty-related conditions diminishes and is substituted by chronic and often complex care needs, such as CHD. The survival rate and quality of life for these patients from childhood into adulthood depends on excellence of medical care. The complexity of surgically repaired heart lesions requires lifelong surveillance.[5] Therefore, all these points should be taken in consideration when planning ideal care for patients with CHD. It is expensive, and it requires investment during a lifelong journey. However, investment is not a single solution; it is a triad which needs to be addressed simultaneously, "*people, process, and technology*". Kozak et al.[4] has shown that there are three major limitations: 1) cost (65%), 2) the need for sedation (60%), and 3) insufficient number of qualified professionals (55%). These address the triad: the investment in new technology in healthcare, the need for professional development, and a process to make the technology effective and impact the quality of care. The training of pediatric cardiologist in today's world requires sub-specialty in imaging diagnosis, which has been advancing too slowly, especially with respect to CMR training.[6] The increasing number and quality of professionals able to perform and interpret results will generate a new cycle, including correct use of CMR in patients with CHD, especially in pediatric populations.

This data has the power to trigger multiple actions in caring for patients with CHD, namely, allocation of resources, professional training, and changes in practices. All these actions coupled with strong care practices move us in the same direction, promoting high quality health care.

Keywords

Heart Defects, Congenital/surgery; Procedures and Techniques Diagnostic; Magnetic Resonance Imaging/methods; Cardiac Catheterization.

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References

1. Penny DJ. Global perspectives on pediatric cardiac critical care. Pediatr Crit Care Med. 2016;17(8):S388–93.
2. Zheleva B, Atwood JB. The invisible child: childhood heart disease in global health. Lancet [Internet]. 2017;389(10064):16–8. Available from: http://dx.doi.org/10.1016/S0140-6736(16)32185-7
3. Stout KK, Daniels CJ, Aboulhosn JA, Bozkurt B, Broberg CS, Colman JM, et al. 2018 AHA/ACC Guideline for the Management of Adults With Congenital Heart Disease: Executive Summary. Circulation. 2018;139(14) è637-e697.
4. Kozak MF, Afiune JY,Crosse-Wortmann. Uso atual de ressonancia magnética cardíaca pediatrica no Brasil. Arq Bras Cardiol. 2021; 116(2):305-312.
5. Morhy SS, Barberato SH, Lianza AC, Soares AM, Leal GN, Rivera IR, et al. Posicionamento sobre Indicações da Ecocardiografia em Cardiologia Fetal, Pediátrica e Cardiopatias Congênitas do Adulto – 2020. Arq Bras Cardiol. 2020; 115(5):987-1005.
6. Helbing WA, Mertens L, Sieverding L. Recommendations from the Association for European Paediatric Cardiology for training in congenital cardiovascular magnetic resonance imaging. Cardiol Young. 2006;16(4):410–2.

Effects of Doxorubicin on Heme Biosynthesis and Metabolism in Cardiomyocyte

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Abstract

Background: **Doxorubicin is associated with cardiotoxicity and late cardiac morbidity. Heme is related to cellular oxidative stress. However, its specific regulation in cardiomyocytes under doxorubicin effects has not yet been documented.**

Objective: **This study seeks to evaluate the changing profiles of rate-limiting enzymes in the heme metabolism pathway under the effect of doxorubicin.**

Methods: **H9c2 cardiomyocytes were incubated with doxorubicin at different concentrations (1,2,5,10μM respectively). The real-time PCR and Western Blot were used to determine the mRNA and protein expression for four pivotal enzymes (ALAS1, ALAS2, HOX-1, and HOX-2) regulating cellular heme metabolism, as well as the levels of heme were detected by ELISA. $p<0.01$ was considered significant.**

Results: **This study observed a dose-dependent changing pattern in heme levels in H9c2 cells with the highest level at the 5μM concentration for doxorubicin, which occurred synchronously with the highest upregulation level of ALAS1, as well as the degradative enzymes, HOX-1, and HOX-2 in mRNA and protein expression. By contrast, ALAS2, contrary to the increasing concentrations of doxorubicin, was found to be progressively down-regulated.**

Conclusion: **The increase in ALAS1 expression may play a potential role in the heme level elevation when H9c2 cardiomyocyte was exposed to doxorubicin and may be a potential therapeutic target for doxorubicin-induced myocardial toxicity. (Arq Bras Cardiol. 2021; 116(2):315-322)**

Keywords: **Doxorubicin; Biosynthesis; Heme; Myocites, Cardiac; Cardiotoxicity; ALAS.**

Introduction

With the continuing progression of anti-tumor drugs and radiotherapy, the survival rate of patients with malignant tumors has been improved, and their survival-span is significantly prolonged. However, the widespread use of anti-tumor drugs is accompanied by an increase in cardiovascular adverse events, which affects patient survival and quality of life. Anthracyclines are drugs derived from streptomycin, including doxorubicin, and epirubicin, which are widely used to treat breast cancer, small cell lung cancer, myeloma, sarcoma, lymphoma, and leukemia. Myocardiopathy and subsequent heart failure are the most serious manifestation of cardiotoxicity caused by anthracycline drugs in chemotherapy. Moreover, the cardiovascular toxicity of anthracyclines is dose-dependent and irreversible.[1,2]

The exact mechanism of anthracycline drugs that induced myocardial toxicity remains unclear, though a variety of theories have been proposed, including the inhibition of DNA replication and RNA transcription, DNA damage caused by free radicals, lipid peroxidation and alkylation, DNA cross-linking, interference with DNA unwinding, inhibition of topoisomerase Ⅱ, among others.

Heme is an important porphyrin ligand, as a supplement of the heme protein, and is responsible for the physiological function of O_2 transport in the body. Many biological functions related to life, such as electron transport, oxygen storage, signal transduction, and gene expression are controlled by different heme proteins. Recent studies found that heme levels increased significantly in rat models of myocardial ischemic heart failure, suggesting that heme may play an important role in ischemic and hypoxic myocardial injury.[3,4] However, there has been no published literature that specifically explored the changing of heme biosynthesis or metabolism in cardiomyocyte under anthracyclines treatment.

Heme biosynthesis is initiated by the formation of 5-aminolevulinic acid (ALA) from glycine (Gly) and succinyl-CoA, catalyzed by ALA synthase (ALAS), which has two isoenzymes: ALAS1 and ALAS2. On the other hand, heme oxygenase (HOX) mediates the first step of heme catabolism, and it cleaves heme to form biliverdin. Two active isoforms of HOX have been identified: the inducible HOX-1 and the less regulated HOX-2.

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The purpose of this study was to elucidate the changing profiles of four pivotal enzymes, aminolaevulinic acid synthase 1 (ALAS1), aminolaevulinic acid synthase 2 (ALAS2), heme oxygenase 1 (HOX-1), and heme oxygenase 2 (HOX-2), in H9c2 cardiomyocyte under doxorubicin treatment.

Methods

Cell culture and doxorubicin treatment

H9c2 cardiomyocytes were purchased from American Type Culture Collection (ATCC, Manassas, VA)and then cultured with DMEM/F12 medium containing 10% fetal bovine serum and 1% double-antibody medium, under the conditions of 37°C and 5% CO_2 in a humidified chamber. The H9c2 cells were then plated onto 6-well plates at 2×10^5 cells/well in a volume of 2 mL and cultured in DMEM/F12 medium containing 10% fetal bovine serum for 24 h. After, different doses of doxorubicin (1,2,5,10 μM, respectively) were added to the plate well. The doxorubicin-untreated cells (treated with saline) represented the control group. After a 24h-incubation at 37ºC, the cells of different wells were harvested separately by centrifugation (10,000 rpm for 10 minutes at 4°C) and used for further study below.

Quantitative real-time PCR

Total RNA was extracted from H9c2 cells of all the groups, using TRIzol (Invitrogen; Thermo Fisher Scientific, Inc., Waltham, MA, USA) and reverse transcribed with the SuperScript Double-Strand Synthesis kit (Invitrogen; Thermo Fisher Scientific, Inc.), according to the manufacturer's instructions, and amplified on a 7500 Fast real-time PCR system with SYBR GreenER qPCR SuperMix Universal (Invitrogen; Thermo Fisher Scientific, Inc., Waltham, MA, USA). Primers used for amplification of ALAS1, ALAS2, HOX-1, and HOX-2 were designed using Primer3 (v. 0.4.0) software. The following primers were used for real-time PCR:

ALAS1-F:TTGCCAAAGTCCGTTTCC

R: TGTAGTCATCTGCCATAGGG 3';

ALAS2-F: TCAAGGGAGAGGAGGGTCAAG

R: ACGAGGCACAGTTGGGTAG

HOX-1-F:TCGACAACCCCACCAAGTT

R:CTGGCGAAGAAACTCTGTCT

HOX-2-F:GCTTACACTCGTTACATGGG

R: CACATGCTCGAACAGGTAGA

GAPDH-F: GATGACATCAAGAAGGTGGTGA

R:ACCCTGTTGCTGTAGCCATATTC.

The reaction conditions were as follows: 95°C for 3 min; 95°C for 30 sec, 55°C for 20sec, and 72°C for 20sec with 40 cycles. Melting curve analyses were performed to verify their amplification specificity. The expression values of all targeted genes from each sample were calculated by normalizing with internal control GAPDH and calculated using the 2-ΔΔCT method.

Western Blot

H9c2 cells were trypsinized, centrifuged for 5 min at 1,000 x g and washed with cold PBS. The H9c2 cells were then resuspended in lysis buffer with protease and phosphatase inhibitors. The cell lysate was kept in ice and vortexed. After centrifugation for 20 min at 13,000×g, the supernatant was separated and stored at −80 °C until use. After denaturation, 20μg of total protein were loaded onto 12% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) gels for protein separation, and electrophoretically transferred to a polyvinylidene difluoride (PVDF) membrane. After blocking with 5%milk in TBST (50mM Tris-HCl, pH 8;154 mM NaCl and 0.1% tween20) for 2 hours at room temperature, the membranes were probed with specific antibodies against ALAS1 (dilution,1:1,000; rabbit polyclonal; cat. no. 16200-1-AP; Proteintech), ALAS2 (dilution,1:1,000; rabbit polyclonal; cat. no. ab136799; Abcam), HOX-1 (dilution,1:1,000; rabbit polyclonal; cat. no. ab230513; Abcam), HOX-2 (dilution,1:500; rabbit polyclonal; cat. no. ab229960; Abcam), and GAPDH (dilution, 1:1,000; clone 6C5; cat. no. ab8245; Abcam) overnight at 4°C. Horseradish peroxidase (HRP)-labeled secondary antibodies (1:1,000 dilution; cat.nos. A0208, A0216; Beyotime) was added, followed by incubation at room temperature for 2 h. Membranes were visualized by enhanced chemiluminescence kits (Biorbyt, Ltd., Cambridge, UK). To quantify the targeting protein expression, the X-ray films were scanned, and band intensities were quantified by ImageJ 1.47 software. The results were normalized to GAPDH.

Intracellular heme measurement

Enzyme-linked immune sorbent assay (ELISA) was employed to determine intracellular heme levels. H9c2 cells of each group were lysed and followed by centrifugation at 12,000 rpm for 15 minutes at 4°C to remove debris. The protein concentration of the cell lysate was quantified by an enhanced BCA Protein Assay kit (Beyotime). The heme in H9c2 cell lysates was measured by using QuantiChrom Heme Assay (BioAssay Systems) following the manufacture's protocol and normalized to a protein concentration of each sample.

Flow cytometry to determine the apoptosis rate in H9c2 cells

Apoptosis was assessed using the Annexin V-FITC/PI Apoptosis Detection kit (KeyGEN, China) according to the manufacturer's protocol. After the intervention, approximately 1×10^5 H9c2 cells of each group were washed and digested with trypsin, and then resuspended with 1x PBS (4°C) and centrifuged at 2,000 rpm for 5-10 minutes to wash the cells. The cells were resuspended in 500μl of the buffer, followed by the addition of 5 μl of Annexin V-FITC and 5 μl of PI. The cells were incubated in the dark for 15 minutes at room temperature. Next, the cells of each group were examined for apoptosis rate by flow cytometry (BD Accuri™ C6). The experiment was repeated three times. The apoptotic rate was quantified as the percentage of cells stained with Annexin V.

Statistical Analysis

Data in the present study are normally distributed, which was verified by Shapiro- Wilk test, and are expressed as mean ± SD. One-way ANOVA, followed by Tukey's post hoc test, was used to examine the statistical significance of differences between groups. Statistical analysis was performed by using the SPSS 24.0 Statistical Package Program for Windows (SPSS Inc., Chicago, IL, USA). A two-sided p-value of <0.01 was considered significant.

Results

The changing of the heme level in H9c2 cells with a different concentration of doxorubicin

As shown in Figure 1, compared with the control group (5088.4±153.1ng/ml), heme levels of H9c2 cells were significantly up-regulated to a 1.27-fold (6493.1±138.8 ng/ml), a 1.56-fold (7498.9±110.2ng/ml), and a maximum 2.34-fold (11896.6±187.3ng/ml) increase in 1μM, 2μM, and 5μM doxorubicin groups, separately ($p<0.01$). This up-regulation trend was dropped back to a 1.95-fold (9911.9±286.8ng/ml) increase in the 10μM doxorubicin group, as compared to the control group ($p<0.01$).

The Effects of doxorubicin on the apoptosis rate of H9c2 cells

The flow cytometry analysis showed that, compared with the control group treated with saline, the apoptosis rate of H9c2 cells treated with different concentrations of doxorubicin was significantly increased, as shown in Figure 2. When incubated with 1, 2, 5, and 10μM doxorubicin for 24h, the total apoptosis rate, including both early and end-stage apoptosis, of H9c2 was increased to 10.6±1.6%, 41.1±1.9%, 60.5±3.6%, and 76.0±2.5%, respectively, as compared to 2.1±0.5% in the control group ($p<0.01$).

Regulation of aminolaevulinic acid synthase 1 (ALAS1) and aminolaevulinic acid synthase 2 (ALAS2) messenger RNA (mRNA) expression in H9c2 cells after doxorubicin treatment

As the first step and rate-limiting enzymes for heme synthesis that occur in the mitochondria, the mRNA expression of ALAS1 and ALAS2 under doxorubicin treatment were evaluated. After incubating with 1μM and 2μM doxorubicin, the mRNA expressions of ALAS1 were down-regulated (though not statistically significant). After treating with 5μM and 10μM doxorubicin, the ALAS1 mRNA expressions were statistically increased to 41.1-fold and 375.3-fold, separately, as compared to the control group. Unlike ALAS1, ALAS2 mRNA expression proved to be progressively and significantly down-regulated (1μM group:0.88-fold, 2μM group: 0.83-fold, 5μM group: 0.49-fold, 10μM group:0.31-fold respectively, as shown in Figure 3A.)

Regulation of mRNA expression for HOX-1 and HOX-2 in H9c2 cells after doxorubicin treatment

The cytoplastic rate-limiting enzymes in heme catabolism, HOX-1 and HOX-2, were examined. It was found that after having been incubated with an increasing level of doxorubicin, the HOX-1 and HOX-2 mRNA exhibited the same regulation pattern, although with different changing levels. No significant change was observed in mRNA expression after 1μM and 2μM doxorubicin treatment, when compared with the control group, for either HOX-1

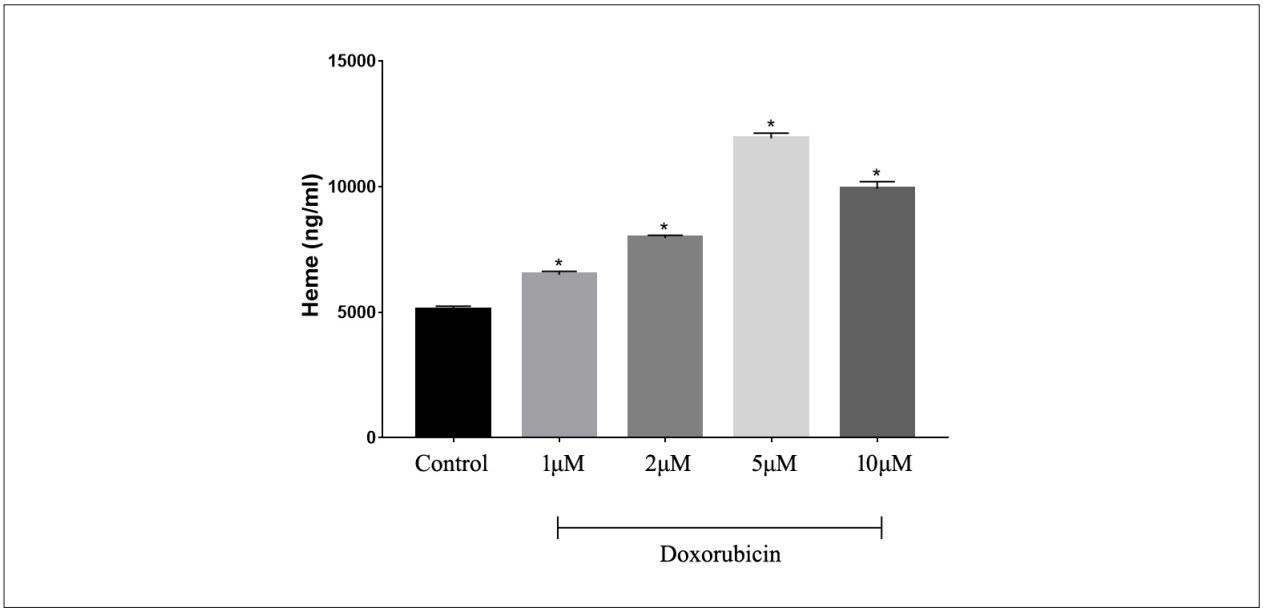

Figure 1 - *Effects of doxorubicin on heme levels in H9c2 cells exposed to saline (control group) or doxorubicin with different concentrations for 24 hours. Heme levels were measured by ELISA. Data are presented as the mean±standard deviation. *p<0.01, compared with the control group.*

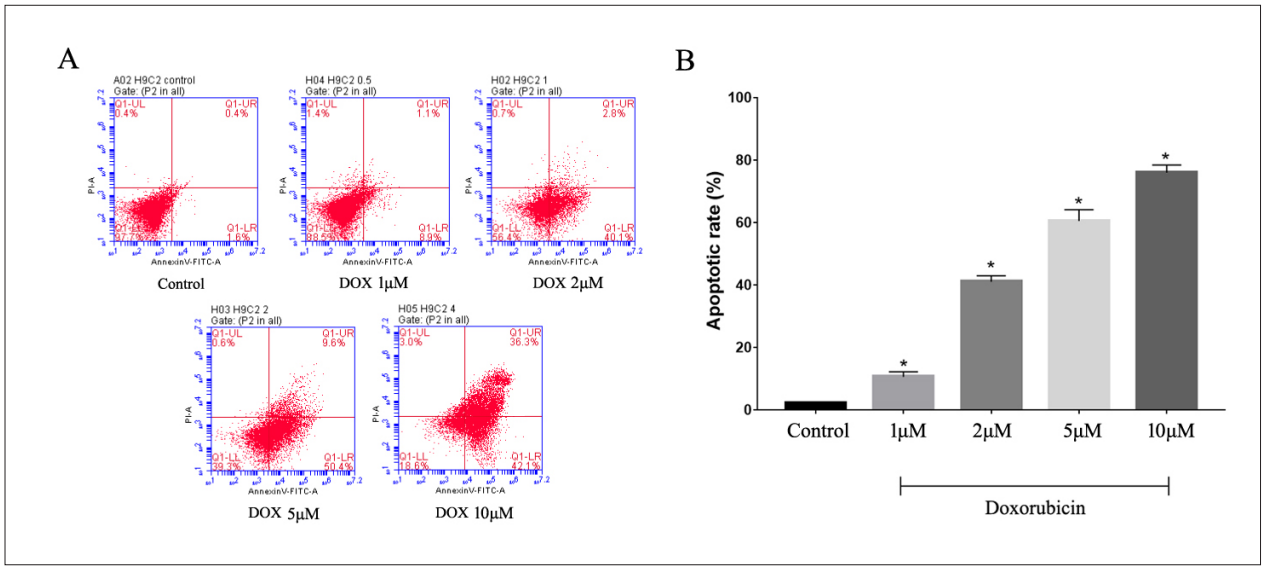

Figure 2 – *Flow cytometry analysis to evaluate the effects of doxorubicin on H9c2 cell viability. H9c2 cells were pretreated with saline (control) and doxorubicin at 1, 2, 5 and 10μM, respectively, for 24h. (A) Representative flow cytometry analyses of five individual experiments corresponding to control and different concentration doxorubicin treatment, respectively. (B) Statistical graph of annexin V-FITC/PI staining. Results was expressed as mean±SD. * p<0.01 vs control group.*

or HOX-2. After incubating with 5μM doxorubicin, the mRNA expression for HOX-1 and HOX-2 significantly up-regulated to 4.3-fold and 15.5-fold changes, respectively ($p<0.01$). But after treatment with 10μM doxorubicin, the up-regulation was declined to the extent of 2.6-fold and 3.2-fold, separately, when compared with the control group ($p<0.01$), as shown in Figure 3B.

Regulation of ALAS1, ALAS2, HOX-1, and HOX-2 protein levels after doxorubicin treatment

Western blot analysis showed that, identical to their mRNA expression pattern, ALAS1 protein levels were significantly down-regulated in the 2μM doxorubicin group and up-regulated in 10μM doxorubicin groups, when compared with the control group. ALAS2 protein levels were found to be progressively down-regulated as the doxorubicin concentration increased from 1μM to 10μM, as shown in Figure 4A.

Protein expression of HOX-1 was slightly down-regulated under 1μM and 2μM doxorubicin treatment, and then sharply up-regulated when compared with the control group. However, inconsistent with the mRNA expression pattern, our study detected a progressive increase in the HOX-2 protein level, with an increase in the doxorubicin concentration from 1μM to 5μM, and then a decline to the baseline level when treated with 10μM doxorubicin (Figure 4B).

Discussion

Doxorubicin is a kind of anthracycline drug, which is an effective broad-spectrum anti-tumor drug. It is widely used in the treatment of various malignant tumors, such as breast cancer, lung cancer, and lymphoma.[5] But the toxic cardiac effects of doxorubicin in a clinical chemotherapy dose is severe and dose-dependent, which can cause cardiomyopathy and congestive heart failure, and thus greatly limits its clinical use.[6] Different from the mechanism of its anti-tumor activity, the primary mechanism of cardiac toxicity induced by doxorubicin, is the generation of iron-mediated reactive oxygen species (ROS) and the subsequent promotion of myocardial oxidative stress.[7] Heme is an essential mediator of the biochemical availability of iron.[8] The function of the heme molecule varies according to the binding protein it coordinates with. It may serve as a mediator of oxygen transport and storage in hemoglobin[9] or myoglobin,[10] whereas it acts as an electron transporter in cytochromes and is the critical source of redox-active iro.[11] Bhoite-Solomon et al. found that free heme is toxic to the myocardium and caused cytolysis through sarcolemma damage in a concentration-dependent manner.[12] In addition to cardiomyocyte, free heme can also be toxic to human epithelial cells and neuron-like cells[13,14] through oxidative stress caused by cell apoptosis or necrosis. Moreover, free heme can cause endothelial cell injury by stimulating the expression of inflammatory factors.[15,16]

However, unlike the abundant studies in the iron-mediated oxidative injury in cardiomyocyte treated with anthracycline drugs, the intracellular heme level variation and the regulation processes of its synthesis and metabolism have not been well evaluated in cardiomyocyte under anthracycline treatment. The present study systematically examined the variation characteristics of biosynthetic and degradative enzymes for heme for the first time.

In the heme biosynthesis pathway, there are eight enzymes involved, among which four are mitochondrial enzymes, and four are cytoplasmic enzymes.[17] For the first step of heme synthesis, glycine and succinyl coenzyme A are condensed into δ-aminolevulinic acid (ALA). This reaction needs to be catalyzed by aminolevulinic acid synthase

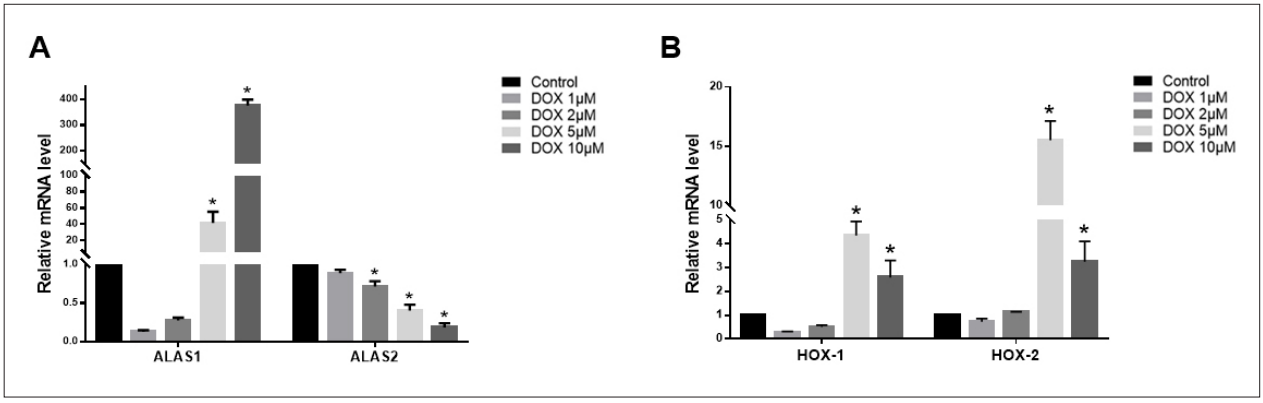

Figure 3 – *(A) mRNA expression changes of ALAS1 and ALAS2 under doxorubicin treatment. ALAS1, aminolaevulinic acid synthase 1; ALAS2, aminolaevulinic acid synthase 2. (B) Characteristics of mRNA expression changes for heme catabolic enzymes under doxorubicin treatment. HOX-1, heme oxygenase 1; HOX-2, heme oxygenase 2. * indicate p<0.01 vs. Control group.*

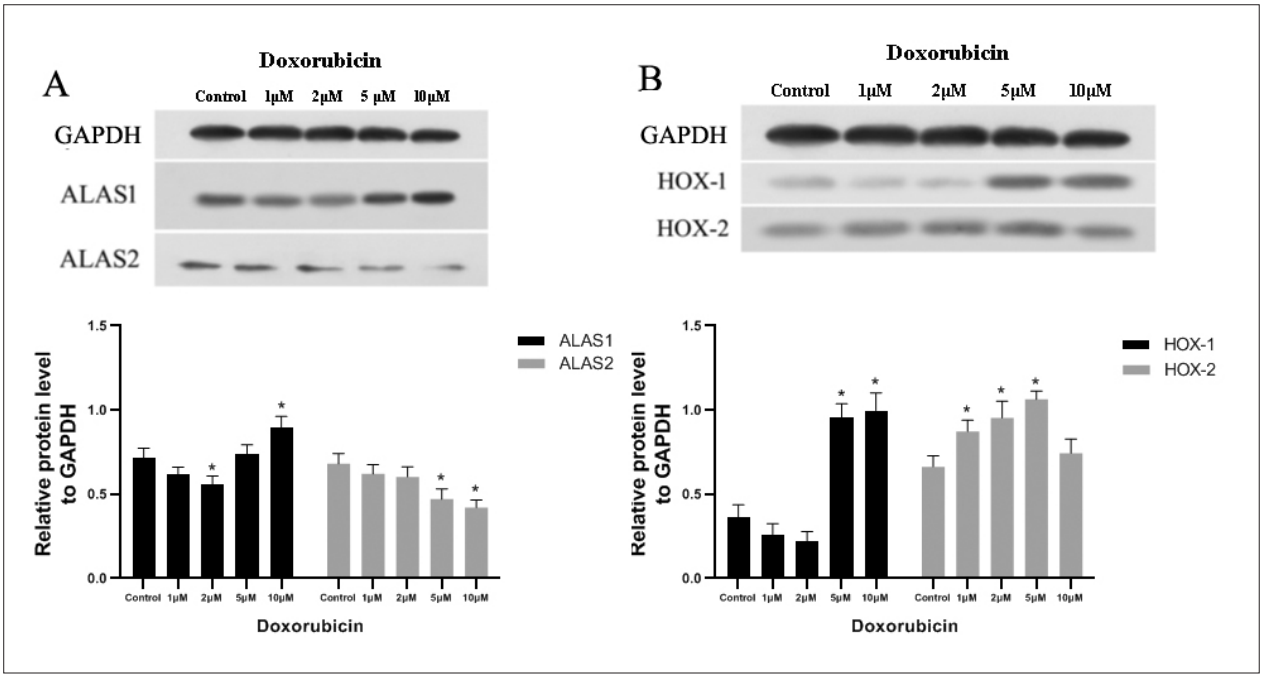

Figure 4 – *Analysis data of western blotting for ALAS (A) and HOX (B) protein level change in H9c2 cells at different concentrations for doxorubicin. ALAS1, aminolaevulinic acid synthase 1; ALAS2, aminolaevulinic acid synthase; HOX-1, heme oxygenase 1; HOX-2, heme oxygenase 2. Each western blot was conducted three times. * indicate p<0.01 vs. control group.*

(ALAS).[18] There are two types of ALAS: ALAS1 and ALAS2. The former has a universal expression, while the latter is dominantly expressed in red blood cell precursor cells.[19] The present study found that not only ALAS1, but also ALAS2, were both expressed in the H9c2 cells at baseline levels. After the treatment with doxorubicin, ALAS1 and ALAS2 mRNA expression exhibit two distinct changing patterns. The ALAS1 mRNA and protein expression at first presented a trend of inhibition (though not statistically significant in our study) with 1μM and 2μM doxorubicin and then showed a dramatic up-regulation pattern with 5μM and 10μM doxorubicin treatment.

