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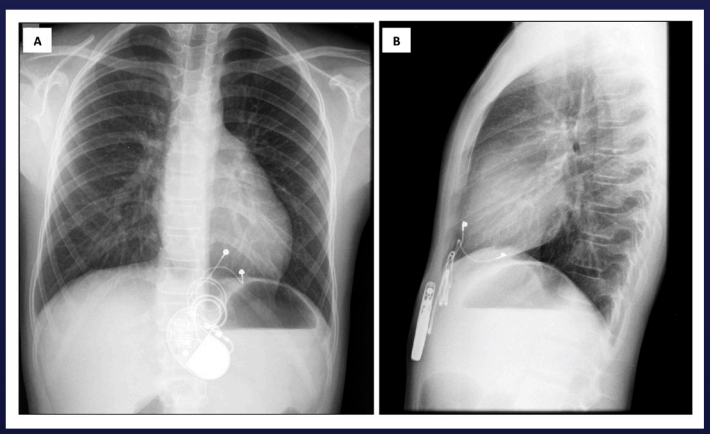

Figure 3 – *Chest radiographic projections displaying the appearance of epicardial pacemaker 10 years later, in anteroposterior (A) and lateral projections (B). Page 337*

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SUPPORT

G-Proteins Agonists and NO/cGMP Blockers: Unexplored Frontiers in the Pharmaceutical Industry

Paulo Roberto B. Evora

Departamento de Cirurgia e Anatomia - Faculdade de Medicina de Ribeirão Preto - Universidade de São Paulo, São Paulo, SP – Brazil

Two unexplored therapeutic frontiers the pharmaceutical industry still must address: 1) to answer the questions about the G-proteins' signal transduction to keep the NO release normal, and 2) to block the amine-resistant inflammatory vasoplegia mediated by NO overproduction. It is important to remember that two Nobel prizes are involved.

G-proteins: potential therapeutic role

The release of nitric oxide (NO) can occur by different pathways involving G-proteins. The Gi-protein is responsible for the mediation of inhibitory effects of receptors in the adenylate cyclase and guanylate cyclase pathways. An early stage of the majority of the responses mediated by receptors is the activation of G-proteins in the cell membrane, which is the target of the modulation of a variety of intracellular events. The role of G-proteins in the pathophysiology of vasospasm after global ischemia and reperfusion is still a matter of investigations. Their participation was documented in a comparative study of vascular relaxation induced by sodium fluoride, which produces biphasic responses in human, bovine, and porcine coronary arteries, causing an endothelium-dependent relaxation and an endothelium-independent contraction. G-protein dysfunction in the endothelium has also been postulated as responsible for the endothelial dysfunction in conditions of endothelial cell regeneration after injury, atherosclerosis, and coronary vasospasm. Myocardial ischemia and reperfusion selectively impair receptor-mediated NO release. However, the ability of the endothelial cell to produce NO or generate endothelium-dependent relaxation to nonnitric oxide-dependent agonists remains intact.[1,2]

In summary: 1. Endothelial cells maintain their capacity to release NO based on their ability in receiving the transduction signal through the membrane; 2. G-proteins have a fundamental role in the signal transduction; 3. This paradigm is extended to all vasotonic cardiovascular diseases that coexist with platelet dysfunction. These data would be highly relevant in the research of G-protein-targeting drugs.

The cGMP/cAMP "crosstalk" is underestimated

At present, clinical management of inflammatory vasoplegia associated with sepsis or anaphylaxis is symptomatic. Volume is expanded using administration of fluids, and low blood pressure is managed using administration of positive inotropes and vasoconstrictors. However, circulatory shock is frequently refractory to high amine concentrations.

Since 1994, blockade of guanylate cyclase by methylene blue (MB) in distributive shock has been the subject of study in our Laboratory of Endothelial Function and has been clinically used by the Cardiovascular Surgery Group, both at Ribeirao Preto Medical School of the University of Sao Paulo (FMRP-USP). There is strong evidence that MB, a guanylate cyclase inhibitor, is a therapeutic option for the treatment of the vasoplegic syndrome. Based on our clinical and laboratory experience, accumulated over a period of 20 years, classic concepts about the use of MB in this condition have been established: 1) Heparin and ACE inhibitors are risk factors; 2) At recommended doses, MB is considered a safe drug (the lethal dose is 40 mg/kg); 3) MB does not cause endothelial dysfunction; 4) The effects of MB appear only in the case of nitric oxide (NO) upregulation; 5) MB is not a vasoconstrictor *per se*; by blocking the cGMP system, it "releases" the cAMP system in a kind of "crosstalk", facilitating the vasoconstrictor effect of noradrenaline; 6) The most commonly used dosage is 2 mg/kg intravenous bolus followed by continuous infusion, since plasma concentration decreases markedly in the first 40 minutes; 7) There is a possible "window of opportunity" for the effectiveness of the MB.[3-5]

In this milieu, one main question comes up: 'What can we do when circulatory shock becomes refractory to the classical therapeutic measures including fluid administration, inotropes, and vasoconstrictors? Responses to this question are currently limited to the accumulated evidence regarding three cAMP-independent vasoconstriction mechanisms: 1) cGMP/NO-dependent vasoconstriction (the most important mechanism); 2) vasopressin administration and; 3) hyperpolarization-dependent vasoconstriction. Why these therapeutic alternatives do not always work?' We believe that there are at least, five aspects pertaining to this inquiry: 1) The lack of consideration of existing 'guidelines' or 'evidence based medicine' regarding the accepted treatment options available; 2) lack of knowledge of different vasodilatation mechanisms; 3) the possibility of a crosstalk between different vasodilatation mechanisms; 4) the soluble guanylyl cyclase (sGC) enzymatic activity and; 5) the common use of MB as a 'rescue' or 'ultimate' therapeutic attempt.[6]

Although there are no definitive multicentric studies, the use of MB is currently the unique, safest, cheapest treatment option for vasoplegic syndrome in cardiac surgery. Nevertheless, the MB "affair" masks the real problem of vasoplegic endothelial dysfunction, whose blockade could be the target of current drugs other than MB.

Keywords

GTP-Binding Proteins; Nitric Oxide; Endothelial Cells; Technology Pharmaceutical; Reference Drugs.

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However, in the scope of an editorial, it must be considered that there is no simple answer to the questions addressed above, since there are multiple factors that influence the decision making in multimillion dollar investments. Even considering the actual and potentialy clinical benefits, one must consider the patent situation of the product and its development, as well as the potential of present and future market. In addition, according to executives of the pharmaceutical industry, there is also a possible competition for funding that often entails internal competition between many lines of research.

These considerations would be speculative, but in our opinion the pharmaceutical industry owes us explanations on: 1) questions about the G-proteins signal transduction to keep NO release normal, and 2) blockage of the amine-resistant inflammatory vasoplegia mediated by NO overproduction. It is important to remember that two Nobel prizes are involved (Figure 1).

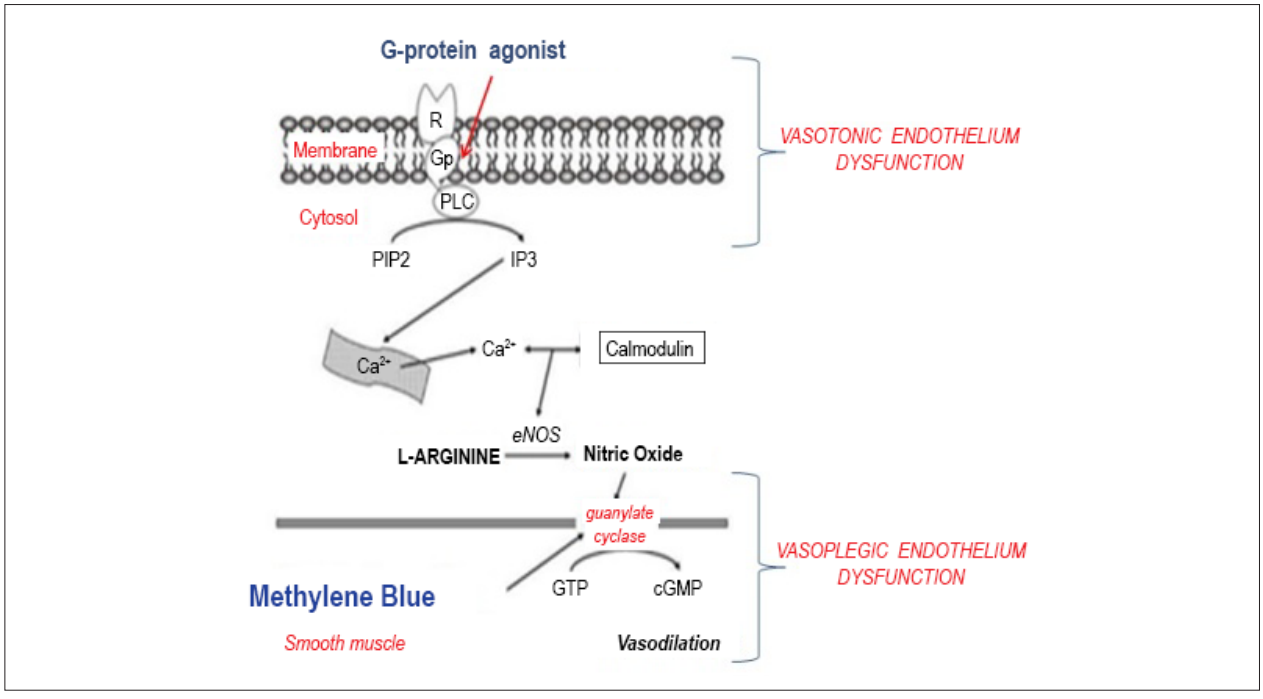

Figure 1 – *Endothelial nitric oxide synthase converts L-arginine to nitric oxide, which activates guanylate cyclase, responsible for the conversion of GTP to cGMP that causes endothelium-dependent vasodilatation commonly associated with circulatory shock mediated by membrane receptors (Adapted from Evora & Simon; Ann Allergy Asthma Immunol. 2007;99:306-313.)*[7]

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Impact of Paclitaxel-Eluting Balloons Compared to Second-Generation Drug-Eluting Stents for of In-Stent Restenosis in a Primarily Acute Coronary Syndrome Population

Guillaume Marquis-Gravel, Alexis Matteau, Brian J Potter, François Gobeil, Nicolas Noiseux, Louis-Mathieu Stevens, Samer Mansour

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Abstract

Background: **The place of drug-eluting balloons (DEB) in the treatment of in-stent restenosis (ISR) is not well-defined, particularly in a population of all-comers with acute coronary syndromes (ACS).**

Objective: **Compare the clinical outcomes of DEB with second-generation drug-eluting stents (DES) for the treatment of ISR in a real-world population with a high proportion of ACS.**

Methods: **A retrospective analysis of consecutive patients with ISR treated with a DEB compared to patients treated with a second-generation DES was performed. The primary endpoint was a composite of major adverse cardiovascular events (MACE: all-cause death, non-fatal myocardial infarction, and target lesion revascularization). Comparisons were performed using Cox proportional hazards multivariate adjustment and Kaplan-Meier analysis with log-rank.**

Results: **The cohort included 91 patients treated with a DEB and 89 patients treated with a DES (74% ACS). Median follow-up was 26 months. MACE occurred in 33 patients (36%) in the DEB group, compared to 17 patients (19%) in the DES group (p log-rank = 0.02). After multivariate adjustment, there was no significant difference between the groups (HR for DEB = 1.45 [95%CI: 0.75-2.83]; p = 0.27). Mortality rates at 1 year were 11% with DEB, and 3% with DES (p = 0.04; adjusted HR = 2.85 [95%CI: 0.98-8.32]; p = 0.06).**

Conclusion: **In a population with a high proportion of ACS, a non-significant numerical signal towards increased rates of MACE with DEB compared to second-generation DES for the treatment of ISR was observed, mainly driven by a higher mortality rate. An adequately-powered randomized controlled trial is necessary to confirm these findings. (Arq Bras Cardiol. 2017; 109(4):277-283)**

Keywords: **Angioplasty, Balloon; Drug-Eluting Stents; Paclitaxel; Coronary Restenosis; Acute Coronary Syndrome.**

Introduction

Drug-eluting stents (DES) are considered as the standard of care in percutaneous coronary intervention across a broad range of lesion complexity,[1,2] indications for revascularization,[3-6] and patient categories.[7] Treatment of in-stent restenosis (ISR) with DES improves outcomes compared to bare-metal stents (BMS) and balloon angioplasty.[8-10] However, the long-term impact of using multiple metal layers in coronary arteries is not fully understood.[11] Moreover, the use of DES requires long-term dual antiplatelet therapy (DAPT), significantly increasing bleeding risk, especially among patients requiring concomitant oral anticoagulation.[12] Finally, despite low contemporary rates, stent thrombosis remains a catastrophic potential adverse event following DES implantation.[13,14]

Drug-eluting balloons (DEB) provide an alternative for revascularization that avoids the risk of thrombosis associated with stenting and reduces the risk of restenosis associated with standard balloon angioplasty and BMS. The use of a DEB for treatment of ISR has a robust cost-effectiveness profile as compared to DES over a one-year period, mainly owing to savings associated with DAPT.[15] Prior studies have suggested that a stent-based drug-elution might not be necessary to prevent recurrent ISR.[16,17] Yet, randomized trials comparing paclitaxel-eluting balloons to DES for ISR treatment have shown conflicting results with regards to angiographic endpoints.[18-23] These studies have assessed clinical outcomes following DEB for ISR mostly as a secondary endpoint, enrolled mainly patients with stable coronary artery disease, and primarily used first-generation DES as the standard therapy for comparison. The objective of the present study was, therefore, to compare the clinical outcomes following DEB to second-generation DES for the treatment of ISR in a population comprised of a majority of patients presenting with an acute coronary syndrome (ACS).

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Methods

A retrospective cohort study was performed, comparing consecutive patients who underwent treatment of ISR using a paclitaxel-eluting balloon (Pantera Lux™, Biotronik, Berlin, Germany) to a random sample control group (1:1) of patients treated with a second-generation DES for ISR between December 2009 and November 2012, at the Centre Hospitalier de l'Université de Montréal (CHUM), an academic tertiary care centre (Canada). The selection of DEB or DES was left at the operator's discretion. Duration of DAPT was in accordance with the current practice guidelines for the specific indication for revascularization. DAPT was prescribed for a minimum of 3 months following elective DEB angioplasty. When performed, follow-up coronary angiography was clinically driven. Data were abstracted from electronic and paper medical records, and completed by telephone interviews. Coronary angiograms were independently reviewed by one investigator.

The primary outcome was a composite endpoint of major adverse cardiovascular events (MACE) including death from any cause, non-fatal myocardial infarction, and target lesion revascularization (TLR) at last follow-up. Secondary outcomes included device thrombosis, and the individual components of the primary outcome.

