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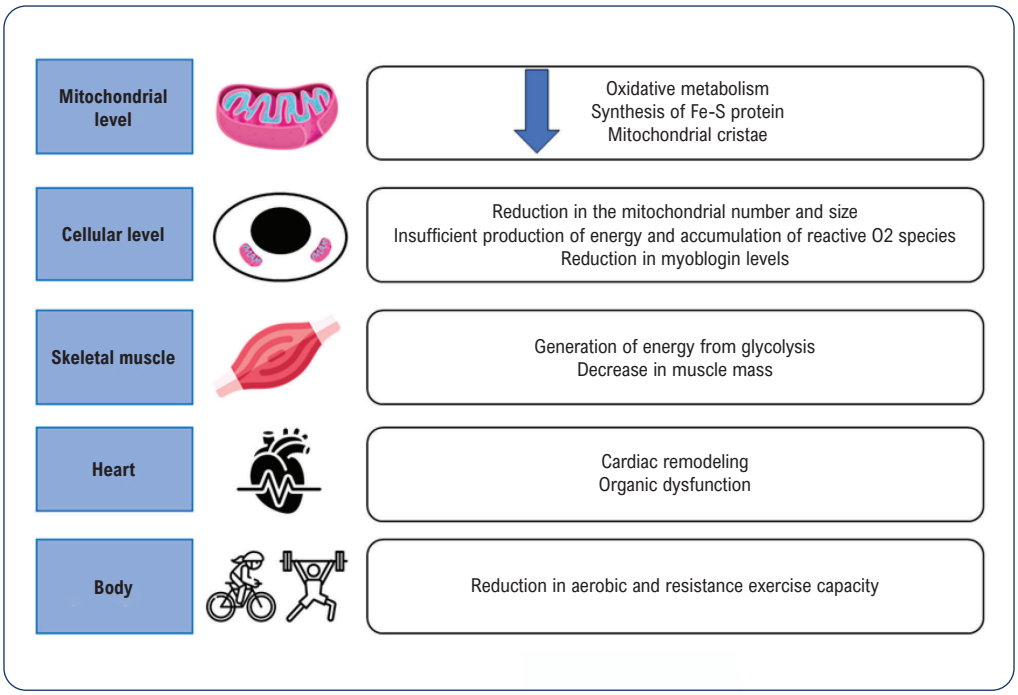

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Original Article

What Should be the First-line Treatment for the Closure of Hemodynamically Significant Patent Ductus Arteriosus in Premature Infants?

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Abstract

Background: **It is important which medicine to use as a first-line treatment to close the duct.**

Objectives: **The aim of this study is to compare the effectiveness and side effects of intravenous (IV) forms of ibuprofen and paracetamol and to contribute to the literature investigating the first drug selected in the medical treatment of patent ductus arteriosus (PDA).**

Methods: **Our study was conducted between January 2017 and December 2019. Premature infants with birth weight (BW) ≤1500 g and gestational age (GA) ≤32 weeks were included in the study. In the study period, all infants with hemodynamically significant patent ductus arteriosus (hsPDA) were given rescue intravenous (IV) ibuprofen as a primary medical treatment or IV paracetamol treatment if there were contraindications for ibuprofen. The patients were divided into two groups: patients receiving IV ibuprofen and patients receiving IV paracetamol.**

Results: **Of these patients, 101 were given IV paracetamol and 169 were given IV ibuprofen. The success rate of PDA closure with first-course treatment was 74.3% in the IV paracetamol group and 72.8% in the IV ibuprofen group (p=0.212).**

Conclusions: **Our results show that IV paracetamol is as effective as IV ibuprofen in the first-line treatment of hsPDA, and can become the preferred treatment for the management of hsPDA.**

Keywords: **Infant, Premature; Ductus Arteriosus, Patent/surgery; Infant, Low Birth Weight; Ibuprofen/therapeutic use; Acetaminophen/therapeutic use.**

Introduction

Hemodynamically significant patent ductus arteriosus (hsPDA) is a common cause of morbidity and mortality affecting more than 40% of premature babies.[1] Prolonged hsPDA disrupts systemic hemodynamics causing negative clinical consequences such as respiratory distress syndrome (RDS), pulmonary hemorrhage, bronchopulmonary dysplasia (BPD), decrease in cerebral oxygenation, neurodevelopmental maturation disorder, intraventricular hemorrhage (IVH), acute renal failure, nutritional intolerance, necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), sepsis, and prolonged length of hospital stay. Therefore, it needs to be treated. If clinical signs of PDA exist, it should be treated.[1,2] Despite being associated with all these negative outcomes, a causative relationship has been questioned since some studies did not show reduction of most of these comorbidities or its consequences with treatment of ductus arteriosus. It is noteworthy that these studies were not designed to define the role of the ductus arteriosus (DA) in the prediction of adverse clinical outcomes but there are still many controversies concerning the treatment (pharmacological, surgical, percutaneous), timing, and the specific subgroups of premature infants that would benefit from the closure of DA.[3-7]

The most commonly used drugs aiming at pharmacological closure are cyclooxygenase (COX) inhibitors, mainly indomethacin and ibuprofen, which block the conversion of arachidonic acid to prostaglandins (PG). The success reported with ibuprofen in the treatment of hsPDA is 70–85%.[2] Negative side effects of ibuprofen and indomethacin therapy such as peripheral vasoconstriction, gastrointestinal bleeding and perforation, decreased platelet aggregation, hyperbilirubinemia and kidney failure have been reported, although they are rare in clinical practice.[1]

Paracetamol, a PG synthase inhibitor, can also be used in the treatment of hsPDA when COX inhibitors are contraindicated or ineffective and have potential side effects.[2] Paracetamol has become an increasingly common alternative to ibuprofen, and studies on paracetamol have also been reported to be successful.[8] The pharmacological treatment

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of hsPDA remains challenging. Reducing the emergence of adverse effects and the need for surgical ligation in this area has strengthened the purpose of identifying other suitable drugs that are safer and more effective than ibuprofen for premature babies.[9] In previous studies comparing the effectiveness of paracetamol and ibuprofen therapy for hsPDA, oral forms have been used.[1,2,10-15] Based on these studies, recent a Cochrane metanalysis states that studies are needed before any suggestions are made for routine use of paracetamol in the treatment of PDA in the newborns. When the results of the included studies were combined, the success rate for paracetamol to close a PDA was higher than that of placebo and similar to that of ibuprofen and indomethacin.[16]

Paracetamol seems to be successful for hsPDA due to possibly fewer side effects as a recovery option where COX inhibitors fail. However, in the first-line treatment of hsPDA, information on the success rate of paracetamol compared to ibuprofen is lacking. Therefore, in this study, we aimed to compare the efficacy and safety of IV ibuprofen and IV paracetamol for pharmacological closure of PDA in premature infants.

Methods

Study Design

This study was conducted between January 2017 and December 2019 in the neonatal intensive care unit (NICU) of Ankara Bilkent City Hospital. This study was designed retrospectively. Ethical committee approval was obtained from the local ethical committee prior to the study. Preterm infants with gestational age (GA) ≤32 weeks, birth weight (BW) ≤1500 g, postnatal age ≥48 hours, and diagnosed with hsPDA were enrolled. Preterm infants with major congenital anomaly, congenital heart disease, ductus dependent congenital heart disease, who died within the first 48 hours after birth, were excluded from the study.

Demographic and Clinical Characteristics

Perinatal variables including GA, BW, gender, Apgar scores (1st and 5th minutes), antenatal steroids administration, 2- and 3-course paracetamol treatment, PDA ligation, gastrointestinal bleeding, pulmonary hemorrhage, RDS, IVH (grade ≥3), NEC (grade≥2), moderate or severe BPD, ROP requiring laser therapy, early-onset neonatal sepsis (EOS), late-onset sepsis (LOS), duration of non-invasive ventilation (NIV), mechanical ventilation (MV) and oxygen (O_2) supplementation, day of full enteral feeding achievement, length of hospital stay and mortality were recorded for all infants.

EOS was defined as ≤72 hours and LOS >after 72 hours in preterm infants hospitalized in the NICU.[17] RDS was diagnosed as requirement for surfactant administration.[18] IVH was searched by cranial ultrasonography performed during the first 7 days of life (intraparenchymal hemorrhage + IVH, large IVH).[19] Bell's criteria were used for the diagnosis and staging of NEC.[20] Infants receiving ≥30% oxygen with/without any positive pressure at postmenstrual age of 36 weeks were diagnosed as moderate or severe BPD.[21] ROP was screened by specialized ophthalmologists based on the international classification revisited.[22]

Laboratory and Radiological Evaluation

Before and 24 hours after the first course of medical treatment, all patients were evaluated for renal and liver function tests including serum creatinine and blood urea nitrogen (BUN), aspartate amino transferase (AST), and alanine amino transferase (ALT), as well as imaging studies involving cranial ultrasonography, and echocardiography (ECHO).

Hemodynamically Significant Patent Ductus Arteriosus

ECHO was performed on all patients at postnatal 72nd hour. Diagnosis of hsPDA was determined according to clinical and ECHO criteria (Table 1).[1,23,24] ECHO examination was performed by a pediatric cardiologist. Doppler ECHO was performed using a GE Vivid 7 Pro, 10S transducer (GE Healthcare, Salt Lake City, Utah). hsPDA was initially treated with either IV paracetamol or IV ibuprofen. Surgical ligation was performed if hsPDA persisted (despite 3 courses of paracetamol or ibuprofen treatment). The non-hsDPA group was selected according to the same exclusion criteria, and consisted of infants without hsPDA.

Table 1 – Hemodynamically Significant Patent Ductus Arteriosus

Clinical characteristics	Murmur
	Hyperdynamic precordium
	Bounding preductal pulses
	Worsening respiratory status
	Wide pulse pressure
	Hypotension
	Metabolic acidosis
Echocardiographic characteristics	Increased left atrium to aorticroot ratio
	Cardiomegaly
	Left-to-right shunting
	Large open ductus (>1.5 mm)
	Reversal of flow in postductal major arteries

Intravenous Treatment of Paracetamol and Ibuprofen

During the study period, IV paracetamol or IV ibuprofen treatment was given as a primary rescue pharmacological treatment to all infants with hsPDA. If ibuprofen was contraindicated, paracetamol was started. Contraindications for ibuprofen treatment were active IVH, thrombocytopenia or other known clotting disorders, severe sepsis, suspected or confirmed NEC, feeding intolerance, intestinal perforation, significant impairment of renal function, and severe hyperbilirubinemia.[14,15,25] The patients were divided into two groups: patients receiving IV paracetamol and patients receiving IV ibuprofen. Each eligible patient received either IV paracetamol (Parol, Atabay Ilac Kimya San., Istanbul, Turkey) at a dose of 15 mg/kg every 6 hours for 5 days or IV ibuprofen (Intrafen; Gen Ilac, Ankara, Turkey) at an initial dose of 10 mg/kg followed by 5 mg/kg at 24 and 48 hours for 3 days.

Patient Follow-up

One day after the treatment, an ECHO evaluation was performed by a pediatric cardiologist. Patients with minimal ductal shunting were followed up regularly by a neonatologist and a pediatric cardiologist. Patients who achieved PDA closure but had signs and symptoms of reopening later during hospitalization were re-evaluated by ECHO and were treated according to their ECHO findings and clinical condition.

Fluid intake was started at 70–80 mL/kg per day and was increased by increments of 10–20 mL/kg each day, to a maximum of 150–160 mL/kg per day for all patients enrolled in the study. Hypotension was treated with dopamine for patients in which fluid treatment had failed. Ventilation was supported according to the severity of respiratory distress, using nasal continuous positive airway pressure or MV. Patients with EOS or LOS were treated according to the NICU protocol.

Data Analysis

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 17 for Windows (SPSS Inc, Chicago, Illinois). Normal distribution of data was performed by using Kolmogorov-Smirnov test. Mann-Whitney U-test for non-parametric continuous variables in independent samples and chi-square or Fisher's exact tests for categorical variables were used for the comparison of the groups. The results were expressed as median (interquartile range) for continuous variables as well as percentage and distribution of frequency for categorical variables. Two-sided p-value of 0.05 was set as the cut-off for statistical significance.

Results

A total of 486 preterm infants with BW ≤1500 g and GA ≤32 weeks were admitted to our NICU during the study period. According to the exclusion criteria, 29 preterm infants were excluded from the study. Of the remaining 457 preterm infants, 284 infants were diagnosed with hsPDA. 14 infants died before medical therapy was initiated. The remaining 270 patients with hsPDA, involving 101 patients receiving IV paracetamol and 169 patients receiving IV ibuprofen, were included in the study and analyzed. Median GA and BW of all eligible patients were 27.7 (2.2) weeks and 1006 (324) g (median [interquartile range]), respectively. The rate of hsPDA was 62.1% (284/457) among preterm infants. The success rate of PDA closure with the first course was 74.3% (75/101) in the IV paracetamol group and 72.8% (123/169) in the IV ibuprofen group (p=0.212). The success rate of PDA closure with the 2nd course was 50% (13/26) in the IV paracetamol group and 50% (23/46) in the IV ibuprofen group. The 2nd course treatment requirement was 27.5% (26/101) in the paracetamol group and 27.2% (46/169) in the ibuprofen group (p=0.312). The success rate of PDA closure with the 3rd course was 53% (7/13) in the IV paracetamol group and 65% (15/23) in the IV ibuprofen group. Third course treatment requirement was 12.8% (13/101) in the paracetamol group and 13.6% (23-169) in the ibuprofen group (p=0.191). The ligation rate was 5.9% in the paracetamol group, and 4.7% in the ibuprofen group (Figure 1). There was no statistical difference between the groups (p=0.303). The results were similar between the paracetamol and the ibuprofen groups in terms of clinical and demographic characteristics, clinical outcomes, hepatic and renal function tests (Table 2, 3 and 4).

Discussion

Our results have shown that IV paracetamol and IV ibuprofen are similarly effective when used as the first-line treatment option to close PDA. Moreover, both IV drugs were well tolerated for side effects on kidney and liver, and gastrointestinal and pulmonary complications. Additionally, there was no difference between the groups in terms of premature morbidity and mortality. Since most (90%) IVH and pulmonary hemorrhage cases occur before 72 hours of life, any treatment starting beyond that period should not be capable of reducing their incidence, therefore no difference between the drugs used in our study would be expected.[26]

Ductus arteriosus is a vital anatomical formation that connects pulmonary and systemic circulation in the fetus. The main factors that cause DA patency in intrauterine life are low oxygen pressure, PG and nitric oxide. Increased oxygen levels and decreased Prostaglandin E2 (PGE2) immediately after delivery allow functional ductal closure. Ductal patency disrupts both hemodynamics in premature infants and contributes to prematurity-related morbidity and mortality.[27] Therefore, once an hsPDA is detected, two main factors (oxygen and PG levels) that provide vasodilation of the ductus should be manipulated to ensure ductal closure. Indomethacin, ibuprofen and paracetamol, which inhibit PG synthesis from arachidonic acid, thus providing vasoconstriction, are used for ductal closure. PG synthase is the main enzyme that converts arachidonic acid into PG. This enzyme has two catalytic activities, including COX (-1, -2, -3) and peroxidase. Indomethacin and ibuprofen inhibit COX-1 and -2 enzymes, and paracetamol inhibits the enzyme COX-3 and peroxidase, thereby inhibiting PG synthesis. While peroxidase, the target enzyme of paracetamol, can be activated at low peroxide levels, COX, the target enzyme of ibuprofen, is activated at higher peroxide levels. Therefore, paracetamol is more effective than ibuprofen in hypoxia.[2]

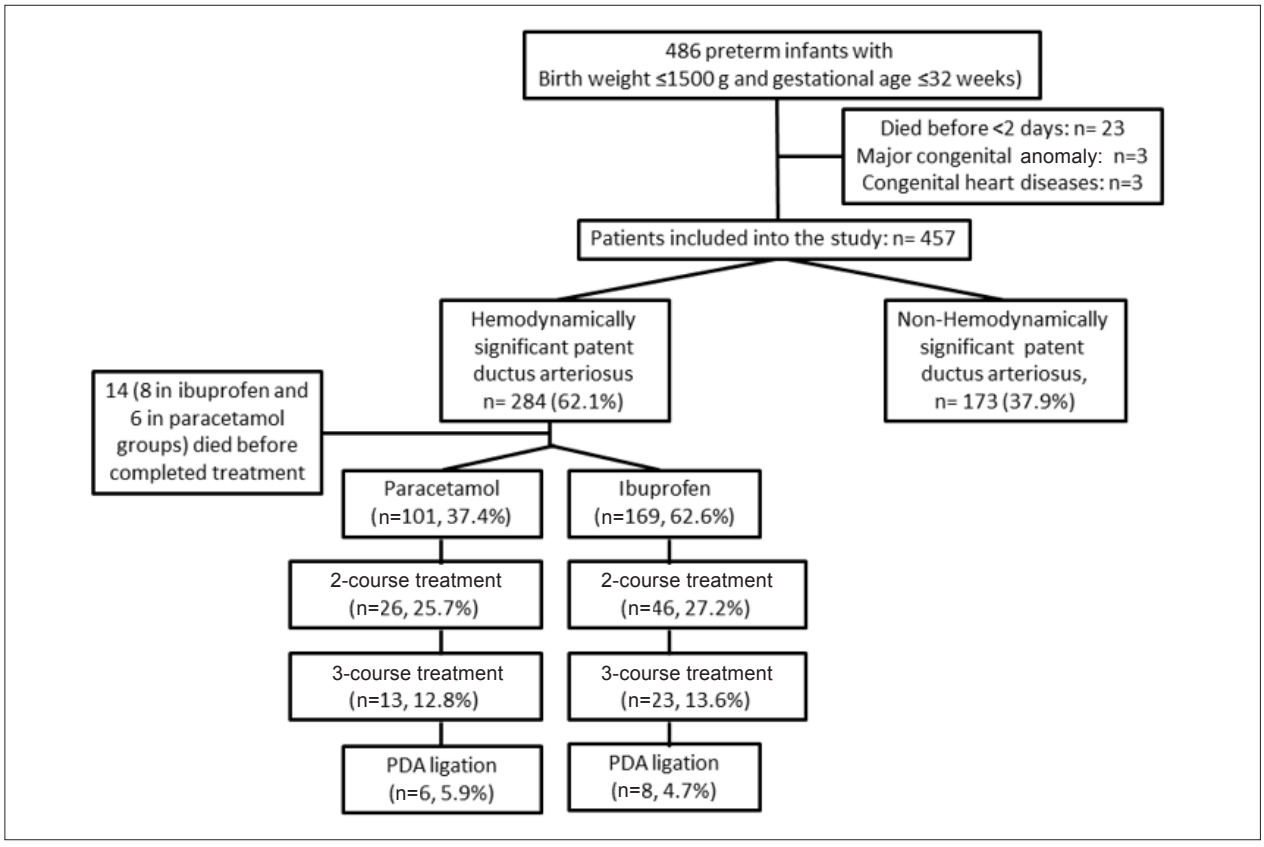

Figure 1 – *Flowchart of the study population. PDA: patent ductus arteriosus.*

Table 2 – Clinical and Demographical Characteristics of the Study Population

Clinical and demographical characteristics	Paracetamol (n: 101, 37.4%)	Ibuprofen (n: 169, 62.6%)	p-value
Gestational age, weeks, [a]	28 (2.8)	28 (2)	0.653
Birth weight, g,[a]	1042 (426)	1020 (290)	0.329
Male,[b]	53 (52.4)	79 (47.6)	0.381
1. min. Apgar,[a]	5 (2)	5 (2)	0.112
5. min. Apgar,[a]	7 (2)	8 (1)	0.153
Antenatal steroids,[b]	71 (70.2)	119 (68.6)	0.124
Duration of MV, days,[a]	3 (8)	2 (5)	0.270
Duration of NIV, days,[a]	12 (16)	9 (12)	0.980
Oxygen supplementation, days,[a]	42 (36)	30 (33)	0.388
Day of full enteral feeding, days,[a]	17 (11)	16 (8)	0.131
Length of stay in hospital, days,[a]	76 (45)	66 (30)	0.861

MV: mechanical ventilation; NIV: non-invasive ventilation.[a] Median (interquartile range),[b] n (%).

Table 3 – Clinical Outcomes of Study Groups

Clinical and demographical characteristics	Paracetamol (n: 101, 37.4%)	Ibuprofen (n: 169, 62.6%)	p-value
RDS,[a]	84 (83.1)	131 (77.5)	0.279
IVH, grade ≥3,[a]	12 (11.8)	13 (7.7)	0.279
NEC, stage ≥2,[a]	3 (2)	4 (2.3)	0.524
BPD,[a]	22 (21.7)	34 (20.1)	0.421
ROP,[a]	15 (14.8)	24 (14.2)	0.255
EOS,[a]	18 (17.8)	28 (16.5)	0.867
LOS,[a]	35 (34.6)	44 (26)	0.454
Gastrointestinal bleeding,[a]	-	4 (2.3)	0.321
Pulmonary hemorrhage,[a]	2 (2)	5 (2.9)	0.514
Mortality,[a]	17 (19.8)	19 (11.2)	0.131
2nd course treatment,[a]	26 (25.7)	46 (27.2)	0.312
3rd course treatment,[a]	13 (12.8)	23 (13.6)	0.191
PDA ligation, [a]	6 (5.9)	8 (4.7)	0.303

[a]n (%). BPD: bronchopulmonary dysplasia; EOS: early neonatal sepsis; PDA: patent ductus arteriosus; IVH: intraventricular hemorrhage; LOS: late onset neonatal sepsis; NEC: necrotizing enterocolitis; RDS: respiratory distress syndrome; ROP: retinopathy of prematurity.

Table 4 – Evaluation of hepatic and renal function tests after the first course of treatment

Laboratory values	Intravenous paracetamol		p-value	Intravenous ibuprofen		p-value	p-value*
	Pre-treatment	Post-treatment		Pre-treatment	Post-treatment		
BUN (mg/dL), [a]	40 (24)	44 (28)	0.352	42 (25)	42 (11-92)	0.926	0.667
Serum creatinine (mg/dL), [a]	0.8 (0.5)	0.8 (0.3)	0.339	0.7 (0.4)	0.8 (0.4)	0.116	0.452
Serum AST (Units/L), [a]	28 (10)	28 (17)	0.758	28 (13)	28 (15)	0.995	0.844
Serum ALT (Units/L), [a]	23 (12)	20 (13)	0.571	24 (14)	22 (12)	0.237	0.707

*ALT: alanine aminotransferase; AST: aspartate amino transferase; BUN: blood urea nitrogen. *p-value for post-treatment measurements between the groups. a Median (interquartile range).*

Considering the side effects of indomethacin and ibuprofen, new treatment methods were needed to reduce the need for ligation. Oral paracetamol was found to be effective in the treatment of PDA in 5 patients with PDA who did not respond to ibuprofen in the first case series reported by Hammerman et al.[28] In the first studies, paracetamol was not used as the first-line drug, but as an alternative drug to cases where COX inhibitors were ineffective or contraindicated.[28] Then, paracetamol was used as the first-line treatment to close the ductus arteriosus.[1,2,10] Previous studies have been conducted to investigate the efficacy and safety of oral ibuprofen compared to oral paracetamol to clarify whether paracetamol can be used as a first-line treatment for ductal closure in preterm infants. Generally, in previous studies, the efficacy and reliability of oral forms of drugs used in hsPDA treatment have been evaluated.[1,29-34]

Our study, in addition to determining the efficacy of IV paracetamol in the treatment of hsPDA, aimed to compare it with IV ibuprofen. Based on our findings, whilst hsPDA closure rates were 74.3% with IV paracetamol, this ratio was 72.8% with IV ibuprofen, and there was no difference in both groups. In many studies, this rate was found to be approximately 70–85%, and was similar to the results of our study. Similar results were found in our study for side effects, complications and clinical outcomes as well.[2] However, it was seen that the number of cases in the groups of previous studies ranged from 10 to 80.[1,2,10,11,35] Therefore, our results might be more robust or stronger and reliable than other studies due to a large number of cases.

Although there is evidence to show that paracetamol is as effective as ibuprofen, there are studies that have found conflicting results. For instance, Lu et al.[12] showed that paracetamol was less effective than ibuprofen for the closure of PDA in newborns, and this effect was reduced even more in very low birth weight (VLBW) or extremely low birth weight babies.[12] Similarly, in a study by Sallmon, it was reported that in parallel with the 27.5% PDA closure rate observed after paracetamol treatment, the total closure rate of PDA was only 21.1% following the administration of paracetamol in VLBW infants.[36] In addition, some studies have reported that paracetamol is not as effective as ibuprofen.[37,38] Generally, paracetamol is used as an alternative option in selected patients, in which the ibuprofen could not be used, such as preterm infants with sepsis, whose general condition is poor, whose organ functions are

not appropriate. Logically, the possible success of paracetamol is decreased for those patients.[15] Therefore, as in our study, it would be more appropriate to evaluate that paracetamol can be used as the first choice based on the results of studies comparing the efficacy of paracetamol and ibuprofen in the treatment of hsPDA. Our study showed that IV paracetamol was similarly effective as IV ibuprofen in the treatment of hsPDA. Therefore, we suggest that IV paracetamol can be used as the first-line treatment for hsPDA as well as IV ibuprofen.

Previous studies have been conducted to compare the efficacy and safety of oral forms of the drugs for the treatment of hsPDA.[1,2,10-13] Also, there are limited studies with IV forms. A study by Roofthooft et al.[14] has reported that IV paracetamol treatment is not effective for PDA closure in VLBW babies after failure of IV ibuprofen treatment.[14] In this study, paracetamol therapy was not recommended for PDA closure for infants >2 weeks of age after birth. However, paracetamol has been reported to be effective when used as a first-line treatment for PDA. Furthermore, Valerio et al.[25] have found that IV paracetamol is effective in closing PDA for both "primary care" and "recovery" therapy.[25] In another IV paracetamol and IV ibuprofen comparison study, it was stated that paracetamol could become the preferred treatment for the management of PDA, mainly due to its more favorable side effect profile.[9] Our results also supported this information. Also, the side effects of ibuprofen are sometimes a disadvantage for its recommendation.[10,12] In some studies, similar to our results, it is reported that there is no difference in terms of the side effect profile of both paracetamol and ibuprofen.[1,2,9,11] In addition, supporting the previous studies, we found that surgical ligation rates were similarly decreased in infants with hsPDA treated either with paracetamol or ibuprofen.[1,2,11]

However, it is still being investigated which drug will be given in the safest and most effective way. Despite all these contradictory results, a recent Cochrane metanalysis by Ohlsson and Shah[16] has stated that further studies are required before routine use of paracetamol for the first-line treatment of hsPDA.[16] We think that the results of our study will shed light on this issue. According to our results, when IV paracetamol was given as the first-line treatment option for PDA closure, it was found to be as effective as IV ibuprofen without any side effects.

Our study had some limitations due to its retrospective nature. Other parameters such as hourly urine output, bilirubin level of patients in the treatment groups could not be evaluated. There is lack of data to recommend the first-line treatment of PDA in terms of morbidities, as there are other factors that should be considered. For example: the only drug that could reduce IVH in studies was early indomethacin. It would be more appropriate to show the efficacy of paracetamol in closing PDA and suggest randomized multicenter studies that could certify its safety and capacity of reducing negative clinical outcomes.

Conclusions

When paracetamol was used as the first-line treatment option for the medical treatment of PDA, it was found to be similarly effective as ibuprofen. Additionally, there was no difference between two drugs in terms of premature morbidity and mortality. Multicenter randomized controlled studies on this subject will help to determine the first-line treatment of hsPDA.

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Author Contributions

Conception and design of the research, Acquisition of data and Writing of the manuscript: Cakir U; Analysis and interpretation of the data, Statistical analysis and Critical revision of the manuscript for intellectual content: Tayman 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.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Zekai Tahir Burak under the protocol number 37/2019 and date 19.03.2019. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Reperfusion Therapy Optimization in Acute Myocardial Infarction with ST-Segment Elevation using WhatsApp®-Based Telemedicine

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Abstract

Background: About 40% of patients with ST-segment elevation myocardial infarction (STEMI) in Brazil do not receive reperfusion therapy.

Objective: The use of a telemedicine network based on WhatsApp® could increase the percentage of patients receiving reperfusion therapy.

Methods: A cross-sectional study analyzed outcomes before and after the organization of a telemedicine network to send the electrocardiogram via WhatsApp® of patients suspected of STEMI from 25 municipalities that are members of the Regional Health Department of Ribeirão Preto (DRS−XIII) to a tertiary hospital, which could authorize immediate patient transfer using the same system. The analyzed outcomes included the percentage of patients who received reperfusion therapy and the in-hospital mortality rate. A p value < 0.05 was considered statistically significant.

Results: The study compared 82 patients before (February 1, 2016 to January 31, 2018) with 196 patients after this network implementation (February 1, 2018 to January 31, 2020). After implementing this network, there was a significant increase in the proportion of patients who received reperfusion therapy (60% vs. 92%), relative risk (RR): 1.594 [95% confidence interval (CI) 1.331 – 1.909], p < 0.0001 and decrease in the in-hospital mortality rate (13.4% vs. 5.6%), RR: 0.418 [95%CI 0.189 – 0.927], p = 0.028.

Conclusion: The use of WhatsApp®-based telemedicine has led to an increase in the percentage of patients with STEMI who received reperfusion therapy and a decrease in the in-hospital mortality rate.

Keywords: ST Elevation Myocardial Infarction; Acute Coronary Syndrome; Telemedicine/trends; Reperfusion/therapy.

Introduction

Cardiovascular diseases are the main cause of mortality worldwide, including in Brazil.[1] ST-segment elevation Myocardial Infarction (STEMI) is responsible for most of the fatal events of this etiology. According to disclosure by DATASUS, 142,982 patients were hospitalized for acute myocardial infarction in 2018 in Brazil.[1] In the last decades, the morbidity and mortality of STEMI have greatly reduced, especially with the development of reperfusion therapies (fibrinolytics and primary angioplasty).[2] However, to obtain this benefit, this coronary event must be recognized early, which is usually based on anamnesis and electrocardiogram (ECG), to allow the organization of the rapid referral of these patients to tertiary centers prepared to offer these types of therapies.

The Brazilian registry of acute coronary syndromes evidenced that only 61.2% of patients with STEMI received reperfusion therapy for treatment (35.9% receiving primary angioplasty and 25.3% receiving fibrinolytic therapy).[3] Hence, a large percentage of patients in our country, especially those in the public system, still do not receive reperfusion therapy in a timely manner. This directly impacts the survival and functional impairment of these patients' left ventricle and the consequent heart failure in many STEMI cases.

The objective of this investigation was to evaluate whether the implantation of a telemedicine network to send the ECG of patients with suspected STEMI through a simple digital communication platform (WhatsApp®) for immediate analysis in a tertiary center increased the percentage of patients receiving reperfusion therapy within the initial 12 hours of the STEMI onset. Additionally, we assessed the impact of organizing the immediate release for hospital transfer of a suspected STEMI patient using the same communication resource on the in-hospital mortality due to this coronary event.

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Methods

This before-and-after cross-sectional study compares the percentage of patients who received reperfusion therapy for the treatment of STEMI within a 12-hour period, before and after the implementation of a network (Rede – Supra) for sending patient data and remote analysis of ECGs of patients with this suspected pathology using an accessible digital communication platform (WhatsApp®) to a tertiary cardiology center.

This network included the 25 municipalities included in the Regional Health Department of Ribeirão Preto (DRS – XIII). In this initial phase, it was decided not to include the city of Ribeirão Preto in the data collection, because due to its location, this city already had greater capacity to refer these patients to a tertiary hospital. Figure 1 shows the municipalities that are part of DRS–XIII, as well as their subdivision into three regions, named: Horizonte Verde, Aquífero Guarani, and Vale das Cachoeiras. The receiving center for these ECGs was located in the Coronary Unit of the Emergency Department of Hospital das Clínicas of Ribeirão Preto Medical School at the University of São Paulo (HCFMRP/USP), located in the city of Ribeirão Preto. This is a tertiary referral hospital for the exclusive care and treatment of emergency cases for this entire region.

This study was approved by the Research Ethics Committee of our hospital and followed the recommendations of the Helsinki declaration.

Implementation of the Supra Network

An initial consultation was carried out with the Regional Council of Medicine, which was in favor of using WhatsApp® to send the ECG between doctors. The project was presented to and approved by the Regional Intergovernmental Commission of the DRS–XIII with the health secretariats of the constituent municipalities.

Two training sessions were conducted with nurses in charge of the emergency care unit in each municipality to demonstrate the importance of early diagnosis and rapid referral of patients with STEMI to a tertiary hospital, since none of these municipalities had primary angioplasty services and fibrinolytic drugs were available in only four of them. A practical training was carried out on how to perform quality ECG, which allows the correct diagnosis and a questionnaire was applied on the resources available in each unit for the care of these patients. After these two activities, the flowchart detailed in figure 2 was presented to the coordinators of these units, containing the guidelines on sending the ECG via WhatsApp® when a STEMI was suspected and the operationalization of the transfer of these patients to the referral hospital (Figure 2).

A dedicated cell phone was also made available for this type of communication. The Assistant Cardiologists of the Coronary Unit of the Emergency Department of HCFMRP/USP were responsible for the assessment of these ECGs. Two standard responses were created: confirmed STEMI, immediate transfer to the Emergency Unit was authorized, and unconfirmed

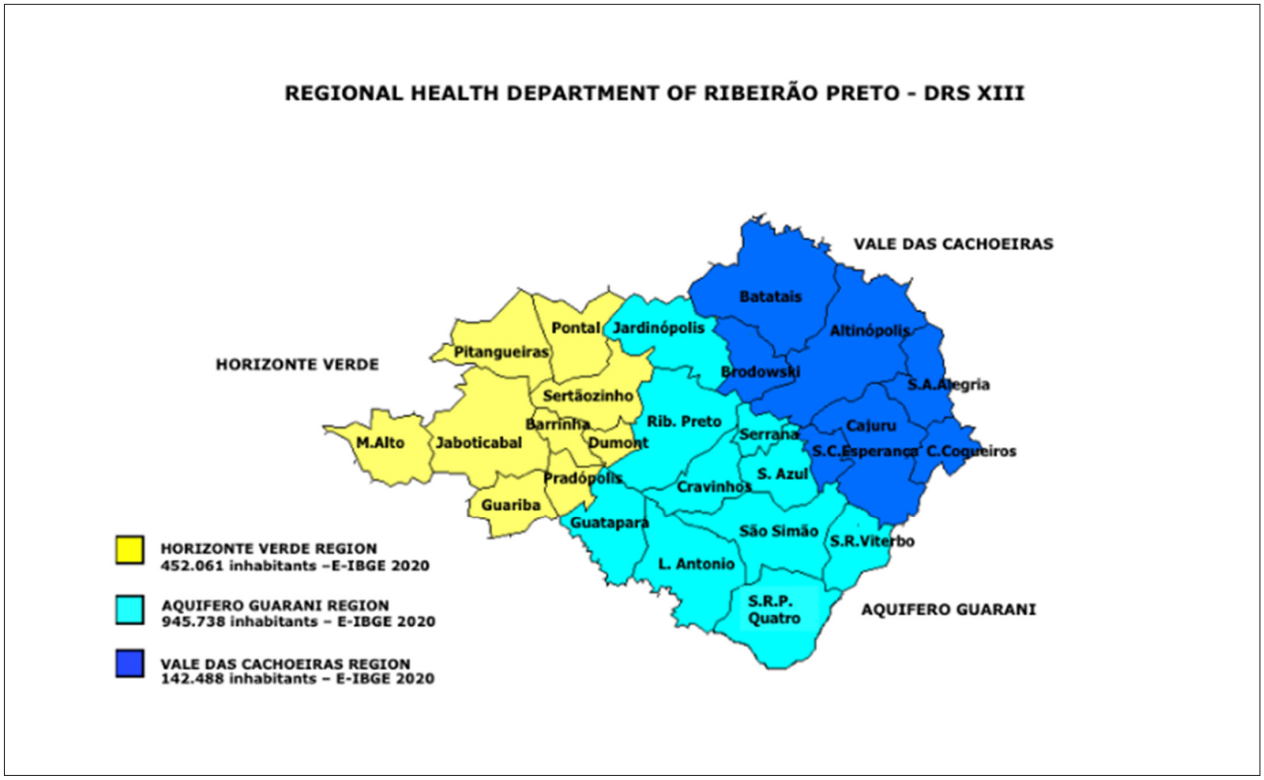

Figure 1 – *Geographic map of the municipalities within the Ribeirão Preto Regional Health Department (DRS – XIII); as well as its subdivision into the regions of Horizonte Verde, Aquífero Guarani, and Vale das Cachoeiras.*

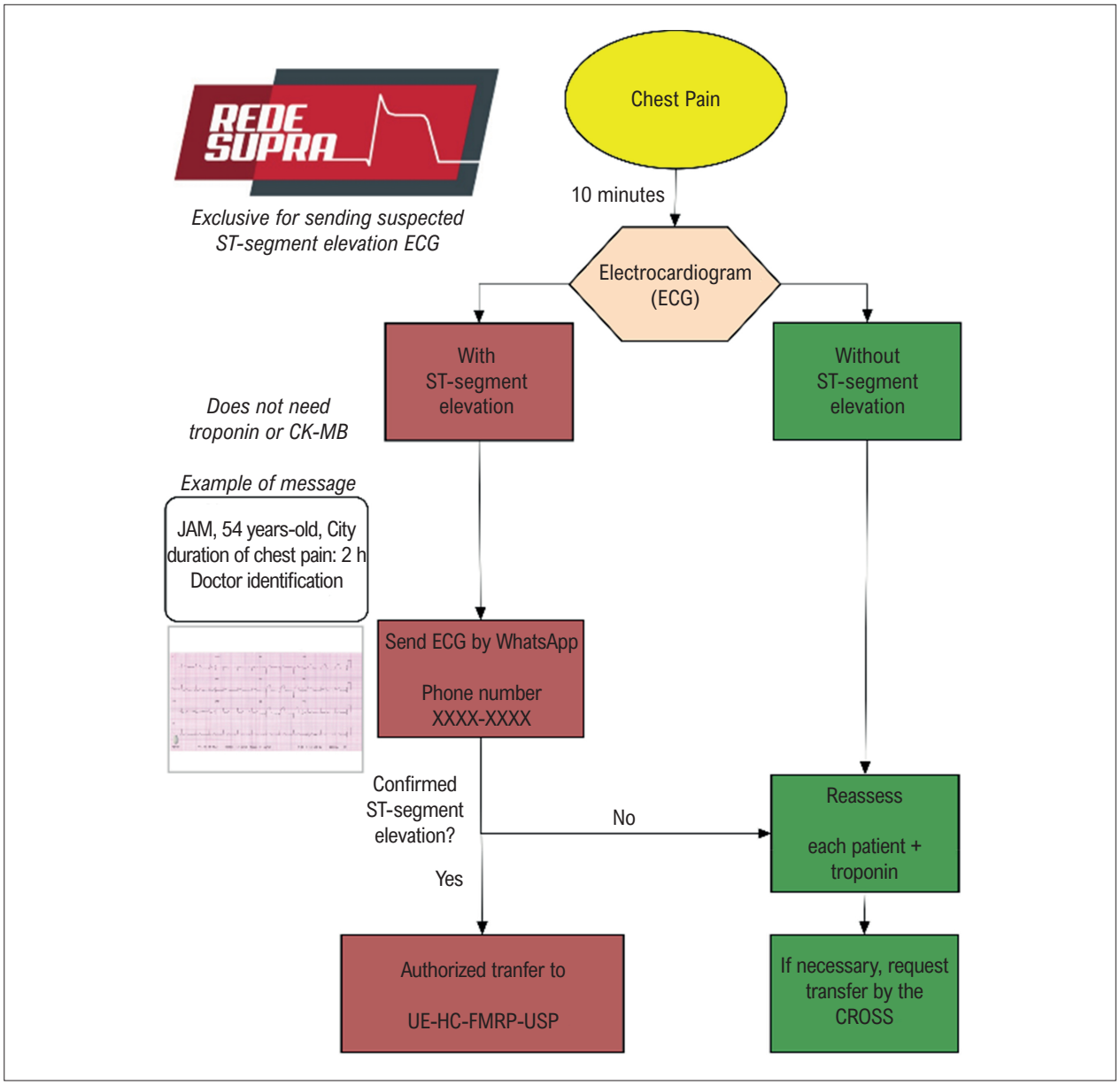

Figure 2 – *Flowchart to guide the operationalization of the telemedicine network based on WhatsApp® for sending electrocardiograms (ECG) of suspected ST-segment elevation Myocardial Infarction (STEMI) and organization of the transfer flow of this patient to the tertiary hospital. UE-HC-FMRP - Emergency Unit, Hospital das Clínicas, Ribeirão Preto School of Medicine; CROSS – Center of Regulation for Health Services Offered by the Health Department of the State of São Paulo.*

STEMI, if necessary was regulated via Health Service Offer Regulation Center (CROSS – *Central de Regulação de Ofertas e Serviços de Saúde*). On February 1, 2018, the dedicated cell phone number was made available to all these municipalities.

Data collection

Retrospective data prior to the implementation of this network were acquired by reviewing the medical records of patients admitted to our hospital with a primary diagnosis of STEMI, identified through the following international code of diseases (ICD−10): I21.0 (acute transmural myocardial infarction of anterior wall), I21.1 (acute transmural myocardial infarction of inferior wall), I21.2 (acute transmural myocardial infarction of other sites), I21.3 (acute transmural myocardial infarction of unspecified site), I22.0 (subsequent myocardial infarction of anterior wall), I22.1 (subsequent myocardial infarction of inferior wall), I22.8 (subsequent myocardial infarction of other sites), I22.9 (subsequent myocardial infarction of unspecified site) The only analyzed cases were those referred by the 25 municipalities that comprise the DRS XIII in the two-year period before the implementation of this telemedicine network. The definition for the diagnosis of STEMI followed the criteria of the Fourth Universal Definition of Myocardial Infarction.[4]

After the implementation of the Rede Supra, the data were prospectively collected by a nurse from the Coronary Unit who weekly reviewed the messages and ECGs sent to this center via WhatsApp® and subsequently checked the information necessary for this study in all patients' records during the two years following the implementation of this network.

The primary assessed outcome was the percentage of patients who received some type of reperfusion therapy (fibrinolytics, primary angioplasty or spontaneous reperfusion) within 12 hours of the onset of chest pain symptoms. The secondary assessed outcomes were the in-hospital mortality rate, as well as the time between chest pain onset and the reperfusion therapy start. For patients with spontaneous reperfusion or for those who did not receive any type of reperfusion therapy, the time between pain onset and hospital admission was considered.

Statistical analysis

To determine the sample size using the chi-square test, it was assumed that 50% of patients from this region received reperfusion therapy before this network was implemented, based on recent historical data from our institution. In addition, it was assumed that this percentage would rise to 80% after the implementation of this network, detecting this difference with power of 80% and a significance level of 5%. Thus, the study would need to include at least 50 patients (before) and 50 patients (after) to test this hypothesis.

The Shapiro-Wilk test was used to assess the type of distribution of quantitative variables. Quantitative variables with normal distribution were expressed as mean ± standard deviation and the other variables as median and interquartile range (IQR). To compare the two quantitative variables with normal distribution, the unpaired Student's *t* test was used. The Mann-Whitney test was employed for those with another type of distribution. Qualitative variables were expressed as frequencies and percentages. To compare between two or more qualitative variables, the chi-square test was used. To evaluate the association between two variables, the relative risk (RR) was calculated, as well as its 95% confidence interval (95% CI). A two-tailed p-value <0.05 was considered statistically significant. The statistical analysis and construction of the graphs were performed using the GraphPad Prism statistical software, version 7.00 (CA, USA).

Results

From February 1, 2018 through January 31, 2020, the ECG of 1847 patients were sent through this network and evaluated. Of these ECGs, 280 (15%) patients were suspected to have STEMI, which was confirmed in 196 (11%) after clinical evaluation and after the ECG was repeated in the hospital setting. The time between receiving the ECG through WhatsApp® and sending the response was less than 10 minutes in the vast majority of cases. The other characteristics of patients whose ECGs were analyzed through this telemedicine network are shown in Table 1.

The demographic and clinical characteristics of patients diagnosed with STEMI treated at our service before and after the implantation of this network are shown in Table 2. There was no difference in relation to age. Despite the predominance of males in the two analyzed periods, the proportion of females clearly increased in the second period. No difference was observed in relation to the personal history of these patients or in relation to the affected left ventricular walls.

After the implantation of the Rede Supra, there was a statistically significant increase in the proportion of patients who received reperfusion therapy for acute treatment of STEMI, 49/82 (60.00%) *vs*. 180/196 (92.00%), RR: 1.594 (95% CI 1.331 – 1.909), p <0.0001, as depicted in Figure 3A. In terms of the type of reperfusion therapy used in the treatment, a statistically significant increase was observed in the proportion of patients treated with primary angioplasty. The proportion of patients who received a fibrinolytic agent or who had spontaneous reperfusion was similar before and after, as shown in Figure 3B.

Moreover, the in-hospital mortality rate of patients with STEMI in our service was significantly reduced, 11/82 (13.40%) *vs*. 11/196 (5.60%), RR: 0.418 (95% CI 0.189 – 0.927), p = 0.028, as depicted in Figure 4A. These values indicate a number needed to treat (NNT) of 12 corresponding to a

Table 1 – Characterization of patients whose electrocardiograms were sent through the Rede Supra via WhatsApp® from February 1, 2018 through January 31, 2020

Characteristics	n = 1847
ECG with suspected ST-elevation, n (%)	280(15)
ECG with confirmed ST-elevation, n (%)	196(11)
Response time, n (%)	
< 10 min	1651(89)
10 – 30 min	125(07)
30 – 60 min	36(02)
> 60 min	35(02)
Age group, n (%)	
< 40 years	268(15)
≤40 – <50 years	261(14)
≤50 – <60 years	379(21)
≤60 – <70 years	395(21)
≥70 years	416(23)
Not informed	128(06)
Gender, n (%)	
Male	1033(56)
Female	541(29)
Not informed	273(15)
Origin, n (%)	
Horizonte Verde	645(35)
Aquífero Guarani	596(32)
Not informed	332(18)
Vale das Cachoeiras	274(15)

ECG: electrocardiogram; min: minutes.

Table 2 – Characteristics of patients at hospital admission before and after the implementation of the Rede Supra

Characteristics	Before (n = 82 patients)	After (n = 196 patients)	p-value
Demographics			
Age, mean ± SD	60 ± 11	61 ± 12	0.676
Male gender, n (%)	65(79)	123(63)	0.007
Personal history, risk factors			
Hypertension, n (%)	46(56)	112(57)	0.873
Diabetes, n (%)	21(26)	57(29)	0.661
Dyslipidemia, n (%)	21(26)	42(21)	0.448
Smoker, n (%)	41(50)	92(47)	0.641
Prior AMI, n (%)	6(07)	21(11)	0.383
Prior angioplasty, n (%)	2(02)	15(08)	0.098
Prior CABG, n (%)	0(00)	00(00)	1.000
Physical examination on admission			
SBP (mmHg), mean ± SD	135 ± 27	122 ± 27	0.0009
DBP (mmHg), mean ± SD	74 ± 15	82 ± 17	<0.0001
HR (beats/min), mean ± SD	80 ± 20	85 ± 18	0.072
SBP <90 mmHg, n (%)	7(09)	8(04)	0.134
Affected LV wall, n (%)			0.155
Anterior	27(33)	90(46)	
Inferior	53(65)	96(49)	
Other	2(02)	10(05)	
Troponin (µg/L), median (IQR)	9.87(3.28 – 20.09)	13.50(5.00 – 30.00)	0.058
Origin, n (%)			0.043
Vale das Cachoeiras	18(22)	68(35)	
Horizonte Verde	29(35)	62(32)	
Aquífero Guarani	35(43)	66(34)	
Hospital ength of stay (days), median (IQR)	5(4 – 9)	5(4 – 9)	0.845

SD: standard deviation; AMI: acute myocardial infarction; CABG: Coronary Artery Bypass Grafting ; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; LV: left ventricle; IQR: interquartile range.

reduction in mortality. The time between chest pain onset and the reperfusion therapy start was significantly reduced from 9 h [IQR 6 - 19] in the previous period, to 4 h [IQR 3 - 6] in the period after the network implementation, p <0.0001.