By contrast, mRNA and protein expression of ALAS2 were progressively suppressed to the lowest level when treated with 10μM doxorubicin, with 69.0% and 35.0% reductions, respectively. This phenomenon indicates that, under the effect of doxorubicin, the regulation of ALAS1 and ALAS2 may occur through the different pathways and seek different targeting bioprocesses. The step-down-regulation of ALAS2 can be explained by the negative feedback from a progressive elevation of heme level. This effect might be achieved by repressing ALAS2 mRNA transcription, as shown in our real-time PCR results, as well as by interrupting ALAS2 formation through a block of the ALAS2 precursor into mitochondria.[20,21] In red blood cells, the expression of ALAS2 is determined by the trans-activation of nuclear factors GATA-1, CACC box, and NF-E2-binding sites in the

promoter area, and its synthesis is regulated by the amount of free iron. [22] However, the regulation mechanism of ALAS2 in cardiomyocyte under doxorubicin treatment will need to be further researched.

In our study, ALAS1, which was supposed to be strictly under negative feedback control at a low level to prevent a high cytotoxic heme level, was overexpressed both in gene and protein aspects, despite the simultaneously existing high heme level. Podvinec et al.[23] reported that drugs that induce cytochromes P450 and other drug-metabolizing related enzymes might simultaneously and transcriptionally up-regulate ALAS1 expression, which is the first step in the heme synthesis, to coordinate with the need of up-regulated cytochrome P450 activity. This process was mediated through two enhancer elements, located 20 and 16 kb upstream of the transcriptional start site of ALAS1, and their interaction with the xenoreceptors NR1I2 and NR1I3.[23] Zordoky et al.[24] revealed that doxorubicin caused a significant induction of several cytochrome P450 genes, such as CYP1A1, CYP1A2, CYP1B1, and CYP2B2 gene expression in a concentration-dependent manner. NR1I2 and NR1I3 have also been proved to be the crucial nuclear receptors mediating the interaction between doxorubicin and metabolizing enzymes.[25] The precise mechanism for the regulation of ALAS expression patterns in the cardiomyocyte will need to be elucidated in future study.

Heme oxidase (HOX) is the rate-limiting enzyme in the process of heme degradation, which can oxidatively degrade the heme molecule to produce carbon monoxide, iron, and biliverdin. Heme oxidase has two isoenzymes, heme oxidase 1 (HOX-1) and heme oxidase 2 (HOX-2). HOX-2 mainly plays a regulatory role under normal physiological conditions, while HOX-2 may protect cells and tissues under oxidative stress.[26]

The HOX-1 expression may be promoted by a variety of stimuli including doxorubicin[27] and intracellular accumulation of heme. Previous studies revealed that HO-1 expression is primarily regulated at the transcriptional level, several regulatory elements have been identified to play important roles in up-regulating HOX-1, including metal response elements (MREs), stress response elements (StREs), AP-1, and NF-B. [28] On the other hand, Bach1 has proven to have a repressor effect on HOX-1 expression.[29] The present study found HOX-1 in H9c2 cardiomyocytes was down-regulated in the first place when treated with low concentration doxorubicin (1μM and 2μM) in H9c2 cells and then significantly up-regulated with 5μM and 10μM doxorubicin incubation. Our research indicates that further studies focusing on the interaction between various regulators and HOX-1 gene elements under different doxorubicin concentration will be needed.

In spite of exhibiting a similar pattern of mRNA expression with HOX-1, the HOX-2 protein level was progressively elevated, along with the doxorubicin concentration, which increased from 1μM to 5μM and abruptly declined below the baseline level when treated with 10μM doxorubicin. The difference in the changing profile of the protein level between HOX-1 and HOX-2 may be due to the difference in their regulation mechanisms.[30,31] In rats, HOX-2 expression is modulated by glucocorticoids through the glucocorticoid responsive element (GRE).[32] To the best of our knowledge, this is the first study on the effect of doxorubicin on HOX-2 expression in cardiomyocytes; however, the precise mechanism of action between doxorubicin and HOX-2 regulation remains a critical, unsolved question.

Study limitations

The lack of results in detecting enzyme activities in H9c2 cells was believed to be the main limitation of our study. Meanwhile, the oxidative stress level, according to the changes in heme metabolism, has not been explored, which may well elucidate the relationship between heme metabolic enzymes and doxorubicin-induced cardiotoxicity. Further studies covering these aspects are warranted to clarify the effect of doxorubicin on the heme biosynthesis and metabolism.

Conclusions

The increase in ALAS1 expression may play a potential role in the heme level elevation when H9c2 cardiomyocyte is exposed to doxorubicin. Although HOXs were upregulated under moderate-high concentration doxorubicin treatment, their degradative effects were overwhelmed by the uncontrolled heme synthesis activation. The specific mechanisms for the loss of negative feedback control to heme formation under doxorubicin treatment and the potential role of ALAS as a therapeutic target against the doxorubicin-induced heme cytotoxicity will need to be studied in future investigations.

Author contributions

Conception and design of the research and Writing of the manuscript: Wang Z; Acquisition of data and Statistical analysis: Wang Z, Gao J, Teng H; Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Wang Z, Peng 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 article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Barbar T, Mahmood SS, Liu JE. Cardiomyopathy Prevention in Cancer Patients. Cardiol Clin. 2019 Nov;37(4):441-7.
2. Cuomo A, Rodolico A, Galdieri A, Russo M, Campi G, Franco R, et al. Heart Failure and Cancer: Mechanisms of Old and New Cardiotoxic Drugs in Cancer Patients. Card Fail Rev. 2019 May 24;5(2):112-8.
3. Sansbury BE, DeMartino AM, Xie Z, Brooks AC, Brainard RE, Watson LJ,et al Metabolomic analysis of pressure-overloaded and infarcted mouse hearts. Circ Heart Fail. 2014;7:634–42.
4. Khechaduri A, Bayeva M, Chang HC, Ardehali H. Heme levels are increased in human failing hearts. J Am Coll Cardiol. 2013;61:1884–93.
5. Rivankar S .An overview of doxorubicin formulations in cancer therapy. J Cancer Res Ther. 2014 Oct-Dec;10(4):853-8.
6. Liu H, Wang H, Xiang D, Guo W. Pharmaceutical Measures to Prevent Doxorubicin-Induced Cardiotoxicity. Mini Rev Med Chem. 2017;17(1):44-50.
7. Cappetta D, De Angelis A, Sapio L, Prezioso L, Illiano M, Quaini F, Rossi F, et al. Oxidative Stress and Cellular Response to Doxorubicin: A Common Factor in the Complex Milieu of Anthracycline Cardiotoxicity. Oxid Med Cell Longev. 2017;2017:1521020.
8. Gao G, Li J, Zhang Y, Chang YZ. Cellular Iron Metabolism and Regulation. Adv Exp Med Biol. 2019;1173:21-32.
9. Kafina MD, Paw BH. Intracellular iron and heme trafficking and metabolism in developing erythroblasts. Metallomics. 2017;9(9):1193-203.
10. Postnikova GB, Shekhovtsova EA. Myoglobin: Oxygen Depot or Oxygen Transporter to Mitochondria? A Novel Mechanism of Myoglobin Deoxygenation in Cells (review). Biochemistry (Mosc). 2018 Feb;83(2):168-83.
11. Yanatori I, Richardson DR, Toyokuni S, Kishi F. How iron is handled in the course of heme catabolism: Integration of heme oxygenase with intracellular iron transport mechanisms mediated by poly (rC)-binding protein-2. Arch Biochem Biophys. 2019 Sep 15;672:108071.
12. Bhoite-Solomon V1, Kessler-Icekson G, Shaklai N. Myocyte injury by hemin. In Vitro Cell Dev Biol Anim. 1993;29A (8):636-42.
13. Nath KA, Balla J, Croatt AJ, Vercellotti GM. Heme protein-mediated renal injury: a protective role for 21-aminosteroids in vitro and in vivo. Kidney Int. 1995;47(2):592-602.
14. Goldstein L, Teng ZP, Zeserson E, Patel M, Regan RF. Hemin induces an iron-dependent, oxidative injury to human neuron-like cells. J Neurosci Res. 2003;73(1):113-21.
15. Merle NS, Grunenwald A, Rajaratnam H, Gnemmi V, Frimat M, Figueres ML, et al. Roumenina LT1,2,Intravascular hemolysis activates complement via cell-free heme and heme-loaded microvesicles. JCI Insight. 2018 Jun 21;3(12). pii: 96910.
16. Camus SM, De Moraes JA, Bonnin P, Abbyad P, Le Jeune S, Lionnet F, et al. Circulating cell membrane microparticles transfer heme to endothelial cells and trigger vasoocclusions in sickle cell disease. Blood. 2015 Jun 11;125(24):3805-14.
17. van der Vorm LN, Paw BH. Studying disorders of vertebrate iron and heme metabolism using zebrafish. Methods Cell Biol. 2017;138:193-220.
18. Brown BL, Kardon JR, Sauer RT, Baker TA. Structure of the Mitochondrial Aminolevulinic Acid Synthase, a Key Heme Biosynthetic Enzyme. Structure. 2018 Apr 3;26(4):580-9.e4.
19. Chiabrando D, Mercurio S, Tolosano E. Heme and erythropoieis: more than a structural role. Haematologica. 2014 Jun;99(6):973-83.
20. Lathrop JT, Timko MP. Regulation by heme of mitochondrial protein transport through a conserved amino acid motif. Science. 1993;259(5094):522-5.
21. Lane DJ, Merlot AM, Huang ML, Bae DH, Jansson PJ, Sahni S, et al. Cellular iron uptake, trafficking and metabolism: key molecules and mechanisms and their roles in disease. Biochim Biophys Acta Mol Cell Res. 2015;1853:1130–44.
22. Peoc'h K, Nicolas G, Schmitt C, Mirmiran A, Daher R, Lefebvre T, et al. Regulation and tissue-specific expression of δ-aminolevulinic acid synthases in non-syndromic sideroblastic anemias and porphyrias. Mol Genet Metab. 2019 Jan 23. pii: S1096-7192(18)30632-2.
23. Podvinec M, Handschin C, Looser R, Meyer UA. Identification of the xenosensors regulating human 5-aminolevulinate synthase. Proc Natl Acad Sci U S A. 2004;101(24):9127-9132.
24. Zordoky BN, El-Kadi AO. Induction of several cytochrome P450 genes by doxorubicinorubicin in H9c2 cells. Vascul Pharmacol. 2008 ;49(4-6):166-72.
25. Hedrich WD, Hassan HE, Wang H. Insights into CYP2B6-mediated drug-drug interactions. Acta Pharm Sin B. 2016 Sep;6(5):413-25.
26. Muñoz-Sánchez J, Chánez-Cárdenas ME. A review on hemeoxygenase-2: focus on cellular protection and oxygen response. Oxid Med Cell Longev. 2014;2014:604981.
27. Zhu XF, Li W, Ma JY, Shao N, Zhang YJ, Liu RM, et al. Knockdown of heme oxygenase-1 promotes apoptosis and autophagy and enhances the cytotoxicity of doxorubicin in breast cancer cells. Oncol Lett. 2015 Nov;10(5):2974-80.
28. Morse D, Choi AM. Heme oxygenase-1: the "emerging molecule" has arrived. Am J Respir Cell Mol Biol. 2002 Jul;27(1):8-16.
29. Kitamuro T, Takahashi K, Ogawa K, Udono-Fujimori R, Takeda K, Furuyama K, et al. Bach1 functions as a hypoxia-inducible repressor for the heme oxygenase-1b gene in human cells. J Biol Chem. 2003 Mar 14;278(11):9125-33.
30. Dunn LL, Midwinter RG, Ni J, Hamid HA, Parish CR, Stocker R. New insights into intracellular locations and functions of heme oxygenase-1. Antioxid Redox Signal. 2014;20:1723–42.
31. Intagliata S, Salerno L, Ciaffaglione V, Leonardi C, Fallica AN, Carota G, et al. Heme Oxygenase-2 (HO-2) as a therapeutic target: Activators and inhibitors. Eur J Med Chem. 2019 Dec 1;183:111703.
32. Liu N, Wang X, McCoubrey WK, Maines MD. Developmentally regulated expression of two transcripts for heme oxygenase-2 with a first exon unique to rat testis: control by corticosterone of the oxygenase protein expression. Gene. 2000 Jan 4;241(1):175-83.

Influence of Doxorubicin Treatment on Heme Metabolism in Cardiomyoblasts: *An In Vitro* Study

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Short Editorial related to the article: Effects of Doxorubicin on Heme Biosynthesis and Metabolism in Cardiomyocyte

The last decades have been marked with potential advances in cancer diagnosis and therapy, leading to a decrease in mortality and increased patient survival.[1] Doxorubicin is a drug that belongs to the anthracycline family, a class of anticancer drugs extracted from streptomycin.[2] Although the mechanism of action of this drug in cancer is complex, it is known that it interferes with the synthesis of DNA and RNA in addition to inducing the production of free radicals that damage the cell membrane and DNA.[3] However, many of the chemotherapeutic agents used in the neoplasms treatment protocols induce several side effects, including cardiac toxicity and negative repercussions in the vascular system such as thrombolytic ischemia, arterial hypertension, ventricular dysfunction and heart failure.[1,4] The cardiotoxic effect of doxorubicin is dose-dependent, and the primary mechanism of toxicity is the induction of oxidative stress in the myocardium, with high production of reactive oxygen (ROS) and nitrogen (RNS) species that trigger DNA damage and deregulation of various processes intracellular.[5]

The heme molecule mediates the iron availability and is essential for numerous biological processes in aerobic organisms. In the cardiovascular system, it plays a crucial role in antioxidant defense, signal transduction, oxygen transport, hemoglobin storage, and mitochondrial electron transport.[6] Four mitochondrial and four cytoplasmic enzymes participate in heme metabolism. For heme synthesis, glycine and succinyl coenzyme A are condensed into δ-aminolevulinic acid (ALA) by the enzymes aminolevulinic acid synthases (ALAS), known as ALAS1 and ALAS2.[7] The degradation of heme is carried out by enzymes called heme oxygenase (HOX), which produces carbon monoxide, biliverdin, and iron. HOX-1 isoenzyme regulates normal physiological conditions while HOX-2 isoenzyme protects the cells from oxidative stress.[8] On the other hand, experimental studies have shown that elevated heme protein levels are related to increased oxidative stress and toxicity in cardiomyocytes.[9,10] However, few studies in the literature verified the influence of anthracyclines on heme protein metabolism in cardiomyocytes.

In this sense, the study published in the Arquivos Brasileiros de Cardiologia of this edition aimed to explore changes in heme biosynthesis in a cardiomyocytes cell lineage treated with doxorubicin.[11] The authors evaluated changes in the protein and gene profile of the enzymes ALAS1, ALAS2, HOX-1, and HOX-2 in cultures of H9C2 cardiomyocytes treated with different concentrations of the doxorubicin for 24 hours.[11] The authors demonstrated that treatment with doxorubicin significantly increased heme levels and that the enzymes ALAS1 and ALAS2 showed different behaviors. Lower doses of doxorubicin inhibited ALAS1 expression in H9C2 cardiomyocytes, and the authors suggest that it is a negative feedback mechanism to prevent cell toxicity induced by high levels of heme. When the dose of the drug was increased, ALAS1 expression also increased, a result corroborated by a previous study.[12] ALAS2 levels decreased as the dose of doxorubicin was increased, and the authors proposed that this mechanism is an effect to counteract the high level of heme.

Regarding the HOX-1 and HOX-2 enzymes, both showed the same behavior at the gene level, with increased expression compared to the control when higher doses of the drug were used. At the protein level, increased levels of HOX-1 were detected only with the highest doses of the doxorubicin, while HOX-2 showed increased levels in a dose-dependent manner.[11] The authors suggested that results related to the protein profile of HOX-1 and HOX-2 may be due to differences in the regulatory mechanisms of these enzymes. Also, few studies have verified the relationship between HOX-2 and doxorubicin in cardiomyocytes.

Although doxorubicin is widely used, many of its cardiotoxic mechanisms remain unclear. The research on which this short editorial is based has shown that treatment with doxorubicin in cardiomyocytes modulates gene and protein levels of crucial enzymes in the synthesis and degradation of heme proteins in a different way. Future studies are needed to elucidate the exact role of these enzymes in cardiomyocytes under treatment with doxorubicin.

Keywords

Doxorubicin/therapeutic use; Anthracyclines; Myocytes, Cardiac; Heme; Hemoglobin E/metabolism.

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References

1. Cappetta D, De Angelis A, Sapio L, Prezioso L, Illiano M, Quaini F, et al. Oxidative Stress and Cellular Response to Doxorubicin: A Common Factor in the Complex Milieu of Anthracycline Cardiotoxicity. Oxid Med Cell Longev. 2017;2017:1–13.
2. Cuomo A, Rodolico A, Galdieri A, Russo M, Campi G, Franco R, et al. Heart Failure and Cancer: Mechanisms of Old and New Cardiotoxic Drugs in Cancer Patients. Card Fail Rev. 2019 May 24;5(2):112–8.
3. Rivankar S. An overview of doxorubicin formulations in cancer therapy. J Cancer Res Ther. 2014;10(4):853.
4. Moslehi JJ. Cardiovascular Toxic Effects of Targeted Cancer Therapies. N Engl J Med. 2016 Oct 13;375(15):1457–67.
5. Nithipongvanitch R, Ittarat W, Cole MP, Tangpong J, Clair DK St., Oberley TD. Mitochondrial and Nuclear p53 Localization in Cardiomyocytes: Redox Modulation by Doxorubicin (Adriamycin)? Antioxid Redox Signal. 2007 Jul;9(7):1001–8.
6. Yanatori I, Richardson DR, Toyokuni S, Kishi F. How iron is handled in the course of heme catabolism: Integration of heme oxygenase with intracellular iron transport mechanisms mediated by poly (rC)-binding protein-2. Arch Biochem Biophys. 2019 Sep;672:108071.
7. Brown BL, Kardon JR, Sauer RT, Baker TA. Structure of the Mitochondrial Aminolevulinic Acid Synthase, a Key Heme Biosynthetic Enzyme. Structure. 2018 Apr;26(4):580–589.e4.
8. Muñoz-Sánchez J, Chánez-Cárdenas ME. A Review on Hemeoxygenase-2: Focus on Cellular Protection and Oxygen Response. Oxid Med Cell Longev. 2014;2014:1–16.
9. Khechaduri A, Bayeva M, Chang H-C, Ardehali H. Heme Levels Are Increased in Human Failing Hearts. J Am Coll Cardiol. 2013 May;61(18):1884–93.
10. Bhoite-Solomon V, Kessler-Icekson G, Shaklai N. Myocyte injury by hemin. Vitr Cell Dev Biol - Anim. 1993 Aug;29(8):636–42.
11. Wang Z, Gao J, Teng H, Peng J. Os efeitos da doxorrubicina na biossíntese e no metabolismo do heme em cardiomiócitos. Arq Bras Cardiol. 2021; 116(2):315-322.
12. Podvinec M, Handschin C, Looser R, Meyer UA. Identification of the xenosensors regulating human 5-aminolevulinate synthase. Proc Natl Acad Sci. 2004 Jun 15;101(24):9127–32.

Value of Left Atrial Diameter with CHA2DS2-VASc Score in Predicting Left Atrial/Left Atrial Appendage Thrombosis in Non-valvular Atrial Fibrillation

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Abstract

Background: **Atrial fibrillation is the most common persistent arrhythmia, and is the main factor that leads to thromboembolism.**

Objective: **To investigate the value of left atrial diameter combined with CHA2DS2-VASc score in predicting left atrial/left atrial appendage thrombosis in non-valvular atrial fibrillation.**

Methods: **This is a retrospective study. 238 patients with non-valvular atrial fibrillation were selected and divided into two groups: thrombosis and non-thrombosis. CHA2DS2-VASc score was determined. P<0.05 was considered statistically significant.**

Results: **Multivariate logistic regression analysis revealed that the history of stroke/transient ischemic attack, vascular disease, CHA2DS2-VASc score, left atrial diameter (LAD), left ventricular end-diastolic dimension (LVEDD) and left ventricular ejection fraction (LVEF) were independent risk factors for left atrial/left atrial appendage thrombosis (p<0.05). Receiver operating characteristic curve analysis revealed that the area under the curve for the CHA2DS2-VASc score in predicting left atrial/left atrial appendage thrombosis was 0.593 when the CHA2DS2-VASc score was ≥3 points, and sensitivity and specificity were 86.5% and 32.6%, respectively, while the area under the curve for LAD in predicting left atrial/left atrial appendage thrombosis was 0.786 when LAD was ≥44.17 mm, and sensitivity and specificity were 89.6% and 60.9%, respectively. Among the different CHA2DS2-VASc groups, the incidence rate of left atrial/left atrial appendage thrombosis in patients with LAD ≥44.17 mm was higher than patients with LAD <44.17 mm (p<0.05).**

Conclusion: **CHA2DS2-VASc score and LAD are correlated with left atrial/left atrial appendage thrombosis in non-valvular atrial fibrillation. For patients with a CHA2DS2-VASc score of 0 or 1, when LAD is ≥44.17 mm, the risk for left atrial/left atrial appendage thrombosis remained high. (Arq Bras Cardiol. 2021; 116(2):325-331)**

Keywords: **Atrial Fibrillation Non Valvar; Stroke; Risk Assessment; Propensity Score; Heart Atria; Atrial Appendage.**

Introduction

Atrial fibrillation (AF) is the most common persistent arrhythmia, and is the major factor that leads to thromboembolism.[1] In recent years, with the aging of the population in China, the incidence of this disease has increased.[2] Therefore, this disease represents a serious threat to people's life and health. When AF occurs, the cardiac atrium cannot regularly and effectively constrict, and blood flow slows down, which greatly increases the risk of left atrial/left atrial appendage thrombosis,[3] and left atrial/left atrial appendage thrombosis further increases the risk of thromboembolism events.[4] Therefore, scientific evaluation of left atrial/left atrial appendage thrombosis is of great significance for guiding treatment and improving the prognosis of patients. CHA2DS2-VASc is a presently and widely used scoring system to assess the risk of stroke in patients with non-valvular AF, and plays an important role in determining high-risk factors and guiding treatment.[5] However, the scoring system relies mainly on patient's history record. A study revealed that[6] left atrial size was closely correlated to left atrial/left atrial appendage thrombosis. However, it remains unclear whether the left atrial diameter combined with the CHA2DS2-VASc scoring system can improve the predictive results of left atrial/left atrial appendage thrombosis. The objective of this study was to analyze the factors related to left atrial/left atrial appendage thrombosis in patients with non-valvular AF, and explore the value of left atrial diameter combined with the CHA2DS2-VASc score in predicting left atrial/left atrial appendage thrombosis, in order to provide reference for clinical practice.

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Data and methods

General data

This was a retrospective study. Data was collected from medical records. A total of 238 patients with non-valvular AF, who were hospitalized in Zhengzhou Cardiovascular Hospital from February 2012 to March 2017, were enrolled into the study. Inclusion criteria: (1) patients diagnosed by electrocardiogram (ECG) or dynamic ECG; (2) patients who underwent transesophageal echocardiography. Exclusion criteria: (1) patients with rheumatic heart disease, valvular AF and paroxysmal AF; (2) patients with acute myocardial infarction and acute decompensated heart failure within 90 days, and patients with previous history of cardiac surgery; (3) patients with pulmonary embolism, deep venous thrombosis, history of administration of anticoagulant drugs, such as warfarin and rivaroxaban, or lipid-lowering drugs, such as statins; (4) patients with malignant tumors, hyperthyroidism, and severe liver and kidney dysfunction. This study was approved by the Ethics Committee of our hospital. All patients provided a signed informed consent.

Methods

Clinical data acquisition

Gender, age, course of AF, smoking and alcohol addiction, chronic disease history, height and weight of all patients were collected, and the body mass index (BMI) was calculated. In addition, fasting blood glucose (FBG), total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), platelet count (Plt), serum uric acid (UA) and other biochemical indicators were collected.

Transthoracic echocardiography and transesophageal echocardiography

All examinations were performed by an experienced sonographer with the title of Chief Physician in our hospital. All patients were routinely informed and signed an informed consent before examination. A Philips iE33 color Doppler ultrasound diagnostic apparatus was used to complete the examination. Transthoracic echocardiography was routinely performed, and the probe frequency was 2.5 MHz. Left atrial diameter (LAD), left ventricular end-diastolic dimension (LVEDD), and left ventricular ejection fraction (LVEF) were measured. Subsequently, local pharyngeal anesthesia with lidocaine was administered. Then, the probe was placed into the esophagus up to the location of the heart, and the probe frequency was 5.0 MHz. The left atrial and left atrial appendage sections were continuously observed to determine whether thrombus was present in the left atrial/left atrial appendage. These patients were divided into two groups: thrombosis group and non-thrombosis group.

CHA2DS2-VASc score

The CHA2DS2-VASc score was calculated according to the basic clinical data of patients:[7] (1) major risk factors (2 points per item): age of ≥75 years old, ischemic stroke, and transient ischemic attack; (2) secondary factors (1 point per item): female, aged 65–74, hypertension, diabetes, vascular disease, and chronic heart failure; (3) a lowest score of 0 and a highest score of 9. The higher the score was, the greater the possibility of thrombosis.

Statistical analysis

Data collation and statistical analyses were conducted using the statistical software SPSS 21.0. Continuous data were expressed as mean±standard deviation (x±SD), and compared between two groups using Student's unpaired *t*-test of normal distribution, and Kolmogorov-Smirnov (K-S) test was used for normal distribution. Categorical data were expressed in rate (%), and compared between two groups using X^2-test. Multivariate logistic regression analysis was performed to analyze related factors that affected the left atrial/left atrial appendage thrombosis. The receiver operating characteristic (ROC) curve was used to analyze the predictive results of left atrial diameter and CHA2DS2-VASc score for left atrial/left atrial appendage thrombosis. $p<0.05$ was considered statistically significant.

Results

Left atrial/left atrial appendage thrombosis

A total of 238 patients with non-valvular AF were enrolled in this study. Among these patients, 151 patients were male and 87 patients were female, and the age of these patients ranged from 29 to 86, with an average age of 61.1±12.4. In these 238 patients, left atrial/left atrial appendage thrombosis occurred in 46 patients, and the incidence was 19.3%.

Comparison of clinical data between the thrombosis group and the non-thrombosis group

Differences in gender, BMI, course of AF, proportions of patients with a history of smoking and alcohol consumption, proportions of patients with diabetes and coronary heart disease, CHA2DS2-VASc score, FBG, TC, TG, LDL-C, Plt, UA and drug therapy between the thrombosis group and non-thrombosis group were not statistically significant ($p>0.05$). In the thrombosis group, the proportion of patients aged ≥75, the proportion of patients with hypertension, the proportion of patients with heart failure, the proportion of patients with a history of stroke/transient ischemic attack, the proportion of patients with a history of vascular disease, and the CHA2DS2-VASc score, LAD and LVEDD were higher than those in the non-thrombosis group, while HDL-C and LVEF were lower than those in the non-thrombosis group, and all differences were statistically significant ($p<0.05$, Table 1).

Related factors that affect left atrial/left atrial appendage thrombosis

With the determination of whether the left atrial/left atrial appendage thrombosis existed as a dependent variable, and the variables with a p-value <0.10 as independent variables, multivariate logistic regression analysis was performed. The results revealed that the history of stroke/transient ischemic

Table 1 – Clinical Data of Thrombosis Group & Non-Thrombosis Group

Index	Thrombosis Group (n=46)	Non-Thrombosis Group (n=192)	t/χ^2	p
Age (n, %)				
<65 yo	18 (39.1)	112 (58.3)		
65–74 yo	15 (32.6)	62 (32.3)		
≥75 yo	13 (28.3)	18 (9.4)	12.668	0.002
Sex (M/F)	32 (69.6)	119 (62.0)	0.921	0.337
BMI (kg/m^2)	26.82±3.70	25.94±3.01	1.696	0.091
Years of AF (A)	4.69±1.69	5.10±1.38	1.718	0.087
Smoke (n, %)	18 (39.1)	71 (37.0)	0.921	0.337
Alcohol drinking (n, %)	11 (23.9)	36 (18.8)	0.624	0.429
Hypertension (n, %)	32 (69.6)	91 (47.4)	7.304	0.007
Diabetes (n, %)	8 (17.4)	44 (22.9)	0.664	0.415
Coronary disease (n, %)	4 (8.7)	8 (4.2)	1.590	0.207
HF (n, %)	7 (15.2)	6 (3.1)	10.508	0.001
Stroke/TIA (n, %)	17 (37.0)	11 (5.7)	101.138	0.000
Vascular disease (n, %)	22 (47.8)	51 (26.6)	7.890	0.005
FBG (mmol/L)	5.72±0.86	6.13±1.43	1.832	0.068
TC (mmol/L)	4.82±0.96	4.66±0.98	1.036	0.301
TG (mmol/L)	1.84±1.02	1.68±0.92	1.055	0.292
LDL-c (mmol/L)	3.00±0.54	2.96±0.86	0.298	0.766
HDL-c (mmol/L)	0.99±0.18	1.16±0.31	3.458	0.001
Plt (×10^9/L)	209.08±34.45	214.43±41.26	0.815	0.416
UA (μmol/L)	333.70±64.68	342.74±70.08	0.798	0.426
CHA2DS2-VASc score	2.26±1.90	1.64±1.48	2.428	0.016
CHA2DS2-VASc group (n, %)			2.635	0.268
0 score	8 (17.4)	55 (28.6)		
1 score	14 (30.4)	56 (29.2)		
≥2 scores	24 (52.2)	81 (42.2)		
LAD (mm)	45.81±6.16	38.55±5.00	6.118	0.000
LVEDD (mm)	51.35±4.38	48.53±4.11	4.133	0.000
LVEF (%)	57.05±10.50	61.84±9.17	3.092	0.002
Drug treatment (n, %)				
β-blockers	15 (32.6)	54 (28.1)	0.362	0.547
ACEI/ARB	21 (45.7)	75 (39.1)	0.670	0.413

BMI: body mass index; HF: heart failure; TIA: transient ischemic attack; FBG: fasting blood glucose; TC: total cholesterol; TG: triglyceride; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; Plt: platelet count; UA: serum uric acid; LAD: left atrial diameter; LVEDD: left ventricular end-diastolic dimension; LVEF: left ventricular ejection fraction; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blockers.

attack, vascular disease, CHA2DS2-VASc score, LAD, LVEDD and LVEF were independent risk factors for left atrial/left atrial appendage thrombosis ($p<0.05$, Table 2).