Endpoints were defined as per the Academic Research Consortium standardized definitions.[24] The local institutional Ethics Committee approved the protocol in compliance with the Declaration of Helsinki, and a waiver of consent was obtained. The study was conducted according to the STROBE statement.[25]

Statistical analyses

Continuous variables were presented as medians with 25-75% interquartile range (IQR). Categorical variables were expressed as proportions. Group comparisons of baseline characteristics were performed using the Pearson χ^2 for categorical variables, and the Kruskal-Wallis test for continuous variables. Unadjusted comparison of the primary outcome between the DEB and DES groups was performed using the log rank test. One-year freedom from MACE and mortality were compared with the Pearson χ^2 test. Freedom from MACE was illustrated using Kaplan-Meier curves. Multivariate Cox regression model was used to assess the impact of DEB on the primary and secondary outcomes. Covariates included in the multivariate model were based on a combination of a stepwise backward selection to identify independent risk factors for MACE in the cohort, and a priori knowledge of predictors of MACE (the latter variables being forced into the model). To limit over-fitting, the number of covariates retained was such that the ratio of events to covariates remained at least ten. From the available baseline and procedural characteristics, the stepwise selection process was used with an entry and stay criteria of 0.20 and 0.05, respectively. Interaction analyses were performed by adding an interaction term in the same multivariate Cox model to evaluate the relationship between DEB and MACE in the following pre-specified subgroups: DEB/DES length (≥ 20 mm or < 20 mm), diameter (≥ 3 mm or < 3 mm), and indication for revascularization (ACS or stable angina). In the DEB group, rates of MACE following treatment of intra-DES and intra-BMS restenosis were compared by using the same multivariate model as an exploratory analysis. Throughout the study, statistical significance was set at a two-sided p-value < 0.05. Statistical analyses were performed with SPSS® Statistics 20.0 (IBM®, Armonk, NY).

Results

From December 2009 to November 2012, DEBs were used in 100 patients, of whom 91 (91%) had follow-up data and were included in the analysis. The DES group included 89 patients treated with 6 zotarolimus-eluting stents (5 Endeavor® and 1 Resolute Integrity®, Medtronic Vascular, Santa Rosa, CA) and 94 everolimus-eluting stents (93 Xience V™, Abbott Vascular, Santa Clara, CA; 1 Promus Element™, Boston Scientific, Natick, MA). Median follow-up was 24 months (IQR: 15 to 32 months) in the DEB group and 27 months (IQR: 20 to 33 months) in the DES group. Baseline clinical characteristics for both groups are presented in Table 1. ACS was the indication for revascularization in 65 patients (71%) in the DEB group and 69 patients (78%) in the DES group (p = 0.35) (total cohort: 134 patients [74%]). Procedural data are shown in Table 2. There were more focal lesions and fewer occlusive lesions in the DEB group compared with the DES group (p = 0.05). Intra-DES reevascularization (compared to intra-BMS revascularizaton) was more frequent in the DEB group (p = 0.01). Preparation of the lesion with a cutting balloon was more frequent in the DEB group (19% versus 2%; p < 0.001), and maximal inflation pressure was higher (median: 16 atm versus 14 atm; p = 0.03) in the DEB group.

The primary outcome occurred in 33 patients (36%) in the DEB group, compared to 17 patients (19%) in the DES group (unadjusted p log-rank = 0.02). At one year, MACE occurred in 18 (23%) and 10 (12%) patients in the DEB and DES groups, respectively (Pearson χ^2 p-value = 0.06). Freedom from MACE at follow-up is illustrated in Figure 1. Covariates included in the final multivariate model were age, body mass index, diabetes, chronic kidney disease stage ≥ 3a (defined as creatinine clearance < 60 mL/min according to the Cockroft-Gault formula), and ACS (versus stable angina) as the indication for revascularization. After multivariate adjustment, no significant difference in the rates of MACE between both groups was present (adjusted HR for DEB = 1.45 [95%CI: 0.75-2.83]; p = 0.27) (Figure 2). Secondary outcomes are shown in Table 3. Two in-hospital deaths occurred in each group. One-year mortality rates were 11% (10 patients) and 3% (3 patients), in the DEB and DES groups respectively (Pearson χ^2 p-value = 0.04). Though numerically higher in the DEB group, all-cause mortality at follow-up (23% versus 7%) was not significantly different after multivariable adjustment (adjusted HR = 2.85; p = 0.06). One-year rates of TLR were 6% (5 patients) and 5% (4 patients), respectively (Pearson χ^2 p-value = 0.75). In the DEB group, there was no significant difference between BMS-ISR and DES-ISR (adjusted HR = 0.90 [95%CI: 0.37-2.20] p=0.82) in terms of MACE.

Table 1 – Baseline characteristics

	Drug-eluting balloon (n = 91)	Drug-eluting stent (n = 89)	p-value
Age (years)	66 (59-71)	66 (56-74)	0.89
Women	21 (23%)	24 (27%)	0.55
Body mass index (kg/m^2)	28 (26-34)	27 (24-30)	0.01
Diabetes	43 (47%)	33 (39%)	0.29
Hypertension	80 (89%)	72 (84%)	0.32
Dyslipidemia	86 (97%)	81 (93%)	0.29
Previous Stroke/TIA	11 (13%)	11 (13%)	0.95
Chronic kidney disease	22 (28%)	26 (33%)	0.46
Previous CABG	26 (29%)	17 (20%)	0.14
Indication			**0.37**
Stable angina	26 (29%)	20 (23%)	
Unstable angina	36 (40%)	37 (42%)	
NSTEMI	26 (29%)	24 (27%)	
STEMI	3 (3%)	8 (9%)	

TIA: transient ischemic attack; CABG: coronary artery bypass graft; NSTEMI: non-ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction.

No modification of the effect of DEB on the occurrence of MACE was observed for balloon-stent diameter (3 mm versus ≥ 3 mm) (p for interaction = 0.92), balloon/stent length (< 20 mm versus ≥ 20 mm) (p for interaction = 0.77) or ACS as the indication for revascularisation (p for interaction = 0.45).

Discussion

In the present study, assessing long-term clinical outcomes in a real-world primarily ACS population, we found that ISR treated with a paclitaxel-eluting balloon, compared to second-generation DES, while not showing a significant difference in overall MACE rates after adjustment, might be associated with a higher all-cause mortality rate. The present study was designed as an exploratory analysis of a real-world population and it can neither prove the clinical superiority or non-inferiority of DEB compared to DES for ISR. Rather, given the paucity of data on the clinical outcomes of DEB compared with current standard practice for this indication, we sought to add to the literature providing comparative clinical data on the use of DEB and second-generation DES in a real-world setting. Strengths of the analysis include an all-comer cohort presenting mostly with ACS, and use of second-generation DES as a comparator, both reflecting more accurately current clinical practice than previous reports.[18,19,21] Though relatively small, the sample size was similar to previous clinical trials of DEB.[18,19,21-23] The results of the present study are relevant for patient care optimization as concerns remain regarding DES for treatment of ISR despite their proven short-term efficacy.

The angiographic efficacy of DEB compared to first-generation DES has previously been demonstrated.[18-21] However, the RIBS IV randomized trial showed that everolimus-eluting stents were associated with improved angiographic outcomes compared to the SeQuent® Please DEB for treatment of DES-ISR.[22] Clinical events in DEB-ISR trials were only reported as secondary endpoints. In addition, only a minority of patients presented with an ACS in these trials, and none enrolled patients with an acute myocardial infarction. In the ISAR-DESIRE-3 trial, rates of MACE (23.5%) in the DEB group at one year were comparable to the rates in our cohort (23%).[20] In the present study, the mortality rate in the DEB group at one year (11%) was higher than in ISAR-DESIRE-3 (2.2%), suggesting that our real-world cohort might have represented a higher-risk population. This hypothesis is supported by the fourfold higher rate of ACS in our cohort (77%) compared to ISAR-DESIRE-3 (19%). In the PEPCAD-II trial, there was, in contrast to our findings, a strong trend towards lower rates of MACE in the DEB group compared to paclitaxel-eluting stent (9% versus 22%, respectively; p = 0.08).[21] However, in addition to being compared to first-generation DES, there were only 5 total deaths in the PEPCAD-II trial, suggesting again a population at lower overall risk than the one in this study.[21] Previous trials (except for RIBS IV) used first-generation DES as comparators, and this might at least in part explain why the signal observed in our study in disfavour of DEB was not observed previously.[18,19,21,23] Patients with ACS might still benefit more from a second-generation DES over a DEB for treatment of ISR, as high local and systemic pro-thrombotic and inflammatory milieu of ACS might not be suitable for DEB use, but this hypothesis remains to be confirmed.

Limitations of the present analysis include its non-randomized, single-centre, retrospective design. Selection bias was likely, and while multivariate modelling appeared to adequately account for known confounders, unmeasured confounding might remain. Additionally, it was not adequately powered to detect

Table 2 – Procedural characteristics

	Drug-eluting balloon (n = 91)	Drug-eluting stent (n = 89)	p-value
Access site			**0.64**
Radial	55 (60%)	59 (67%)	
Femoral	34 (37%)	28 (32%)	
Radial + femoral	1 (1%)	0 (0%)	
Brachial	1 (1%)	1 (1%)	
Coronary territory			**0.31**
Left main	3 (3%)	4 (5%)	
Left anterior descending	28 (31%)	29 (33%)	
Circumflex	27 (30%)	16 (18%)	
Right coronary artery	33 (36%)	40 (45%)	
DES ISR	55 (66%)	28 (42%)	0.01
Intra-CABG ISR	10 (11%)	8 (9%)	0.66
ISR pattern			**0.01**
Focal	52 (61%)	40 (46%)	
Diffuse	26 (31%)	25 (29%)	
Proliferative	4 (5%)	4 (5%)	
Occlusive	3 (4%)	18 (21%)	
Adjunctive procedures			
Rotational atherectomy	0 (0%)	1 (1%)	0.33
Thrombectomy	3 (3%)	7 (8%)	0.18
Cutting balloon	17 (20%)	2 (2%)	< 0.01
Balloon/stent diameter (mm)	3.00 (3.00-3.50)	3.00 (2.75-3.50)	0.61
Balloon/stent length (mm)	20 (20-30)	28 (18-30)	< 0.01
Maximal inflation pressure (atm)	16 (12-19)	14 (12-16)	0.03

DES: drug-eluting stent; ISR: in-stent restenosis; CABG: coronary artery bypass graft.

differences in rare clinical endpoints, such as device thrombosis. However, the sample size in this study is on par with those from prior clinical trials of DEB for the treatment of ISR.[16-19,21,23] Also, the current analysis lacks information on the duration of DAPT following ISR angioplasty. Future trials should address the efficacy of DEB in the setting of ACS and seek to define current clinical practice regarding DAPT following DEB, as the duration of DAPT and its associated costs and complications may prove to be the determining factors in the event of ongoing clinical equipoise between DEB and second-generation DES.

Conclusion

In conclusion, the present study showed that in a population with a high proportion of ACS, a non-significant numerical increase in MACE was observed with the use of DEB to treat ISR compared to second-generation DES. It was mainly driven by a concerning trend toward higher mortality with the use of DEB. Confirmation of these results by an adequately-powered randomized trial in the ACS population with clinically-driven endpoints is paramount to appropriately clarify the role of DEB in the interventional cardiology armamentarium.

Author contributions

Conception and design of the research: Marquis-Gravel G, Matteau A, Potter BJ, Mansour S; Acquisition of data: Marquis-Gravel G; Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Marquis-Gravel G, Matteau A, Potter BJ, Gobeil F, Noiseux N, Louis-Mathieu S, Mansour S; Statistical analysis: Marquis-Gravel G, Potter BJ, Mansour S; Writing of the manuscript: Marquis-Gravel G, Mansour S.

Potential Conflict of Interest

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

Sources of Funding

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Study Association

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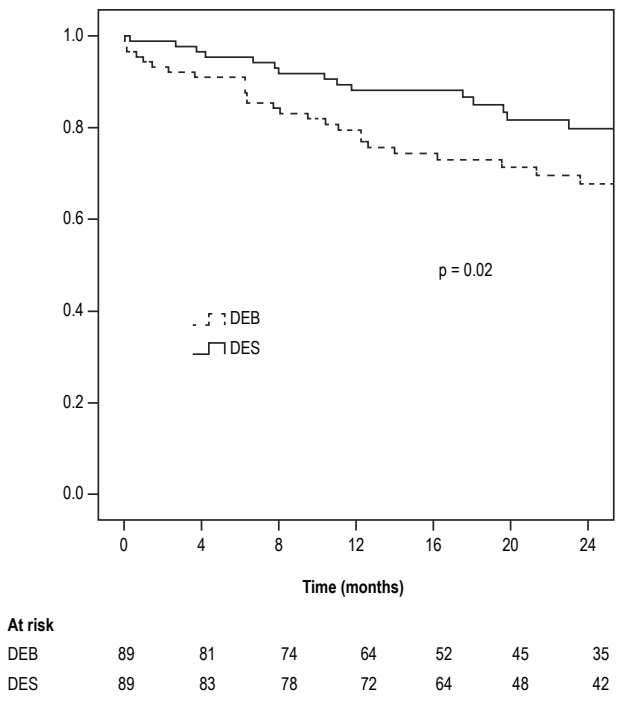

Figure 1 – *Unadjusted freedom from major adverse cardiovascular event. DEB: drug-eluting balloon; DES: drug-eluting stent.*

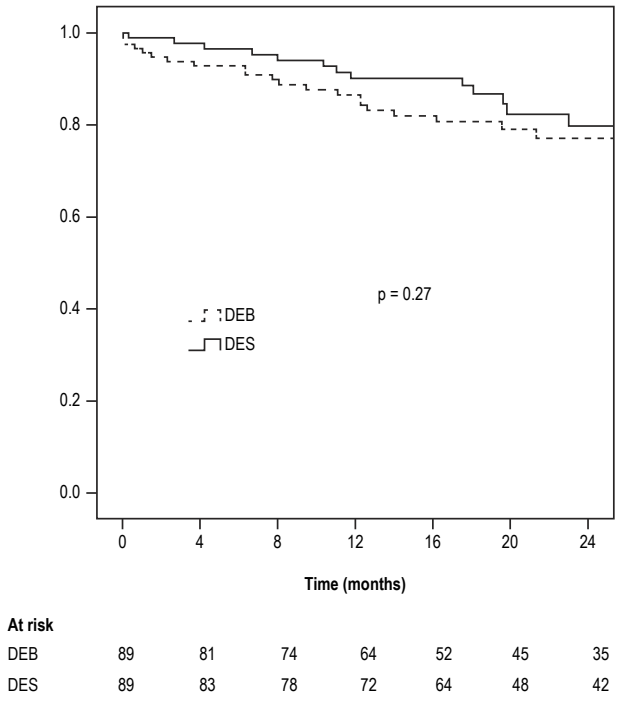

Figure 2 – *Adjusted Cox proportional hazards model analysis of major adverse cardiovascular event. DEB: drug-eluting balloon; DES: drug-eluting stent.*

Table 3 – Primary and secondary outcomes following treatment of in-stent restenosis

	Drug-eluting balloon (n = 91)	Drug-eluting stent (n = 89)	Adjusted hazards ratio* (95% confidence interval)	p-value
MACE	36%	19%	1.45 (0.75-2.83)	0.27
All-cause death	23%	7%	2.85 (0.98-8.32)	0.06
Non-fatal myocardial infarction	9%	6%	1.40 (0.43-4.6)	0.58
Target-lesion revascularization	10%	8%	1.29 (0.44-3.76)	0.64
Binary restenosis	13%	9%	1.03 (0.37-2.88)	0.95
Lesion thrombosis	1%	0%	78.96 (N/A)	0.67
All-cause revascularization	24%	16%	1.23 (0.57-2.63)	0.60

*MACE: major adverse cardiovascular events. *Adjusted Cox proportional hazards model, including age, body mass index, diabetes, chronic renal disease, and acute coronary syndrome as the indication for revascularization.*

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Non-Sustained Ventricular Tachycardia Episodes Predict Future Hospitalization in ICD Recipients with Heart Failure

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Abstract

Background: Implantable cardioverter-defibrillator (ICD) therapy is well known to reduce mortality in selected patients with heart failure (HF).

Objective: To investigate whether monitored episodes of non-sustained ventricular tachycardia (NSVT) might predict future HF hospitalizations in ICD recipients with HF.