Discussion

This investigation found that the implementation of a telemedicine network using an accessible digital communication platform (WhatsApp®) to send the ECG for specialized analysis and the organization of the influx of patients with suspected STEMI to a tertiary referral hospital for treatment of this pathology, was associated with a significant increase in the proportion of patients who received reperfusion therapy, a reduction in the time to implement this therapy, and a significant reduction in the in-hospital mortality rate.

Scientific evidence has demonstrated that the rapid initiation of reperfusion therapy to treat STEMI significantly reduces complications, mainly by minimizing myocardial damage.[5,6] Based on this observation, the organization of regional care networks for patients with STEMI is recommended in an attempt to expedite their treatment.[7-9]

In developing countries, such as Brazil, a significant percentage of patients with STEMI still do not receive reperfusion therapies within an adequate time window. Thus, a Brazilian report on acute coronary syndrome[3] showed that about 40% of patients with STEMI did not receive any reperfusion therapy, and these rates may be even higher in certain regions of Brazil.[10] Several factors explain this occurrence, such as the patient's delay in seeking medical care, underdiagnosis and difficulties in the regulatory influxes for referring these patients to tertiary cardiology centers.[11] On the other hand, the organization of a telemedicine network can improve performance for these two latter factors.[12,13]

Telemedicine facilitates the prompt sending of the ECG to an analysis center, allowing this test to be interpreted by an

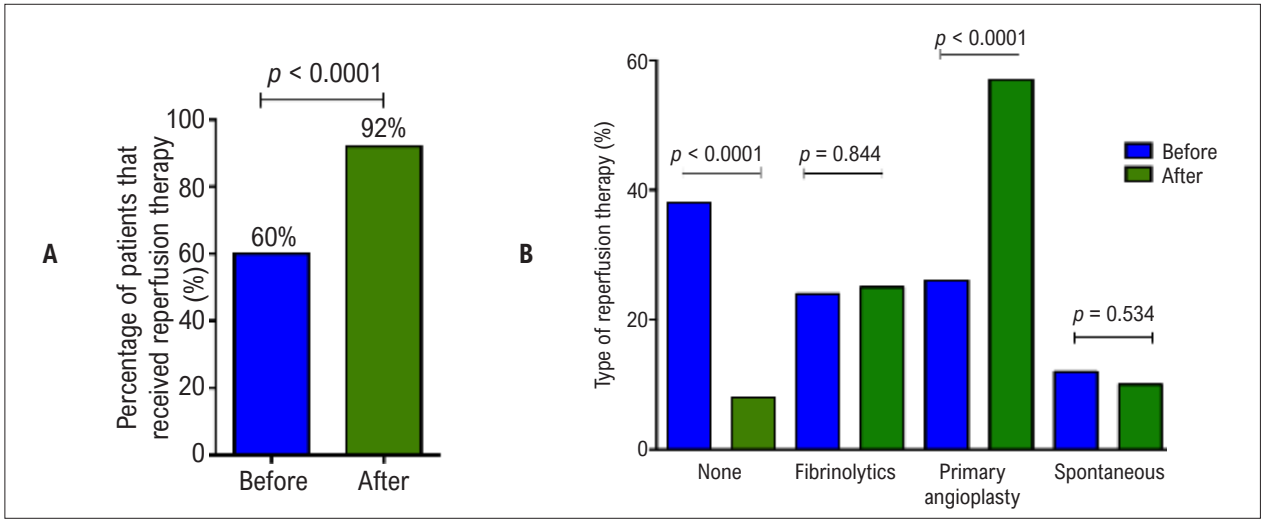

Figure 3 – *Bar graph showing the percentage of patients who received some type of reperfusion therapy before and after the implementation of the Rede Supra (A); as well as the types of reperfusion therapy received for the treatment of acute ST-segment elevation Myocardial Infarction (STEMI) (B). Spontaneous - coronary recanalization was spontaneous without fibrinolytics or primary angioplasty.*

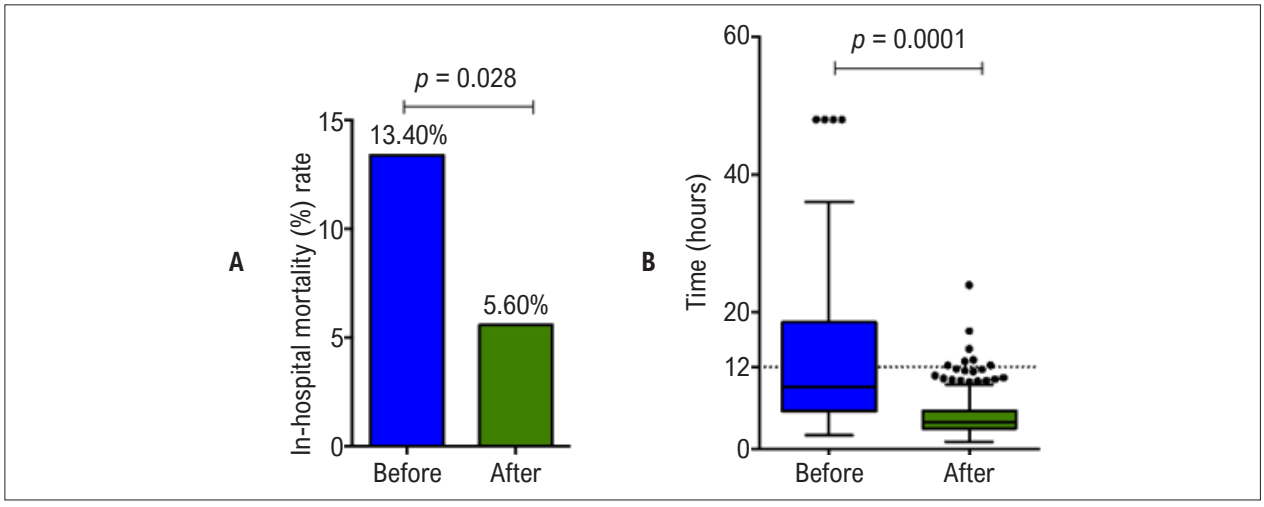

Figure 4 – *Bar graph illustrating in-hospital mortality (A) and boxplot showing the time between symptom onset and the start of reperfusion therapy (B) of patients with confirmed diagnosis of ST-segment elevation Myocardial Infarction (STEMI) before and after the implementation of the Rede Supra.*

experienced cardiologist and, thus, optimizing the transfer of patients who really should be referred to tertiary centers. For example, in this case series, STEMI was suspected in only 15% of all ECGs sent through the network, thus optimizing the existing resources for rapid transfer and effective treatment of this group of patients. Prior to the implementation of the Rede Supra, the diagnosis of STEMI was not confirmed in many referred patients, resulting in an overload of the health system and making it difficult to refer patients who really need to be transferred.

The present results corroborate those of a recent systematic review and meta-analysis that included 16,960 patients and evidenced a positive impact of telemedicine, with a reduction in the in-hospital mortality rate, (RR: 0.63; 95% CI 0.55 – 0.72, p <0.001), as well as a reduction in door-to-balloon time, with an average difference of -28 min (95% CI -35 – -20 min) for the treatment of STEMI.[14] According to the results of the present investigation, the reduction observed for in-hospital mortality should be interpreted as resulting from the combination of the earlier treatment associated with the expansion of primary angioplasty as the main treatment for these patients.

The present results are also in line with those of other Brazilian authors regarding the use of telemedicine in the care of STEMI. Caluza et al.[15] showed a reduction in mortality from 26.14% to 7.31%, p = 0.0028 in emergency rooms in the metropolitan region of São Paulo after the implementation of a network with a central contact to send ECGs. Matsuda et al.[16] also detected a reduction in in-hospital mortality very similar to that observed in the present investigation (15.00% vs. 5.60%) with the use of telemedicine to send the ECG in

another region of the city of São Paulo. Marcolino et al.[17] reported an important reduction in in-hospital mortality (12.30% vs. 7.10%, p <0.001) with the implementation of a telemedicine network for the treatment of infarction in the Belo Horizonte region. Figueiras Filho et al.[18] also observed an increase in the percentage of patients with STEMI who received reperfusion therapy (29.10% vs. 53.80%, p <0.001), and a reduction in 30-day mortality (19.80% vs. 5.10%, p <0.001) with the network implementation for infarction care supported by telemedicine resources in the city of Salvador.

In addition to the implementation of the network, the establishment of a continuous feedback between all units belonging to this network is a fundamental aspect. A prospective and multicenter German study reported that systematic feedback improved quality indexes in STEMI care, including a reduction of in-hospital mortality (10.80% vs. 6.80%; p = 0.024).[19]

An essential aspect to be highlighted from this investigation was the use of an accessible digital communication platform, such as WhatsApp®, with low-cost installation/maintenance and that does not require training for its use, which greatly facilitates its dissemination to other regions of the country. It is worth mentioning that the image quality obtained by this platform never hindered the analysis of the ECG; when there were difficulties, they were related to the ECG performance technique and not to the ECG transmission. In addition, the intercommunication messages between professionals, as well as the ECG images, can be maintained in the system's security record.

The Brazilian Society of Cardiology (SBC) published in 2019 a guideline on telemedicine, in which it makes clear the importance of information and communication technologies to expand access to health services in Brazil.[20] Furthermore, we reinforce that after the establishment of the General Data Protection Act in our country, an expanded discussion on the security of medical information exchange through WhatsApp® should be conducted.

Limitations

This was an observational, non-randomized study, and the data before the implementation of this telemedicine network were collected retrospectively through hospitalization records, which may have led to the loss of data from some patients. Only in-hospital mortality was assessed, and outcomes after hospital discharge were not analyzed. Information on the social and educational level of the patients included in this investigation was not evaluated. However, the establishment of this network mainly minimized the delaying in referring the patient within the health system and did not implement any intervention to reduce the patient's delay in seeking medical assistance, so the educational level of the studied population had little repercussion on these results.

Conclusion

The implementation of a telemedicine network based on an accessible communication platform, such as WhatsApp®, for sending and analyzing ECGs, and for organizing the referral influx of patients with suspected STEMI to a tertiary hospital had immediate positive impacts, with an increase in the percentage of patients who received reperfusion therapy and with less delay, in addition to a significant reduction in the in-hospital mortality rate.

Author Contributions

Conception and design of the research: Pintyá JP, Miranda CH; Acquisition of data: Teixeira AB, Zancaner LF, Ribeiro FFF, Pintyá JP, Miranda CH; Analysis and interpretation of the data: Teixeira AB, Zancaner LF, Ribeiro FFF, Pintyá JP, Schmidt A, Maciel BC, Marin-Neto JA, Miranda CH; Statistical analysis: Miranda CH; Writing of the manuscript: Teixeira AB, Miranda CH; Critical revision of the manuscript for intellectual content: Schmidt A, Maciel BC, Marin-Neto JA.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade de São Paulo Faculdade de Medicina de Ribeirão Preto under the protocol number 2.951.321. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Exercise Testing In Patients with Sickle Cell Disease: Safety, Feasibility and Potential Prognostic Implication

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Abstract

Background: Patients with sickle cell disease (SCD) are at increased risk for cardiovascular complications. Exercise testing is used as a prognostic marker in a variety of cardiovascular diseases. However, there is a lack of evidence on exercise in SCD patients, particularly regarding its safety, feasibility, and possible prognostic role.

Objectives: We used the maximal treadmill test to determine safety and feasibility of the exercise testing in SCD patients. Additionally, the factors associated with exercise duration, as well as the impact of exercise-induced changes on clinical outcome, were also assessed.

Methods: One-hundred thirteen patients with SCD, who underwent exercise testing, were prospectively enrolled. A comprehensive cardiovascular evaluation, including echocardiography and B-type natriuretic peptide (BNP) levels, were obtained. The long-term outcome was a composite endpoint of death, severe acute painful episodes, acute chest syndrome, or hospitalization for other SCD-related complications. Cox regression analysis was performed to identify the variables associated with the outcome. A p-value<0.05 was considered to be statistically significant.

Results: The mean age was 36 ± 12 years (range, 18-65 years), and 62 patients were women (52%). Ischemic electrocardiogram and abnormal blood pressure (BP) response to exercise were detected in 17% and 9%, respectively. Two patients experienced pain crises within 48 hours that required hospitalization. Factors associated with exercise duration were age, sex, tricuspid regurgitation (TR) maximal velocity, and E/e' ratio, after adjustment for markers of disease severity. During the mean follow-up of 10.1 months (ranging from 1.2 to 26), the endpoint was reached in 27 patients (23%). Independent predictors of adverse events were hemoglobin concentration, late transmitral flow velocity (A wave), and BP response to exercise.

Conclusions: Exercise testing in SCD patients who were clinically stable is feasible. Exercise duration was associated with diastolic function and pulmonary artery pressure. Abnormal BP response was an independent predictor of adverse events.

Keywords: Anemia, Sickle Cell; Vasculitis;Hemolysis; Vascular Occlusion; Hypertension; Prognosis; Exercise.

Introduction

Sickle cell disease (SCD) is an increasing global health problem associated with life-threatening complications and progressive organ damage.[1-4] Although the number of patients with SCD is expected to increase with treatment improvement, life expectancy is reduced by about 3 decades, even with the best medical care.[1] This condition is characterized by the presence of abnormal erythrocytes damaged by hemoglobin S, leading to a multisystem disorder.[2,5] The pathophysiological hallmark of SCD is hemoglobin polymerization, causing vaso-occlusion with ischemia-reperfusion injury and hemolysis.[5,6] Chronic complications result from two main mechanisms including large-vessel vasculopathy and progressive ischemic organ damage.[1,2,5]

In recent decades, early diagnosis and effective treatment have greatly prolonged the survival of patients with SCD[7] and thus cardiovascular complications have been increasingly detected. Chronic anemia is associated with several well-described cardiac changes in patients with SCD, including left ventricular dilation, increased mass, and impaired diastolic function.[8-10] In addition, intravascular hemolysis may lead

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to precapillary pulmonary hypertension, which is one of the major complications of SCD, with severe consequences on the right-side heart chambers.[3,11-17]

Patients with SCD are at increased risk for myocardial ischemia and sudden death, especially with the aging of the affected population.[6,11,18] Chest pain is usually attributed to vascular occlusive crisis, and the diagnosis of myocardial infarction is frequently missed, occasionally made only upon autopsy.[18] Therefore, ischemic heart disease may be present in a significant number of patients with SCD.

Exercise testing has been used widely to detect myocardial ischemia in patients with chest pain syndromes or potential symptom equivalents.[19] However, the metabolic changes induced by exercise may stimulate erythrocyte sickling and promote vascular occlusions.[20,21] This fact raised a dilemma of either recommended exercise for these patients or deprives them from beneficial effects of physical activity. Although previous studies showed a normal exercise tolerance in SCD patients,[22,23] they had several limitations, including a small number of patients and the use of a six-minute walk test to assess functional capacity. Therefore, there is a lack of evidence to indicate exercise programs for SCD patients. Furthermore, it is unclear whether exercise-induced parameters obtained from symptom-limited exercise tests are associated with adverse outcomes in the SCD setting.

Therefore, in this study, we sought to 1) verify the exercise tolerance in patients with SCD; 2) determine the factors associated with the duration of exercise testing; 3) examine the impact of exercise-induced cardiovascular response on clinical outcome; and 4) assess the feasibility and safety of exercise testing in the population with SCD.

Methods

Study population

This was a single center study in which patients with SCD, confirmed by hemoglobin electrophoresis, were prospectively enrolled. Patients who were unable to perform exercise testing due to orthopedic or other organic problems associated with SCD (pain episodes, severe venous insufficiency, cardiovascular or respiratory decompensation) were excluded.

B-type natriuretic peptide (BNP) levels were measured using standard radioimmunoassay in all patients immediately before exercise testing. The research protocol was approved by the Ethics Committee of the Federal University of Minas Gerais and written informed consent was obtained from all patients.

Exercise testing protocol

Symptom-limited exercise was performed on a treadmill (Centurium 200, Micromed, Brazil), using a modified Bruce protocol, which, in the initial stages, presents smaller increments in the effort load , allowing for better adaptation and tolerance to exercise. This protocol is derived from the standard Bruce protocol and presents 3-minute stages, which are different only in the first stage, which presents normal initial velocity of the first stage original protocol, changing only in the slope (first 3 minutes, without inclination). The second stage is similar to the first stage of Bruce, and, after this it follows the usual protocol. Thus, the relation between workload and O_2 consumption is around 0.5 MET / minute until the third, and thereafter ± 1.2 MET / minute.[19]

A 13-lead ECG was continuously monitored and recorded in each minute, and cuff blood pressure was recorded manually at rest, during the last 30 seconds of each stage and during the 6-min recovery period. After achieving maximal workload, all patients spent 1 minute in a cool-down period at a speed of 2.4 km per hour and a grade of 2.5 percent. After 1 min, all of the patients completed the recovery phase in the supine position.

The test reached the maximal level, with patients remaining on the treadmill until they reached the subjective parameters (dyspnea, fatigue, chest pain or lower limbs, inability to follow the treadmill) of exercise intolerance or usual contraindications for its continuation (such as sustained arrhythmias). The peak VO_2 and METs were estimated at the exercise peak. Presence of ST-T changes, heart rate and blood pressure responses, and arrhythmias were evaluated. Abnormal exercise blood pressure response was defined as either no elevation or increase in systolic blood pressure at peak of exercise < 20 mmHg or a drop in exercise systolic blood pressure below the resting value.[24] ST-segment changes were considered indicative of ischemia when there was a horizontal or down-sloping ST-segment depression ≥ 1 mm at 60–80 ms after the J point.[19]

Oximetry was performed at rest and during the exercise test using two oximeters: OHMEDA 3800, GE and HELLCOR OXIMAX N-600X, one on each index finger. All exams were performed and analyzed by an experienced cardiologist.

Echocardiographic evaluation

Echocardiographic assessment was performed according to recommendations of the American Society of Echocardiography,[25] using a commercially available echocardiograph (GE Vivid Q, Horten, Norway). LV ejection fraction was calculated according to the modified Simpson's rule, and LV mass was calculated using Devereux's formula.[26] Diastolic function was assessed by pulsed-wave Doppler examination of mitral inflow, and by tissue Doppler imaging.[27] Early diastolic velocity (e') at the medial and lateral border of the mitral annulus were obtained, and the ratio between peak mitral E and e' (E/e') was calculated. Right ventricular function was assessed using peak systolic velocity at the tricuspid annulus by means of tissue Doppler imaging,[28] tricuspid annular motion, and fractional area change, which was calculated as (RV end-diastolic area – RV end-systolic area)/RV end-diastolic area x 100. Maximal tricuspid regurgitation (TR) velocity was obtained at the 4-chamber or parasternal views. All measurements were performed by a single investigator, blinded to clinical data, and were averaged from 3 beats.

Endpoint definitions

The primary endpoint was exercise duration, and the secondary endpoint was combined into the following events: (1) death related to SCD, (2) all-cause mortality, (3) three or more acute painful episodes that require hospitalization, (4)

acute chest syndrome characterized by a newly pulmonary infiltrate detected by chest radiography associated with chest pain, fever, tachypnea, wheezing, cough, and hypoxemia, and (5) hospitalization for another SCD-related complication, especially a life-threatening infection.

The date of enrollment in the study was defined as the date on which exercise testing was performed. The inclusion period was from August 2015 to September 2016, and the follow-up ended on November 2017. Follow-up data were obtained during clinical follow-up appointment or telephone interviews.

Statistical analysis

The study was designed to achieve 90% power to detect a 15% prevalence of ECG abnormalities suggested of myocardial ischemia in the overall population with SCD. We assumed that at least 10 patients will have ischemic ST-T abnormalities, returning an estimated sample size of 93.

Categorical data were presented as numbers and percentages, continuous data were expressed as mean ± standard deviation (SD) or median and interquartile range, depending on the pattern of distribution of each variable. Shapiro-Wilk test was performed to evaluate the distribution of the continuous variables.

To determine the factors associated with exercise testing duration, linear regression models with univariate and multivariate analyses were performed. Assumptions for linear regression analysis were verified with no significant violations observed.

Cox regression analysis was performed to determine the characteristics that were independently associated with composite endpoint. Clinical, laboratory, echocardiographic, and exercise testing variables that were clinically relevant or significantly associated with events in the univariate analysis were included in the multivariate logistic regression model. The variables that entered into the final model were age, gender, laboratory (reticulocytes and hemoglobin concentrations), echocardiographic (TR maximal velocity, E/e' ratio, and LV indexed mass), and exercise testing (abnormal pressure response and presence of ischemia) parameters. A p-value<0.05 was considered to be statistically significant.

Statistical analysis was performed using SPSS, version 22.0 (SPSS Inc., Chicago, Illinois).

Results

Clinical characteristics of the study population

A total of 120 outpatients were included, but 7 were unable to perform the exam in an exercise testing room, leaving 113 patients who completed the study protocol. Of these, 71 were carriers of hemoglobin (Hb) SS, 40 HbSC, and 2 with sickle cell-beta zero thalassemia (Hb S-β^0-thal). The mean age of the patients was 36.2 ± 12.4 years (range, 18-65 years), and 62 patients were women (52%). The majority of the patients are asymptomatic, in NYHA functional class (FC) I (77%), whereas 24 (20%) were in class II and 4 (3%) in class III. The clinical characteristics of the study population are summarized in Table 1. Sixteen patients (13%) had hypertension, and 43 patients (36%) had renal dysfunction. Hospitalization in the past year occurred in 25 patients (21%), 2 or more times in 11 patients (9%).

Stroke was previously diagnosed in 16 patients (13%), who were under hypertransfusion and were without significant motor sequelae. The most frequently used medications were folic acid (93%), hydroxyurea (62%), and angiotensin-converting enzyme inhibitors or angiotensin receptors blockers (23%). Seven patients (6%) were taking furosemide. All patients who were clinically stable presented mild anemia with hemoglobin levels of 9.9 ± 2.2 g/dl (Table 1). B-type natriuretic peptide concentrations were within the normal range.

The echocardiographic measurements are demonstrated in Table 1. The majority of the patients had normal ventricular dimensions with preserved systolic function. Left atrial volume was increased, whereas other parameters to assess diastolic function were normal, especially tissue Doppler-derived E/e' ratio, which was within the normal range. Similarly, right ventricular dimensions and tricuspid regurgitation maximal velocity jet were also within the normal range. Only 2 patients presented a tricuspid regurgitation jet velocity ≥3 m/s.

Exercise testing

Ischemic ST abnormalities compatible with criteria for ischemia during the effort were detected in 19 patients (17%). Exercise testing characteristics are presented in Table 2.

In the overall population, subjective assessment of functional capacity during anamnesis by NYHA functional class (FC) was associated with that measured by exercise testing. Functional capacity was measured in METs, with the mean value of 8.9 ± 2.8, range from 1.5 to 17.3. The patients in class I achieved 9.4 METs whereas those in class III achieved less than 4 METs. The relationship between functional class as assessed by anamnesis and ergometry is shown in Figure 1.

Supraventricular premature contractions were frequent during exercise, isolated in 16% of the cases, and complexes with some episodes of paroxysmal supraventricular tachycardia in 17% of the patients. Isolated ventricular premature contractions occurred in 14 patients (12%). Abnormal blood pressure response was found in 10 patients (9%), with a mean increase of systolic blood pressure of 14 mmHg, when compared to those with anormal response, in whom the mean increase of blood pressure was 29 mmHg (p=0.002). Following the exercise testing, within 48 hours, two patients (1.8%) experienced pain crises that required hospitalization for treatment.

Factors associated with exercise duration

In the overall population, the exercise duration was 9.2 minutes, ranging from 1.1 to 15.5 minutes. Several clinical, laboratory, and echocardiographic variables were tested for a possible association with exercise tolerance (Table 3). The potential predictors that were selected for the multivariate model were age, gender, oximetry at rest, hemoglobin concentration, and echocardiographic parameters of LV diastolic function, RV function, and pulmonary pressure assessed by TR maximal velocity. TR maximal velocity and E/e' ratio were the main factors associated with exercise time in the univariate analysis. In the

multivariate linear regression analysis, including the laboratory markers of disease severity, TR maximal velocity and E/e' ratio emerged as important factors associated with exercise duration, after adjustment for age and gender (Table 4).

Predictor of adverse events

During a mean follow-up of 10.1 months (range, 1.2 to 26), the endpoint was reached in 27 patients (23%): 4 patients died (one death was unrelated to SCD), 8 were hospitalized due to ≥ 3 acute painful episodes, 11 had acute chest syndrome, and 4 were hospitalized with other SCD-related complications.

Several variables were tested for a possible association with an adverse outcome (Table 4). The potential predictors that were selected for the multivariate model were genotype Hb SS, Hemoglobin levels, left ventricular mass, left atrial volume, right atrial area, tricuspid regurgitation peak velocity, peak transmitral A velocity, BNP levels, and abnormal blood pressure response to exercise. In the multivariate analysis, the independent predictors of adverse events were hemoglobin concentration, peak transmitral A velocity, and abnormal blood pressure response to exercise. The cumulative incidence of adverse events by systolic blood pressure response is shown in Figure 2.

Discussion

This study sought to provide some information on exercise tolerance in SCD patients. As there is a lack of evidence in the literature about exercise testing in SCD, our results show

Table 1 – Baseline Characteristics of the Study Population

Variables*	Value
Body surface area (m^2)	1.7 ± 0.2
Heart rate (bpm)	75.8 ± 13.6
Systolic/diastolic blood pressures (mmHg)	117.4 ± 14.6/73.2 ± 4.3
Hemoglobin (g/dl)	9.9 ± 2.2
Reticulocytes (% of erythrocytes)	5.6 [3.6/8.7]
Leukocyte count ($x10^3$/l)	8.6 ± 3.0
Lactate dehydrogenase (U/l)	575 [413/833]
Aspartate aminotransferase (U/l)	23 [16/32]
Ferritin (ng/ml)	181 [75/388]
Total bilirubin (mg/dl)	1.7 [1.1/3.0]
Creatinine (mg/dl)	0.7 [0.6/0.8]
B-type natriuretic peptide (BNP, pg/ml)	27 [11/62]
Echocardiographic measurements	
Left ventricular end-diastolic diameter (mm)	51 [48/56]
Left ventricular end-systolic diameter (mm)	33[30/37]
Left ventricular ejection fraction (%)	63 [59/65]
Indexed LV mass (g/m^2)	103.2 [85/130]
Peak early diastolic transmitral flow velocity (E,cm/s)	93.1 ± 22.2
Peak late transmitral flow velocity (A, cm/s)	55.9 ± 16.9
Deceleration time (ms)	206.0 ± 41.6
E/A ratio	1.8 ± 0.7
E/e' ratio †	6.8 ± 2.2
Indexed left atrial volume (mL/m^2)	42.1 ± 14.8
Right ventricular fractional area changing (%)	44.2 ± 5.8
Right ventricular peak systolic velocity (cm/s)	14.5 ± 3.0
Tricuspid annular motion (mm)	25.9 ± 4.3
Right ventricular myocardial performance index	0.12 ± 0.07
Tricuspid regurgitation maximal velocity‡ (m/s)	2.2 ± 0.3
Right atrial area (cm^2)	16.2 ± 3.4

**Values are expressed as the mean value ± SD, or median [interquartile range]. e': early diastolic mitral annular velocity at septal and lateral mitral annulus, E/A: ratio of early to late transmitral flow velocity. † E/e': ratio of the early diastolic transmitral flow velocity to early diastolic mitral annular velocity (average at septal and lateral mitral annulus). ‡Peak systolic velocity at the tricuspid annulus by tissue Doppler imaging.*

Table 2 – Patient characteristics during exercise testing

Variables*	Value
Oximetry (%)	95 [92/96]
Peak HR (beats/min)	158.4 ± 21.0
Peak HR (% predicted)	86.9 ± 10.0
Peak VO_2 ($ml.Kg^{-1}.min^{-1}$)	31.0 ± 9.7
MET	8.9 ± 2.8
Presence of ischemia	20 (17)
Supraventricular premature beats	40 (33)
Ventricular premature beats	17 (14)
Abnormal blood pressure response	11 (9)
Changes in systolic blood pressure (mmHg) †	27.5 ± 14.9
Delta of systolic pressure/exercise duration (mmHg/min) ‡	3.1 ± 1.5

**Values are expressed as the mean value ± SD, number (percentage) of patients, or median [interquartile range]. † Systolic blood pressure at peak - at rest. ‡ Systolic blood pressure at peak - at rest / exercise time; HR: heart rate; MET: metabolic equivalent for task.*

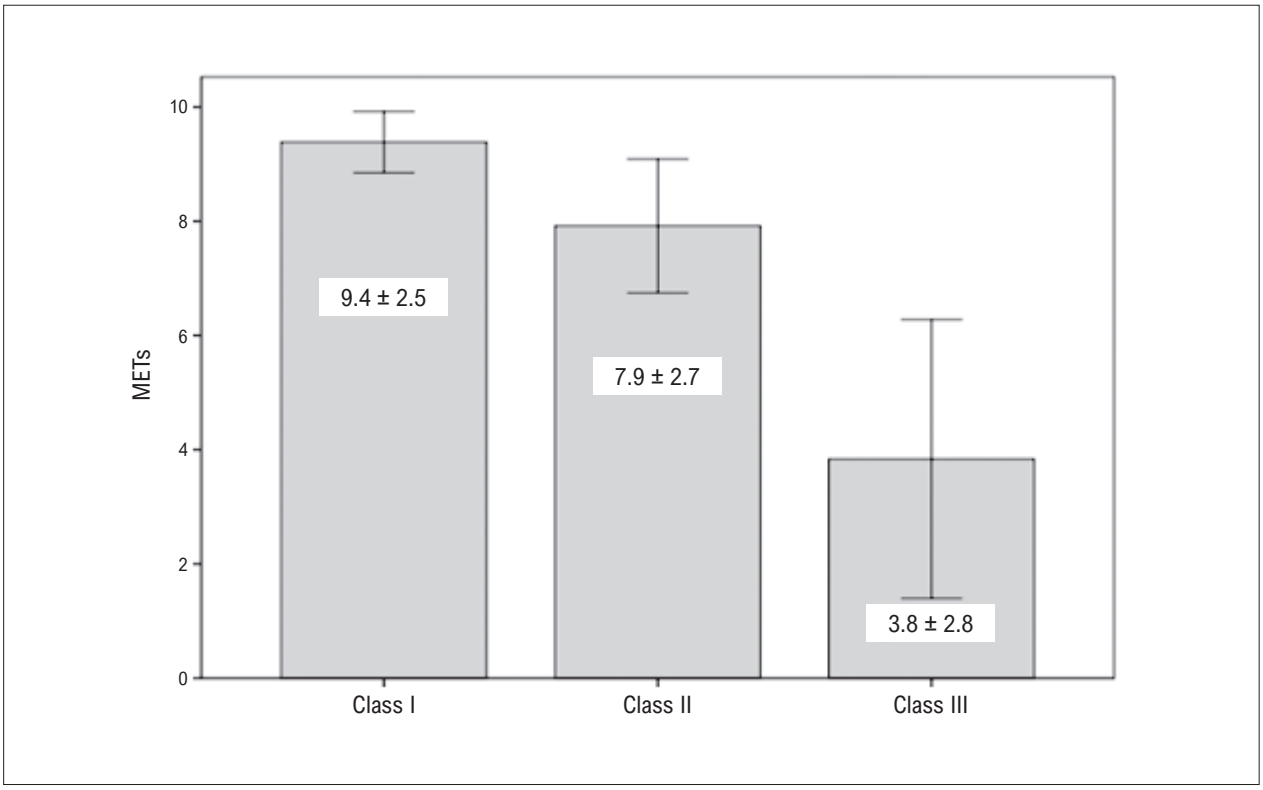

Figure 1 – *Association between functional capacity by NYHA functional class assessed by anamnesis and exercise capacity measured by ergometry.*

that exercise testing in chronic compensated patients with SCD is feasible, relatively safe, and can be performed in a hospital environment with an experienced team. Moreover, exercise testing provides useful information for the management of patients with SCD.

There is a lack of evidence to indicate an exercise program for patients with SCD. The major question faced by healthcare professionals involved in SCA management is the safe level of physical exercise they should recommend for their patients.[21]

As physical activity is known to induce metabolic changes that can potentially precipitate a vaso-occlusive crisis, patients are usually encouraged to exercise on a symptom-limited basis. The presence of anemia induces a faster transition from aerobic to anaerobic metabolism during exercise, which may stimulate the polymerization of hemoglobin S and promote microvascular occlusions.[29,30] Additionally, the dehydration that occurs during

Table 3 – Factors associated with exercise time

Variables	Univariate		Multivariate	
	Beta	p-value	Beta	p-value
Age (years)	-0.067	0.001	-0.038	0.045
Male gender	1.386	0.003	1.195	0.006
Beta-blockers	-2.158	0.014	…	…
Leg ulcers	-1.242	0.034	…	…
Previous stroke	-1.475	0.042	…	…
Indexed LA volume (mL/m^2)	-0.049	0.002	…	…
Peak A velocity (cm/s)	-0.032	0.025	…	…
Deceleration time (ms)	-0.017	0.004	…	…
E/e' ratio	-0.358	<0.001	-0.224	0.018
TR maximal velocity (m/s)	-2.675	<0.001	-1.810	0.015
Indexed LV mass (g/m^2)	-0.015	0.014	…	…
Systolic blood pressure (mmHg)	-0.045	0.005	…	…
Oximetry (%) at rest	0.240	0.022	…	…
B-type natriuretic peptide (pg/ml)	-0.006	0.001	…	…
Hemoglobin (g/dl)	0.387	<0.001	…	…
Ferritin (ng/ml)	-0.001	0.001	…	…
Lactate dehydrogenase (IU/l)	-0.002	0.004	…	…
Proteinuria	1.436	0.005	…	…

LA: left atrial; LV: left ventricular; TR: tricuspid regurgitation.

Table 4 – Cox proportional-hazards analysis for predicting adverse outcomes in patients with sickle cell disease

Variables	Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Genotype Hb SS	2.546 (1.020-6.351)	0.045	…	…
Hemoglobin (g/dl)	0.803 (0.664-0.970)	0.023	0.688 (0.552-0.858)	0.001
LV mass (g/m^2)	1.007 (1.000-1.015)	0.055	…	…
LAV (mL/m^2)	1.022 (0.999-1.046)	0.060	…	…
Right atrial area (cm^2)	1.143 (1.042-1.255)	0.005	…	…
TAM (mm)	1.098 (1.008-1.197)	0.033	…	…
TR velocity (m/s)	3.729 (1.474-9.433)	0.005	…	…
Peak A velocity (cm/s)	0.976 (0.955-0.998)	0.031	0.964 (0.933-0.997)	0.034
Abnormal SBP response	4.110 (1.346-12.550)	0.013	4.990 (1.316-18.921)	0.018
BNP (pg/ml)	1.001 (1.000-1.003)	0.052	…	…

CI: confidence interval; HR: hazard ratio; LAV: left atrial volume; LV: left ventricular; SBP: systolic blood pressure; TAM: tricuspid annular motion; TR: tricuspid regurgitation; BNP: B-type natriuretic peptide.

exercise, associated with the acute episodes of tissue hypoxia, may also contribute to the sickling of the red blood cells. Therefore, although our study and others have demonstrated relative safety of physical activity in SCD,[21] it is not risk-free. We observed two complications after the test, reinforcing the need for medical care, including hydration, to perform exercise testing in this vulnerable population.

However, recent evidence suggests that SCD patients may practice physical activities even if specific recommendations about exercise duration and intensity are needed.[21, 30]

The presence of arrhythmias during exercise varies greatly in the literature. In our study, 16% of the patients presented supraventricular arrhythmias, which is higher than expected

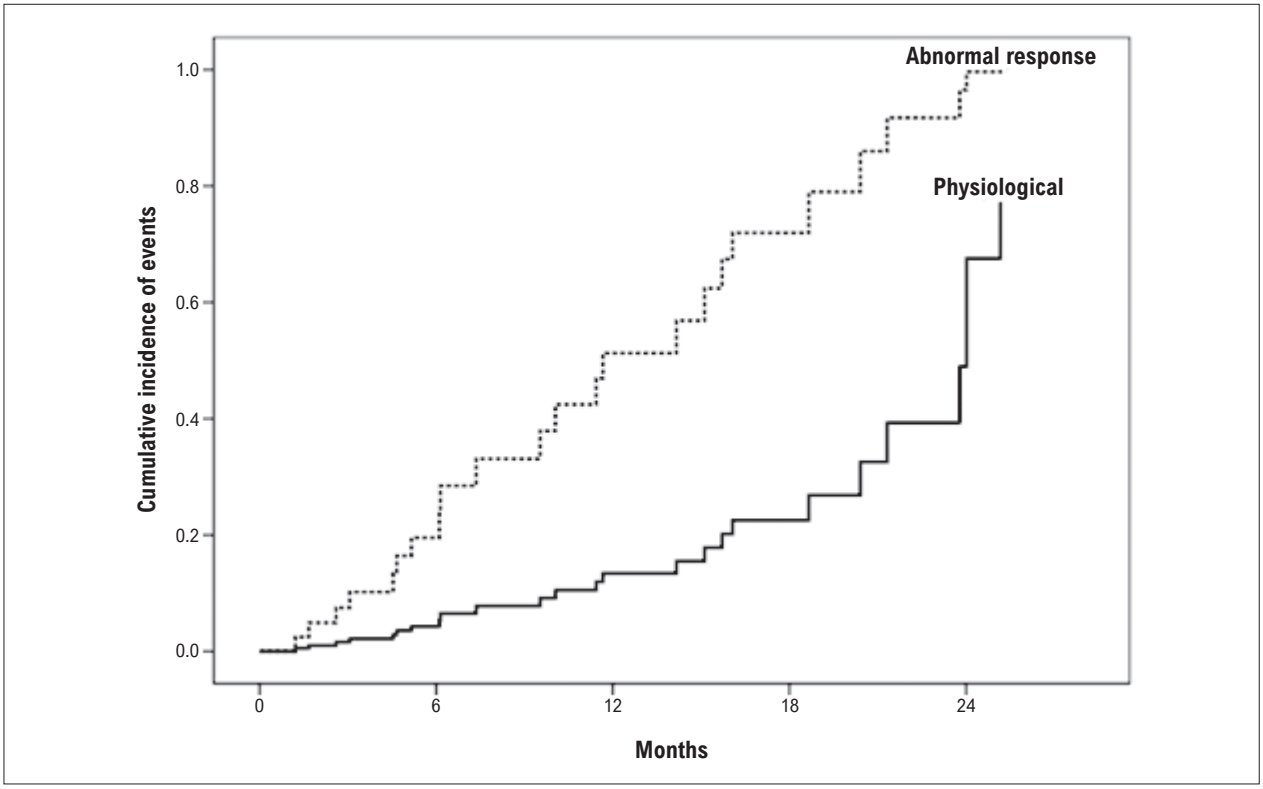

Figure 2 – *Cumulative incidence of adverse events in patients with SCD who presented abnormal blood pressure response to exercise as compared to those with a physiological response (p-value of 0.027).*

for this group of patients.[19,31] This is probably due to left atrial enlargement and diastolic dysfunction often seen in SCD, which are the main factors associated with these arrhythmias,[32] adjusted by age. The prevalence of ventricular arrhythmias was similar to data from the literature.[19] The presence of ischemic changes of the ST-segment, suggesting that myocardial ischemia is considered frequent in SCD, ranging from 10-50%.[6,11,33] We found a prevalence of 17%, with no other findings indicating obstructive coronary disease.

Determinants of exercise tolerance in patients with SCD

Accentuated impairment in exercise capacity has consistently been found in SCD patients. Several factors contribute to exercise intolerance, including possible cardiac filling abnormalities, chronic anemia, pulmonary vascular disease, peripheral vascular disease related to microvascular occlusion.[11,21,34,35] Three main mechanisms for exercise limitation in SCA were proposed: anemia, pulmonary vascular disease, and peripheral vascular disease and/or myopathy.[21] Indeed, in our study, the tricuspid regurgitation velocity that estimates pulmonary artery systolic pressure remained as an important determinant of exercise duration after adjustment for age and gender. Similarly, a tissue Doppler-derived E/e' ratio, which is a marker of high LV filling pressure was an independent factor associated with exercise duration.

In agreement with our findings, a previous study showed that a reduction in the 6-min walk distance was independently associated with echocardiographic measures of pulmonary hypertension, expressed by tricuspid regurgitation velocity, and with measures of diastolic dysfunction, suggesting two major independent determinants of exercise intolerance.[36]

In the general population, abnormalities of left ventricular diastolic function, measured by E/e' ratio, are independently associated with exercise capacity.[37] Although males had a greater exercise capacity than females, the magnitude of this difference decreased with age. Compared to those with normal diastolic function, patients with mild diastolic dysfunction (impaired relaxation) had a progressive increase in the magnitude of reduction in exercise capacity with advancing age.[37] In the present study with asymptomatic patients with mild diastolic dysfunction, age was inversely correlated with exercise capacity.

Abnormal blood pressure response and adverse outcomes in SCD

The mean arterial pressure should normally increase by near 40% during incremental exercise as a result of the increase in cardiac output, with a progressive increase in systolic blood pressure.[24] Abnormal blood pressure responses are relatively common, and their potential clinical value has increasingly drawn attention.[38] Although difficult to determine on the basis of varying definitions, the prevalence of exercise hypotension has been reported in up to 6%.[39]

Exercise-induced hypotension has long been considered a poor prognostic sign in those with established cardiovascular disease.[40-42] A systematic review and meta-analysis showed that a hypotensive response predicts longer-term fatal and non-fatal cardiovascular events and all-cause mortality.[43] This was observed irrespective of disease presentation, mode of exercise undertaken, intensity of exercise, or how exercise hypotension was defined. In agreement, we found that abnormal blood response was an independent predictor of adverse events, after adjustment for well-known prognostic factors.

Several mechanisms have been proposed to explain the association between the increased risk of adverse cardiovascular outcomes and an insufficient rise, or drop, in blood pressure during incremental exercise testing.[38,42] During exercise, decreased systolic blood pressure below resting values has been linked to underlying cardiovascular disease, including left ventricular dysfunction, coronary artery disease, and aortic outflow obstructions.[42,43] Abnormalities in the autonomic nervous system during exercise testing are likely observed in patients who appear with decreased systolic blood pressure responses. Autonomic imbalance has been related to the development of heart failure, and similar disturbances possibly occur in those with decreased exercise systolic blood pressure response.[44] A previous study showed that even modest elevations in systolic blood pressure during exercise stress testing are associated with a decreased risk of all-cause death and myocardial infarction.[42] However, the etiology of exercise-induced hypotension is multifactorial and complex.

In the setting of SCD, systemic blood pressure is reported to be lower in SCD patients without comorbidities, when compared to the general population.[45] SCD patients with blood pressure values above the expected range for this population – "relative systemic hypertension" – had increased risk of stroke and death.[46]. The exact mechanism by which exercise induced abnormal blood pressure response in SCD patients is related to adverse outcomes needs to be defined. Myocardial ischemia induced by exercise may cause left ventricular dysfunction. Indeed, a previous study reported that left ventricular end-diastolic volume decreased most markedly with exercise in patients exhibiting ischemic ECG.[47] On the other hand, another investigation found that the patients who had ischemic responses when exercising also showed an elevated double product (systolic blood pressure x heart rate) with an excessive elevation in blood pressure, suggesting increased myocardial oxygen demand during exercise in this population.[48]

Pulmonary hypertension is also associated with exercise limitation and poor prognosis in SCD patients.[21] Although in our study the pulmonary pressure response to exercise was not assessed, its excessive elevation during exercise may contribute to right ventricular dysfunction, reduction in cardiac output, with consequent hypotensive response to exercise. Indeed, the relationship between adverse outcome and abnormal blood pressure response to exercise in SCD patients is complex, likely mediated by chronic complications, including anemia, pulmonary vascular disease, and left ventricular diastolic dysfunction.

Study limitations

The study has some limitations. The sample size was estimated to detect ECG abnormalities related to myocardial ischemia in SCD, which limits the analysis regarding the predictors of adverse events. The patients enrolled in this study are referred from an outpatient clinic, including a wide spectrum of the SCD, but with a small number of more severe disease subgroups, particularly with pulmonary hypertension, which limits its external validity.

A total of 34% of the patients had an SC subtype, which limited our conclusions for the entire population of SCD. In addition, the use of the cardiopulmonary exercise test would be the ideal tool to study the determinants of functional capacity in these patients. Another limiting factor is related to the measurement of blood pressure during exercise. It is well described the difficulty of this measurement during physical activity, which may compromise the reproducibility of our finding.

Conclusions

Exercise testing in SCD patients who were clinically stable is relatively safe and feasible, providing valuable clinical information, and may be helpful in aerobic conditioning. Exercise-induced ischemic electrocardiographic changes were frequent, whereas pain crises after exercise were uncommon. The main determinants of exercise duration were left ventricular diastolic function and pulmonary artery pressure estimated by tricuspid regurgitation velocity. Abnormal blood response was an independent predictor of adverse events. Further studies are needed to determine the safety of the exam in larger samples, together with the underlying mechanisms associated with the increased risk of adverse events in patients with SCD with decreased systolic blood pressure response during exercise stress testing.

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Author Contributions

Conception and design of the research: Araújo CG, Resende MBS, Januário JN, Ribeiro ALP, Nunes MCP; Acquisition of data: Araújo CG, Resende MBS, Tupinambás JT, Dias RCTM, Barros FC, Vasconcelos MCM, Januário JN, Nunes MCP; Analysis and interpretation of the data and Statistical analysis: Araújo CG, Resende MBS, Ribeiro ALP, Nunes MCP; Obtaining financing: Januário JN, Ribeiro ALP, Nunes MCP; Writing of the manuscript: Araújo CG, Ribeiro ALP, Nunes MCP; Critical revision of the manuscript for intellectual

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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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Can We Perform the Maximal Treadmill Test on Individuals with Sickle Cell Disease?

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Short Editorial related to the article: Exercise Testing in Patients with Sickle Cell Disease: Safety, Feasibility and Potential Prognostic Implication

Sickle cell disease (SCD) may present a stable clinical condition with the advancement of pharmacological treatment and available technologies for early diagnosis.[1] However, if not diagnosed and treated early, it may lead to progressive organ damage and even fatal complications.[2] Therefore, it is important to develop different instruments to assess the SCD prognosis. The maximal treadmill test (MTT), widely used in different diseases, such as heart failure, can play an important role in the risk stratification of these patients, since they usually have chest pain associated with vessel occlusion, causing myocardial ischemia and, consequently, sudden death, something very common in these individuals.[3,4]

However, patients with SCD need to exercise caution when performing physical exercises, especially at high-intensity, as these may lead to metabolic disorders that could favor erythrocyte sickling and promote vascular occlusions.[5] This fact raised a discussion and a dilemma between recommending physical exercise for these patients or depriving them of the positive effects that physical exercise is capable of promoting.[6,7] Due to the association described above, between physical exercising and ischemia in SCD individuals, it is necessary to perform an exercise test.[8] However, we get to the paradox of risk versus benefit. Can individuals with SCD safely perform a MTT to provide answers about the cardiovascular impact induced by exertion in the occurrence of clinical outcomes? This is what Araújo et al.,[9] Below we will describe the main study characteristics and its main results.

This is an observational study that aimed to assess the safety and feasibility of a MMT in SCD patients. In addition, factors associated with test duration and the impact of changes caused by the test on clinical outcomes were evaluated. For the development of the study, 133 patients with SCD were included. In addition to undergoing an exercise stress assessment, they underwent a comprehensive cardiovascular assessment, including echocardiography, as well as B-type natriuretic peptide (BNP) levels. The long-term outcome (24 months) was a combination of events, such as mortality, severe pain crises, acute chest syndrome, or hospital admissions for other complications associated with the disease.