The value of LAD and CHA2DS2-VASc score in predicting left atrial/left atrial appendage thrombosis

The ROC curve analysis revealed that when the CHA2DS2-VASc score was used to predict left atrial/left atrial appendage thrombosis, the area under the curve (AUC) was 0.593 (95% CI: 0.495–0.690). When the CHA2DS2-VASc score was ≥3, sensitivity and specificity were 86.5% and 32.6%, respectively. When LAD was used to predict left atrial/left atrial appendage thrombosis, the AUC was 0.786 (95% CI: 0.704–0.868). When LAD was ≥44.17 mm, sensitivity and specificity were 89.6% and 60.9%, respectively (Figure 1).

Table 2 – Related factors of thrombus in left atrium or left atrial appendage

Index	B	SE	Wals χ^2	p	OR (95%CI)
Stroke/TIA	3.597	1.165	9.528	0.002	36.498 (3.718~358.322)
Vascular disease	1.280	0.574	4.979	0.026	3.597 (1.168~11.071)
HDL-c	2.574	1.021	6.354	0.012	13.124 (1.773~97.142)
CHA2DS2-VASc score	-0.441	0.171	6.610	0.010	0.644 (0.460~0.901)
LAD	-0.246	0.058	18.025	0.000	0.782 (0.698~0.876)
LVEDD	-0.173	0.063	7.432	0.006	0.841 (0.743~0.953)
LVEF	0.066	0.027	5.925	0.015	1.068 (1.013~1.126)

TIA: transient ischemic attack; HDL-C: high-density lipoprotein cholesterol; LAD: left atrial diameter; LVEDD: left ventricular end-diastolic dimension; LVEF: left ventricular ejection fraction.

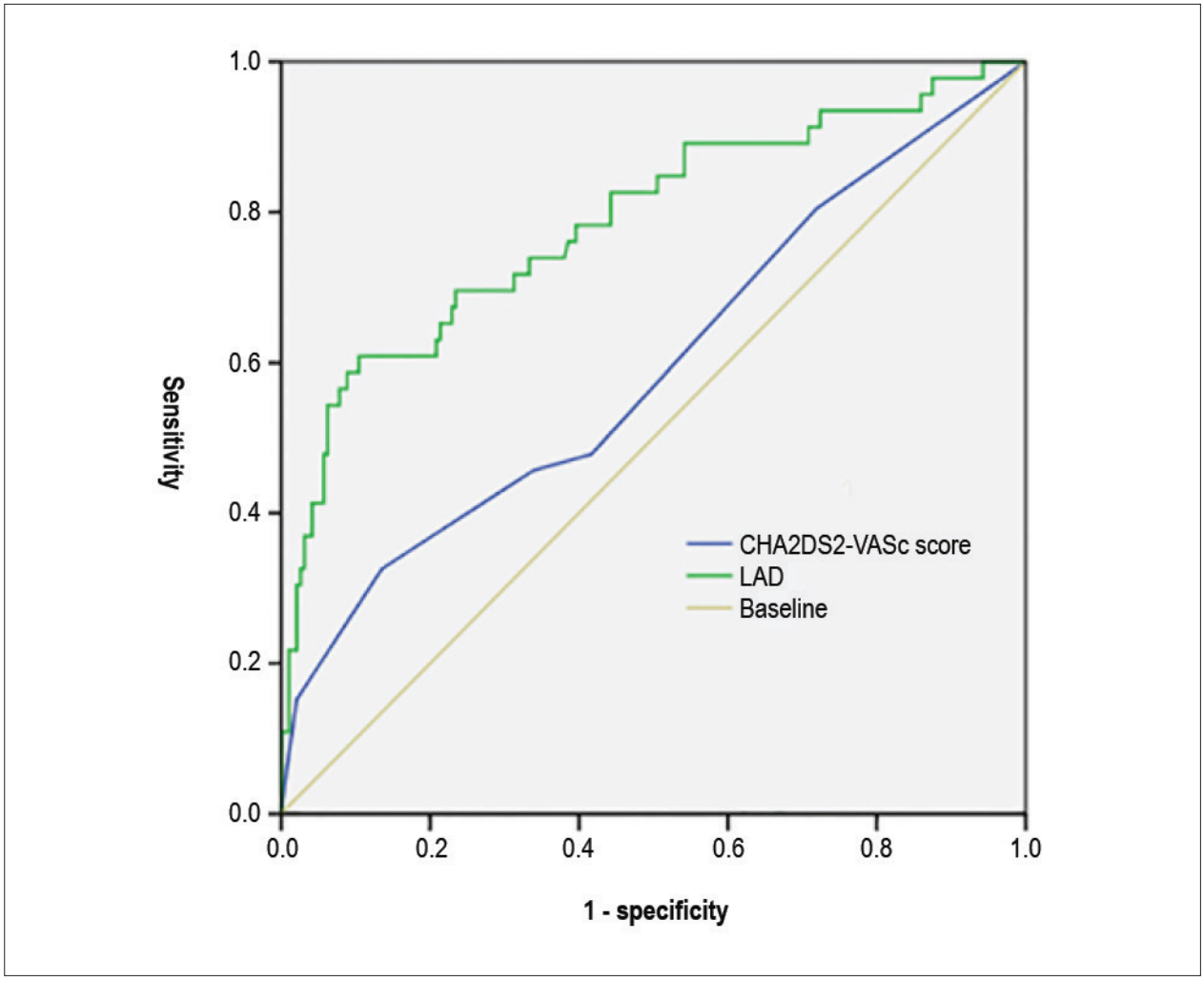

Figure 1 – *The ROC curve analysis results showed that when the CHA2DS2-VASc score was used to predict left atrial/left atrial appendage thrombosis, the area under the curve was 0.593 (95% CI: 0.495–0.690). When the CHA2DS2-VASc score was ≥3, sensitivity and specificity were 86.5% and 32.6%, respectively. When LAD was used to predict left atrial/left atrial appendage thrombosis, the area under the curve was 0.786 (95% CI: 0.704–0.868). When LAD was >44.17 mm, sensitivity and specificity were 89.6% and 60.9%, respectively.*

Effect of LAD on the risk of left atrial/left atrial appendage thrombosis in patients in the different CHA2DS2-VASc groups

In the different CHA2DS2-VASc groups, the incidence of left atrial/left atrial appendage thrombosis in patients with LAD ≥44.17 mm was higher than that in patients with LAD <44.17 mm, and the difference was statistically significant ($p<0.05$, Table 3).

Discussion

As the most common arrhythmia type in the Internal Medicine-Cardiovascular Department, AF is a risk factor that leads to thromboembolism.[8] Compared with the non-AF population, the risk of stroke in patients with AF is increased by five times.[9] In addition, a study revealed that[10] the thrombus that caused stroke in AF patients mostly came from the left atrial /left atrial appendage. Left atrial/left atrial appendage thrombosis is an independent risk factor for stroke in patients with non-valvular AF.[11] This may significantly increase the risk of thromboembolic events, and is a direct indicator of anticoagulant therapy in AF patients.[12] Therefore, early detection of left atrial/left atrial appendage thrombosis or high-risk factors for left atrial/left atrial appendage thrombosis is of great significance for guiding treatment and improving the prognosis of AF patients. In this study, 238 AF patients, who did not receive anticoagulation and lipid-lowering therapy, were enrolled. The transesophageal echocardiography results revealed that the incidence of left atrial/left atrial appendage thrombosis was 19.3%. This is similar to 18.6%, reported by Shuanglun Xie et al.,[13] and 20.7%, reported by Weiwei Fu et al.[14] These results reveal that the incidence of left atrial/left atrial appendage thrombosis is relatively high in AF patients without anticoagulation and lipid-lowering therapy.

The CHA2DS2-VASc scoring system was established by further optimizing the CHADS2 scoring system, which is a clinical method commonly used to assess the risk of stroke in AF patients at present, and also used to guide clinical treatment.[15] A study revealed that[16] a CHA2DS2-VASc score of ≥2 is an independent risk factor for left atrial/left atrial appendage thrombosis in AF patients. This study revealed that the CHA2DS2-VASc score was higher in the thrombosis group than in the non-thrombosis group. However, the difference in the distribution of CHA2DS2-VASc scores between the two groups was not statistically significant. Univariate and multivariate analysis revealed that the CHA2DS2-VASc score is an independent risk factor for left atrial/left atrial appendage thrombosis. Furthermore, these results reveal that the CHA2DS2-VASc score is correlated to left atrial/left atrial appendage thrombosis. The ROC curve analysis revealed that the AUC was 0.593 (95% CI: 0.495–0.690). When the CHA2DS2-VASc score was ≥3, sensitivity and specificity were 86.5% and 32.6%, respectively. These results showed that for patients with a CHA2DS2-VASc score of ≥3, the possibility of left atrial/left atrial appendage thrombosis should be highly alerted. However, this study also revealed that when the CHA2DS2-VASc score was 0 or 1, left atrial/left atrial appendage thrombosis still occurred in 9 and 15 patients, respectively. Furthermore, these results revealed that for low-risk patients with a CHA2DS2-VASc score of 0 or 1, there was still a risk of stroke. These results suggested that the CHA2DS2-VASc score has some limitations in predicting left atrial/left atrial appendage thrombosis.

A study revealed that[17] morphological changes in the left atrium and left atrial appendage might increase the risk of thromboembolism in AF patients. When AF occurs, the bigger the cardiac atrium, the more easily thrombosis forms.[18] In this study, LAD in AF patients was compared. The results revealed that LAD was greater in the thrombosis group than in the non-thrombosis group, which was an independent risk factor for left atrial/left atrial appendage thrombosis. The ROC curve analysis revealed that when LAD was used to predict left atrial/left atrial appendage thrombosis, the AUC was 0.786 (95% CI: 0.704–0.868), and when LAD was ≥44.17 mm, sensitivity and specificity were 89.6% and 60.9%, respectively. These results revealed that LAD size was correlated to left atrial/left atrial appendage thrombosis. Hence, when LAD was ≥44.17 mm, this had good sensitivity and specificity in predicting left atrial/left atrial appendage thrombosis. In this study, we used LAD as the index to predict left atrial/left atrial appendage thrombosis. Recently, left atrial volume has been used as a measure of left atrial enlargement.[19] This index might be included in future studies. In this study, patients were further stratified according to the CHA2DS2-VASc score, in order to analyze the effect of LAD on left atrial/left atrial appendage thrombosis. These results revealed that regardless of whether the CHA2DS2-VASc score was 0, 1 or ≥2, LAD ≥44.17 mm significantly increased the risk of left atrial/left atrial appendage thrombosis. These results revealed that further assessment of LAD on the basis of the CHA2DS2-VASc score would be helpful for evaluating the risk of left atrial/left atrial appendage thrombosis and guiding anticoagulation therapy.

Table 3 – The effect of left atrial diameter on the risk of thrombosis in left atrium/left atrial appendage in patients with different CHA2DS2-VASc groups (mm).

CHA2DS2-VASc group	n	left atrial/left atrial appendage thrombus (n, %)		OR	χ^2	p
		LAD≥44.17	LAD<44.17			
0 score	63	6/12 (50.0)	3/51 (5.9)	8.500 (95% *CI*: 1.856~38.938)	9.524	0.002
1 score	73	11/16 (68.8)	4/57 (7.0)	9.797 (95% *CI*: 2.747~34.943)	15.466	0.000
≥2 score	102	11/19 (57.9)	11/83 (13.3)	4.368 (95% *CI*: 1.651~11.559)	9.712	0.002

However, considering that this study is a single-center, small-sample size study, there may be some shortcomings in sample representativeness. Hence, multi-center and large-sample size cohort studies are needed to further clarify the relationship between the CHA2DS2-VASc score and LAD in predicting left atrial/left atrial appendage thrombosis and guiding anticoagulation therapy.

Conclusion

In summary, the CHA2DS2-VASc score and LAD are correlated to left atrial/left atrial appendage thrombosis in patients with non-valvular AF. For patients with a CHA2DS2-VASc score of 0 or 1, LAD size should be further considered. When LAD was ≥44.17 mm, the risk of left atrial/left atrial appendage thrombosis is still relatively high, and it is necessary to conduct further anticoagulation therapy.

Author contributions

Conception and design of the research, Obtaining financing and Critical revision of the manuscript for intellectual content: Yi-Qiang Y; Data acquisition, Analysis and interpretation of the data, Statistical analysis and Writing of the manuscript: Zhang Y.

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

This study is not associated with any thesis or dissertation.

References

1. Garwood CL, Korkis B, Grande D, Hanni C, Morin A, Moser LR. Anticoagulation bridge therapy in patients with atrial fibrillation: recent updates providing a rebalance of risk and benefit. Pharmacotherapy. 2017;37(6):712-24.
2. Wan H, Wu S, Wang J, Yang Y, Zhu J, Shao X, et al. Body mass index and the risk of all-cause mortality among patients with nonvalvular atrial fibrillation: a multicenter prospective observational study in China. Eur J Clin Nutr. 2017;71(4):494-9.
3. Wyrembak J, Campbell KB, Steinberg BA, Bahnson TD, Daubert JP, Velazquez EJ, et al. Incidence and predictors of left atrial appendage thrombus in patients treated with nonvitamin K oral anticoagulants versus warfarin before catheter ablation for atrial fibrillation. Am J Cardiol. 2017;119(7):1017-1022.
4. Chen YY, Liu Q, Liu L, Shu XR, Su ZZ, Zhang HFet al. Effect of metabolic syndrome on risk stratification for left atrial or left atrial appendage thrombus formation in patients with nonvalvular atrial fibrillation. Chin Med J (Engl). 2016;129(20):2395-2402.
5. Zhao LD, Hong J. New research progress of risk evaluation scores of stroke and bleeding in patients with atrial fibrillation. Chin J Integr Tradit West Med Intens Crit Care. 2017;24(2):213-216.
6. Boyd AC, McKay T, Nasibi S, Richards DA, Thomas L. Left ventricular mass predicts left atrial appendage thrombus in persistent atrial fibrillation. Eur Heart J Cardiovasc Imaging. 2013;14(3):269-75.
7. Zhu WG, Xiong QM, Hong K. Meta-analysis of CHADS2 versus CHA2DS2-VASc for predicting stroke and thromboembolism in atrial fibrillation patients independent of anticoagulation. Tex Heart Inst J. 2015;42(1):6-15.
8. Almutairi AR, Zhou L, Gellad WF, Lee JK, Slack MK, Martin JR, et al. Effectiveness and safety of non-vitamin K antagonist oral anticoagulants for atrial ribrillation and venous thromboembolism: A systematic review and meta-analyses. Clin Ther. 2017;39(7):1456-78.
9. Harel Z, Chertow GM, Shah PS, Harel S, Dorian P, Yan AT, et al. Warfarin and the risk of stroke and bleeding in patients with atrial fibrillation receiving dialysis: a systematic review and meta-analysis. Can J Cardiol. 2017;33(6):737-46.
10. Chanda A, Reilly JP. Left atrial appendage occlusion for stroke prevention. Prog Cardiovasc Dis. 2017;59(6):626-35.
11. Doukky R, Garcia-Sayan E, Patel M, Pant R, Wassouf M, Shah S, et al. Impact of diastolic function parameters on the risk for left atrial appendage thrombus in patients with nonvalvular atrial fibrillation: a prospective stud. J Am Soc Echocardiogr. 2016;29(6):545-553.
12. Lobo R, McCann C, Hussaini A, Meany TB, Kiernan TJ. Left atrial appendage thrombus with resulting stroke post-RF ablation for atrial fibrillation in a patient on dabigatran. Ir Med J. 2014;107(10):329-30.
13. Xie SL, Chen YY, Liu Q, Zhang YJ, Shu XR, Su ZZ, et al. Effect of metabolic syndrome on risk stratification of left atrial thrombus formation in patients with nonvalvular atrial fibrillation. Chin J Cardiac Arrhythm. 2015;19(2):87-93.
14. Fu WW, Li GD, Wang Z. Relationship between high-density lipoprotein cholesterol and left atrial/left atrial appendage thrombus in non-valvular atrial fibrillation patients. J Tianjin Med Univ. 2015;21(2):498-502.
15. Doorn S, Debray TPA, Kaasenbrood F, Hoes AW, Rutten FH, Moons KGM, et al. Predictive performance of the CHA2DS2-VASc rule in atrial fibrillation: a systematic review and meta-analysis. J Thromb Haemost. 2017;15(6):1065-77.
16. Ma JW, Ma XH, Cui LJ, Li Z. The predictive value of CHADS2 and CHA2DS2-VASc score in left atrial or left atrial appendage thrombus in patients with non-valvular atrial fibrillation. Tianjin Med J. 2015;43:304-8.
17. Qi SY, Tian Y, Shi L, Wang YJ, Lu XY, Chen RM, et al. Left atrial appendage morphology and thromboembolic risk in patients with atrial fibrillation and CHADS2 score ≤ 1: a case-control study. Chin J Cardiac Arrhythm. 2015;19:94-98.
18. Taina M, Vanninen R, Hedman M, Jäkälä P, Kärkkäinen S, Tapiola T, et al. Left atrial appendage volume increased in more than half of patients with cryptogenic stroke. PLoS One. 2013;8(11):e79519.
19. Arsanjani R, Flint N, Beigel R, Khachatryan T, Shalev A, Shturman A, et al. Comparison of accuracy of left atrial area and volume by two-dimensional trans-thoracic echocardiography versus computed tomography. Am J Cardiol. 2019;123(7):1180-4.

Beyond CHA2DS2-VASc for Predicting the Risk of Thromboembolism and Stroke - Not That Simple!

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Short Editorial relatet to the article: Value of Left Atrial Diameter with CHA2DS2-VASc Score in Predicting Left Atrial/Left Atrial Appendage Thrombosis in Non-valvular Atrial Fibrillation

Ischemic stroke can result from a variety of causes, such as atherosclerosis of the cerebral circulation, occlusion of cerebral small vessels, and cardiac embolism.[1] Of these causes, cardioembolic stroke has a particular significance because cardiac embolism causes more severe strokes than other ischemic stroke subtypes.[2] In about 20% of patients who have had ischemic stroke, a major risk cardiac source, such as atrial fibrillation (AF) and/or left ventricular thrombi, is identified. Thus, assessing the presence of AF, and the risk of thromboembolism associated to cardiac lesions play a key role in stroke prevention. [3]

Age, male gender, hypertension, diabetes mellitus, valvular heart disease, congestive heart failure, coronary heart disease, chronic kidney disease, inflammatory disorders, sleep apnea, and tobacco use have all been established as risk factors for both AF[4] and stroke.[5] However, it may be that other atrial factors besides AF can result in thromboembolism, and in some cases, AF may be a lagging marker of these other thrombogenic atrial abnormalities. AF often occurs in the setting of atrial abnormalities such as mechanical dysfunction in the left atrial appendage.[6] These abnormalities of atrial substrate have recently been associated with stroke risk independently of AF. The CHA2DS2-VASc (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack (TIA), vascular disease, age 65 to 74 years, sex category) score is a validated tool to predict the risk of stroke and systemic emboli in patients with non-valvular atrial fibrillation and has been widely used to guide clinical practice.[7-10]

Left atrial appendage (LAA) represents one of the main sources of cardiac thrombi responsible for stroke in patients with AF[11] and this is probably due to the anatomical characteristics of this structure, which facilitate slower blood flow inside it. An interesting finding is that LAA thrombosis can occur even in patients with a lower CHA2DS2VASc score (< 2) and this may be related to its morphology. The relationship between the findings of transesophageal echocardiography and the CHA2DS2-VASc score has not yet been established, since most studies evaluate the association in the presence of thrombus with the score.[12,13] Linhares et al.,[14] recently presented interesting results suggesting that the thrombogenic morphology of LAA identified in transesophageal echocardiography (TEE) presented a higher risk of stroke regardless of the CHA2DS2VASc score.[14]

However, it remains unclear whether another parameter, the left atrial diameter (LAD) combined with the CHA2DS2-VASc scoring system can improve the predictive results of left atrial/left atrial appendage thrombosis. Zhang Y e Yi-Qiang Y,[15] in a retrospective study including 238 patients with non-valvular atrial fibrillation, proposed to investigate the value of left atrial diameter combined with CHA2DS2-VASc score in predicting the left atrial/left atrial appendage thrombosis in non-valvular atrial fibrillation. The authors have found that the receiver operating characteristic curve analysis revealed that the area under the curve for the CHA2DS2-VASc score in predicting left atrial/ left atrial appendage thrombosis was 0.593 when the CHA2DS2-VASc score was ≥ 3 points, and the sensitivity and specificity was 86.5% and 32.6%, respectively, while the area under the curve for LAD in predicting left atrial/ left atrial appendage thrombosis was 0.786 when LAD was ≥ 44.17 mm, and the sensitivity and specificity was 89.6% and 60.9%, respectively. Additionally, they have found that among the different CHA2DS2-VASc groups, the incidence of left atrial/ left atrial appendage thrombosis in patients with a LAD of ≥ 44.17 mm was higher than in patients with a LAD < 44.17 mm.

Rather than a definitive answer to this intriguing question, the paper by Zhang Y and Yi-Qiang Y[15] mostly represents an important hypothesis generator. The findings are interesting indeed. However, the readers should consider important aspects that may limit the generalizability and clinical application of these findings at the present moment. First,

Keywords

Risk Factors; Diabetes; Hypertension; Atherosclerosis; Atrial Fibrillation; Stroke; Embolism and Thrombosis; Cerebrovascular Circulation.

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the sensitivity of the predictive model remained moderate even after the addition of the LAD parameter; second, the specificity of the model was too low to be suggested as a standard tool; third, due to the large confidence intervals observed in the analysis of the association of the different different CHA2DS2-VASc groups, LAD and occurrence of thrombosis, a considerable uncertainty still remains in these results. Finally, larger prospective studies are needed to better understand the role of cardiac parameters, such as LAD and the risk of thromboembolism.

References

1. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24(1):35-41.
2. Lin HJ, Wolf PA, Kelly-Hayes M, Beiser AS, Kase CS, Benjamin EJ, et al. Stroke severity in atrial fibrillation. The Framingham Study. Stroke 1996;27(10):1760-4.
3. Hart RG, Diener HC, Coutts SB, Easton JD, Granger CB, O'Donnell MJ, et al. Embolic strokes of undetermined source: the case for a new clinical construct. Lancet Neurol.2014;13(4):429-38.
4. Andrade J, Khairy P, Dobrev D, Nattel S. The clinical profile and pathophysiology of atrial fibrillation: relationships among clinical features, epidemiology, and mechanisms. Circ Res 2014;114(9):1453-68.
5. Elkind MS. Inflammatory mechanisms of stroke. Stroke 2010;41(10 Suppl):S3-8.
6. Warraich HJ, Gandhavadi M, Manning WJ. Mechanical discordance of the left atrium and appendage: a novel mechanism of stroke in paroxysmal atrial fibrillation. Stroke 2014;45(5):1481-4.
7. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest 2010;137(2):263-72.
8. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. Eur Heart J. 2012;33(12):1500-10.
9. Mason PK, Lake DE, DiMarco JP, Ferguson JD, Mangrum JM, Bilchick K, et al. Impact of the CHA2DS2-VASc score on anticoagulation recommendations for atrial fibrillation. The Am J Med. 2012;125(6):603 e1-6.
10. Olesen JB, Torp-Pedersen C, Hansen ML, Lip GY. The value of the CHA2DS2-VASc score for refining stroke risk stratification in patients with atrial fibrillation with a CHADS2 score 0-1: a nationwide cohort study. Thromb Haemost. 2012;107(6):1172-9.
11. Di Biase L, Santangeli P, Anselmino M, Mohanty P, Salvetti I, Gili S, et al. Does the left atrial appendage morphology correlate with the risk of stroke in patients with atrial fibrillation? Results from a multicenter study. J Am Coll Cardiol. 2012;60(6):531-8.
12. Bayard YL, Omran H, Neuzil P, Thuesen L, Pichler M, Rowland E, et al. PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion) for prevention of cardioembolic stroke in non-anticoagulation eligible atrial fibrillation patients: results from the European PLAATO study. EuroIntervention.2010;6(2):220-6.
13. Dawson AG, Asopa S, Dunning J. Should patients undergoing cardiac surgery with atrial fibrillation have left atrial appendage exclusion? Interact Cardiovasc Thorac Surg. 2010;10(2):306-11.
14. LInhares RR, Moreira DAR, Peixoto LB, Cruz AP, Garcia LP, Barreto RB, et al. Association between Morphodynamic Variables by Transesophageal Echocardiography and CHA2DS2-Vasc Values. Int J Cardiovasc Sci. 2019;32(5):460-470.
15. Zhang Y e Yi-Qiang Y. Valor do Diâmetro do Átrio Esquerdo com Escore CHA2DS2-Vasc na Predição da Trombose Atrial Esquerda/Trombose de Apêndice Atrial Esquerdo na Fibrilação Atrial Não Valvar. Arq Bras Cardiol. 2021; 116(2):325-331.

Atrial Fibrillation (Part 2) - Catheter Ablation

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Abstract

More than 20 years since its initial use, catheter ablation has become a routinely performed procedure for the treatment of patients with atrial fibrillation (AF). Initially based on the electrical isolation of pulmonary veins in patients with paroxysmal AF, subsequent advances in the understanding of pathophysiology led to additional techniques not only to achieve better results, but also to treat patients with persistent forms of arrhythmia, as well as patients with structural heart disease and heart failure.

Significant technological advances, especially in 3D electroanatomic mapping, intracardiac echocardiography use and how energy is delivered to the tissue (cryoablation and tissue contact force with radiofrequency) have allowed a significant reduction in the rate of complications and in the use of ionizing radiation.

Currently, ablation is the most efficient treatment for patients with AF, and an excellent alternative to the use of antiarrhythmic drugs, whose development has been insignificant in recent decades.

With the pioneering observations made by Haissaguerre et al.,[1] the pivotal role of arrhythmogenic foci located in the pulmonary veins (PV) in the pathophysiology of the initiation and maintenance of AF episodes was shown. The concept of focal AF was then established, where atrial arrhythmia that diffusely affects both atria have a well-determined origin, and is therefore susceptible to therapeutic interventions. Techniques using catheter ablation were developed and improved to eliminate AF-generating foci through circumferential ablation around the PVs,[2-4] with higher success and performance rates compared to the best pharmacological therapy.[5-10]

The aim of this article is to review the advances in catheter ablation for AF and describe to the clinical cardiologist state-of-the-art indications, techniques, results and complications.

Keywords

Arrhythmias Cardiac; Fibrilation Atrial; Catheter Ablation/methods; Echocardiography/methods.

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Ablation Strategies

Over the last 20 years, several ablation strategies have been used to control AF. In common, there is a current consensus that the isolation of all PVs is fundamental in all groups of patients (paroxysmal, persistent or long-standing persistent AF).[11-15] Isolation must be electrically proven by circular mapping inside the PVs (Figures 1 and 2), as this step is paramount for the success of the procedure. Recent studies have shown that the procedure should be performed on uninterrupted oral anticoagulation, a strategy proven to reduce thrombotic and hemorrhagic complications.[16-18]

In patients with paroxysmal AF, PV isolation is usually all that is needed, targeting additional sites only in specific situations (e.g., triggering foci mapped outside the PVs). Some centers routinely perform isolation of the superior vena cava[19,20] since it can also be, albeit rarely, *a* triggering AF-inducing source. Most publications show favorable results, with success rates above 70%.[6,7,9]

PV isolation can be performed using: 1) radiofrequency (RF) energy, through point-by-point focal applications (Figure 1 – A), ideally with catheters with contact force sensors at the tip (Figure 1 – B), or 2) freezing (cryoablation), using a balloon catheter positioned in the antrum of the PVs, capable of performing ablation simultaneously around the entire circumference in contact with the tissue (Figure 1 - D). A randomized study (Fire and ICE)[21] directly comparing the two strategies for the treatment of paroxysmal AF showed similar results. These findings were replicated in a second randomized study (CIRCA-DOSE)[22] that compared two cryoablation regimens (4 min vs. 2 min freezings) to the use of contact force-guided RF to isolate the PVs in patients with paroxysmal AF; in this study, there was a >98% reduction in AF burden demonstrated through continuous electrocardiographic monitoring. It is important to note that the Cryo balloon catheter is not commonly used for ablation at sites other than around the PVs; when necessary, an RF catheter should be used for that (Figure 1 - C).