Methods: We examined 104 ICD recipients (mean age: 60 ± 10.1 years, 80.8 % male) with HF who were referred to our outpatient clinic for device follow-up. After device interrogation, patients were divided into NSVT positive and negative groups. The primary endpoint was the rate of hospitalization within the next 6 months after initial ICD evaluation.

Results: Device evaluation demonstrated at least one episode of monitored NSVT in 50 out of 104 patients. As expected, no device therapy (shock or anti-tachycardia) was needed for such episodes. At 6 months, 24 patients were hospitalized due to acute decompensated HF. Hospitalization rate was significantly lower in the NSVT negative as compared with positive groups (38% versus 62%; adjusted hazard ratio [HR] 0.166 ; 95% CI 0.056 to 0.492; p = 0.01).

Conclusions: Monitored NSVT bouts in ICD recordings may serve as a predictor of future HF hospitalizations in ICD recipients with HF suggesting optimization of therapeutic modalities in these patients along with a close supervision in the clinical setting. (Arq Bras Cardiol. 2017; 109(4):284-289)

Keywords: Heart Failure; Tachycardia, Ventricular; Defibrillators, Implantable; Hospitalization.

Introduction

Implantable cardioverter defibrillator (ICD) therapy has been regarded as the mainstay of sudden cardiac death (SCD) prevention among patients with HF, and significantly reduces overall mortality in these patients.[1,2] In clinical practice, diminution of rehospitalizations in a given patient with HF serves as a predictor of favorable outcome, and may potentially mirror the optimality of therapeutic strategy as well. In line with this notion, ICD therapy was also suggested to be associated with lower HF readmission rates.[3]

Non-sustained ventricular tachycardia (NSVT) has been one of the most common challenges in clinical cardiology. It is generally defined as 3 or more consecutive beats arising below the atrioventricular node with a rate >120 beats/min and lasting less than 30 s.[4,5] The ICD has treatment as well as monitorization options for NSVT. NSVT is associated with an increased risk for sustained tachyarrhythmia[5] and is also a risk factor for SCD in patients with left ventricular dysfunction and hypertrophic cardiomyopathy.[6-8] In other terms, NSVT is a common finding in Holter monitoring of patients with HF and is associated with a poor outcome.[9] The present study aims to investigate the potential impact of NSVT episodes on the incidence of future HF hospitalizations among ICD recipients with HF.

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Methods

Study Population and enrolment

This observational prospective study was performed between November 2015 and May 2016 at Cardiology Clinic of the Trakya University Hospital, in Edirne, Turkey. ICD records contain data between previous index evaluation and the current day. Previous ICD follow-up of study patients were done 6 months before the study beginning day. NSVT was defined in monitored zone of ICD as 4 or more consecutive beats arising below the atrioventricular node with a rate > 167 beats/min and shorter than 16 beats (Figure 1). Patients who had NSVT episodes were defined as group-I and who had not any arrhythmia episodes were defined as group-II.

The patients with decompensated heart failure at the time of enrollment, atrial fibrillation-flutter, primary valvular pathology, advanced chronic obstructive pulmonary disease, recent infection, malignancy, blood dyscrasia, autoimmune or inflammatory disease, renal failure and hepatic failure were excluded from the study. Additionally, to discriminate

Not Have VT-NS		Have VT-NS	
Treated		**Treated**	
VF	0	VF	0
FVT (off)		FVT (off)	
VT	0	VT	0
		AT/AF (Monitor)	
Monitored		**Monitored**	
VT (133-167 bpm)	0	VT (133-167 bpm)	0
VT-NS (> 4 beats, > 167 bpm)	0	VT-NS (> 4 beats, > 167 bpm)	2
SVT: VT/VF Rx Withheld	0	SVT: VT/VF Rx Withheld	0
AT/AF	0	AT/AF	0

Figure 1 – *NSVT positive and negative definition of ICD record.*

ventricular arrhythmias and supraventricular arrhythmias more accurately, only patients with dual chamber ICD were selected, and patients receiving any ICD therapy (Shock or ATP) or monitored VT (133-167 bpm) were excluded from the study.

Information including age, gender, diabetes mellitus, hypertension and hyperlipidemia was gathered. The definition of HT was a systolic blood pressure (BP) value of ≥ 140 mmHg and/or a diastolic BP value of ≥ 90 mmHg at least on > 2 BP measurements or being on an antihypertensive therapy.[10] The definition of DM comprised a blood sugar value of ≥ 126 mg/dl (7.0 mmol/l) in the fasting state or being on an antidiabetic therapy[11] whereas the status of hyperlipidemia was based on the presence of a blood cholesterol level of ≥ 200 mg/dl or a triglyceride level of ≥ 150 mg/dl in the fasting state. The study was approved by the local ethics committee, and was implemented in complete concordance with the Declaration of Helsinki on human research. All subjects gave written informed consent to participate.

Follow-up and data collection

Implantable cardiac defibrillator interrogation was performed in the beginning of the study. All ICD's zones were as VT (167-200 bpm) with discriminators and VF (> 200 bpm). Standard VT was defined as sustained tachycardia with a cycle interval ranging 300 to 360 msec. VF was defined as when the cycle interval was shorter than 300 msec. NSVT was defined as a regular rhythm wide complex tachycardia lasting four or more beats, higher rate than 167 bpm and shorter than 16 beats. Two independent electrophysiologists blinded to study design performed ICD interrogations, reviewed, and classified the arrhythmia episodes. When no consensus was reached, a third physician was included, and the final judgment was based on the majority decision.

At enrolment, a detailed patient history and the medications were noted. Echocardiography was performed for the evaluation of left ventricular ejection fraction, and the device follow-up results were collected in ICD follow-up unit. Clinical follow-up visits were scheduled at monthly. At each follow-up visit, the same physician blinded to the cause for the patient's presentation evaluated signs and symptoms of HF deterioration by auscultation and examination for leg edema and jugular vein distension. A chest X-ray was performed to detect signs of pulmonary congestion and when cardiac decompensation suspected, patient was admitted to inpatient clinic.

Statistical analysis

Continuous variables were expressed as mean (standard deviation) if the distribution was normal and as median (interquartile range) if the distribution was abnormal. The normality of distribution for continuous variables was confirmed with the Kolmogorov-Smirnov test. Categorical variables were expressed as number and percentages. A $\chi 2$ test or Fisher's exact test was performed to compare the categorical variables. Non-paired student's t-test or Mann- Whitney U test was used for continuous variables, as appropriate. Cox regression analysis was used to evaluate the relationship between variables and NSVT episodes. The results of the Cox analysis were presented as hazard ratios (HR) and 95% confidence intervals (CI). Receiver operating characteristic curve analysis was used to determine the optimum cutoff levels of the NSVT episodes to predict hospital admission. All statistical analyses were performed with SPSS software version 17.0 (SPSS Inc., Chicago, IL). A p value of 0.05 was considered statistically significant.

Results

NSVT episodes were observed in 50 out of 104 patients (48 %) at the initial ICD evaluation. Study population were categorized into two subgroups if there were or not a NSVT episode (group I: 54 patients with NSVT and group II: 50 patients without NSVT). The baseline characteristics of the study population are shown in Table 1. Baseline characteristics were comparable between the two groups. The results of hematological and biochemical parameters are listed in Table 2. Laboratory parameters were also comparable between the groups.

Table 1 – Baseline demographic and clinical features in ICD patients with and without NSVT

	Group I NSVT (-) (n = 54)	Group II NSVT (+) (n = 50)	p
Male, n (%)	(42) (77.7)	(42) (84.0)	0.42
Age (years, mean ± SD)	60 ± 10.1	61 ± 10.1	0.72
Hypertension, n (%)	25 (46)	24 (48)	0.86
Diabetes, n (%)	15 (27)	12 (24)	0.66
Device			
CRT, n (%)	11 (20)	6 (12)	0.24
ICD, n (%)	43 (80)	44(78)	
Ischemic Etiology, n (%)	25 (46)	30 (60)	0.16
Secondary Prevention, n (%)	21 (38)	17 (34)	0.60
Ejection Fraction (%)	28 ± 5.1	28 ± 5.7	0.98
Angiotensin-converting enzyme inhibitors, n (%)	42 (77)	40 (80)	0.78
Spironalactone, n (%)	29 (53)	34 (68)	0.13
Digoxin, n (%)	11 (20)	13 (26)	0.50
Diuretics, n (%)	30 (55)	35 (70)	0.13
Beta-blocker, n (%)	47 (87)	46 (92)	0.24
Statin, n (%)	27 (50)	28 (56)	0.56
Amiodarone, n (%)	7 (12)	2 (4)	0.10
Ivabradine, n (%)	8 (14)	8 (16)	0.86

NSVT: nonsustained ventricular tachycardia; ICD: implantable cardioverter-defibrillator; CRT: cardiac resynchronization therapy; SD: standart deviation.

Tabela 2 – Comparison of biochemical and hematological characteristics and hospitalization in ICD patients with and without NSVT

	Group I NSVT (-) (n = 54)	Group II NSVT (+) (n = 50)	p
Glucose, mg/dL	124 ± 70.1	114 ± 40.1	0.40
Cratinine, mg/dL	1.01 ± 0.34	0.9 ± 0.24	0.63
Sodium, mg/dL	135 ± 17.3	137 ± 3.9	0.52
Potassium, mg/dL	4.5 ± 0.53	4.5 ± 0.57	0.98
Low-density lipoprotein, mg/dL	107 ± 39.9	106 ± 36.1	0.97
High-density lipoprotein, mg/dL	40 ± 12.4	38 ± 12.8	0.57
Asparate transaminase, mg/dL	28 (14-113)	26 (8-65)	0.53
Alanine transaminase, mg/dL	25 (5-115)	25 (3-71)	0.95
Hemoglobin, g/dL	12.9 ± 1.72	13 ± 2.04	0.82
Platelet, x 10^3/L	244 ± 90.6	235 ± 63.6	0.54
White blood cell, x 10.9 /µl	8.1 ± 2.32	8,9 ± 3.02	0.14
TSH, mU/L	2.1 ± 1.75	2.2 ± 2.85	0.80
Free T3, ng/dL	2.5 ± 0.75	2.7 ± 0.81	0.31
Free T4, ng/dL	1.1 ± 0.32	1.1 ± 0.25	0.67
Hospitalization, n (%)	5 (9)	19 (38)	0.001

NSVT: nonsustained ventricular tachycardia; ICD: implantable cardioverter-defibrillator; HET: thyroid stimulant hormone.

At 6 months following the initial ICD interrogation, 24 patients were eventually hospitalized due to HF decompensation. Hospitalization was significantly lower in the NSVT negative versus positive groups (38% versus 62%; adjusted hazard ratio [HR] 0.166 ; 95% CI 0.056 to 0.492; p = 0.01) (Table 2). Patients were rehospitalized due to HF

more frequently within the first month as compared with the following months. Totally, 10 out of 24 hospitalized patients were admitted within the first month. Moreover, 8 out of these 10 were in group II (Figure 2). Analysis of receiver operating characteristic (ROC) for NSVT episodes (area under curve 0.816, 95% CI 0.650 to 0.812, p < 0.001) demonstrated that a total NSVT number of ≥ 19 had a strong discriminatory power to predict future HF hospitalization (Sensitivity 67%, Specificity 88%) (Figure 3).

Discussion

The present study clearly demonstrates that monitored NSVT episodes in the initial ICD recordings appear to be associated with HF decompensation and re-hospitalization during the 6 months after the index evaluation with a predominantly higher rate of admissions within the first as compared with the following months.

Previous studies suggested NSVT as an important prognostic determinant for arrhythmic events.[12,13] NSVT and frequent ventricular premature beats were previously shown to have a significant association with a higher arrhythmia risk in patients with dilated cardiomyopathy[14] More importantly, NSVT is strongly associated with an increased SCD risk in the setting of hypertrophic cardiomyopathy.[8,15] Even though the potential association of NSVT with further malignant arrhythmic events has been clarified to some extent, relationship between heart failure decompensation and NSVT is yet to be thoroughly elucidated.

Ventricular arrhythmias are frequently encountered in patients with HF[9] with an overall incidence of NSVT ranging between % 30 and %80.[16,17] NSVT is also common in ambulatory ECG recordings of HF patients and is associated with poor outcome.[9] NSVT was suggested as an independent predictor of total mortality in patients with HF.[16] Moreover, NSVT was found to be predictive for ICD-derived arrhythmias in patients with ischemic or nonischemic cardiomyopathy.[18]

Exact mechanisms linking NSVT to adverse outcomes remain unclear. One such mechanism for this association may be ascribed to sympathetic hyperactivation: During a NSVT episode, the blood pressure may fall drastically eliciting a subsequent sympathetic burst, which, in turn, might disturb cardiac structure and performance in the long term as a result of repetitive arrhythmic episodes ultimately leading to a state of progressive heart failure and cardiac decompensation.[19]

Secondly, increased sympathetic activity is a predictor of malign arrhythmias[20] and a trigger of adverse myocardial remodeling. Accordingly, NSVT might be considered as a consequence of progressive myocardial failure associated with enhanced sympathetic activation or other triggers. In other words, an existing primary condition or abnormality manifesting as a progressive myocardial failure may ultimately predispose to malignant arrhythmias including NSVT. For exemple, electrical storm is an ominous finding in ICD recipients and is associated with worsening HF leading to an increased risk for sudden and non-sudden cardiac mortality.[21,22]

In the present study, we found a significant relationship between monitored NSVT episodes and hospitalization rates at 6 months. Our study has important clinical implications; Pacemakers are successful rhythm detection devices and ICD follow-up serves as an easy way to detect a long-term rhythm record of patients. NSVT detection in ICD recordings of patients with HF may be an important tool for the prediction of decompensated heart failure development in the near future. Rates of HF rehospitalization may be substantially diminished through close monitoring and optimization of medical therapy in these patients.

There are some limitations of the present study. This was a single-centre study, and included limited number of patients. Because of the sample size and inadequate power, it seems quite possible that some associations might have gone undetected.