We need to draw attention to the results found, such as ischemic changes on exertion, which were detected in 17% (19) of the patients, and also to abnormal blood pressure (BP) responses during the test, detected in 9% (10). These data already bring us an alert to the ergometric evaluation in this population. Regarding more severe acute responses, such as pain crises, 48 hours after the test, two patients required hospitalization. The factors associated with the test duration include age, sex, maximum tricuspid regurgitation velocity (TRV) and E/e' ratio, all standardized markers of disease severity. 23% of the patients had some adverse clinical outcome, with a mean follow-up period of 10.1 months (ranging from 1.2 to 26). Independent predictors of adverse events were hemoglobin concentration, late transmitral flow velocity (A wave), and BP response to physical exertion.

We will cite some limitations of the present study, in order to improve the conduct of future studies, as the topic is very interesting and lacks robust scientific literature. One of the limitations is that the sample size was estimated to detect electrocardiographic abnormalities related to myocardial ischemia in SCD individuals, however, without taking into account the analysis of predictors of adverse events. When it comes to scientific studies, we must pay attention to internal and external validity, which determines the power to extrapolate the data to a larger sample.[10] This study was very well conducted. However, it does not have good external validity, as patients were referred from an outpatient clinic with SCD, but with a small number of more severe subgroups, especially those with pulmonary hypertension, limiting external validity to patients with more severe conditions. The suggestion is to conduct a randomized clinical trial in the future with subgroups of different levels of disease severity for better external validation and consequently improve the quality of evidence.[11]

What can be positively highlighted is that the MMT for SCD patients is relatively safe and feasible, offering valuable clinical information, in addition to being useful in the assessment of aerobic condition. Furthermore, it is possible to conclude that test duration is associated with diastolic function and pulmonary artery pressure and that an abnormal BP response was an independent predictor of adverse events. This information is supportive when performing a MMT in SCD patients.

Keywords

Sickle Cell Anemias; Exercise Test.

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Cost-Effectiveness Analysis of CCTA in SUS, as Compared to Other Non-Invasive Imaging Modalities in Suspected Obstructive CAD

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Abstract

Background: **The Brazilian public health system does not include computed tomography angiography (CTA).**

Objective: **Rank, according to the Brazilian public health system, the cost-effectiveness of different strategies for the diagnosis of coronary artery disease (CAD), combining exercise tests (ET), myocardial scintigraphy (MS), stress echocardiography (SE), and CTA in a hypothetical intermediate pre-test probability cohort of patients.**

Methods: **This study implemented a cost-effectiveness analysis through a decision tree. The incremental cost-effectiveness ratio (ICER) and net benefit were analyzed by adopting multiple thresholds of willingness to pay, from 0.05 to 1 GDP per capita per correct diagnosis. In sequential tests, a second confirmatory test was performed only when the first was positive.**

Results: **After excluding dominated or extended dominance diagnostic strategies, the efficiency frontier consisted of three strategies: ET, ET followed by SE, and SE followed by CTA, the last being the most cost-effective strategy. Through the net benefit, the ranking of the most cost-effective strategies varied according to willingness to pay.**

Conclusions: **Using current concepts of health technology assessment, this study provides a ranking for decision-making concerning which diagnostic strategy to use in a population with an intermediate pre-test risk for CAD. With a feasible cost estimate adopted for CTA, the impact of including this to the list of the diagnostic arsenal would represent a cost-effective strategy in most of the evaluated scenarios with broad variations in the willingness to pay.**

Keywords: **Coronary Disease; Stable Angina; Cost-Benefit Analysis; Diagnostic Techniques, Cardiovascular.**

Introduction

Cardiovascular disease was the cause of 17.7 million deaths in 2015, representing 31% of all deaths worldwide. Of these, it is estimated that 7.4 million occur due to coronary artery disease (CAD).[1,2] In Brazil, according to most recent health indicators, approximately 490,000 deaths were reported from 2007 to 2011.[3] It is estimated that the prevalence of light angina and mild to severe angina in the Brazilian population is, respectively, 7.6% and 4.2%,[4] and the costs related to cardiovascular diseases grow as the population ages, estimated, in 2015, for Brazil, at a total of R$37.1 billion, or approximately 0.7% of the gross domestic product (GDP).[5]

Coronary angiography (CA) is the "gold standard" for the diagnosis of CAD; however, it is an invasive exam and associated with complications.[6,7] Ideally, non-invasive tests should select which patients should be referred for invasive diagnostic confirmation, but the current strategy is flawed, as demonstrated in a massive record of 398,978 patients referred for the CA, of which only 37% presented obstructive CAD, even though non-invasive tests were conducted in 85% of the patients (mostly functional).[8] One Brazilian study corroborates these findings, in which 61% of the patients with functional tests with high-risk criteria did not present obstructive CAD.[9] New diagnostic tests with greater accuracy or sequential diagnostic strategies have the potential to reduce the diagnostic errors and the unnecessary number of CAs.

Identifying the most cost-effective diagnostic strategy for obstructive CAD can bring clinical and economic benefits for the Brazilian Unified Health System (SUS, in Portuguese). Today, in addition to the CA, the diagnostic tests for CAD available at SUS are: myocardial scintigraphy (MS), stress echocardiography (SE), and exercise tests (ET). The computed tomography angiography (CTA) is an exam that is still not included in SUS, although it does present high-accuracy diagnoses, when compared to the other exams.[10–13]

The present study aims to rank the cost-effectiveness of the different CAD diagnostic strategies, considering the non-invasive tests available at SUS, and the CTA, testing varied thresholds of the willingness to pay for a pre-defined 30% intermediate pre-test probability population within the realm of SUS.

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Methods

The incremental cost-effectiveness ratio (ICER) has been routinely used by health technology assessment agencies worldwide to summarize the results of economic assessments and establish the cost-effectiveness of technologies. However, a new methodology of cost-effectiveness assessment was proposed: the *net monetary benefit* (NMB), or the *net health benefit* (NHB).[14] This latter methodology has advantages over the ICER, as it does not require a base comparison to estimate the gains and incremental costs, and as it is easier to calculate. The efficiency or "benefit" of each strategy can be measured in different forms, such as years of lives saved, or by the number of correct diagnoses obtained with a diagnostic strategy. Based on a pre-defined willingness to pay, the "profit" obtained with the intervention is estimated. For example, if a decision-maker is willing to pay R$10,000 per year per saved life, a technology that increases survival in 5 years would be "worth" R$50,000. If the interventional price were less than R$50,000, it would be beneficial. For a hypothetical value of R$30,000, such an intervention would be providing an NMB of R$20,000 (5 x R$10,000–R$30,000). Likewise, considering the same willingness to pay, we would expect a minimum gain of 3 years of life with such an investment (30,000/R$10,000), but, as it provides 5 years of survival, we will have an NHB of 2 years. The greater the monetary or health gain, the greater the cost-effectiveness of that technology or diagnostic strategy, as its incorporation will bring savings and gains in health.

The cost-effectiveness of the diagnostic tests for obstructive CAD (CTA, MS, SE, and ET) was assessed using a combination of 11 diagnostic strategies and the impact on a hypothetical cohort of 1,000 individuals with a 30% prevalence of CAD (intermediate probability). A negative test represented the end of the study. In cases in which the diagnostic strategy involved sequential tests, a second confirmatory test was carried out only if the first test was positive. The sum of true negative tests (negative test in patients without CAD>50%) with true positive tests (positive tests in patients with CAD>50%) represented the total correct diagnoses.

To define the most cost-effective strategy, two analyses were adopted: the efficiency frontier, one based on the ICER and one based on the NHB. As there is no cost-effectiveness threshold established in Brazil, all of the technologies that were not dominated or without extended dominance were presented through an efficiency frontier. With the strategies ranked according to their costs or benefits, the dominated strategy will simply be that which is less efficient and more expensive.

The second stage of the ICER analysis involves the identification of strategies with extended dominance. The undominated strategies were ranked in an ascending order of costs, and the ICER was calculated by comparing the costs and incremental effectiveness related to the prior least costly strategy. The less efficient strategies and those with a lower ICER were considered non-cost-effective by extended dominance.

The most cost-effective strategy, by definition, is that which presents the highest ICER, within the threshold of the willingness to pay established by the decision-maker. In the case of the NHB, the most cost-effective strategy will be that which brings the highest net gain in number of correct diagnoses, according to each threshold of willingness to pay. For both analyses, it was necessary to estimate the costs and the effectiveness (quantity of correctly diagnosed tests) of the different strategies.

The most cost-effective strategies were also ranked according to the variation of pre-test probabilities between 10% and 60% in different thresholds of willingness to pay for a correct diagnosis (table attached here and available at Mendeley Data), the Brazilian GDP per capita using as a base value. All of the calculations were done in Excel®.

Costs

The estimation of costs (Table 1) was created by means of a *top-down* approach, and the cost of each strategy was based on the unit cost of each test. For the tests available at SUS, the costs were obtained through SIGTAP (Management System for the Table of Procedures, Medications and OPM) from SUS.[3] For CTA, the *bottom-up* micro-cost approach was used to quantify the resources necessary for its fulfillment (appendix 1).

Effectiveness

The accuracy of each test was estimated based on a literature review carried out on September 20, 2019, with a search for meta-analyses about the accuracy of diagnostic tests in the MEDLINE, The Cochrane Library, Lilacs databases, with no restrictions on languages. The studies were selected separately by two reviewers (P.B. and L.T.); disagreements were resolved by consensus. If at the end of the selection of the studies there was more than one article selected, the study with the best quality evaluation, according to AMSTAR.[15] was used. The search strategy and the flowchart

Table 1 – Costs of diagnostic tests in ascending order

Test	Unit cost (SIGTAP)
Exercise test	R$ 30.00
Stress echocardiogram	R$ 165.00
Computed tomography angiography	R$ 452.05
Stress and at-rest myocardial scintigraphy	R$ 791.59

Values extracted from the SIGTAP table in 2020[3]

of the selection of evidence is available, respectively, in appendixes 2 and 3.

Sensitivity analysis

To evaluate the impact of uncertainties of the values inserted in the model, a deterministic sensitivity analysis was performed. The confidence and interquartile intervals were used as the maximum and minimum values of each piece of information contained in the model as of the literature review, as shown in Table 2.

Ethical Consideration

No studies were performed on human beings, nor were confidential, institutional, or personal data used. The entire study is based on data published in electronic databases. This project received the following report from the Research Ethics Committee (REC): "This study is a systematic review of the literature that does not require an assessment on the part of the REC"; logged under report number: 2.421.181.

Results

In the ICER analysis, among the 11 diagnosed strategies, 7 dominated strategies were identified, that is, strategies with a higher cost and a lower number of correct diagnoses (Table 3).

The four undominated strategies were listed in ascending order of costs, and it was identified that the ET + CTA strategy was the least effective (least number of correct diagnoses) and with a higher ICER than the SE + CTA strategy (Table 4), and was thus not considered to be cost-effective (extended dominance).

Thus, the efficiency frontier was constructed based on the three most cost-effective strategies, ET, ET+SE, and SE+CTA (Figure 1).

Based on the sensitivity analysis, shown in the Tornado Graph (Figure 2), the parameters with greater impact on the results were sensitivity and specificity of the exercise test, the cost of the CTA, and the prevalence of CAD.

The NHB ranking enables the assessment of all of the strategies without the need to exclude dominated or extended

Table 2 – Parameters and values adopted in the ICER model for CAD diagnostic strategies

Parameter	Accuracy	Lower Limit	Upper Limit	Reference
ET Sensitivity	0.80	0.48	0.85	Banerjee et al.,2012[16]
ET Specificity	0.63	0,63	0.88	Banerjee et al.,2012[16]
SE Sensitivity	0.81	0.70	0.87	Banerjee et al.,2012[16]
SE Specificity	0.84	0.73	0.94	Banerjee et al.,2012[16]
MS Sensitivity	0.88	0.88	0.89	Jaarsma et al., 2012[17]
MS Specificity	0.61	0.59	0.62	Jaarsma et al., 2012[17]
CTA Sensitivity	0.93	0.93	0.94	Haase et al., 2019[18]
CTA Specificity	0.84	0.84	0.85	Haase et al., 2019[18]

Exercise Test and Stress Echocardiogram: (Banerjee, Newman, Van Den Bruel, & Heneghan, 2012); Scintigraphy (Jaarsma et al., 2012); CTA (Haase et al., 2019). ET: exercise test; MS: myocardial scintigraphy; CTA: computed tomography angiography; SE: stress echocardiogram.

Table 3 – Projection of the strategies in 1,000 patients in order of cost, with the number of correct diagnoses and the identification of the dominated strategies

Strategy	Cost	Correct diagnosis	Observation
ET	R$ 30,000.00	681	
ET + SE	R$ 112,335.00	853	
SE	R$ 165,000.00	831	Dominated
ET + CTA	R$ 255,572.95	884	
SE + CTA	R$ 325,477.75	909	
CTA	R$ 452,050.00	871	Dominated
CTA + ET	R$ 463,732.00	884	Dominated
CTA + SE	R$ 516,301.00	909	Dominated
CTA + MS	R$ 760,295.15	904	Dominated
MS	R$ 791,590.00	691	Dominated
MS + CTA	R$ 1,034,340.85	904	Dominated

ET: exercise test; MS: myocardial scintigraphy; CTA: computed tomography angiography; SE: stress echocardiogram. Year 2020 as reference for the presented values.

Table 4 – Identification of extended dominance in the undominated diagnostic strategies for CAD

Strategy	Cost	Correct diagnosis	ICER	
ET	R$ 30,000.00	681.00	NA	
ET + SE	R$ 112,335.00	852.96	R$ 478.80	
ET + CTA	R$ 255,572.95	883.75	R$ 4,651.19	Extended dominance
SE + CTA	R$ 325,477.75	909.49	R$ 2,716.44	

ET: exercise test; MS: myocardial scintigraphy; CTA: computed tomography angiography; SE: stress echocardiogram. Year 2020 as reference for the presented values; ICER: incremental costeffectiveness ratio.

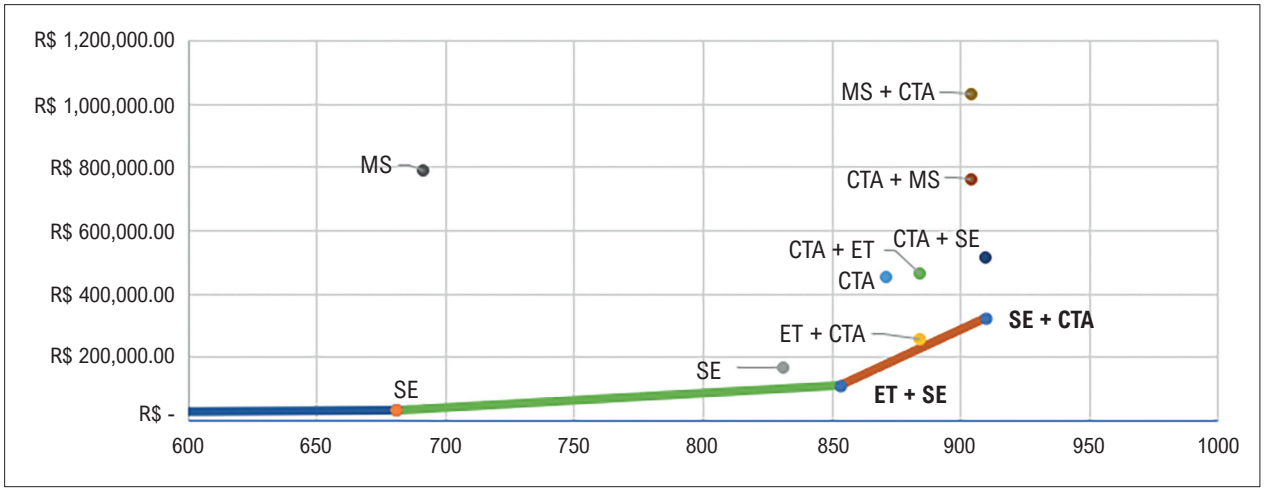

Figure 1 – *Efficiency frontier of diagnostic strategies for CAD (costs and number of correct diagnoses per 1,000 individuals). ET: exercise test; MS: myocardial scintigraphy; CTA: computed tomography angiography; SE: stress echocardiogram.*

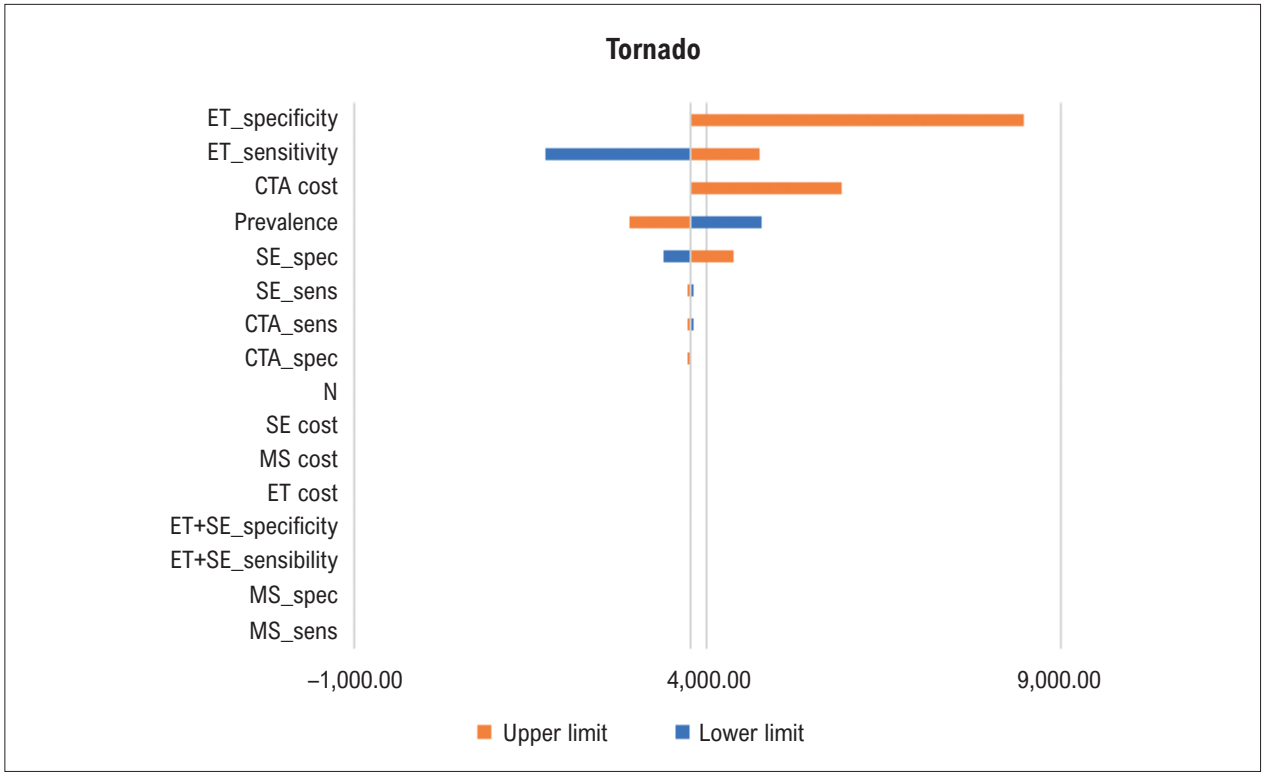

Figure 2 – *Tornado Diagram – impact on the ICER values of each parameter evaluated separately in their upper and lower limits.*

dominance strategies. Table 5 presents the ranking of more cost-effective strategies according to the variation of pre-test probabilities between 10% and 60% in different thresholds of willingness to pay for a correct diagnosis, using the Brazilian GDP per capita as the base value, which, according to the most recent IBGE 2017 census is R$ 31,833.50.[19]

Discussion

The SE + CTA strategy presents the best rate of correct diagnosis (909.49), in other words, the best effectiveness, and therefore the greatest certainty in the clinical guidance of the patients, be it for CA, or be it to eliminate the diagnosis. The definition of the best strategies to investigate obstructive CAD result in the best diagnostic certainty, thus minimizing the number of false-negatives (loss of diagnosis), as well as false-positives (reducing the number of "white" catheterisms and their complications).[20,21] Diagnostic errors in this scenario are associated with unnecessary invasive exams, in addition to leading to complications, such as acute myocardial infarction and death due to the lack of adequate treatment in a disease of high mortality.[1,2,20] The accuracy of the diagnostic tests should be analyzed in light of their costs, primarily when we consider a new technology in a publicly financed health system, such as SUS.

The ICER has been used by health technology assessment agencies worldwide to summarize the results of economic assessments of health interventions. Even in countries like Brazil, where there is no explicitly defined ICER threshold for decision-making, its impact on decisions is highly relevant. However, alternative resolute measures based on the concept of net benefit are being presented, and this is the first study to assess the cost-benefit of diagnostic strategies for CAD through an analysis of net benefit in health.

There are important distinctions between the ICER and the NHB. The ICER requires the comparison of two strategies, regardless of the total number of evaluated strategies. In the NHB, the net benefit measures are calculated for each strategy individually, that is, it eliminates the need to compare pairs and the need to eliminate dominated strategies. What is necessary is a defined threshold of the willingness to pay to calculate the measure of net benefits, but they are not necessary to calculate the ICER, although without a threshold of cost-effectiveness, its interpretation would be limited. No cost-effectiveness threshold has been established in Brazil in the process of the incorporation of technologies. In this study, the most cost effective strategy, according to the efficiency frontier, was the combination of the stress echocardiogram, followed by the computed tomography angiography, given that it is the undominated strategy with the highest ICER value and within a threshold.

The NHB criterion allows for the ranking of all of the strategies in such a way as to aid the decision-maker in choosing which strategy to follow, based on the availability of the exams/professionals, budget, and willingness to pay for a correct diagnosis. The CTA, although it is the only exam not included today in SUS, is the most prevalent exam among the most cost-effective strategies, only failing to reach first place when the willingness to pay is less than 0.2 GDP per capita per correct diagnosis. Separately, not considering sequential exams, the most cost-effective exam is the stress echocardiogram, up to the threshold of 0.1 GDP per capita per correct diagnosis, surpassed by the CTA in the upper thresholds.

When varied in different pre-test probabilities (10% to 60%), we find that the CTA is the most cost-effective test (combined or not with other methods) in 79% of the scenarios analyzed in this study, which is in accordance with cost-effectiveness studies of CTA conducted in developed countries[20-23] and with the recent updates from the UK's *National Institute for Heath and Care Excellence* guidelines from 2017[22,24] and the European Society of Cardiology (ESC) guidelines.[25] Updated in 2019, this guideline determines that the CTA can be used as the first-line exam in the evaluation of suggestive symptoms of obstructive CAD, substituting functional imaging exams. In the UK, which has a health system financed with public resources (like SUS in Brazil) based on cost-effectiveness analyses for their reality, the CTA was recommended as the first-line exam, substituting functional exams.[22,24] This decision should be taken based on the reality of each country and each health system, with the aim of the present study being to foster the understanding of the diagnostic strategies of thoracic pain within the reality of SUS.

The choice of diagnostic strategy should take into consideration not only the cost-effectiveness for the finding of the coronary obstruction, but also the clinical outcomes. Major randomized studies, such as PROMISE and SCOT HEART, have brought information mainly about the prognosis of those patients who began the CAD investigation with CTA. There was a greater certainty in the diagnosis and, with this, a greater

Table 5 – Ranking of the diagnostic strategies by threshold of willingness to pay for correct diagnosis according to the net benefit criteria, in relation to the different pre-test probabilities

	0.05 GDP pc	0.1 GDP pc	0.2 GDP pc	0.3 GDP pc	0.4 GDP pc	0.5 GDP pc	1 GDP pc
10%	ET + SE	ET + SE	SE + CTA	SE + CTA	SE + CTA	SE + CTA	SE + CTA
20%	ET + SE	ET + SE	SE + CTA	SE + CTA	SE + CTA	SE + CTA	SE + CTA
30%	ET + SE	CTA + ET	SE + CTA	SE + CTA	SE + CTA	SE + CTA	SE + CTA
40%	ET + SE	CTA + ET	SE + CTA	SE + CTA	SE + CTA	SE + CTA	SE + CTA
50%	SE	CTA + ET	CTA	CTA	CTA	CTA	CTA
60%	SE	SE	CTA	CTA	CTA	CTA	CTA

ET: exercise test; MS: myocardial scintigraphy; CTA: computed tomography angiography; SE: stress echocardiogram; GDP: gross domestic product.

introduction of preventive medicine therapies, considering a real possibility in the reduction of events, such as long-term infarctions, in addition to documenting a lesser number of CAs without obstructive disease in this group of patients.[26,27] In this context, it is important to highlight that the large randomized ISCHEMIA study failed to demonstrate any reduction in deaths or limb infarctions in the functional exams.[28] By contrast, the anatomical evaluation enables the diagnosis of atherosclerosis and refers the patient to a better clinical treatment, with the possibility of a reduction in infarctions and deaths.[26,27,29] The final guideline of the Brazilian Society of Cardiology (SBC) from 2014 recommends beginning the investigation of obstructive CAD with functional exams, followed by CTA should such exams be inconclusive or contraindicated.[30]

Among the functional methods, the MS is one of the most commonly used tests in Brazil and worldwide to diagnose CAD.[31,32] It is estimated that, in SUS, approximately 54% of the elective nuclear medicine exams are of myocardial perfusion.[32] However, the strategies that include MS were dominated in our study, which proved to be the most expensive and the least effective.

The ET + SE and SE + CTA strategies present percentages of false-positives similar to 4% (Table 2:2, attached here), whereas the percentage of false-negatives varies considerably among the strategies. For example, the ET + SE strategy presents a false-negative rate of 1.3%, while the ET + CTA strategy presents a false-negative rate of 0.4% (three-fold less than the ET + SE), thus presenting less incorrect diagnoses. Although it has an extended dominance in the effectiveness frontier, in the analysis of the NHB, we observed that the ET + CTA strategy loses to the ET + SE strategy only within the margin of 0.05 to 0.1 GDP per capita (table NHB attached here). Asymmetric economic characteristics between regions and cities in Brazil make the availability of equipment and qualified workforce heterogeneous. For example, in 2019, among the nearly six million CT exams performed in SUS, 51% were concentrated in the Southeast region and less than 6% in the North.[33] The ranking of the diagnostic options presented in this work can aid decision-makers by combining local data on infrastructure, willingness to pay, and diagnostic accuracy. The CTA is less well-known and makes use of a more expensive machinery than does the SE, which may well limit its use as a first-line exam in scenarios with a lower budget, in which the ideal would be to begin with a lower cost and less complex exam, with the results used as referrals for more expensive and complex exams. As the ET is more well-known than the SE, one should consider that the ET + CTA strategy may well be more executable in the Brazilian public health system than would be the SE + CTA strategy, despite the minor drop in effectiveness from that of the ET as compared to that of the SE. The present study mainly analyzed patients in a 30% pre-test probability, as this is the prevalence of disease normally found in the outpatient diagnostic laboratories (considered mild-low). After performing the sensitivity tests, the results of cost-effectiveness do not reveal substantial changes when we vary the pre-test probability. In addition, the pre-test probability between 10% and 60% was ranked according to the willingness to pay, considering that the CTA was not found as a cost-effective option only when we considered the value of 0.05 GDP per capita per correct diagnosis.

Among the limitations of this study, discrepancies were found among the articles, mainly regarding the definition of obstructive CAD, in which the studies about CTA and MS define coronary obstruction as being above 50% by means of coronary angiography, while the study that includes exercise tests and stress echocardiogram includes articles with obstructive CAD references above 50% or 70%. To minimize possible biases, systematic reviews, meta-analyses, and quality analyses of the articles were performed. A recent cost-effectiveness study, with data from SUS, presented, as its main limitation, the determination of the CTA value as the cost paid by SUS for a simple chest CT, extrapolating data from the supplementary health system.[34] Our study attempts to reach the real value of the costs of CTAs (approximately 3 times the value of the chest CT), since this value has a major impact on the assessment of comparative strategies. Finally, the accuracy of the tests varies with the quality of the equipment and of the responsible staff. Future studies can verify the impact of the adoption of this flow chart of decision-making through the prospective follow-up by computing clinical and economic data from real world results.

Conclusion

In scenarios like that of Brazil, with budget restrictions and heterogeneity in the supply of diagnostic tests, the identification of cost-effective strategies can guide health managers and decision-makers to manage their resources in a more efficient manner. Using up-to-date concepts of health technology assessments, this study provides a ranking for decision-making regarding which diagnostic strategy to use in a population with an intermediate pre-test risk for CAD. With a feasible cost estimate adopted for CTA, it can be concluded that the impact of including this to the list of diagnostic arsenal would represent a cost-effective strategy in most of the evaluated scenarios with broad variations in the willingness to pay.

Author Contributions

Conception and design of the research and Critical revision of the manuscript for intellectual content: Carmo PB, Rey HCV, Gottlieb I; Acquisition of data: Carmo PB, Trocado L; Analysis and interpretation of the data: Carmo PB, Magliano C, Rey HCV, Camargo G, Gottlieb I; Statistical analysis: Magliano C; Writing of the manuscript: Carmo PB, Magliano C, Camargo G, Gottlieb I.

Potential Conflict of Interest

Dr. Gabriel C. Camargo - Works in a private company performing CTA. Dr. Ilan Gottlieb - Works in a private company performing CTA

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Study Association

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*Supplemental Materials

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It is Time for Coronary Computed Tomography Angiography to be Incorporated into the SUS

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Short Editorial related to the article: Cost-Effectiveness Analysis of CCTA in SUS, as Compared to Other Non-Invasive Imaging Modalities in Suspected Obstructive CAD

In the evaluation of patients with stable coronary artery disease (CAD), also called chronic coronary syndrome (CCS), complementary tests are used both for diagnostic and prognostic purposes.[1,2] Anatomical (coronary angiography and coronary CT angiography) and functional (exercise testing, stress echocardiography, rest and stress myocardial perfusion imaging by scintigraphy, magnetic resonance, and positron emission tomography) tests are available. Coronary angiography, the gold standard, is invasive and therefore, indicated for clinically more severe patients, or those with poor prognostic findings in non-invasive testing, when myocardial revascularization is considered or planned.[3]

The choice for the most appropriate diagnostic test is an important and challenging issue for the cardiologist in the clinical evaluation of CCS. The first step in this decision-making process is the assessment of the pre-test probability (PTP) of CAD. As recommended by the current SCC guidelines,[3,4] patients classified as having high PTP should receive medical therapy and undergo testing for prognostic information. The patients with low PTP should be assessed for an alternative diagnosis more likely than CAD. Patients with PTP calculated between 15-85% are in the intermediate range, where the complementary tests are more useful and important for CAD diagnosis.[5] In addition to diagnostic accuracy and PTP, the selection of a non-invasive test depends on the clinical characteristics of patients, local expertise, and the availability of tests.[4] In Brazil, it is estimated that up to 80% of the population depends exclusively on medical care provided by the public health system (SUS).[6] In this context of managing economic resources, physicians and health managers should focus on the most cost-effective options for the diagnosis of CAD.

The article by Carmo et al.[7] assesses just the intermediate and low-intermediate PTP (10-60%) scenario, via two different methods of cost-effectiveness analysis, using up-to-date concepts of health technologies (incremental cost-effectiveness ratio and the net benefit). The strategies with sequential tests were performed when the first test was positive. The results were presented according to the variation of PTP at different thresholds of willingness to pay for a correct diagnosis. Although coronary computed tomography angiography (CTA) is not yet available in SUS, it was the most cost-effective strategy in this study, either alone or in sequential testing, except in the lower thresholds of willingness to pay, in which was overwhelmed by stress echocardiogram (SE).[7]

Another interesting finding concerns the use of exercise testing (ET), which was placed in the background in international guidelines,[4] but showed to be an excellent cost-effective option in lower PTPs and lower willingness to pay thresholds, especially when followed by SE in case the ET was positive.[7] Given the large economic differences between regions in Brazil, in locations with less availability of resources and health financing, ET could remain the main diagnostic screening strategy for CAD.

Myocardial scintigraphy (MS), widely used in SUS, proved to be more expensive and less effective than CTA and SE in all scenarios evaluated, appearing as a negative spotlight in the diagnostic strategy in CAD. Furthermore, CTA was able to reveal non-obstructive CAD even in patients with moderate and severe myocardial ischemia in functional tests, such as 15% of those initially selected for the ISCHEMIA trial.[8] Another advantage of CTA is the possibility of non-invasive quantification of the fractional flow reserve, capable of detecting flow-limiting obstructive coronary lesions, reducing the number of false-positive results.[9] These findings highlight the usefulness of CTA in significantly reducing the number of CCS patients referred to coronary angiography and, therefore, decreasing the costs and possible complications of the invasive testing.

The main results of the analysis performed by the authors are based on the estimated CTA price in which SUS would pay for, that can be underestimated, since the ATC versus MS costs readily available online in many supplementary healthy services are comparable. This would lead to an important limitation of this manuscript if confirmed afterwards. Another gap is the intermediate-high PTP scenario (60-85%), not evaluated in this study, where MS could be able to show a better competitiveness, considering its good performance in confirming the diagnosis of functionally significant CAD in this higher PTP range.[10]

This article shows relevant evidence that may be applied by SUS health managers and physicians in the decision-making process of the diagnostic methods chosen for CAD. It might also be used as a future reference for local guidelines, that similarly to other international guidelines[1,11] may consider

Keywords

Cost-Benefit Analysis; Stable Angina; Coronary Artery Disease; Computed Tomography Angiography; Unified Health System; Diagnostic Imaging/methods;

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the recommendation of ATC as a first-line diagnostic test for CAD, as an alternative to functional imaging. It should be noted, however, that functional testing remains irreplaceable in objectively assessing the degree of functional limitation and the patient's response to therapy.[3,4] Finally, there is still room for the rational use of all available methods in diagnosing obstructive CAD in clinical practice, but there is no longer any reason why CTA should not be incorporated into the SUS.

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Clinical Profile and 30-Day Outcomes of Patients with Bicuspid Aortic Valve Undergoing Aortic Valve and/or Aorta Surgery

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Abstract

Background: The bicuspid aortic valve (BAV) affects 0.5 to 2% of the population and is associated with valve and aortic alterations. There is a lack of studies on the profile of these patients in the Brazilian population.

Objective: To describe the profile of patients with BAV undergoing valve and/or aortic surgery in a tertiary cardiology center, in addition to the outcomes related to the intervention.

Methods: Retrospective cohort including 195 patients (mean age 54±14 years, 73.8% male) diagnosed with BAV who underwent surgical approach (valvular and/or aorta) from 2014 to 2019. Clinical data, echocardiographic and tomographic studies were evaluated, as well as characteristics of the intervention and events in 30 days. A value of p<0.05 was considered statistically significant.

Results: We found a high prevalence of aortic aneurysm (56.5%), with a mean diameter of 46.9±10.2 mm. Major aortic regurgitation was found in 25.1% and major aortic stenosis in 54.9%. Isolated aortic valve surgery was performed in 48.2%, isolated aortic surgery in 6.7% and combined surgery in 45.1%. The 30-day mortality was 8.2%. In the multivariate analysis, the predictors of the combined outcome at 30 days (death, atrial fibrillation and reoperation) were age (OR 1.044, 95% CI 1.009-1.081, p=0.014) and left ventricular mass index (OR 1.009, 95% CI 1.000-1.018, p=0.044).

Conclusion: Patients with BAV approached in our service have a higher incidence of aortopathy, with the additional need to evaluate the aorta with computed tomography or magnetic resonance imaging.

Keywords: Aortic Valve; Thoracic Surgery; Aortic Valve Stenosis.

Introduction

The bicuspid aortic valve (BAV) is the most prevalent congenital heart disease, affecting 0.5 to 2% worldwide.[1-3] Life expectancy is similar to general population, but these patients have hemodynamic, cellular, molecular and genetic changes that are intrinsically related to repercussions on the aortic valve and aorta, requiring early surgical intervention.[4-7] Furthermore, the prevalence and progression of these defects are proportional to age, with the greater risk of cardiovascular outcomes in patients older than 30 years.[8]

Such complex etiopathogenicity of BAV generates a heterogeneity of clinical presentations. In addition, there is a lack of information on the clinical profile of patients with BAV undergoing cardiac surgery, especially in the Brazilian population.

Objective

This study aims to describe the profile of patients with BAV undergoing valve and/or aortic surgery in a tertiary cardiology center, in addition to the outcomes related to the intervention.

Methods

Study population: Retrospective cohort of patients over 18 years old with a diagnosis of BAV who underwent surgical approach to the aorta and/or aortic valve between the years 2014 to 2019. All patients underwent transthoracic echocardiography analysis and evaluation of the ascending aorta and aortic arch by computed tomography or magnetic resonance imaging before surgery. The surgical indication was based on institutional protocols, following current guidelines for the treatment of valvular heart disease and aortic diseases.[9,10] Patients without documentation of aortic assessment or pre-procedure echocardiogram were excluded. The study protocol was reviewed and approved by the local institutional ethics committee.

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Study protocol: Preoperative data of the population such as age, sex, medications in use, presence of symptoms, surgical risk by EuroSCORE II, comorbidities, anatomical characteristics of the aorta by computed tomography or magnetic resonance imaging, cardiac and valve anatomy by echocardiogram, and laboratory data on hemoglobin and creatinine were evaluated. In the 30-day outcomes, data on perioperative mortality and complications were analyzed, in addition to the 30-day composite endpoint of mortality, atrial fibrillation and surgical reoperation.

Statistical analysis: The SPSS version 26 program (IBM, Armonk, NY) was used for statistical analysis, with simple descriptive analyzes of frequency and percentage for categorical variables, with a description of mean and standard deviation or median and interquartile range for continuous variables. Data normality distribution was analyzed using the Kolmogorov-Smirnov test. For comparative analysis between groups, the chi-square test or Fisher's exact test was used to assess categorical variables, as appropriate. For comparison of continuous variables, unpaired Student's t-test or Mann-Whitney test was used, as appropriate. Univariate analysis of predictors related to the 30-day composite endpoint of mortality, atrial fibrillation and reoperation was performed with binary logistic regression. In the univariate analysis, those with a p-value <0.05 were selected and included in the multivariate binary logistic regression model. The relationship of the presence of aortic stenosis or regurgitation with the left ventricular mass index was evaluated using the linear regression method, and the necessary assumptions for the use of this technique were verified (variability and distribution of errors). A value of $p<0.05$ was considered statistically significant.

Results

Characteristics of the population: 195 consecutive patients with BAV who underwent surgery during this period were included. The mean age was 54±14 years, mostly male and with a high prevalence of comorbidities such as systemic arterial hypertension, diabetes, and chronic kidney disease. The characteristics of the studied population are shown in Table 1. In the assessment of the aorta, 187 (95.9%) patients underwent computed tomography, and the remainder (4.1%) underwent magnetic resonance imaging, with 76.4 % of aortic ectasia (aorta > 38 mm), and 56.5% with aortic aneurysm (aorta > 45 mm), with a mean diameter of the ascending aorta of 46.9 ± 10.2 mm (Figure 1). By echocardiographic assessment, the mean preoperative left ventricular ejection fraction was 59 ± 11%, with severe aortic regurgitation in 25.1% and severe aortic stenosis in 54.9%. Patients with aortic stenosis had a mean transaortic gradient of 49.1 ± 17.0 mmHg and aortic valve area of 0.79 ± 0.19 cm^2. Surgical indication for aortic valve disease occurred in 62.6% of the cases, 33.3% for aortopathy and the remainder for coronary artery disease or mitral valve disease.

Acute aortic dissection was described in 5.6% of the patients, who had larger aortic diameters than those without acute dissection (54.95 ± 21.36 vs. 46.81 ± 8.81 mm, $p=0.010$).

Surgical characteristics and clinical outcomes: Data related to surgery and clinical outcomes are described in Table 2. In 45.1%, the procedure was combined aorta and aortic valve surgery. Of these, 53.4% underwent Bentall de Bono surgery, 33% underwent modified Bentall de Bono surgery with implantation of a biological prosthesis, and the remaining underwent surgery with aortic valve preservation. In 94 (48.2%) patients, isolated aortic valve surgery was performed and 13 (6.7%) patients underwent isolated aortic surgery. In the patients undergoing aortic valve surgery, biological prosthesis was implanted in 60.4%, mechanical prosthesis in 30.2%, aortic valve repair in 8.8%, and one patient underwent transcatheter approach (TAVI). The 30-day mortality was 8.2%, higher than predicted by the EuroSCORE II (1.61 [0.93-3.02] %). In the postoperative period, 21.5% of patients had acute renal failure, 15,7% had atrial fibrillation, and 9.7% required reoperation. The outcomes according to the type of valve lesion (severe aortic stenosis, severe aortic regurgitation, severe mixed aortic disease and moderate mixed aortic disease) are described in Supplementary Table 1.

Predictors of the Composite Endpoint: The univariate analysis of predictors of 30-day composite endpoint of death, atrial fibrillation and reoperation are described in Table 3 and Supplementary Table 2. In the multivariate analysis, age and left ventricular mass index remained independent predictors of the combined outcome. Although the presence of aortic stenosis or regurgitation was not predictor of endpoint, we found a relationship of these variables with the left ventricular mass index ($B=18.52$, 95% CI=3.96-33.09, $p=0.013$ and $B=61.80$, 95% CI=44.73-78.87, $p<0.001$; respectively). The multivariate analysis excluding the patient undergoing TAVI found the same composite endpoint predictors described above and is shown in Supplementary Table 3.

Comparison according to intervention indication: The comparison of patients according to indication for surgery by aortic diameter or valve disease is shown in Table 4. Patients in whom intervention was indicated due to disease of the aorta were less symptomatic and had less cardiac remodeling, with a smaller mass index of LV, smaller left atrium diameter, thinner septum, and posterior wall. As expected, patients with an indication for disease of the aorta had larger aortic diameters and indexed aortic diameters. Patients indicated for valvular heart disease had a higher proportion of combined surgery. We did not find differences between groups regarding outcomes.

Discussion

The main findings of this study were: (1) 76.4% of patients with BAV had associated aortopathy, (2) because it is a tertiary center, high morbidity is highlighted, with 56.9% hypertensive and 46.7% of patients with coronary artery disease, therefore, we found a higher intervention mortality than predicted by the EuroSCORE II and (3) age and left ventricular mass index were predictors of

Table 1 – Baseline characteristics of the studied population

Variables	n=195
Clinical features	
Age, years	54.7±14.1
Female Sex	51 (26.2)
Body Surface Area, m²	1.88±0.21
Hypertension	111 (56.9)
Diabetes	25 (12.8)
Previous atrial fibrillation	15 (7.7)
Chronic kidney Disease*	44 (22.6)
Coronary Artery Disease	39 (46.7)
Previous Endocarditis	9 (4.6)
Angina	46 (23.6)
Dyspnea NYHA III or IV	112 (59.1)
EuroSCORE II, %	1.61 (0.93-3.02)
Beta-Blocker	90 (46.2)
Diuretics	95 (48.7)
ACEi	59 (30.3)
BRA	64 (32.8)
Statins	75 (38.5)
Laboratory	
Hemoglobin, mg/dL	13.9±1.7
Creatinine, mg/dL	1.14±0.56
Characteristics of the aorta	
Larger diameter of the thoracic aorta, mm	46.9±10.2
Larger indexed thoracic aorta diameter, mm/m²	25±6
Aortic diameter > 38 mm	149 (76.4)
Aorta diameter > 45 mm	100 (56.5)
Acute dissection	11 (5.6)
Coarctation	11 (5.6)
Echocardiogram	
Aortic sinus, mm	37.4±6.8
Left atrium diameter, mm	40.5±7.2
Septum, mm	12±4
Posterior wall, mm	11±1
LV mass index, g/m²	142±53
LV diastolic diameter, mm	56.8±10.7
LV systolic diameter, mm	38.3±9.4
LV ejection fraction, %	59±11
Aortic valve area, cm²†	0.82±0.22
Maximum transaortic gradient, mmHg†	54±33
Mean transaortic gradient, mmHg†	42±19
Severe aortic regurgitation	48 (25.1)
Severe aortic stenosis	104 (53.3)
Severe mixed aortic disease	16 (15.5)
Surgical indication	
Severe aortic stenosis	78 (40,0)
Severe aortic regurgitation	44 (22,6)
Aorta	65 (33,3)
Coronary or mitral valve	8 (4,1)

*Data presented as mean ± standard deviation, median (interquartile range) or n (%). *Chronic kidney disease was defined as creatinine clearance <60ml/kg/min. †Parameters described only in patients with aortic stenosis. ARB: Angiotensin II receptor blocker; ACE inhibitors: Angiotensin-Converting Enzyme Inhibitor; NYHA: New York Heart Association; LV: left ventricle.*

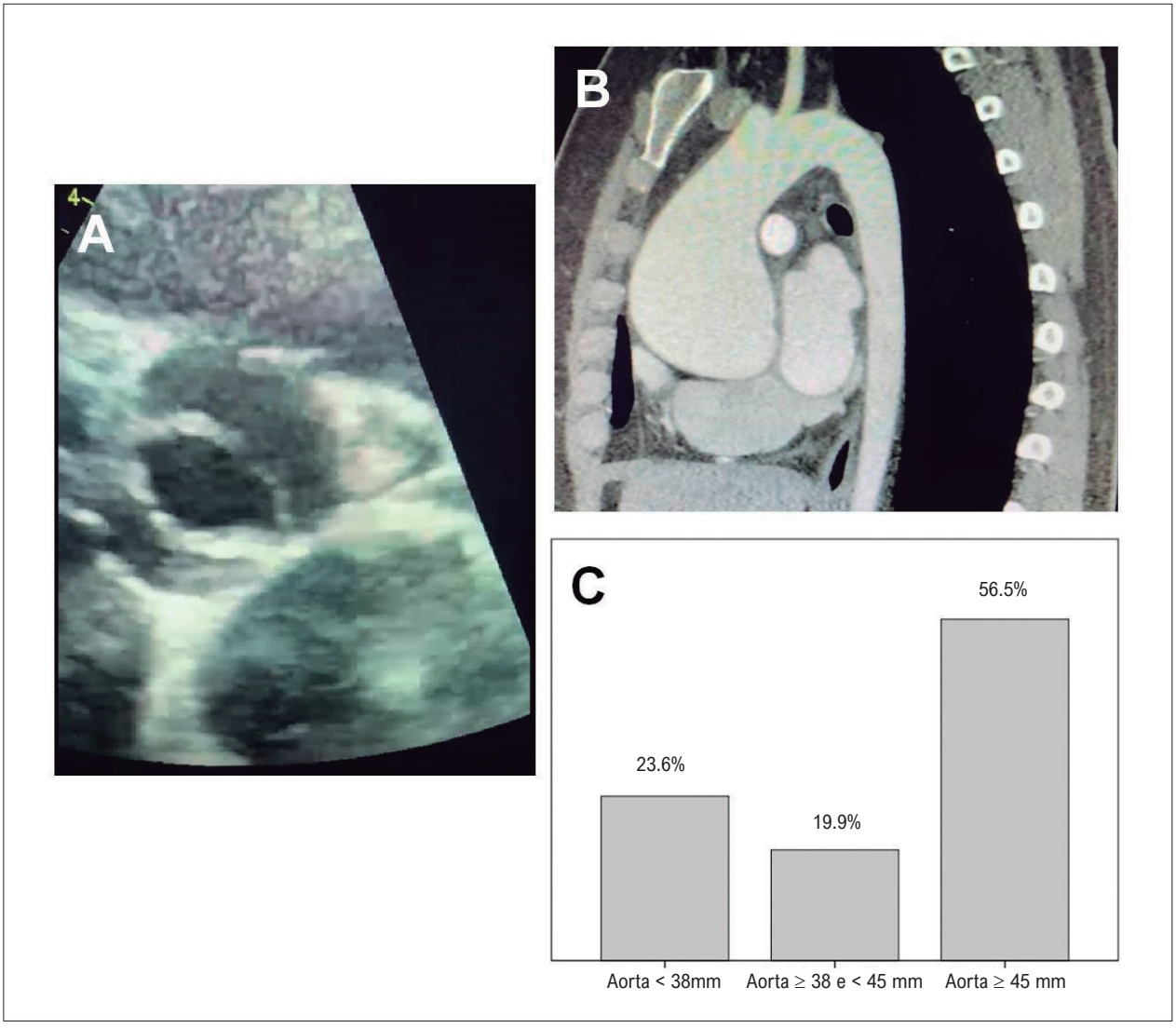

Figure 1 – *A) Transverse parasternal window of transthoracic echocardiogram showing bicuspid aortic valve. B) Computed tomography of the aorta showing dilation of the ascending aorta. C) Incidence of patients with bicuspid aortic valve and aorta smaller than 38 mm, aorta between 28 and 45 mm, and aorta greater than or equal to 45 mm.*

the composite endpoint of death, atrial fibrillation, and reoperation within 30 days.