In persistent and long-standing persistent forms of AF, additional electrical conduction barriers are often created, as stand-alone PV isolation is usually insufficient and associated with high recurrence rates.[23-25] Several strategies have been studied,[26-37] the most frequently used being: ablation of triggers outside the PVs, linear lesions in the left atrium (LA) and extensive RF applications at sites depicting fractionated electrograms during AF (most commonly observed in the posterior LA wall, septum, LA roof, mitral annulus, base of the left atrial appendage (LAA) and inside the coronary sinus). During RF applications at these sites, AF conversion to regular atrial tachycardias or even to sinus rhythm may occur.

The negative results of the randomized Star AF II[38] study should be noted. The study compared the addition of linear lesions and ablation of fragmented potentials to PV isolation in

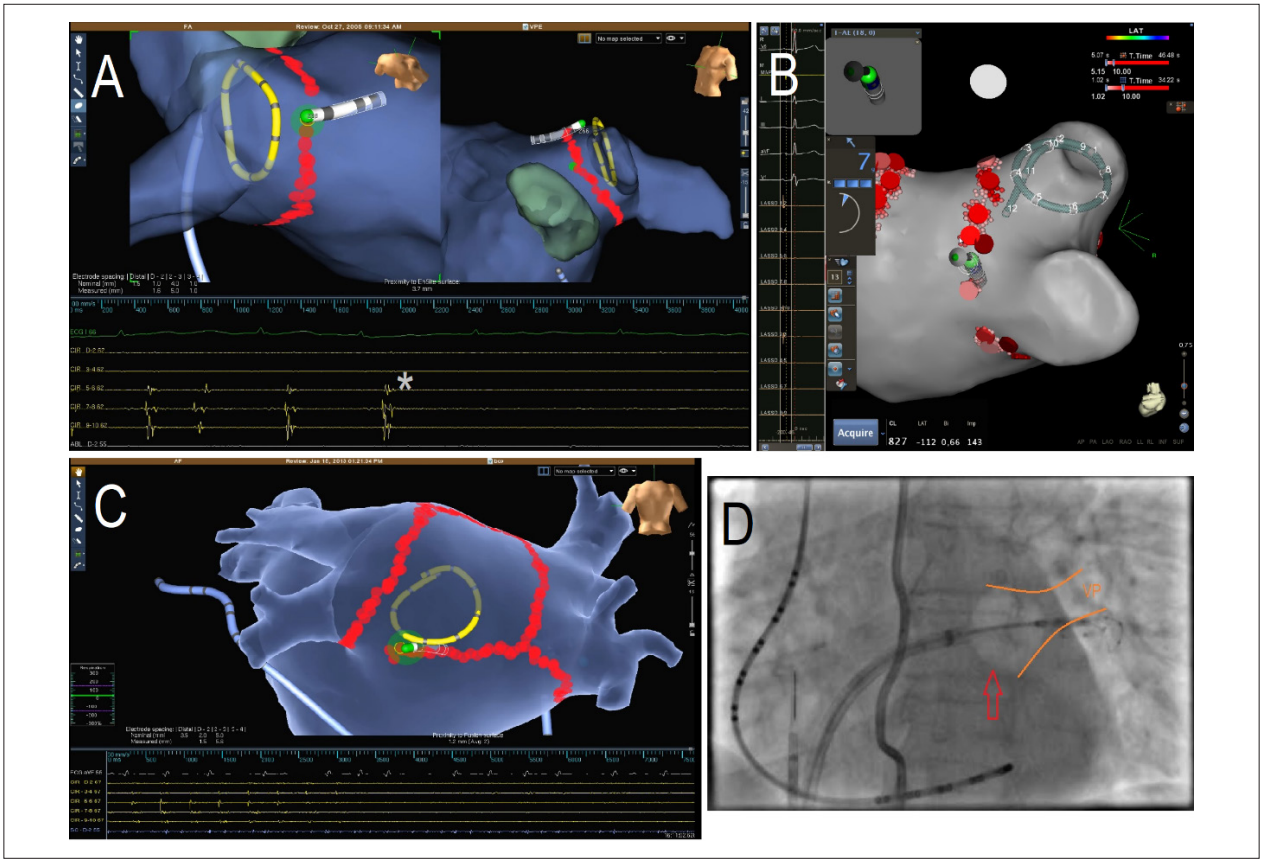

Figure 1 – *Catheter ablation for the treatment of paroxysmal AF. A) Isolation of left VPs by circumferential ablation (RF point-by-point) guided by 3D electroanatomic mapping (NAVx system — Abbott), demonstrating the elimination of electrograms (*) recorded by a circular catheter inside the PVs. B) Isolation of the right PVs (CARTO system — Biosense Webster) with a contact force-sensing catheter (shown by the force vector and force quantification = 7 g); the circular mapping catheter is inside the right superior PV. C) Persistent AF ablation (NAVx system — Abbott) demonstrating the additional linear RF lesions to isolate the LA posterior wall (roof and inferior lines), leading to the elimination of electrograms (recorded by the circular mapping catheter). D) Fluoroscopic imaging during cryoablation for isolation of the left superior PV, demonstrating the balloon catheter (arrow) inflated and in contact with the vein ostium. Balloon ablation along the PV circumference is performed simultaneously, which is usually restricted to PV isolation — when additional ablation is required, an RF catheter should be used.*

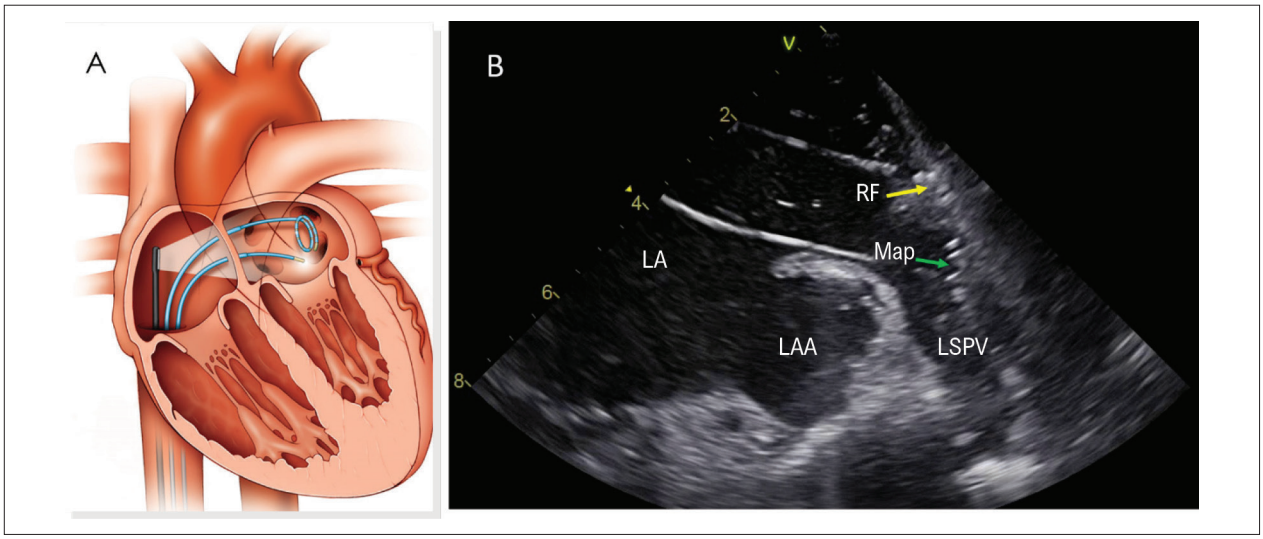

Figure 2 - *Use of intracardiac echo (ICE) during AF ablation. A) Schematic diagram showing the ICE catheter in the right atrial cavity with the ultrasound beam directed to guide the two transeptal punctures and positioning of circular mapping and ablation catheters in LA. B) ICE image demonstrating PV antral positioning and tissue contact during RF delivery around the left superior PV (VPSE). LA: left atrium; LAA: left atrial appendage; Map: mapping catheter; RF: ablation catheter.*

patients with persistent AF. In this study, there was no difference in the rates of sinus rhythm maintenance at 18 months between the groups (59% for PVI only vs. 49% and 46% in the other groups, without statistical significance). Therefore, many centers still perform PV isolation only, even in patients with persistent AF.

A more aggressive strategy for eliminating AF triggers was also tested in a randomized controlled trial (BELIEF Trial),[39] by electrical isolation of the left atrial appendage (LAA). Isolation of this structure in addition to conventional ablation was associated with a 55% reduction in the relative risk of AF recurrence in patients with long-term persistent AF. LAA isolation is currently performed selectively as it requires extensive RF applications and its association with increased risk of embolic phenomena (due to the loss of LAA contraction leading to slow flow and thrombus formation). Patients with electrically isolated LAA should be permanently anticoagulated, regardless of the CHADSVASC score, and should undergo occlusion of this structure if anticoagulation is contraindicated.[40]

Therefore, more persistent forms of AF with significant atrial remodeling require modification of the atrial substrate, implying a greater number, sites and extent of RF applications. There is no consensus in the literature on the best strategy to be used (Table 1). The evolution of AF to persistent forms represent progression of a pathological process (atrial myopathy)[41,42] and should motivate earlier intervention, ideally when AF is still paroxysmal, and LA remodeling is not yet present. A large retrospective study with more than 4,500 patients analyzed the impact of time between the diagnosis of AF and ablation therapy.[43] The results are striking, demonstrating that the earlier the ablation is performed the better the results – establishing the so called "oncological concept of AF", that is, the best results are obtained when treatment is done in the early stages of the disease (PV isolation in paroxysmal AF). In more advanced diseases (persistent and long-standing persistent AF), treatment is usually much more extensive and associated with worse results. A message to cardiologists and clinicians caring for AF patients is that the sooner the better.

Technologies to guide ablation

Regardless of the strategy used, imaging-based mapping methods are often used in addition to traditional electrophysiological mapping. Two types of technology are appropriate in this setting:

a) Electroanatomic mapping – this form of 3D mapping allows to accurately define the anatomy of the atrial cavities and the PVs, depict the functional substrate by measuring tissue voltage, mark the RF lesions spots (figure 1) on the constructed map and color-code the electrical activation information obtained. It is also possible to navigate on images of the true anatomy obtained by computed tomography or magnetic resonance imaging. 3D mapping is especially useful to reduce exposure to fluoroscopy and to make easy to show electrical activation of the arrhythmia circuit or focus as well as the RF lesions performed to treat them. Two systems are currently available in Brazil: CARTO — Biosense Webster and NavX — Abbott.

b) Intracardiac echocardiogram (ICE) – through an ultrasound catheter initially positioned (but not limited to) in the right atrium, it is possible to obtain detailed real-time images of cardiac anatomy[44,45] and visualize precise and safe manipulation of catheters through the various cardiac structures (Figure 2). Its use also allows the safe performance of transeptal punctures under direct visualization and the early detection of acute complications (pericardial effusion, thrombi). A recent study with more than 100,000 patients undergoing AF ablation showed the importance of this imaging method in significantly reducing the risk of a severe complication: cardiac perforation.[46] In this contemporary series, failure to use ICE was the greatest risk factor for cardiac perforation (RR 4.85).

These non-fluoroscopic imaging tools have been increasingly used in the EP laboratory over the years and can even guide the entire ablation procedures, completely avoiding the use of X-rays.[47] Initially reported approximately 10 years ago, "Zero-Fluoro" techniques are increasingly used in the electrophysiological community because they have been shown as safe and effective as traditional methods guided by fluoroscopy.[48-50]

Recurrences

Two main factors justify AF recurrences after ablation:

1. Reconnection or recurrent conduction in the PVs – for circumferential lesions to provide permanent PV isolation, contiguous fibrous tissue formation should form usually four to eight weeks after the acute injury (energy-induced tissue edema). If the lesion is not deep enough in the atrial wall, there may be remaining viable tissue after edema resorption. It only takes a small recovered segment to restore electrical PV-LA connection.

2. Occurrence of ectopic foci outside the PVs (non-PV triggers) – these occur more commonly (but not only) in persistent forms of AF or in patients with significant atrial remodeling.

PV reconnection is easily solved with new RF applications in conduction gaps. Reintervention is usually quick, easy and safe. In paroxysmal AF, it increases the control rates of AF in approximately 95% of cases. With the use of catheters with contact-force sensors, it has become an increasingly rare phenomenon[51-53] as RF lesions tend to be deeper and permanent.[54]

Non-PV triggers represent a more diffuse atrial substrate; their recognition and extensive ablation are necessary to improve outcomes, without which arrhythmia control is usually not possible.[33,54,55] They are most commonly located at the LA posterior wall, LAA and coronary sinus[32,54] — structures that can also be isolated by RF applications. It is certainly possible to maintain sinus rhythm in the long term, even if more than one intervention if necessary.

Patient Selection and Results

The selection of patients for catheter ablation of AF is currently mainly based on the failure of medical therapy (Table 2). According to the last HRS/EHRA/ECAS/APHRS/SOLAECE consensus of experts in 2017,[11] the primary indication for AF ablation is the presence of symptomatic paroxysmal or persistent AF, refractory or intolerant to at least one class I or III antiarrhythmic drug. There is solid evidence for improved quality-of-life parameters in these patients.[5,56]

AF ablation can be performed in patients with various types of heart disease (coronary artery disease, left ventricular

Table 1 – Atrial fibrillation Ablation Strategies

For PV Isolation:	
Class I – A	PV isolation is recommended for all AF ablation procedures
Class I – B	Demonstration of PV entrance block
Class IIa – B	Monitor for PV reconnection for 20 minutes after initial isolation
Class IIb – B	Adenosine administration 20 minutes after PV isolation Pacing along the circumferential ablation line Demonstration of PV exit block
In addition to PV isolation:	
Class I – B	CTI ablation in patients with history of typical flutter or if the arrhythmia is inducible during AF ablation
Class I – C	If linear lesions are performed, bidirectional block should be demonstrated
Class IIa – C	If reproductible non-PV triggers are identified, ablation should be considered When using a contact force-sensor catheter, a minimum of 5-10 g is reasonable
Class IIb – B	LA posterior wall isolation can be considered for initial or redo procedures for persistent or long-standing persistent AF High dose Isoproterenol for non-PV trigger detection and ablation can be considered for initial or redo procedures for paroxysmal, persistent, or long-standing persistent AF

PV: pulmonary vein; AF: atrial fibrillation; ICT: cavo-tricuspid isthmus; LA: left atrium.

Table 2 – Indications for atrial fibrillation ablation

Symptomatic AF, refractory or intolerant to at least 1 antiarrhythmic drug (class I or III):	
Class I – A	Paroxysmal AF
Class IIa – B	Persistent AF
Class IIb – C	Long-standing persistent AF
Symptomatic AF, before initiation of antiarrhythmic drugs (Class I or III):	
Class IIa – B	Paroxysmal AF
Class IIa – C	Persistent AF
Class IIb – C	Long-standing persistent AF
Indications for patient populations underrepresented in clinical trials:	
Class IIa – B	Congestive heart failure Older patients (≥ 75 years) Hypertrophic cardiomyopathy Younger patients (≤ 45 years) Brady-tachy syndrome
Class IIa – C	Athletes with AF
Class IIb – C	Asymptomatic AF

AF: atrial fibrillation.

hypertrophy, heart failure) and clinical presentations of AF (paroxysmal, persistent or long-lasting persistent), but the best results are obtained for patients with structurally normal hearts. In the largest randomized study that compared ablation with pharmacological therapy (CABANA),[7] survival free of recurrent AF is significantly better (HR 0.53) in ablated patients compared to those who remained on multiple antiarrhythmic drugs. Nevertheless, in this study, there was no reduction in a combined hard endpoint (death, stroke, severe bleeding or cardiac arrest) in the "intention-to-treat" analysis, although there were problems with large crossover rates for the ablation group (27%). In this study, the subgroups that benefited the most were the youngest (<65 years) and patients with congestive heart failure.

The selection of patients with persistent and long-standing persistent forms of AF follows the same reasoning, but the decision should be individualized according to parameters of remodeling such as LA size or volume[57] (which is an important predictor of recurrence) and AF duration. Persistent AF is a heterogeneous disease, with different degrees of atrial fibrosis and with influence of the autonomic nervous system and other pathophysiological processes still poorly understood,

which explains the heterogeneous results observed with different ablation strategies. Targeting this type of AF requires an individualized definition of the substrate and mechanisms involved.[58,59]

It is important to note that even with the strategy of extensive RF applications described above, higher recurrences rates and need for reinterventions are observed. In the experience of Natale et. al., 60% of patients maintained sinus rhythm without drugs after the first procedure.[54] In those undergoing a second intervention, 80% maintained sinus rhythm. Table 3 summarizes some of the main published studies.

Catheter ablation is less effective in certain subgroups of patients,[60] where advances in pathophysiological knowledge are still needed: dilated and fibrous atria, persistent or long-standing AF, hypertrophic cardiomyopathy, amyloid infiltrate, obesity and sleep apnea.

Long-term follow-up of patients undergoing catheter ablation shows the occurrence of late recurrences,[61-63] around 7% per year in the first 5 years. It should be noted that the estimation of the actual success of ablation is hampered by inconsistencies and heterogeneities in the definitions of success and recurrences in the different published studies. As an example, most studies consider as a recurrence any atrial arrhythmia lasting more than 30 seconds, a definition with clearly little clinical significance. In this scenario, the AF burden should be more valued and clinically meaningful in future research.

Table 3 – Trials in atrial fibrillation ablation

Trial (year)	Type	Ablation Strategy	N	Follow-up months	Sinus Rhythm Maintenance	p-value
Paroxysmal AF						
Thermocool AF (2010)	Randomized Ablation or AAD; multicentric	PVI CFAE and lines optional	167	12	66%/16%	<0.001
STOP AF (2013)	Randomized Cryoablation or AAD; multicentric	PVI	245	12	70%/7%	<0.001
SMART AF (2014)	Non-randomized; contact force-sensors; multicentric;	PVI CFAE and lines optional	172	12	72.5%/NA	<0.0001
TOCCASTAR (2015)	Randomized contact force-sensors or not; multicentric	PVI CFAE, non-PV triggers and lines optional	300	12	67.8%/69.4%	0.0073*
RAAFT-2 (2014)	Randomized Ablation or AAD (1st line); multicentric	PVI non-PV triggers optional	127	24	45%/28%	0.02
MANTRA-PAF (2012)	Randomized Ablation or AAD (1st line); multicentric	PVI + roof lines mitral and ICT lines optional	294	24	AF burden: 13%/19%	-
FIRE and ICE (2016)	Randomized RF or Cryo; multicentric	PVI	762	12	64.1% (RF)/65.4% (Cryo)	-
CIRCA DOSE (2019)	Randomized RF or Cryo 4 min or Cryo 2 min; multicentric	PVI	346	12	53.9% (RF)/52.2% (Cryo 4 min)/51.7% (Cryo 2 min)	0.87
Persistent AF						
TTOP (2014)	Randomized Ablation or AAD / DCC	PVI + CFAE	210	6	56%/26%	< 0.001
SARA (2014)	Randomized Ablation or AAD; multicentric	PVI CFAE and lines optional	146	12	70%/44%	0.002
STAR AF II (2015)	Randomized 3 ablation strategies; multicentric	PVI; PVI + CFAE; PVI + lines	589	18	59%/49%/46%	0.15
Paroxysmal or Persistent AF						
CABANA (2019)	Randomized Ablation or AAD; multicentric	PVI additional ablation optional	2204	48.5	69%/50%	-

*AF: atrial fibrillation; RF: radiofrequency; AAD: antiarrhythmic drugs; PVI: pulmonary vein isolation; CFAE: complex fractionated atrial electrograms; DCC: direct current cardioversion; * non-inferiority.*

As new technologies and experiences tend to promote permanent PV isolation, recurrence is currently more frequently observed due to the appearance of non-PV triggers, which should be identified and addressed[32,33,54,64]. Therefore, it is important to maintain periodic monitoring of patients and it is prudent to maintain anticoagulant therapy in patients at higher risk who do not have contraindications.

Table 4 summarizes adjuvant care to maximize the safety and efficacy of the ablation procedure.

Special Situations

International guidelines published in 2016 and 2017 and updated in 2019 and 2020 by different international societies (SBC/HRS/EHRA/ECAS/APHRS/ACC/AHA/ESC/EHRA)[11-13,15] almost consensually recommend ablative treatment in special situations (Table 2):

1) Ablation as first-choice therapy:

Increasing safety and efficacy allow ablation to be offered as first-line therapy for treatment (even before the use of antiarrhythmic drugs) in some special situations (athletes, young people, normal hearts).[65,66] It is a Class IIa indication for patients with symptomatic paroxysmal or persistent AF. Other appropriate situations for this strategy are patients with symptomatic pauses upon arrhythmia interruption (brady-tachy syndrome)[67] or in competitive athletes, who may have contraindications to antiarrhythmic drug use.

2) AF in patients with Heart Failure (HF):

HF may predispose to AF occurrence through various mechanisms, such as increased left ventricular filling pressures or LA dilatation and fibrosis, leading to atrial structural and electrical remodeling. AF can increase mortality in patients with left ventricular dysfunction.[68] Treatment of AF in this subset of patients is of critical importance[69-73] given the limitations of Amiodarone, the only antiarrhythmic drug available for this subgroup. In the most recent European guidelines published in 2020, AF ablation in patients with HF received a Class Ia[15] indication based on comparative studies with Amiodarone (AATAC)[69] and the publication of randomized studies such as AMICA[74] and CASTLE-AF,[75] the latter performed in patients with severe HF (mean EF 32%), demonstrating a significant reduction in mortality or hospitalization for HF (38%) and cardiovascular mortality (51%). These unprecedented findings confirm the negative prognosis of AF in this population and open a new frontier of indications for ablation in centers with adequate experience and infrastructure. Recent positive results are encouraging, with demonstration of improvement in ventricular function and reversal of atrial remodeling.[76]

3) AF in the elderly:

There are studies that have focused on reporting the results of AF ablation in older individuals. The age limit for the definition of elderly ranged from ≥70, 75 or 80 years. However, the number of elderlies in these studies was relatively small, with five of the seven studies enrolling less than 100 patients and the largest series reporting on 261 patients. Overall, the results of these studies provide evidence that ablation meets safety and efficacy criteria in this population,[77,78] despite a reduction in AF-free survival rates with every decade of age (Class IIa).

4) AF in asymptomatic patients and reduced risk of stroke:

Ablation of AF (paroxysmal or persistent) in truly asymptomatic patients can be considered[79] despite the lack of definitive evidence of significant changes in hard outcomes – particularly in the risk of thromboembolic phenomena/stroke. It should be performed by experienced operators and after a detailed discussion of the risks and benefits (Class IIb). There is solid evidence of reduction of hospitalizations[80] and resource utilization, with favorable cost-effectiveness.[10] In this scenario, patients with a higher probability of success should be prioritized (young people, paroxysmal AF, without significant atrial remodeling).

Several retrospective observational studies point to a significant reduction in thromboembolic risks in patients with CHADVASC score ≤3 undergoing successful AF ablation,[81-87] many of them reporting favorable outcomes even in patients who discontinued anticoagulant therapy. Data from the KP-RHYTHM[88] study, proving that the risk of stroke is proportional to the burden of AF in paroxysmal patients, regardless of

Table 4 – Adjunctive Strategies for atrial fibrillation ablation

Not directly related to the AF ablation procedure:	
Class IIa – B	Weight loss Evaluate BMI for ablation procedure Screen for sleep apnea signs and symptoms Treat sleep apnea
Class IIb – C	Interruption of AAD before ablation to improve long-term results is not clear AAD use during blanking period (3 months) after ablation to improve results is not clear
Reducing risk during ablation procedure:	
Class I – B	**Clear delineation of PV ostia to avoid energy delivery inside the PVs**
Class I – C	Reduce the energy power delivered in the LA posterior wall near the esophagus
Class IIa – C	Use a temperature sensor probe in the esophageal lumen and guide energy titration

AF: atrial fibrillation; AAD: antiarrhythmic drugs; BMI: body mass index; PV: PV: pulmonary vein; LA: left atrium.

CHADVASC score, and a metanalysis from randomized studies[89] suggesting reduced mortality and hospitalizations, are compatible with the hypothesis of risk reduction after a successful ablation.

It should be emphasized, however, that there is no direct evidence from randomized studies specifically designed for this purpose; the CABANA[7] trial did not show any reduction in a combined endpoint in a heterogeneous population (paroxysmal and persistent AF) comparing ablation versus drug treatment. The recently published EAST-AFNET 4[90] demonstrated a significant benefit in cardiovascular outcomes with a strategy of early rhythm control compared to heart rate control, but in this important randomized study, only 20% of patients were treated with ablation.

All current guidelines recommend that ablative treatment should not aim at discontinuation of anticoagulant therapy,[11-14] which should have its indication based on the baseline risk of the patient (usually indicated in patients with CHADSVASC score ≥ 2). All patients undergoing ablation should use anticoagulants for a minimum period of 2 months regardless of risk factors, and its continuation should be individualized by the risk score.

The ongoing OCEAN[91] study compares the maintenance of anticoagulation therapy (Rivaroxaban) with Aspirin in patients at moderate to severe risk undergoing ablation and maintaining sinus rhythm for at least 1 year after the procedure. The results should help refine indications of long-term anticoagulation after ablation.

Complications

The ablation procedure is associated with low complication rates in centers of excellence with high volume and experience, with major complications individually lower than 1% in highly experienced centers.[11] Table 5 summarizes the main complications and their incidences as reported in the literature.

It is important to be aware of a late complication (in the first weeks) related to esophageal injury due to its proximity to the LA posterior wall. During energy application in this region, power and/or time should be reduced, in addition to monitoring the luminal esophageal temperature (Table 4). An available alternative consists of different methods of mechanical esophageal deviation to increase its distance from the site of energy delivery.[92-95] There are reports of atrio-esophageal fistulas, with a high mortality rate.[96-100] Fortunately, this is a rare complication, with an estimated incidence of approximately 0.04%. Its early recognition is critical to avoid a fatal outcome.[99,101-103]

Future Perspectives

The use of high-power RF with short duration has been advocated to produce better quality tissue lesions,[104,105] besides causing wider and shallower lesions and therefore less risk of collateral damage (especially to the esophagus). This technique was associated with shorter RF application and LA instrumentation times and low complication rates,[106,107] boosting further investigations of catheters that can cause more permanent lesions within seconds of energy delivery.[108]

There are great expectations for the development of a new energy source for ablation: "electroporation". Unlike thermal energies (RF, cryotherapy, laser, ultrasound and microwave), which damages all tissues indiscriminately, pulsed field ablation (PFA) or "electroporation," which is a non-thermal ablation modality in which ultrafast electric fields (<1 s) are applied to target tissue selectively, destabilizing cell membranes and culminating in cell death. This is possible because tissues have different thresholds for necrosis. This technology is already in use to treat unresectable solid tumors in close proximity to blood vessels or nerves, given their different resistance to pulsed electric fields.[109,110] Cardiomyocytes have one of the lowest tissue injury thresholds, and PFA can therefore be applied during catheter ablation, limiting collateral damage to nearby structures such as the esophagus[111] and phrenic nerve.[112]

Table 5 – Complications Related to AF Ablation

Complications	Incidence	Diagnostic test
Death	<0.1% – 0.4%	-
Coronary stenosis / occlusion	<0.1%	Coronary angiogram
Atrio-esophageal fistula	0.02% – 0.11%	CT/MRI; avoid endoscopy with air insufflation
Air embolism	<1%	Clinical or angiography
PV stenosis	<1%	CT/MRI
Stiff LA syndrome	<1.5%	Echo; cardiac catheterization
Permanent phrenic nerve paralysis	0% – 0.4%	Chest X-Ray; fluoroscopy; Sniff test
Stroke/TIA	0% – 2%	CT/MRI; cerebral angiography
Vascular complications	0.2 – 1.5%	Vascular ultrasound; CT
Cardiac tamponade	0.2% – 5%	Echo
Pericarditis	0% – 5%	Clinical; ECG; Echo
Gastroparesis	0% – 17%	Endoscopy; barium swallow; gastric emptying evaluation

CT: computed tomography; MRI: magnetic resonance; PVI: pulmonary vein; LA: left atrium; TIA: transient ischemic attack; ECG: electrocardiogram.

Initial experience in patients undergoing ultra-fast PV isolation is very promising, with permanent isolation rates never reported before (100%).[113] This technology has great potential to replace RF and other thermal energies for catheter treatment of AF.

The recently published ERADICATE-AF[114] study evaluated the additional effect of catheter renal denervation in 302 hypertensive patients undergoing AF ablation, randomized to simply PV isolation or combined with renal artery ablation. The addition of denervation resulted in better AF-free survival at 12 months (72% vs. 56%). These findings certainly need to be replicated in a blinded model of renal denervation, but modulation of the autonomic nervous system is an important pathophysiological mechanism that should be further explored.

Conclusions

Catheter ablation is the most effective method for rhythm control in patients with AF, associated with significant improvement in symptoms, AF burden, quality of life and hospital admissions. It is associated with low complication rates when performed in experienced centers. Its role in reducing thromboembolic events and mortality still needs definitive proof in future randomized studies.

Author contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Saad EB, d'Avila A; Writing of the manuscript: Saad EB.