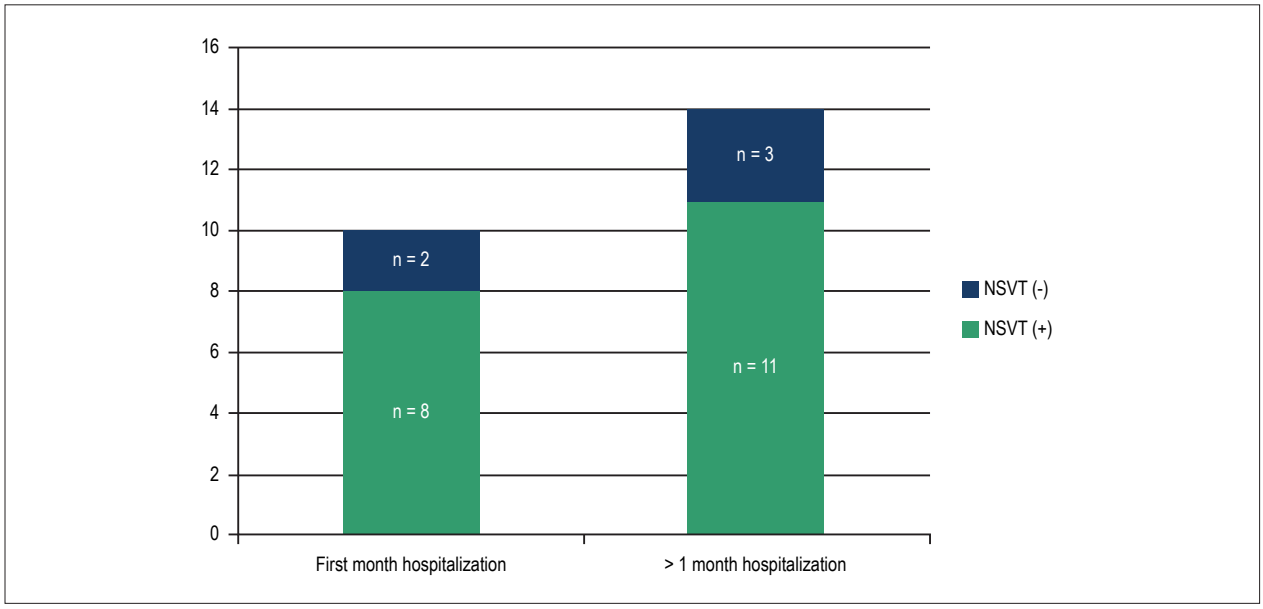

Figure 2 – *Time to hospital admission of study patients due to decompensation.*

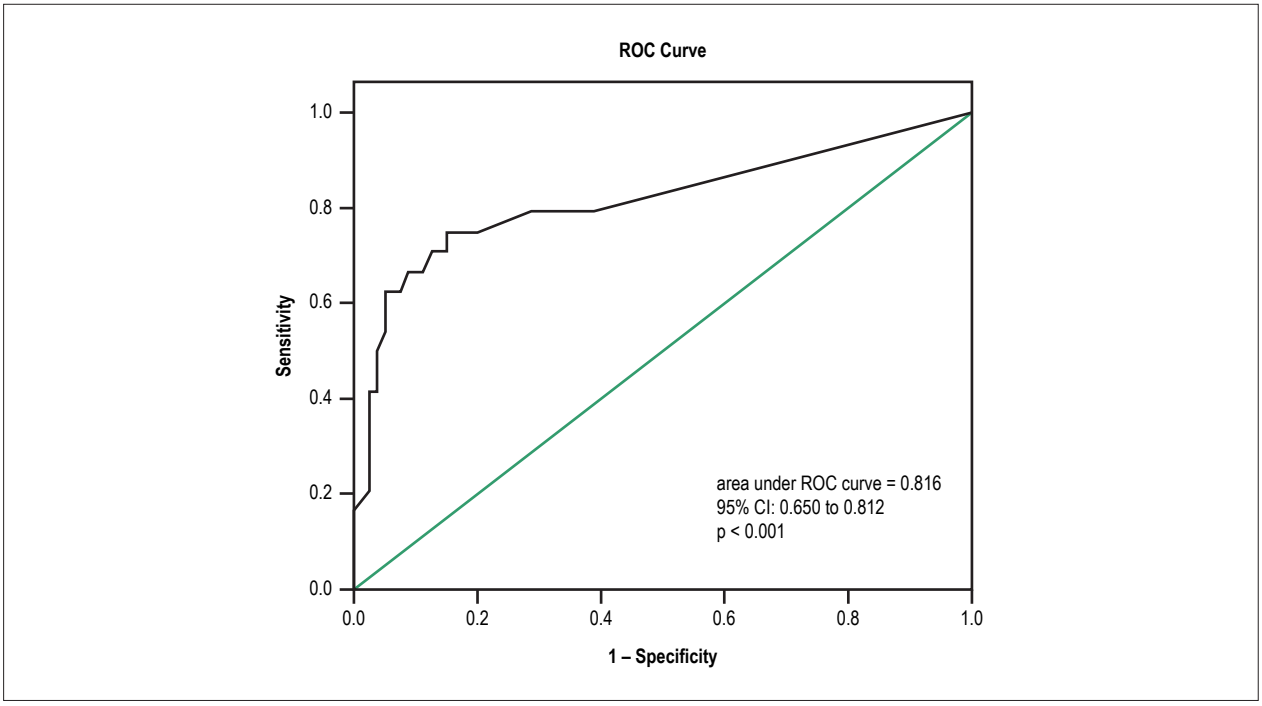

Figure 3 – *ROC curve analysis between hospitalization and non sustained ventricular tachycardia episodes.*

Moreover, the potential impact of other arrhythmias including PVCs was not taken into account. Further prospective studies are needed to substantiate the prognostic role of NSVT episodes in the prediction of future heart failure decompensation.

Conclusion

Non-sustained ventricular tachycardia episodes may predict future heart failure decompensation in ICD recipients with HF. Detection of NSVT episodes in ICD recordings may entail optimization of medical therapy as well as close supervision of these patients in an effort to preclude future HF admissions.

Author contributions

Conception and design of the research: Uçar FM, Yilmaztepe MA; Acquisition of data: Uçar FM, Taylan G, Aktoz M; Analysis and interpretation of the data: Uçar FM, Yilmaztepe MA, Taylan G, Aktoz M; Statistical analysis: Uçar FM, Taylan G; Obtaining financing: Uçar FM, Aktoz M; Writing of the manuscript: Uçar FM; Critical revision of the manuscript for intellectual content: Uçar FM, Yilmaztepe MA, Aktoz M.

Potential Conflict of Interest

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

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Do We Need to Personalize Renal Function Assessment in the Stratification of Patients Undergoing Cardiac Surgery?

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Abstract

Background: **Renal dysfunction is an independent predictor of morbidity and mortality in cardiac surgery. For a better assessment of renal function, calculation of creatinine clearance (CC) may be necessary.**

Objective: **To objectively evaluate whether CC is a better risk predictor than serum creatinine (SC) in patients undergoing cardiac surgery.**

Methods: **Analysis of 3,285 patients registered in a prospective, consecutive and mandatory manner in the Sao Paulo Registry of Cardiovascular Surgery (REPLICCAR) between November 2013 and January 2015. Values of SC, CC (Cockcroft-Gault) and EuroSCORE II were obtained. Association analysis of SC and CC with morbidity and mortality was performed by calibration and discrimination tests. Independent multivariate models with SC and CC were generated by multiple logistic regression to predict morbidity and mortality following cardiac surgery.**

Results: **Despite the association between SC and mortality, it did not calibrate properly the risk groups. There was an association between CC and mortality with good calibration of risk groups. In mortality risk prediction, SC was uncalibrated with values > 1.35 mg /dL ($p < 0.001$). The ROC curve showed that CC is better than SC in predicting both morbidity and mortality risk. In the multivariate model without CC, SC was the only predictor of morbidity, whereas in the model without SC, CC was not only a mortality predictor, but also the only morbidity predictor.**

Conclusion: **Compared with SC, CC is a better parameter of renal function in risk stratification of patients undergoing cardiac surgery. (Arq Bras Cardiol. 2017; 109(4):290-298)**

Keywords: **Renal Insufficiency/prevention & control; Myocardial Revascularization; Hospital Mortality; Creatinine/analysis; Indicators of Morbidity and Mortality; Risk Factors.**

Introduction

Cost-effectiveness analysis in cardiac surgery reveals the impact of complication prevention and incorporation of new technologies in health system.[1] High rates of complications and hospital mortality have been reported in patients with renal dysfunction who undergo myocardial revascularization surgery.[2] Therefore, a more reliable, individualized assessment of renal function may lead to better optimization and allocation of resources that may help physicians and patients choose the best time and type of treatment.

In this context, several studies have shown a direct correlation of preoperative renal failure with morbidity and mortality following cardiac surgery.[3,4] For a better estimate of kidney failure degree, current risk scores, such as EuroSCORE II, have included creatinine clearance (CC) calculation.[5-7] However, EuroSCORE II has been shown to become more complex and flawed when adapted to current lines of work, as revealed by internal validation.[8,9] For this reason, we have concerns relating to how to choose international scores and more and more complex models.

To estimate mortality risk, Brazilian models include serum creatinine (SC) values only, even as categorical variable.[10,11] Hence, EuroSCORE II, recently validated in Brazil,[12] includes CC levels as a predictive variable, aiming to improve the performance of the original version of EuroSCORE.[13] However, pitfalls in calibration tests of the instrument may be related to inaccurate measurements of some variables in our settings. In light of this, and due to the higher complexity of estimating CC as compared with SC for physicians and other healthcare professionals, the real need for estimating this parameter is questionable. Unfortunately, to our knowledge, there are no studies available on the impact of CC *versus* SC on morbidity and mortality after cardiac surgery.

In light of this gap in the literature, the aim of our study was to objectively assess the importance of CC *versus* SC in the stratification of patients undergoing cardiac surgery in a prospective, multicentric, mandatory registry of patients undergoing cardiac surgery in the state of Sao Paulo, Brazil.[14]

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Methods

Sample

Cross-sectional study based on Sao Paulo Registry of Cardiovascular Surgery (REPLICCAR), performed at Heart Institute (InCor) of the General Hospital of the University of Sao Paulo Medical School. All patients who consecutively underwent emergency coronary and/or valve surgery in 10 hospitals in the state of Sao Paulo in the period from November 2013 to January 2015 were included in the analysis. Before the start of the study, the presence of SC, CC and EuroSCORE II in all patients was confirmed. The sample should have included a minimum of 100 events for statistical significance; the study was started with 224 deaths and 263 morbidities registered.

Inclusion and exclusion criteria

Inclusion criteria:

All patients aged ≥ 18 years, who underwent elective surgery during the pre-established period for:

- Valve surgery (substitution or plastic surgery);
- Myocardial revascularization surgery (MRS) (with or without extracorporeal circulation)
- Combined surgery (MRS and valve surgery).

Exclusion criteria:

Other types of surgeries performed in combination with valve and/or MRS.

Data collection, definition and organization

Collected data are fed in to REPLICCAR by a trained person in each of the 10 centers participating in the project. Data were inserted online to the website *bdcardio.incor.usp.br* by username and password, into four different interfaces: preoperative, intraoperative, discharge and 30 days after discharge. A total of 68 variables were collected by patient, and follow-up was performed by telephone. Data completion and veracity were controlled by registry governance and administration. CC was calculated by the Crockcroft-Gault equation for estimation of glomerular filtration rate using SC, age, sex, and body weight.

EuroSCORE II values used in REPLICCAR is calculated on the website http://www.euroscore.org/calc.html. Outcome measures were hospital morbidity and mortality in the period from surgery to evaluation at 30 days, or to hospital discharge. Morbidity included severe acute renal failure (sARF), stroke and acute myocardial infarction (AMI).

Statistical analysis

Continuous variables were expressed as mean ± standard deviation and categorical variables as percentages. Fisher exact test was used for contingency tables. Calibration was calculated by the Hosmer Lemeshow test, indicating that the model was adequately adjusted when $p > 0.05$. In the calibration of CC and SC, we analyzed the difference between expected and observed mortality and morbidity by nonlinear least squares (NLS). Therefore, a positive NLS indicates that the outcomes were better than expected. In addition to NLS, we evaluated the adjusted rate between observed and expected outcomes, the ´risk adjusted mortality quotient` (RAMQ). A RAMQ lower than 1 suggests that surgical outcome was better than the average outcome. CC and SC accuracy was analyzed by the area under the ROC curve. Using multiple logistic regression analysis, two multivariate models were built for mortality and two multivariate models were built for morbidity, one model using the variable CC, and the other using the variable SC. Regression analysis was performed by the stepwise selection method. Models with the dichotomous variable CC < 55mL/min were also tested. A P value < 5% was considered significant. Statistical analysis was performed using the SPSS desktop statistical software, version 22.0 for Windows (IBM Corporation Armonk, New York).

Ethics and Consent form

This work was approved as a subproject of the online registry number 9696 of the Ethics Commission for Research Project Analysis (CAPPesq) of HCFMUSP, entitled "Heart surgery programs innovation using surgical risk stratification at the São Paulo State Public healthcare system: SP-Score-SUS study".

Results

Subjects

Of 3,285 patients, 224 patients (6.8%) died and 263 (7.9%) had some morbidity. Mean age was 60.47 ± 12.3 years, and 1,195 (36.3%) were women. Mean body mass index was 26.7 ± 4.5 kg/m^2. Reoperations were performed in 399 (12.1%) patients. A total of 1,428 (43.4%) patients with functional class III-IV and 1,180 (35.8%) emergency patients underwent surgery. Mean ejection fraction was 58.3 ± 11.2%. Mean SC and CC values were 1.25 ± 1.1 mg/dL and 72.6 ± 29.5 mL/min, respectively. Mean EuroSCORE II was 2.6 ± 4.3. A total of 1,862 (56.7%) MRS alone, 1,065 (32.4%) valve surgery alone and 358 (10.9%) MRS combined with valve surgery was performed.

Association between SC and mortality

There was an association between SC and mortality ($p = 0.0003$). However, the model with SC subgroups did not adjust well for mortality in the Hosmer-Lemeshow test (H-L, $p < 0.0001$), Table 1.

Our results showed that, although expected mortality by SC was associated with observed mortality in our sample, when SC was ≥ 1.60, expected mortality by the variable became significantly disproportionate (RAMQ > 2), underestimating the observed mortality. On the other hand, there is a similar number of patients between the groups (see supplementary figure A), which confirms the disproportion between OM and EM for higher SC levels.

Association between creatinine clearance and mortality

There was a significant association between CC and mortality ($p < 0.0001$) and the model with CC subgroups adjusted well in the Hosmer-Lemeshow mortality test (H-L, $p = 0.277$), Table 2.

Table 1 – Expected mortality (EM) by serum creatinine adjusted for observed mortality (OM)

Serum creatinine	Cases	%	OM	EM	RAMQ (OM/EM)
< 0.80	341	10.4	15	20.96	0.72
0.80-0.87	346	10.5	16	21.72	0.74
0.88-0.93	310	9.4	9	19.69	0.46
0.94-0.99	235	7.1	10	15.07	0.66
1.00-1.03	322	9.8	19	20.78	0.91
1.04-1.10	350	10.6	16	22.83	0.70
1.11-1.20	381	11.6	22	25.2	0.87
1.21-1.34	325	9.9	21	21.87	0.96
1.35-1.59	319	9.7	28	22.02	1.27
≥ 1.60	364	11.1	68	33.86	2.01
Total	3293	100,0	224	224	

RAMQ: Risk Adjusted mortality quotient.

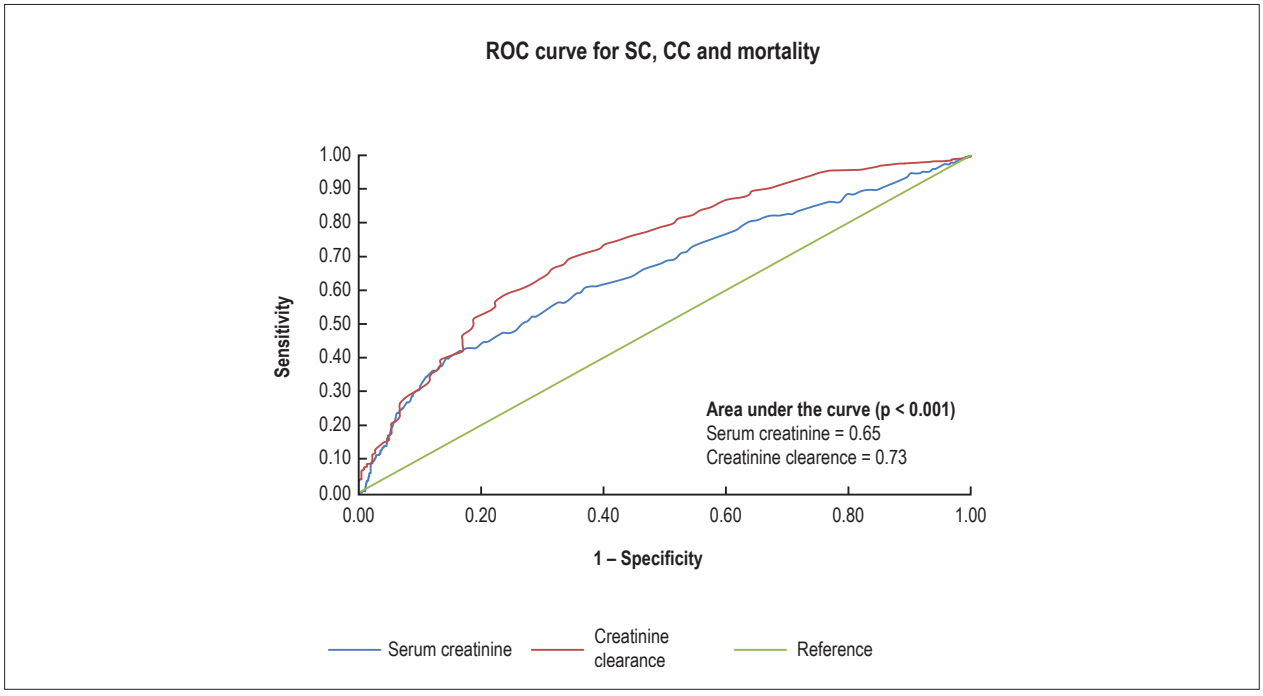

Figure 1 – *ROC curve for serum creatinine, creatinine clearance and mortality.*

In calibration, using creatinine clearance as predictive variable of the groups formed by the Hosmer Lemeshow test, there was no significant difference between expected mortality by CC and observed mortality (p = 0,277). Also, there is a similar number of patients between the groups (see supplementary figure B) that confirms that CC is a good predictor of mortality.