BAV is a defect in embryogenesis of the aortic valve not fully clarified, but with several theories about its origin, from changes in fetal transvalvular flow leading to failure in the separation of the cusps to more current theories relating genetic factors and failure of cell migration in some phases of embryogenesis.[11-13] The fusion of the cusps leads to the turbulence of the valve flow, thus predisposing to early aortic valve degeneration. Turbulent flow is also responsible for asymmetrical stress on the aortic wall, which may predispose to dilation of the aorta.[4] In addition to this hemodynamic change in the outflow tract that explain the aortopathy associated with valve degeneration, microscopic changes also occur such as reduced fibrillin-1, matrix disruption, apoptosis and increased metalloproteinases justifying the presence of aortic dilatation in patients with valve function unchanged.[6,7,14]

The indication for an intervention in BAV may be related to severe aortic valve disease associated with symptoms or prognostic factors – an indication similar to other valve diseases or aortopathy itself. The indication for intervention in the aorta varies according to the case. In patients with aortic dilatation without valve disease, frequent follow-up is indicated for those with an aortic diameter greater than 45mm or an increase of 0.3cm/year. The 2014 European Society of Cardiology Guidelines for Diagnosis and Management of Aortic Diseases indicate an intervention for patients with aortic diameter >55mm alone and >50mm in the presence of prognostic factors.[10] The American Heart Association guidelines do not define a specific cut-off value for isolated aortic intervention, guiding a case-by-case assessment of patients with aortic

Table 2 – Surgery characteristics and clinical outcomes

Variable	n=195
Procedure	
Combined surgery (Aorta and aortic valve)	88 (45.1)
Bentall de Bono	47 (53.4)
Modified Bentall de Bono	29 (33.0)
Aortic valve repair	12 (13.6)
Isolated aorta surgery	13 (6.7)
Aortic valve surgery	94 (48.2)
Biological prosthesis	80 (85.1)
Mechanical prosthesis	9 (9.5)
Valve repair	4 (4.2)
TAVI	1 (1.0)
Combined myocardial revascularization	24 (12.3)
Outcomes in 30 days	
Mortality	16 (8.2)
Bleeding	28 (14.4)
Blood transfusion	41 (21)
Acute kidney injury*	42 (21.5)
Reoperation	19 (9.7)
Stroke	4 (2.1)
Cardiac tamponade	8 (4.1)
Combined outcome (death + atrial fibrillation + reoperation)	55 (28.2)
Length of stay in the ICU, days	5.1±5.8

*Data presented as mean ± standard deviation or n (%). *Acute kidney injury defined as an increase in creatinine ≥0.3 mg/dl. TAVI:Transcatheter aortic bioprosthesis implantation; ICU: Intensive Care Unit.*

Table 3 – Predictor analysis for the 30-day composite endpoint of death, atrial fibrillation, and re-approach

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
Age, years	1.051 (1.023-1.078)	<0.001	1.044 (1.008-1.082)	0.016
Body surface area, m^2	0.214 (0.047-0.974)	0.046	0.178 (0.019-1.658)	0.130
Hemoglobin, mg/dL	0.812 (0.673-0.978)	0.029	0.871 (0.680-1.116)	0.276
Angiotensin II receptor blocker	1,916 (1.003-3.660)	0.049	0.680 (0.297-1.557)	0.362
Left atrium diameter, mm	1,078 (1.028-1.131)	0.002	1.072 (0.995-1.155)	0.067
LV mass index, g/m^2	1.007 (1.001-1.014)	0.017	1.009 (1,000-1.018)	0.044
LV ejection fraction, %	0.960 (0.933-0.987)	0.004	0.981 (0.945-1.018)	0.305
Moderate or severe tricuspid regurgitation	6,550 (1,923-22,309)	0.003	0.528 (0.095-2.950)	0.467
Moderate or severe mitral regurgitation	2.603 (1.035-6.549)	0.042	2,646 (0.633-11.069)	0.183
Aortic valve surgery	3.257 (1.042-10.175)	0.042	2.972 (0.505-17.504)	0.229

OR: odds ratio; LV: left ventricle.

Table 4 – Comparison of patients according to indication for intervention by aortic diameter or valve disease

Variables	Indication by the diameter of the aorta (n=65)	Indication for valve disease (n=130)	p
Clinical features			
Age, years	57.3±14.5	53.4±13.8	0.072
Body Surface Area, m²	1.88±0.22	1.88±0.21	0.917
Women	14 (21.5)	37 (28.5)	0.300
Hypertension	43 (66.2)	68 (52.3)	0.066
Diabetes mellitus	8 (12.2)	17 (13.1)	0.880
Dyslipidemia	21 (32.3)	37 (28.5)	0.580
Chronic kidney disease*	20 (30.8)	24 (18.5)	0.053
EuroSCORE II, %	1.96 (0.97-4.43)	1.35 (0.89-2.66)	0.045
Laboratory			
Hemoglobin, mg/dl	14.0±1.6	13.8±1.7	0.395
Creatinine, mg/dl	1.23±0.82	1.10±0.36	0.132
Symptoms			
Angina	13 (20)	33 (25.4)	0.520
Dyspnea NYHA III and IV	23 (35.4)	89 (68.4)	<0.001
Medications			
Beta-blocker	42 (64.6)	48 (36.9)	<0.001
ACEi	16 (24.6)	43 (33.1)	0.250
BRA	24 (36.9)	40 (30.8)	0.349
Spironolactone	2 (3.1)	18 (13.8)	0.020
Loop diuretic	27 (41.5)	68 (52.3)	0.185
Aortic Characteristics			
Larger diameter of the aorta	53.6±11.1	43.1±7.4	<0.001
Larger diameter of the indexed aorta	28.7±6.9	23.0±4.8	<0.001
Echocardiogram			
Aortic sinus, mm	41.0±7.1	35.7±6.0	<0.001
Left atrium diameter, mm	38.9±6.7	41.2±7.3	0.035
Septum, mm	11.0±1.7	12.3±4.8	0.012
LV posterior wall, mm	10.1±1.5	11.0±1.9	0.001
LV mass index, g/m²	126.1±44.7	150.8±55.3	0.002
LV diastolic diameter, mm	54±9	57±11	0.064
LV systolic diameter, mm	36±8	39±9	0.136
LV ejection fraction, %	60±8	58±12	0.089
Mean transaortic gradient, mmHg	34±18	44±18	0.019
Aortic valve area, cm²	0.91±0.27	0.80±0.20	0.137
Severe aortic stenosis	18 (27.7)	86 (66.2)	<0.001
Severe aortic regurgitation	10 (15.4)	38 (29.2)	0.047
Moderate or severe tricuspid regurgitation	3 (4.6)	10 (7.7)	0.554
Moderate or severe mitral regurgitation	3 (4.6)	18 (13.8)	0.059
Surgery			
Isolated aorta	13 (20)	0 (0)	<0.001
Isolated aortic valve	0 (0)	95 (73.1)	<0.001
Combined surgery	52 (80)	35 (26.9)	<0.001
Outcome in 30 days			
Death	5 (7.7)	11 (8.5)	0.854
Postoperative atrial fibrillation	8 (13.6)	23 (17.6)	0.388
Reoperation	8 (12.3)	11 (8.5)	0.403
Combined outcome (death + atrial fibrillation + reoperation)	17 (26.2)	38 (29.2)	0.653

*Data presented as mean ± standard deviation, median (interquartile range) or n (%). *Chronic kidney disease was defined as creatinine clearance <60 ml/kg/min. ARB: Angiotensin II receptor blocker; ACE inhibitors: Angiotensin-Converting Enzyme Inhibitor; NYHA: New York Heart Association; LV: left ventricle.*

diameter between 40 and 50 mm.[15] Both guidelines indicate surgery in patients with aorta diameter > 45mm if primary aortic valve intervention is indicated.[10,15]

In our study, 93% of patients had valve disease with an indication for intervention, a percentage similar to the study by Tzemos et al (95.7%).[8] Regarding the incidence of aortic aneurysm, there is significant variability in the literature that can be explained, among other factors, by the extreme heterogeneity in the definition of aortic dilation, ranging between 40 and 45mm.[16-18] Despite this, the prevalence of aortic aneurysm defined by an aorta larger than 45mm in our population exceeded that described in the literature (56.5% vs. 20-30%, respectively), reinforcing the need to assess the aorta with computed tomography or magnetic resonance in all patients with BAV.[8,19,20] In addition, our population had a high prevalence of systemic arterial hypertension, diabetes mellitus and coronary artery disease compared to other studies with patients with BAV.[5,8] A relevant finding was the high incidence of acute dissection (5.6%), described in the literature in 0.5-1% of patients with BAV in several surgical outcomes and long-term follow-up studies.[8,14] In line with the literature, we identified that patients with dissection had larger aortic diameters than those without such alteration (54.9 ± 21.3 vs. 46.8 ± 8.8 mm, p=0.010).[20]

It is noteworthy that combined surgery (aorta + valve) was not associated with a worse prognosis when compared to isolated valve surgery. Furthermore, the patients in our series had 30-day mortality higher than that predicted by the EuroSCORE II (8.2% vs. 2.77±4.07%, respectively). In addition to the fact that the EuroSCORE II does not have specific validation for the Brazilian population with BAV, the high mortality can still be justified by a selection bias, given that our center is a national reference. Furthermore, there is a tendency to care for more symptomatic patients (24.1% in functional class III/IV), with a higher incidence of comorbidities (46.7% with coronary artery disease) and with greater cardiac repercussion (left ventricular mass index mean of 142±53 g/m^2).

Increased left ventricular mass index and age were identified as independent predictors of postoperative outcomes, the latter being also described in other observational cohorts of patients with BAV.[8,19,21] Such studies also demonstrate the impact of valve degeneration on the prognosis, which was not confirmed in our study in the multivariate analysis. However, the increase in the left ventricular mass index was correlated with significant aortic stenosis and regurgitation, being an indirect marker of valve repercussion in the left cardiac chambers.

Limitations

The main limitation of this study is inherent to its observational design. Thus, data that could negatively influence the surgical outcome and outcomes (such as cardiopulmonary bypass time, hospital stay, use of vasoactive drugs, circulatory support, infection rate, among others) were not available for analysis in all patients. Furthermore, short-term follow-up does not allow us to extrapolate our findings beyond the 30 days. However, the number of patients evaluated is large for the pathology, being the largest sample in the national literature to date. Another bias arises from the fact that our institution is a reference for surgical treatment of patients with valve disease and aortopathy and thus may not faithfully represent the behavior of the disease in the general population. However, it makes us better understand the characteristics of the pathology in a highly complex population. In addition, the short inclusion period (2014 to 2019) ensured the homogeneity of surgical techniques and intervention recommendations. Another point to be mentioned is that the histopathological analysis of the aorta was not routinely performed in the patients in our study. However, due to the high association of aortopathy with BAV, demonstrated in previous studies, we can infer that those aortic alterations are related to valve disease.[6,7,14]

Conclusion

In patients with BAV, we found a higher incidence of aortopathy than described in the literature, showing the syndromic heterogeneity of BAV and the need for additional assessment of the aorta with computed tomography or magnetic resonance imaging.

Author Contributions

Conception and design of the research and Analysis and interpretation of the data: Kirschbaum M, Rosa VEE, Fernandes JRC, Santis A, Accorsi TD, Sampaio RO, Tarasoutchi F; Acquisition of data: Kirschbaum M, Sampaio BPA, Thevenard G, Quintanilha NR; Statistical analysis and Writing of the manuscript: Kirschbaum M, Rosa VEE, Tarasoutchi F; Critical revision of the manuscript for intellectual content: Kirschbaum M, Rosa VEE, Sampaio BPA, Thevenard G, Quintanilha NR, Fernandes JRC, Santis A, Accorsi TD, Sampaio RO, Tarasoutchi F.

Potential Conflict of Interest

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

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the USP – Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo – HCFMUSP under the protocol number SDC 5094/20/123. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

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*Supplemental Materials

For additional information, please click here.

Clinical Profile and Outcomes in 30 Days of Patients with Bicuspid Aortic Valve Undergoing Aortic Valve and/or Aortic Surgery

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Short Editorial related to the article: Clinical Profile and 30-Day Outcomes of Patients with Bicuspid Aortic Valve Undergoing Aortic Valve and/or Aorta Surgery

This short editorial is motivated by the results presented and discussed in an excellent article carried out at INCOR.[1] The authors emphasize a lack of Brazilian population, strengthening the relevance question since the bicuspid aortic valve (BAV) affects 0.5 to 2% of people and is associated with valve and aortic changes. The bicuspid aortic valve (BAV) is defective embryogenesis of the aortic valve that is not fully understood, even several theories about its origin. These theories include:[2,3]

1) Alteration in fetal transvalvular flow leading to failure in cusp separation;
2) Genetic factors;
3) Cell migration failure in some stages of embryogenesis.

Arterial stiffness is an essential predictor of aortopathy and myocardial remodeling in 41 patients with a bicuspid aortic valve, and it might be increased in childhood. For this reason, there has been growing interest in the follow-up of patients with ABV since childhood. A recent article was published in the Brazilian Archives of Cardiology, a very well-written article by Pelin Kosger et al.[4] To assess arterial stiffness and left ventricular myocardial function in forty-four children with a well-functioning bicuspid aortic valve. The investigation revealed that According to the oscillometric pulse wave analysis, the children with a well-functioning bicuspid aorta valve had similar arterial stiffness to that of their healthy peers. The ascending aorta diameter was established as an independent predictor of left ventricular myocardial function. Arterial stiffness may not be a severe risk factor in pediatric patients without marked ascending aorta dilation.[4]

The INCOR study is a retrospective cohort including 195 patients (mean age 54±14 years, 73.8% male) with a diagnosis of BAV who underwent surgical approach (valvular and aorta) from 2014 to 2019. Clinical echocardiography and tomography data were evaluated, in addition to the characteristics of the intervention and events within 30 days. The results revealed:

1) High prevalence of aortic aneurysm (56.5%), with a mean diameter of 46.9±10.2 mm;
2) Major aortic regurgitation in 25.1% and significant aortic stenosis in 54.9%. Isolated aortic valve surgery was performed in 48.2%, isolated aortic surgery in 6.7%, and combined surgery in 45.1%. The 30-day mortality was 8.2%.

In the multivariate analysis, the predictors of the combined outcome at 30 days (death, atrial fibrillation, and reoperation) were age (OR 1.044, 95% CI 1.009-1.081, p=0.014) and left ventricular mass index (OR 1.009, 95% CI 1.000-1.018, p=0.044). Perhaps the most critical finding was that patients with BAV have a higher incidence of aortopathy, with the additional need to assess the aorta with computed tomography or magnetic resonance imaging. Another fact that deserves to be highlighted was the discussion that, in general, the characteristics of the Brazilian population do not present marked differences compared to data from other countries, and the organization of international guidelines is more coherent. There remains the endless old story of the incidence of Rheumatic Fever, differentiated according to the social level of country populations development.

The authors point out that the main limitation of this study is inherent to its observational design. Thus, data that could negatively influence the surgical outcome and impact events (such as cardiopulmonary bypass time, hospital stay, use of vasoactive drugs, circulatory support, infection rate, among others) were not available for analysis in all patients. Furthermore, the short-term follow-up (30 months) does not allow the findings to be extrapolated beyond this period. We wait for the middle and long time outcomes evaluations.

Currently, no treatments prevent the bicuspid valve from developing stenosis or regurgitation. Statins to lower cholesterol may help some people. However, my capital doubt is, which I believe shared by most cardiac surgeons, arose in the evidence that bicuspid aortic valves are associated with aortic dilations. Is it justified to associate the surgical approach to the aorta in all cases of bicuspid aortic valves? The guidelines do not present a definitive direction, and it can be assumed as a tendential logical behavior, but difficult to fit into the principles of Hippocrates ("mutilate to the minimum, rebuild to the maximum...")

Keywords

Bicuspid Aortic Valve

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Telemonitoring in Heart Failure – A Single Center Experience

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Abstract

Background: The natural history of heart failure is a progressive decline and recurrent hospital admissions. New strategies to timely detect decompensations are needed. The use of telemonitoring in heart failure is inconsistent.

Objectives: This study aimed to evaluate the impact of this telemonitoring program (TMP) in hospitalizations and emergency department admissions.

Methods: This is a retrospective observational study, that analyzed data of all the patients who enrolled in the TMP program from January 2018 to December 2019. Demographic, clinical, and TMP-related data were collected. The number of hospitalizations and emergency department admissions from the year before and after enrollment were compared, using the Wilcoxon test. A two-sided $p<0.05$ was considered significant.

Results: A total of 39 patients were enrolled, with a mean age of 62.1 ± 14 years and a male predominance (90%). The most common causes of heart failure were ischemic and dilated cardiomyopathy. The mean ejection fraction was 30% and the median time of disease duration was 84 months (IQR 33-144). Patients who were enrolled for less than one month were excluded, with a total of 34 patients analyzed. Patients were followed in the TMP for a median of 320 days. The number of emergency department admissions was reduced by 66% ($p<0.001$), and the number of hospitalizations for heart failure was reduced by 68% ($p<0.001$). The TMP had no impact on the number of hospitalizations for other causes.

Conclusions: This trial suggests that a TMP could reduce health service use in patients with heart failure.

Keywords: Heart Failure/physiopathology; Telemonitoring; Hospitalization; Emergency Services.

Introduction

Heart Failure (HF) is a major public health problem, with rising incidenc and a significant mortality and morbidity.[1] In Portugal, the prevalence is estimated to be 4.36%.[2] The natural history of this disease is worsening symptoms and diminishing functional capacity over time, with episodes of acute decompensation, often leading to hospital admissions. After the first admission, up to 50% of the patients will be readmitted within six months after discharge[3] and 17-45% will die in the first year.[4] Repeated hospitalizations for HF have a negative impact on prognosis, being an independent predictor of mortality.[5]

The main strategies to prevent hospitalization are adequate pharmacological treatment, patient education, structured follow-up, and self-monitoring.[6] Various strategies have been tried to timely identify signs of clinical deterioration, allowing for an intervention before the acute exacerbation takes place. Telemonitoring is the use of technology to remotely monitor patients at home.[7] It was first proposed in the 2016 European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic HF, with a class II, level of evidence B recomendation.[6] Studies have shown that programs of telemonitoring could reduce the rate of emergency and hospital admissions, lengths of hospital stays, and even HF-related mortality.[8-11] Other possible advantages are involving patients and families in disease management, timely optimization of medical therapy, increased compliance, and improvement in the patients' quality of life.[9] However, these results are inconsistent, as other studies show null results.[12,13] This is most likely due to differences in the study populations, healthcare systems, and types of telemonitoring.[14]

Objectives

The aim of this study is to evaluate the impact of non-invasive remote telemonitoring in Portuguese patients with advanced heart failure in emergency and hospital admissions.

Material and methods

Study Design

This is a retrospective, observational, before and after study of patients enrolled in an advanced heart failure telemonitoring program (TMP). This means that each patient is his own control, comparing events in the one year before entering the program and during the period of TMP.

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Patient Selection

To be included in the TMP, patients had to be over 18 years of age, have a diagnosis of HF and be able to comply with the medical devices. We selected data on patients who enrolled in the program between January 1, 2018, and November 30, 2019. Participants followed up for less than a month were excluded from the analysis.

Telemonitoring Protocol

The telemonitoring process consisted of daily measurements of physiological data, namely body weight, blood pressure, heart rate, oxygen saturation, and body temperature, plus a weekly performance of a three-lead electrocardiogram.

After selection, patients and caregivers received training on how to use the devices and transmit data. Basal values were defined as a median of the first three values registered. The deviations that would trigger an alert were defined by the medical team (Table 1).

Two types of alerts were defined. Technical alerts were failure on data transmission or no data reported, and they were fixed by a technician. Clinical alerts were a measurement above or below the preset limits. A nurse would call the patients with a clinical alert to ask about symptoms and apply the Morisky-Green test to measure medication adherence. If the clinical alert was validated, the referring physician would contact the patient to decide on the best management strategy.

Data Collection

Data on patient demographics and disease characteristics were obtained from electronic medical records. We collected data on all-cause hospitalization and heart failure hospitalization, as well as emergency department admissions, from the year before entering the program and enrollment period.

Statistical analysis

Baseline data were summarized using descriptive statistics: means and standard deviation for continuous data with normal distribution, medians and interquatile range for skewed data, and percentages for categorical data. The Shapiro-Wilk test was used to assess the normality of distribution. Comparative analysis between before and after enrollment in the program was done using the Wilcoxon test. A two-sided $p<0.05$ was considered significant. All analyses were performed using data analysis and statistical software (SPSS).

Results

A total of 39 patients were included in the program. Baseline characteristics are presented in table 2. The mean age was 62 years, ranging from 34 to 90 years old. There was a male predominance. Most patients had ischemic or dilated cardiomyopathy, with a median disease duration of 84 months (IQR: 33-144). Mean left ventricular ejection fraction was 29%± 9.3% and no patient presented with preserved ejection fraction. Atrial fibrillation was present in more than two-thirds of the patients.

Patients were monitored for a median of 320 days (IQR: 166-486). During that period, three patients dropped out of the program, one was submitted to a heart transplant, and five died while on the program. The causes of death were worsening HF in two patients and infection in the other three. For these subjects, all events up to the time of discontinuation were accounted for in the main analysis. The remaining 25 were still enrolled in the TMP by the time of this analysis.

Compliance was good, with 58% of patients reporting all data at least 75% of the time and 75% reporting at least one parameter for more than 75% of the time.

There were a total of 2,928 clinical alerts, but only 31 were confirmed as clinically relevant, mainly changes in weight and heart rate. The remaining 98.9% alerts were considered non-significant due to the absence of symptoms or wrong measurements. The significant alerts are defined as mild, moderate, or severe, according to the deviation from the preset limits. In these cases, the doctor would call the patient and decide on management, as represented in figure 1. Half of the patients were observed in the emergency department, but the remaining cases were resolved by therapeutic changes, a visit to the HF clinic, or simple monitoring.

The total number of emergency department visits decreased from 100 admissions in the year prior to the enrollment, to 34 during the telemonitoring program (reduction of 66%, p <0.001). Hospitalizations for HF decreased from 71 to 23 (68%, p<0.001) and the number of days in hospital also decreased significantly, from 692 days to 178 days. No

Table 1 – Definition of the variables reported and deviations that trigger an alert

	Normal	Alert
Peripheral saturation of O_2 (SpO_2)	Δ < 4% of basal	Δ ≥ 4% and SpO_2 < 92%
Heart Rate	50-100 ppm	<50 or > 100
Systolic blood pressure	Δ ≤ 20% of basal	Δ > 20% of basal
Diastolic blood pressure	Δ ≤ 20% of basal	Δ > 20% of basal
Body weight	Δ <1Kg	Δ ≥ 1 Kg in 24h or ≥ 2Kg in 3 days
Temperature	≤ 37.5ºC	>37.5ºC
Three-lead electrocardiogram	HR 50-100	HR <50 or > 100

HR: Heart rate. Kg: kilogram.

Table 2 – Population baseline characteristics

	n=34*
Age, years	**62 ± 14**
Male gender, n (%)	**30 (88%)**
Etiology, n (%)	
Ischemic heart disease	13 (38,3%)
Dilated cardiomyopathy	14 (41,2%)
Alcohol-related	3 (8,9%)
Idiopathic	7 (20,7%)
Post-chemotherapy	1 (2,9%)
Post-myocarditis	2 (5,8%)
Familial	1 (2,9%)
Hypertrophic cardiomyopathy	3 (8,9%)
Left ventricular non-compaction cardiomyopathy	1 (2,9%)
Congenital heart disease	1 (2,9%)
Right ventricular arrhythmogenic dysplasia	1 (2,9%)
Amyloidosis	1 (2,9%)
Left ventricular ejection fraction, n (%)	
Normal (>50%)	0 (0%)
Mildly impaired (40-50%)	8 (23,5%)
Moderately impaired (30-40%)	9 (26,5%)
Severely impaired (<30%)	17 (50%)
NYHA class, n (%)	
I	0 (0%)
II	15 (44,1%)
III	18 (53%)
IV	1 (2,9%)
Atrial Fibrillation, n (%)	22 (64,7%)
Medications, n (%)	
Beta blocker	30 (88,2%)
ACE inhibitor or ARB	12 (35,3%)
ARN inhibitor	15 (44,1%)
Aldosterone-receptor antagonist	31 (91,2%)

*NYHA: New York Heart Association; ACE: angiotensin- converting enzyme; ARB: angiotensin-receptor blocker; ARN: angiotensin receptor-neprilysin. * Data presented as mean ± standard deviation or n, (%)*

differences were found in admissions due to other causes. These results are represented in figure 2.

No adverse events were caused by the monitoring system.

Discussion

Recently, home-based telemonitoring has emerged as an add-on option to HF management, providing regular and reliable vital signs and symptoms of community-based patients. This is the first study to test this hypothesis in the Portuguese population. We found a 68% significant reduction in hospitalizations due to worsening HF and a 66% reduction in emergency department visits for all-causes. Another important point is the reduction in hospital length of stay, probably the result of both the early identification of the decompensation and early discharge with close monitoring of the patient. This is particularly relevant due to the limitation of beds in the hospitals. These results support previous studies that have shown benefits from remote telemonitoring.

Daily weight monitoring is a class I recommendation in the management of HF,[6] because fluid retention is a sign of clinical decline and non-compliance to diuretic treatment. In our study, this was the most commonly significant clinical alert identified, leading to an intervention, mainly therapeutic changes, clinical visits, or emergency department admissions. However, Zhang et al.[15] demonstrated that measuring weight alone has limited value.

In 2019, telemonitoring programs were further endorsed by the European Society of Cardiology (ESC),[16] mainly due to two publications. The TIM-HF2 trial[17] demonstrated that a regular home assessment of weight, blood pressure, heart rate, oxygen saturation, electrocardiogram, and general health status could reduce the proportion of days lost due to unplanned CV (mainly HF) hospitalizations or death ($p = 0.046$) as well as all-cause mortality (HR 0.70; $p = 0.028$). A Cochrane review[18] of 25 trials concluded that telemonitoring reduced all-cause mortality by 20% and HF hospitalization by 30%.

The ESC stated that the protocol used in the TIM-HF2 trial should be tried in other countries to test for reproducibility.[16] The population studied in TIM-HF2 trial was similar to ours in terms of gender distribution, NYHA class and heart failure etiology. However, their population was 8 years older and they had 25% of patients with preserved ejection fraction, while we had none. The telemonitoring program is very similar to our own and our positive results may indicate that it is an effective method of remote monitoring.

Distant patient management should not be limited to monitoring vital signs. The medical team can use that data to individualize care, provide patient education, and timely introduce or uptitrate disease-modifying therapies. This approach might lead to a more significant impact on prognosis.

In other studies, the degree of compliance ranged from 80% to 90%,[7,14] which is better than our numbers. This is probably because patients are less compliant in everyday clinical practice than in clinical trials. In Portugal, as shown by the HLS-EU-PT,[18] 61% of the surveyed population has an inadequate general health literacy level. This can be a barrier to an effective disease treatment, as these patients have a more difficulty understanding of the disease and its management.[19] Some studies have also shown that it leads to poor medication adherence and increased hospitalization. By entering such a program, patients and caregivers, are given more knowledge and responsibility on disease management.[20] This can probably help to explain why, even though the number of significant clinical alerts

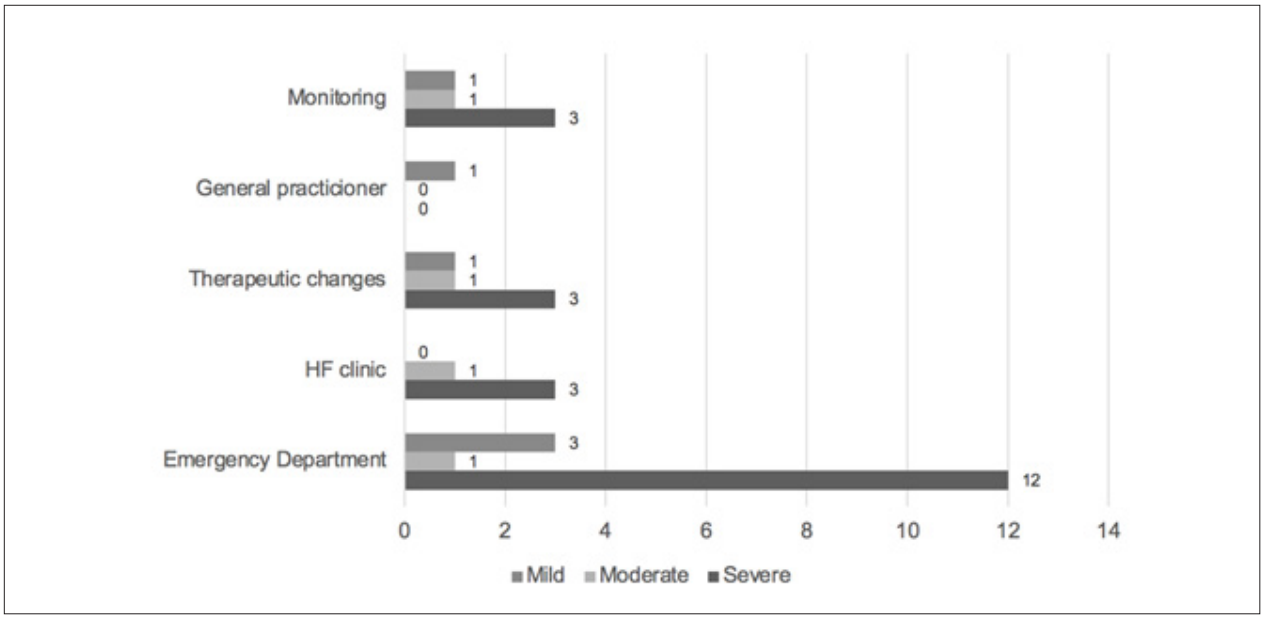

Figure 1 – *Medical decision management after a relevant clinical alert and telephone contact with the patient.*

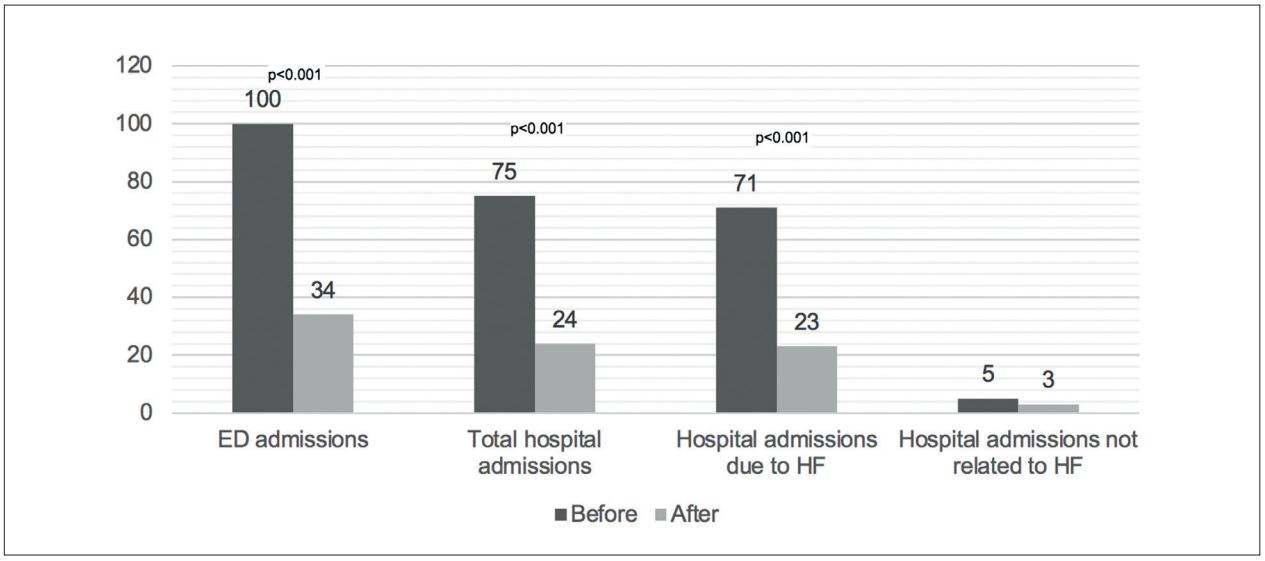

Figure 2 – *Comparative analysis using the Wilcoxon test revealed a significant reduction in emergency room admissions and hospitalizations due to heart failure, when compare the numbers from the previous year with the numbers when joining the telemonitoring program.*

is low, the number of hospital admissions for HF reduces greatly.

Some studies have shown that age does not have an impact on these results, with patients over 75 years of age having the same benefit as younger patients.[21] This is important because we have an aging population with a high prevalence of HF and frequent hospital admissions.

The main limitations of this paper are those associated with a before-and-after study, mainly history threat, that is defined as other events that could affect outcomes. In this type of study other variables, such as medication changes or other interventions, are not recorded. We also have a small sample size. However, this study can still produce preliminary evidence for intervention effectiveness in a population with relatively severe heart failure. Another limitation is that admissions occurring in hospitals outside the National Health System were not recorded, although they are uncommon.

Further research should focus on identifying the most important biological parameters to monitor, which subgroups of patients will benefit the most from this approach and which are the most cost-effective programs.

Conclusions

Our non-invasive telemonitoring program has significantly reduced HF hospitalizations and emergency department admissions, as well as days in hospital for HF. Implementation of such a program should be considered to improve the outcomes for patients with heart failure.

Author Contributions

Conception and design of the research: Cruz IO, Costa S, Franco F, Gonçalves L; Acquisition of data and Writing of the manuscript: Cruz IO; Analysis and interpretation of the data and Statistical analysis: Cruz IO, Teixeira R; Critical revision of the manuscript for intellectual content: Costa S, Teixeira R, Franco F, Gonçalves L.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

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

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Is There a Role for Telemonitoring in Heart Failure?

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Short Editorial related to the article: Telemonitoring in Heart Failure – A Single Center Experience

Heart failure (HF) is the leading cause of cardiovascular hospitalization in the world. Mortality rate ranges from 5% to 15%, and up to 50% of patients are readmitted in the emergency department in 90 days after discharge.[1] Different strategies have been implemented in recent years to avoid readmission, and telemedicine is a growing field in this scenario. The use of telecommunication technologies brings potential advantages when compared to in-person care, overcoming organizational and geographic barriers. However, divergent results in randomized trials evaluating the efficacy of telemedicine in reducing heart failure hospitalizations and mortality[2] discouraged the routine use of digital resources in clinical practice until the COVID-19 pandemic.

In this issue of Arquivos Brasileiros de Cardiologia, retrospective observational research evaluated the impact of an advanced telemonitoring program in a heart failure population.[3] Thirty-nine patients were included, and the researchers compared the number of hospitalizations one year before the program, with hospitalizations during the program. The program used vital signs and variables such as heart rate, blood pressure, weight variation, peripheral blood oxygenation, temperature, and a seminal 3-derivation electrocardiogram. Thirty-four patients were included in the final analysis. The authors reported a 66% reduction in emergency department admissions and a reduction of 68% in heart failure hospitalizations, considering the patients themselves as controls.

The small number of participants, the retrospective observational nature of the study, and the absence of simultaneous control participants make these results only hypothesis generating results, but they do run in line with current literature. Although randomized controlled trials (RCTs) in the last decade showed divergent results regarding the efficacy of telemedicine in heart failure,[2] systematic reviews showed a reduction in hospitalizations and mortality among this population. A Cochrane systematic review in 2015, including only RCTs, evaluated the use of structured telephone support or non-invasive home telemonitoring compared to standard practice for people with heart failure.[4] This study showed that non-invasive telemonitoring reduced all-cause mortality (RR 0.80, 95% CI 0.68 to 0.94) and heart failure-related hospitalizations (RR 0.71, 95% CI 0.60 to 0.83). Another systematic review, also including only RCTs and 11,450 patients, published in 2020, confirmed similar results.[5]

Current guidelines also diverge in the class of recommendation on telemedicine with heart failure patients. The Guideline of the Brazilian Society of Cardiology on Telemedicine in Cardiology advise cardiologists to use noninvasive telemonitoring strategies with structured telephone support in heart failure to reduce hospitalizations (class IA recommendation) and mortality (class IIA recommendation),[6] which is in alignment with the Emerging Topics Update of the Brazilian Heart Failure Guideline - 2021 (class IIA recommendation for mortality and hospitalizations).[7] The European Society of Cardiology Heart Failure guideline, however, does not provide any recommendation on non-invasive remote monitoring,[8] while the American Heart Association recommend effective systems to coordinate HF care to provide the guideline-recommended medical therapy and prevent hospitalizations (class I recommendation).[9]

This retrospective research does not clear doubts about efficacy of telemedicine in heart failure, however it draws attention to a relevant theme not only in heart failure, but in all clinical areas. In-person evaluation became limited in the healthcare system after the new coronavirus, leading to a growing need for alternative means of clinical evaluation.[10] The COVID-19 pandemic boosted the development of remote monitoring tools, and new trials need to be designed to analyze the role of telemedicine after these global changes and to encourage the routine use of this tool in clinical practice.

Keywords

Heart Failure/physiopathology; Telemonitoring; Hospitalization; Emergency Services

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Factors That Impact the Decision to Perform Left Ventriculography in Coronary Artery Disease

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Abstract

Background: **Left ventriculography is an invasive method for assessment of left ventricular systolic function. Since the advent of noninvasive methods, its use has been questioned, as it carries some risk to the patient.**

Objective: **To assess which factors are independently associated with the decision to perform ventriculography in patients with coronary artery disease.**

Methods: **Analytical, retrospective, database review study of electronic medical records comparing 21 predefined variables of interest among patients undergoing coronary angiography. P-values <0.05 were considered significant.**

Results: **We evaluated 600 consecutive patients undergoing coronary angiography. Left ventriculography was performed in the majority of cases (54%). After multivariate analysis, patients with chronic coronary syndrome (OR 1.72; 95% CI: 1.20–2.46; p < 0.01) were more likely to undergo the procedure. Patients with known ventricular function (OR 0.58; 95% CI: 0.40–0.85; p < 0.01); those with a history of CABG (OR 0.31; 95% CI: 0.14–0.69; p < 0.01) or hypertension (OR 0.58; 95% CI: 0.36–0.94; p = 0.02); and those with higher creatinine levels (OR 0.42; 95% CI: 0.26–0.69; p < 0.01) had greater odds of not undergoing ventriculography.**

Conclusions: **In patients undergoing coronary angiography, a diagnosis of chronic coronary syndrome was independently associated with greater likelihood of left ventriculography, while having previously determined ventricular function, a history of hypertension or CABG, and higher creatinine levels were associated with a decreased likelihood of undergoing this procedure.**

Keywords: **Cardiovascular Diseases; Coronary Artery Disease; Ventricular Function, Left; Ventriculography/methods; Coronary Angiography/methods; Hypertension; Myocardial Revascularization/surgery.**

Introduction

Invasive left ventriculography has been used to assess left ventricular function for over 50 years, and has long been the gold standard for this purpose.[1] However, the arsenal of noninvasive imaging modalities has been expanding, offering a variety of new and sophisticated techniques. In an attempt to improve application of available techniques, criteria for the appropriate use of diagnostic methods in certain clinical situations were recently published. These criteria state that both echocardiography and ventriculography are appropriate to assess left ventricular function during the initial presentation of an acute coronary syndrome.[2]

Ventriculography, however, can lead to complications. Contrast-induced nephropathy (CIN) occurs in approximately 1% of patients without predisposing factors, and in 10% to 30% of those with risk factors. This risk increases with higher doses of contrast.[3-11] Severe anaphylactic reactions may occur in 0.1% of patients.[12] Other complications include embolization, arrhythmias, cardiac tamponade, and a 30% increase in radiation exposure.[12] Currently, however, the risk of complications such as allergic reactions, volume overload, and CIN has been greatly reduced by the use of nonionic, low-osmolarity contrast media.[13,14]

Some studies have questioned whether invasive diagnostic methods may be overused.[1,15] In addition to cost concerns caused by duplication of test requests, patients are being exposed to unnecessary risk if an alternative, noninvasive method is available. Authors have also noted that the indications for ventriculography vary across geographic regions and hospitals, reflecting differences in clinical practice and uncertainty about the role of this method in cardiovascular diagnosis.[1]

In practice, the decision to perform ventriculography even when other, noninvasive methods for assessing ventricular function are available, has been made on a case-by-case basis, at the discretion of the interventional cardiologist or attending physician.[16]

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Guidelines for management of coronary syndrome recommend the assessment of left ventricular function, preferably via a noninvasive method.[17-26] Despite still considering ventriculography to be appropriate, the literature does not specifically establish its current role, nor in which situations it should be prioritized over noninvasive techniques.[2]

Therefore, the present study sought to assess which factors are associated with the decision to perform left ventriculography in patients with coronary artery disease undergoing coronary angiography.

Methods

This was an analytical, retrospective study. Medical records were retrieved and analyzed consecutively until the defined sample size of patients undergoing coronary angiography (n = 600) was reached. All interventions were performed at the catheterization laboratory of Santa Casa de Misericórdia/Hospital Santa Izabel, Salvador, Bahia, from January 1, 2017 through January 31, 2018. We also consulted the department database and the imaging reporting system to obtain information missing from the electronic medical record. As the department database only includes those patients undergoing angioplasty, we evaluated only those whose coronary angiography resulted in a subsequent angioplasty.

For the present study, adult patients (18 years or older) with suspected coronary artery disease were selected regardless of gender or whether angiography was performed electively or on an emergency basis. Patients whose records were more than 10% incomplete after a review of the electronic medical record and department database would have been excluded, but no such cases occurred.

This study was conducted in compliance with the ethical principles laid out in Brazilian National Health Council Resolution 466/12. The study protocol was submitted to the Research Ethics Committee of Santa Casa de Misericórdia da Bahia/Hospital Santa Izabel for appreciation (certificate no. 92940318.1.0000.5520) and approved with opinion no. 2,793,589. Given the retrospective, chart-review design of the study and since the patients in question were no longer being actively followed, we filed for a waiver of informed consent and submitted documentation ensuring that participants would not be identified. The interventional cardiologists who performed the procedures were identified by a code, to which only the authors had access.

Participants were divided into two groups: patients who underwent ventriculography and those who did not. In these two groups, 21 candidate variables for prediction of ventriculography were collected and analyzed. These variables were selected on the basis of previous studies and of our perception of the plausibility of their interfering with the decision to perform the procedure. We selected variables related to sociodemographic characteristics, such as gender (female/male), age (in full years), ethnicity (white/nonwhite), body mass index, and payer (if public, Unified Health System – SUS; if out-of-pocket or insured, non-SUS), and medical history, such as diabetes, metformin use, hypertension, acute myocardial infarction, previous coronary angioplasty, previous coronary artery bypass grafting (CABG), or heart failure. We also included variables related to the history of present illness and the procedure itself, such as shift (day/night); contrast volume (in mL); diagnosis on admission (chronic coronary syndrome/acute coronary syndrome); presence of hemodynamic instability; whether left ventricular function was known (previously determined by imaging); interventional cardiologist who performed the procedure; baseline creatinine; presence of mechanical complications; and presence of severe coronary artery disease (defined in this study as three-vessel disease or left main coronary artery disease).

Sample size calculation

To allow inclusion of the 21 variables of interest in the logistic regression model, and considering a minimum of 10 patients per variable, we estimated a minimum sample size of 420 patients.

Furthermore, based on a previous study by Hung-Hao Lee et al.,[15] who reported that 44% of patients with acute myocardial infarction and 56% of controls underwent ventriculography, to obtain a statistical power of 80% at an alpha level of 5%, we established a sample size of 544 patients. For added safety, we planned to include 600 patients.

Statistical analysis

Categorical variables were expressed as absolute and relative frequencies. Continuous variables were expressed as means and standard deviations (SD), if symmetrically distributed, or as medians and interquartile ranges (IQR) otherwise. The Kolmogorov-Smirnov test was used to confirm or reject the assumption of normality. In the search for variables predictive of ventriculography, we performed a univariate analysis. Categorical variables were compared using Pearson's chi-square test; normally distributed continuous variables, with Student's *t*-test for independent samples; and nonparametric variables, with the Mann–Whitney *U* test. Variables that reached $p < 0.05$ in these tests were carried forward into the multivariate logistic regression model, aiming to identify those variables for which an independent association remained after adjustment for the others. An alpha level of less than 5% ($p < 0.05$) was considered statistically significant on multivariate analysis. The Statistical Package for the Social Sciences, Version 14.0 for Windows (SPSS Inc.; Chicago, IL, USA), was used for data tabulation and analysis.

Results

A total of 600 patients who underwent coronary angiography from January 1, 2017, to January 31, 2018, were selected. Of these, 324 patients (54.0%) underwent ventriculography.

Analysis of sociodemographic characteristics revealed that 365 patients (60.8%) were male; 479 (79.8%) self-reported their ethnicity as nonwhite; and 324 (54.0%) were covered by the Unified Health System. The mean age was 65.5 ± 11.0 years, and the median (IQR) BMI was 26 (24–29) kg/m^2.

Regarding comorbidities, 248 patients (41.3%) had diabetes; 106 (17.7%) reported taking metformin; 505 (84.2%)

had hypertension; 145 (24.2%) had a history of MI; 84 (14.0%) had undergone angioplasty in the past; 35 (5.8%) had a history of CABG; and 38 (6.3%) reported having a diagnosis of congestive heart failure (CHF).

Regarding variables related to current clinical status and the procedure, 539 patients (89.8%) underwent angiography during the day shift; 202 (33.7%) had known ventricular function; 283 (47.2%) had chronic coronary syndrome; 18 (3.0%) were hemodynamically unstable at the time of the procedure; and 54 (9%) had severe CAD. The median (IQR) contrast volume administered was 80 (60–100) mL, and the baseline creatinine was 0.8 (0.6–1.0) mg/dL. There were no cases of mechanical complications in this sample. Each of the interventional cardiologists was responsible for 12 (2.0%) to 111 (18.5%) procedures.

Table 1 shows the distribution of variables and their comparison in the groups with and without ventriculography.

Among the variables of interest, nine were statistically significant ($p < 0.05$): payer; age; hypertension; history of CABG; known left ventricular function; diagnosis on admission; hemodynamic instability; baseline creatinine; and interventional cardiologist. These variables were included in the logistic regression model. Table 2 shows the final logistic regression model, which defined the independent predictors of indication for left ventriculography.

We observed that, after adjusting for the other variables, having a diagnosis of chronic (versus acute) coronary artery disease was independently associated with greater odds of undergoing ventriculography, while those with known ventricular function, previous CABG, hypertension, and higher baseline creatinine were more likely to not undergo ventriculography.

Discussion

In our study, left ventriculography was performed in the majority of patients who underwent coronary angiography (54%). This is consistent with the literature, although there is substantial variation between centers.[1,15]

The findings of this study suggest some factors that may influence the decision to perform left ventriculography. A diagnosis of chronic coronary syndrome was independently associated with greater odds of undergoing the procedure. Having known left ventricular function, hypertension, a history of CABG, and increased baseline creatinine were associated with greater odds of not undergoing left ventriculography. The few similar studies we found in the literature also reported some factors that correlated with use of this method, albeit with great variation. However, there seems to be a trend toward performing ventriculography in more stable patients and avoiding it in those with renal failure.[1,15]

Patients with known ventricular function and higher creatinine levels were less likely to undergo ventriculography. Although most patients had normal serum creatinine levels, we found a significant association when we analyzed this parameter as a continuous variable. This appears to be a rationally based decision, possibly with the aim of sparing the patient from an unnecessary procedure or a higher contrast volume.