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References

1. Haissaguerre M, Jais P, Shah DC, Hocini M, Quiniou G, Garrigue S, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med*. 1998; 339(10): 659-66.
2. Kanagaratnam L, Tomassoni G, Schweikert R, Pavia S, Bash D, Beheiry S, et al. Empirical pulmonary vein isolation in patients with chronic atrial fibrillation using a three-dimensional nonfluoroscopic mapping system: long-term follow-up. *Pacing Clin Electrophysiol*. 2001; 24(12): 1774-9.
3. Kanj MH, Wazni OM, Natale A. How to do circular mapping catheter-guided pulmonary vein antrum isolation: the Cleveland Clinic approach. *Heart Rhythm*. 2006; **3**(7): 866-9.
4. Verma A, Marrouche NF, Natale A. Pulmonary vein antrum isolation: intracardiac echocardiography-guided technique. *J Cardiovasc Electrophysio.l* 2004; 15(11): 1335-40.
5. Mark DB, Anstrom KJ, Sheng S, Piccini JP, Baloch KN, Monahan KH, et al. Effect of Catheter Ablation vs Medical Therapy on Quality of Life Among Patients With Atrial Fibrillation: The CABANA Randomized Clinical Trial. *JAMA*. 2019; 321(13): 1275-85.
6. Packer DL, Kowal RC, Wheelan KR, Irwin JM, Champagne J, Guerra PG, et al. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front (STOP AF) pivotal trial. *J Am Coll Cardio.l* 2013; 61(16): 1713-23.
7. Packer DL, Mark DB, Robb RA, Monahan KH, Bahnson TD, PooleJE, et al. Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation: The CABANA Randomized Clinical Trial. *JAMA*. 2019; 321(13): 1261-74.
8. Reynolds MR, Walczak J, White SA, Cohen DJ, Wilber DJ. Improvements in symptoms and quality of life in patients with paroxysmal atrial fibrillation treated with radiofrequency catheter ablation versus antiarrhythmic drugs. *Circ Cardiovasc Qual Outcomes*. 2010;3(6): 615-23.
9. Wilber DJ, Pappone C, Neuzil P, Paola A, Marchlinski F, Natale A, et al. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. *JAMA*. 2010; 303(4): 333-40.
10. Saad EB, Tayar DO, Ribeiro RA, Junqueira SM, Jr., Andrade P, d'Avila A. Healthcare Utilization and Costs Reduction after Radiofrequency Ablation For Atrial Fibrillation in the Brazilian Private Healthcare System. *Arq Bras Cardiol*. 2019; 113(2): 252-7.
11. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm*. 2017;14(10): e275-e444.
12. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland Jr JC, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. *Circulation*. 2019; 140(2):e125-e51.
13. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016; 37(38): 2893-962.
14. Magalhaes LP, Figueiredo MJO, Cintra FD, Saad EB, Kuniyoshi RR, Lorga Filho AM, et al. Executive Summary of the II Brazilian Guidelines for Atrial Fibrillation. *Arq Bras Cardiol* 2016; 107(6): 501-8.
15. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2020.
16. Silva MA, Futuro GMC, Mercon ES, Vasconcelos D, Agrizzi RS, Elias Neto J, et al. Safety of Catheter Ablation of Atrial Fibrillation Under Uninterrupted Rivaroxaban Use. *Arq Bras Cardiol*. 2020; 114(3): 435-42.
17. Saad EB, Costa IP, Costa RE, Inacio Jr LA, Slater C, Camiletti A, et al. Safety of ablation for atrial fibrillation with therapeutic INR: comparison with transition to low-molecular-weight heparin. *Arq Bras Cardiol*. 2011; 97(4): 289-96.
18. Calkins H, Willems S, Gerstenfeld EP, Verma A, Schilling R, Hohnloser SH, et al. Uninterrupted Dabigatran versus Warfarin for Ablation in Atrial Fibrillation. *N Engl J Med*. 2017; 376(17):1627-36.

19. Arruda M, Mlcochova H, Prasad SK, Kilicaslan F, Saliba W, Patel D, et al. Electrical isolation of the superior vena cava: an adjunctive strategy to pulmonary vein antrum isolation improving the outcome of AF ablation. *J Cardiovasc Electrophysiol.* 2007; 18(12):1261-6.

20. Gianni C, Sanchez JE, Mohanty S, Trivedi C, Rocca DG, Al-Ahmad A, et al. Isolation of the superior vena cava from the right atrial posterior wall: a novel ablation approach. *Europace.* 2018; 20(9): e124-e32.

21. Kuck KH, Brugada J, Furnkranz A, Metzner A, Ouyang F, Chun KR, et al. Cryoballoon or Radiofrequency Ablation for Paroxysmal Atrial Fibrillation. *N Engl J Med.* 2016; 374(23):2235-45.

22. Andrade JG, Champagne J, Dubuc M, Deyell MW, Verma A, Macle L, et al. Cryoballoon or Radiofrequency Ablation for Atrial Fibrillation Assessed by Continuous Monitoring: A Randomized Clinical Trial. *Circulation.* 2019; 140(22):1779-88.

23. Oral H, Knight BP, Tada H, Ozaydin M, Chugh A, Hassan S, et al. Pulmonary vein isolation for paroxysmal and persistent atrial fibrillation. *Circulation.* 2002;105(9):1077-81.

24. Parkash R, Tang AS, Sapp JL, Wells G. Approach to the catheter ablation technique of paroxysmal and persistent atrial fibrillation: a meta-analysis of the randomized controlled trials. *J Cardiovasc Electrophysiol.* 2011; 22(7):729-38.

25. Wynn GJ, Das M, Bonnett LJ, Panikker S, Wong T, Gupta D. Efficacy of catheter ablation for persistent atrial fibrillation: a systematic review and meta-analysis of evidence from randomized and nonrandomized controlled trials. *Circ Arrhythm Electrophysiol.* 2014; **7**(5):841-52.

26. Scott PA, Silberbauer J, Murgatroyd FD. The impact of adjunctive complex fractionated atrial electrogram ablation and linear lesions on outcomes in persistent atrial fibrillation: a meta-analysis. *Europace.* 2016; 18(3): 359-67.

27. Romero J, Gianni C, Natale A, Di Biase L. What Is the Appropriate Lesion Set for Ablation in Patients with Persistent Atrial Fibrillation? *Curr Treat Options Cardiovasc. Med* 2017; 19(5): 35.

28. Mohanty S, Mohanty P, Trivedi C, Gianni C, Rocca DG, Biasi L, et al. Long-Term Outcome of Pulmonary Vein Isolation With and Without Focal Impulse and Rotor Modulation Mapping: Insights From a Meta-Analysis. *Circ Arrhythm Electrophysiol.* 2018; 11(3): e005789.

29. Hung Y, Lo LW, Lin YJ, Chang SL, Hu YF, Chung FP, et al. Characteristics and long-term catheter ablation outcome in long-standing persistent atrial fibrillation patients with non-pulmonary vein triggers. *Int J Cardiol.* 2017; 241: 205-11.

30. Bai R, Di Biase L, Mohanty P, Trivedi C, Russo AD, Themistoclakis S, et al. Proven isolation of the pulmonary vein antrum with or without left atrial posterior wall isolation in patients with persistent atrial fibrillation. *Heart Rhythm.* 2016; 13(1): 132-40.

31. Pambrun T, Denis A, Duchateau J, Sacher F, Hocini M, Jais P, et al. MARSHALL bundles elimination, Pulmonary veins isolation and Lines completion for ANatomical ablation of persistent atrial fibrillation: MARSHALL-PLAN case series. *J Cardiovasc Electrophysiol.* 2019; 30(1): 7-15.

32. Santangeli P, Zado ES, Hutchinson MD, Riley MP, Lin D, Frankel DS, et al. Prevalence and distribution of focal triggers in persistent and long-standing persistent atrial fibrillation. *Heart Rhythm.* 2016; 13(2): 374-82.

33. Hayashi K, An Y, Nagashima M, Hiroshima K, Ohe M, Makihara Y, et al. Importance of nonpulmonary vein foci in catheter ablation for paroxysmal atrial fibrillation. *Heart Rhythm.* 2015; 12(9):1918-24.

34. Kottkamp H, Berg J, Bender R, Rieger A, Schreiber D. Box Isolation of Fibrotic Areas (BIFA): A Patient-Tailored Substrate Modification Approach for Ablation of Atrial Fibrillation. *J Cardiovasc Electrophysiol.* 2016; **27**(1): 22-30.

35. Thiyagarajah A, Kadhim K, Lau DH, Emami M, Linz D, Khokhar K, et al. Feasibility, Safety, and Efficacy of Posterior Wall Isolation During Atrial Fibrillation Ablation: A Systematic Review and Meta-Analysis. *Circ Arrhythm Electrophysiol.* 2019; 12(8):e007005.

36. Di Biase L, Burkhardt JD, Mohanty P, Sanchez J, Mohanty S, Horton R, et al. Left atrial appendage: an underrecognized trigger site of atrial fibrillation. *Circulation.* 2010; 122(2):109-18.

37. Brooks S, Metzner A, Wohlmuth P, Lin T, Wissner E, Tilz R, et al. Insights into ablation of persistent atrial fibrillation: Lessons from 6-year clinical outcomes. *J Cardiovasc Electrophysiol.* 2018; 29(2): 257-63.

38. Verma A, Jiang CY, Betts TR, Chen J, Deisenhofer I, Mantovan R, et al. Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med.* 2015;372(19):1812-22.

39. Di Biase L, Burkhardt JD, Mohanty P, Mohanty S, Sanches JE, Trivedi C, et al. Left Atrial Appendage Isolation in Patients With Longstanding Persistent AF Undergoing Catheter Ablation: BELIEF Trial. *J Am Coll Cardiol.* 2016; 68(18):1929-40.

40. Di Biase L, Mohanty S, Trivedi C, Romero J, Natale V, Briceno D, et al. Stroke Risk in Patients With Atrial Fibrillation Undergoing Electrical Isolation of the Left Atrial Appendage. *J Am Coll Cardiol.* 2019; 74(8): 1019-28.

41. Marrouche NF, Wilber D, Hindricks G, Jais P, Akoum N, Marchlinsk F, et al. Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF study. *JAMA.* 2014; 311(5):498-506.

42. Goette A, Kalman JM, Aguinaga L, Akar J, Cabrera JA, Chen AS, et al. EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: Definition, characterization, and clinical implication. *Heart Rhythm.* 2017; 14(1): e3-e40.

43. Bunch TJ, May HT, Bair TL, Johnson DL, Weiss JP, Crandall BG, et al. Increasing time between first diagnosis of atrial fibrillation and catheter ablation adversely affects long-term outcomes. *Heart Rhythm.* 2013; 10(9): 1257-62.

44. Enriquez A, Saenz LC, Rosso R, Silvestry FE, Callans D, Marchlinski FE, et al. Use of Intracardiac Echocardiography in Interventional Cardiology: Working With the Anatomy Rather Than Fighting It. *Circulation.* 2018; 137(21): 2278-94.

45. Saad EB, Costa IP, Camanho LE. Use of intracardiac echocardiography in the electrophysiology laboratory. *Arq Bras Cardiol.* 2011; 96(1): e11-7.

46. Friedman DJ, Pokorney SD, Ghanem A, Marcello S, Kalsekar I, Yadalam S, et al. Predictors of Cardiac Perforation With Catheter Ablation of Atrial Fibrillation. *JACC Clin Electrophysiol.* 2020; **6**(6): 636-45.

47. Heidbuchel H, Wittkampf FH, Vano E, Ernst S, Schilling R, Picano E, et al. Practical ways to reduce radiation dose for patients and staff during device implantations and electrophysiological procedures. *Europace.* 2014; 16(7): 946-64.

48. Lerman BB, Markowitz SM, Liu CF, Thomas G, Ip JE, Cheung JW. Fluoroless catheter ablation of atrial fibrillation. *Heart Rhythm.* 2017; 14(6): 928-34.

49. Razminia M, Willoughby MC, Demo H, Keshmiri H, Wang T, D'Silva O, et al. Fluoroless Catheter Ablation of Cardiac Arrhythmias: A 5-Year Experience. *Pacing Clin Electrophysiol.* 2017; 40(4): 425-33.

50. Saad EB, Slater C, Inacio LAO, Jr., Santos GVD, Dias LC, Camanho LEM. Catheter Ablation for Treatment of Atrial Fibrillation and Supraventricular Arrhythmias Without Fluoroscopy Use: Acute Efficacy and Safety. *Arq Bras Cardiol.* 2020; 114(6): 1015-26.

51. Natale A, Reddy VY, Monir G, Wilber DJ, Lindsay BD, McElderry HT, et al. Paroxysmal AF catheter ablation with a contact force sensing catheter: results of the prospective, multicenter SMART-AF trial. *J Am Coll Cardiol.* 2014; 64(7): 647-56.

52. Reddy VY, Dukkipati SR, Neuzil P, Natale A, Albenque AP, Kautzner J, et al. Randomized, Controlled Trial of the Safety and Effectiveness of a Contact Force-Sensing Irrigated Catheter for Ablation of Paroxysmal Atrial Fibrillation: Results of the TactiCath Contact Force Ablation Catheter Study for Atrial Fibrillation (TOCCASTAR) Study. *Circulation.* 2015; 132(10): 907-15.

53. De Pooter J, Strisciuglio T, El Haddad M, Wolf M, Phlips T, Vandekerckhove Y, et al. Pulmonary Vein Reconnection No Longer Occurs in the Majority of Patients After a Single Pulmonary Vein Isolation Procedure. *JACC Clin Electrophysiol*. 2019; 5(3): 295-305.

54. Gokoglan Y, Mohanty S, Gunes MF, Trivedi C, Santangeli P, Gianni C, et al. Pulmonary Vein Antrum Isolation in Patients With Paroxysmal Atrial Fibrillation: More Than a Decade of Follow-Up. *Circ Arrhythm Electrophysiol*. 2016; 9(5)e003660.

55. Della Rocca DG, Mohanty S, Trivedi C, Di Biase L, Natale A. Percutaneous Treatment of Non-paroxysmal Atrial Fibrillation: A Paradigm Shift from Pulmonary Vein to Non-pulmonary Vein Trigger Ablation? *Arrhythm Electrophysiol Rev.* 2018; 7(4): 256-60.

56. Blomstrom-Lundqvist C, Gizurarson S, Schwieler J, Jensen SM, Bergfeldt L, Kenneback G, et al. Effect of Catheter Ablation vs Antiarrhythmic Medication on Quality of Life in Patients With Atrial Fibrillation: The CAPTAF Randomized Clinical Trial. *JAMA*. 2019; 321(11): 1059-68.

57. Njoku A, Kannabhiran M, Arora R, Reddy P, Gopinathannair R, Lakkireddy D, et al. Left atrial volume predicts atrial fibrillation recurrence after radiofrequency ablation: a meta-analysis. *Europace*. 2018; 20(1): 33-42.

58. Mohanty S, Mohanty P, Di Biase L, Trivedi C, Morris EH, Gianni C, et al. Long-term follow-up of patients with paroxysmal atrial fibrillation and severe left atrial scarring: comparison between pulmonary vein antrum isolation only or pulmonary vein isolation combined with either scar homogenization or trigger ablation. *Europace*. 2017; 19(11): 1790-7.

59. Fochler F, Yamaguchi T, Kheirkahan M, Kholmovski EG, Morris AK, Marrouche NF. Late Gadolinium Enhancement Magnetic Resonance Imaging Guided Treatment of Post-Atrial Fibrillation Ablation Recurrent Arrhythmia. *Circ Arrhythm Electrophysiol*. 2019; 12(8): e007174.

60. Al-Khatib SM, Benjamin EJ, Buxton AE, Calkins H, Chung MK, Curtis AB, et al. Research Needs and Priorities for Catheter Ablation of Atrial Fibrillation: A Report From a National Heart, Lung, and Blood Institute Virtual Workshop. *Circulation*. 2020; 141(6): 482-92.

61. Steinberg JS, Palekar R, Sichrovsky T, Arshad A, Preminger M, Musat D, et al. Very long-term outcome after initially successful catheter ablation of atrial fibrillation. *Heart Rhythm*. 2014; 11(5): 771-6.

62. Takigawa M, Takahashi A, Kuwahara T, Okubo K, Takahashi Y, Watari Y, et al. Long-term follow-up after catheter ablation of paroxysmal atrial fibrillation: the incidence of recurrence and progression of atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2014; 7(2): 267-73.

63. Tilz RR, Heeger CH, Wick A, Saguner AM, Metzner A, Rillig A, et al. Ten-Year Clinical Outcome After Circumferential Pulmonary Vein Isolation Utilizing the Hamburg Approach in Patients With Symptomatic Drug-Refractory Paroxysmal Atrial Fibrillation. *Circ Arrhythm Electrophysiol*. 2018; 11(2): e005250.

64. Lin D, Santangeli P, Zado ES, Bala R, Hutchinson MD, Riley MP, et al. Electrophysiologic findings and long-term outcomes in patients undergoing third or more catheter ablation procedures for atrial fibrillation. *J Cardiovasc Electrophysiol*. 2015; 26(4): 371-7.

65. Morillo CA, Verma A, Connolly SJ, Kuck KH, Nair GM, Champagne J, et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation (RAAFT-2): a randomized trial. *JAMA*. 2014; 311(7): 692-700.

66. Walfridsson H, Walfridsson U, Nielsen JC, Johannessen A, Raatikainen P, Janzon M, et al. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation: results on health-related quality of life and symptom burden. The MANTRA-PAF trial. *Europace*. 2015; 17(2): 215-21.

67. Khaykin Y, Marrouche NF, Martin DO, Saliba W, Schweikert R, Wexman M, et al. Pulmonary vein isolation for atrial fibrillation in patients with symptomatic sinus bradycardia or pauses. *J Cardiovasc Electrophysiol*. 2004; 15(7): 784-9.

68. Swedberg K, Olsson LG, Charlesworth A, Cleland J, Hanrath P, Komajda M, et al. Prognostic relevance of atrial fibrillation in patients with chronic heart failure on long-term treatment with beta-blockers: results from COMET. *Eur Heart J*. 2005; 26(13): 1303-8.

69. Di Biase L, Mohanty P, Mohanty S, Santangeli P, Trivedi C, LakkiReddy D, et al. Ablation Versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device: Results From the AATAC Multicenter Randomized Trial. *Circulation*. 2016; 133(17): 1637-44.

70. Hunter RJ, Berriman TJ, Diab I, Kamdar R, Richmond L, Baker V, et al. A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). *Circ Arrhythm Electrophysiol*. 2014; **7**(1): 31-8.

71. Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med*. 2008; 358(25): 2667-77.

72. Lobo TJ, Pachon CT, Pachon JC, Pachon EI, Pachon MZ, Pachon JC, et al. Atrial fibrillation ablation in systolic dysfunction: clinical and echocardiographic outcomes. *Arq Bras Cardiol*. 2015; 104(1): 45-52.

73. Scanavacca M, Bocchi EA. Catheter Ablation for Atrial Fibrillation in Patients with Heart Failure. *Arq Bras Cardiol*. 2018; 110(4): 300-2.

74. Kuck KH, Merkely B, Zahn R, Arentz T, Seidl K, Schluter M, et al. Catheter Ablation Versus Best Medical Therapy in Patients With Persistent Atrial Fibrillation and Congestive Heart Failure: The Randomized AMICA Trial. *Circ Arrhythm Electrophysiol*. 2019; 12(12): e007731.

75. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, et al. Catheter Ablation for Atrial Fibrillation with Heart Failure. *N Engl J Med*. 2018; 378(5): 417-27.

76. Sugumar H, Prabhu S, Voskoboinik A, Young S, Gutman SJ, Wong JR, et al. Atrial Remodeling Following Catheter Ablation for Atrial Fibrillation-Mediated Cardiomyopathy: Long-Term Follow-Up of CAMERA-MRI Study. *JACC Clin Electrophysiol*. 2019; 5(6): 681-8.

77. Nademanee K, Amnueypol M, Lee F, Drew CM, Suwannasri W, Schwab MC, et al. Benefits and risks of catheter ablation in elderly patients with atrial fibrillation. *Heart Rhythm*. 2015; 12(1): 44-51.

78. Santangeli P, Di Biase L, Mohanty P, Burkhardt JD, Horton R, Bai R, et al. Catheter ablation of atrial fibrillation in octogenarians: safety and outcomes. *J Cardiovasc Electrophysiol*. 2012; 23(7): 687-93.

79. Kalman JM, Sanders P, Rosso R, Calkins H. Should We Perform Catheter Ablation for Asymptomatic Atrial Fibrillation? *Circulation*. 2017; 136(5): 490-9.

80. Guo J, Nayak HM, Besser SA, Beaser A, Aziz Z, Broman M, et al. Impact of Atrial Fibrillation Ablation on Recurrent Hospitalization: A Nationwide Cohort Study. *JACC Clin Electrophysiol*. 2019; 5(3): 330-9.

81. Saad EB, d'Avila A, Costa IP, Aryana A, Slater C, Costa RE, et al. Very low risk of thromboembolic events in patients undergoing successful catheter ablation of atrial fibrillation with a CHADS2 score ≤3: a long-term outcome study. *Circ Arrhythm Electrophysiol*. 2011; 4(5): 615-21.

82. Proietti R, AlTurki A, Di Biase L, China P, Forleo G, Corrado A, et al. Anticoagulation after catheter ablation of atrial fibrillation: An unnecessary evil? A systematic review and meta-analysis. *J Cardiovasc Electrophysiol*. 2019; 30(4): 468-78.

83. Themistoclakis S, Corrado A, Marchlinski FE, Jais P, Zado E, Rossillo A, et al. The risk of thromboembolism and need for oral anticoagulation after successful atrial fibrillation ablation. *J Am Coll Cardiol*. 2010; 55(8): 735-43.

84. Bunch TJ, May HT, Bair TL, Weiss JP, Crandall BG, Osborn JS, et al. Atrial fibrillation ablation patients have long-term stroke rates similar to patients without atrial fibrillation regardless of CHADS2 score. *Heart Rhythm*. 2013; 10(9): 1272-7.

85. Bunch TJ, Crandall BG, Weiss JP, May HT, Bair TL, Osborn JS, et al. Patients treated with catheter ablation for atrial fibrillation have long-term rates of death, stroke, and dementia similar to patients without atrial fibrillation. *J Cardiovasc Electrophysiol.* 2011; **22**(8): 839-45.

86. Kalbfleisch SJ. Atrial fibrillation ablation, stroke, and mortality: Evaluating the effects of therapy in the era of big data. *Heart Rhythm.* 2017; 14(5): 643-4.

87. Saliba W, Schliamser JE, Lavi I, Barnett-Griness O, Gronich N, Rennert G. Catheter ablation of atrial fibrillation is associated with reduced risk of stroke and mortality: A propensity score-matched analysis. *Heart Rhythm.* 2017; 14(5): 635-42.

88. Go AS, Reynolds K, Yang J, Gupta N, Lenane J, Sung SH, et al. Association of Burden of Atrial Fibrillation With Risk of Ischemic Stroke in Adults With Paroxysmal Atrial Fibrillation: The KP-RHYTHM Study. *JAMA Cardiol.* 2018; **3**(7): 601-8.

89. Asad ZUA, Yousif A, Khan MS, Al-Khatib SM, Stavrakis S. Catheter Ablation Versus Medical Therapy for Atrial Fibrillation: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Circ Arrhythm Electrophysiol.* 2019; 12(9): e007414.

90. Kirchhof P, Camm AJ, Goette A, Brandes A, Eckardt L, Elvan A, et al. Early Rhythm-Control Therapy in Patients with Atrial Fibrillation. *N Engl J Med.* 2020 Oct 1;383(14):1305-1316.

91. Verma A, Ha ACT, Kirchhof P, Hindricks G, Healey JF, Hill MD, et al. The Optimal Anti-Coagulation for Enhanced-Risk Patients Post-Catheter Ablation for Atrial Fibrillation (OCEAN) trial. *Am Heart J.* 2018; 197: 124-32.

92. Mateos JC, Mateos EI, Pena TG, Lobo TJ, Mateos JC, Vargas RN, et al. Simplified method for esophagus protection during radiofrequency catheter ablation of atrial fibrillation--prospective study of 704 cases. *Rev Bras Cir Cardiovasc.* 2015; 30(2): 139-47.

93. Bhardwaj R, Naniwadekar A, Whang W, Mittnacht AJ, Palaniswamy C, Koruth JS, et al. Esophageal Deviation During Atrial Fibrillation Ablation: Clinical Experience With a Dedicated Esophageal Balloon Retractor. *JACC Clin Electrophysiol.* 2018; 4(8): 1020-30.

94. Iwasawa J, Koruth JS, Mittnacht AJ, Tran VN, Palaniswamy C, Sharma D, et al. The impact of mechanical oesophageal deviation on posterior wall pulmonary vein reconnection. *Europace.* 2020; 22(2): 232-9.

95. Palaniswamy C, Koruth JS, Mittnacht AJ, Miller MA, Choudry S, Bhardwaj R, et al. The Extent of Mechanical Esophageal Deviation to Avoid Esophageal Heating During Catheter Ablation of Atrial Fibrillation. *JACC Clin Electrophysiol.* 2017; 3(10): 1146-54.

96. Vasconcelos JT, Filho S, Atie J, Maciel W, Souza OF, Saad EB, et al. Atrial-oesophageal fistula following percutaneous radiofrequency catheter ablation of atrial fibrillation: the risk still persists. *Europace.* 2017; 19(2): 250-8.

97. Calkins H, Natale A, Gomez T, Etlin A, Bishara M. Comparing rates of atrioesophageal fistula with contact force-sensing and non-contact force-sensing catheters: analysis of post-market safety surveillance data. *J Interv Card Electrophysiol.* 2019.

98. Gunes MF, Gokoglan Y, Biase L, Gianni C, Mohanty S, Horton R, et al. Ablating the Posterior Heart: Cardioesophageal Fistula Complicating Radiofrequency Ablation in the Coronary Sinus. *J Cardiovasc Electrophysiol.* 2015; 26(12): 1376-8.

99. Mohanty S, Santangeli P, Mohanty P, Biase L, Trivedi C, Bai R, et al. Outcomes of atrioesophageal fistula following catheter ablation of atrial fibrillation treated with surgical repair versus esophageal stenting. *J Cardiovasc Electrophysiol.* 2014; **25**(6): 579-84.

100. Han HC, Ha FJ, Sanders P, Spencer R, Teh AW, O'Donnell D, et al. Atrioesophageal Fistula: Clinical Presentation, Procedural Characteristics, Diagnostic Investigations, and Treatment Outcomes. *Circ Arrhythm Electrophysiol.* 2017; 10(11).

101. Wu TC, Pisani C, Scanavacca MI. Approaches to the Diagnosis and Management of Atrial-Esophageal Fistula After Catheter Ablation for Atrial Arrhythmias. *Curr Cardiovasc Risk Rep.* 2019; 13.

102. Pappone C, Vicedomini G, Santinelli V. Atrio-Esophageal Fistula After AF Ablation: Pathophysiology, Prevention & Treatment. *J Atr Fibrillation.* 2013; **6**(3): 860.

103. Kim YG, Shim J, Lee KN, Lim JY, Chung JH, Jung JS, et al. Management of Atrio-esophageal Fistula Induced by Radiofrequency Catheter Ablation in Atrial Fibrillation Patients: a Case Series. *Sci Rep.* 2020; 10(1): 8202.

104. Bhaskaran A, Chik W, Pouliopoulos J, Nalliah C, Qian P, Barry T, et al. Five seconds of 50-60 W radio frequency atrial ablations were transmural and safe: an in vitro mechanistic assessment and force-controlled in vivo validation. *Europace.* 2017; 19(5): 874-80.

105. Leshem E, Zilberman I, Tschabrunn CM, Barkagan M, Contreras-Valdes FM, Govari A, et al. High-Power and Short-Duration Ablation for Pulmonary Vein Isolation: Biophysical Characterization. *JACC Clin Electrophysiol.* 2018; 4(4): 467-79.

106. Winkle RA, Moskovitz R, Hardwin Mead R, Engel G, Kong MH, Fleming W, et al. Atrial fibrillation ablation using very short duration 50 W ablations and contact force sensing catheters. *J Interv Card Electrophysiol.* 2018; 52(1): 1-8.

107. Winkle RA, Mohanty S, Patrawala RA, Mead RH, Kong MH, Engel G, et al. Low complication rates using high power (45-50 W) for short duration for atrial fibrillation ablations. *Heart Rhythm.* 2019; 16(2): 165-9.

108. Reddy VY, Grimaldi M, De Potter T, Vijgen JM, Bulava A, Duytschaever MF, et al. Pulmonary Vein Isolation With Very High Power, Short Duration, Temperature-Controlled Lesions: The QDOT-FAST Trial. *JACC Clin Electrophysiol.* 2019; 5(7): 778-86.

109. Rubinsky B, Onik G, Mikus P. Irreversible electroporation: a new ablation modality--clinical implications. *Technol Cancer Res Treat.* 2007; 6(1): 37-48.

110. Davalos RV, Mir IL, Rubinsky B. Tissue ablation with irreversible electroporation. *Ann Biomed Eng.* 2005; 33(2): 223-31.

111. Koruth JS, Kuroki K, Kawamura I, Brose R, Viswanathan R, Buck ED, et al. Pulsed Field Ablation vs Radiofrequency Ablation: Esophageal Injury in a Novel Porcine Model. *Circ Arrhythm Electrophysiol.* 2020 Mar;13(3):e008303.