Analysis of the ROC curve (Figure 1), which measures the accuracy of the variable in discriminating between patients who died and those who survived, revealed that, when SC was used as predictive variable, the accuracy of the model was 0.65. However, when CC was used as predictive variable, the accuracy of the model in predicting mortality reached 0.73 (p < 0.001).

Association between SC and morbidity (stroke, AMI, sARF)

There was an association between SC and morbidity (p < 0.0001). However, the model with SC subgroups did not adjust well to morbidity in the Hosmer-Lemeshow test (H-L, p < 0.0001), Table 3.

Table 2 – Expected mortality (EM) by creatinine clearance adjusted for observed mortality (OM)

Creatinine clearance	Cases	%	OM	EM	RAMQ (OM/EM)
≥ 109	333	10.1	5	3.14	1.59
95-108	339	10.3	9	7.14	1.26
85-94	343	10.4	11	10.31	1.07
77-84	310	9.4	13	12.26	1.06
70-76	328	10.0	6	16.13	0.37
64-69	319	9.7	20	19.3	1.04
57-63	333	10.1	24	24.52	0.98
49-56	341	10.4	34	31.17	1.09
39-48	323	9.8	34	37.86	0.90
< 38	324	9.8	68	62.17	1.09
Total	3293	100.0	224	224	

RAMQ: Risk Adjusted mortality quotient.

Table 3 – Expected morbidity by serum creatinine adjusted for observed morbidity

		morbi = 1		morbi = 0	
Group	Total	Observed	Expected	Observed	Expected
1	341	13	23.80	328	317.20
2	346	14	24.83	332	321.17
3	310	13	22.59	297	287.41
4	235	16	17.34	219	217.66
5	322	14	23.95	308	298.05
6	350	23	26.40	327	323.60
7	381	20	29.26	361	351.74
8	325	32	25.53	293	299.47
9	319	32	25.90	287	293.10
10	364	86	43.42	278	320.58

RAMQ: Risk Adjusted mortality quotient.

Although we observed an association between expected morbidity by SC and observed morbidity in the sample, calibration by Hosmer-Lemeshow test showed a significant difference between expected mortality by SC and observed mortality in the groups.

Association between CC and morbidity (stroke, AMI, sARF)

There was an association of CC with morbidity ($p < 0.0001$). CC subgroups adjusted well to morbidity in the Hosmer-Lemeshow test (H-L, $p < 0,346$), Table 4.

In addition to the association between expected morbidity by CC and observed morbidity in the sample, calibration by the Hosmer-Lemeshow test showed that there was no significant difference between expected mortality by CC and observed mortality in the groups.

Analysis of the ROC curve (Figure 2) showed that, when SC was used as predictive variable, accuracy of the model was 0.68 only. Nevertheless, when CC was used as predictive variable, accuracy of the model to predict observed mortality was 0.70 ($p < 0,001$).

Multivariate model for mortality

In the upper part of the Table 5, we can see that when a multivariate model for mortality without CC was generated, the independent predicting variables were age, hematocrit, pulmonary artery pressure, type of hospitalization and functional class, but not SC. However, in the lower part of the table, when we created a multivariate model without SC, CC was in the model, achieving an accuracy of 0.768.

Table 4 – Expected morbidity by creatinine clearance adjusted for observed morbidity

		morbi = 1		morbi = 0	
Group	Total	Observed	Expected	Observed	Expected
1	333	7	5.30	326	327.70
2	339	12	10.68	327	328.32
3	343	16	14.52	327	328.48
4	310	18	16.47	292	293.53
5	328	19	20.86	310	307.14
6	319	17	24.08	302	294.92
7	333	21	29.56	312	303.44
8	341	39	36.18	302	304.82
9	323	41	42.06	282	280.94
10	324	74	63.30	250	260.70

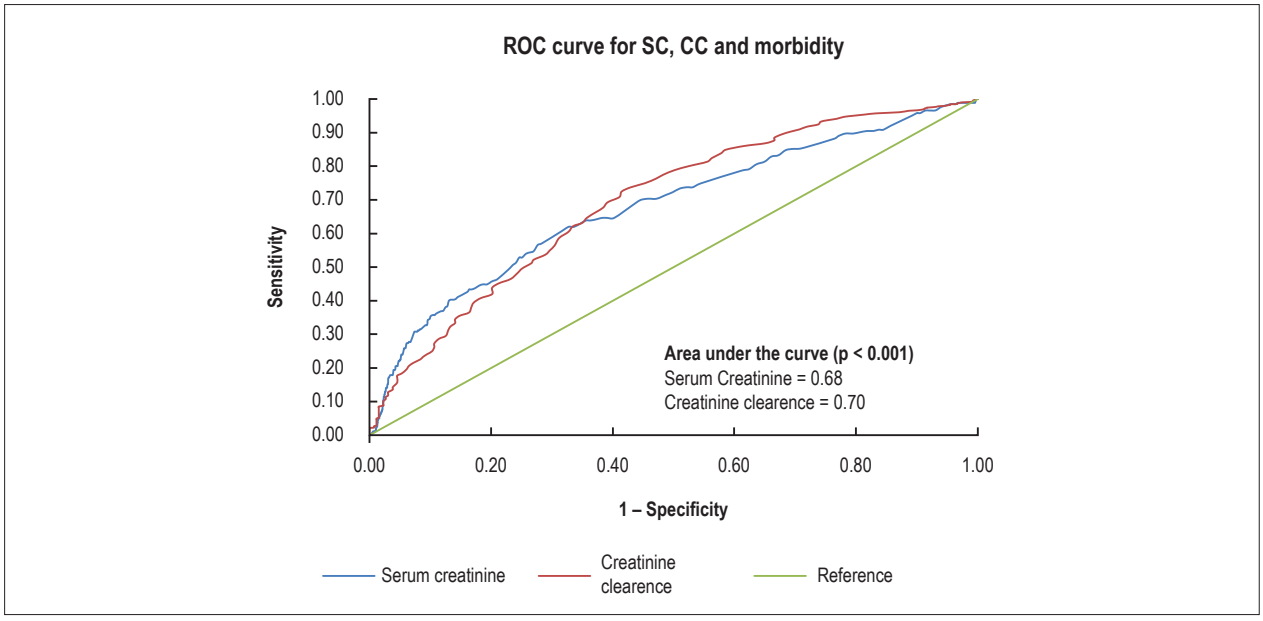

Figure 2 – *ROC curve for serum creatinine, creatinine clearance and morbidity.*

Multivariate model for morbidity

We can see in the upper part of the Table 6 that, when we created a multivariate model for morbidity without CC, the independent predicting variables were age, hematocrit, and SC, achieving an accuracy of 0.68. However, in the lower part of the table, it is shown that when we created a multivariate model without SC, CC was in the model, achieving an accuracy of 0.70.

Discussion

'In patients undergoing cardiac surgery, renal function has an influence on mortality prediction.[2] Many preoperative risk predictive models in patients undergoing cardiac surgery have confirmed the importance of renal function as a mortality predictor. In these models, ARF, necessity of dialysis and SC, used as categorical variables, are considered risk factors.

SC levels are affected by numerous factors that are independent of glomerular filtration rate: tubular secretion and reabsorption, endogenous production, irregular diet, extrarenal elimination, laboratory diagnostic techniques, and medications.[15,16] Since assessment of renal function based on SC is associated with several limitations,[16,17] and measurement of urinary CC takes a long time, many equations to estimate glomerular filtration rate using SC, body weight, age, sex and ethnic characteristics have been developed. All these equations, however, exhibit some limitations.

Table 5 – Multivariate model for mortality

Without Creatinine clearance:

		Confidence interval 95%	
Effect	**Risk estimation**	**Lower limit**	**Highest Limit**
Age	1.047	1.028	1.066
Hematocrit	0.924	0.891	0.958
Pulmonary artery pressure	1.020	1.008	1.032
Urgency Emergency	2.341	1.518	3.611
Functional class III/IV	2.136	1.063	4.292

Accuracy = 0.762

Multivariate model for mortality without Serum creatinine:

		Confidence interval 95%	
Effect	**Risk estimation**	**Lower limit**	**Highest Limit**
Age	1.038	1.019	1.058
Hematocrit	0.935	0.900	0.971
Pulmonary artery pressure	1.018	1.006	1.030
Creatinine clearance	0.989	0.978	0.999
Urgency Emergency	2.163	1.393	3.358
Functional class III/IV	2.087	1.037	4.198

Accuracy = 0.768

Table 6 – Multivariate model for morbidity

Without Creatinine clearance:

		Confidence interval 95%	
Effect	**Risk estimation**	**Lower limit**	**Highest Limit**
Age	1.028	1.011	1.046
Hematocrit	0.940	0.908	0.973
Serum creatinine	1.127	1.018	1.240

Accuracy = 0.68

Modelo multivariado para morbidade sem Serum Creatinine:

		Confidence interval 95%	
Effect	**Risk estimation**	**Lower limit**	**Highest Limit**
Creatinine clearance	0.971	0.962	0.980

Accuracy = 0.70

The most frequently used method to assess renal function in Medicare and in the national transplant waiting list in the US[18] is the Cockcroft-Gault formula. This formula is not absolutely precise (e.g. in elderly patients) and may either overestimate or underestimate the renal function.[15,19] Many studies on heart and renal failure showed a good correlation between CC estimated by the Cockcroft-Gault formula and the glomerular filtration rate.[20,21] Due to its wide acceptance, this formula was chosen to be used in REPLICCAR.

It is worth mentioning that we performed binary analysis of CC (< 55 mL/min), which did not show any difference in comparison with continuous analysis of the variable. Nevertheless, in patients with SC ≥ 1.35 mg/dL, observed mortality was greater than expected mortality, reaching values

two times greater than in patients with SC ≥ 1.60 mg/dL. Although SC has been used by Brazilian health care centers,[22,23] even as a criteria of ARF stage classification,[24] it should be analyzed with caution due to its lack of calibration in predicting mortality. This should start with the inclusion of CC in local risk scores, in which SC is still used as a binary data.

CC had greater predictive power for both mortality and morbidity than SC, assessed by the area under the ROC curve. However, there are difficulties in detecting differences between the variables by analysis of the standard deviation of the ROC curve. To address this issue, we constructed multivariate models by multiple regression to first evaluate the influence of CC on other variables, and then the influence of SC. In mortality model, regression analysis showed that when CC was excluded, SC was not an independent predicting variable, which suggests its inefficacy in this analysis. On the other hand, when SC was excluded, CC was not only an independent predicting variable, but also the only predictor in this model. This reinforces the importance of CC in the preoperative assessment, which has also been demonstrated in other studies performed in Brazil.[24] Therefore, local models should also follow the tendency to include CC, similar to international scores.

Estimation of expected morbidity and mortality by the risk models, as well as their relationship with observed morbidity and mortality using NLS and RAMQ, represent effective analytical tools in the assessment of potential influence on morbidity and mortality (e.g. in detecting diseases in the preoperative period, choosing the type of surgery etc.).

CC, which is currently considered in EuroSCORE II, even as categories, has already been included in REPLICCAR as continuous variable and undoubtedly should be included in future risk models developed in Brazil. Therefore, there should be a preference for the use of CC, calculated by the Cockcroft-Gault equation over SC in the preoperative assessment of renal function.

The only clear limitation of this study is the fact that this was not a randomized study, which could specifically evaluate the impact of each variable. Although prospective registry is the most robust method for this type of analysis, it is worth to note that these results should be validated before being applied in other types of procedures and populations, as in pediatric population.

Conclusion

This study shows that SC values greater than 1.6 underestimate the risk of hospital morbidity and mortality in patients undergoing coronary and/or valve surgery in Sao Paulo state. We encourage the calculation of CC for a more accurate, individualized assessment of renal function, aiming a better planning and optimization of perioperative care.

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Author contributions

Conception and design of the research: Nakazone M, Pomerantzeff PMA, Arthur CPS; Acquisition of data: Mejia OAV, Goncharov M, Dallan LAO, Osternack D, Jatene FB, Arthur CPS; Analysis and interpretation of the data: Mejia OAV, Lisboa LAF, Goncharov M, Dallan LAO, Nakazone M, Pomerantzeff PMA; Statistical analysis: Mejia OAV, Goncharov M; Writing of the manuscript: Arthur CPS; Critical revision of the manuscript for intellectual content: Mejia OAV, Lisboa LAF, Dallan LAO, Nakazone M, Osternack D, Pomerantzeff PMA, Jatene FB.

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.