On the other hand, some variables are not so intuitively explained. In our sample, ventriculography was performed more often in patients with chronic coronary syndrome than in those with acute coronary syndromes, who, in theory, might need more immediate evaluation. This can be partially explained by the fact that many stable patients undergo the procedure electively and thus bring with them reports of past imaging performed at outside hospitals, sometimes with incomplete data or of questionable quality.

When evaluating the contrast volume used in the two groups, we found that patients undergoing ventriculography used a median of only 3 mL additional contrast. This was a striking finding, as approximately 30 mL of additional contrast is generally used when performing ventriculography as compared to angiography alone. One possible explanation would be a tendency of interventional cardiologists to avoid the technique altogether in those patients who had already received a large volume of contrast during coronary angiography.

Current guidelines suggest that ventriculography can be used to help identify the culprit artery.[19,22,24] As our study was retrospective, we were unable to identify this particular use of the method. Another possible use of ventriculography mentioned is for evaluation of mechanical complications.[2] In our sample, there were no patients with mechanical complications; therefore, this potential use was also not evaluated.

Despite variation in the individual decision to perform ventriculography by interventional cardiologists, which was significant on univariate analysis, there was no independent association after adjustment for other variables.

The process of deciding whether to perform a diagnostic test involves several aspects, including the degree of evidence and information available in the literature, the clinical condition of the patient, the surrounding circumstances, and even the beliefs of the physician who orders the test. Current international and Brazilian guidelines do not establish objective criteria for the preferential performance of invasive left ventriculography over noninvasive methods for the assessment of ventricular function in patients with coronary artery disease. We believe this is due to a lack of evidence in the literature; however, it forces the physician to make an individual decision at the time of angiography, which can lead to significant variation in management across centers.

This study has some limitations. Data were collected retrospectively, leading to difficulties in obtaining accurate information. In addition, the database included only patients undergoing angioplasty; therefore, we only evaluated patients whose coronary angiography resulted in a subsequent angioplasty, which may have introduced selection bias. Data were entered by different providers from different sectors, with no standardization regarding the timing of requests for laboratory tests and imaging, making comparisons difficult. To minimize this issue, we carried out an active search for supplemental information through different means, including the hospital's electronic medical record, the catheterization laboratory database, and the radiology reporting system. In case of stable patients admitted for elective angiography, information on demographic data, presence of comorbidities, and current medications was provided by patients themselves

Table 1 – Distribution of variables and their association with the decision to perform ventriculography

Variable	Total cases N=600	No ventriculography N=276	Ventriculography N=324	p-value
Male sex N (%)	365	169 (46.3)	196 (53.7)	0.86
Nonwhite ethnicity N (%)	479	219 (45.7)	260 (54.3)	0.83
Unified Health System N (%)	324	130 (40.1)	194 (59.9)	< 0.01
Age* mean ± SD	65.5 ± 11.0	66.6 ± 11.5	64.7 ± 10.5	0.03
BMI Median (IQR)	26 (24-29)	25 (24-29)	26 (24-29)	0.71
Diabetes N (%)	248	121 (48.8)	127 (51.2)	0.28
On metformin N (%)	106	46 (43.4)	60 (56.6)	0.59
Hypertension N (%)	505	244 (48.3)	261 (51.7)	0.01
Prior MI N (%)	145	73 (50.3)	72 (49.7)	0.25
Prior angioplasty N (%)	84	41 (48.8)	43 (51.2)	0.63
Prior CABG N (%)	35	26 (74.3)	9 (25.7)	< 0.01
CHF N (%)	38	16 (42.1)	22 (57.9)	0.73
Day shift N (%)	539	246 (45.6)	293 (54.4)	0.68
Known LV function N (%)	202	109 (54.0)	93 (46.0)	< 0.01
Diagnosis of CCS N (%)	283	115 (40.6)	168 (59.4)	0.01
Instability N (%)	18	12 (66.7)	6 (33.3)	0.09
Severe CAD N (%)	54	25 (46.3)	29 (53.7)	1.00
Contrast volume Median (IQR)	80 (60-100)	77 (56-100)	80 (60-100)	0.15
Creatinine** Median (IQR)	0.8 (0.6-1.0)	0.8 (0.7-1.1)	0.7 (0.6-0.9)	< 0.01
Interventional cardiologist*** N (%)	–	–	–	< 0.01
A	27	13 (48.1)	14 (51.9)	
B	56	40 (71.4)	16 (28.6)	
C	57	12 (21.0)	45 (79.0)	
D	12	8 (66.6)	4 (33.4)	
E	21	13 (61.9)	8 (38.1)	
F	92	38 (41.3)	54 (58.7)	
G	111	46 (41.4)	65 (58.6)	
S	44	33 (75.0)	11 (25.0)	
I	30	12 (40.0)	18 (60.0)	
J	51	13 (25.5)	38 (74.5)	
L	98	47 (48.0)	51 (52.0)	

*BMI: body mass index; CABG: coronary artery bypass grafting; CAD: coronary artery disease; CCS: chronic coronary syndrome; CHF: congestive heart failure; LV: left ventricle. *(N = 594), **(N = 592), ***(N = 599). Source: Own work.*

Table 2 – Logistic regression adjusted for variables with p < 0.05 on univariate analysis

Variable	OR (95%CI)	p-value
Known LV function	0.58 (0.40–0.85)	<0.01
Diagnosis of chronic coronary syndrome	1.72 (1.20–2.46)	<0.01
History of CABG	0.31 (0.14–0.69)	<0.01
Hypertension	0.58 (0.36–0.94)	0.02
Baseline creatinine (mg/dL)	0.42 (0.26–0.69)	<0.01

Logistic regression adjusted by payer, age, hypertension, history of coronary artery bypass grafting (CABG), known left ventricular (LV) function, diagnosis on admission, hemodynamic instability, baseline creatinine, and interventional cardiologist. Source: Own work.

upon admission. In hospitalized patients, this information was recorded by physicians in each patient's progress notes.

Despite these limitations, the present study identified variables that may interfere with the decision to perform left ventriculography during cardiac catheterization in real-world clinical practice, outside the controlled environment of clinical trials.

Conclusions

In patients with coronary artery disease undergoing coronary angiography, a diagnosis of chronic coronary syndrome was independently associated with greater odds of undergoing left ventriculography. Having known left ventricular function (determined by other imaging methods), hypertension, a history of CABG, and increased baseline creatinine were associated with greater odds of not undergoing left ventriculography.

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Author Contributions

Conception and design of the research: Santos CCL, Feitosa GS, Feitosa Filho GS; Acquisition of data: Santos CCL, Oliveira RP, Sena J, Oliveira AD, Ferreira MG, Santos Filho A; Analysis and interpretation of the data: Santos CCL, Feitosa Filho GS; Statistical analysis and Obtaining financing: Santos CCL; Writing of the manuscript: Santos CCL, Feitosa Filho GS; Critical revision of the manuscript for intellectual content: Santos CCL, Oliveira RP, Sena J, Oliveira AD, Ferreira MG, Santos Filho A, Guissoni H, Brito JC, Feitosa GS, Feitosa Filho GS.

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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Original Article

Racial Differences in Blood Pressure Control from Users of Antihypertensive Monotherapy: Results from the ELSA-Brasil Study

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Abstract

Background: **It seems that the worst response to some classes of antihypertensive drugs, especially angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, on the part of the Black population, would at least partially explain the worse control of hypertension among these individuals. However, most of the evidence comes from American studies.**

Objectives: **This study aims to investigate the association between self-reported race/skin color and BP control in participants of the Longitudinal Study of Adult Health (ELSA-Brasil), using different classes of antihypertensive drugs in monotherapy.**

Methods: **The study involved a cross-sectional analysis, carried out with participants from the baseline of ELSA-Brasil. Blood pressure control was the response variable, participants with BP values ≥140/90 mmHg were considered out of control in relation to blood pressure levels. Race/skin color was self-reported (White, Brown, Black). All participants were asked about the continuous use of medication. Association between BP control and race/skin color was estimated through logistic regression. The level of significance adopted in this study was of 5%.**

Results: **Of the total of 1,795 users of antihypertensive drugs in monotherapy at baseline, 55.5% declared themselves White, 27.9% Brown, and 16.7% Black. Even after adjusting for confounding variables, Blacks using angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blocker (ARB), thiazide diuretics (thiazide DIU), and beta-blockers (BB) in monotherapy had worse blood pressure control compared to Whites.**

Conclusions: **Our results suggest that in this sample of Brazilian adults using antihypertensive drugs in monotherapy, the differences in blood pressure control between different racial groups are not explained by the possible lower effectiveness of ACEIs and ARBs in Black individuals.**

Keywords: **Antihypertensive Agents; Hypertension; Continental Population Groups.**

Introduction

Several studies have shown that the prevalence and severity of hypertension are higher in Blacks than in Whites;[1] additionally, the data indicate that among hypertensive patients, Blacks, in general, have poorer blood pressure control than Whites.[1] The Black-White difference in blood pressure control seems to be larger for some classes of antihypertensive drugs.[2] Hypertension disproportionately affects more Black individuals; additionally, the control of blood pressure levels also seems more difficult in these individuals when compared to the White population[1]. It seems that the worst response to some classes of antihypertensive drugs by the Black population would at least partially explain the worse control of hypertension among these individuals.[2]

Studies show that a portion of the Black population has a low production of renin; thus, by a compensatory mechanism, the body increases the vascular production of angiotensin II, and as a consequence there is an increase in the effects of aldosterone.[2,3] Several monotherapy studies indicate that Black patients have less reduction in blood pressure (BP) with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blocker inhibitors (ARBs) compared to

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White patients.[4-7] In addition, when comparing the classes of calcium channel blockers (CCBs) and thiazide diuretics (DIUs), indicated as the first choice for hypertension treatment in the Black population, the use of ACEIs in monotherapy was associated with an increased risk of cardiovascular events in these individuals.[8-10]

In this sense, the American, European therapeutic guidelines do not recommend ACEIs or ARBs as monotherapy, as first choice medication in the treatment of hypertension in Black individuals, since they are medications that act in the renin-angiotensin-aldosterone pathway.[11,12]

However, although the treatment of BP has been widely studied in African-Americans,[1,2,5,6] the same is not true for Black Brazilians. There is still a great scarcity of studies on this topic in the country, and as such, we extrapolate the data mainly from the United States of America (USA). However, this extrapolation requires some caution, as there are differences between the American and the Brazilian Black populations, especially with regard to the high miscegenation in Brazil,[13] socioeconomic conditions, and cardiovascular risk,[14,15] which makes this field an important research area.

ARBs and ACEIs are among the most frequently used antihypertensive drugs among Brazilian adults,[16] regardless of race/skin color, mainly because they are distributed free of charge by the Brazilian public health system (SUS). Results from the National Survey on Access, Use and Promotion of Rational Use of Medicines in Brazil (PNAUM), showed that about 21% of the respondents used ACEIs (enalapril or captopril) and 20% used ARB (losartana).[17] The prevalence of ACEI and ARB monotherapy use in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) baseline was 12.4 % and 11.0%, respectively.[16] Thus, the present study aimed to investigate the association between self- reported race/skin color and BP control in participants of the ELSA-Brasil, using different classes of antihypertensive drugs in monotherapy.

Methods

Study design and Population

ELSA-Brasil is a prospective cohort composed of 15,105 public employees, active or retired, from seven public institutions of higher education and/or research from six Brazilian state capitals. More information on the study design and cohort profile can be found in the articles published by Aquino et al.[19] and Schmidt et al.[20]

The present study involved a cross-sectional analysis, carried out with participants from the baseline (2008-2010) of ELSA-Brasil. All participants who were users of ACEIs, ARBs, CCBs, beta-blockers (BBs), and thiazide DIUs in monotherapy, who answered the questionnaire on the use of medications, had information available on self-reported race/skin color, and on the values of blood pressure levels, were included.

Of the 4,412 participants using antihypertensive drugs, participants who did not present information on self-reported race/skin color (n = 56) and those who declared themselves Asian or indigenous (n = 154) were excluded, in addition to those participants who used antihypertensive drugs in polytherapy (n = 2,407). Thus, the analytical sample was composed of 1,795 antihypertensive users in monotherapy. All participants signed an informed consent form, and the study was approved by the ethics committees of each institution involved.

Study Variables

Blood pressure control

Blood pressure levels were measured after a five-minute rest, with the participant sitting in a quiet room at a controlled temperature. The two-way cuff and oscillometric device (Omron HEM 705CPINT) were used.[20,21] Three measurements were taken after one-minute intervals, and the average of the last two was considered to be the BP of each participant.[21] The participants were classified into two groups according to whether or not they had BP control. Those with systolic BP<140 mmHg and diastolic BP<90 mmHg were considered controlled. Participants with BP values≥140/90 mmHg were considered out of control in relation to blood pressure levels.[22]

Self-reported race/skin color

All participants were asked: "*The Brazilian Census (IBGE) uses the terms 'Black', 'Brown, 'White', 'Asian', and 'indigenous' to classify people's skin color or race. If you had to answer the IBGE Census today, how would you rate yourself regarding your color or race?*", with the following response options: Black, Brown, White, Asian, and Brazilian Indigenous. In the present study, only participants who claimed to be White, Black, or Brown were included, due to low numbers of the other categories.

Class of antihypertensive drugs

All participants were asked about the continuous use of medication in the previous two weeks[23] and were instructed to take prescriptions and/or medications used to the research center.

The antihypertensive medication reported by the participants were classified according to the following classes: angiotensin receptor blockers (ARBs) (candesartan, irbesartan, losartan, olmesartan, telmisartan, valsartan); Beta-blockers (beta blockers with beta-1 selectivity (atenolol, bisoprolol, nebivolol, metoprolol) and non-selectable blockers (propranolol, nadolol, pindolol)); dihydropyridine calcium channel blockers (amlodipine, felodipine, isradipine, lacidipine, lercanidipine, nifedipine, nimodipine, nitrendipino, manidipino) and non-dihydropyridine (diltiazem, verapamil); thiazide diuretics (chlortalidone, hydrochlorothiazide, indapamide); and angiotensin-converting enzyme inhibitors (captopril, benazepril, delapril, fosinopril, lisinopril, enalapril, perindopril, ramipril, trandolapril).

Demographic and socioeconomic characteristics, health-related lifestyles, anthropometric, and clinical conditions

Information on the demographic and socioeconomic characteristics of the participants was obtained through structured questionnaires.[18] In the present study, the

following sociodemographic variables were considered: sex, age (on a continuous scale), and education (categorized into: Undergraduate complete, Secondary complete, and < Secondary complete)

Excessive consumption of alcoholic beverages was assessed and defined using the type of drink usually consumed, frequency, and consumption patterns. The information obtained in the questionnaire was summarized and defined in grams of alcohol consumed per week. Excessive consumption >210 g of alcohol per week was considered for men, and >140 g per week for women.[24]

Body mass index (BMI) (kg/m^2) was obtained by measuring height and weight, and was classified into three categories: <25 (normal weight); ≥25 and <30 (overweight); and ≥30 (obesity). Diabetes Mellitus (DM) was defined by self-report of previous diagnosis or use of medication to treat diabetes; by fasting glucose ≥126 mg/dL; by the glucose tolerance test ≥200 mg/dL; or by glycated hemoglobin ≥6.5 %.[25]

All participants answered how long they had been using the reported antihypertensive medication. Time was classified into years of use.

Statistical Analysis

Initially, the demographic and socioeconomic characteristics, health-related lifestyle habits, anthropometric, and clinical conditions of the participants were distributed according to the total population and the three self-reported race/skin color categories. They were described using proportions for categorical variables, and mean and standard deviation for continuous variables. The comparison between groups was performed using the chi-square test for categorical variables and the One-Way ANOVA test for continuous variables. Association between BP control and race/skin color was estimated through logistic regression.

The covariables (demographic and socioeconomic characteristics, excessive alcohol consumption, BMI (continuous), DM, and time of use of antihypertensive drugs) were entered into the models step by step with forward elimination. Crude and adjusted odds ratios (OR) and their respective 95% confidence intervals (95% CI) were estimated. We investigated whether self-reported race/skin color (reference category: Whites) was associated with BP control among the 1,795 users of the five classes of antihypertensive drugs in baseline monotherapy. After univariate analysis, the crude ORs (Model 0) were adjusted for age, sex, and education (Model 1). Model 1 was then adjusted for excessive alcohol consumption (Model 2), and finally Model 2 was adjusted for BMI, DM, and time of use of antihypertensive drugs (Model 3). All variables that remained statistically associated with the response variable ($p < 0.05$) were maintained in the final model after all adjustments. All analyses were performed using software Stata (version 14.0).

Results

Of the total of 1,795 users of antihypertensive drugs in monotherapy at baseline, 995 (55.5 %) declared themselves White. Both in the total population and in the three racial groups, women were the majority. The average age among Whites was 57 (9.0) years, and 55 (8.2) years between the Brown and Black populations. Complete higher education was significantly more frequent among the White as compared to the Black and Brown populations. The frequency of DM and obesity was significantly higher among Black individuals, followed by the Brown and White participants. Excessive alcohol consumption was not significantly different between the three racial groups (Table 1).

The percentage of participants who had uncontrolled BP was higher among Black individuals followed by the Brown and White participants (38.8 %, 32.5 %, and 22.0 % respectively; $p < 0.05$). The Black participants had a higher frequency of use of ACEIs (30.8 %), thiazide DIUs (23.4 %), and CCBs (11.0 %), when compared to the other races. The percentage of use of ARBs (28.0 %) and BBs (27.8 %) was higher among the White participants (Table 1).

The percentage of participants who had no BP control was higher among users of ACEIs, followed by users of CCBs, thiazide DIUs, ARBs, and BBs (33.2 %, 31.4 %, 28.2 %, 26.9 %, and 21.2% respectively; $p < 0.05$). Higher systolic blood pressure levels were presented among CCB users, followed by ACEIs. Users of ACEIs had higher mean diastolic blood pressure levels, followed by users of thiazide DIUs and ARBs. The average time of use of antihypertensive drugs was higher among CCB users (Table 2). More information on the distribution of study participants according to self-reported race/skin color and antihypertensive drugs classes can be seen in Table 1 of the appendix.

When investigating the association between self-reported race/skin color and BP control among users of ACEIs in monotherapy, even after adjusting for all variables, the chances of the Brown and Black populations having uncontrolled BP were 2.7 (95%CI: 1.7;4.3) and 2.2 (95%CI:1.3;3.4) higher, respectively, when compared to Whites. Among the users of ARBs, BBs, and thiazide DIUs, only Black individuals had a statistically higher chance of having uncontrolled BP when compared to Whites, after adjustment for confounding variables. Among CCB users, the self-reported race/skin color was not statistically associated with uncontrolled BP (Table 3).

Discussion

This study innovates by investigating racial disparities in blood pressure control in monotherapy users of different classes of antihypertensive drugs in a sample with great racial diversity among adult Brazilian public servants. Our results do not corroborate with most of those found by the studies developed mainly with American populations,[8,12,13,26] which show that Black users of ACEIs and ARBs have worse blood pressure control when compared to users of BBs, CCBs, and thiazide DIUs. Black users of antihypertensive drugs in monotherapy from the baseline of ELSA-Brasil, had a greater chance of having uncontrolled BP not only in the ACEI and ARB classes, but also in all others, with the exception of the CCB class.

The most recent American guideline for the treatment of hypertension[12] recommends including a thiazide diuretics or calcium channel blockers for Black adults with hypertension without heart failure or chronic kidney

Table 1 – Distribution of users antihypertensive in monotherapy at baseline according to socioeconomic characteristics; health-related lifestyle habits and presence of morbidities; control of blood pressure; blood pressure levels. class of drugs and time of use of antihypertensive drugs distributed according self-reported race/skin color categories. n (%). mean (SD) ELSA-Brasil*. (2008-2010) (N= 1.795)*

Variables	Overall (N=1.795)	White(N=995)	Brown (N=501)	Black (N=299)	p value‡
Gender	832 (46.4)	486 (48.8)	230 (45.9)	116 (38.8)	0.009
Male	963 (53.6)	509 (51.2)	271 (54.1)	183 (61.2)	
Female					
Age (years)	**56 (8.7)**	**57 (9.0)**	**55 (8.2)**	**55 (8.1)**	**0.023§**
Education					
Undergraduate complete	972 (54.1)	699 (70.2)	203 (40.5)	70 (23.4)	0.001
Secondary complete	583 (32.5)	228 (22.9)	205 (40.9)	150 (50.2)	
< Secondary complete	240 (13.4)	68 (6.8)	93 (18.6)	79 (26.4)	
Excessive drinking[1]					
No	1.650 (92.0)	902 (90.7)	467 (93.4)	281 (94.0)	0.079
Yes	143 (8.0)	92 (9.3)	33 (6.6)	18 (6.0)	
Diabetes					
No	1.273 (71.0)	735 (74.0)	348 (69.5)	190 (63.5)	0.002
Yes	521 (29.0)	259 (26.0)	153 (30.5)	109 (36.5)	
Body mass index (BMI)					
Normal weight	458 (25.5)	267 (26.8)	132 (23.3)	59 (19.8)	0.012
Overweight	780 (43.5)	444 (44.6)	212 (42.3)	124 (41.6)	
Obesity	556 (31.0)	284 (28.5)	157 (31.4)	115 (39.6)	
Blood pressure control					
Controlled	1.297 (72.3)	776 (78.0)	338 (67.5)	183 (61.2)	0.001
Out of control	498 (27.7)	219 (22.0)	163 (32.5)	116 (38.8)	
Means of systolic blood pressure levels	128 (17.3)	126 (16.7)	130 (16.5)	133 (19.2)	0.004
Mean diastolic blood pressure levels	79 (10.5)	81 (10.5)	81 (10.5)	82 (10.8)	0.362
Class of antihypertensive drugs					
ACEI	500 (27.9)	266 (26.7)	142 (28.3)	92 (30.8)	0.001
Thiazide DIU	291 (16.2)	123 (12.4)	98 (19.6)	70 (23.4)	
CCB	121 (6.7)	51 (5.1)	37 (7.4)	33 (110.0)	
ARB	439 (24.5)	278 (28.0)	114 (22.7)	47 (15.7)	
BB	444 (24.7)	277 (27.8)	110 (22.0)	57 (19.1)	
Time of use of antihypertensive drugs (years)	4.0 (4.3)	4.2 (4.2)	3.9 (4.5)	3.5 (4.1)	0.106§

Differences in total N for each variable are due to missing values. † The Longitudinal Study of Adult Health (ELSA-Brasil). [1] Excessive drinking defined as >210 g alcohol/week for men and 140 g alcohol/week for women. [2] Reference values for blood pressure control: Controlled (<140/90 mmHg), Out of control (≥140 / 90 mmHg) ‡ p-value resulting from the Chi-square test § p-value resulting from the ANOVA test. Blood pressure (BP), Angiotensin converting enzyme inhibitors (ACEI), Angiotensin receptor blocker (ARB), Calcium channel blocker (BCC), Beta blocker (BB), Thiazide diuretic (Thiazide DIU)

disease. This recommendation is supported by results of studies carried out with an American population that have frequently shown that Black individuals, possibly because they have low renin production, have worse blood pressure control when treated with medications that act on the renin-angiotensin system. Furthermore, this population has worse cardiovascular outcomes when treated with these antihypertensive drugs.[3,4,27,28]

In addition to the lower production of renin among Black individuals, the lower response of ACEIs, compared to thiazide DIUs, CCBs, and BBs can be explained by other factors. It has been suggested that this lower response is attributed to a high sodium intake in Black individuals who are more sensitive to salt, in which the response to ACEIs would be somewhat weakened. Others have suggested that hypertension in the Black population may not have a mechanism independent of

Table 2 – Distribution of users of antihypertensive drugs in monotherapy at baseline according to socioeconomic characteristics; health-related lifestyle habits and presence of morbidities; control of blood pressure; blood pressure levels and time of use of antihypertensive distributed according to how antihypertensive classes. n (%). mean (SD)ELSA-Brasil[†]. (2008-2010) (N= 1.795)[*]

Variables	ACEI (N=500)	Thiazide diuretic (N=291)	BCC (N=121)	ARB (N=439)	BB (N=444)	p value[‡]
Gender						
Male	289 (57.8)	84 (28.9)	59 (48.8)	227 (51.7)	173 (38.9)	0.001
Female	211 (42.2)	207 (71.1)	62 (51.2)	212 (48.3)	271 (61.1)	
Age (years)	55 (8.4)	55 (8.5)	55 (8.5)	57 (8.6)	55 (8.9)	0.668[§]
Education						
Undergraduate complete	230 (46.0)	119 (40.9)	65 (53.7)	291 (53.7)	267 (60.1)	0.001
Secondary complete	188 (37.6)	114 (39.2)	36 (29.7)	112 (25.5)	133 (23.0)	
< Secondary complete	82 (16.4)	58 (19.9)	20 (16.5)	36 (8.2)	44 (9.9)	
Excessive drinking[1]						
No	449 (89.8)	275 (94.8)	113 (93.4)	400 (91.3)	413 (93.0)	0.104
Yes	51 (10.2)	15 (5.2)	8 (6.6)	38 (8.7)	31 (7.0)	
Diabetes						
No	307 (61.4)	219 (75.3)	83 (68.6)	306 (69.7)	358 (80.8)	0.001
Yes	193 (38.6)	72 (24.7)	38 (31.4)	133 (30.3)	85 (19.2)	
Body mass index (BMI)						
Normal weight	115 (23.0)	75 (25.8)	38 (31.4)	93 (21.2)	137 (30.9)	0.001
Overweight	212 (42.4)	102 (35.1)	55 (45.5)	206 (46.9)	205 (46.3)	
Obesity	173 (34.6)	114 (39.2)	28 (23.1)	140 (31.9)	101 (22.8)	
Blood pressure control						
Controlled	334 (66.8)	209 (71.8)	83 (68.6)	321 (73.1)	350 (78.8)	0.001
Out of control	166 (33.2)	82 (28.2)	38 (31.4)	118 (26.9)	94 (21.2)	
Means of systolic blood pressure levels	130 (18.6)	128 (15.4)	131 (15.1)	128 (16.5)	125 (17.7)	0.001[§]
Mean diastolic blood pressure levels	82 (11.3)	80 (9.14)	79 (10.0)	80 (9.9)	77 (10.8)	0.001[§]
Time of use of antihypertensive drugs (years)	4.5 (4.5)	3.6 (4.5)	4.8 (4.5)	2.6 (2.6)	4.7 (4.9)	0.001

Differences in total N for each variable are due to missing values. [†] The Longitudinal Study of Adult Health (ELSA-Brasil). [1] Excessive drinking defined as >210 g alcohol/week for men and 140 g alcohol/week for women. [2] Reference values for blood pressure control: Controlled (<140/90 mmHg), Out of control (≥140 / 90 mmHg) [‡] p-value resulting from the Chi-square test [§] p-value resulting from the ANOVA test. Blood pressure (BP), Angiotensin converting enzyme inhibitors (ACEI), Angiotensin receptor blocker (ARB), Calcium channel blocker (BCC), Beta blocker (BB), Thiazide diuretic (Thiazide DIU)

angiotensin.[29] Moreover, this increase in sensitivity to salt may also explain the better control of blood pressure among Black users of thiazide DIUs.[30] Other studies have shown a significant increase in the risk of adverse effects associated with ACEIs in Black individuals, for example coughing, which contributes to the greater discontinuation of treatment with ACEIs among this group when compared to other races.[31]

In the 1990s, a study by Saunders and collaborators showed that, among the Black population, the CCB class, as compared to BBs and ACEIs, was more effective in controlling both systolic and diastolic blood pressure levels.[32] In addition, several other more recent studies mainly developed among Black Americans, have shown that CCBs, as compared to ACEIs, ARBs and BBs, were more effective in reducing the risk of several cardiovascular events, such as acute myocardial infarction, strokes, and cardiac insufficiency.[8,11,12,26] In our study, among CCB users on monotherapy, Brown and Black individuals were not more likely to have uncontrolled blood pressure levels when compared to Whites. Although this lack of association can be explained by the low sampling power in this group (we have only 121 CCB users on monotherapy), the results are in line with the literature, which recommends CCBs as one of the first choices for the treatment of hypertension in the Black population.

In this sense, our results, which in summary showed that the greater chance of having uncontrolled BP in Black individuals is not restricted to users on ACEIs and ARBs in

Table 3 – Crude and adjusted odds ratios (OR) * in blood pressure control+ of users of antihypertensive drugs in monotherapy in the baseline of the ELSA-Brasil1 2008-2010 (n=1.795)

Class of antihypertensive drugs		Multivariate		
	Model 0	Model 1	Model 2	Model 3
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
ACEI (n=500)				
White	Ref.	Ref.	Ref.	Ref.
Brown	2.9**(1.9;4.5)	2.8**(1.8;4.4)	2.8**(1.8;4.4)	2.7**(1.7;4.3)
Black	2.5**(1.5;4.1)	2.3**(1.3;3.9)	2.3**(1.3;3.9)	2.2**(1.3;3.4)
ARB (n=439)				
White	Ref.	Ref.	Ref.	Ref.
Brown	1.3 (0.8;2.1)	1.1 (0.6;1.9)	1.1 (0.6;1.9)	1.2 (0.7;2.2)
Black	2.4** (1.25;4.51)	1.9 (0.9;4.0)	2.0 (1.0;4.1)	2.2** (1.0;4.7)
BCC (n=121)				
White	Ref.	Ref.	Ref.	Ref.
Brown	0.8 (0.3;2.1)	0.7 (0.3;1.9)	0.7 (0.2;1.9)	0.7 (0.2;2.1)
Black	1.3 (0.5;3.2)	1.0 (0.4;2.9)	1.0 (0.4;2.9)	1.1 (0.4;3.5)
BB (n=444)				
White	Ref.	Ref.	Ref.	Ref.
Brown	1.3 (0.8;2.3)	1.3 (0.7;2.3)	1.3 (0.7;2.3)	1.2 (0.6;2.2)
Black	2.3**(1.2;4.3)	2.1**(1.0;4.1)	2.1**(1.0;4.2)	2.1**(1.0:4.4)
Thiazide DIU (n=291)				
White	Ref.	Ref.	Ref.	Ref.
Brown	1.6 (0.9;3.0)	1.5 (0.8;2.9)	1.6 (0.8;3.2)	1.7 (0.9;3.4)
Black	2.2**(1.2:4.2)	1.9 (1.0;4.0)	2.1**(1.0;4.5)	2.4**(1.1;5.1)

** Odds Ratios (OR). + Reference category is blood pressure controlled (<140/90 mmHg)** p < 0,05. 1 The Longitudinal Study of Adult Health (ELSA-Brasil). Model 1: Adjusted for age, gender, and education. Model 2: Model 1 was then adjusted for excessive alcohol consumption. Model 3: Model 2 was adjusted for BMI, diabetes mellitus, and time of use of antihypertensive drugs. Angiotensin-converting enzyme inhibitors (ACEI), Angiotensin receptor blocker (ARB), Calcium channel blocker (BCC), Beta blocker (BB), Thiazide diuretic (Thiazide DIU)*

monotherapy, which is also found among users of thiazide DIUs and BBs, corroborate other studies that show that the possible explanations for Black individuals having worse BP control go beyond the physiological issue that would involve classes of medication. Socioeconomic differences, such as a low level of education, is one of the main determinants of the occurrence and the worse control of arterial hypertension,[33,34] and may partly explain the differences between the Black, Brown, and White populations. In addition, social contexts or "neighborhoods" in which people live can contribute substantially to racial disparities in health[35,36] and can play an important role in explaining the relationship between race/skin color and control of arterial hypertension.

In fact, previous studies developed at the ELSA-Brasil baseline have already shown racial disparities in the prevalence and control of hypertension. Chor et al. showed that individuals who claimed to be Black had poorer blood pressure control compared to those who claimed to be White, even among users of antihypertensive drugs.[16] Barber et al. investigated the association between residential segregation and cardiometabolic risk factors, which included the presence of hypertension. The authors concluded that, despite having no statistically significant difference, the Black and Brown populations were more likely to live in economically segregated neighborhoods in relation to Whites and individuals who lived in these neighborhoods were 26% more likely to have hypertension.[36] In addition, Baldo et al. also show that Black and Brown participants in the ELSA-Brasil baseline had greater arterial stiffness when compared to Whites. However, this difference was explained by the average blood pressure levels and the age of the participants, suggesting that therapeutic approaches should focus on the control of blood pressure levels, especially among Black individuals.[37]

It is important to highlight that, in our study, Black participants have the highest frequency of ACEI use, which would not be expected, since we tend to follow the guidelines based on Black American studies. However, the guidelines also recommend ACEIs or ARBs for individuals with diabetes,[11,12,22] which can explain this result, since our Black participants have the highest frequency of DM.

Pena and colleagues showed that, in Brazil, skin color assessed phenotypically has a very weak correlation with the degree of ancestry.[38] In this sense, ancestral results would help to better understand the racial disparities in the control of blood pressure from a genetic perspective. However, self-reported race/skin color is a phenotype that reaches beyond the genetics and the lived experience, thus reflecting the subjects' perceptions of their own ethnic racial belonging.[39]

The present work innovates when investigating racial disparities in blood pressure control among users of different classes of antihypertensive drugs in a sample of adult Brazilian public servants; however it does have some limitations that should be highlighted. First, we had no information on the dose of antihypertensive treatment, and it is well-known that there are differences in dose optimization between different classes of the drug. Second, although monotherapy is more often used for milder cases, the staging of arterial hypertension can influence therapeutic options, with some classes more indicated at the beginning of treatment and others preferably in more advanced stages.[12] However, there was no information on the hypertension staging. Third, although the uncontrolled BP was defined based on the values adopted by the national and international guidelines for the treatment and control of hypertension, it was based on a specific measurement of blood pressure levels. In this sense, false-positive and false-negative results can appear, which could interfere in our results.

Fourth, although the results are true for monotherapy, studies will show that the low effectiveness of ACEIs among Black individuals is reversed by the association of these medications with thiazide DIUs and CCBs.[40,41] However due to the low sampling power, especially among new users, we have not tested combined therapy in the present study. Finally, although we have made adjustments for the main variables, this does not control unmeasured confounders.

Conclusion

As far as we know, this is the first study to investigate racial disparities among users of different classes of antihypertensive drugs in monotherapy in a sample of Brazilian adults. In conclusion, our results suggest that the differences in blood pressure control between different racial groups are not explained by the possible lower effectiveness of ACEIs and ARBs in Black individuals, because this occurs within other classes of antihypertensive drugs. These results suggest caution in making antihypertensive treatment decisions based strictly on the race of the patients and provide relevant information that can guide decision-making for the treatment and control of arterial hypertension in the Brazilian context, suggesting that higher lack of BP control in Black individuals may be more related to social determinants than to the antihypertensive class used. Policies that act on adequate access to treatment and patient education should therefore be addressed.

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: Sousa CT, Ribeiro A, Barreto SM, Giatti L, Brant L, Lotufo P, Chor D, Lopes AA, Mengue SS, Baldoni AO, Figueiredo RC

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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Influence of Racial Composition on Blood Pressure Control in the Brazilian Population: The Need for New Perspectives Beyond Drug Treatment

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Short Editorial related to the article: Racial Differences in Blood Pressure Control from Users of Antihypertensive Monotherapy: Results from the ELSA-Brasil Study

"Of all the forms of inequality, injustice in health care is the most shocking and inhumane"

Martin Luter King, 1966

In the context of cardiovascular health, some racial characteristics have been frequently associated with worse blood pressure (BP) control. For example, Black adults have more severe resistant hypertension as compared with other ethnic groups.[1-3] A lot of this evidence has been gathered from populations where there had been little racial mixing and, for this reason, understanding the impact of specific racial characteristics of the Brazilian population on the occurrence, diagnosis, and control of hypertension is imperative.[4,5]

The study by Sousa et al.[6] provides a new perspective on the influence of race on the treatment and control of BP in Brazilian adults. Using a robust database of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), the authors evaluated the association of self-reported race/skin color with BP control in individuals under different monotherapy antihypertensive regimens. This publication complements previous studies of the group on the influence of ethnicity on several aspects of hypertensive disease.[7,8]

Black individuals using angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), thiazide diuretics (TD) and beta blockers showed a worse BP control than White individuals. After statistical treatment of the data, the authors concluded that the differences in BP control between the racial groups could not be explained by a possible lower efficacy of ACEI and ARBs in Black patients. Despite the observational nature of the study, it starts to reveal some important topics about the management of hypertensive patients belonging to specific groups (in this case, Black population), and put forward some hypotheses that need to be investigated, mainly those related to racial health inequality and its repercussions.

Racial mixing, characteristic of the Brazilian population, raises important socioeconomical questions, and important challenges to health care in the country.[4,5] From the perspective of social determinants of health and disease processes, factors related to racial composition of the population (including racism) can contribute to health inequality, and thereby negatively influence the outcomes.[1,2,9,10] Difficulty in accessing health services, preventive and protective measures, and adequate treatment may be common. According to the 2019 Brazilian National Household Sample Survey (PNAD, Pesquisa Nacional por Amostra de Domicílios), 9.4% of respondents self-reported as Black, and 46.8% as *Pardo*.[11]

Also, we need to mention some features that strongly contribute to the management of chronic diseases in the Brazilian Unified Health System:[12] the accelerated population aging and increasing social inequality, associated with the marked increase of chronic morbidities in our population (approximately 26 million people aged ≥ 50 years report more than two chronic conditions, where hypertension is present in most of them).[13] There is also the increase in the incidence of all non-communicable diseases from 2013 to 2019, as reported in the Brazilian National Health Survey (PNS).[4]

In fact, data stratified by race/ethnicity from the 2019 PNS showed that Black and *pardo* individuals, mainly women (57.8%), reported worse health status. Besides, White people reported higher attendance at medical appointments than Black people, regardless of sex.[4] As compared with the 2013 PNS, a higher proportion of Black hypertensive patients who self-reported use of medications, performance of complementary tests and visits to specialists was found in the 2019 PNS. These patients also showed higher rates of attendance at medical care, especially in public services and primary health centers, although they were seen by different physicians at the last visit from the ones in previous consultations.[5] Also, a Brazilian study showed that living in economically segregated neighborhoods, where Black and Pardo people are more likely to live, is associated with higher odds of hypertension (26%) and diabetes (50%) as compared

Keywords

Hypertension; Ethnic Groups; Chronic Disease

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with living in other areas. Thus, economically segregated neighborhoods may represent potential environment for promoting racial inequalities regarding the occurrence of cardiometabolic risk factors.[7]

Therefore, extending the findings of Sousa et al.,[6] the Brazilian population urgently calls for further studies that provide a wider perspective of care, from access to health services, medications, diagnostic tests, and specialists, to a longitudinal, coordinated multidisciplinary care and self-care strategies consistent with their socioeconomic, demographic and cultural characteristics.

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Epicardial Adipose Tissue in Heart Failure Phenotypes – A Meta-Analysis

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Abstract

Background: Epicardial adipose tissue (EAT) is increased in comorbidities common in heart failure (HF). In this sense, EAT could potentially mediate effects that lead to an impaired cardiac function.

Objectives: This meta-analysis aims to investigate if the amount of EAT in all-types of HF and each HF phenotype is significantly different from control patients.

Methods: This meta-analysis followed the Meta-analysis Of Observational Studies in Epidemiology guidelines. The search was performed in the MEDLINE, Embase, and Lilacs databases until November 2020. Two authors performed screening, data extraction, and quality assessment. A p-value <0.05 was defined as statistically significant.

Results: Eight observational studies were included, comprehending 1,248 patients in total, from which 574 were controls, 415 had HF with reduced ejection fraction (HFrEF) and 259 had HF with mid-range or preserved ejection fraction (HFmrEF or HFpEF). The amount of EAT was not different between all types of HF and the control group (SMD = -0.66, 95% CI: -1.54 to 0.23, p =0.14). Analyzing each HF phenotype separately, patients with HFrEF had a reduced EAT when compared to the controls (SMD= -1.27, 95% CI: - 1.87 to -0.67, p <0.0001), while patients with HFmrEF or HFpEF showed an increased EAT when compared to controls (SMD= 1.24, 95% CI: 0.99 to 1.50, p <0.0001).

Conclusion: The amount of EAT was not significantly different between all types of HF and the control group. In patients with HFrEF, the EAT volume was reduced, whereas in HFpEF and HFmrEF, the amount of EAT was significantly increased. PROSPERO registration number: CRD42019134441.

Keywords: Heart Failure/physiopathology; Pericardium/diagnostic, imaging; Adipose Tissue; Cytotoxins; Metanalisis.

Introduction

Epicardial adipose tissue (EAT) is a visceral fat depot localized around the myocardium.[1,2] EAT secretes several proinflammatory chemokines and cytokines, collectively called adipokines.[3] In addition, due to the close relation of EAT and the myocardium, epicardial fat may promote mechanical and local inflammatory effects on the cardiac muscle and coronary vessels.[4]

It is also known that EAT is increased in systemic diseases, which can promote a systemic proinflammatory state, such as obesity and diabetes, common in heart failure (HF) patients, mainly in HF with preserved ejection fraction (HFpEF).[5-7] In this sense, EAT may mediate deleterious effects on the myocardium, which can lead to an impaired cardiac function.[8]

Previous studies have shown that EAT is lower in HF patients than in healthy patients.[9] However, a recent study published by van Worden et al., which submitted 64 patients with HF with mid-range ejection fraction (HFmrEF) or HFpEF to cardiac magnetic resonance (CMR) showed that HF patients had a higher EAT volume than the control group.[4] Despite the relevance of this association, there are no systematic reviews or meta-analyses that weigh the available evidence and bring conclusions and discussions about this topic. Therefore, the present study aims to perform a meta-analysis to investigate the association between EAT and each HF phenotype.

Methods

A meta-analysis was performed using the criteria established by the Meta-analysis of Observational studies in the Epidemiology Group (MOOSE) recommendations.[10] The protocol of this meta-analysis was registered in PROSPERO, logged under the following registration number: CRD42019134441.

Search strategies

Two investigators (ETOC, LMSB) searched the MEDLINE, the Lilacs, and the Embase database for studies that investigated EAT in patients with HF, until November 2020. The search strategy was made by a combination of English terms and Medical Subject Heading (MeSH) descriptors, consisting of four keywords [(epicardial adipose OR epicardial fat) AND (heart failure OR cardiac insufficiency)]. A manual search of references was also used to identify possible studies for inclusion. Each title and abstract were independently analyzed by the two investigators, who selected the articles that would

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be relevant to the review. After, full texts of the remaining articles were reviewed to select which would be included in the quantitative analysis. In case of disagreement, the decision was made by discussion and consensus of the authors.

Inclusion criteria

Eligible studies were required to meet the following criteria: 1) Population: the study included human subjects with HF; 2) Intervention: the study measured EAT and left ventricular ejection fraction (LVEF) with computerized tomography, echocardiography, or CMR; 3) Comparison group: the study included patients without HF; 4) Outcomes: the study reported means and 95% confidence intervals (CI) or standard deviation of EAT in patients with HF and the control group; 5) Study Design: this was an observational study.

Data extraction

Data extraction was performed by two investigators, using a standard form (PMH, OSC), and cross-checked by a third author (ETOC). Extracted data included: 1) First author's last name, publication year; 2) Characteristics of the included studies: number of patients, country of the study, study arms, etiology of HF, New York Heart Association class of the included patients, the ejection fraction of the included patients, age, body mass index, method of EAT measurement, and main findings 3) Outcome results: means, 95% CI, and standard deviation of EAT in patients with HF, and the control group.

Quality assessment

The risk of bias in the studies was evaluated by the NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE CASE CONTROL STUDIES, which analyzes the selection of participants in each study, the comparability of cases and controls, and the exposure. Quality assessment was performed by two investigators, using a standard questionnaire (PMH, OSC), in case of divergence, a conclusion was reached by consensus. The quality of studies was considered good if they scored between 7-8 points, satisfactory if they scored between 5-6 points, and unsatisfactory if they scored from 0 to 4 points. Quality assessment of the included studies is reported in Tables 1 and 2.

Statistical analysis

The association between EAT and HF was measured by Standard Mean Difference (SMD) with 95% CI, due to different units of measurement used across the studies. Subsequently, standard errors were determined from the corresponding 95% CIs or directly obtained from the study. The inverse variance method was used to weigh studies for the combined overall statistics. Statistical significance was defined at p-value < 0.05. Heterogeneity between studies was assessed using the Cochrane Q and I^2 statistics and then evaluated by I^2 values. I^2 values less than 30% were defined as low heterogeneity; less than 60% were considered moderate heterogeneity; and more than 60% were determined as high heterogeneity.[11] The random-effects model was chosen based on differences in the population of the studies, which included different phenotypes of HF, as well as patients with several comorbidities and from numerous countries. A sensitivity analysis was performed by leaving out studies and checking the consistency of the overall effect estimate. A meta-regression was not performed because of the small number of studies included. The results are reported in forest plots with 95% CI. All analyses were done using Review Manager 5.3 software.

Results

Study selection

Initially, a total of 188 studies were identified in the databases, 179 in MEDLINE and 9 in Embase, and 0 in the Lilacs database. In the duplicate analysis, 3 duplicates were identified, which were excluded. After a careful reading of titles and abstracts, 170 of 185 studies were excluded because they were not related to the present review or were not original studies. Full texts of the remaining 15 studies were analyzed, and 8 of them were included in the meta-analysis. Of the 7 studies excluded, 3 were excluded because they did not analyze EAT in HF and control patients, 3 were excluded because did not report means and 95% CI or standard deviation of EAT in patients with HF and the control group, and 1 was excluded because it did not analyze LVEF. The flow diagram of the study selection is depicted in Figure 1.

Characteristics of the included studies

Eight studies[4,7,9,12-16] were included in this review, seven of which were prospective single-center observational studies and one single-center retrospective observational study[14] (Tables 1 and 2).

Overall, 1,248 patients were included in our meta-analysis, of which 574 were controls and 674 patients with HF. Of the 674 HF patients included, 415 had HF with reduced ejection fraction (HFrEF) and 259 had HFpEF or HFmrEF. Four studies[7,9,12,13] used CMR to measure the EAT, two studies[14,16] used echocardiography, one study[15] used computerized tomography (CT), and one study used CMR and echocardiography to evaluate de EAT.[4] Studies have also used different LVEF cut-off points to define HF phenotypes, as shown in detail in Tables 1 and 2.

Quality of the included studies

All eight studies included in this review were graded as good by the NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE CASE CONTROL STUDIES, having received seven to eight stars out of nine, as shown in Table 1.

Association of Epicardial Adipose Tissue and Heart Failure

In random-effects analyses, the amount of EAT was not associated with HF when all the phenotypes of HF were analyzed (SMD= -0.66, 95% CI: -1.54 to 0.23, p =0.14), as shown in Figure 2. The heterogeneity test showed that there were significant differences between studies ($p<0.00001$, $I^2=97\%$). A sensitivity analysis was performed; however, it was not possible to remove the heterogeneity from the meta-analysis.