112. Koruth JS, Kuroki K, Iwasawa J, Viswanathan R, Brose R, Buck ED, et al. Endocardial ventricular pulsed field ablation: a proof-of-concept preclinical evaluation. *Europace.* 2020 Mar 1;22(3):434-9

113. Reddy VY, Neuzil P, Koruth JS, Petru J, Funosako M, Cochet H, et al. Pulsed Field Ablation for Pulmonary Vein Isolation in Atrial Fibrillation. *J Am Coll Cardiol.* 2019; 74(3): 315-26.

114. Steinberg JS, Shabanov V, Ponomarev D, Losik D, Ivanickiy E, Kropotkin E, et al. Effect of Renal Denervation and Catheter Ablation vs Catheter Ablation Alone on Atrial Fibrillation Recurrence Among Patients With Paroxysmal Atrial Fibrillation and Hypertension: The ERADICATE-AF Randomized Clinical Trial. *JAMA.* 2020; 323(3): 248-55.

Cardiopulmonary Transplantation: When to Indicate?

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Introduction

Cardiopulmonary transplantation (CPT) peaked in the late 1980s and early 1990s, with almost 300 transplants performed each year worldwide. With the advances in the treatment of heart and lung failure, this number has dropped considerably, and in 2017 only 62 CPTs were performed worldwide.[1,2] There is a huge discussion about the profile of patients who can benefit from CPT and the best time for its indication.

Case report

We describe the case of a 46-year-old female patient diagnosed with atrioventricular communication (AVC), who underwent surgical correction in 2006 and developed secondary pulmonary hypertension in the late postoperative period. Her personal history was: stroke in 2014, with right hemiplegia, chronic atrial fibrillation, and biliary lithiasis. Referred to the transplant service, the patient was put on a waiting list for the procedure after a multidisciplinary discussion. She evolved with need for hospitalization due to dyspnea and worsening of heart failure, from functional class II to IV (according to the New York Heart Association, NYHA). A chest computed tomography (CT) scan showed chronic pulmonary thromboembolism (PTE) of the main arteries and interlobar branches. A transthoracic echocardiogram showed severe right ventricular (RV) dysfunction with pulmonary artery systolic pressure (PASP) of 129 mmHg, presence of transeptal bidirectional flow, and at least two orifices compatible with *ostium secundum* type atrial septal defect, measuring 10 mm and 8 mm, respectively.

The patient evolved with progression of cardiac dysfunction and worsening of clinical picture (dyspnea on minimal exertion, central cyanosis), increased pulmonary artery systolic pressure (PASP = 153mmHg) and need for continuous inotropic use (milrinone). A cardiac magnetic resonance imaging (MRI) was performed and identified return of the AVC (Figure 1) and PTE in the right pulmonary artery (Figure 2).

Keywords

Heart–Lung Transplantation/trends; Pulmonary Embolism; Hypertenson Pulmonary; Atrial Fibrillation; Lithiasis; Stroke.

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After a discussion at the Technical Chamber of the State Transplant Center, the patient was prioritized in the transplant wait line and, after five months of hospitalization, the CPT was performed at Hospital Israelita Albert Einstein (HIAE). The donor was an 18-year-old male, whose cause of brain death had been hemorrhagic stroke.

The surgical incision was made by anterior thoracotomy with Clamshell-type transverse sternotomy, and the installation of extracorporeal circulation (ECC) through cannulation in the ascending aorta and drainage in the superior and inferior vena cava. During cardiectomy, phrenic nerves were identified bilaterally and released with safety margins.

During pneumonectomy, the region of the recurrent laryngeal nerve was preserved to prevent injuries. The implantation of the cardiopulmonary block started with bronchial anastomoses, followed by the aorta and vena cava. The graft ischemia time was 255 minutes and the ECC time was 195 minutes. After being removed from ECC, the patient was submitted to a thromboelastogram (TEG) and a coagulogram, corrected according to result with platelets, fibrinogen and prothrombin complex, in addition to two red blood cell concentrates.

The patient was admitted to the intensive care unit (ICU) in mechanical ventilation, receiving 0.5 micro/kg/min of norepinephrine; 0.06 micro/kg/min of vasopressin; 3.7 micro/kg/min of dobutamine. The prophylaxis used was meropenem and vancomycin and, in induction, methylprednisolone and basiliximab. For immunosuppression, we used Tacrolimus, prednisone and mycophenolate.

The patient was extubated on the second postoperative day, with a PO_2/FiO_2 ratio of 400. In the first 72 hours after transplantation, the patient had primary graft dysfunction I (PGD), only due to a radiological alteration without clinical repercussion. She remained in the ICU for four days and was discharged on the 34th postoperative day. Currently, she is under outpatient follow-up, reporting a good quality of life.

Discussion

The International Society for Heart and Lung Transplantation (ISHLT) reports that the major indication for CPT is pulmonary hypertension, due to idiopathic pulmonary arterial hypertension or secondary to congenital heart disease (such as Eisenmenger Syndrome), which represents 60% a 70% of transplants in the past three decades, followed by Cystic Fibrosis, with 14.9%.[3,4]

The option for isolated heart and lung transplantation for patients who would previously be treated with CPT, as well as advances in the treatment of pulmonary hypertension, are reflected in the decrease in number of CPTs performed.

Preoperative exams must be carefully analyzed, as patients who will be referred and submitted to CPT may

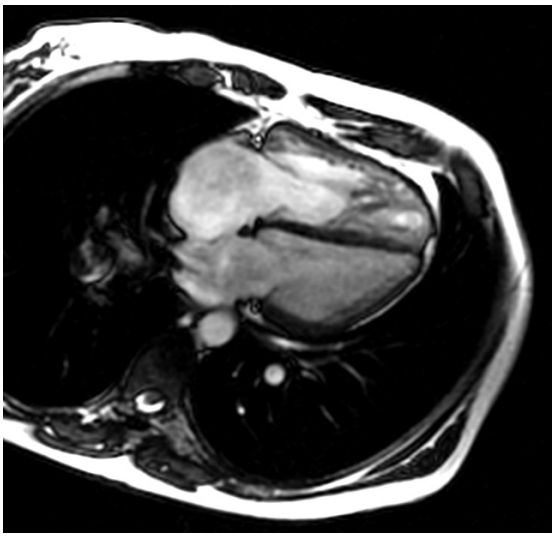

Figure 1 – *Cardiac magnetic resonance imaging showing interatrial communication.*

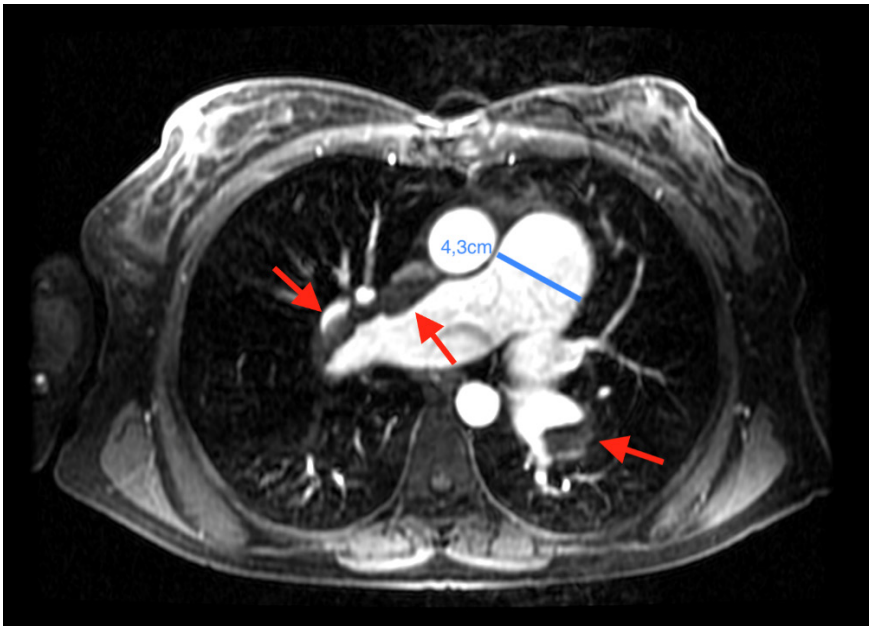

Figure 2 – *Cardiac magnetic resonance imaging showing thromboembolism in the right pulmonary artery (red arrow) and an enlarged pulmonary artery trunk.*

have involvement of other organs, such as liver and kidney, in addition to chronic systemic venous congestion. Another point to be verified is whether the recipient has a positive immune panel, because previous transfusion procedures could sensitize the patient.[5]

The postoperative management of CPT is similar to that of patients undergoing lung transplantation alone. Common causes of death in the first 30 days are graft failure, technical complications, and infection. Bronchiolitis obliterans syndrome (BOS) and pulmonary allograft dysfunction remain the main causes of mortality in the first year.[6]

There is a discussion in the international literature about the need and indication for CPT or when to recommend lung or heart transplantation alone. In Brazil, the 3rd Brazilian Guidelines on Cardiac Transplantation advises that, in cases of fixed pulmonary hypertension, CPT can be considered.[7] However, some points must be taken into account: anatomy, worsening of ventricular failure, hypertension, clinical

conditions and hemodynamics of the patient, worsened quality of life, cardiac index and renal dysfunction.[8]

A disadvantage of CPT is the use of one donor for a patient, while a bilateral or two unilateral heart and lung transplantation could be performed in two or three patients.[9]

There are many patients in Brazil who can benefit from CPT, whether due to congenital heart disease or Pulmonary Arterial Hypertension (PAH) of any etiology, in which the involvement is severe and irreversible.[10,11]

Conclusion

CPT should be considered as a therapeutic option for carefully selected patients. The time for referral for transplantation, before the disease gets worse, is of utmost importance to achieve good results. The management of these patients requires complex and multidisciplinary care. There is a hidden demand in our population that can benefit from this type of transplantation.

Author contributions

Conception and design of the research: Fernandes PMP; Acquisition of data: Reis FP, Abdalla LG; Writing of the manuscript: Faria GF; Critical revision of the manuscript for intellectual content: Fernandes PMP, Afonso Junior JE, Bacal F.

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References

1. Webb W R, Howard H S. Cardio-pulmonary Transplantation. Surg Forum. 1957;8:313–7.
2. Reitz BA, Wallwork JL, Hunt SA, Pennock JL, Billingham ME, Oyer PE, et al. Heart-Lung Transplantation: Successful Therapy for Patients with Pulmonary Vascular Disease. N Engl J Med. 1982 Mar 11;306(10):557–64.
3. K. Khush K, Cherikh WS, Chambers DC, Goldfarb S, Hayes D, Kucheryavaya AY, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-fifth Adult Heart Transplantation Report—2018; Focus Theme: Multiorgan Transplantation. J Heart Lung Transplant. 2018;37(10):1155–68.
4. Goldfarb SB, Hayes D, Levvey BJ, Cherikh WS, Chambers DC, Khush KK, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Twenty-first Pediatric Lung and Heart-Lung Transplantation Report—2018; Focus Theme: Multiorgan Transplantation. J Heart Lung Transplant. 2018;37(10):1196–206.
5. Brouckaert J, Verleden SE, Verbelen T, Coosemans W, Decaluwé H, De Leyn P, et al. Double-lung versus heart-lung transplantation for precapillary pulmonary arterial hypertension: a 24-year single-center retrospective study. Transpl Int.2019;37(10):196-206.
6. Toyoda Y, Toyoda Y. Heart-lung transplantation: Adult indications and outcomes. J Thorac Dis. 2014;6(8):1138–42.
7. Bacal F, Marcondes-Braga FG, Rohde LEP, Xavier Júnior JL, de Souza Brito F, Moura LZ, et al. 3ª Diretriz Brasileira de Transplante Cardíaco. Arq Bras Cardiol. 2018; 111(2):230-89
8. Idrees JJ, Pettersson GB. State of the Art of Combined Heart-Lung Transplantation for Advanced Cardiac and Pulmonary Dysfunction. Vol. 18, Current Cardiol Rep. Current Medicine Group LLC 1; 2016. p. 1–9.
9. Le Pavec J, Hascoët S, Fadel E. Heart-lung transplantation: current indications, prognosis and specific considerations. J Thorac Dis. 2018;26(10:5946-52.
10. Associação Brasileira de Transplantes de Orgãos . (ABTO). Dimensionamento dos Transplantes no Brasil e em cada estado [cited 2020 May 26];1–89. Available from: www.abto.org.br
11. Pêgo-Fernandes PM. Heart-lung transplantation: a necessity. J Bras Pneumol. 2020 May;46(3):e20190273–e20190273.

Why not Think about Non-Invasive Brain Stimulation to Control Blood Pressure?

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In 2007, Ridding and Rothwell[1] asked in their editorial: "Is there a future for the therapeutic use of transcranial magnetic stimulation?", drawing attention to the number of studies and hypotheses being built around non-invasive brain stimulation (NIBS). In fact, at the time, the focus of the use of NIBS was on neurological and psychiatric diseases. As the understanding of the physiology of the nervous system on the cardiovascular system was broadened, other ideas emerged. In their hypothesis, Cogiamanian et al. (2010)[2] drew attention to the possibility of treating arterial hypertension using NIBS - repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). From 2010 to the present, many questions have been answered about the real effects of NIBS, through experimental and clinical research.[3,4] The understanding we have today of the physiological effects that brain stimulation techniques have on neuronal cells and associating them with the complex neural control of the cardiovascular system, we ask ourselves: is there a possibility of this effective treatment approach for systemic arterial hypertension? If we think about the low cost, easy patient adherence, few side effects, it seems reasonable for us the need for studies that investigate this possible approach. For some years now, the relationship between the pathophysiological mechanisms of arterial hypertension and the central and peripheral nervous system has been further studied and thinking of the descending blood pressure (BP) control and regulation mechanisms, various areas of the brain (sensory motor cortex, pre-cortex - frontal medial and the insular cortex) control several functions such as: modulation of the autonomic response, somatic vasomotor mechanisms, variations in BP, among others.

Studies have shown that NBIS can influence cardiac autonomic behavior, through the variability of the R intervals of the electrocardiogram, favoring the increase in cardiac sympathetic or parasympathetic activity, depending directly on the applied stimulus.[5] Apparently, anodic stimulation applied to the motor control area increases the sympathetic tone, while anodic stimulation in the temporal lobe increases the parasympathetic tone (Insular cortex).[6,7] However, little has been explored in response to NIBS on arterial sympathetic activity. It is well known that BP is controlled by cardiac output (heart rate and stroke volume) and by the arterial resistance system. The central action of cardiac and peripheral modulation by the autonomic system through NIBS can be a non-pharmacological feasibility in BP control, with great plausibility. The direct action on pressure reduction was only verified when deep brain stimulation was performed in the periventricular/periaqueductal gray matter region in humans.[8] However, in studies with tDCS carried out in normotensive individuals, it failed to show any hypotensive effect.[9] A light at the end of the tunnel for the effect of NIBS on BP was verified in a study using tDCS in athletes. Higher post-aerobic exercise hypotension was found when tDCS was applied before exercise in athletes, with no effect on sedentary individuals.[10] However, the short, medium and long-term effect of NIBS in hypertensive individuals, mainly due to idiopathic causes, needs to be better verified.

It is known that hypertensive patients have greater cardiac and vascular sympathetic tone.[2]

It is possible that cardiac effects are more expected with the application of NIBS than peripheral ones, thereby we can expect the likelihood that the decreased sympathetic response in hypertensive patients facilitates hypotension or improve the pharmacological and non-pharmacological effect in the clinical treatment.

In view of this relationship between BP and cortical activity, NIBS seems to be a tool with good potential to be explored, as the effects of invasive brain stimulation (deep brain stimulation and spinal cord stimulation) have already been demonstrated with good results in the control of BP.[8] The reduction in BP is seen as a reaction after non-invasive magnetic stimulation. This letter draws attention to this hypothesis due to the few experimental and clinical studies that have tested this possibility and the clinical studies that we have, did not address systemic arterial hypertension more strongly.

Keywords

Blood Pressure; Transcranial Magnetic Stimulation; Transcranial Direct Current Stimulation; Transcranial Magnetic Non-Invasive/methods.

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References

1. Ridding MC, Rothwell JC. Is there a future for therapeutic use of transcranial magnetic stimulation? Nature Rev Neurosc. 2007;8(7)559-67.
2. Cogiamanian F, Brunoni AR, Boggio PS, Fregni F, Ciocca M, Priori A. Non-invasive brain stimulation for the management of arterial hypertension. Med Hypothes. 2010;74(2):332-6.
3. Lefaucher JP,Antal A, Aayache S,Benninger D, Brunelin J, Cogiamanian F, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). Clin Neurophysiol. 2017;128(1):56-92.
4. Lefaucher JP, Aleman A, Baekun C, Jenninger DA, Brunelin D, Lazzaro V, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnectic stimulation (rTMS): An update (2014-2018). Clin Neurophysiol. 2020;131(2):474-528.
5. Makovac E, Thayer JF, Ottaviani C. A meta-analysis of non-invasive brain stimulation and autonomic functioning: Implications for brain-heart pathways to cardiovascular disease. Neurosc Biobehav Rev. 2017;74(Pt B):330-41.
6. Clancy JA, Johnson R, Raw R, Deuchars SA, Deuchars J. Anodal transcranial direct current stimulation (tDCS) over the motor cortex increases sympathetic nerve activity. Brain Stimulation. 2014;7(1):97-104.
7. Oppenheimer SM, Gelb A, Girvin JP, Hachinski VC. Cardiovascular effects of human insular cortex stimulation. Neurology. 1992;42(9): 1727-32.
8. Green AL, Wang S, Owen SL. Deep brain stimulation can regulate arterial blood pressure in awake humans. Neuroreport 2005;8(16):1741–5.
9. Vandermeeren Y, Jamart J, Ossemann M. Effect of tDCS with an extracephalic reference electrode on cardio-respiratory and autonomic functions. BMC Neurosci. 2010;16(4):11:38.
10. Montenegro RA, Farinatti Pde T, Fontes EB, Soares PP, Cunha FA, Gurgel JL, et al. Transcranial direct current stimulation influences the cardiac autonomic nervous control. Neurosci Lett. 2011;15:497(1):32-6.

COVID-19 Chain of Survival 2020

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Abstract

The term *Chain of Survival* provides a useful metaphor for the elements involved in the COVID-19 management. The 5 links of the COVID-19 Chain of Survival are:

• SCIENCE - Evidence-based medicine (public policies and policies)

• AWARENESS - Increasing population sensitization and awareness

• TRAINING - Individual or team training for healthcare professionals

• STRUCTURE - Equip and structure the pre-hospital and in-hospital phases of COVID-19 management

• RETURN - Return of patients and healthcare professionals

A strong Chain of Survival can improve the chances of survival and recovery for victims of COVID-19.

Initiative: Brazilian Society of Cardiology (SBC) and Brazilian Association of Emergency Medicine (ABRAMEDE).

Note: The COVID-19 Chain of Survival is aimed at providing information and not at replacing the clinical judgement of physicians, who should determine the appropriate treatment for their patients.

Introduction

In December 2019, the Municipal Health and Sanitation Commission of Wuhan, Hubei Province, China, reported a group of 27 cases of pneumonia of unknown etiology, 7 of which were severe. In January 2020, the Chinese authorities identified a new virus in the *Coronaviridae* family that has been named 'new coronavirus', 2019-nCoV, and, subsequently, SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2). The disease associated with the new coronavirus has been called COVID-19.[1] Since then, COVID-19 has spread, affecting 35 628 628 individuals worldwide by the first fifteen days of October, having the United States and Brazil as its epicenter, with 9 385 506 and 5 566 049 cases, respectively. Regarding the number of deaths in the same period, 1 215 756, Brazil ranks second, with 160 496 deaths.[2]

The emergency measures to treat patients with COVID-19 and restrain the outbreak are number one priority in those countries. However, those measures might result in collateral damage for patients with other acute diseases, in addition to worsening the socioeconomic conditions in those countries.

The Chain of Survival refers to a chain of events that should occur in rapid sequence to maximize the chances of surviving COVID-19 and restoring the health and social flows. It is a simple metaphor to demonstrate the population's vital role in controlling COVID-19, in addition to the role played by healthcare professionals in that control. It suggests that each link of the chain is critical and depends on the preceding one, and that the chain of survival is not only strong when all its links are consolidated, but it might help save lives through the effective approach to its links.

General principles

This article addresses the major challenges faced by healthcare technicians, who, with health managers and physicians, have responded to the ever-changing needs regarding COVID-19 management, providing adequate healthcare environments to infected individuals as well as protection to other patients and care providers.

This pandemic has highlighted the importance of the healthcare systems and hospitals, as well as the need for their constant management as a major part of governance in this challenging and complex situation.

This article aims at creating and describing the structural components of a COVID-19 Chain of Survival. The recommendations in this document are based on evidence available at the time of its elaboration and on expert opinions. Because the knowledge about COVID-19 rapidly evolves, the protocols for the safe return of medical care and invasive and non-invasive procedures are constantly evolving and adapting. This project has been idealized by the Brazilian Society of Cardiology and the Brazilian Association of Emergency Medicine (ABRAMEDE) to serve as reference for their associates. The recommendations presented, however, should not be used as the sole base to define local protocols; other updated sources should be considered as knowledge in the field evolves.

Keywords

COVID-19; Coronavirus; Betacoronavirus, Evidence Based Medicine; Survival; Medical Care.

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Systematic, organized and coordinated effort in the community continues to be the most powerful recommendation we can make to save individuals affected by COVID-19. The metaphor of the links in a chain has proved to be successful in many aspects regarding cardiopulmonary resuscitation.[3,4] The use of the COVID-19 Chain of Survival can identify weak spots not only in the healthcare system 'links' but also in the fight against the pandemic, and, thus, contribute to optimize the treatment of critical patients with COVID-19. Therefore, all individuals involved are important and should work in harmony. Major health managers, healthcare professionals, technicians, clinical engineers, risk managers and pharmacists, among others, should work as in an orchestra, with dynamic system management.

Surviving severe COVID-19 depends on a sequence of critical interventions. If one of such critical interventions is neglected or delayed, the chances of survival decrease. The term 'Chain of Survival' is used to describe that sequence. Figure 1 shows the 5 interdependent links in the COVID-19 Chain of Survival.

• **SCIENCE: Evidence-based medicine (policies and public policies)** – The chain of command in the health system and the COVID-19 challenge

An essential point is to participate in the public debate, learning with the pandemic and objectively assessing the governance of health systems. The discussion will necessarily continue, as it should in a democracy, but it is paramount to learn the lessons of this challenging period.

Evidence-based medicine is the explicit and conscientious use of the best scientific evidence for the decision-making regarding patient care. Evidence-based medicine aims at uniting the physician's experience, the patient values and preferences, and the best scientific evidence available.[5-7] The COVID-19 pandemic has had personal and political repercussions, yielding impassioned discussions and true clashes in the agonism and antagonism of new/old drugs or treatments. This scenario, however, does not change the demand for better evidence deriving from randomized clinical trials specifically designed to determine the evidence-based modalities of treatment to reduce the COVID-19 spread and prevent the burden of future outbreaks.[5-7]

• **AWARENESS: Increasing population sensitization and awareness**

Although several therapies have been suggested, no specific option has been able to successfully treat COVID-19 or prevent SARS-CoV-2 infection so far. The only feasible intervention that has proven to reduce the transmission rate seems to be the use of strict social distancing measures for the general population.[5] The results of systematic reviews and metanalyses have supported the physical distancing of at least 1 meter and have provided quantitative estimates for contact tracing models. The ideal use of face masks, proper hand hygiene, and face/eye protection against contact in public places seem to have an impact.[5,6] MacIntyre et al.,[8] in a randomized study comparing the use of cloth masks and medical masks in healthcare workers, have found a significantly higher rate of respiratory infection among cloth masks users. Other studies and recommendations,[8-12] involving simulation applied to population distribution and COVID-19 transmission, have shown that the continuous use of face masks (filtering 20-50% of exhaled air) by the general population, even when asymptomatic, significantly reduces COVID-19 spread, with beneficial effects regardless of the population groups associated with higher risk. That reduction can be potentially optimized when social distancing is associated. Therefore, it is plausible and necessary to consider that all individuals should wear masks when exposed to agglomerations and other high-risk situations, especially because of the higher transmissibility in the early asymptomatic phase of COVID-19.

Figure 1 – *COVID-19 Chain of Survival.*

• TRAINING: Individual and team training for healthcare professionals

The interruption of permanent medical education goes beyond medical residence. The cancellation of medical congresses, courses and symposia, the reduction in clinical teams due to absence of contaminated professionals, the reluctance to attend trainings, the confinements, the taking on colleague's tasks, and the increase in the workload during the COVID-19 pandemic have required the implementation of technologies, as well as adjustments and immediate action to minimize the educational gap.[13,14]

Teleconferences had already been introduced as a useful tool for continuing education long before COVID-19 appearance. With the pandemic, their prominent use involved in exchanging learning strategies between institutions[13-18] made teleconferences the fundamental mean to provide permanent clinical education, proving their usefulness. Several apps and multimedia conferencing have allowed not only clinical departments to implement lectures and clinical sessions, but also medical schools to continue their activities. In addition, hospitals and clinical units could continue to issue reports and discuss their cases.

Simulation-based medical education has been an adequate tool for learning during the COVID-19 pandemic, provided some adjustments were made, such as the reduction in the number of participants, use of personal protection equipment, and disinfection of mannequins.[19-22]

• STRUCTURE: Equip and structure the pre-hospital and in-hospital phases of COVID-19 management

In face of the immediate need to manage a novel disease, telemedicine has enabled interdisciplinary and distance learning.[23] In Brazil, intensive care and emergency physicians could provide remote care to patients with COVID-19, indirectly contributing to evidence-based clinical management.[24-26] The Tele UTI project is a collaborative initiative of five private philanthropic hospitals to provide care to 2500 intensive care beds from the Brazilian Unified Public Health System, under the leadership of the Hospital Israelita Albert Einstein. The project consists in daily remote medical visits to intensive care patients, with emphasis on severe acute respiratory syndrome and suspected COVID-19 cases.[27]

• RETURN: Return of patients and healthcare professionals

The return of routine medical visits and social life should be aligned with social policies and follow the recommendations of competent authorities. It is mandatory that the medical community and the society remain vigilant and pay careful attention to new evidence and possible new outbreaks.[26]

The following measures are imperative in healthcare settings: proper physical structure to ensure physical distancing by using floor signaling in association with physical barriers, such as acrylic or glass panels; alcohol gel provision; banners and posters displayed at strategic places with information on hand hygiene, cough etiquette, and COVID-19 major signs and symptoms.[26-29] Last but not least, the economy recovery and the social adequacy to the 'new today' are fundamental.

Towards post-COVID-19: Lessons and challenges to hospitals and health infrastructure

There is evidence of possible repetitions of viral attacks soon. Prevention and preparedness are essential, especially for the healthcare sector.

Conclusion

The first lesson to be learned is that this challenging period requires courage to change: those who work in the healthcare sector must rethink the architectonic models. Technicians have made miracles by adapting the current hospitals to promptly meet the new demand and should be included in future planning and design processes. The governance of the health systems must consider the need for less fragmentation and stronger national coordination. It is worth considering that we currently must be even more sustainable, aiming at prevention and preparedness, with an economic development focused on respect to people, the community, and the environment. We should, thus, remember Machiavelli and take advantage from a dramatic crisis.

The concept of the COVID-19 Chain of Survival highlights several important principles, and any frail link in the chain reduces the survival rates. A weak component of the system is the major reason for variability in the survival rates.

Although all links should be strong, the unavoidable question persists: which is the most important? Recognizing the emergency and starting the chain are certainly essential; thus, if that does not occur, the survival decreases.

Because 'Structure' is the only 'sufficient' intervention, that is, the link that treats COVID-19, it is often referred as 'the most important factor in determining survival'. However, the efficacy of the chain cannot be assessed based on only one individual link; the chain should be assessed as a whole. In fact, the truth is even more satisfactory and suitable for the concept of the Chain of Survival, in which each link matters.

A strong Chain of Survival can improve the chances of survival and recovery for COVID-19 victims.

Author contributions

Conception and design of the research: Timerman S; Writing of the manuscript: Timerman S, Guimarães HP, Rochitte CE, Polastri TF; Critical revision of the manuscript for intellectual content: Timerman S, Guimarães HP, Rochitte CE, Polastri TF, Lopes MACQ.