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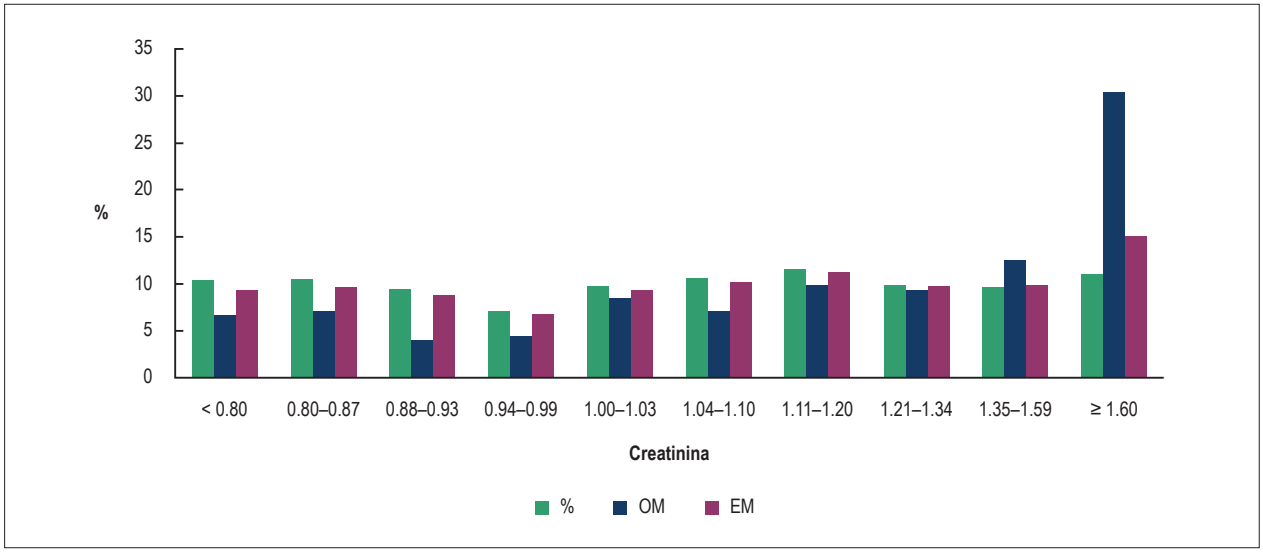
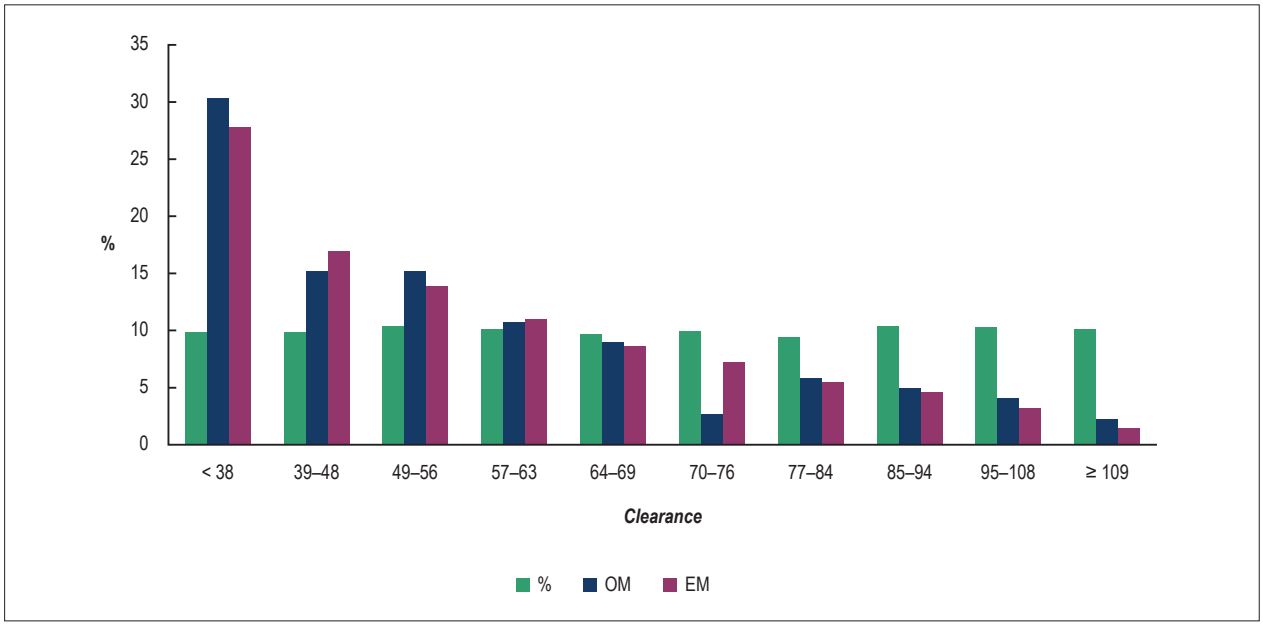


Supplementary Figure A – *Percentage of patients, observed mortality (OM) and expected mortality (EM) for serum creatinine groups.*



Supplementary Figure B – *Percentage of patients, observed mortality (OM) and expected mortality (EM) for serum creatinine clearance groups.*

Pre-Frailty Increases the Risk of Adverse Events in Older Patients Undergoing Cardiovascular Surgery

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Abstract

Background: **Frailty is identified as a major predictor of adverse outcomes in older surgical patients. However, the outcomes in pre-frail patients after cardiovascular surgery remain unknown.**

Objective: **To investigate the main outcomes (length of stay, mechanical ventilation time, stroke and in-hospital death) in pre-frail patients in comparison with no-frail patients after cardiovascular surgery.**

Methods: **221 patients over 65 years old, with established diagnosis of myocardial infarction or valve disease were enrolled. Patients were evaluated by Clinical Frailty Score (CFS) before surgery and allocated into 2 groups: no-frailty (CFS 1–3) vs. pre-frailty (CFS 4) and followed up for main outcomes. For all analysis, the statistical significance was set at 5% ($p < 0.05$).**

Results: **No differences were found in anthropometric and demographic data between groups ($p > 0.05$). Pre-frail patients showed a longer mechanical ventilation time (193 ± 37 vs. 29 ± 7 hours; $p<0.05$) than no-frail patients; similar results were observed for length of stay at the intensive care unit (5 ± 1 vs. 3 ± 1 days; $p < 0.05$) and total time of hospitalization (12 ± 5 vs. 9 ± 3 days; $p < 0.05$). In addition, the pre-frail group had a higher number of adverse events (stroke 8.3% vs. 3.9%; in-hospital death 21.5% vs. 7.8%; $p < 0.05$) with an increased risk for development stroke (OR: 2.139, 95% CI: 0.622–7.351, $p = 0.001$; HR: 2.763, 95%CI: 1.206–6.331, $p = 0.0001$) and in-hospital death (OR: 1.809, 95% CI: 1.286–2.546, $p = 0.001$; HR: 1.830, 95% CI: 1.476–2.269, $p = 0.0001$). Moreover, higher number of pre-frail patients required homecare services than no-frail patients (46.5% vs. 0%; $p < 0.05$).**

Conclusion: **Patients with pre-frailty showed longer mechanical ventilation time and hospital stay with an increased risk for cardiovascular events compared with no-frail patients. (Arq Bras Cardiol. 2017; 109(4):299-306)**

Keywords: **Aging; Cardiovascular Surgery; Adverse Events; Fragility.**

Introduction

Frailty is characterized as a multidimensional syndrome with decline in physiologic and cognitive status.[1] In addition, pre-frailty and frailty have been described as biological syndromes resulting from the dysregulation of multiple metabolic pathways.[1-3]

Recent data have revealed a significant association between pre-frailty and the risk of cardiovascular disease - with 25–50% more cardiovascular events in frail older individuals than in healthy elderly subjects[2] - irrespective of any classical cardiometabolic risk factors, suggesting that pre-frailty should be targeted as a potentially reversible risk factor for cardiovascular diseases in the older population.[1]

In recent years, the number of older patients undergoing cardiovascular surgery has increased, and the number of complications from cardiovascular surgery in this population is higher compared with younger patients.[4,5] A comprehensive preoperative assessment is essential in order to determine the risks and benefits of surgical intervention in this population; however, current methods of risk stratification have some limitations.[6,7]

Frailty has also been consistently identified as a major predictor of adverse outcomes in older surgical patients.[4,8] Higher levels of frailty lead to increased risk during the postoperative period, with more time on mechanical ventilation, longer hospital stay, and more postoperative complications (stroke and death) compared with patients with low frailty levels.[3] However, most studies have focused exclusively on demonstrating that patients with frailty are more susceptible to adverse events than patients without frailty after cardiovascular surgery,[8] while the outcomes for patients in early stages of frailty (pre-frailty) are still unknown.

Therefore, we aimed to investigate the main outcomes after cardiovascular surgery in pre-frail patients compared with non-frail patients. We hypothesized that pre-frail patients have a higher incidence of cardiovascular events compared with non-frail patients. Early detection of pre-frailty enables a more careful preoperative classification of these individuals and encourages the development of prevention programs in this population.

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Methods

The present investigation was conducted as a prospective observational study. A convenience sample of 283 patients over 65 years of age were enrolled in this study. All patients had an established diagnosis of cardiovascular disease (myocardial infarction, valve regurgitation or stenosis), determined by previous electrocardiogram and/or Doppler echocardiography, and all had surgical indications (coronary artery bypass [CAB], valve replacement or valve repair, or combined surgery). Patients with prior neurological disease (previous stroke or muscular dystrophies), cognitive impairment resulting from previous injury, frailty score ≥ 5, non-elective/emergency surgery procedures and patients who refused to participate in the study were excluded.

Twenty-four hours before elective surgery, frailty of all patients was assessed by Clinical Frailty Score (CFS) (Chart 1), which was performed by a single physiotherapist, previously trained. All patients were able to participate in the assessment in an active way. Then, the patients were allocated into two groups: no-frailty (CFS 1∼3) and pre-frailty (CFS 4).[9,10] The CFS is a practical, efficient and validated scale that measures frailty. It was developed to provide clinicians with an easily applicable tool to stratify older adults according to level of vulnerability.[11]

All patients were admitted to the intensive care unit (ICU) after undergoing cardiovascular surgery. Heart rate, mean arterial pressure, and oxyhemoglobin saturation by pulse oximetry (SpO_2) were measured with a Dixtal monitor (DX 2010®), and all of them were followed up (60 days) for hospital discharge or major adverse cardiovascular events: stroke, infection and in-hospital death. In addition, length of stay, duration of mechanical ventilation, use of vasopressor agents, and the need for home-based physiotherapy services after hospital discharge were also evaluated.

The study was approved by the Institutional Ethics Committee (registration number – 1048554). Written informed consent was obtained from all participants.

Statistical analysis

Statistical analysis was carried out using the SPSS program (version 20; SPSS Inc.). Data are expressed as mean ± standard deviation and percentage, as appropriate. The Kolmogorov-Smirnov test was used to determine normality of the data distribution; the non-paired t test and the χ^2 test were used to assess differences in categorical data.

The survival variables were compared using the log rank test, and Kaplan–Meier survival curves were constructed. Subsequently, Cox regression models were used to assess the relationship between baseline (surgery data) frailty and mortality. Follow-up time was calculated in days from the date of the baseline measurement to the date of a major adverse cardiovascular event. The odds ratio (OR), hazard ratio (HR), and 95% confidence intervals (95% CIs) were calculated. For all of the analysis, the statistical significance was set at 5% ($p < 0.05$).

Results

A total of 283 patients who underwent elective cardiovascular surgery were enrolled in this study, and of these 62 patients were excluded: 11 patients refused to participate, 17 patients had a CFS > 5, 22 patients had their post-surgery data lost, and 12 patients underwent non-elective/emergency surgical procedures. Thus, 221 patients were included in the study: 144 with pre-frailty and 77 without frailty.

Baseline characteristics are shown in Table 1. There were a higher percentage of male patients in both groups, and body mass index was slightly increased in the pre-frail group than in patients without frailty. None of the patients had heart failure or renal insufficiency prior to surgery. Moreover, there were no differences in CAB or valve replacement surgery between groups (Table 1). In addition, cardiopulmonary bypass time and cross-clamping time during procedures (extracorporeal circulation) were similar between pre-frailty and no-frailty groups (Table 1).

No differences in hemodynamic values or blood samples were observed between the groups after admission to the ICU (Table 1). However, pre-frailty group had a higher number of patients using vasopressor medications compared with no-frailty group (Table 2). A longer time in mechanical ventilation, with more patients in prolonged ventilation, as well as longer ICU and total hospital length of stay was observed in the pre-frailty group compared with the group

1 Very Fit – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 Well – People who have no active disease symptoms but are less fit than category 1. Often, they exercise or are very active occasionally, e.g. seasonally.

3 Managing Well – People whose medical problems are well controlled, but are not regularly active beyond routine walking.

4 Vulnerable – While not dependent on others for daily help, often symptoms limit activities. A common complaint is being "slowed up", and/or being tired during the day.

5 Mildly Frail – These people often have more evident slowing, and need help in high order IADLs (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 Moderately Frail – People need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (cuing, standby) with dressing.

7 Severely Frail – Completely dependent for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 Very Severely Frail – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9 Terminally ill - Approaching the end of life. This category applies to people with a life expectancy <6 months, who are not otherwise evidently frail.

Chart 1 – *Clinical Frailty Scale. Adapted from Rockwood[9] and McDermid.[10]*

Table 1 – Patients' characteristics

	No-frailty (n = 77)	Pre-frailty (n = 144)	p value
Anthropometrics/Demographics			
Male, n (%)	52 (67.5%)	93 (64.5%)	0.26
Age, years	70 ± 2	72 ± 4	0.42
Weight, kg	69.3 ± 9.8	73.4 ± 14.3	0.02
Height, m	1.64 ± 0.09	1.63 ± 0.10	0.76
BMI, kg/m^2	25.4 ± 2.6	27.1 ± 3.9	0.001
LVEF, %	54 ± 12	55 ± 11	0.52
Euro Score	2 ± 0.5	6 ± 0.4	< 0.001
ASA	2 ± 0.3	3 ± 0.6	< 0.001
Main comorbidities			
Hypertension, n (%)	58 (75.3%)	120 (83.3%)	0.01
Type II Diabetes, n (%)	27 (35%)	56 (38.8%)	0.12
Dyslipidemia, n (%)	33 (42.8%)	66 (45.8%)	0.38
Smoker, n (%)	14 (18.2%)	16 (11.1%)	0.09
Surgical data			
Coronary artery bypass, n (%)	41 (53.2%)	83 (57.6%)	0.65
Valve replacement, n (%)	25 (32.4%)	42 (29.2%)	0.42
Coronary artery bypass + valve replacement, n (%)	11 (14.2%)	19 (13.2%)	0.71
Activated partial thromboplastin time, s	27 ± 6	25 ± 7	0.19
Cardiopulmonary bypass time, min	100 ± 40	90 ± 39	0.17
Cross-clamp time, min	73 ± 26	63 ± 31	0.12
Baseline hemodynamic and blood measurements			
HR, bpm	97 ± 22	93 ± 19	0.21
MAP, mmHg	98 ± 11	101 ± 14	0.43
Hemoglobin, g/dL	10.7 ± 2.1	10.8 ± 1.7	0.68
Hematocrit, %	33.2 ± 6.0	33.9 ± 8.7	0.49
Platelets, mm^3	143,126 ± 60,725	146,726 ± 53,742	0.64
Creatinine, mg/dL	1.16 ± 0.50	1.27 ± 0.54	0.54
hs-CRP, mg/L	8.8 ± 0.8	9.0 ± 0.8	0.86
PaO_2, mmHg	118 ± 5	117 ± 9	0.90
$PaCO_2$, mmHg	42 ± 11	39 ± 8	0.06
HCO_3^-, mmol/L	22 ± 2	21 ± 3	0.53
SpO_2, %	96 ± 4	97 ± 3	0.37

Definition of abbreviations: BMI: body mass index; LVEF: left ventricular ejection fraction; ASA: American society of anesthesiologists; HR: heart rate; MAP: mean arterial pressure; hs-CPR: high sensitive c-reactive protein; PaO_2: arterial oxygen pressure; $PaCO_2$: arterial carbon dioxide pressure; HCO_3^-: bicarbonate; SpO_2: oxyhemoglobin saturation by pulse oximetry. Values are expressed in mean ± standard deviation or frequency. Non-paired t student test was applied to variables described as mean ± standard deviation and the χ^2 test was used to assess differences of frequencies in categorical variables.

without frailty. In addition, in the pre-frailty group, there was a higher incidence of cardiovascular events and a greater number of patients with stroke and in-hospital deaths than in the no-frailty group (Table 2).

Kaplan–Meier analysis showed that cumulative events were significantly higher in patients with pre-frailty, both in stroke (Figure 1) and in-hospital deaths (Figure 2). Moreover, the OR and HR indicated an increased risk for stroke and in-hospital deaths in patients with higher frailty scores (pre-frailty group; Table 3).