Table 1 – Characteristics of the included studiess

Study	Country	Definition of HF# and/or HF# subtypes	Control group definition	Measurement method	Quality
Doesch et al.[12]	Germany	Presence of LVEF ≤35% on echocardiography and signs and symptoms of HF. These patients were classified in HF due ICM or DCM.	Healthy patients	CMR	Good
Doesch et al.[9]	Germany	Patients with LVEF <50% on echocardiography in the absence of significant CAD (coronary artery stenosis ≥ 50% or history of coronary revascularization or previous MI).	Healthy patients	CMR	Good
Doesch et al.[7]	Germany	History of symptomatic HF and LVEF ≤ 35% on echocardiography. The ischemic etiology was defined as the presence of any epicardial coronary vessels with ≥75% stenosis or history of MI or coronary revascularization. DCM was based on end-diastolic diameter >56mm and a normal coronary angiography performed within the previous 6 months.	Healthy patients	CMR	Good
Flüchter et al.[13]	Germany	Patients with previous HF subclassified in ischemic and dilated etiologies.	Healthy patients	CMR	Good
Obokata et al.[14]	The United States	HFpEF was defined by clinical symptoms of HF, LVEF >=50%, directly measured elevation in LV filling pressures (at rest>15mmHg and/or with exercise ≥25mmHg). Non-obese HFpEF was defined by BMI <30kg/m^2. Obese HFPEF was defined by the presence of class II or greater obesity (BMI ≥35kg/m$^{2)}$.	Non-obese patients free of HF	Echocardiography	Good
Khawaja et al.[15]	The United States	Patients with LVEF ≤55%. This group was subdivided into patients with moderate LV dysfunction (LVEF 35% to 55%) and a group with severe LV dysfunction (LVEF ≤55%).	Patients without history of HF or LV dysfunction on echocardiogram	CT	Good
Tabakci et al.[16]	Turkey	NICMP was defined as LVEF ≤45 with normal coronary epicardial arteries seen in angiography.		CMR	Good
van Woerden et al.[4]	The Netherlands	Patients with LVEF >= 40% on echocardiography, NT-proBNP >125ng/L and echocardiographic evidences of LV hypertrophy, LV diastolic dysfunction, or left atrial dilatation according to ESC criteria. HFmrEF were defined by LVEF 40–50 and HFpEF patients were defined by LVEF >50%.	Healthy patients	CMR	Good

BMI: body mass index; CAD: coronary artery disease; CMR: cardiac magnetic resonance; CT: computerized tomography; DCM: dilated cardiomyopathy; HF: heart failure; HFmrEF: heart failure with mid-range ejection fraction; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; ICM: ischemic cardiomyopathy; LV: left ventricle; LVEF: left ventricular ejection fraction; MI: myocardial infarction; NICMP: nonischemic dilated cardiomyopathy; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association.

Performing a subgroup analysis evaluating the association between the amount of EAT with HFrEF, our meta-analysis showed that EAT was significantly lower in HFrEF patients than in the control group (SMD= -1.27, 95% CI: - 1.87 to -0.67, p <0.0001), as shown in Figure 3. The heterogeneity test showed that there were significant differences between studies (p<0.00001, I^2=92%). Although a sensitivity analysis was performed, it was not possible to remove the heterogeneity from the meta-analysis.

In addition, another subgroup analysis was performed to evaluate the association between the amount of EAT with HFpEF or HFmrEF. In this meta-analysis, the EAT volume was greater in HFpEF and HFmrEF than in the control group (SMD= 1.24, 95% CI: 0.99 to 1.50, p <0.0001), as shown in Figure 4. The heterogeneity test showed that there were no significant differences between studies (p = 0.85, I^2=0%).

Discussion

To the best of our knowledge, this is the first meta-analysis that investigated the association between EAT and HF. In our analysis, there was no significant relation between EAT and all-types of HF. However, in a subgroup analysis including only patients with HFrEF, the EAT volume was significantly reduced in HFrEF when compared to the control group. Furthermore, after performing an analysis including patients with HFpEF or HFmrEF, our results showed that the amount of EAT was significantly greater in the HFpEF or HFmrEF group than in the controls.

Anatomy and Measurement of the Epicardial Adipose Tissue

EAT is a visceral adipose tissue with close anatomical and physiological correlation with the myocardium and coronary arteries. It is located behind the visceral pericardium, in direct

Table 2 – Characteristics of the included studies (continued)

Study	Arms	N	Age, year	Male Sex (%)	BMI	EF	EAT| volume, weight or thickness
Doesch et al.[12]	HF (EF ≤ 35%)	41	63 ± 12	88	27 ± 4	27 ± 9	44 ± 11 (g)
	Controls	16	61 ± 11	75	28 ± 5	57 ± 6	67 ± 10 (g)
Doesch et al.[9]	DCM (EF 35-50%)	28	57,2 ± 13,4	79	26,6 ± 4,6	43,6 ± 6,9	50.0 ± 21.9 (ml) / 25.0 ± 10.4 (ml/m^2) / 47.0 ± 20.6 (g) / 23.5 ± 9.8(g/m^2)
	DCM (EF ≤35%)	84	60,1 ± 14,0	77	27,3 ± 4,8	23,0 ± 6,7	50.2 ± 13.9 (ml) / 25.7 ± 7.0 (ml/m^2) / 47.2 ± 13.1 (g) / 24.2 ± 6.6 (g/m^2)
	All DCM	112	59,4 ± 13,9	78	27,2 ± 4,7	58,7 ± 5,2	50.2 ± 16.2 (ml) / 25.5 ± 8.0 (ml/m^2) / 47.2 ± 15.2 (g) / 24.0 ± 7.5 (g/m^2)
	Controls	48	60,9 ± 9,8	77	27,3 ± 6,0	58,7 ± 5,2	66.0 ± 15.3 (ml) / 33.5 ± 6.4 (ml/m^2) / 62.1 ± 14.4 (g) / 31.7 ± 5.6 (g/m^2)
Doesch et al.[7]	HF|	66	63 ± 12	82	27 ± 4	27 ± 9	46 ± 11 (ml) / 43 ± 11 (g) / 24 ± 5 (ml/m^2)
	Controls	32	57 ± 11	78	28 ± 4	58 ± 5	71 ± 13 (ml) / 67 ± 13 (g) / 36 ± 5 (ml/m^2)
Flüchter et al.[13]	HF	43	61,9±12,4	81,3	27,0 ± 4,4	25,9 ± 6,8	51.0 ± 20.9 g / 3.5 ± 1.5(mm)- (Long-axis) / 2.9 ± 1.3(mm)-(Short-axis) /3.2 ± 1.2(mm)- (Longaxis/Short-axis)
	Controls	28	56,6 ± 10,9	78,6	27,5 ± 4,2	58,8 ± 4,2	64.6 ± 21.2 g / 3.8 ± 1.5(mm)- (Long-axis) / 4.3 ± 1.3(mm)-(Short-axis) /4.1 ± 1.1(mm)- (Longaxis/Short-axis)
Obokata et al.[14]	Controls	71	62 ± 10	42	25,4 ± 2,8	63 ± 4	6 ± 2 mm / 632 (517 - 768) ml
	Non-obese HFpEF (EF>50%)	96	70 ± 10	36	26,0 ± 2,7	63 ± 6	7±2 mm / 797 (643 - 979) ml
	Obese HFpEF (EF>50%)	99	65 ± 11	36	40,8 ± 5,6	63 ± 6	10±2 mm / 945 (831 - 1105) ml
Khawaja et al.[15]	HF (EF<55%)	60	54,2 ± 12,2	19	30,7 ± 11,5	NR	83.5 ± 67.1 (cm^3)
	HF (EF 35-55%)	43	53,4 ± 12,2	35	29,5 ± 4,7	NR	96.1 ± 73.9 (cm^3)
	HF (EF≤35%)	17	59,8 ± 14,4	53	31,3 ± 13,6	NR	52.2 ± 29.7 (cm^3)
	Controls	321	55,8 ± 10,4	70	29,6 ± 6,7	NR	114.5 ± 98.5 (cm^3)
Tabakci et al.[16]	DCM	93	49,9 ± 13,9	69	27,7 ± 3,3	32,0 ± 8,5	4.1 ± 0.8 mm
	Controls	38	51,1 ± 10,0	61	28,3 ± 3,4	62,9 ± 4,9	6.1 ± 1.8 mm
van Woerden et al.[4]	HF	64	70 ± 10,7	63	29,6 ± 5,7	54,3 ± 8,5	107.0 ± 27.7 (mL/m^2)
	Controls	20	66 ± 5,5	65	27,2 ± 4,6	59,7 ± 5,4	76.9 ± 11.5 (mL/m^2)

BMI: body mass index; DCM: dilated cardiomyopathy; EAT: epicardial adipose tissue; EF: ejection fraction; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; NR: not reported. All studies adopted a significance level of p-value < 0.05.

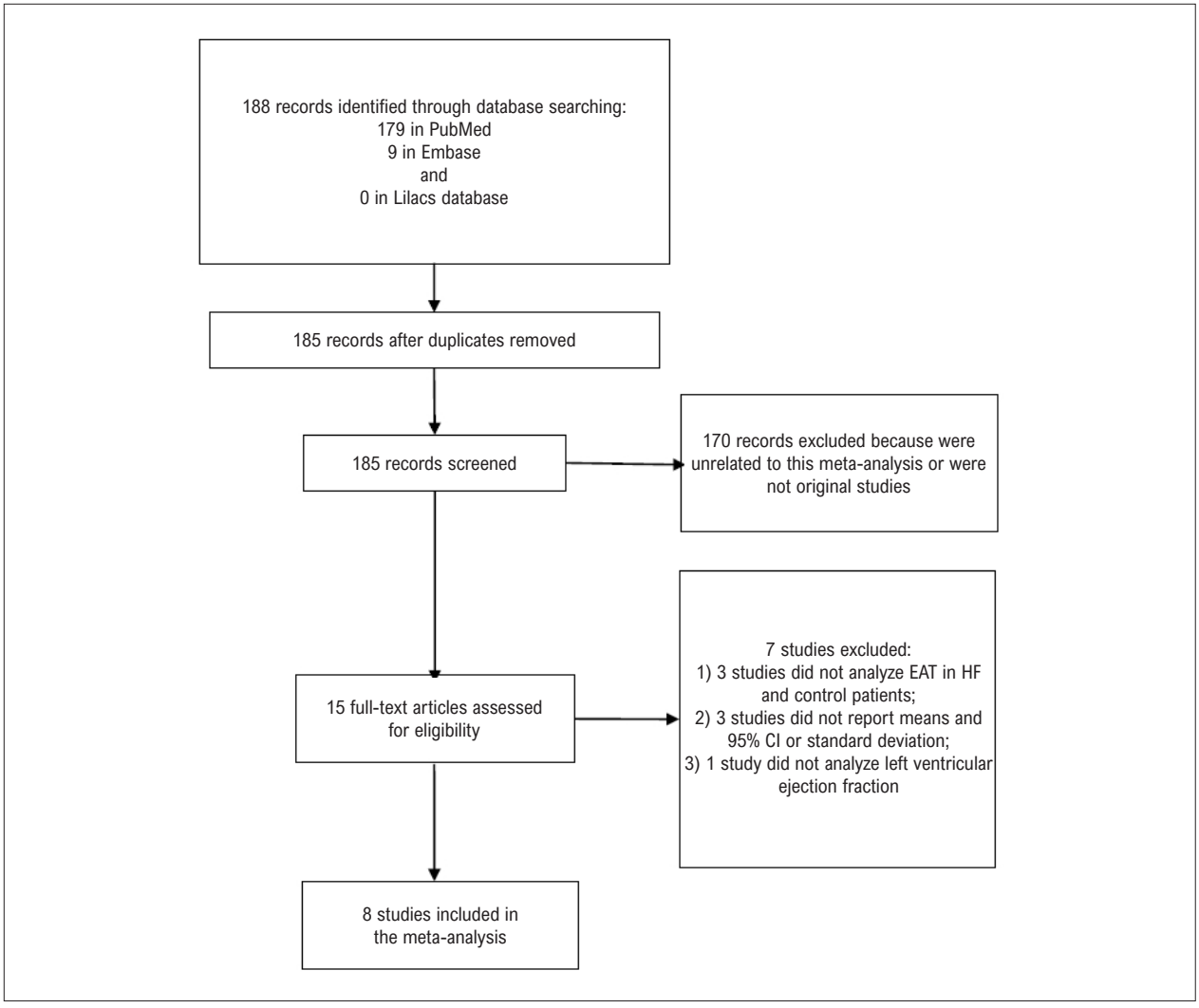
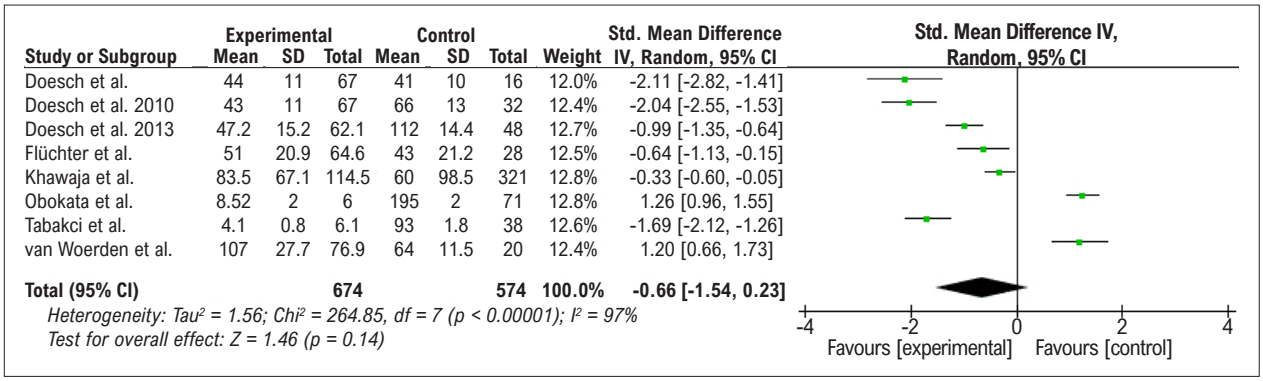


Figure 1 – *Flow diagram of the study selection.*



Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Doesch et al.	44	11	67	41	10	16	12.0%	-2.11 [-2.82, -1.41]
Doesch et al. 2010	43	11	67	66	13	32	12.4%	-2.04 [-2.55, -1.53]
Doesch et al. 2013	47.2	15.2	62.1	112	14.4	48	12.7%	-0.99 [-1.35, -0.64]
Flüchter et al.	51	20.9	64.6	43	21.2	28	12.5%	-0.64 [-1.13, -0.15]
Khawaja et al.	83.5	67.1	114.5	60	98.5	321	12.8%	-0.33 [-0.60, -0.05]
Obokata et al.	8.52	2	6	195	2	71	12.8%	1.26 [0.96, 1.55]
Tabakci et al.	4.1	0.8	6.1	93	1.8	38	12.6%	-1.69 [-2.12, -1.26]
van Woerden et al.	107	27.7	76.9	64	11.5	20	12.4%	1.20 [0.66, 1.73]
Total (95% CI)			**674**			**574**	**100.0%**	**-0.66 [-1.54, 0.23]**

Heterogeneity: Tau² = 1.56; Chi² = 264.85, df = 7 (p < 0.00001); I² = 97%
Test for overall effect: Z = 1.46 (p = 0.14)

Figure 2 – *Forest plot showing that the amount of EAT is not associated with all-types of HF. In the Standard Mean Difference column, the red dots to the left of the vertical line represented the studies that found a reduced amount of EAT in HF. The red dots to the right of the vertical line represented the studies that found an increased amount of EAT in HF. The black diamond represents the pooled analysis, and because it touches the vertical line, the result is not statistically significant. Chi2: chi-square statistic; CI: confidence interval; df: degrees of freedom; HF: heart failure; I2: I-square heterogeneity statistic; IV: inverse variance; p: p value; SD: standard deviation; SE: standard error; Std: standard; Z: Z statistic.*

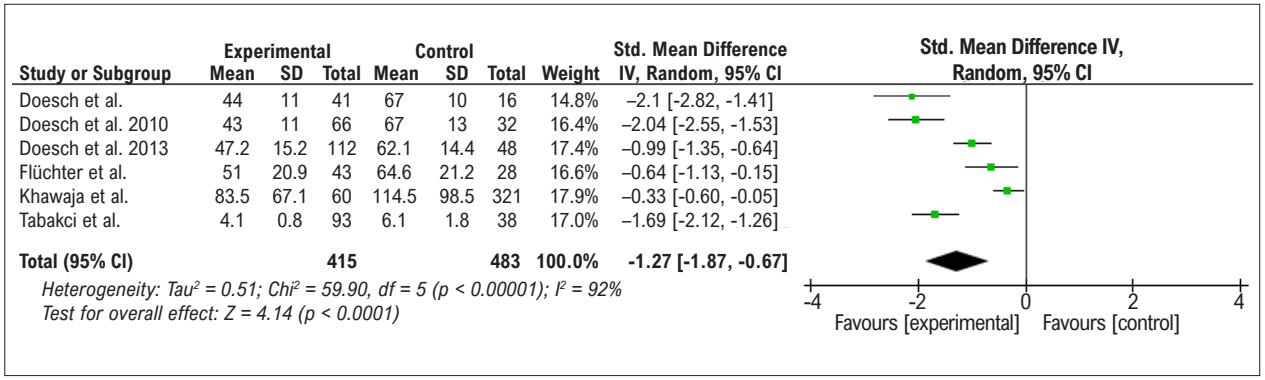


Figure 3 - *Forest plot showing that the amount of EAT is reduced in HFrEF. In the Standard Mean Difference column, the red dots to the left of the vertical line indicated that the amount of EAT is reduced in HFrEF. The black diamond does not touch the vertical line, showing statistical significance. Chi2: chi-square statistic; CI: confidence interval; df: degrees of freedom; HF: heart failure; I2: I-square heterogeneity statistic; IV: inverse variance; p: p value; SD: standard deviation; SE: standard error; Std: standard; Z: Z statistic.*

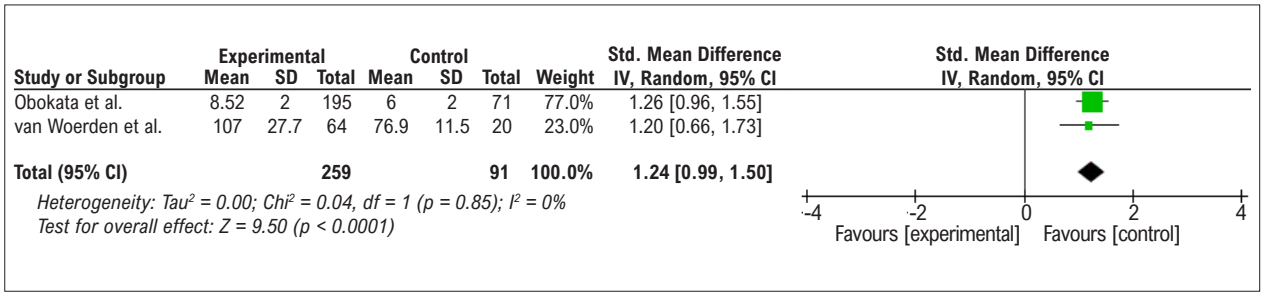


Figure 4 - *Forest plot showing that the amount of EAT is associated with HFpEF or HFmrEF. In the Standard Mean Difference column, the red dots on the right of the vertical line indicated that the amount of EAT is increased with HFpEF and HFmrEF phenotypes. The black diamond does not touch de vertical line showing statistical significance. Chi2: chi-square statistic; CI: confidence interval; df: degrees of freedom; I2: I-square heterogeneity statistic; IV: inverse variance; p: p value; SD: standard deviation; SE: standard error; Std: standard; Z: Z statistic.*

contact with the cardiac muscle, with no fascia between them, sharing the same coronary vascularization.[17,18] Previous studies have also shown that this fat depot is associated with body mass index levels, waist circumference, insulin resistance, and other metabolic syndrome traits, but may also contribute to systemic inflammation beyond traditional cardiovascular risk factors.[19,20,21] Thus, due to the close anatomical relation among EAT, the myocardium, and coronary arteries, EAT may have an impact on the pathophysiology of cardiovascular diseases, such as coronary artery disease, atrial fibrillation, and HF.[18,22]

Magnetic Resonance Imaging (MRI), CT, and echocardiography can adequately assess the amount of EAT, MRI being the gold-standard.[23] Although echocardiographic measurements have a good correlation with MRI, spatial variation in the echocardiographic window is a critical issue that needs attention when evaluating EAT thickness.[23] To minimize this problem, anatomical landmarks, such as the position of the interventricular septum and the aortic annulus, should always be used when assessing EAT thickness with the echocardiogram.[23]

Epicardial Adipose Tissue and Heart Failure with Reduced Ejection Fraction

In our meta-analysis, we found that in patients with HFrEF, EAT was significantly reduced when compared to the controls. For patients with HFrEF, EAT may be reduced due to systolic dysfunction and high levels of b-type natriuretic peptide (BNP) in this phenotype. In fact, when myocardium becomes dysfunctional, it develops abnormal metabolic needs.[24,25] In this sense, the role of EAT as a source of energy or cytokine homeostasis would decrease, and the EAT would be less found.[24,25] Moreover, in patients with HFrEF with a severely reduced ejection fraction, the reduced EAT volume may indicate a decreased buffering capacity for excess fatty free acids (FFA), as well as a lower capacity to adjust to special energy demands of the dysfunctional heart.[7]

Another possible pathway for EAT reduction is the fact that natriuretic peptides are capable of stimulating lipolysis in adipocytes.[24,26-28] Since patients with HFrEF often have high levels of BNP,[16] even when compared to HFpEF and HFmrEF, this might lead to lower amounts of EAT in HFrEF, as observed in this study.

Epicardial Adipose Tissue and Heart Failure with Preserved or Mid-Range Ejection Fraction

In this meta-analysis patients with HFpEF and HFmrEF demonstrated a higher amount of EAT, which was significantly different when compared to the control patients. Our results are in agreement with a previous meta-analysis, which showed an association between EAT and diastolic dysfunction,[29] a functional cardiac dysfunction that can lead to HFpEF and is also present in these patients. Differently from HFrEF, HFpEF is a highly heterogeneous syndrome and, to date, there are no therapies that can effectively reduce the risk of mortality in patients with this condition.[30] An emerging pathophysiological model of HFpEF shows that this HF phenotype comes from a comorbidity-induced systemic inflammation that leads to endothelial dysfunction, myocardial fibrosis, and cardiomyocyte stiffening, which ultimately results in HFpEF.[31]

Physiologically, EAT promotes several protective cardiac effects, due to its anti-atherosclerotic and anti-inflammatory properties, as well as a high FFA release and uptake rates.[32] However, in this comorbidity-induced inflammation model, obesity, diabetes, and other comorbidities that are common in patients with HFpEF may abnormally increase EAT, overloading fat cells.[7,33] Consequently, these dysfunctional fat cells start to release pro-inflammatory adipokines into circulation, which can lead to a chronic systemic inflammatory state.[5,34] This state is associated with several alterations, such as arterial stiffening, endothelial dysfunction of arterioles, and fibrosis.[4]

Moreover, since EAT is located under the pericardium, it could cause a remarkable influence on the diastolic function,[18,29] due to mechanical restraint effects, reducing LV distensibility, which restricts LV filling and functional capacity.[35-40]

Further Directions

Although this meta-analysis shows that the amount of EAT volume is associated with HFpEF and HFmrEF, the inflammatory state and the secretion of pro-inflammatory cytokines of this fat depot in HF must be investigated. Furthermore, studies that investigate if changes in EAT volume are associated with changes in left ventricular dynamics will elucidate the relation between EAT and cardiac function. Moreover, translational studies and clinical trials that study therapies and interventions targeting EAT are warranted.

Limitations

This meta-analysis has several limitations. First, since our meta-analysis only included observational studies, it carries an inherent bias of this study design. Moreover, to analyze all evidence available, our meta-analysis included studies using different imaging methods that assessed EAT, which could have contributed to the high heterogeneity found in our results. The fact that included studies analyzed patients from different continents and several HF etiologies might also have led to the significant heterogeneity observed in our results. Finally, the subgroup analysis of patients with HFpEF and HFmrEF included a small number of studies, which highlights the need for further studies that provide new insights into this association.

Conclusion

In our analysis, there was no significant relation between EAT and HF. However, in a prespecified subgroup analysis including only patients with HFrEF, the EAT volume was reduced in HFrEF when compared to the control group. In addition, after performing an analysis including patients with HFpEF or HFmrEF, EAT was significantly higher in HFpEF or HFmrEF than in the controls. Therefore, EAT could be further studied in translational studies to better understand the pathophysiology of HFpEF and HFmrEF and, possibly, provide a novel therapeutic target for HFpEF and HFmrEF therapies.

Author Contributions

Conception and design of the research: Correia ETO, Barbetta LMS, Mesquita ET; Acquisition of data: Correia ETO, Barbetta LMS, Costa OS, Miranda PH; Analysis and interpretation of the data: Correia ETO, Barbetta LMS; Statistical analysis: Correia ETO; Writing of the manuscript and Critical revision of the manuscript for intellectual content: Correia ETO, Barbetta LMS, Costa OS, Miranda PH, Mesquita ET.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

Ethics approval and consent to participate

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

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Subclinical Left Atrial and Ventricular Dysfunction in Acromegaly Patients: A Speckle Tracking Echocardiography Study

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Abstract

Background: **Although it is known that the left ventricular (LV) ejection fraction (EF) measured by echocardiography is preserved in patients with acromegaly, there is not enough information about the LV and left atrial strain (LV-GLS and LAS).**

Objective: **This study aimed to evaluate the left ventricular (LV) and left atrial (LA) functions with strain echocardiography (SE) in patients with acromegaly.**

Methods: **This study included 50 acromegaly patients with active disease and 50 healthy controls with similar age, gender, and body surface area. In addition to routine echocardiography examinations, LV-GLS and LAS measurements were performed with SE.**

Results: **LAS and LV-GLS values were significantly lower in patients with acromegaly ($p<0.05$ for all). In bivariate analysis, systolic blood pressure, N-terminal prohormone of brain natriuretic peptide, Insulin-like growth factor-1, LA diastolic diameter, and LVMI levels were found to be positively correlated with both LAS and LV-GLS ($p<0.05$). IGF-1 level was strongly correlated with LAS and LV-GLS ($p<0.001$ and $\beta=0.5$ vs. $p<0.001$ and $\beta=0.626$, respectively); 48% of patients with acromegaly have reduced LV-GLS (<20%). Left ventricular mass-index (LVMI) independently determines the presence of reduced LV-GLS and each 1g/m² increase in LVMI level increases the likelihood of reduced LV-GLS by 6%.**

Conclusion: **Although LV ejection fraction is normal in patients with acromegaly, LAS and LV-GLS values were significantly reduced. Apart from LVMI increase, another finding of cardiac involvement may be LAS and LV-GLS decrease. Therefore, in addition to routine echocardiography, LAS and LV-GLS may be useful to evaluate early signs of cardiac involvement before the occurrence of irreversible cardiac changes.**

Keywords: **Echocardiography/methods; Acromegaly; Cardiovascular Diseases; Myocardial, Deformability; Diagnostic, Imaging; Stroke Volume**

Introduction

Acromegaly is a chronic disease characterized by increased Insulin-like growth factor 1 (IGF-1) synthesis in the liver due to a growth hormone (GH) secreting pituitary adenoma, and excessive protein synthesis and excess tissue growth due to these hormones.[1] Chronic high IGF-1 levels cause specific structural and functional changes.[1] If left untreated, it causes mortality, and the most common cause of mortality is cardiovascular (CV) diseases.[1,2]

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Strain is a measure of deformation against a power in a matter. It is defined in radial, circumferential, and longitudinal dimensions. Assessment of myocardial deformation by strain echocardiography (SE), in terms of two-dimensional speckle tracking echocardiography (2D-STE) or tissue Doppler imaging (conventional strain), can provide peerless information on both regional and global ventricular functions.[3] Deformation imaging can even detect minimal functional changes and provides early stage diagnosis. Left atrium (LA) deformation parameters and left ventricular global longitudinal strain (LV-GLS) have proven to be strongly correlated with LA and LV systolic functions in different clinical scenarios, respectively.[4-8] It has been demonstrated that many patients with normal LV ejection fraction (LVEF) have reduced LV systolic function with the use of LV-GLS.[3,9,10]

In patients with acromegaly, systolic function is evaluated with LVEF. However, impairment in LVEF is only seen in the later stages of the disease and in the minority of patients.[11-14]

Recently, a limited number of studies have evaluated LV-GLS and LA strain in patients with acromegaly and preserved LVEF.[5-8] Contradictory results were obtained in these studies. LV-GLS was found to be decreased in two studies conducted by the same authors;[8,9] whereas, another study reported LV-GLS to be similar to healthy controls.[5] Evaluation of LA deformation measures in patients with acromegaly with 3D-STE have been performed in a study; however, no clear information was provided regarding the change in global LA strain.[8]

Due to the feasibility of simultaneous measurements of LA deformation and LV-GLS, in addition to traditional echocardiography, this study aimed to evaluate the LV and LA functions with SE in patients with active acromegaly and preserved LVEF.

Methods

Study population

In this cross-sectional study, 50 patients (33 male, 17 female; mean age 46.1 ± 6.2 years) with active acromegaly (1-De novo patients, 2-Patients after surgery without remission, 3-Patients on medical treatment without remission) and age, gender, body mass index (BMI), and body surface area (BSA) matched with 50 healthy controls (31 male, 19 female; mean age: 44.6 ± 5.1 years). Patients aged over 18 years with active acromegaly were enrolled in the study. The patients included in the study are shown in the flow-chart (Figure 1). Current guideline information was used for the diagnosis, treatment, and classification of patients with acromegaly.[1] Remission of acromegaly was defined as a normal glucose-suppressed serum GH less than 0.38 μg/liter (<1 mU/liter), a serum GH less than 1.9 μg/liter (<5 mU/liter), and a normal IGF-1 for age.[1] Patients with a history of coronary artery disease (CAD) and myocardial infarction, cardiac arrhythmia, systolic heart failure or LVEF <50%, heart valve disease, pulmonary embolism, thyroid dysfunction, pregnancy (known or suspected), active malignancy, and kidney and liver dysfunction, as well as patients who refused to participate in the study were not included in the study. The local ethics committee approved the study protocol (Cukurova University Faculty of Medicine Ethics Committee, 03.05.2019-88), and written informed consent was taken from each participant.

After the assessment of detailed medical history and a complete physical examination, the baseline characteristics of the patients, including age, sex, hypertension (HT), diabetes mellitus (DM), hyperlipidemia, current smoking status, family history of cardiac disease, and medications were recorded for all patients. Participants' BMI and BSA parameters were calculated.

Glucose, blood urea nitrogen, creatinine, total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, triglyceride, aspartate aminotransferase, alanine aminotransferase, white blood cells, hemoglobin, high sensitive C reactive protein, and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were measured using an automated chemistry analyzer (Abbott Aeroset, MN, USA) with appropriate commercial kits (Abbott). Serum GH was assessed by an automated chemistry analyzer (Abbott Aeroset, MN, USA), using appropriate commercial kits (Abbott) and

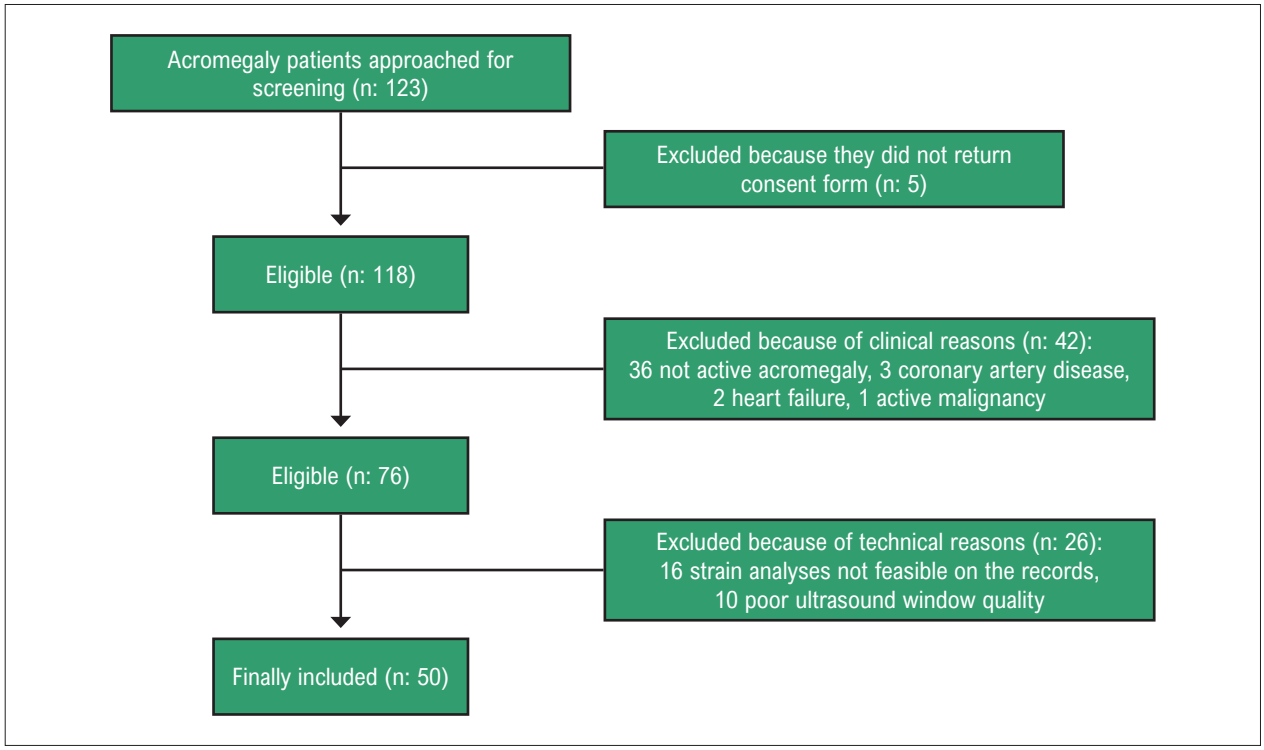

Figure 1 – *Flow-chart for inclusion and evaluation of patients in the study.*

reference value of GH was between 0.014 -5.219 ng/ml. The serum total IGF-1 level was assessed by an automated chemistry analyzer (Abbott Aeroset, MN, USA), using appropriate commercial kits (Abbott), and the reference value of IGF-1 varies according to age and sex. Serum GH and IGF-1 levels were measured at the same time of echocardiography examination for each subject.

Echocardiographic assessment

Echocardiographic evaluation was made by using a 2.5-3.5 MHz transducer EPIQ 7C (Philips Healthcare 3000 Minuteman Road, Andover, MA USA). Echocardiographic evaluation was performed within the first week for patients who met the inclusion criteria. Echocardiographic evaluations of all patients were performed in the left lateral decubitus position with electrocardiography and blood pressure monitoring. All images were taken with at least 3 repetitive cycles from the standard parasternal long and short axis, apical 4 chamber, 5 chamber, and 2 chamber views according to the suggestions of the American Society of Echocardiography.[15] LV diastolic diameter, LV systolic diameter, interventricular septum (IVS) thickness, posterior wall (PW) thickness, LA diastolic diameter were measured from the parasternal long axis image from two-dimensional image windows. Devereux formula was used for LV mass measurement.[16] Afterwards LV mass-index (LVMI) was calculated by dividing LV mass to BSA. LVMI value > 115 gr/m^2 in men and > 95 gr/m^2 in women were considered LV hypertrophy.[17]

In the SE procedure, all patients were in normal sinus rhythm. LA and LV myocardial deformation parameters were calculated by using STE over two-dimensional gray scale images. Two-dimensional gray scale apical 4 chambers (A4C), apical 2 chambers (A2C), and apical 3 chambers (A3C) were recorded after expiration by holding one's breath. At least three cardiac cycles were recorded for each image, and attention was paid to consider at least 60-80 fps, according to the guidelines of European Society of Cardiology.[18] Segments with insufficient image quality and cardiac cycles containing premature beats were excluded from the measurements.

QLAB version 10.5 (Philips, Andover, MA, USA) software was used for LV and LA analyses. The software has automatically followed the wall movements throughout the entire cardiac cycle after the LV endocardium has been marked frame by frame with manual drawing method (manual tracking) on the two-dimensional images. LV-GLS values were calculated from the images with 2D-STE. After manually marking 2 basal and 1 apical parts of LV, the remaining endocardial borders were automatically marked by the software and the appropriate epicardial border was also automatically drawn. When the automatically drawn LV boundaries are not suiTable for analysis, the borders were manually corrected for proper analysis. After analysis, the software divided LV A2C, A3C, A4C recordings to six segments, and an 18-segment model was used to calculate LV-GLS (Figure 2).

LA myocardial deformation parameters were also calculated from the images of 2D-STE using LV strain software.[19] Apical four chamber view images of the LA were obtained using standard anatomic landmarks to ensure optimal acquisition and avoid foreshortening with conventional 2-dimensional echocardiography, at relatively high frame rates (60–80 fps). The LA endocardial border tracing was started at the endocardial border of the mitral annulus, to the LA endocardial border, extrapolating across the pulmonary veins, and/or LA appendage orifices, up to the opposite mitral annulus side by experienced echocardiographers blinded to clinical information. The software then automatically generated an epicardial LA silhouette, which delineated a region of interest in each apical view. Manual adjustment of the region of interest was allowed to encompass the entire LA myocardial layer, followed by automated segmental tracking. After tracking, the LA deformation indices, such as longitudinal strain and its first derivation SR curves, were obtained from a non-foreshortened apical four chamber view.[20] We used the R wave as a starting point (R-R gating) for deformation analysis. Longitudinal strain and strain rate curves were generated in all segments, and the average of the segments was calculated for the corresponding time points (Figure 3). Using these curves, peak positive LA strain (LAS) and peak systolic strain rates (LASR) were calculated. LAS and LASR represent reservoir function of the LA. All the echocardiographic images were stored digitally and reviewed offline, with deformation measures performed by an experienced cardiologist, blinded to the data, using Philips QLAB version 10.5 software analysis.

Statistical analyses

Statistical analyses were conducted using SPSS, version 23.0, (SPSS Inc. Chicago, Illinois). Data are expressed as mean ± SD for continuous variables and percentage for categorical variables. The Shapiro-Wilk test was used to test normality, and a p-value >0.05 was defined as normally distributed data. Continuous variables that showed normal distribution were compared using the Student's t test and ANOVA, whereas the Mann-Whitney U and Kruskal-Wallis tests were used for non-normally distributed samples. Categorical variables and frequencies were compared by means of the chi-square test. Statistical significance was defined as a p-value <0.05 for all comparisons. In our study, parameters that differed in patients with <20% for LV-GLS were found in univariate analysis. Therefore, Backward: LR logistic regression analysis was performed to determine the parameters that independently determined patients with <20% for LV-GLS. Pearson's and Spearman's correlation were used to examine the relationship between continuous variables. Variables with a p-value <0.05 in the bivariate analysis were tested in the linear regression analysis. Results were expressed as the p-value and hazard ratio (HR) in a 95% CI.

Results

Fifty-eight patients with active acromegaly were included in the study. Eight patients who met the exclusion criteria and could not perform ideal echocardiographic examination were excluded from the study. Forty-five patients included in the study were De novo acromegaly patients. The other three patients were after surgery without remission and two patients were on medical treatment without remission. The study data were divided into two groups, with and without acromegaly (healthy controls). Cohen kappa values that

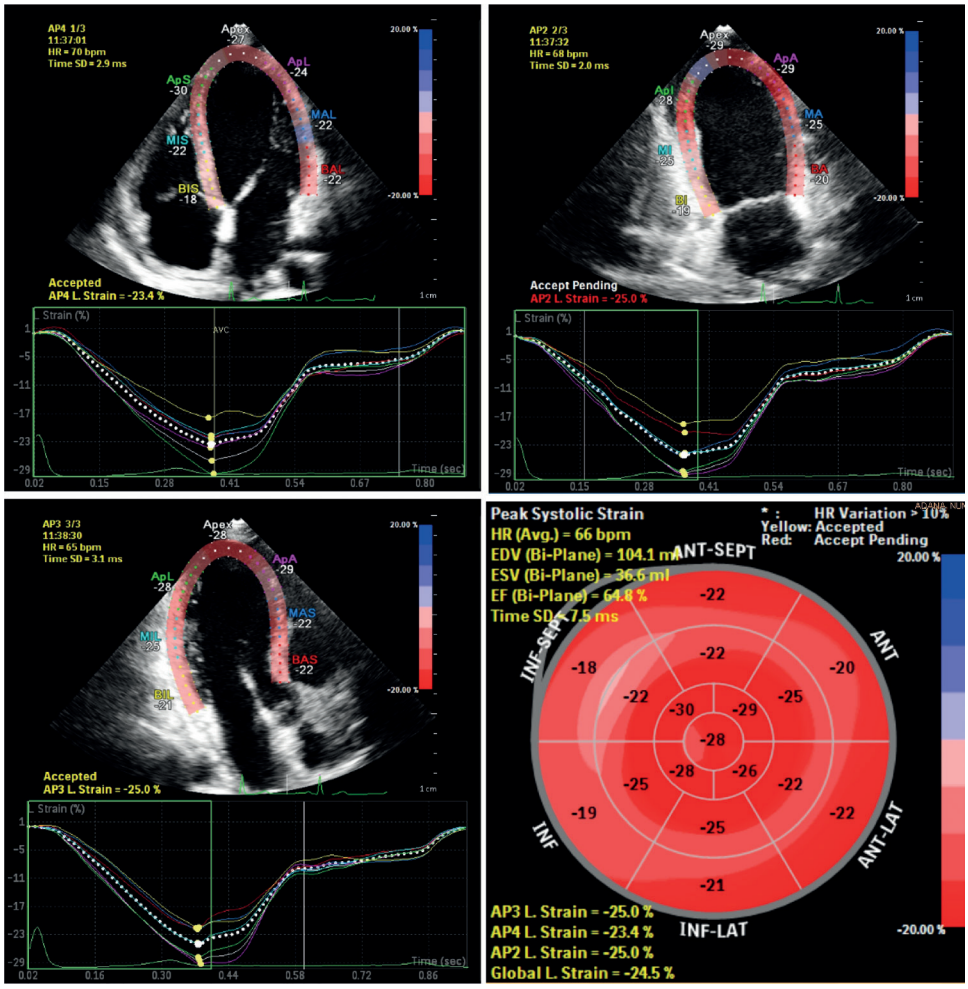

Figure 2 – *Left ventricular global longitudinal strain (LV-GLS) measurement by strain echocardiography in patient with acromegaly.*

evaluate interobserver and intraobserver variability were over 90% for all echocardiography measurements.

Demographic, clinical, and laboratory data

When demographic data were compared between the study groups; age, gender, BMI, and BSA were similar between the groups. The frequency of HT and DM in patients with acromegaly was determined to be 28% and 32%, respectively. In terms of clinical parameters, systolic and diastolic blood pressures and heart rate were higher in patients with acromegaly. Plasma glucose, NT-proBNP, IGF-1, and growth hormone levels were found to be significantly higher in patients with acromegaly. Other laboratory parameters were similar between the two groups (Table 1).

Echocardiographic data

IVS and PW end-diastolic thickness and LVMI values were found to be significantly higher in patients with acromegaly (Table 2). LV diameters and LVEF values were found to be similar between the groups with and without acromegaly. LAS and LV-GLS values were significantly lower in patients with acromegaly (Figure 4-5).

When the limit value was taken as <20% for LV-GLS, it was found that LV-GLS levels were decreased in 48% of the acromegaly group. When the demographic, clinical, and laboratory data of patients with decreased and normal LV-GLS acromegaly were compared, it was determined that patients with low LV-GLS had higher rates of HT (45.8% vs 11.5% and p = 0.008) and higher LVMI values (123 gr/m^2 vs 94.6 gr/m^2 and p <0.008). In the multivariate logistic regression analysis, it was found that the LVMI value and IGF-1 levels independently predict the reduced LV-GLS value (p = 0.003, OR: 1.060 and CI: 1.019 - 1.102 and p = 0.012, OR: 1.056 and CI: 1.023 - 1.098). According to this analysis, every 1 gr/m^2 increase in LVMI value and every 1 ng/dL increase in IGF-1 level increases the probability of decreased LV-GLS by 6% and 5.6%, respectively.

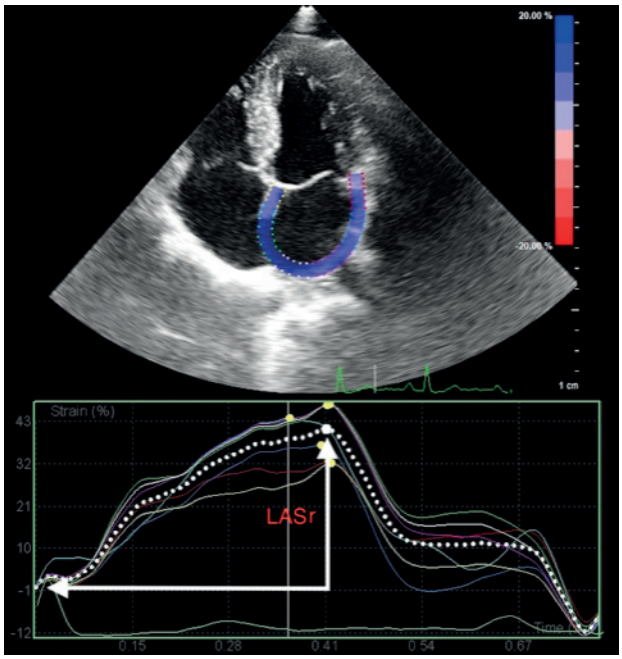

Figure 3 – *Left atrial deformation parameter measurement by strain echocardiography in patient with acromegaly.*

Determination of LA deformation measurement

Correlation analysis was performed to determine the parameters associated with LA deformation. Parameters related to LAS in correlation analysis were summarized in Table 3. Linear regression analysis was performed to determine the presence of independent relationships of LAS. In linear regression analysis; systolic BP, NT-proBNP, IGF-1, LA end-diastolic diameter, and LVMI were found to be positively and significantly associated with LAS. Statistically, the strongest correlation was found to be between LAS and IGF-1 levels (Table 3 and Figure 6).

Determination of LV-GLS-related parameters

Correlation analysis was performed to determine the parameters associated with LV-GLS. Parameters related to LV-GLS in the correlation analysis were summarized in Table 4. Linear regression analysis was performed to determine the presence of independent relationships of LV-GLS related parameters. In linear regression analysis; systolic blood pressure, NT-proBNP, IGF-1, LA end-diastolic diameter and LVMI were found to be positively and significantly associated with the LV-GLS value. Statistically, the strongest correlation was found to be between the LV-GLS and IGF-1 levels (Table 4 and Figure 7).

Discussion

To the best of our knowledge, our study is the first study to evaluate LV-GLS and LAS together in patients with acromegaly. The main finding of our study was that LV and LA systolic functions in SE were found to be impaired despite the preservation of LV systolic functions in conventional echocardiography. Another important finding was that the IGF-1 level, which is one of the most important parameters of acromegaly disease activity, was strongly correlated with LAS and LV-GLS. In addition, in our study, it was found that 48% of patients with acromegaly had silent impaired LV systolic function detected with SE and this condition was closely and independently related to LVMI value and IGF-1 level.

Acromegaly is one of the secondary causes of HT. HT and DM are common in these patients due to the metabolic effects of the disease.[7,11,21,22] In patients with acromegaly, fibrosis and hypertrophic changes occur in different degrees of LV and LA myocardium, with both increasing frequency of HT and DM, and an increasing IGF-1 level. LVH is common and can be seen in 25-85% of all patients with acromegaly.[5,23,24] In our study, 50% of the patients with acromegaly had LVH. In patients with acromegaly, cardiac changes due to increased hormones and associated HT and DM are called acromegalic cardiomyopathy (CMP).[25] This disease consists of 3 phases; i) an increase in LV and right ventricle (RV) contractility and LVH accompanied by increased IGF-1, ii) diastolic dysfunction as a result of decreased LV elasticity, iii) typical cardiomyopathy appearance with LV dilatation and decreased LVEF.[26] LVEF decrease and LV dilatation, which is the 3rd stage of the disease, are seen in only 1-10% of the patients with acromegaly.[11-14] However, it is important to evaluate LV functions of these patients with a new diagnostic method as early as stage 1, before irreversible cardiac changes occur.