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References

1. Jimenez AJ, Garcia DE. Recomendaciones de Actuación frente a casos de infección por El nuevo coronavirus (SARS-COV-2). In: Guimarães HP, Lobo SMA, Shubert DU, Dal-Pizzol F. Recomendações em Medicina de Emergência e Medicina Intensiva para o atendimento a COVID-19. São Paulo: Editora dos Editores,2020, p.269-320.
2. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU).[Acesso em 04 ezembro 2020] Disponivel em : https://coronavirus.jhu.edu/map.html
3. Gullo A. Cardiac Cardiac arrest, chain of survival and Utstein style Eur J Anaesthesiol. 2002 Sep; 19(9): 624-33.
4. Iwami T, Nichol G, Hiraide A, Hayashi Y, Nishiuchi T, Kajino K,et al. Continuous improvements in "chain of survival" increased survival after out-of-hospital cardiac arrests: a large-scale population-based study. Circulation. 2009 Feb 10;119(5):728-34
5. Remuzzi A, Remuzzi G. COVID-19 and Italy: what next? Lancet 2020; 395: 1225–8.
6. Pascarella G, Strumia A, Piliego C, Bruno F, Del Buono R. COVID-19 diagnosis and management: a comprehensive review. J Intern Med. 2020 May 13: 10.1111.
7. Malay SD. COVID-19, Pandemic, and Social Distancing J Foot Ankle Surg. 2020 May-June; 59(3): 447–8.
8. MacIntyre CR, Seale H, Dung TC, Tham DC, Hlen ND. A cluster randomised trial of cloth masks compared with medical masks in healthcare workers. BMJ Open, 2015;5(4):e006577.
9. Chu DK, Akl AE, Duda S, Solo K, Yaacoub S, Schünemann HJ. COVID-19 Systematic Urgent Review Group Effort (SURGE) study authorsPhysical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis. Lancet. 2020 Jun 27;395(10242):1973-87
10. Eikenberry SE, Mancuso M, Iboi E, Phan T, Einkenberry K, Kuang Y, e al.et al. To mask or not to mask: Modeling the potential for face mask use by the general public to curtail the Covid-19 pandemic. Infect Dis Model, 2020;5:293-308.
11. Mahase E. Covid-19: What is the evidence for cloth masks?. BMJ, 2020;369:m1422.
12. Javid B, Weekes MP, Matheson NJ. Covid-19: should the public wear face masks?. BMJ, 2020;369:m1442.
13. Dedeilia A , Sotiropoulos MG, HanrahanJG , Deep J, Dedeilias P, Sideris M. Medical and Surgical Education Challenges and Innovations in the COVID-19 Era: A Systematic Review. In Vivo. 2020 Jun;34(3 Suppl):1603-11.
14. Tomlinson J, Shaw T, Munro A, Johnson R, Madden DL, Phillips R, et al. How does tele-learning compare with other forms of education delivery? A systematic review of tele-learning educational outcomes for health professionals. N S W Public Health Bull .2013;24:70-5.
15. Spitzer RF, Kives S, Ornstein M, Caccia N, Stephens D, Flood C, et al. Videoconferencing for resident teaching of subspecialty topics: the pediatric and adolescent gynecology experience at the Hospital for Sick Children. J Pediatr Adolesc Gynecol .2008;21(6):343-6.
16. Stokes DC: Senior medical students in the COVID-19 response: An opportunity to be proactive. Acad Emerg Med.2020; 27(4):343-5.
17. Rakowsky S, Flashner BM, Doolin J, Reese Z, Shpilsky J, Yang S, et al. Five Questions for residency leadership in the time of COVID-19: Reflections of chief medical residents from an internal medicine program. Acad Med. 2020;95(8):1152-4.
18. Kogan M, Klein SE, Hannon CP, Nolte MT: Orthopaedic education during the COVID-19 pandemic. J Am Acad Orthop Surg.2020;323(21):2131-2.
19. Rose S: Medical Student Education in the Time of COVID-19. JAMA, 2020 323(21):2131-2.
20. Mian A, Khan S: Medical education during pandemics: a UK perspective. BMC Med 18(1):100.
21. Brandão CFS, Vaccarezza G, Bizario JCS, Goes AFT. Clinical simulation strategies for knowledge integration relating to initial critical recognition and management of COVID-19 for use within continuing education and health related academia in Brazil: a descriptive study. Sao Paulo Med. J.,138(5):385-92.
22. Deng A, Wang JJ, Tsui BCH. Keeping trainees safe in a pandemic: the evolving role of medical simulation training. Can J Anaesth. 2020;67(9):1292-3.
23. Hollander JE, Carr BG. Virtually Perfect? Telemedicine for Covid-19. N Engl J Med. 2020;382(18):1679-81.
24. Guimarães HP, Couto TB, Corrêa TD, Rodrigues RR, Timerman S, Garrido AP, et al. Cardiorespiratory arrest care in critically patients with suspected or confirmed infection by COVID-19: recommendations and training. Einstein (São Paulo);2020 agosto 2020 (in press).
25. Carvalho CRR, Scudeller PG, Rabello G, Gutierrez MA, Jatene FB. Use of telemedicine to combat the COVID-19 pandemic in Brazil. Clinics. 2020;75:e2217
26. Hospitais Proadi-SUS. Tele UTI.[Acesso em 2020 16 agosto] Disponível em:https://hospitais.proadi-sus.org.br/covid19/conheca-as-iniciativas-da-forca-tarefa/12/tele-uti
27. Lockhart SL, Naidu JJ, Badh CS, Duggan LV. Simulation as a tool for assessing and evolving your current personal protective equipment: lessons learned during the coronavirus disease (COVID-19) pandemic. Can J Anesth. 2020; 67(7):895-6.
28. Bittencourt MS, Generoso G, Melo PHMC, Bittencourt DP, Miranda EJFP, Mesquita ET, et al. Protocolo de reconexão dos serviços de cardiologia com os pacientes durante a pandemia de COVID-19: Posicionamento – Protocolo de reconexão dos serviços de cardiologia com os pacientes durante a pandemia de COVID-19 – 2020. [Acesso em 2020 03 Outubro). Disponível em: https://www.portal.cardiol.br/post/protocolo-de-reconex%C3%A3o-dos-servi%C3%A7os-decardiologia-com-os-pacientes-durante-a-pandemia-de-covid-19.
29. Timerman S, Starbelli TMV, Facciolli T, Kalil RK. Atlantica Hotels Safe & Clean Protocol e Chancela InCor .[Accessed in 2020 Oct 20] Available from:https://www.atlanticahotels.com.br/comunicado-covid-19/

Emerging Topics in Heart Failure: Sodium-Glucose Co-Transporter 2 Inhibitors (SGLT2i) in HF

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Research letter related to Heart Failure Summit Brazil 2020 / Heart Failure Department - Brazilian Society of Cardiology

Possible Mechanisms of Action

Sodium-glucose co-transporter 2 inhibitors (SGLT2i) inhibit glucose reabsorption in proximal convoluted tubules, resulting in glycosuria and reduced blood glucose levels. However, this effect does not seem to explain the benefits of SGLT2i in patients with heart failure (HF).[1,2]

Its benefits also do not seem to be directly related to its effects on classic cardiovascular risk factors (SAH, DM, DLP), since outcome reduction in the EMPA-REG study was not dependent on the baseline metabolic/hemodynamic profile of the patients or their variation throughout the study.[3]

One of the most accepted mechanisms for explaining the mode of action of SGLT2i in HF is improved parietal tension of the left ventricle secondary to a decrease in pre- (effect of natriuresis and osmotic diuresis) and afterload (improvement in endothelial function and reduction of blood pressure).[4-6] Metabolic mechanisms include improved cardiomyocyte metabolism and bioenergetics (increased ketogenesis and increased β-hydroxybutyrate levels),[7] myocardial sodium-hydrogen pump inhibition (which leads to a higher concentrations of calcium in the mitochondria),[8] reduced cardiac necrosis and fibrosis (inhibition of collagen synthesis)[9] and changes in cytokine production and epicardial fatty tissue.[10]

However, there are still questions about the real contribution of these mechanisms.

Their benefits exist with or without DM, which calls the role of ketogenesis into question.

Keywords

heart failure; SGLT2i.

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The diuretic effect of SGLT2i was not observed in DAPA-HF (either by potentiating diuretics or reducing natriuretic peptide levels).[11] Thus, better knowledge of the main mechanisms still depends on studies in experimental models and other studies in progress, such as EMPEROR-preserved, EMPA-HEART and DELIVER.

The possible mechanisms of action of this therapeutic class are summarized in the figure below (Figure 1).

New evidence about HF prevention

The first large study on this therapeutic class (EMPA-REG OUTCOME) was published in 2015.[12] It evaluated empagliflozin in DM2 patients with established cardiovascular disease who were receiving normal treatment. Among those who received empagliflozin, there was a significant reduction in major adverse cardiovascular events (MACE: CV death, non-fatal MI or non-fatal stroke) (hazard ratio [HR]: 0.86 95% CI: 0.74-0.99) and a surprising reduction in hospitalization for HF (HHF) (HR: 0.65 (95%CI: 0.50-0.85). The CANVAS Program,[13] published in 2017, evaluated canagliflozin in DM2 patients with a high risk of cardiovascular events who were receiving normal treatment. It found a reduction in the combined primary endpoint (MACE: CV death, non-fatal MI or non-fatal stroke) and a 33% reduction in HHF (HR = 0.67, 95%CI: 0.52-0.87), as well as fewer combined renal events.

The DECLARE-TIMI 58 trial[14] evaluated dapagliflozin in DM2 patients with established atherosclerotic disease or multiple risk factors for atherosclerotic disease who were receiving normal treatment. There was no reduction in the combined primary outcome (MACE: CV death, MI or stroke). There was a 17% reduction in the combined outcome of cardiovascular mortality and HHF, and a 27% reduction (HR: 0.73 (95%CI: 0.61-0.88) in HHF. More recently, the VERTIS–CV trial[15] evaluated ertugliflozin (not yet marketed in Brazil) in DM2 patients with established cardiovascular disease who were receiving normal treatment. Although there was no reduction in the combined primary outcome (MACE: CV death, myocardial infarction or stroke),a 30% reduction in HHF was observed.

Taken together, the available data demonstrate the effectiveness of SGLT2i for reducing the incidence of HF in groups of DM2 patients.

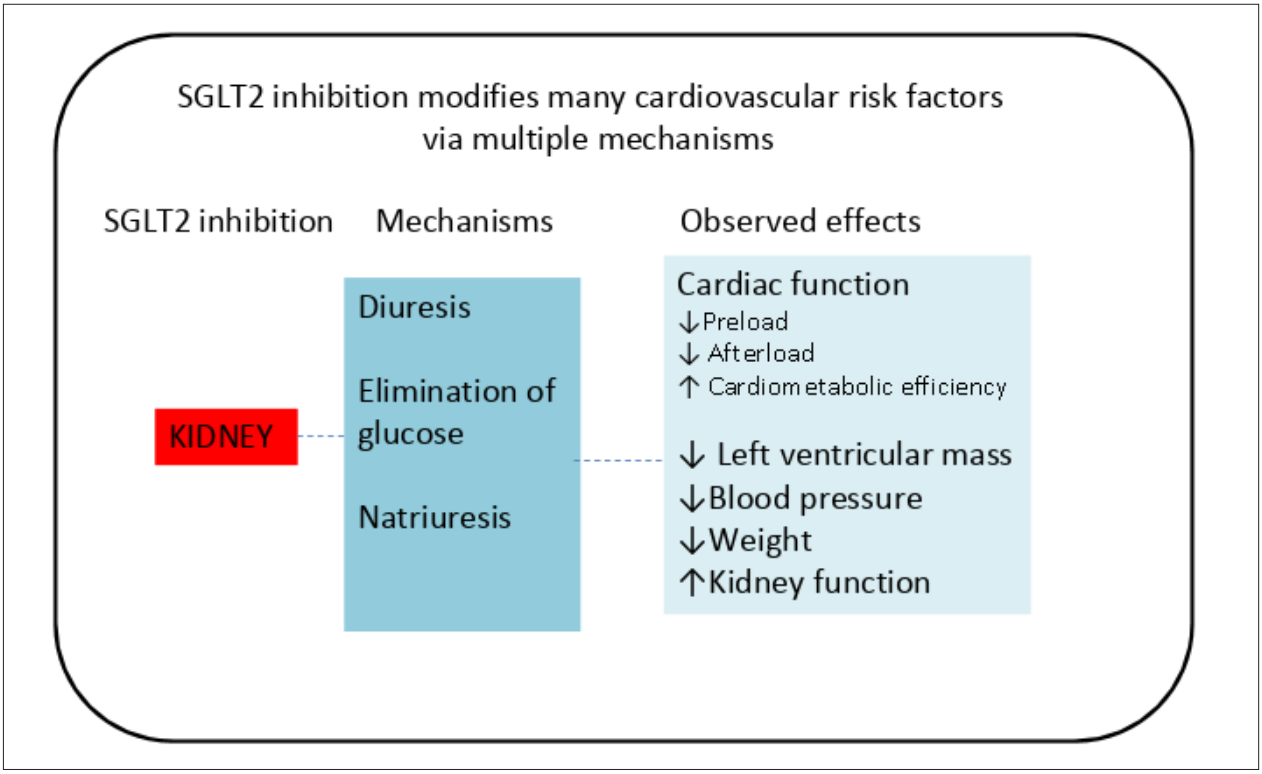

Figure 1 – *SGLT2i: mechanisms of action.*

When assessed in isolation, the other outcomes showed benefits for the group that received the medication. For the combined outcome of cardiovascular mortality and HHF, the HR of HHF was 0.73 (95%CI: 0.61-0.88) and the HR was 0.83 (95%CI: 0.73-0.95). For renal failure or mortality, the HR was 0.53 (95%CI: 0.43-0.66).

There was a HR of 0.86 (95%CI: 0.74-0.99)The results for the combined primary outcome (MACE: CV death, non-fatal MI or non-fatal stroke).

New evidence about HF treatment in patients with and without DM

HF prevention in diabetics

HF is the second leading cause of cardiovascular disease in DM2. The prevalence of HF is 9-22%, which is four times the prevalence in the general population and is generally higher in females (relative risk reduction (RRR) 1.95 vs. 1.75).[16] Recent data suggest that, in DM2 patients, body mass index has a greater impact on the development of HF in than glycated HB itself, which is unlike the AMI/stroke outcome.[16]

Therefore, the different mechanisms of hypoglycemic drugs should be considered for this outcome in general, not just for glycemic control.[17] It has been shown that DPP-4 inhibitors are a neutral class in all aspects of cardiovascular disease. As a class, GLP1 agonists reduced the risk of atherosclerotic cardiovascular disease (reduced AMI and/or stroke).[18] However, SGLT2i showed a definite benefit by reducing HHF.[19] Recently, the DAPA-HF and EMPEROR-Reduced trials demonstrated increased benefits in HF patients (both diabetic and non-diabetic) with reduced ejection fraction. These studies found that, as an add-on therapy to pharmacological treatment optimized for HF, SGLT2i reduced HHF and cardiovascular mortality.[19]

Thus, a meta-analysis of combinations demonstrated that a potential ideal treatment regimen with reduced CV and HF outcomes could be a combination of GLP1-a and SGLT2i in a history of metformin therapy.[17,19]

SGLT2i in ICFER - which, for whom, and when

In the VERTIS-CV trial, SGLT2i (ertugliflozin) reduced hospitalization for HF in diabetic patients with vascular disease due to atherosclerosis.[15] In the EMPEROR-Reduced trial, SGLT2i (empagliflozin) reduced the combined primary outcome of HHF/cardiovascular death and the secondary outcomes HHF and decline in renal function, as well as improved quality of life, reduced glycated hemoglobin and NT-proBNP.[20]

In the DAPA-HF trial, dapagliflozin reduced the combined outcome of hospitalization/urgent visit due to HF and cardiovascular death, the secondary outcomes cardiovascular death/HHF, total HHF/cardiovascular death, all-cause mortality, and improved quality of life.[21] Likewise, in the DECLARE-TIMI trial, dapagliflozin reduced renal events,[14] while in the DAPA-CKD trial it reduced the risk of sustained decline in renal function in patients with chronic kidney

disease, whether diabetic or not.[7] Subanalysis of the DAPA-HF trial showed reduced progression of renal function decline in HF patients,[8] while pre-specified analysis of the EMPA-REG OUTCOME trial showed that SGLT2i (empagliflozin) reduced the progression of renal function decline in diabetics.[3] Finally, in the CREDENCE trial, canagliflozin reduced the progression of renal function decline.[22]

Figure 2 summarizes the unquestionable benefits of SGLT2i (i.e. reduced hospitalization) presented in the main studies.

The most recent SBC Brazilian Heart Failure guideline, coordinated by the Department of Heart Failure (DHF), was published in 2018 and little was known about the role of iSGLT2 in the therapeutic management of HF.[23] It was a consensus in the DHF that the time had come to revisit it. For that purpose, preparatory meetings were held, topic divisions were made among the different collaborators and a virtual meeting took place on December 4, 2020, due to the COVID-19 pandemic. This meeting was attended by renowned experts in the HF area, who provided updates, offered their opinions and included new therapeutic options. The iSGLT2 have been incorporated into the therapeutic management of HF, gathered together in a single table that will be published shortly.

List of participants of the Heart Failure Summit Brazil 2020 / Heart Failure Department - Brazilian Society of Cardiology

Aguinaldo Freitas Junior, Andréia Biolo, Antonio Carlos Pereira Barretto, Antônio Lagoeiro Jorge, Bruno Biselli, Carlos Eduardo Lucena Montenegro, Denilson Campos de Albuquerque, Dirceu Rodrigues de Almeida, Edimar Alcides Bocchi, Edval Gomes dos Santos Júnior, Estêvão Lanna Figueiredo, Evandro Tinoco Mesquita, Fabiana G. Marcondes-Braga, Fábio Fernandes, Fabio Serra Silveira, Felix José Alvarez Ramires, Fernando Atik, Fernando Bacal, Flávio de Souza Brito, Germano Emilio Conceição Souza, Gustavo Calado de Aguiar Ribeiro, Humberto Villacorta Jr., Jefferson Luis Vieira, João David de Souza Neto, João Manoel Rossi Neto, José Albuquerque de Figueiredo Neto, Lídia Ana Zytynski Moura, Livia Adams Goldraich, Luís Beck-da- Silva, Luís Eduardo Paim Rohde, Luiz Claudio Danzmann, Manoel Fernandes Canesin, Marcelo Bittencourt, Marcelo Westerlund Montera, Marcely Gimenes Bonatto, Marcus Vinicius Simões, Maria da Consolação Vieira Moreira, Miguel Morita Fernandes da Silva, Monica Samuel Avila, Mucio Tavares de Oliveira Junior, Nadine Clausell, Odilson Marcos Silvestre, Otavio Rizzi Coelho Filho, Pedro Vellosa Schwartzmann, Reinaldo Bulgarelli Bestetti, Ricardo Mourilhe Rocha, Sabrina Bernadez Pereira, Salvador Rassi, Sandrigo Mangini, Silvia Marinho Martins, Silvia Moreira Ayub Ferreira, Victor Sarli Issa.

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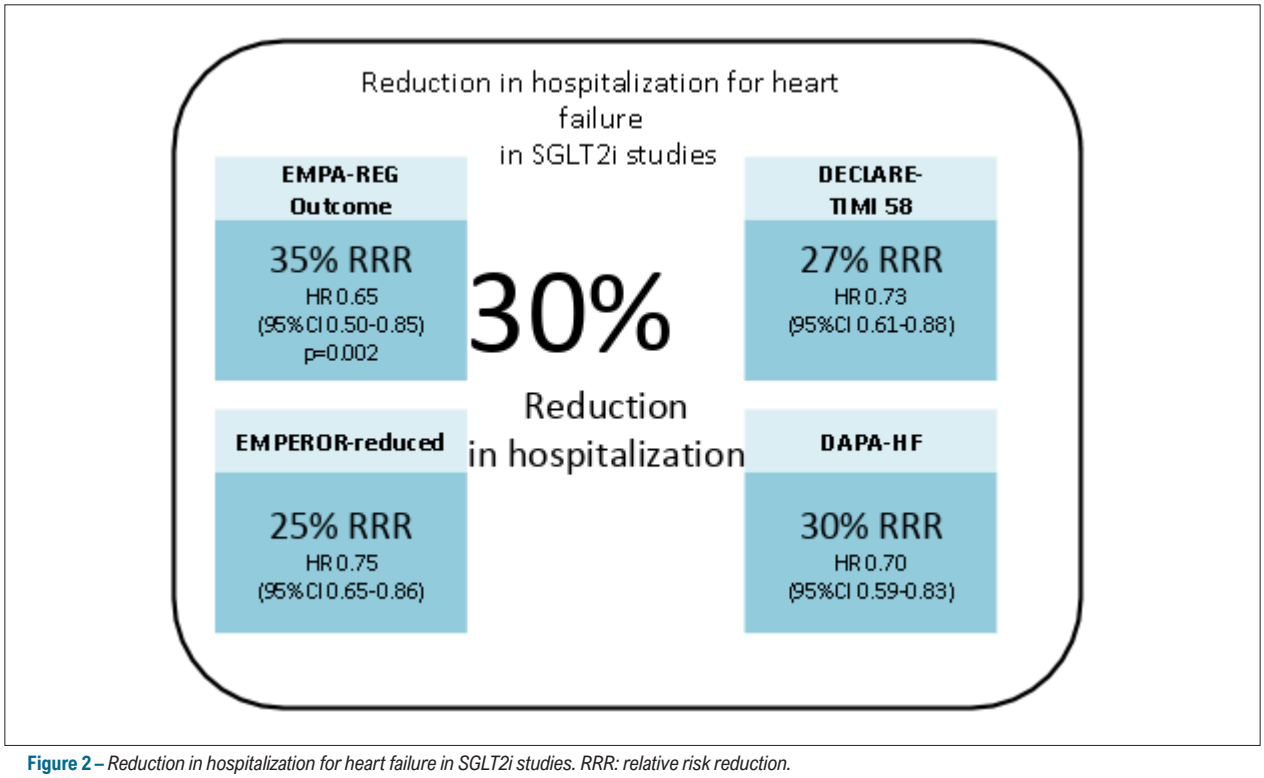

Figure 2 – *Reduction in hospitalization for heart failure in SGLT2i studies. RRR: relative risk reduction.*

Research Letter

Potential Conflict of Interest

Dr. Edimar Bocchi - Consultancy/lecture fee: Boehringer Ingelheim, Astra Zeneca. Research grant: Astra Zeneca. Research projects: Boehringer Ingelheim, Astra Zeneca.

Dr. Lidia Zytynski Moura - Speaker and advisory board at Astra Zeneca.

Dr. Carlos Eduardo Lucena Montenegro - Speaker at Astra Zeneca.

Dr. José Albuquerque de Figueiredo Neto - Speaker at Astra Zeneca.

Dr. Denilson Campos de Albuquerque - Emperor study researcher. Advisory board and speaker to Boehringer Ingelheim and Astra Zeneca.

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References

1. Verna, S., McMurray, J.J.V. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. Diabetologia, 2018.
2. Lopaschuk, GD and Verma S. Mechanisms of Cardiovascular Benefits of Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitors: A State-of-the-Art Review. JACC Basic Transl Sci, 2020; 5(6):632-644.
3. Fitchett D, Inzucchi SE, Cannon CP et al. Empagliflozin Reduced Mortality and Hospitalization for Heart Failure Across the Spectrum of Cardiovascular Risk in the EMPA-REG OUTCOME Trial. Circulation, 2019; 139(11): 1384–1395.
4. Wanner C, Lachin JM, Inzucchi SE et al (2018) Empagliflozin and clinical outcomes in patients with type 2 diabetes mellitus, established cardiovascular disease, and chronic kidney disease. Circulation 137:119–129.
5. Verma S, McMurray JJV, Cherney DZI (2017) The metabolodiuretic promise of sodium-dependent glucose cotransporter 2 inhibition: the search for the sweet spot in heart failure. JAMA Cardiol 2:939–940.
6. Sattar N, McLaren J, Kristensen SL et al. (2016) SGLT2 inhibition and cardiovascular events: why did EMPA-REG Outcomes surprise and what were the likely mechanisms? Diabetologia 59:1333–1339.
7. Ferrannini E, Mark M, Mayoux E (2016) CV protection in the EMPA-REG OUTCOME Trial: a "Thrifty Substrate" hypothesis. Diabetes Care 39:1108–1114.
8. Baartscheer A, Schumacher CA, Wust RC et al. Empagliflozin decreases myocardial cytoplasmic Na+ through inhibition of the cardiac Na+ /H+ exchanger in rats and rabbits. Diabetologia 2017; 60:568–573.
9. Fedak PW, Verma S, Weisel RD, Li RK. Cardiac remodeling and failure from molecules to man (part II). Cardiovasc Pathol 2005;14: 49–60.
10. Packer M. Do sodium-glucose co-transporter-2 inhibitors prevent heart failure with a preserved ejection fraction by counterbalancing the effects of leptin? A novel hypothesis. Diabetes Obes Metab. 2018; 20(6):1361-1366.
11. Packer M. Lessons learned from the DAPA-HF trial concerning the mechanisms of benefit of SGLT2 inhibitors on heart failure events in the context of other large-scale trials nearing completion. Cardiovasc Diabetol. 2019;18(1):129.
12. Zinman B, Wanner C, Lachin JM et al. for the EMPA-REG OUTCOME Investigators: Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes N Engl J Med 2015; 373:2117-2128
13. Neal B, Perkovic V, Mahaffey KW et al. CANVAS Program Collaborative Group. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med. 2017 Aug 17;377(7):644-657. doi: 10.1056/NEJMoa1611925
14. Wiviott SD, Raz I, Bonaca MP et al. DECLARE–TIMI 58 Investigators. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019 Jan 24;380(4):347-357. doi: 10.1056/NEJMoa1812389
15. Cannon CP, Pratley R, Dagogo-Jack S et al. VERTIS C Investigators. Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. N Engl J Med. 2020 Oct 8;383(15):1425-1435. doi: 10.1056/NEJMoa2004967.
16. Ohkuma T, Komorita Y, Peters, SAE. et al. Diabetes as a risk factor for heart failure in women and men: a systematic review and meta-analysis of 47 cohorts including 12 million individuals. Diabetologia 62, 1550–1560 (2019).
17. Rawshani A, Rawshani A, Franzén S, et al. Risk Factors, Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2018;379(7):633-644. doi:10.1056/NEJMoa1800256
18. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials Lancet. 2019 Jan 5;393(10166):31-39. doi:10.1016/S0140-6736(18)32590-X
19. Sinha B, Ghosal S. Meta-analyses of the effects of DPP-4 inhibitors, SGLT2 inhibitors and GLP1 receptor analogues on cardiovascular death, myocardial infarction, stroke and hospitalization for heart failure. Diabetes Res Clin Pract. 2019;150:8-16. doi:10.1016/j.diabres.2019.02.014
20. Packer M, Anker SD, Butler J, Bocchi E et al. EMPEROR-Reduced Trial Investigators. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020 Oct 8;383(15):1413-1424. doi: 10.1056/NEJMoa2022190.
21. McMurray JJV, Solomon SD, Inzucchi SE et al DAPA-HF Trial Committees and Investigators. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019 Nov 21;381(21):1995-2008. doi: 10.1056/NEJMoa1911303
22. Perkovic V, Jardine MJ, Neal B, et al. CREDENCE Trial Investigators. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med. 2019 Jun 13;380(24):2295-2306. doi: 10.1056/NEJMoa1811744.
23. Comitê Coordenador da Diretriz de Insuficiência Cardíaca, Rohde LEP, Montera MW, Bocchi EA, et al. Diretriz Brasileira de Insuficiência Cardíaca Crônica e Aguda. Arq Bras Cardiol. 2018 Sep;111(3):436-539

The Challenges of Heart Failure Yesterday, Today and Tomorrow and the 20 Years of DEIC

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The Department of Heart Failure of the Brazilian Society of Cardiology (DEIC) completes 20 years in 2020 and represents a robust legacy of scientific activities and associations of Brazilian cardiology.

Its foundation represented an important milestone in the fight against heart failure (HF), a complex progressive and often fatal clinical syndrome. HF should be addressed in a multidisciplinary way, supported by translational science and good practices (clinical guidelines and protocols), involving patients, families, caregivers, managers and the whole society, in view of its social impacts in Brazil and in the world.

With population aging and increased survival of patients with cardiovascular diseases, the prevalence of HF is increasing globally, with about 26 million people affected worldwide, in addition to thousands of undiagnosed cases.[1] HF is the leading cause of hospitalization in the world and this results in an overload at all levels of care. It is estimated that HF affects approximately 2.5 million people in Brazil and a recent study has revealed its financial impact in Brazil, with an estimated expenditure of BRL 22.1 million/US$ 6.8 million in 2015.[2] Besides, the study revealed a substantial loss of well-being. Of the 521,941 years of life lost adjusted for disability, adjusted for comorbidities, there are 270,806 years of healthy life lost due to disability and 251,941 years of life lost as a result premature death.

DEIC was created under the leadership of Professor Maria da Consolação Vieira Moreira and had the support of Professor Gilson Soares Feitosa, then president of the Brazilian Society of Cardiology (1999–2001), mobilizing leaders from all over Brazil, particularly the professor Edimar Alcides Bocchi, leading the Heart Failure Study Group (GEIC) in 2000. On July 6, 2001, chaired by Professor Maria da Consolação, the 1st Brazilian Symposium on Heart Failure was held in Belo Horizonte during the 12_{th} Congress of Society of Cardiology of Minas Gerais (Chart 1).

With a successful history, built by HF leaders in Brazil, due to the growing number of members and relevance in scientific productivity, GEIC gradually became the Department of Heart Failure (DEIC), finally created in 2011, in the administration of Professor Fernando Bacal. This important fact occurred during the 10th Brazilian Congress of Heart Failure, celebrating 11 years since the foundation of GEIC, in the city of Belo Horizonte (Chart 1).

Since its foundation, congresses of high scientific quality and international exchange have been held annually, providing the Brazilian medical community with the improvement of the state of the art of multidisciplinary care and treatment of HF. In the last congresses, we have had more than 1,000 registrants and about 200 papers have been presented, allowing exchanges of experiences with renowned specialists from various locations, from Brazil and the world. In 2020, due to the impacts of the pandemic of the new coronavirus, DEIC, in a revolutionary way, held a virtual congress — Heart Failure Summit Brazil 2020 — to present and discuss the main advances that, in the last 12 months, transformed the HF and will be reasons for changes to our HF Guideline due to be released in the first half of 2021 (Chart 2).

Fulfilling its scientific role, DEIC has an important project of Guidelines and Updates, intended to demonstrate strategies and propose evidence-based recommendations. The first HF Guideline, in the form of a consensus, was published in 1992, before the DEIC was created. It was published in São Paulo and was coordinated by the esteemed master Dr. Michel Batlouni (Chart 3).