Discussion

In the present study, we investigated the relationship between pre-frailty and adverse postoperative outcomes following cardiovascular surgery. The main and new findings of the present study were: 1) Pre-frailty patients have more cumulative events than no-frailty patients, both in stroke and in-hospital deaths, and 2) Pre-frailty patients have longer mechanical ventilation time and hospital stay compared with the no-frailty patients. These findings are strongly relevant, as there are no previous studies that have demonstrated a relationship between pre-frailty and adverse postoperative outcomes in cardiovascular surgery.

Our results contribute to understanding whether the extent of premorbid deficit accumulation adds prognostic value in patients after cardiovascular surgery. Currently, more than half of all cardiovascular surgeries are performed on patients over 75 years.[12] A recent systematic review[13] showed that the incidence of frailty increased steadily with age (65–69 years: 4%; 70–74 years: 7%; 75–79 years: 9%; 80–84 years: 16%; and older than 85 years: 26%), as a consequence of age-related decline in many physiological systems, which collectively results in vulnerability to sudden changes in health status triggered by minor stressor events.[2] It also has been demonstrated that these patients have an increased risk of falls, prolonged hospitalization and mortality after surgery.[14] Moreover, previous data have shown that each one-point increase in frailty score is associated with increased incidence of functional limitation and higher mortality risk in six months.[15] A prospective study showed that 47% of a total cohort of 5,210 patients over 65 years of age were classified as pre-frailty (phenotype model), with an increased mortality rate (23%) during seven years of follow-up.[16] Sundermann et al.[17] reported that pre-frailty patients have an intermediate outcome between frailty and no-frailty patients. In addition, pre-frailty has been associated with a four-fold higher risk of becoming frail over a four-year follow-up period[16]. Sergi et al.[1] found that patients with pre-frailty have more cardiovascular diseases compared with no-frailty patients. However, most of frailty studies on postoperative outcomes have only compared frailty versus no-frailty patients.[1,18,19] In this context, the present study extends the knowledge regarding pre-frailty patients. Over a short follow-up period, pre-frailty patients who underwent cardiovascular surgery had more major adverse cardiovascular events and in-hospital deaths than no-frailty patients. Thus, our study presents new evidence suggesting that pre-frailty patients should be better evaluated and rehabilitated prior to cardiovascular surgery.

In our study, pre-frailty patients undergoing cardiovascular surgery had a higher incidence of stroke. In fact, this is a common finding in the scientific literature, and has been

Table 2 – Prospective data observed at the intensive care unit and until hospital discharge in no-frail and pre-frail groups

	No-frailty (n = 77)	Pre-frailty (n = 144)	p value
Length of stay			
Intensive care unit, days	3 ± 1	5 ± 1	0.03
Total time hospitalization, days	9 ± 3	12 ± 5	< 0.001
Mechanical ventilation			
Time in Mechanical ventilation, hours	29 ± 7	193 ± 37	0.001
Prolonged time in mechanical ventilation, n (%)	0	21 (14.5%)	0.001
Vasopressor			
Noradrenaline, n (%)	26 (33.8%)	46 (31.9%)	0.87
Dobutamine, n (%)	8 (10.4%)	29 (20.1%)	0.03
Dopamine, n (%)	14 (18.2%)	15 (10.4%)	0.08
Nitroglicerine, n (%)	8 (10.4%)	20 (13.8%)	0.24
Adverse events			
Infection, n (%)	4 (5.2%)	7 (4,8%)	0.69
Stroke, n (%)	3 (3.9%)	12 (8.3%)	0.02
In-hospital deaths, n (%)	6 (7.8%)	31 (21.5%)	0.001
Home care facility			
Physiotherapy, n (%)	0	67 (46.5%)	< 0.001

Values are expressed in mean ± standard deviation or frequency. Non-paired t student test was applied to variables described as mean ± standard deviation and the χ^2 test was used to assess categorical data differences in frequency variables.

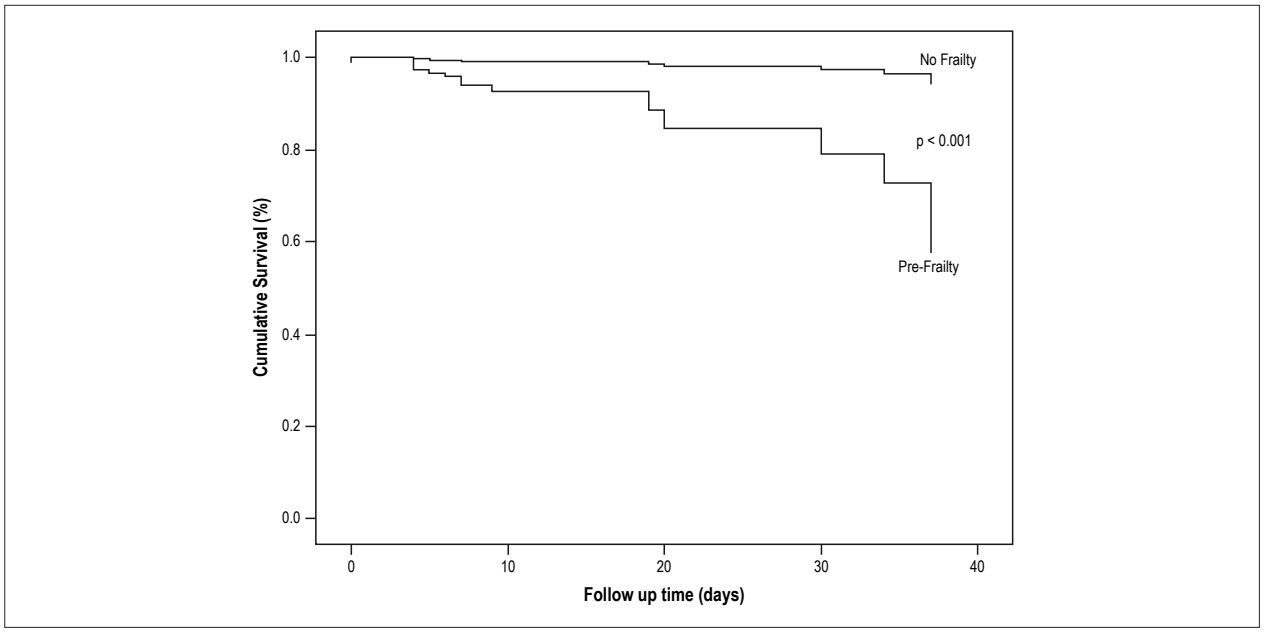

Figure 1 – *Cumulative survival of stroke events between no-frail and pre-frail groups.*

related to aging[20] and intraoperative period, although previous studies have not evaluated frailty or pre-frailty.[21] Actually, frailty patients undergoing non-cardiovascular surgery had more intraoperative cerebral desaturation compared with no-frailty patients,[22] and older patients with comorbidities such as hypertension and diabetes might be at increased risk due to changes in autoregulation of cerebral blood flow.[23] Our data are in line with current literature that suggests that pre-frailty patients undergoing a valve replacement present a higher incidence of stroke compared to patients submitted to CAB, this fact can be explained due to the higher cardiopulmonary bypass and anoxia time during surgery. Interestingly, 25% of pre-frailty patients with stroke progressed to death during the hospitalization period, demonstrating that patient's pre-morbid health status is an important point to be evaluated and may influence the prognosis after a critical event. Furthermore, they were more likely to experience cerebrovascular events and prolonged mechanical ventilation. In this context, it is highly likely that these findings explain the high incidence of stroke in the pre-frailty group in our study. Also, the higher percentage of hypertension and diabetes observed in this group might be related to an increased incidence of cerebrovascular events in these patients.

It is well established that prolonged mechanical ventilation has been related to new deficits or worsening of pre-existing deficits associated with the frailty syndrome in critically ill patients, that persist even after resolution of the critical condition,[24] regardless of the use of invasive or non-invasive ventilation.[15,25] Our patients with pre-frailty had higher mechanical ventilation time. In fact, increased mechanical ventilation time might be a consequence of the main complications found in our study.

Moreover, prolonged mechanical ventilation is associated with impaired functionality, longer hospitalization period and higher incidence of in-hospital deaths.[26] It has been demonstrated that more than 80% of these patients require a second hospitalization within 12 months of discharge from the ICU[26] with high incidence of six-month mortality.[27,28] Furthermore, those patients who survive may have worsened functional capacity for almost five years after hospital discharge.[29] Although it is out of scope of our study to follow up patients after hospital discharge, the pre-frailty group had longer hospital length of stay, required treatment in skilled or assisted-living facility, including physiotherapy and rehabilitation after discharge. Together, these findings suggest that this group is on increased risk of re-hospitalization and/or death in a short period of time.

Clinical implications

Frailty is recognized as a multi-dimensional syndrome characterized by the loss of reserves (physical and cognitive) that result in vulnerability. The CFS is an easy-to-use frailty scale for risk stratification of older adults that enables the assessment of frailty-related outcomes even in the preoperative period, and may improve treatments and interventions, prevent possible complications, and reduce the length of stay.

Our study presents important clinical findings, as frailty is a reversible condition when treated in the early stages with interventions such as exercise. These interventions are effective and might delay the transition from pre-frailty to frailty.[30] Exercise prior to cardiovascular surgery may also contribute to better recovery in ICU.

In addition, our study emphasizes the need to incorporate a frailty evaluation before cardiovascular surgery, in order to better understand the risks to these older patients and to guide specific interventions in the preoperative period to minimize the risk of adverse events, even in patients in the early stages of frailty.

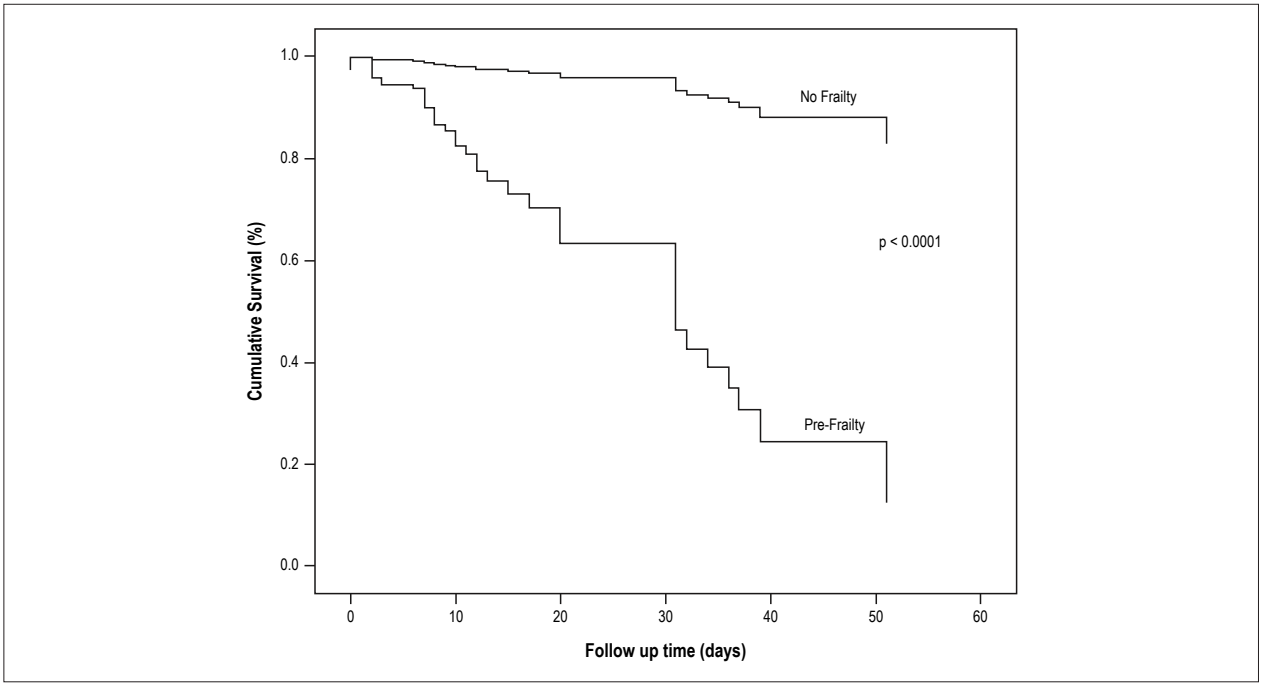

Figure 2 – *Cumulative survival of in-hospital deaths events between no-frail and pre-frail groups.*

Table 3 – Odds ratio and hazard ratio for stroke and in-hospital deaths in the pre-frail group

	OR	95%CI	p value
Stroke	2.139	0.622 – 7.351	0.001
In-hospital deaths	2.763	1.206 – 6.331	0.0001
	HR	**95%CI**	**p value**
Stroke	1.809	1.286 – 2.546	0.001
In-hospital deaths	1.830	1.476 – 2.269	0.0001

OR: odds ratio; HR: hazard ratio; IC: interval of confidence.

Study limitations

This study has some limitations that should be addressed. There is a blank in the recent literature regarding the best evaluation criteria for frailty. There is significant heterogeneity among frailty criteria in clinical trials, thus making it more difficult to recognize and identify frailty in post-surgical patients.[31]

Pre-frailty group had a larger number of patients than no-frailty group. To rule out the possibility that this issue might affect our findings, statistical power for the main outcomes was calculated and revealed a power of 99.98% for total time hospitalization and 74.22% for in-hospital death.

A recent study showed that widely used scores (Acute Physiology Score and Acute Physiology and Chronic Health Evaluation) failed to predict higher death risk.[32] However, frailty, when associated to traditional risk scales (ASA, Eagle and Lee), is an independently predictor of postoperative complications, length of stay, and requirement of skilled or assisted-living care after hospital discharge in older surgical patients.[8] Our study took care to evaluate some types of risk scale: CFS, ASA and EuroScore, and all of them were increased in patients that had worse outcomes. Furthermore, frailty was able to predict major cardiovascular events in post-cardiac surgery, even in patients with early stages of frailty.

There are two frailty models: phenotype and cumulative deficit models. We decided to use just the CFS because it is readily available at the bedside and is easier to understand and use than other frailty assessment tools. Moreover, the CFS has been considered an optimal tool for use on admission to the ICU.[10]

Conclusion

Patients with pre-frailty showed longer mechanical ventilation time, longer ICU and hospital length of stay, and higher requirement for home-based physiotherapy services than no-frailty patients after cardiovascular surgery.

Moreover, the presence of pre-frailty on pre-operative period predicts more cumulative events (stroke or in-hospital death). However, it remains unknown whether pre-frailty treatment before cardiovascular surgery is effective to prevent cumulative outcomes.

Author contributions

Conception and design of the research: Rodrigues MK, Oliveira MF; acquisition of data: Marques A, Umeda IIK, Oliveira MF; analysis and interpretation of the data: Rodrigues MK, Marques A, Lobo DML, Umeda IIK, Oliveira MF; statistical analysis: Rodrigues MK, Lobo DML; writing of the manuscript: Rodrigues MK, Marques A, Lobo DML; critical revision of the manuscript for intellectual content: Umeda IIK, Oliveira MF.

Potential Conflict of Interest

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

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Angiotensin-Converting Enzyme ID Polymorphism in Patients with Heart Failure Secondary to Chagas Disease

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Abstract

Background: Changes in the angiotensin-converting enzyme (ACE) gene may contribute to the increase in blood pressure and consequently to the onset of heart failure (HF). The role of polymorphism is very controversial, and its identification in patients with HF secondary to Chagas disease in the Brazilian population is required.

Objective: To determine ACE polymorphism in patients with HF secondary to Chagas disease and patients with Chagas disease without systolic dysfunction, and to evaluate the relationship of the ACE polymorphism with different clinical variables.

Methods: This was a comparative clinical study with 193 participants, 103 of them with HF secondary to Chagas disease and 90 with Chagas disease without systolic dysfunction. All patients attended the outpatient department of the General Hospital of the Federal University of Goias general hospital. Alleles I and D of ACE polymorphism were identified by polymerase chain reaction of the respective intron 16 fragments in the ACE gene and visualized by electrophoresis.