Evaluation of LV systolic function with LV-GLS is relatively new and still quite uncommon. LV-GLS is mostly used to evaluate subclinical or silent cardiac involvement of systemic

Table 1 – Demographic, clinical, and laboratory parameters of acromegaly patients and healthy controls

Variable	Acromegaly patients n=50	Healthy controls n=50	p
Age (year)	46.1 ± 6.2	44.6 ± 5.1	0.295
Gender (female)	17	19	0.418
Hypertension, n (%)	14 (28%)	–	–
Diabetes mellitus, n (%)	16 (32%)	–	–
Current smoker, n (%)	15 (30%)	–	–
Hyperlipidemia, n (%)	7 (14%)	–	–
Systolic blood pressure (mmHg)	130 ± 19	110 ± 10	<0.001
Diastolic blood pressure (mmHg)	81 ± 11	67 ± 6.4	<0.001
Heart rate (pulse/minute)	81 ± 11	67 ± 4.1	<0.001
Body mass index (kg/m^2)	28.1 ± 2.3	27.6 ± 1.6	0.164
Body surface area (m^2)	2.01 ± 0.10	2.00 ± 0.09	0.569
White blood cell (µL)	7.3 ± 1.9	7.5 ± 1.6	0.656
Hemoglobin (gr/dL)	13.1 ± 1.8	12.9 ± 1.2	0.420
Plasma glucose (mg/dL)	109 ± 23	92 ± 5.6	<0.001
Blood urea nitrogen (mg/dL)	32.9 ± 16.6	29.5 ± 4.1	0.149
Creatinine (mg/dL)	0.75 ± 0.42	0.64 ± 0.10	0.138
Total cholesterol (mg/dL)	197 ± 59	217 ± 60	0.095
Low density lipoprotein (mg/dL)	135 ± 45	148 ± 44	0.157
High density lipoprotein (mg/dL)	44.3 ± 15.3	48.2 ± 8.1	0.125
Triglyceride (mg/dL)	165 ± 77	191 ± 108	0.180
Aspartate aminotransferase (u/L)	20.6 ± 7.4	18.9 ± 3.4	0.143
NT-proBNP (pg/mL)	365 ± 297	74 ± 6.7	<0.001
hs-CRP (mg/dL)	1.69 ± 1.35	0.43 ± 0.31	<0.001
Alanine aminotransferase (u/L)	16.8 ± 8.9	15.9 ± 2.9	0.298
IGF-1 (ng/dL)	376 ± 181	72 ± 7.5	<0.001
Growth hormone (ng/mL)	9.21 ± 14.4	1.01 ± 0.52	<0.001

hs-CRP: High sensitive C reactive protein; IGF-1: Insulin-like growth factor 1; NT-proBNP: N-terminal pro-brain natriuretic peptide.

Table 2 – Echocardiography parameters of acromegaly patients and healthy controls

Variable	Acromegaly patients n=50	Healthy controls n=50	p
IVS end-diastolic thickness (mm)	12.3 ± 1.92	9.9 ± 1.21	<0.001
PW end-diastolic thickness (mm)	11.9 ± 1.32	9.7 ± 1.01	<0.001
LV end-diastolic dimension (mm)	46.7 ± 4.5	47.3 ± 4.3	0.516
LV end-systolic dimension (mm)	31.1 ± 4.2	31.5 ± 4.2	0.656
LA end-diastolic dimension (mm)	35.3 ± 4.2	33.1 ± 2.6	0.002
LV ejection fraction (%)	57.8 ± 4.1	58.9 ± 5.3	0.259
LV mass index (gr/m2)	108 ± 28	82± 17	<0.001
LV hypertrophy, n (%)	25 (50%)	0 (0%)	<0.001
LAS (%)	21.5 ± 1.36	23.5 ± 1.06	<0.001
LV-GLS (%)	−20.4 ± 1.45	−22.8 ± 0.83	<0.001
LV-GLS < 20%, n (%)	24 (48%)	0 (0%)	<0.001

IVS: Interventricular septum; LA: Left atrial; LV-GLS: Left ventricular global longitudinal strain; LV: Left ventricular; PW: posterior wall; LAS: peak positive LA strain.

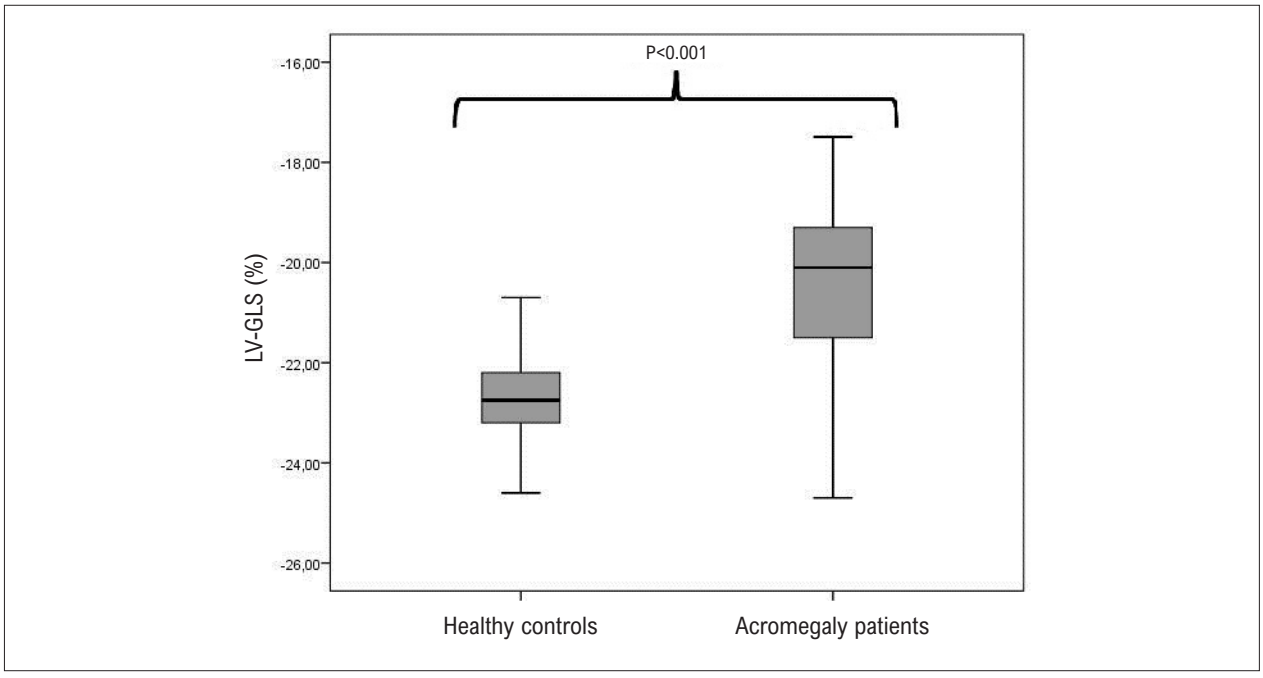

Figure 4 – *The Boxplot graphic showed that left ventricular global longitudinal strain (LV-GLS) in patient with acromegaly and healthy controls.*

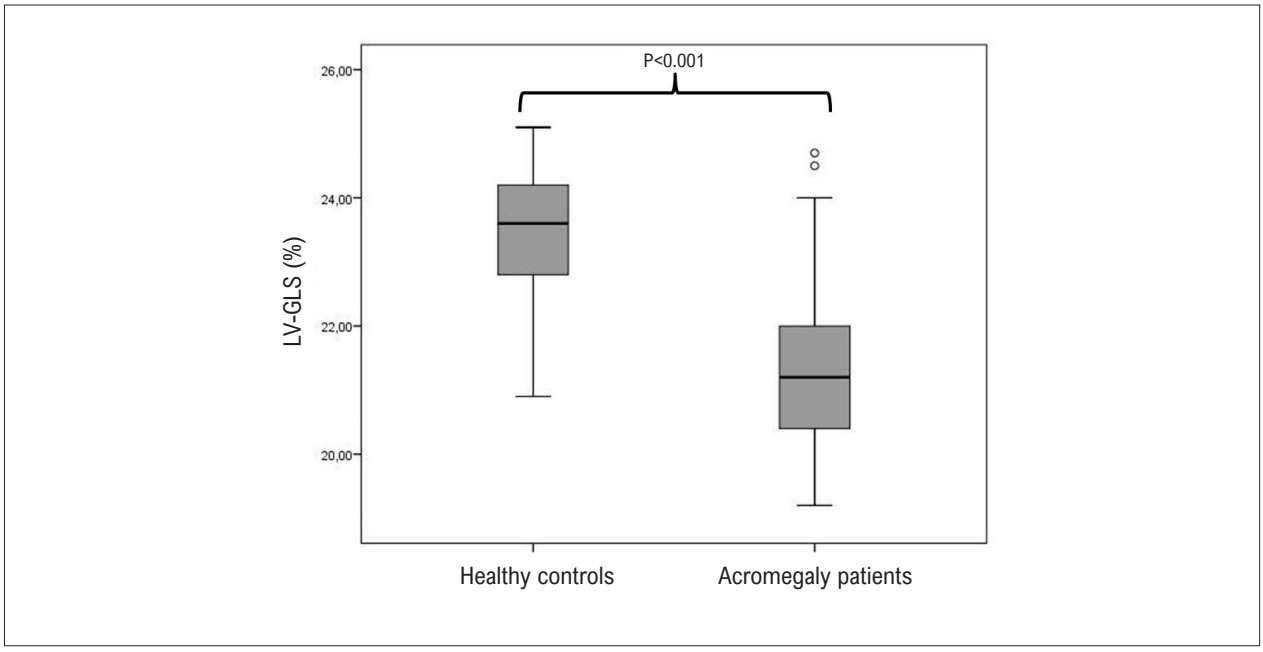

Figure 5 – *The Boxplot graphic showed that peak positive LA strain (LAS) in patient with acromegaly and healthy controls.*

diseases with normal LVEF.[27-30] Cardiovascular mortality increases in patients with acromegaly.[1,2] Decreased LV-GLS values have proven to be associated with sudden cardiac death and life-threatening arrhythmia.[31] The fact that SE is easily accessible and inexpensive gives it an important advantage over other methods. However, the most important limitation is that the image quality must be very good. Although SE was used frequently to evaluate LV functions in the first place; in the last few years, many studies evaluated LA functions with strain echocardiography.[4]

Several studies have evaluated LV-GLS in patients with acromegaly and normal LVEF, and contradictory results have been obtained.[5-7] The first study was conducted by Volschan et al.[5] in 2017 in 37 patients with active acromegaly, and it

Table 3 – The parameters associated with LA-GLS and linear regression analysis for parameters significantly correlated with LAS

	Univariate analysis		Multivariate analysis	
	p	r	p	β
Systolic blood pressure	<0.001	0.427	0.001	0.278
Diastolic blood pressure	<0.001	0.362	0.470	0.102
Heart rate	<0.001	0.360	0.840	0.023
Plasma glucose	<0.001	0.418	0.255	0.133
Creatinine	0.018	0.225	0.712	0.064
NT-proBNP	<0.001	0.445	0.013	0.237
IGF-1 (ng/dL)	<0.001	0.531	<0.001	0.531
Growth hormone (ng/mL)	0.025	0.225	0.408	0.096
LA end-diastolic dimension	<0.001	0.662	<0.001	0.378
LV mass index	<0.001	0.623	<0.001	0.503

LA: Left atrial; LAS: peak positive LA strain; LV: left ventricular; IGF-1: Insulin-like growth factor 1; NT-proBNP: N-terminal pro-brain natriuretic peptide. $R^2_{Adjusted}$ *= 0,684 and p< 0.001 in multivariate analyses.*

was found that the LV-GLS value did not change or even increased with no statistical significance when compared to healthy controls. In another study conducted in 2018, it was reported that there was a decrease in LV-GLS value in acromegaly patients, and this situation was related to LVH.[7] In another study conducted and published very recently by the same authors, LV-GLS was reported to be lower in patients with acromegaly, similar to the previous study.[6] Our study supports two studies showing that the LV-GLS value is decreased in patients with acromegaly. In addition to previous studies, we also showed a significant decrease in LA-GLS in the same patient group. The cut-off value for reduced LV-GLS was accepted as <20%.[15] In our study, 48% of the patients with acromegaly were under <20%. In other words, LV systolic functions of half of the patients with acromegaly were impaired. Increased LVMI and IGF-1 were found to be strongly associated with decreased LV-GLS in acromegaly patients.[5,7] Serum IGF-1 and GH levels were not related in patients with reduced LV-GLS in the same studies.[5,7] In our study, similar to the previous study, LVMI was found to predict patients with reduced LV-GLS; moreover, IGF-1 levels were significantly related to reduced LV-GLS. In our study, it was found that every 1 gr/m² increase in LVMI increased the risk of reduced LV-GLS by 6%. In additional to this, every 1 ng/dL increase in IGF-1 level increased the probability of decreased LV-GLS by 5.6%. LVMI, which is the most objective finding of the cardiac involvement in patients with acromegaly, is also the most closely associated parameter with decreased LV-GLS. Therefore, intervention to HT, DM, and LVMI as early as possible may be the most logical way to delay future systolic dysfunction in patients with acromegaly.

Impaired LV-GLS in patients with acromegaly can be explained by two pathophysiological mechanisms. The first is the effect of HT and DM. LV-GLS reduction has been demonstrated previously with the cardiac effects of HT and DM even in the asymptomatic period before any CV disease.[27,28] In our study, the prevalence of HT and DM in patients with acromegaly is 28% and 32%, respectively. The prevalence of HT was significantly higher in patients with decreased LV-GLS. This indicates that LV-GLS is affected by the presence of HT. The second mechanism may be LV heterotrophy and myocardial fibrosis due to increased IGF-1 in patients with acromegaly without HT and DM.[23,25] An increased IGF-1 value may be associated with disease activity and cardiac involvement. In our study, the IGF-1 level, which is one of the most important parameters of acromegaly activity, was strongly correlated with LV-GLS.

There is limited data on LA function and size in patients with acromegaly.[8,32] In a previous study, it was reported that LA volume and mechanical functions were similar to healthy controls, and serum IGF-1 and GH levels were not associated with LA mechanical function in patients with acromegaly.[32] In another recent study, an increase in LA volume was reported in patients with acromegaly.[8] In our study, LA volume was not evaluated, but LA diastolic diameter was increased in patients with acromegaly.

Although there is no study in the literature evaluating LAS with 2D-STE in acromegaly patients, LA strain imaging was performed in only one study with 3D-STE.[8] Kormanyos et al.[8] reported that LA global and mean segmental strain values were increased and LA circumferential strain values was decreased. A similar finding was demonstrated for right atrium in another study by the same authors.[33] It has been reported that the IGF-1 level and the LA circumferential strain value were positively correlated.[8] Our study was the first to demonstrate a decrease in LAS, and its strong and positive correlation with IGF-1, which is one of the disease activity parameters.

Limitations

As a single-center non-randomized study, our patient cohort might be different from other centers. The sample size is relatively small and our results need to be confirmed in future, large multi-center prospective trials. CV mortality and morbidity are high in patients with acromegaly.[1] However; we did not evaluate the prognosis. In addition, the effect

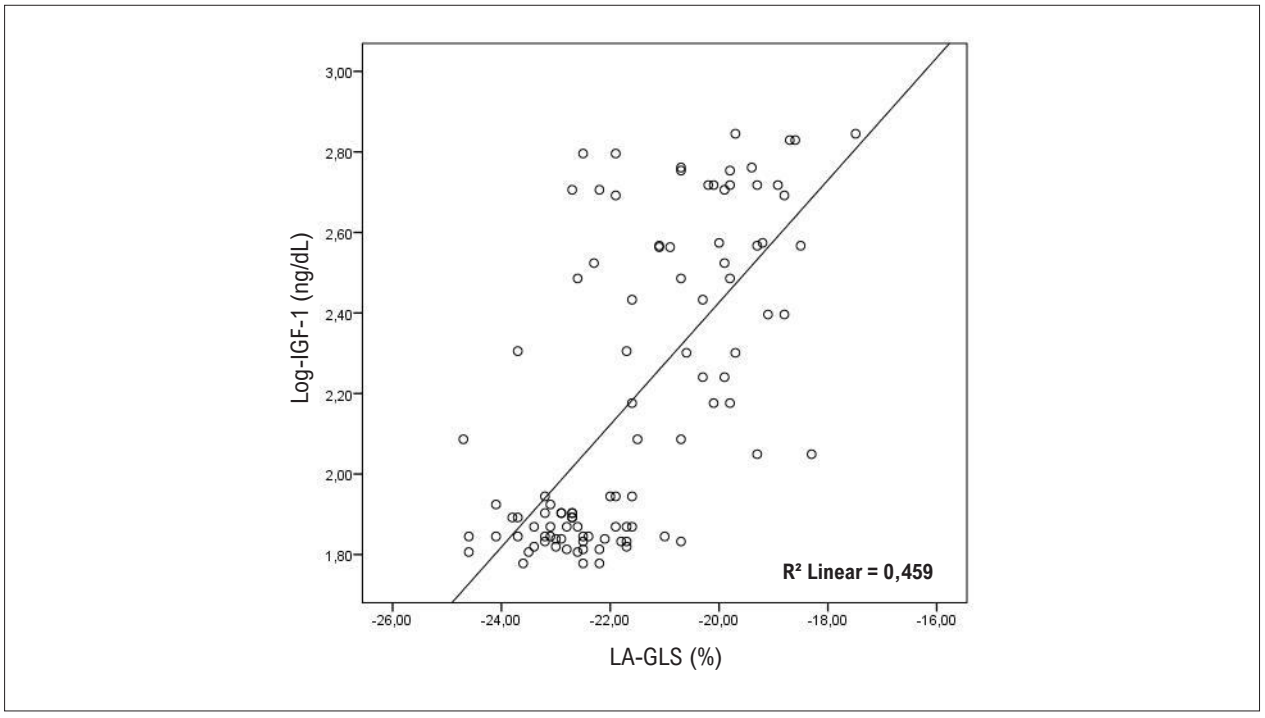

Figure 6 – *Scatter plot diagram of the relationship of peak positive LA strain (LAS) with insulin-like growth factor 1 (IGF-1). A 10-logarithmic scale of IGF-1 value was obtained.*

Table 4 – The parameters associated with LV-GLS and linear regression analysis for parameters significantly correlated with LV-GLS

	Univariate analysis		Multivariate analysis	
	p	r	p	β
Age	0.026	0.223	0.844	0.017
Body mass index	0.033	0.213	0.256	0.092
Systolic blood pressure	<0.001	0.509	<0.001	0.300
Diastolic blood pressure	<0.001	0.462	0.605	0.076
Heart rate	<0.001	0.408	0.426	0.081
Plasma glucose	<0.001	0.442	0.172	0.146
Creatinine	0.015	0.243	0.263	0.090
NT-proBNP	<0.001	0.478	0.011	0.176
IGF-1	<0.001	0.626	<0.001	0.626
Growth hormone (ng/mL)	<0.001	0.429	0.050	0.207
LA end-diastolic dimension	0.001	0.341	0.009	0.199
LV mass index	<0.001	0.623	<0.001	0.548

IGF-1: Insulin-like growth factor 1; NT-proBNP: N-terminal pro-brain natriuretic peptide; LV-GLS: Left ventricular global longitudinal strain. $R^2_{Adjusted} = 0,641$ and p< 0.001 in multivariate analyses.

of treatment on LV-GLS and LAS was not evaluated due to the absence of follow-up. In our study, we did not have the information regarding the pathophysiologic insight of reduced LV-GLS due to the lack of histopathological evaluation with myocardial biopsy. Sleep apnea is common in patients with acromegaly,[1] and it has an adverse effect on LV functions. However, we were not able to do polysomnography in all patients. The most important types of cardiac involvement are LVH and myocardial fibrosis in patients with acromegaly. Myocardial fibrosis can be best assessed with cardiac magnetic resonance imaging. If we had been able to perform cardiac magnetic resonance imaging, we would have been able to evaluate the association of late gadolinium enhancement with LA-GLS and LV-GLS. Diastolic

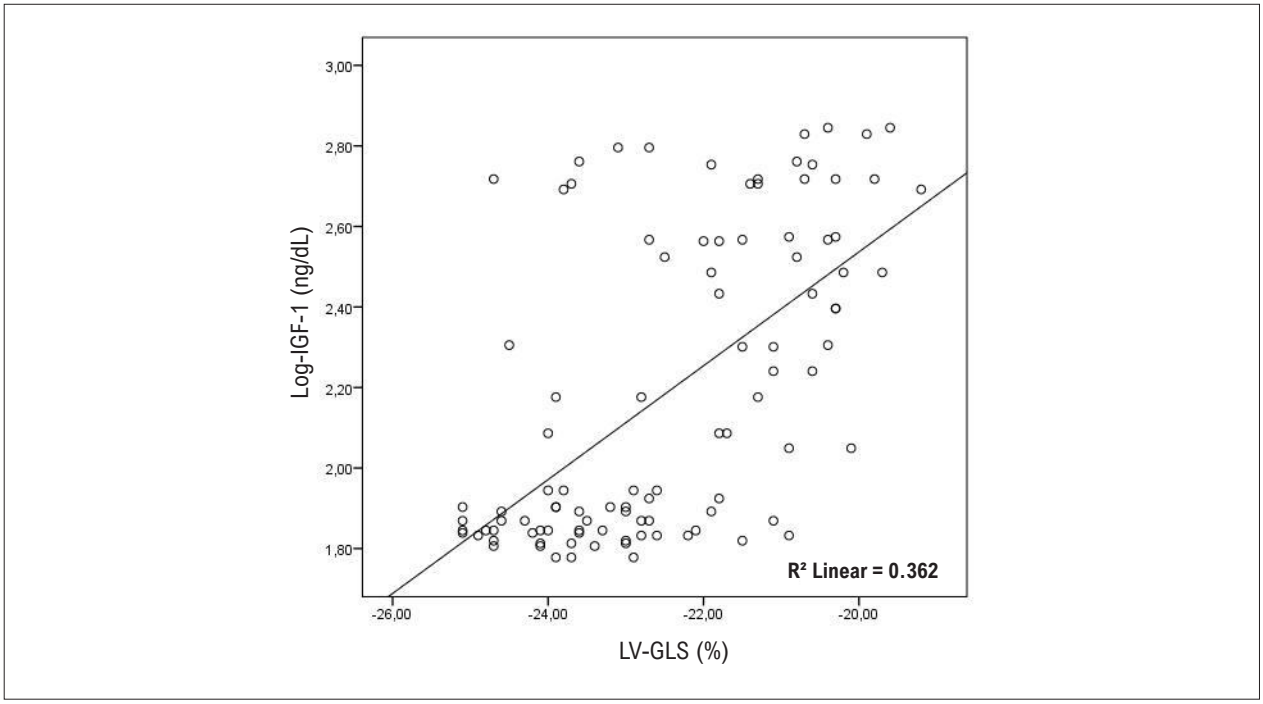

Figure 7 - *Scatter plot diagram of the relationship of left ventricular global longitudinal strain (LV-GLS) with Insulin-like growth factor 1 (IGF-1). A 10-logarithmic scale of IGF-1 value was obtained.*

dysfunction was also common (50.5%) in patients with acromegaly.[3,4] Therefore; we did not evaluate the diastolic dysfunction in these patients groups.

It was shown in previous studies that LA and LV volume and volume index increased in patients with acromegaly.[6,8] In our study, we only measured LV diameter and LA end-diastolic diameter. If we also measured the LA and LV volume index, there could be changes especially in the parameters related to LA-GLS.

Conclusion

Although LVEF is normal in patients with acromegaly, LAS and LV-GLS detected with 2D-STE are significantly lower and are closely related to plasma IGF-1 levels. Apart from an increase in LVMI, another finding of cardiac involvement may be the decrease in LAS and LV-GLS. Therefore, in addition to routine echocardiography, LAS and LV-GLS may be useful to evaluate early signs of cardiac involvement before the occurrence of irreversible cardiac changes in patients with acromegaly.

Author Contributions

Conception and design of the research and Statistical analysis: Koca K, Koc M, Icen YK, Baykan AO, Kaypakli O; Acquisition of data: Sumbul HE, Icen YK, Gulumsek E, Koca F, Ozturk HÁ; Analysis and interpretation of the data: Koca K, Gulumsek E, Koca F, Ozturk HA; Writing of the manuscript: Koca K, Koc M, Koca F, Baykan AO, Kaypakli O; Critical revision of the manuscript for intellectual content: Koca K, Sumbul HE, Kaypakli O.

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.

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Iron Deficiency in Heart Failure with Reduced Ejection Fraction: Pathophysiology, Diagnosis and Treatment

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Abstract

Iron deficiency (ID) is an important comorbidity in heart failure with reduced ejection (HFrEF) and is highly prevalent in both anemic and non-anemic patients. In HFrEF, iron deficiency should be investigated by measurements of transferrin saturation and ferritin. There are two types of ID: absolute deficiency, with depletion of iron stores; and functional ID, where iron supply is not sufficient despite normal stores. ID is associated with worse functional class and higher risk of death in patients with HFrEF, and scientific evidence has indicated improvement of symptoms and quality of life of these patients with treatment with parenteral iron in the form of ferric carboxymaltose. Iron plays vital roles such as oxygen transportation (hemoglobin) and storage (myoblogin), and is crucial for adequate functioning of mitochondria, which are composed of iron-based proteins and the place of energy generation by oxidative metabolism at the electron transport chain. An insufficient generation and abnormal uptake of iron by skeletal and cardiac muscle cells contribute to the pathophysiology of HF. The present review aims to increase the knowledge of the pathophysiology of ID in HFrEF, and to address available tools for its diagnosis and current scientific evidence on iron replacement therapy.

Clinical issue

Heart failure (HF) is a global health problem that affects 26 million people in the world.[1] In Brazil, the number of patients with HF was approximately 2,846,000 in 2015, with increasing prevalence with age.[2]

In a Brazilian registry of patients hospitalized for HF in different parts of the country, in-hospital mortality was 12.6%.[3] In addition to the high in-hospital mortality, it is estimated that nearly 50% of patients diagnosed with HF will die within five years.[4,5] Also, HF has a strong economic impact, leading to a cost of 22.1 billion Brazilian reals in 2015.[2]

Anemia is a common problem in HF with reduced ejection fraction (HFrEF).[6] It is defined as hemoglobin (Hb) levels <13.0 g/dL in men and <12.0 g/dL in women.[7] The most common causes of anemia are iron deficiency (ID), chronic diseases, dilutional anemia and renal failure.[8] ID is a common comorbidity in HF, affecting nearly half of HF patients;[9,10] it is not restricted to anemic patients, since 46% of patients without anemia with stable HF has ID.[11]

ID in HF is more commonly seen in patients with more advanced disease (worse functional class and higher brain natriuretic peptide levels) and in female patients.[11,12] The presence of ID affects the prognosis. In an observational study with 546 patients with HFrEF, ID was a strong independent predictor of death or need for heart transplantation, increasing the risk for these outcomes by nearly 60%.[12] In another cohort composed of 1,506 European patients with chronic HF, ID (without anemia) was also considered a predictor of death.[11] The high prevalence and the strong prognostic power of ID in HF warrant a better understanding of its pathophysiology, diagnosis and treatment.

Pathophysiology

Iron – Absorption, distribution and functions in the body

Iron is a metabolically active micronutrient with unique biochemical features. It has two oxidation states – ferrous (+2) and ferric (+3), found inside and outside cells, respectively.[13]

Mean daily intake of iron is 10-20mg/day, although only 10-20% of dietary iron is actually absorbed through specific transportation systems, especially duodenal enterocytes. Iron can be eliminated from the body by desquamation of intestinal mucosal cells, menstruation, or other blood losses. However, because of the lack of a physiologically regulated excretion system for iron in the body, the regulation of its absorption through the duodenum plays a crucial role in iron homeostasis in the body.[14] Most iron required for erythropoiesis (20-25 mg) is derived from recycling of senescent erythrocytes from macrophage phagocytosis in the reticuloendothelial system.[13,15]

Regarding iron distribution in human body, approximately 65% of the mineral is found in hemoglobin of erythrocytes, and nearly 10% is found in myoglobin of muscle fibers. The remaining is stored in the liver, macrophages of the reticuloendothelial system, and bone marrow.[16]

Iron plays a fundamental role in oxygen transport by hemoglobin and in oxygen storage in the myoglobin of skeletal and cardiac muscle cells. Iron acts as a component of enzymes involved in oxidation (oxidative phosphorylation) and of iron-sulfur and heme proteins in the respiratory chain of mitochondria. Iron participates in the synthesis and degradation of proteins, lipids and ribonucleic acids.[13,17]

Keywords

Iron; Iron Deficiency; Heart Failure, Systolic.

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Iron is a potentially toxic metal as it causes the reduction of oxygen molecules in the cells, resulting in the formation of oxygen reactive species. Thus, iron requires an intracellular and an extracellular neutralizer, in the form of ferritin and transferrin, respectively.[9]

Transferrin is a glycoprotein that acts as a storage depot and mediates the transport of soluble iron. Transferrin receptor 1 (TfR1) mediates the uptake of transferrin-bound iron by receptor-mediated endocytosis.[16]

Iron is stored in the liver, bone marrow and spleen in the form of ferritin, which is the main storage protein of iron. Concentrations of tissue ferritin increase in situations of iron overload or inflammation.[13]

Hepcidin is a hormone peptide produced mainly by hepatocytes and is considered the main regulator of iron metabolism.[15] Its synthesis is regulated by changes in iron requirements in the body. Hepcidin directly acts on ferroportin, a transmembrane protein that transports iron. Ferroportin is located on the surface of duodenal enterocytes, responsible for iron absorption, and on hepatocytes and macrophages, responsible for iron storage. When hepcidin binds ferroportin, the transporter is degraded in lysosomes, resulting in reduced iron release.[13,15,18]

In an experimental study, rats receiving a diet deficient in iron for 12 weeks exhibited increased heart weight and size compared with the control group. Analysis by microscopy revealed abnormal sarcomere structure and mitochondrial ultrastructural aberrations in myocardial tissue.[19]

Iron depletion may have deleterious effects in the body, involving since basic structures, such as mitochondria and cells, until more complex ones (Figure 1).[13,20]

A study on patients with advanced HF undergoing heart transplantation demonstrated depletion of myocardial iron in these patients as compared with healthy controls, suggesting that myocardial iron depletion may play a role in the pathogenesis and progression of HF.[21] ID causes HF, and HF itself seems to induce ID, suggesting the theory of a vicious cycle.[10] The development of ID may be resultant of reduced iron uptake due to malnutrition and volume overload, hemorrhage associated with antiplatelet and anticoagulants, and disturbances in iron utilization and storage caused by inflammation in HF.[22,23]

Patients with chronic inflammatory conditions such as HF, chronic renal disease, cancer, and inflammatory bowel disease are at higher risk of developing ID.[9] in HF patients, hepcidin production in the liver is increased, affecting iron absorption in the gastrointestinal tract and iron mobilization from iron stores, including the reticuloendothelial system.[13,23,24]

Diagnosis

The distinction between ID anemia and anemia of chronic disease is difficult. In the absence of inflammation, serum

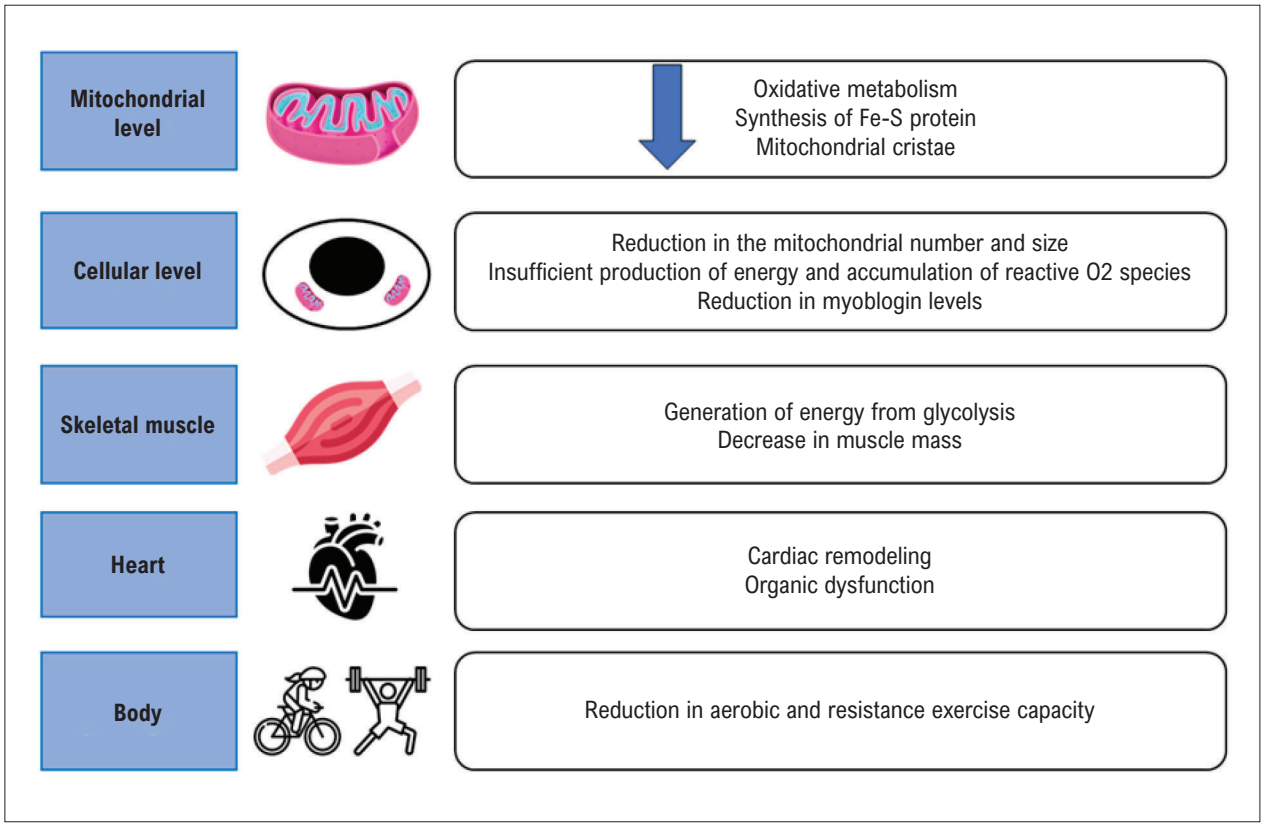

Figure 1 – *Harmful effects of iron deficiency at different levels of organism complexity (adapted from Jankowska et al.[13] and Stugiewicz et al.[20]). Fe-S: iron-sulfur; O2: oxygen.*

levels of ferritin < 30 ng/mL are indicative of ID.[25] In a study on patients with advanced anemia, bone marrow aspiration was performed, and ID was confirmed in 73% of patients. Mean ferritin was 75 ng/mL in iron deficient patients, and 211 ng/mL in non-iron deficient patients. As ferritin is an acute-phase protein, their levels may be either normal of increased in HF, even in situations of ID. Thus, the use of conventional biomarkers and conventional cut-off points obtained from patients with non-inflammatory conditions to identify ID in HF is questionable.[26]

There are two types of ID: absolute deficiency, which reflects depletion of iron stores, with preserved iron homeostasis and erythropoiesis; and functional ID, where iron supply is not sufficient to meet the requirements despite normal or even excess reserve, because iron is trapped inside cells of the reticuloendothelial system and is not available for cellular metabolism.[13]

In patients with HFrEF, absolute ID was defined as ferritin < 100mg/L, and functional ID as ferritin of 100-299 mg/L and transferrin saturation (TSAT) < 20%.[27-29]

Iron deficiency – a therapeutic target

Several randomized clinical trials (RCTs) of treatment of ID in stable and chronic HFrEF have been performed (Table 1). The IRON-HF[30] was the first RCT to compare the use of oral iron, intravenous iron and placebo. No statistically significant difference was found in changes of peak VO2 between the groups. Due to prolonged recruitment and financing issues, the trial was stopped before planned. In another study, the IRONOUT-HF, therapy with oral iron was compared with placebo and, again, no difference in peak VO2 was observed between the groups.[31] These studies corroborate the fact that oral iron supplementation has no clinical benefit in patients with HFrEF and ID.

While the first interventional studies with intravenous iron used ferric hydroxide saccharate complex,[32,33] more recent trials used ferric carboxymaltose, another form of parenteral iron. In 2009, the FAIR-HF, considered the largest RCT comparing intravenous administration of ferric carboxymaltose with placebo. Primary outcomes of interest were New York Heart Association (NYHA) functional class and Patient Global Assessment (PGA) at 24 weeks. PGA is a rating scale on which patients rate disease severity and progression. In the ferric carboxymaltose arm, 47% showed improvement in NYHA functional class (to I or II) at 24 weeks, compared with 30% of those who received placebo (OR =2.40; 95%CI 1.55-3.71; p<0.001). PGA at week 24 was better in the interventional group, where 50% of patients reported a moderate or marked improvement, compared with 28% in the placebo group (OR for improvement 2.51; 95% CI 1.75-3.61; p<0.001). Results were similar in patients with and without anemia.[34]

The CONFIRM-HF study was performed in nine countries in Europe, including 301 patients, with a longer follow-up period (52 weeks) compared with the FAIR-HF. Both studies compared the use of intravenous ferric carboxymaltose with placebo. Primary outcome was improvement in six-minute walk test at 24 weeks compared with baseline. There was an increase in distance walked by 33 ± 11 meters in the group who received carboxymaltose, until the end of the follow-up period at 52 weeks. The effect was observed in both anemic and non-anemic patients, reinforcing the idea that ID is a valid independent therapeutic target.[35] This difference of more than 30 meters in the last six months of study was robust and clinically significant, especially considered that in previous interventional studies, benefits of this magnitude have been reported with cardiac resynchronization by a systematic review.[36] Lower risk of hospitalization was also found in decompensated HF (HR 0.39; 95%CI 0.19–0.82; p=0.009). No difference was found in cardiovascular mortality outcome (HR 0.96; 95%CI, 0.42-2.16; p=0.91).

In a meta-analysis with five RCTs and 851 patients comparing intravenous iron with placebo, no difference found in cardiovascular mortality (OR 0.80; 95%CI 039-1.63; p=0.54) or all-cause mortality (OR 0.83; 95%CI 0.43-1.59; p=0.57). Hospitalization for HF was less frequent in patients treated with intravenous iron (OR 0.28; 95%CI 0.16-0.50; p<0.0001). It is worth pointing out that 89% of patients included in this meta-analysis received parenteral iron in the form of ferric carboxymaltose.[37]

Another meta-analysis with four RCTs and 839 patients compared administration of intravenous carboxymaltose with placebo; there was a reduction in cardiovascular hospitalizations and cardiovascular mortality (RR 0.59; 95%CI 0.40–0.88; p=0.009) in the intervention group. When cardiovascular mortality was analyzed alone, no difference was found between the groups (RR 0.84; 95%CI, 0.43-1.66; p=0.620).[38] Based on the results of the CONFIRM-HF study and other meta-analyses, ferric carboxymaltose has been considered effective in reducing HF or cardiovascular hospitalizations in stable, symptomatic, patients with reduced left ventricular ejection fraction (LVEF).

Then, ID has become a therapeutic target in stable HFrEF, independent of the presence of anemia. The European guidelines on HF[27] have considered intravenous administration of ferric carboxymaltose a IIa recommendation for improvement of symptoms, exercise capacity, and quality of life in NYHA class II/III patients.[27] In the next year, the American (American College of Cardiology/AHA) guidelines on HF gave a class II b recommendation for intravenous iron in HFrEF.[29] In 2018, the Brazilian guidelines on HF were published, which addressed ID in HFrEF, independent of the presence of anemia. Intravenous administration of iron was given a IIa recommendation to improve exercise capacity and quality of life and reduce hospitalizations.[8]

Therefore, it is important to identify candidates for iron replacement therapy (Figure 2), by screening of all patients with stable HF and ejection fraction ≤45% by measurement of serum ferritin and TSAT.[10,27] The safety of parenteral iron is still unknown in HF patients with hemoglobin > 15g/dL.

The diagnosis of ID in acute HF is still a challenge. In an observational study with 47 patients with acute HF, iron profile was measured at admission and on day 30. The prevalence of ID was 83% at admission, with a decrease to 68% on day 30. Median ferritin and TSAT were 93μg/L (IQR: 76–107 μg/L) and 13% (IQR: 6–20%), respectively, on admission, and 159 μg/L (IQR: 134–190 μg/L; p <0.0001 compared with admission) and 17% (IQR: 12–23%; p =0.0176) respectively on the 30th day, without iron replacement therapy. This study demonstrates that

Table 1 – Randomized clinical trials on treatment of iron deficiency in patients with heart failure

	Toblli et al.[33]	FERRIC-HF[32]	FAIR-HF[34]	IRON-HF[30]	CONFIRM-HF[35]	EFFECT-HF[58]	IRONOUT-HF[31]
n	FHS: 20 Placebo: 20	FHS: 24 Placebo: 11	FC: 304 Placebo: 155	FHS: 10 SF: 7; Placebo: 6	FC: 150 Placebo: 151	FC: 86 Standard therapy: 86	FP: 111 Placebo: 114
Bliding	Double-blind	Open	Double-blind	Double-blind	Double-blind	Open	Double-blind
Center (s)	Multicentric	Single-center	Multicentric	Multicentric	Multicentric	Multicentric	Multicentric
Symptoms (NYHA functional class)	II-IV	II-III	II-III	II-IV	II-III	II-III	II-IV
LVEF	≤35%	≤45%	≤40% or ≤45%	<40%	≤45%	≤45%	≤40%
ID definition	Ferritin<100ng/mL and/or TSAT<20%	Ferritin<100ng/mL or ferritin 100-299ng/mL + TSAT<20%	Ferritin<100ng/mL or ferritin 100-299ng/mL + TSAT<20%	Ferritin < 500 µg/L and TSAT<20%	Ferritin<100ng/mL or ferritin 100-299ng/mL + TSAT<20%	Ferritin<100ng/mL or ferritin 100-299ng/mL + TSAT<20%	Ferritin<100ng/mL or ferritin 100-299ng/mL + TSAT<20%
Hb	<12.5 g/dL	<12.5 g/dL (anemic), 12.5-14.5 g/dL(non-anemic)	9-13.5 g/dL	9-12 g/dL	<15 g/dL	<15 g/dL	9-13.5 g/dl
Iron pathway	Injectable	Injectable	Injectable	Injectable and oral	Injectable	Injectable	Oral
Type of iron	FHS	FHS	FC	FHS and FS	FC	FC	PF
Correction phase (dosage)	200mg/week 5 weeks	200mg/week 4 weeks	200mg/week*	SHF 200mg/week SF 200mg 3xd	500-2000mg week 0 and 6	500-2000mg week 0 and 6	150mg 2xd 16sem
Maintenance phase (dosage)	-	200mg/month	200mg/month	-	500mg every 12 weeks†	500mg every 12 weeks†	-
Treatment duration	5 weeks	16 weeks	24 weeks	5 weeks (SHF) 8 weeks (FS)	36 weeks	12 weeks	16 weeks
Follow-up	24 weeks	18 weeks	24 weeks	12 weeks	52 weeks	24 weeks	16 weeks
Primary outcome of interest	Change in NT-proBNP and CRP	Change in pVO2	Change in NYHA FC and PGA	Change in pVO2	Change in the six-minute walk test distance	Change in pVO2	Change in pVO2
Difference in primary outcome	Yes	No	Yes	No	Yes	Yes	N

** Calculated using the Ganzoni equation. † if iron deficiency persists. FC: ferric carboxymaltose; ID: iron deficiency; LVEF: left ventricular ejection fraction; Hb: hemoglobin; CRP: C-reactive protein; IP: iron polysaccharide; PGA: Patient Global Assessment; pVO2: peak oxygen consumption; FS: ferrous sulfate; FHS: ferric hydroxide saccharate; TSAT: transferrin saturation; NT-proBNP: N-terminal B-type natriuretic peptide fragment; NYHA: New York Heart Association.*

biomarkers of iron metabolism are not steady in acute HF, even in a short period of observation, making the diagnosis of ID in acutely decompensated HF questionable.[39]

Other laboratory tests may be used in the investigation of ID, such as soluble transferrin receptor (sTfR) and hepcidin. In the scenario of acute IC, a sTfR ≥1.59ng/mL and a hepcidin < 14.5ng/mL seem adequate to detect ID.[40] In addition, sTfR was found to have a prognostic value in HF, as increased sTfR levels were associated with worse NYHA functional class ($p<0.05$).[41]

Myocardial iron

The diagnosis of ID in HF is relatively easy to be made, as it depends on laboratory tests (ferritin and TSAT) only. In a study with pretransplant patients with advanced HF, ventricular myocardial biopsies were performed to measure myocardial iron in the explanted failing hearts, compared to non-failing hearts, and to assess the correlation of myocardial iron with serum markers. No correlation was found of myocardial iron with TSAT, ferritin, or serum iron,[42] reinforcing that the metabolism of systemic iron and myocardial iron are partly independent.[43]

Cardiac magnetic resonance

Cardiac magnetic resonance (CMR) is a useful tool in the assessment of patients with HF, that provides information regarding its etiology and prognosis.[44] Anderson et al.[45] developed the cardiovascular T2-star (T2*) magnetic resonance technique, and demonstrated that a myocardial

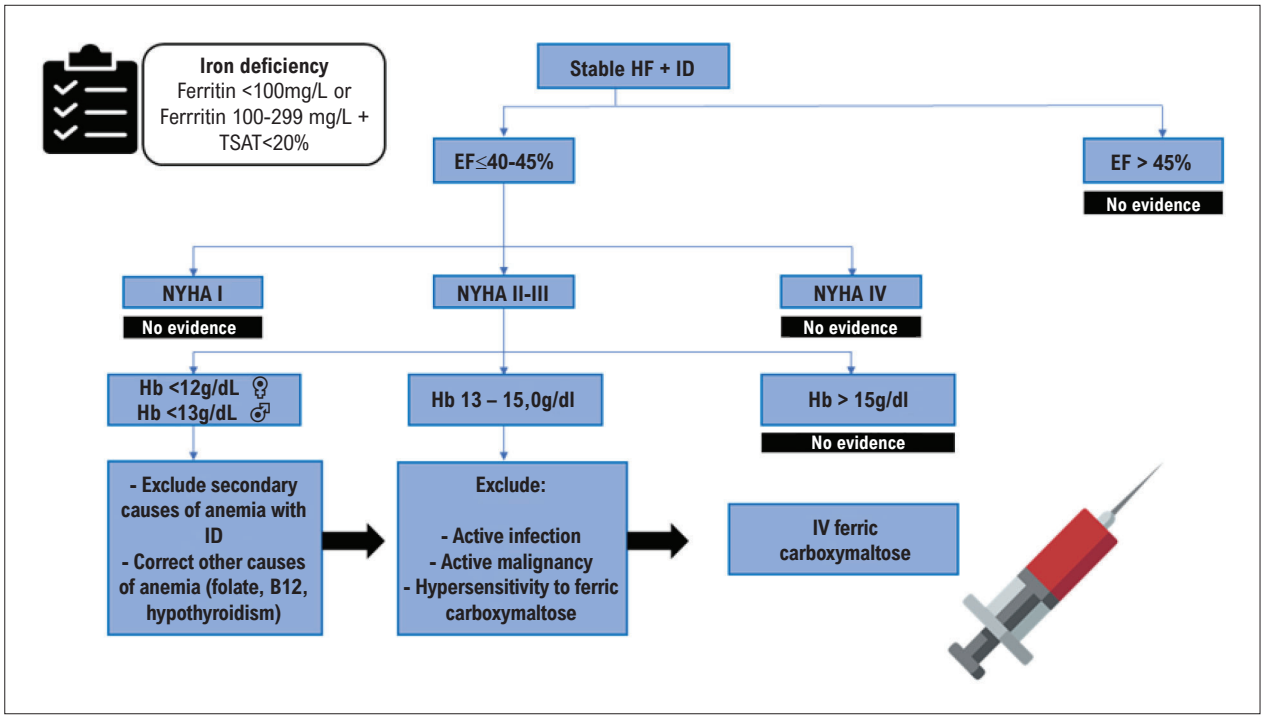

Figure 2 – *Diagnostic and therapeutic algorithm for patients with heart failure and iron deficiency (adapted from Rocha et al.)10. ID: iron deficiency; NYHA: New York Heart Association; EF: ejection fraction: Hb: hemoblogin; B12: vitamina B12; IV: intravenous; TSAT: transferrin saturation.*

T2* of <20 ms was associated with myocardial iron overload and ventricular dysfunction.[45]

As myocardial T2* was shown to be useful in the evaluation of myocardial iron overload, studies have been made to test its utility in detecting myocardial ID also. In a case-control study with HF patients undergoing CMR, a higher T2* seemed to be related with lower myocardial iron content.[46] In a double-blind RCT with symptomatic HF patients (NYHA II and III), ejection fraction < 50% and ID, patients received either ferric carboxymaltose or placebo. Primary outcome was changes in magnetic resonance T2* and T1 at seven and 30 days of treatment. T2* (ms) was significantly lower in the ferric carboxymaltose arm on day seven (36.6 [34.6–38.7] versus 40 [38–42.1], p=0.025) and day 30 (36.3 [34.1–38.5] versus 41.1 [38.9–43.4], p=0.003). These changes in T2* were suggestive of myocardial iron repletion with ferric carboxymaltose administration.[47]

So far, the cut-off point of T2* for detecting myocardial ID has not been established, and hence the usefulness of this non-invasive tool in the assessment of patients with ID still requires further investigation.