In 2014, the 1st Brazilian Registry of Heart Failure — Clinical Aspects, Quality of Care and Hospital Outcomes — BREATHE was published. It was organized by Professor Denilson Campos de Albuquerque and outlined a picture of HF in hospitalized patients around the country, identifying the incorporation of diagnostic methods and therapeutic interventions. The Brazilian Registry of Takotsubo Syndrome, led by Professor Marcelo Westerlund Montera, is currently underway.

DEIC has taken a contemporary stance and expanded its technical and scientific scope, working on chronic HF,

Keywords

Heart Failure/trends; Demographic Aging; Translational Medical Research; Guidelines; Scientific Production.

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acute HF (emergency room/cardiovascular intensive care unit), advanced HF (heart transplantation/mechanical circulatory support), HF in children and adolescents and cardiomyopathies. In Cardiomyopathy, we had the pioneering spirit of teachers Marco Aurélio Dias, Francisco Manes Albanesi, Raul Carlos Pareto Junior, Antonio Carlos Pereira Barreto, Charles Mady, who helped train leaders in HF.

Over the last five years, the following study groups were created in important thematic areas: GETAC (Heart Transplant and Mechanical Circulatory Assistance Study Group), GEICPED (Study Group on HF in Children and Adults with Congenital Heart Diseases) and GEMIC (Cardiomyopathy Study Group). From a modern perspective, we are organizing ourselves to build an ecosystem for inter and multidisciplinary collaboration and cooperation in different sub-areas, which has been a trend in the following international HF societies: HFA-ESC (https://www.escardio.org/Sub-specialty-communities/Heart-Failure-Association-of-the-ESC-(HFA) and HFSA (https://hfsa.org/) (Chart 4).

In 2004, the GEIC for the Youth was created to encourage the scientific and associative development of young cardiologists interested in HF. The first meeting held at the Brazilian Congress of Heart Failure in Salvador (2004), since then, has been changing each year and adding new leaders and now bringing innovation and entrepreneurship to our attendees.

Reaffirming its social role, with community actions and health policies, in the 73rd Brazilian Congress of Cardiology (2018), DEIC president Salvador Rassi and scientific director Evandro Tinoco Mesquita made official the National Day of Alert against Heart Failure,[3] celebrated on the 9th of July. The date was chosen because it was the day of birth of Carlos Chagas, our patron. This first "modern cardiologist" confirms the quote from the late Professor Nelson Botelho, as he used a translational view bringing the bench closer to the bed and connecting a look at population health in Chagas disease. Besides, we created the Carlos Chagas commendation from DEIC for colleagues outstanding in teaching/education, assistance, innovation, science and associations. In collaboration with REBRIC (Brazilian Network of Heart Failure) we work not only with alerts against HF, but also with the application of literacy, building tools for self-care and improvement of clinical outcomes (https://www.rebric.com.br/).

The next decade brings us new challenges: firstly, cementing the paths to a new area of expertise in cardiology — the HF specialist. In the present decade, in line with a contemporary view well established in other countries, several initiatives were introduced to promote and train HF specialists, ensuring education with technical and scientific quality.

In addition, a broader look at prevention in HF involves understanding the model of chronic cardiometabolic disease,[4] making it essential to combine systemic arterial hypertension, obesity, dyslipidemia and diabetes mellitus in the genesis, progression and treatment of HF. Lastly, the need for comprehensive care of HF, involving general practitioners, geriatricians, internists, intensivists and palliative care specialists. Besides, advances in artificial intelligence,[5] digital medicine and genomics are building personalized cardiovascular medicine in HF that will transform the concepts of prevention, diagnosis and treatment, as it has been developed in cardiac amyloidosis and hereditary cardiomyopathies. The COVID-19 pandemic further establishes the concept of cardiovascular surveillance,[6,7] as studies that used cardiac resonance imaging found that, even in people without symptoms, there is a degree of aggression to the heart that should be studied regarding the future risk of developing dilated cardiomyopathy and symptomatic heart failure.

To celebrate the 20 years of DEIC, we gathered the achievements of our brilliant story and applauded the cardiologists, whose work and dedication were responsible for the excellence and success of the department. It is a great honor to revive and revere the past, envisioning a future with the challenge of producing new ideas and renewing ourselves (Figure 1).

Chart 1 – GEIC/DEIC Presidents.

First GEIC Board	GEIC/DEIC Presidents
President: Edimar Alcides Bocchi	**2000-2001**: Edimar Alcides Bocchi
Vice President: Denílson Campos Albuquerque	**2002-2003:** Edimar Alcides Bocchi
Secretary: Fábio Vilas-Boas Pinto	**2004-2005:** Fábio Vilas-Boas Pinto
Scientific Director: Maria da Consolação V Moreira	**2006-2007:** Nadine Oliveira Clausell
Members of the Scientific Committee:	**2008-2009:** Marcelo Westerlund Montera
Evandro Tinoco Mesquita	**2010-2011:** Fernando Bacal
Dirceu Rodrigues de Almeida	**2012-2013:** João David de Souza Neto
Fernando Bacal	**2014-2015:** Dirceu Rodrigues de Almeida
Marco Aurélio Silva (*in memoriam*)	**2016-2017:** Luis Eduardo Paim Rohde
Nadine Oliveira Clausell	**2018- 2019:** Salvador Rassi
Salvador Rassi	**2020-2021:** Evandro Tinoco Mesquita

Chart 2 – GEIC/DEIC Symposia and Congresses.

1st Brazilian Symposium on Heart Failure	**10th Brazilian Congress of Heart Failure**
July 6, 2001 - Belo Horizonte MG	June 9 to 11, 2011 — Belo Horizonte MG
1st Brazilian Symposium on Heart Failure	**11th Brazilian Congress of Heart Failure**
November 28 to 30, 2002 - Rio de Janeiro RJ	May 31 to June 2, 2012 — Gramado RS
2nd Brazilian Symposium on Heart Failure	**12th Brazilian Congress of Heart Failure**
November 21, 2003 - São Paulo SP	June 6 to 8, 2013 — Porto de Galinhas PE
3rd Brazilian Symposium on Heart Failure	**13th Brazilian Congress of Heart Failure**
November 25 to 27, 2004 - Salvador BA	August 7 to 9, 2014 — Ribeirão Preto SP
4th Brazilian Symposium on Heart Failure	**14th Brazilian Congress of Heart Failure**
June 23 to 25, 2005 — Gramado RS	June 18 to 20, 2015 — Rio de Janeiro RJ
5th Brazilian Congress of Heart Failure	**15th Brazilian Congress of Heart Failure**
July 06 to 08, 2006 — Goiânia GO	August 11 to 13, 2016 — Campos do Jordão SP
6th Brazilian Congress of Heart Failure	**16th Brazilian Congress of Heart Failure**
June 28 to 30, 2007 — Fortaleza CE	May 11 to 13, 2017 — Gramado RS
7th Brazilian Congress of Heart Failure	**17th Brazilian Congress of Heart Failure**
June 26 to 28, 2008 — Búzios RJ	June 28 to 30, 2018 — Goiânia GO
8th Brazilian Congress of Heart Failure	**18th Brazilian Congress of Heart Failure**
June 11 to 13, 2009 - São Paulo SP	August 8 to 10, 2019 — Fortaleza CE
9th Brazilian Congress of Heart Failure	**Heart Failure Summit Brazil 2020 (DIGITAL)**
June 10 to 12, 2010 — Curitiba PR	September 19, 2020

Chart 3 – Consensuses and Guidelines

- Brazilian Consensus for the Treatment of Heart Failure — 1992
- Heart Failure Guidelines and Updates: 1999, 2002, 2005, 2009, 2012, 2018
- Heart Transplant Guidelines: 1999, 2010, 2018
- Onco-Oncology Guideline: 2011
- Guideline on Myocarditis and Pericarditis: 2013
- Guideline on Heart Failure and Heart Transplantation in Fetuses, Children and Adults with Congenital Heart Diseases: 2014
- Guideline on Mechanical Circulatory Assistance: 2016

Chart 4 – Medical Residency Programs and Specialization Courses in Advanced HF and Heart Transplantation

1. Instituto Dante Pazzanese de Cardiologia
Continuing Education on Heart Transplant in Adults
2. Sociedade Beneficente Israelita Brasileira Hospital Albert Einstein
Continuing Education on Transplant and Heart Failure
3. Instituto do Coração (Incor) - HCFMUSP
- Specialized complementation program: Congestive Heart Failure and Ventricular Assist Devices
- Heart Transplant Residency
4. Universidade Federal de São Paulo - UNIFESP
Medical Residency at Escola Paulista de Medicina - Optional Year: Heart Transplant
5. Hospital de Clínicas de Porto Alegre
Medical Residency - Additional Year: Heart Transplant
6. Instituto de Cardiologia do Rio Grande do Sul/ Fundação Universitária de Cardiologia
Medical Residency - Additional year for heart transplant education
7. Instituto de Medicina Integral Professor Fernando Figueira – IMIP
Specialized Complementation Program — COMESP. Heart Transplant and Advanced Heart Failure.

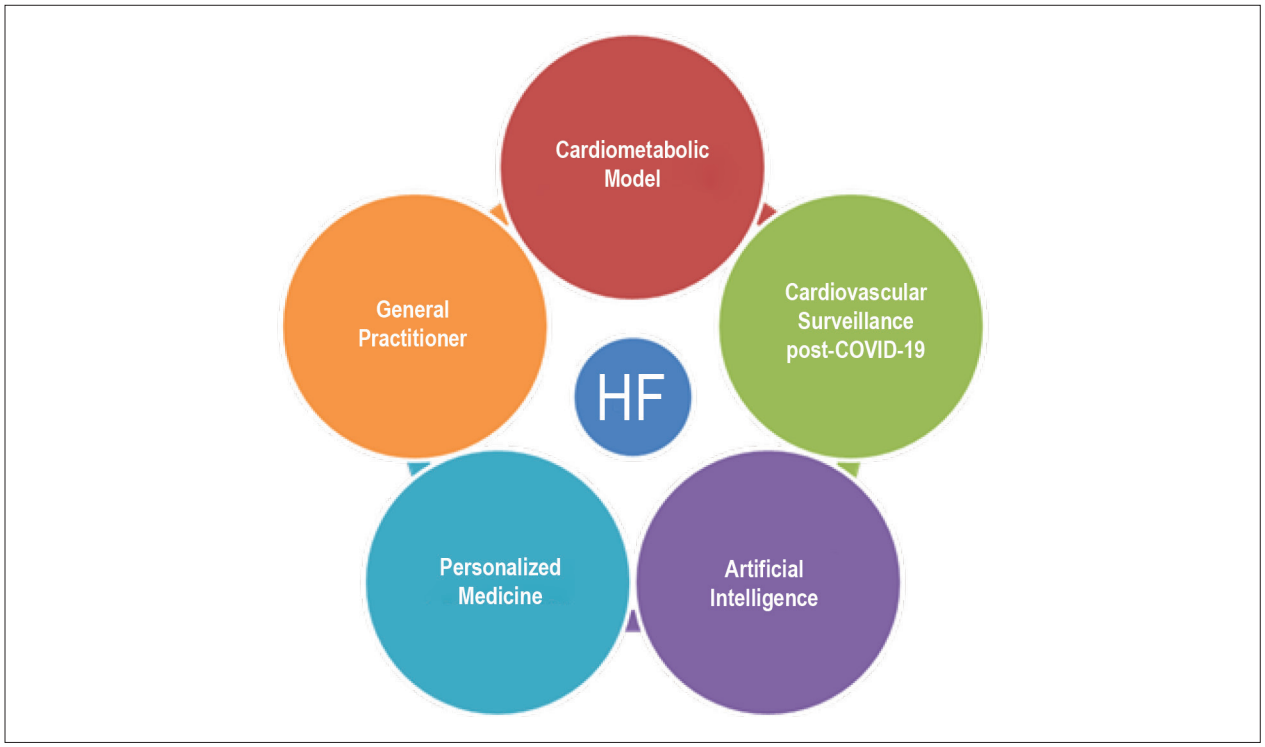

Figure 1 – *Challenges of DEIC 2020–30*

Author contributions

Conception and design of the research and Critical revision of the manuscript for intellectual content: Mesquita ET, Mendes AP, Moura L, Figueiredo Neto JA, Marcondes-Braga FG, Bacal F, Moreira MCV, Clausell NO; Acquisition of data: Mesquita ET, Mendes AP, Moreira MCV; Analysis and interpretation of the data: Mesquita ET, Mendes AP; Writing of the manuscript: Mesquita ET, Mendes AP, Moura L, Figueiredo Neto JA, Marcondes-Braga FG, Bacal F, Clausell NO.

Potential Conflict of Interest

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Study Association

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

References

1. Ferreira JP, Krausy S, Mitchellz S, Perel P, Pineiro D, Chioncel O, et al. et al. World Heart Federation Roadmap for Heart Failure. Global Heart. 2019; 14(3):197-214.
2. Stevens B, Pezzullo L, Verdian L, Tomlinson J, George A, Bacal F. Os custos das doenças cardíacas no Brasil. Arq. Bras. Cardiol. 2018; 111(1):29-36.
3. Mesquita ET, Grippa de Souza ALAA, Rassi S. Dia de alerta da insuficiência cardíaca: um tributo ao gênio Carlos Chagas. Arq Bras Cardiol. 2019; 113(1):5-8.
4. Mechanick JI, Farkouh ME, Newman JD, Garvey T. Cardiometabolic-based chronic disease adiposity and dysglycemia drivers. J Am Coll Cardiol. 2019; 75(5):525-38.
5. Souza Filho EM, Fernandes FA, Soares CLA, Seixas FL, Santos AA, Gismondi RA, Inteligência artificial em cardiologia: conceitos, ferramentas e desafios – "quem corre é o cavalo, você precisa ser o jóquei". Arq Bras Cardiol. 2020; 114(4):718-25.
6. Figueiredo Neto JA, Marcondes-Braga FG, Moura LZ, Figueiredo AM, Figueiredo V, Rocha RM, et al. Doença de coronavírus-19 e o miocárdio. Arq Bras Cardiol. 2020; 114(6):1051-7.
7. Fernandes F, Ramires FJA, Fernandes FD, Simões MV, Mesquita ET. Afecções pericárdicas em pacientes com COVID-19: uma possível causa de deterioração hemodinâmica. Arq Bras Cardiol. 2020; 115(3):569-573.

Radiologic-Electrocardiography Correlation in Wellens Syndrome

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Wellens Syndrome,[1] also known as "Anterior Descending Coronary T-wave syndrome", was described in 1982 by Dr. Henrick Joan Joost (Hein) Wellens, a Dutch physician who also contributed to the characterization of the reentry mechanism in Wolff–Parkinson–White syndrome (WPWS).

Originally described during hospital admission (60% at admission and 40% at the follow-up) of patients with unstable angina, it was characterized by the occurrence of 2 electrocardiographic patterns, with pattern A in 25% of patients and B in 75% of patients.

Pattern A shows the occurrence of biphasic T-wave in leads V2 and V3 and can be found from V1 to V6, whereas pattern B shows inverted and symmetrical T-wave in V2 and V3, with both patterns occurring without the association of Q-waves or pathological QS complexes, with normal R-wave progression and without evidence of ventricular hypertrophy.

These electrocardiographic findings are not very sensitive (69%) but are highly specific (89%)[2] for important obstructive disease in the proximal segment of the anterior descending coronary artery, which if not properly addressed, can determine extensive anterior infarction and high risk of mortality.

Therefore, the performance of provocative ischemia tests is discouraged in the presence of electrocardiographic findings of Wellens Syndrome.[3]

In our service, we conducted the investigation of two patients: patient (1) male gender, smoker, complaining of intermittent atypical pain at rest (CCS-IV) who, after undergoing a coronary artery angiotomography as the first diagnostic test, had an episode of pain, being referred to a 12-lead electrocardiogram that showed pattern A of Wellens Syndrome. Female patient (2), with CCS2 angina, with a positive family history (mother had an infarction at 35 years old) came with an electrocardiogram showing pattern B of Wellens Syndrome (Figure 1, 1A and 1B), and the angiotomography confirmed the same findings as in patient 1. Both angiotomography images show segmental plaque, with signs of vulnerability determining significant proximal obstruction of the proximal segment of the anterior descending artery, promptly at the reading (Figures 2, 3, 4 and 5). The plaque with characteristics of vulnerability was partially calcified, showing a large volume, positive remodeling and low attenuation.

After being referred to the emergency department, the patients' condition was confirmed at the coronary angiography, and an anterior descending artery angioplasty was successfully performed (Figure 6).

To the best of our knowledge, this is the first report of an electrocardiogram-angiotomography correlation for Wellens Syndrome.

Author contributions

Conception and design of the research: Fonseca EKUN, Heringer Filho N, Montemor ML, Ávila LFR, Rochitte CE; Acquisition of data: Fonseca EKUN, Heringer Filho N, Rochitte CE; Analysis and interpretation of the data: Fonseca EKUN, Heringer Filho N, Ávila LFR, Rochitte CE; Writing of the manuscript: Fonseca EKUN, Heringer Filho N, Montemor ML; Critical revision of the manuscript for intellectual content: Fonseca EKUN, Heringer Filho N, Montemor ML, Ávila LFR, Rochitte CE.

Potential Conflict of Interest

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

Sources of Funding

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Study Association

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

Ethics approval and consent to participate

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

Keywords

Electrocardiography; Coronary Vessels; Computed Tomography Angiography; Myocardial Infarction; Coronary Angiography.

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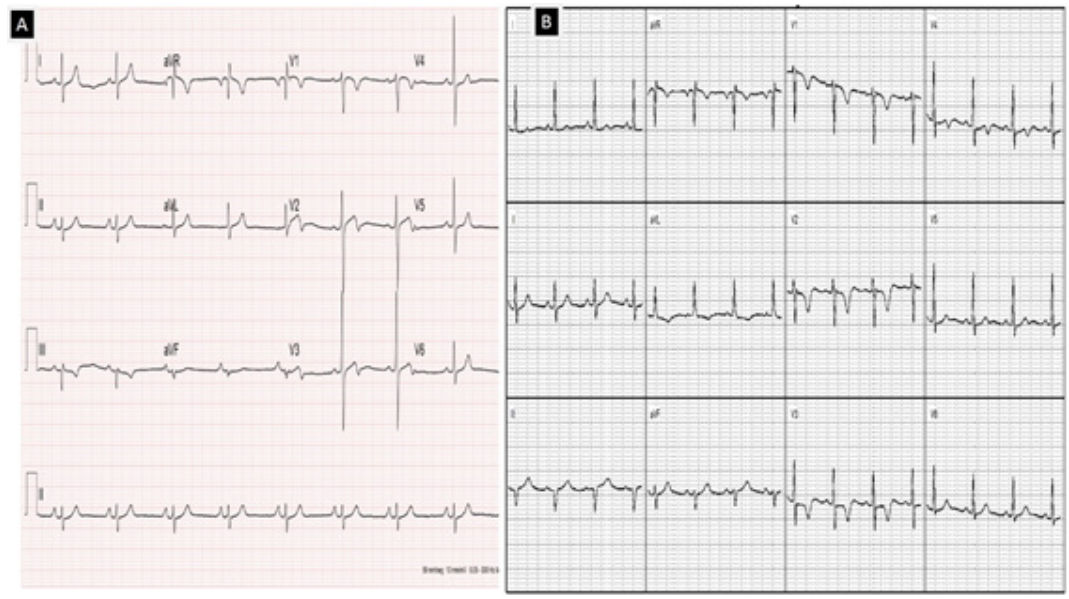

Figure 1 – *ECG images of both patients, showing the patterns of Wellens syndrome (Patient 1 - A / Patient 2 - B).*

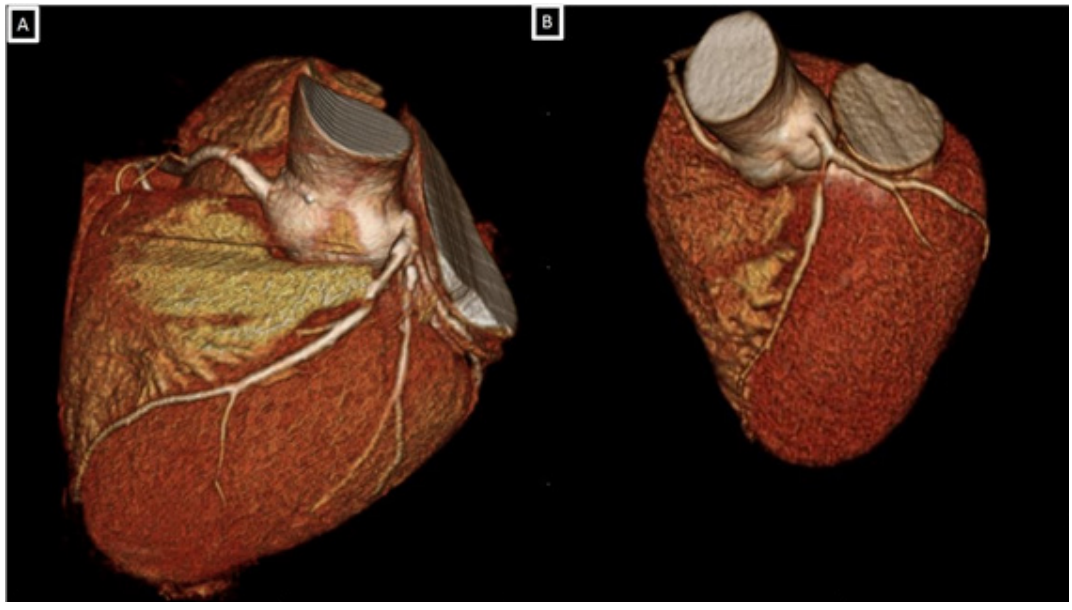

Figure 2 – *Three-dimensional reconstruction (volume-rendering technique) showing important luminal reduction in the proximal segment of the anterior descending artery in both patients (Patient 1 - A / Patient 2 - B).*

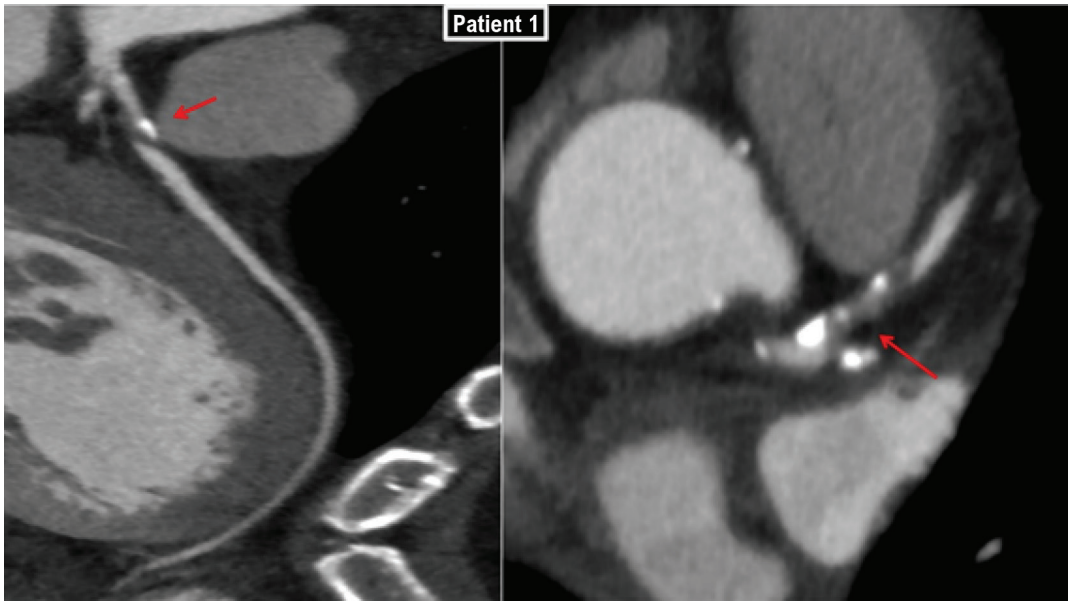

Figure 3 – *Angiotomography of the coronary arteries. Left image - curved reconstruction showing mixed plaque in the proximal segment of the descending artery (red arrows), resulting in marked luminal reduction. Right image - axial image of the proximal segment of the anterior descending artery, on the lesion topography (red arrow), showing critical luminal reduction in patient 1.*

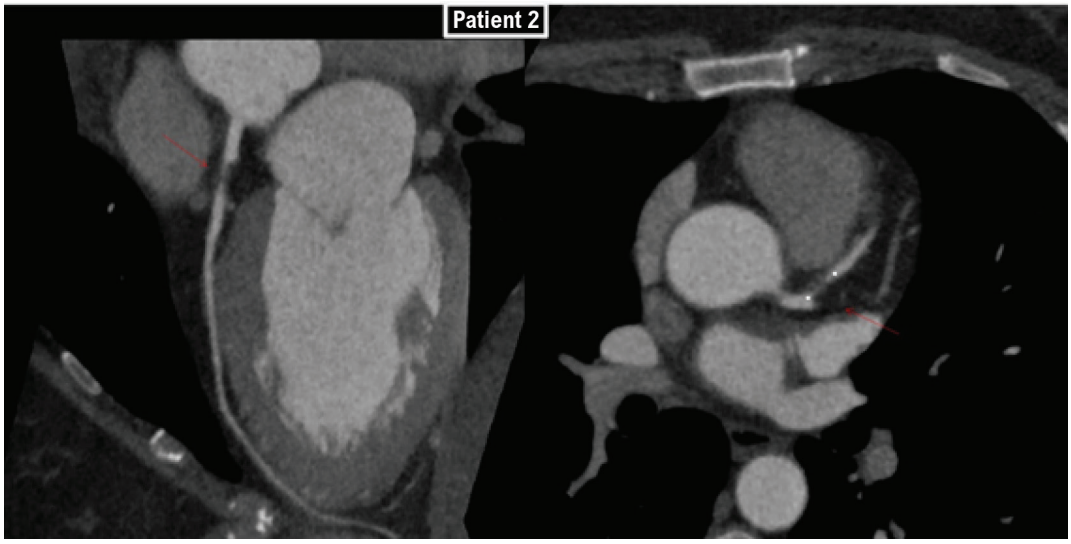

Figure 4 - *Angiotomography of the coronary arteries. Left image - curved reconstruction showing mixed plaque in the proximal segment of the descending artery (red arrows), resulting in marked luminal reduction. Right image - axial image of the proximal segment of the anterior descending artery, on the lesion topography (red arrow), showing critical luminal reduction in patient 2.*

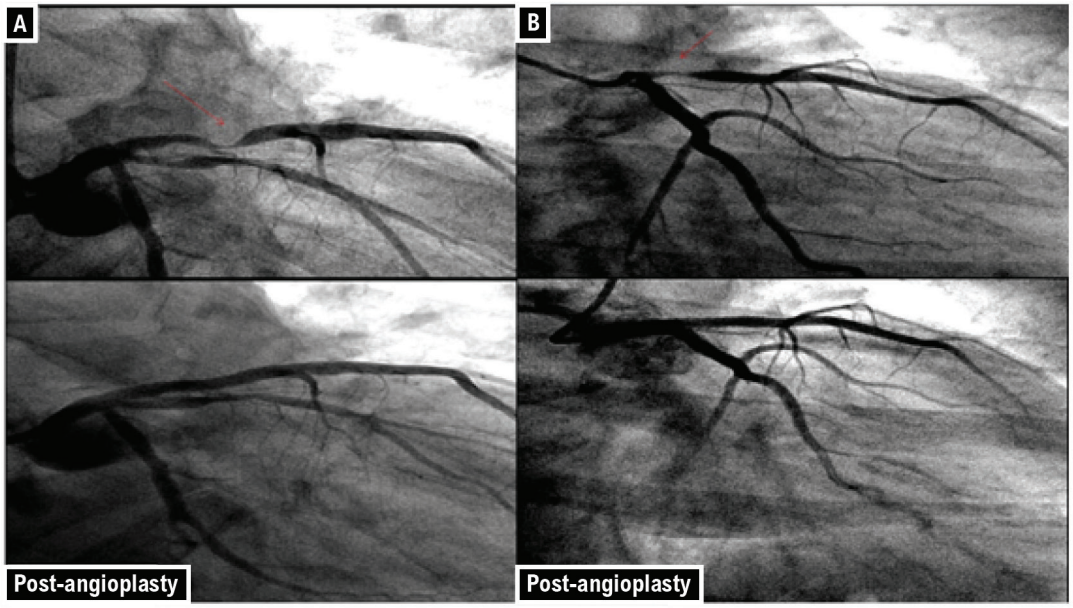

Figure 5 - *Coronary angiography. Top image - critical lesion in the proximal segment of the descending artery, confirming the tomographic findings. Bottom image – post-treatment image showing effective recanalization of the lesion. (Patient 1 - A / Patient 2 - B)*

References

1. de Zwann C, Bar FW, Wellens HJ: Characteristic electrocardiographic pattern indicating a critical stenosis high in left anterior descending coronary artery in patients admitted because of impending myocardial infarction. Am Heart J 1982;103(4 Pt2):730-6.
2. Haines DE, Raabe DS, Gundel WD, Wackers FJ. Anatomic and prognostic significance of new T-wave inversion in unstable angina. Am J Cardiol 1983;52(1):14–8.
3. Rhinehardt J, Brady WJ, Perron AD, Mattu A. Electrocardiographic manifestations of Wellens syndrome. Am J Emerg Med. 2002 Nov;20(7):638-43.