Treatment

Recommended therapeutic dosages of ferric carboxymaltose are described in Table 2. After correction of ID, reevaluation of serum iron markers (ferritin and TSAT) once-twice a year.[23]

Ferric carboxymaltose has been shown to be cost effective by changes in functional class and reduction in hospitalization rates.[48] Since the number of infusions of ferric carboxymaltose is relatively lower, as compared with other intravenous formulations, the total cost of treatment may be lower,[49] in addition to a good safety profile. The therapy is rarely discontinued due to undesirable effects. The most common adverse effects (1-10% of the cases) are flushing, seizure, arterial hypertension, headache, hypophosphatemia, and local reaction on the site of infusion (skin discoloration, pain, irritation).[50] Patients should be monitored for at least 30 minutes after intravenous injection for the occurrence of adverse effects. Contraindications to the use of ferric carboxymaltose are: hypersensitivity to carboxymaltose and its excipients; severe hypersensitivity to other parenteral formulations containing iron; non-iron-deficiency anemia; and evidence of iron overload or disturbances in iron utilization.[23]

Treatment of ID in acute HF

Unlike other trials above mentioned, that included stable outpatients, the recently published multicentric RCT AFFIRM-AHF included patients with LVEF < 50% and ID hospitalized for acute HF. After stabilization and before hospital discharge, participants received ferric carboxymaltose or placebo for 24 weeks. The primary composite outcome was total admissions for HF and cardiovascular death within 52 weeks, which was not different between the groups (RR 0.79; 95%CI, 0.62-1.01; p=0.059). The outcome of cardiovascular death alone was not different (HR 0.96; 95%CI, 0.70-1.32; p=0.81), whereas total admissions for HF was lower in the carboxymaltose (RR 0.74; 95%CI, 0.58-0.94; p=0.013).[51,52] This is a relevant, up-to-date scientific evidence, as it corroborates the indication of ferric

Table 2 – Dose of intravenous ferric carboxymaltose in patients with heart failure and iron deficiency[10]

Weight and Hb	Correction phase		Maintenance phase			
	Week 0	Week 6	Week 12	Week 24	Week 36	Week >36
35-70 Kg and Hb <10g/dL	1000 mg	500 mg	500mg if ID persists	500mg if ID persists	500mg if ID persists	No evidence
35-70 Kg and Hb ≥10g/dL	1000 mg	0 mg				
> 70 Kg and Hb <10g/dL	1000 mg	1000 mg				
> 70 Kg and Hb ≥10g/dL	1000 mg	500 mg				

Table adapted from Rocha et al.[10] ID: iron deficiency; Hb: hemoglobin; HF: heart failure.

carboxymaltose supplementation for patients hospitalized for HFrEF and ID, aiming at reducing the risk for readmissions for HF.

Areas of uncertainty

The criteria to define ID adopted in several RCTs have been arbitrarily established, without validation with iron staining on bone marrow aspirate smears, which is considered the gold-standard method. Grote Beverborg et al.[53] conducted a study with HF patients with LVEF ≤ 45% undergoing myocardial revascularization surgery (n=42) and performed measurements of iron-related markers (serum iron, ferritin, TSAT) and bone marrow aspiration with iron staining. Bone marrow ID was found in 40% of the HF patients. Based on the diagnosis of ID confirmed by bone marrow aspiration, TSAT ≤ 19,8% had a sensitivity of 94.1% and a specificity of 84%, and serum iron ≤13 μmol/L had a sensitivity of 94% and specificity of 88%. On the other hand, ferritin ≤145 ng/mL had a sensitivity of 70.6% and specificity of 60%.[53] Although this was a small study, it raised the question on whether TSAT and serum iron would be more important for the diagnosis of ID than ferritin.

Most patients included in RCTs (FAIR, CONFIRM and EFFECT) had absolute ID (80=90%), whereas functional ID was poorly represented.[10] In a cross-sectional study, patients with HFrEF were categorized into the following: impaired iron transport (TSAT < 20%); absolute ID (ferritin < 100 μg/L); and normal iron status. Patients with isolated impaired iron transport had higher N-terminal pro b-type natriuretic peptide (NT-proBNP) levels (OR 2.1 [1.5–2.9] p<0.001) and worse quality of life (OR 1.7 [1.2–2.5]; p=0,005) as compared with patients with normal iron status, and no difference in NT-proBNP levels compared with patients with absolute ID and normal iron status.[54] These findings highlight the importance of including patients with TSAT<20% or functional ID in RCTs.

The currently available RCTs do not have enough power to evaluate the benefit of intravenous iron in reducing mortality in patients with stable HFrEF. The ongoing double-blind, placebo-controlled study FAIR-HF 2,[55] aims to evaluate whether ferric carboxymaltose can reduce the primary composite endpoint of hospitalization for HF and cardiovascular death in patients with HFrEF and ID.

Most of the evidence available to date is based on studies with patients with reduced ejection fraction. There is a gap in knowledge for patients with HF and preserved ejection fraction (HFpEF). In a systematic review and meta-analysis of 1,877 with HFpEF, the prevalence of ID was 59%. Patients with ID had worse functional class, exercise capacity and quality of life compared with those without ID. No difference was found regarding risk of death or hospitalization.[56] Another RCT, the FAIR-HFpEF,[57] currently in progress, aims to evaluate the efficacy and safety of ferric carboxymaltose administration in patients with HFpEF and ID.

Conclusions

ID is a very common comorbidity in patients with HFpEF that has become a therapeutic target. Intravenous ferric carboxymaltose improves symptoms, exercise capacity and quality of life in symptomatic patients with stable HFrEF and LVEF ≤45%, in both anemic and non-anemic patients. There is also evidence of a reduction in the risk of HF. On the other hand, oral iron formulations have no clinical benefits in patients with HFrEF and ID. So far, there is no clinical evidence supporting ferric carboxymaltose administration in patients with HFrEF.

Author Contributions

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Ethics approval and consent to participate

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

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Medical Residency in Brazil in the Era of Chronic Diseases: The Need for Cardiometabolic Medicine Residency

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Introduction

Cardiovascular diseases (CVD) are the leading cause of death in Brazil, significantly decreasing life expectancy, impairing quality of life, and causing a great impact on the Brazilian Unified Health System. However, it is important to highlight the enormous progress in cardiovascular research and in Brazilian cardiology over the past 6 decades, which have contributed to the increase in life expectancy from 54.[1] years in 1960 to 75.6 years in 2018.[1]

Whereas in the last century, cardiology waged a major battle against acute diseases, such as endocarditis and acute myocardial infarction, medical research has made breakthrough advancements in the management of these conditions. Nonetheless, at the same time, the era of chronic diseases emerged, in which primary drivers (e.g., genetics, environment, and behavior), metabolic drivers (e.g., obesity, diabetes, high cholesterol, and hypertension), co-morbidities (e.g., non-alcoholic fatty liver disease and chronic kidney disease [CKD]), and clinical endpoints (e.g., coronary heart disease, heart failure, and atrial fibrillation) were modeled to improve patient outcomes. As an effort to improve this concept, Mechanick et al.[2,3] introduced the Cardiometabolic-Based Chronic Disease (CMBCD) model, which focused on the impact of primary and metabolic drivers on the development of CVD, identifying key targets to reduce progression from risk (Stage 1 CMBCD) to pre-disease (Stage 2 CMBCD), disease (Stage 3 CMBCD), and complications (Stage 4 CMBCD). This classification is depicted in Figure 1 and marks a new era in the care of cardiometabolic diseases.

This novel cardiometabolic framework, coupled with the need for physician participation in a team care model of patients with cardiometabolic diseases, comprised of a specialist physician, nutritionist, physical educator, physical therapist, psychologist, as well as new structured lifestyle modalities, pharmacotherapies, and technologies, mandates the training of a new generation of cardiometabolic medicine (CM) physicians. In this paper, the rationale behind the creation of a CM fellowship in Brazil will be detailed, with preliminary proposals to be vetted in future discussions.

Keywords

Diabetes Mellitus; Obesity; Hypertension; Internship and Residency

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The present case of brazilian cardiology training and opportunities for improvement

A cardiology fellowship in Brazil typically lasts for 2 years, during which fellows obtain experience in common procedures in both outpatient and inpatient care settings, with the option to pursue subsequent super-fellowships and further specialization. However, there are key improvements to be made, based on the increasing prevalence of cardiometabolic diseases, risk factor unawareness, significant proportion of patients not adequately treated, increased impact of inadequately treated risk factors on the burden of CVD, and a healthcare infrastructure not yet poised to address this problem.

Possible Pathways to Success

Many experts have advocated the introduction of a CM fellowship, which would provide physicians a solid background for diagnosis and treatment of chronic diseases, focusing on topics of cardiology, endocrinology, hepatology, nephrology, and lifestyle medicine.[4-7] This would help physicians provide comprehensive care to patients with multiple risk factors and conditions, reducing fragmentation into different specialties, which can compromise, delay, and increase the cost of care. Several articles have proposed various structures for CM fellowship programs. Soroosh et al.[4] proposed three pathways. First, there would be a training structure consisting of 2 to 3 years of primary fellowship in CM after internal medicine (IM) residency, during which in-depth topics in cardiology and endocrinology would be covered. The cardiology component would include electrocardiography, approaches to hypertension, prevention of atherosclerotic disease (AD), vascular medicine procedures, and other cardiovascular imaging methods.[4] The endocrinology component would consist of guideline-directed comprehensive diabetes and obesity care, as well as the management of metabolic syndrome (MS), lipoprotein disorders, male hypogonadism, and thyroid diseases.[4] This program would include a formal structured training, including tobacco cessation, sleep hygiene, behavioral medicine and stress reduction, exercise physiology, management of alcohol abuse disorder, and community engagement.[4] The second pathway proposed by Soroosh

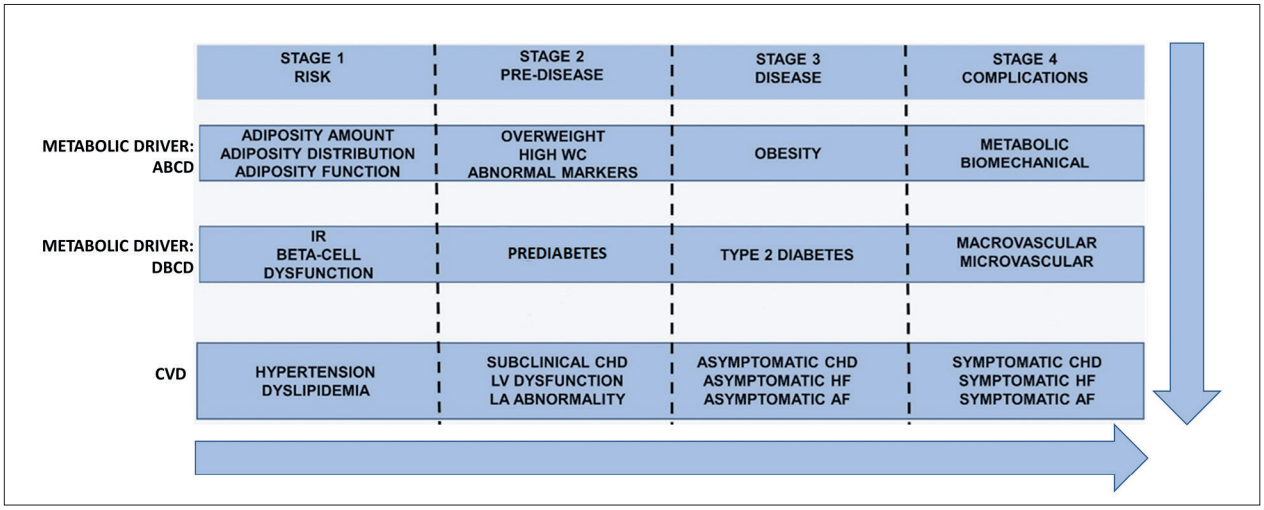

Figure 1 – *Cardiometabolic-Based Chronic Disease: metabolic drivers and stages. Adapted from (2). AF: atrial fibrillation; CHD: coronary heart disease; HF: heart failure; IR: insulin resistance; LA: left atrial; LV: left ventricular; WC: waist-circumference.*

et al.[4] would be a 1-year cardiometabolic training program after IM, endocrinology, cardiology, or nephrology fellowship. In this option, the first 6 months of this super-fellowship would be focused on core cardiometabolic topics, and the next 6 months would be customized by the fellow. Finally, the third pathway approached by Soroosh et al.[4] would be concurrent training in CM with courses of varying length during time allocated to a formal training program in cardiology, endocrinology, etc., with the advantage that any physician would be able to specialize in CM, but it would not be as in-depth as the other models. In another approach, McCarthy et al.[5] proposes a 1-year training program in CM, available as a fellowship for clinicians, such as cardiologists, endocrinologists, and nephrologists. The fellow would undergo rotations in cardiology, endocrinology, and nephrology outpatient clinics, in addition to 1 month in the women's cardiology, vascular and sleep medicine, and weight management outpatient clinics. Throughout the year, topics related to lifestyle changes, cardiac rehabilitation and nutritional approaches, diabetes, antihyperglycemic and hypolipemic therapies, coronary artery calcium quantification, cardiac computerized tomography, approach to hypertension, CKD, and exercise physiology would be covered. Beyond that, Eckel et al.,[6] in another paper, proposed a 3-year fellowship program in CM, after IM residency, covering topics in endocrinology and cardiology. In this model, the topics of obesity, MS, diabetes and lipoprotein disorders, and the pharmacological therapies of these conditions would be covered. Regarding cardiology topics, the focus would be on primary and secondary prevention of AD, cardiac rehabilitation, interpretation of echocardiogram and electrocardiogram, and risk stratification, as well as a strong approach to hypertension associated with vascular medicine. Moreover, during this training, lifestyle medicine subjects would be constantly addressed. Finally, Reiter-Brennan et al.,[7] in another publication, proposed a broad training program, after 2 or 3 years of medical practice, with a more in-depth study of endocrinology and cardiology, plus such topics as biostatistics, epidemiology, and behavioral psychology. The main pillar of the cardiovascular section would be the care related to AD, including primary and secondary prevention, risk factors, methods of risk stratification and quantification of artery calcification; cardiac rehabilitation would also be covered. In the endocrine section, diabetes, hypertension management, MS, obesity, and lipoprotein disorders would be covered. In addition to these, another pillar of this training would be a strong approach to lifestyle changes, with emphasis on the physiology of nutrition and exercise. Core competencies that should be covered in CM residencies and fellowships are covered in Figure 2.

Given the proposals suggested by these authors and considering the disparities and specificities of the Brazilian population and medical training, in our view, two proposals are most promising to establish a cardiometabolic fellowship in Brazil. A first approach would be to institute CM training after IM or Family Medicine (FM). Another way would be to establish a 1-year fellowship program after completing cardiology, endocrinology, nephrology, or hepatology fellowships. These two pathways are illustrated in Figure 3.

Conclusions

Due to the significant increase in the prevalence and incidence of cardiometabolic diseases, the Brazilian Societies of IM, FM, Cardiology, Endocrinology, Hepatology, and Nephrology must begin a thorough discussion centered on the creation of a formal proposal of a medical fellowship in CM to be discussed at the Brazilian Medical Association and presented in the National Medical Residency Commission for approval. In that way, proper training can be offered to a new class of physicians that will unify the care of multiple chronic diseases under one specialty, stimulating research in this area and reducing the risk of CVD development.

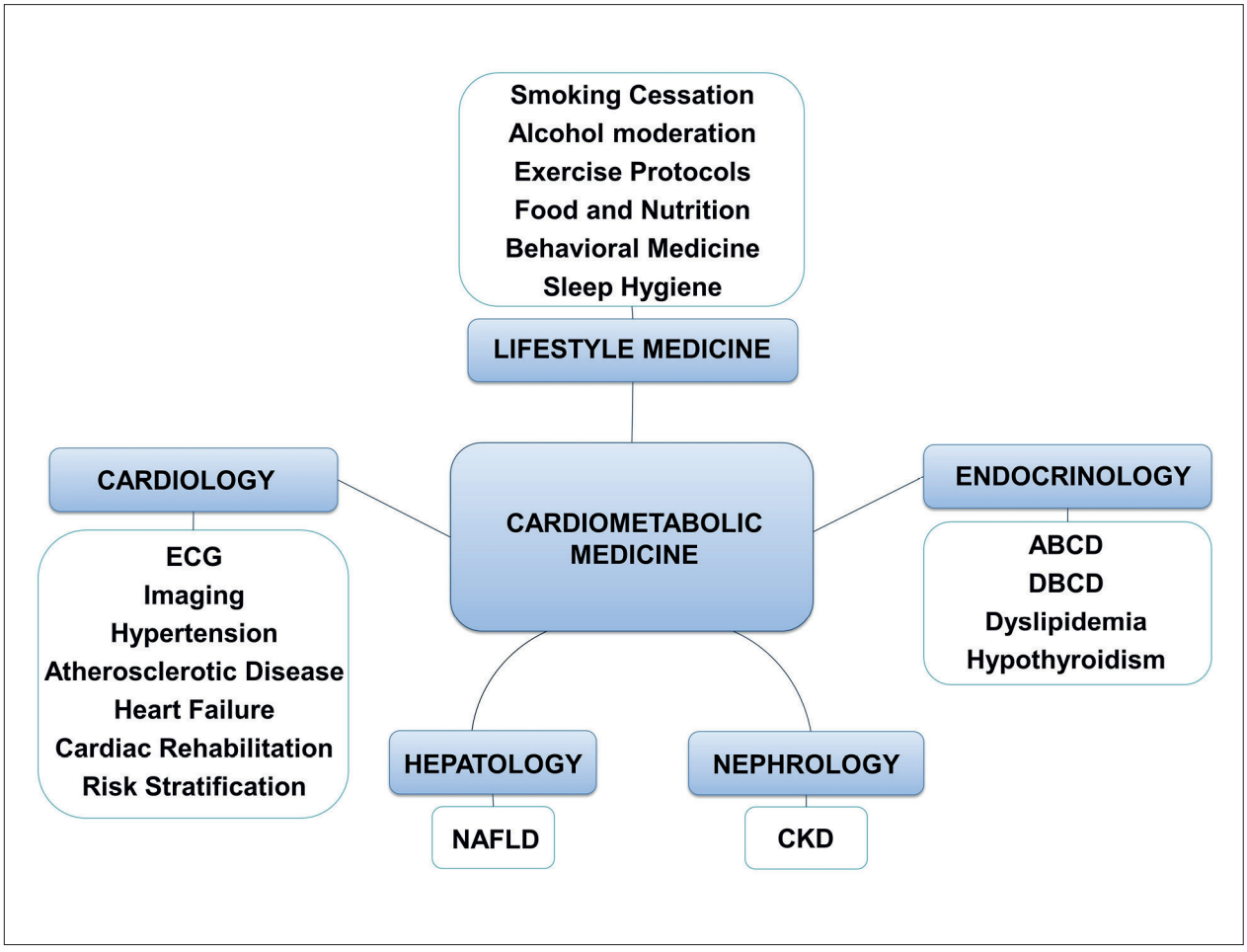

Figure 2 – *Core components of cardiometabolic medicine fellowship. ABCD: Adiposity-Based Chronic Disease; CKD: chronic kidney disease; DBCD: Dysglycemia-Based Chronic Disease; ECG: electrocardiogram; NAFLD: non-alcoholic fatty liver disease.*

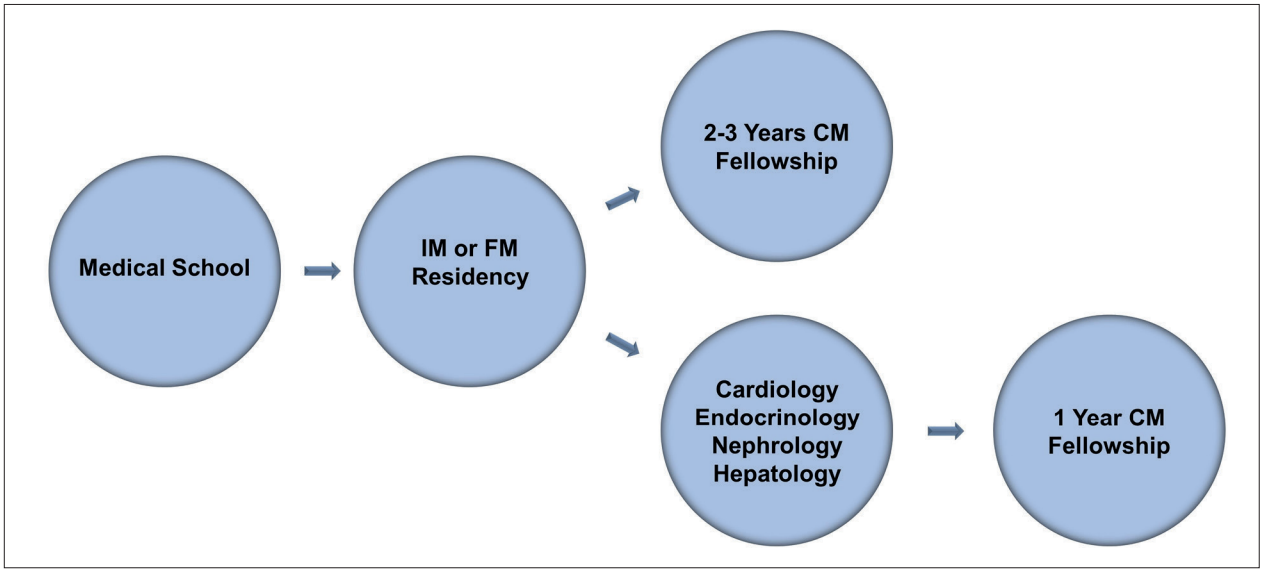

Figure 3 – *Possible training pathways of a cardiometabolic medicine fellowship in Brazil. CM: cardiometabolic medicine; FM: family medicine; IM: internal medicine.*

Author Contributions

Conception and design of the research: Correia ETO; Writing of the manuscript and Critical revision of the manuscript for intellectual content: Correia ETO, Barbetta LMS, Toledo MG, Mesquita ET, Mechanick JI.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

Ethics approval and consent to participate

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

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An Unusual Cause of Hypoxemia after Orthopedic Surgery on an Elderly Patient

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Introduction

Various conditions can cause post-operative hypoxemia, especially in elderly patients. However, a new symptomatic cardiac shunt is a very rare and unexpected complication in this setting. This study presents a case of refractory hypoxemia after orthopedic surgery due to right-to-left (R-L) shunt via a patent foramen ovale (PFO).

Case Report

A 71-year-old male underwent elective left hip replacement surgery, under loco-regional anesthesia. His medical history included obesity, hypertension, diabetes mellitus, and a stroke. He had no history of cardiopulmonary disease.

The first postoperative day was complicated by ileus (Figure 1). Diet was restarted four days later, but abdominal distention and reduced bowel movements persisted. On postoperative day 15, the patient presented severe refractory hypoxemia, with an O_2 saturation (O_2sat) of 75%, improving only to 86% on high-flow oxygen therapy (F_iO_2 90-100%). Despite this, he was calm, showing no signs of respiratory distress. Blood pressure was 110/75 mmHg, heart rate was 76 bpm, and temperature was 36ºC. Cardiac and pulmonary auscultation were normal. There was no jugular venous distension, peripheral edema, or cyanosis.

Arterial blood gas analysis confirmed severe hypoxemia, with a pO_2 of 38 mmHg on F_iO_2 of 28%, improving only to 49 mmHg on F_iO_2 100%. Blood analysis was unremarkable, except for elevated d-dimers (1608 ng/mL). Electrocardiogram and bedside echocardiogram were normal. The patient underwent chest computed tomography (CT) angiography, which showed no signs of pulmonary embolism or significant parenchymal lung disease. The following days, he maintained an O_2sat of 85-89%, despite high-flow oxygen nasal cannula, regardless of upright, supine, or left lateral decubitus body position.

Keywords

Foramen Ovale, Patent; Hypoxia; Vascular Closure Devices

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A ventilation/perfusion (VQ) lung scan was performed, demonstrating the absence of VQ imbalance, but revealing a brain and kidney uptake of tracer, suggesting an R-L shunt (Figure 2A). Transoesophageal echocardiography (TOE) revealed an interatrial septal aneurysm and a PFO with a large resting R-L shunt visible by color Doppler and agitated saline injection (Figure 2B). Upon review of CT images, bowel distention was verified to have caused left hemidiaphragm elevation, changing the supra-hepatic inferior vena cava axis and heart position (and, consequently, the interatrial septal position) horizontally. (Figure 2C) On contrast imaging, early opacification of the left cardiac chambers was noted.

On postoperative day 32 the patient underwent right heart catheterization. Pulmonary artery pressures (PAP) were normal (systolic: 34mmHg; diastolic: 9mmHg; mean: 20mmHg). An occlusion test was performed by inflating a sizing balloon on the PFO (Figure 3A) - systemic O_2sat increased from 77% to 95%, and arterial pO_2 increased from 41 to 70 mmHg in room air, while maintaining a normal PAP (Table 1). Closure was performed with a 14 mm Amplatzer® ASD occluder device (Figure 3B). On follow-up TOE, no residual leak was noted. The patient was later discharged on dual antiplatelet therapy, with an O_2sat of 98% in room air. Clopidogrel was stopped 1 month after the procedure. He remains asymptomatic at 1-year follow-up.

Discussion

The prevalence of PFO in the general population is estimated to be ~25%.[1] In most cases, the interatrial shunt is hemodynamically trivial. However, in rare circumstances, a R-L shunt through a PFO may cause clinically significant arterial deoxygenation by mixing venous and arterial blood. These patients usually present a platypnea-orthodeoxia syndrome, a rare condition characterized by dyspnea and arterial deoxygenation induced by an upright position and typically relieved by lying supine.[2]

The occurrence of R-L interatrial shunting is usually associated with spontaneous or induced pulmonary hypertension. The occurrence of this shunt with normal pulmonary artery pressure is very uncommon, but has been described in previous case reports. This occurs by preferential blood flow streaming from the inferior vena cava into the left atrium, through the PFO, even in the absence of an interatrial pressure gradient. A prominent Eustachian valve and right chamber anatomy modification can act as contributing factors. Such a syndrome has been described in patients with mechanical conditions, causing atrial or septal

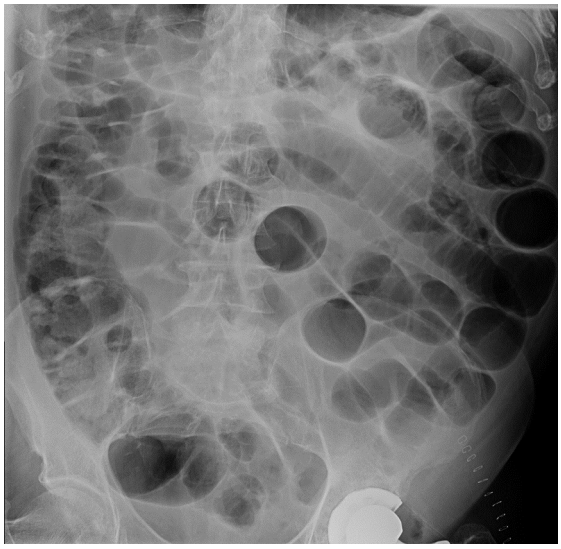

Figure 1 – *Abdominal radiography demonstrating bowel distention.*

deformity, such as kyphoscoliosis,[3] restrictive lung disease, previous pneumonectomy,[4] pleural effusion,[5] diaphragmatic paralysis and ascension,[6] ascending aorta aneurysm,[3] or post-thoracotomy.[7] In these cases, the anatomic relationship between the atrial septum and the inferior vena cava was changed, facilitating desaturated blood flow redirection through the PFO.

The history of symptoms can be short and may have an acute onset with rapid worsening within a few days. As such, the diagnosis of an arterial deoxygenation syndrome is usually a "rule-out" diagnosis.[2] Common causes of acute hypoxemia must be first excluded, such as pneumonia, acute heart failure, pulmonary embolism, or other structural lung disease. In our case, transthoracic echocardiography had missed the diagnosis. The first hint came from the VQ lung scan, requested to rule out pulmonary embolism or other VQ imbalances, which revealed kidney and brain uptake of tracer, a finding that is diagnostic of a R-L shunt.[8] TOE confirmed the R-L shunt through the streaming of blood flow from the inferior vena cava to the PFO. Upon review of CT images, we found that the abdominal distention due to postoperative ileus had

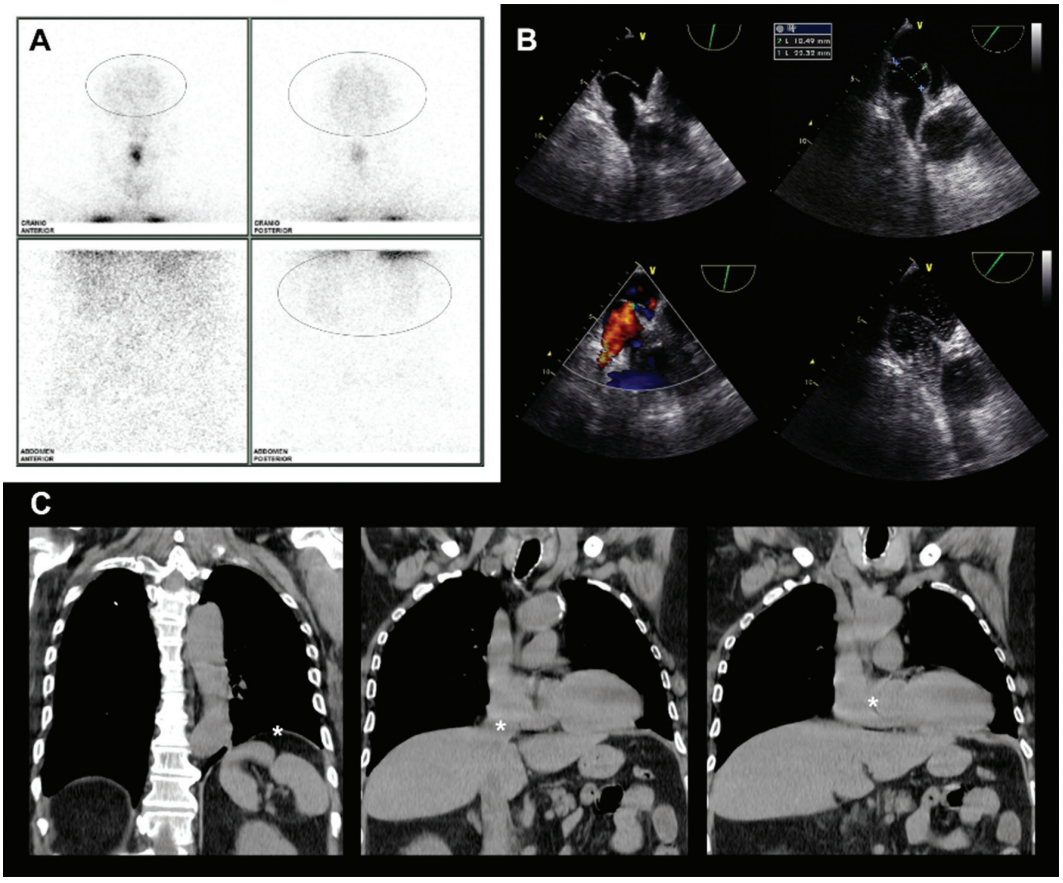

Figure 2 – Panel A: *V/Q scan demonstrating brain and kidney uptake of 99mTc-macroaggregated albumin;* Panel B: *TOE demonstrating PFO and interatrial septal aneurysm, with a large resting R-L shunt visible by color Doppler and agitated saline injection;* Panel C: *CT imaging demonstrating left hemidiaphragm elevation*, changing the supra-hepatic inferior vena cava axis* and the heart position* horizontally.*

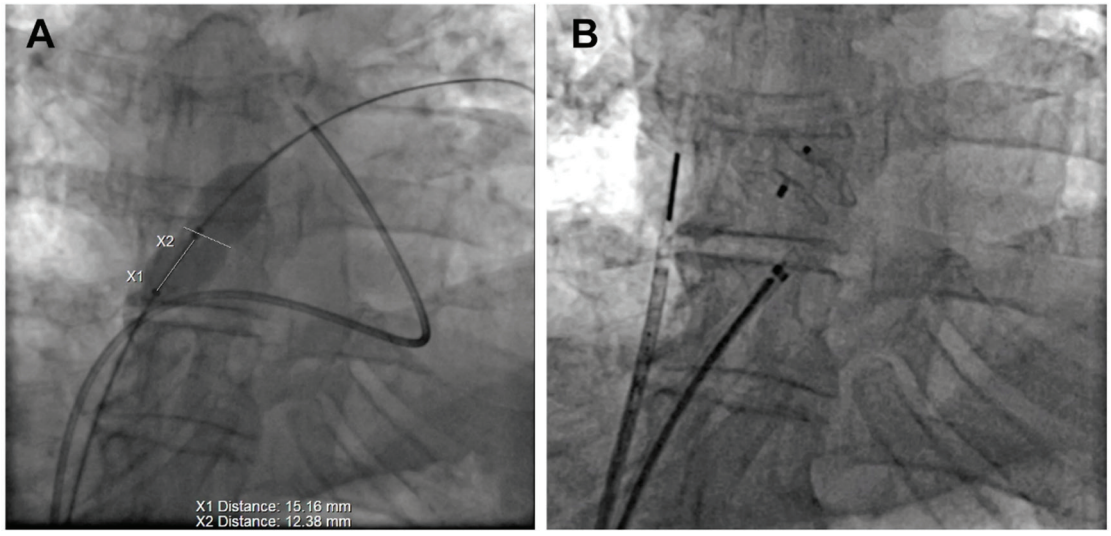

Figure 3 – Panel A: *PFO occlusion test performed by inflating sizing balloon on the PFO;* Panel B: *Deployment of a 14 mm Amplatzer® ASD occluder device.*

Table 1 – Blood gas analysis during right heart catheterization

	Before balloon occlusion		After balloon occlusion	
	Pulmonary artery	Radial artery	Pulmonary artery	Radial artery
pH	7.46	7.47	7.41	7.41
pCO^2 (mmHg)	30	26	32	29
pO^2 (mmHg)	25	**41**	32	**70**
O^2 sat (%)	52	**83**	65	**95**
HCO^{3-} (mmol/L)	21	19	20	20

caused diaphragm elevation and cardiac deformation, which in this case was responsible for the blood streaming. After an extensive review of the literature, we found that this is the first reported case of an arterial deoxygenation syndrome due to PFO under these circumstances. Another unique feature of this case was the severe hypoxemia while lying supine, as opposed to the typical relief of deoxygenation in the supine position of patients with platypnea-orthodeoxia syndrome. This suggests that the anatomic deformation leading to blood streaming was independent of the body position.

A potential limitation of the documentation of this case was that a thorough blood gas analysis in different body positions was not performed. This was due to the fact that severe hypoxemia had already been documented in decubitus, with no significant change in pulse oximetry in the sitting or standing position, so additional radial puncture seemed clinically futile at the time.

Conclusion

The present case illustrates the diagnosis and successful treatment of a rare cause of hypoxemia and highlights the mechanisms causing abnormal cardiac flow and impaired oxygenation with cardiac R-L shunts, which in rare cases can occur despite normal chamber pressures.

Author Contributions

Conception and design of the research and Critical revision of the manuscript for intellectual content: Carvalho P, Meireles D, Martins J, Costa MA, Briosa A; Acquisition of data and Analysis and interpretation of the data: Carvalho P, Meireles D, Martins J, Costa MA; Writing of the manuscript: Carvalho P.

Potential Conflict of Interest

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

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Impact of the First Wave of the COVID-19 Pandemic on Cardiovascular Surgery in Brazil: Analysis of a Tertiary Reference Center

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Introduction

The novel viral respiratory infection caused by coronavirus disease 2019 (COVID-19), initially known as 2019-nCoV, emerged in late December 2019 in Wuhan, China and quickly spread throughout Asia, Europe, and USA, characterizing the situation as a pandemic.[1] In May 2020, the World Health Organization declared Brazil a new epicenter of the coronavirus pandemic.

With the alarming levels of spread and severity of COVID-19, major disruptions in routine hospital services have occurred, as hospitals adjust in order to increase the capacity to care for patients with SARS-CoV-2.[2] In this context, elective surgeries were postponed in order to optimize health resources and staffing issues and to protect patients from in-hospital viral transmission.[3]

Although surgical volume reduction and higher mortality rates have been observed in patients operated on during the first wave of the pandemic period, the impact caused by the COVID-19 pandemic, specifically in cardiovascular surgery, has not yet been fully documented and understood.[4] Aiming to clarify these questions and to create grounding for future actions of resuming cardiovascular surgery units, a retrospective analysis of surgical data was conducted in a high-volume referral center for cardiovascular surgery in Brazil, the epicenter of the COVID-19 pandemic in Latin America.

Patients and Methods

In this retrospective study, the institutional database was used to review all patients who had undergone cardiovascular surgery in 2019 and 2020. The outcomes of two periods were compared, one period from 1 March to 31 July 2019 and the other from 1 March to 31 July 2020, which includes the early stage and the first wave peak of the COVID-19 pandemic in Brazil. This study was approved by the institutional review board under number 4.487.975 on 4 January 2021.

Patients included in this study underwent major adult cardiovascular surgery or congenital heart surgery, and they were categorized into three preoperative states: elective, urgent, and emergency surgery, according to the EuroSCORE II definition.5 Patients undergoing heart transplantation or salvage procedures were excluded from this analysis.

The primary endpoints were overall cardiovascular surgery volume and in-hospital mortality, comparing the two selected periods and the different months of early 2020. In-hospital mortality included patients who died within 30 days of operation and those who died later during the same hospitalization period.

Statistical analysis

Categorical variables were expressed as frequencies and percentages and compared by Pearson's chi-square test or Fisher's exact test between periods. A two-sided α of less than 0.05 was considered statistically significant. All statistical analyses were performed with SPSS, version 25.0.

Results

From 1 January to 31 October 2020, 1,056 patients underwent cardiovascular surgery at our institute. With the advance of the pandemic in early 2020, there was a reduction in the number of surgeries starting in March, with recovery starting in July. In January 2020, 218 cardiovascular surgeries were performed, and at the peak of the pandemic, in May, only 47 cardiovascular surgeries were performed. In October, the surgical volume returned to 122 cardiovascular procedures. The overall postoperative in-hospital mortality also changed significantly, from 7.8% in January to 23.4% in May, and it returned to 6.6%, in October 2020 (Figure 1, Panel A).

Comparing the pandemic period (March to July) of 2020 with the same period (March to July) of 2019, there was a 65.8% reduction (from 1,085 to 371, in 2019 and 2020, respectively) in the total number of cardiovascular surgeries performed. In March 2020 (early pandemic period), the reduction in cardiovascular surgery volume was 24.4%, and, in May 2020 (pandemic peak), it was 80.0%. Postoperative in-hospital mortality had an inverse correlation with a significant

Keywords

COVID-19; Thoracic Surgery; Hospitalization; Tertiary Healthcare/trends; Mortality; Elective Surgical Procedures; Heart Defects Congenital /surgery; Pandemics

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increase from 5.5% (March to July 2019) to 13.7% (March to July 2020), p < 0.001. In May 2019, postoperative in-hospital mortality was 4.3%, and in May 2020 (pandemic peak), it was 23.4% (p < 0.001) (Figure 1, Panel B).

Preoperative status also changed during the pandemic period. In 2019, about two thirds (66.4%) of cardiovascular surgery procedures were elective. During the pandemic period, there was an inversion, with about two thirds (65.2%) of surgical procedures being urgent or emergency. In the pandemic peak (May 2020), the urgent/emergency procedures represented 85.1% of total cardiovascular surgeries, with a 95.5% reduction in elective procedures. However, both surgical statuses decreased during the pandemic period. Elective procedures decreased 82.1%, and urgent/emergency procedures decreased 33.7% (Supplemental Material, Table S1). With the increase in the proportion of urgent and emergency procedures in the pandemic period, compared to the same period in 2019, there was also an increase in surgical risk (EuroSCORE II) from 2.02 to 7.82 among patients undergoing coronary artery bypass graft, from 3.04 to 9.22 among patients undergoing valve surgery, and from 2.90 to 9.70 among patients undergoing combined coronary and valve surgery.

Specific analysis of the most commonly performed cardiovascular surgeries, during the pandemic period, confirmed an average reduction of 70% in the surgical volume, regardless of the type of heart procedures. However, the increase in in-hospital mortality was different depending on the type of procedure performed. Among surgeries for acquired heart diseases (coronary artery bypass graft, valve surgery, and aortic surgery), observed in-hospital mortality was significantly higher. However, in congenital heart surgeries, the increase in observed in-hospital mortality was not significant (Supplemental Material, Table S2).

Considering only the pandemic period (March to July 2020), 39/357 (10.9%) patients had postoperative COVID-19, distributed as follows: 13/99 (13.1%) among patients undergoing coronary artery bypass graft, 14/79 (17.7%) among those undergoing valve surgery, 8/48 (16.7%) among those undergoing aortic surgery, and 2/113 (1.8%) among those undergoing congenital heart surgeries. The patients who had COVID-19 had significantly higher in-hospital mortality than those who did not (35.9% versus 11.6%, p < 0.001). However, even those who did not have COVID-19 still had higher in-hospital mortality when compared to the same period in 2019 (11.6% versus 5.3%, p < 0.001) (Table 1).

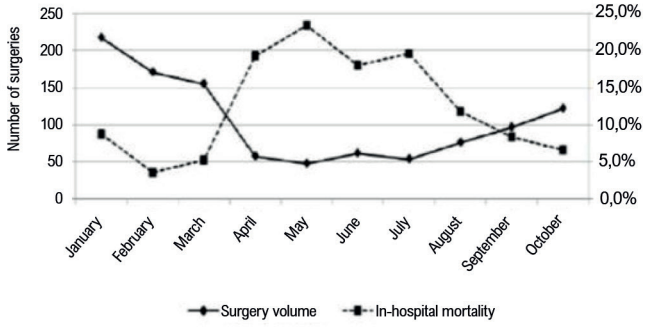
Discussion

The retrospective analysis of a national representative database of a high-volume center in Brazil showed a reduction in the overall volume of cardiovascular surgery, with an increase in the rates of urgent or emergency procedures, as well as a significant increase in postoperative in-hospital mortality during the first wave of the COVID-19 pandemic period.

Surgical practice was significantly impacted in all specialties worldwide during the pandemic period. This was due to the adaptations the healthcare system necessarily underwent in order to attend increased demand of patients with SARS-Cov-2.[3,6]

With the pandemic spread and the major disruptions in hospital routines, there was an increase in observed mortality in cardiovascular surgery procedures. COVIDSurg collaborative, a multi-center cohort of surgeries, included 50 patients who underwent cardiac surgery, and 30-day mortality was 34%, among the patients who had perioperative SARS-CoV-2 infection.4 In the pandemic period, we observed in-hospital mortality of 13.7%, and it was 35.9% among patients who had postoperative COVID-19. Although during the pandemic period there was an increase in the proportion of urgent and emergency procedures and an increase in

A



B

Months	2019	2020		2019	2020	
	Volume	Volume	Variation	Mortality	Mortality	p
	n	n		n	n	
March	205	155	- 24.4%	12 (5.9%)	8 (5.2%)	0.776(1)
April	220	57	- 74.1%	16 (7.3%)	11(19.3%)	0.006(1)
May	235	47	- 80.0%	10 (4.3%)	11(23.4%)	<0.001(2)
June	207	61	- 70.5%	13 (6.3%)	11(18.0%)	0.005(1)
July	218	51	- 76.6%	12 (5.5%)	10(19.6%)	0.003(2)
Total	1085	371	- 65.8%	60 (5.5%)	51(13.7%)	<0.001(1)

(1) Pearson's chi-square test (2) Fisher's exact test

Figure 1 – *Panel A: Impact of the first wave of pandemic period with reduced cardiovascular surgery volume and increased postoperative in-hospital mortality in 2020. Panel B: Cardiovascular surgery volume and in-hospital mortality, comparing March to July of 2019 and 2020 (pandemic period).*

Table 1 – In-hospital mortality of patients with and without COVID-19, in commonly performed cardiovascular surgery procedures, during the pandemic period peak (March to July) of 2020.

Surgery	Total March to July 2020		With COVID-19		Without COVID-19		Total March to July 2019		With versus without COVID-19 (2020)	2019 versus without COVID-19 (2020)
	Volume	Mortality	Volume	Mortality	Volume	Mortality	Volume	Mortality	p	p
	n	n (%)	n	n (%)	n	n (%)	n	n (%)		
CABG	99	13 (13.1%)	13	5 (38.5%)	86	8 (9.3%)	325	9 (2.8%)	0.013(2)	0.013(2)
Valve	79	9 (11.4%)	14	3 (21.4%)	65	6 (9.2%)	318	12 (3.8%)	0.194(2)	0.098(2)
CABG + Valve	18	6 (33.3%)	2	2 (100%)	16	4 (25.0%)	37	4 (10.8%)	0.098(2)	0.224(2)
Aortic	48	13 (27.1%)	8	2 (25.0%)	40	11 (27.5%)	111	12 (10.8%)	1.000(2)	0.012(1)
Congenital	113	10 (8.8%)	2	2 (100%)	111	8 (7.2%)	271	19 (7.0%)	0.007(2)	0.946(1)
Total	357	51 (14.3%)	39	14 (35.9%)	318	37 (11.6%)	1062	56 (5.3%)	<0.001(1)	<0.001(1)

CABG: coronary artery bypass graft. (1) Pearson's chi-square test (2) Fisher's exact test

the EuroSCORE II, the observed mortality was still higher than the expected mortality. This increase in postoperative observed mortality could be associated directly with SARS-CoV-2 infection and indirectly due to the overall scenario of hospital disruptions.[4]

In congenital heart surgery, there was no significant difference in-hospital mortality between the two periods (7.0% versus 8.8%). Two reasons may explain this difference. In-hospital flows from congenital heart surgery were already separated, and they remained more isolated during the pandemic. Another factor is that, although children are just as likely as adults to become infected with SARS-CoV-2, they have fewer symptoms and less severe disease.[7,8]

As the pandemic COVID-19 decreases, many institutions are studying appropriate strategies to restart the routine cardiovascular surgery and reevaluate the waitlist to minimize mortality during the waiting period. All recommendations from public health authorities regarding COVID-19 containment must continue to be followed in order to minimize disease spread, ensure patient safety, and protect health care workers.[9,10] Patients awaiting elective cardiac surgery need to be proactively managed, reprioritizing those with high-risk anatomy or whose clinical status is deteriorating.[3,4] With continuous learning, information exchange, collected data, and known results, we can implement an incident prevention structure that allows the collaborative creation of quality and safety measures for the next step of resuming cardiovascular surgery, minimizing problems during another wave of infection.

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Author Contributions

Conception and design of the research: Lisboa LA, Mejia OAV; Acquisition of data: Lisboa LA, Mejia OAV, Arita ET, Guerreiro GP, Silveira LMV, Miana L, Caneo LF; Analysis and interpretation of the data: Lisboa LA, Mejia OAV, Arita ET, Guerreiro GP, Silveira LMV, Brandão CMA, Dias RR, Dallan LRP, Miana L, Caneo LF; Statistical analysis: Arita ET; Writing of the manuscript: Lisboa LA; Critical revision of the manuscript for intellectual content: Mejia OAV, Brandão CMA, Dias RR, Dallan LRP, Miana L, Caneo LF, Jatene MB, Dallan LAO, Jatene FB.

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Instituto do Coração Faculdade de Medicina da Universidade de São Paulo under the protocol number 4.487.975. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

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*Supplemental Materials

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