Results: In the group of HF patients, 63% were male, whereas 53.6% of patients with Chagas disease without systolic dysfunction were female (p = 0.001). The time from diagnosis varied from 1 to 50 years. Distribution of DD, ID and II genotypes was similar between the two groups, without statistical significance (p = 0.692). There was no difference in clinical characteristics or I/D genotypes between the groups. Age was significantly different between the groups (p = 0.001), and mean age of patients with HF was 62.5 years.

Conclusion: No differences were observed in the distribution of (Insertion/Deletion) genotype frequencies of ACE polymorphism between the studied groups. The use of this genetic biomarker was not useful in detecting a possible relationship between ACE polymorphism and clinical manifestations in HF secondary to Chagas disease. (Arq Bras Cardiol. 2017; 109(4):307-312)

Keywords: Chagas Disease; Polymorphism, Genetic; Heart Failure; Chagas Cardiomyopathy.

Introduction

Chagas disease has characteristics of an endemic disease and is an important cause of dilated heart disease and heart failure (HF) in regions of low socioeconomic level, leading to high mortality and morbidity rates. Early diagnosis and treatment are important to improve survival rates and quality of life.[1]

Chagas disease was considered the main cause of HF in central-western region of Brazil.[2,4] Sudden cardiac death affects approximately 50% of patients with HF secondary to Chagas disease.[5]

Most human health problems, including HF, have a multifactorial etiology, influenced by environmental and genetic factors, and life style. Multifactorial disorders are characterized by phenotypic contributions of several genes that interact to each other and to environmental factors. Many disorders manifested in adults are inherited in an autosomal dominant fashion, including familial cardiomyopathy.[6]

Angiotensin-converting enzyme (ACE) gene (21 kb) is located in the chromosome 17, long arm, region 23, and contains 24 introns.[7] It would be ideal to predict the individual response to therapy as well as the potential adverse effects of drugs in the treatment of HF. With advances in molecular biology and genetics, there has been an increasing need for a redefinition of diseases based on their biochemical processes rather than their phenotypic features. Hence, knowledge and treatment of heart diseases, and isolation and characterization of the genes involved may not be a panacea anymore, but rather, a starting point for an individualized treatment.

In this context, the present study aimed to determine the distribution of the ACE gene polymorphism (I/D) in HF secondary to Chagas Disease, compare it with that in Chagas Disease patients free of systolic dysfunction, and evaluate its relationship with clinical variables.

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Ethical aspects

The study was analyzed and approved by the Research Ethics Committee of the General Hospital of the Federal University of Goias on December 16th, 2014 (approval number 908870).

Study design

This was a comparative, clinical study conducted with two groups of patients (group A and group B) attending the cardiology and the Chagas disease outpatient clinics of the General Hospital of the Federal University of Goias. Patients were recruited to the study from February 2014 to October 2015.

Patients

A total of 193 outpatients were consecutively recruited, 103 with chagasic heart disease (group A) and 90 Chagas disease patients without systolic dysfunction (group B).

Inclusion criteria

Group A: patients with symptomatic HF (according to Framingham criteria) secondary to Chagas disease; group B: patients with diagnosis of Chagas disease, free of systolic dysfunction.

Exclusion criteria

Cardiac dysfunction in group B.

Clinical and laboratory parameters

All clinical data were collected from patients' medical records. Recent laboratory, echocardiography and Doppler echocardiography results were used to determine patients' current health status.

In HF patients, functional class was determined using the New York Heart Association criteria, by the outpatient medical staff. With respect to Doppler echocardiography, the following parameters were analyzed: left atrium (LA), left ventricular systolic diameter (LVSD), left ventricular diastolic diameter (LVDD), and left ventricular ejection fraction (LVEF).

Genotyping

Eight-mL blood samples were collected and stored in two tubes containing EDTA anticoagulant. Then, DNA extraction was performed, followed by ACE polymorphism genotyping by polymerase chain reaction (PCR), which was classified as D/D (deletion/deletion), I/D (insertion/deletion) or I/I (insertion/insertion).

Genotyping method was adapted from Lindpaintner et al.[8] For a final volume of 25 μL, 1 mM of primers, 200 mM of nucleoside triphosphates (dATP, dCTP, dGTP, dTTP), 1.3 mM of magnesium chloride, 50 mM of potassium chloride, 0.5 unit of Taq DNA polymerase and 20 ng of DNA were added. The sense primer GCCCTGCAGGTGTCTGCAGCATGT and the antisense primer GGATGGCTCTCCCCGCCTTGTCTC were used to amplify the alleles D and I, resulting in amplicons of 319 pb and 597 pb, respectively. The protocol of DNA amplification was composed of an initial denaturation at 94°C for 5 minutes, followed by 35 cycles – 30 seconds at 94°C, 45 seconds at 56°C, 2 minutes at 72°C. Then, the amplification products of D and I alleles were subjected to 1.5% agarose gel electrophoresis stained with 0.5 mg/mL ethidium bromide for 10 minutes. Due to the preferential amplification of D allele in heterozygous samples, all samples with a DD genotype were reanalyzed using the primers TGGGACCACAGCCGCGCCTACCAC and TCGGCCCTCCCACCACCATGCTAA (sense and antisense, respectively), at the same conditions of PCR, except for the annealing temperature of 67°C. Analysis of the PCR products by 1.5% agarose gel electrophoresis revealed an amplicon of 335pb with the allele I. The results were captured using the Image Master VDS® video documentation system (Pharmacia Biotech, EUA).

Statistical analysis

Descriptive analysis was used for characterization of the variables – categorical variables were described in percentages; continuous variables with normal distribution were described in mean ± standard deviation, and continuous variables without normal distribution were described in median and interquartile ranges. The Kolmogorov-Smirnov Z test was used to identify those variables with a normal distribution. Differences between groups A and B were calculated using the chi-square test or the unpaired Student's t-test, and the Mann-Whitney test as appropriate. The association between the variables of exposure to HF was measured by Odds Ratio (OR) and respective 95% confidence intervals. Differences between the groups were considered statistically significant when $p < 0.05$. Analyses were performed using the SPSS program, version 18.0.

Results

There was a significant difference in sex distribution between the groups ($p = 0.023$), and 63% of HF patients were men. Mean age of HF patients was 62.5 years ± 11.1 years, with significant difference between the groups ($p = 0.00$). Sociodemographic and clinical characteristics of patients are described in Table 1.

All patients with HF were receiving drug treatment and 73.2% were smokers, which was statistically different from group B ($p = 0.004$). With respect to the comorbidities associated with HF, there was a predominance of dyslipidemia (75%). Mean heart rate was higher in HF patients ($p = 0.030$) as compared with group B.

Megaesophagus was prevalent in group B only (61.7%), with significant difference between the groups ($p = 0.017$). The time elapsed since the diagnosis of Chagas disease was also statistically different between the groups ($p = 0.001$).

Genetic profile of the study population

In order to determine the prevalence of ACE polymorphism genotype between groups A and B, we analyzed the frequency of the DD, ID and II genotypes (Table 2). There was no statistically significant difference in the observed-to-expected genotype frequencies between the groups (0.692).

Table 1 – Sociodemographic and clinical characteristics of the sample

Variables	Group A		Group B		OR	95CI%	p-value
	n	%	n	%			
Sex							
Male	51	63.0	30	37.0	1.96	1.09-3.52	0.023[a]
Female	52	46.4	60	53.6			
Mean age (SD)	62.5	(11.1)	51.3	(11.9)			0.000[b]
Origin							
Goiania	59	54.6	49	45.4	1.12	0.64-1.98	0.692[a]
Others	44	51.8	41	48.2			
Median time elapsed from diagnosis of Chagas disease (interquartile range)	15	(8-25)	9.5	(5-17)			0.002[c]
Smoking							
Yes	30	73.2	11	26.8	2.95	1.38-6.32	0.004[a]
No	73	48.0	79	52.0			
Alcohol consumption							
Yes	21	42.0	29	58.0	0.34	0.28-1.03	0.061[a]
No	82	57.3	61	42.7			
Median heart rate (interquartile range) (bpm)	65	(60-80)	65	(60-80)			0.290[c]
Megaesophagus							
Yes	18	38.3	29	61.7	0.45	0.23-0.87	0.017[a]
No	85	58.2	61	41.8			
Megacolon							
Yes	9	64.3	5	35.7	1.63	0.53-5.05	0.395[a]
No	94	52.5	85	47.5			
Dyslipidemia							
Yes	15	75.0	5	25.0	2.90	1.01-8.32	0.041[a]
No	88	50.9	85	49.1			
Diabetes mellitus							
Yes	6	54.5	5	45.5	1.05	0.31-3.57	0.936[a]
No	97	53.3	85	46.7			

SD: standard deviation; Group A: patients with heart failure secondary to Chagas disease; Group B: patients with Chagas disease free of systolic dysfunction; bpm: beats per minute; OR: odds ratio; [a] chi-square test; [b] unpaired t-test; [c] Mann Whitney test

Table 2 – I/D polymorphism in groups A and B

Genotype	Group A		Group B		p-value
	N	%	N	%	
DD	17	50.0	17	50.0	0.692[a]
ID	59	56.2	46	43.8	
II	27	50.0	27	50.0	

DD: deletion/deletion; ID: insertion/deletion; II-insertion/insertion; group A: patients with heart failure secondary to Chagas disese; Group B: patients with Chagas disease without systolic dysfunction. a chi-square test.

Mean values of echocardiographic variables and genotypes were not statistically different between the groups. ID genotype carriers had greater mean LVDD as compared with other genotype carriers.

With respect to repeated measures of categorical data, there was no significant difference in functional class or I/D genotype (p = 0.472) between the groups. There were only four patients in functional class IV; functional class II was present in 86 patients, 52.3% of them belonged to ID genotype.

Megaesophagus was present in group B, with no difference in the number of patients with and without megaesophagus. Dyslipidemia was associated with a 5-time increased risk for HF patients. Genotypes DD, ID and II were not considered as a risk factor for HF, since their distribution was not statistically different between the groups.

Discussion

There are many conflicting results in the literature on what polymorphisms are involved in the susceptibility to the development and worsening of HF. In the present study, the role of ACE gene polymorphism (I/D) in patients with chagasic heart disease and in Chagas disease patients free of systolic dysfunction. In this population, ACE polymorphism was not associated with sociodemographic and clinical characteristics.

Male gender was predominant (63%) in our sample, similar to data reported in the literature.[9,10] The incidence of HF increases with age, and is more frequent among men.[11] The epidemic increase in HF among the older population has been associated with improved survival.[12]

There was no statistically significant difference in the genotype distribution between men and women in group A, which is in accordance with the study by Zhang et al.[13]

Current literature suggests an association of allele D with predisposition to HF,[14-16] which is in disagreement with our findings. HF patients had lower blood pressure than patients with Chagas disease without systolic dysfunction (p = 0.000), which is in agreement with the study by Yang et al.[17] who investigated ACE I/D genotype in a Chinese population. There were no significant differences in the frequency of alleles or genotypes between the groups in both sexes. HF patients with low blood pressure are at higher risk of death, despite adequate drug therapy.[18]

An independent association has been reported between DD genotype and worse echocardiographic outcomes, and between ID genotype and echocardiographic profile (increased left ventricular ejection fraction and decreased left ventricular diameters).[19] These findings are in disagreement with ours, as we did not find an association between D/I genotypes and echocardiographic findings.

In our study, although we investigated a population with different characteristics, no interaction between I/D and HF was found. This is in accordance with a previous study[20] including 241 patients in Saudi Arabia, in which ACE gene polymorphism was not associated with congenital heart disease.

HF is a common clinical condition with high morbidity and mortality rates. It affects 1.5-2.0% of the general population, and its prevalence increases with age, affecting approximately 10% of individuals aged over 65 years.[21] These data corroborate our findings, which showed that patients with HF were significantly older than patients with Chagas disease without systolic dysfunction.

In addition, Yang et al.[22] compared the distribution of I/D genotypes in 701 individuals of both sexes. No difference was found in the frequencies of genotypes and alleles in male and female between individuals aged over 90 years and a control group aged less than 60 years.

In the analysis of I/DI genotypes and LVSD, we did not find any relationship between these parameters. This is in disagreement with a national study[23] reporting increased LVSD in DD genotype patients, which was associated with increased mortality and morbidity in HF patients of different etiologies.

There was a possible interaction between ACE polymorphisms in chronic HF progression.[24] Allele D was associated with HF progression and higher mortality rate as compared with allele I.[24,25] These data are in contrast to our results, in which I/D genotypes were not associated with HF severity.

In our study, ACE polymorphism was not associated with the severity or progression of HF secondary to Chagas disease. This is in agreement with previous studies[26,27] in which ACE polymorphism was not associated with HF development or progression of Chagas cardiomyopathy.

Distribution of I/D genotypes was not different between groups A and B in our analysis. Individual genetic differences may lead to different risk profiles and small sample sizes, particularly in studies of association, with inadequate power to detect genetic contributions, which may explain the disagreement between studies.

DNA analysis tests may provide the identification of one or more genetic variants associated with increased risk for HF, and thereby contribute to preventive measures including changes in lifestyle and therapies that take into account the genetic profile.

Based on the potential use of the genetic marker in the clinical practice and the inconclusive results regarding the role of ACE polymorphism as a risk factor for the development of HF secondary to Chagas disease, this genetic marker was shown not to be useful in the clinical practice. The lack of association between I/D genotypes may indicate that ACE polymorphism does not act in the pathogenesis of ventricular dysfunction caused by Chagas disease.

Conclusion

There was no difference in the frequencies of I/D genotypes in patients with HF secondary to Chagas disease as compared with Chagas disease patients free of systolic dysfunction. No relationship was found between ACE polymorphism and clinical outcome measures.

Study limitations

The number of patients included in the present study may be considered small as compared with the estimated number of patients with Chagas disease in our country. Socioeconomic factors may interact with genetic factors and affect HF outcomes. Our findings were obtained from public health patients, which may limit the extrapolation of the results to other populations.

Further large, prospective studies involving larger samples sizes are needed to determine which variables may be related to HF secondary to Chagas disease.

Author contributions

Conception and design of the research, acquisition of data and statistical analysis: Silva SJ; Analysis and interpretation of the data and writing of the manuscript: Silva SJ, Rassi S, Pereira AC; Obtaining financing: Silva SJ, Pereira AC; Critical revision of the manuscript for intellectual content: Rassi S, Pereira AC.

Potential Conflict of Interest

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Study Association

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Twenty-four hour Blood Pressure in Obese Patients with Moderate-to-Severe Obstructive Sleep Apnea

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Abstract

Background: Obesity, systemic arterial hypertension (SAH) and obstructive sleep apnea (OSA) are closely related. Up to 70% of patients with OSA may be asymptomatic, and there is evidence that these patients have cardiovascular disease, especially nocturnal SAH.

Objectives: The aim of this study was to evaluate 24-hour blood pressure circadian variation in asymptomatic, obese individuals with moderate-to-severe OSA and compare it with that in individuals with mild OSA or without OSA.

Methods: Eighty-six obese subjects aged between 30 and 55 years (BMI 30-39 kg/m^2), with casual blood pressure < 140/90 mmHg and without comorbidities were recruited. Eighty-one patients underwent clinical and anthropometric assessment, ambulatory blood pressure monitoring (ABPM), and Watch-PAT. Participants were divided into two groups, based on the apnea-hypopnea index (AHI): group 1, with AHI < 15 events/hour, and group 2 with AHI ≥ 15 events/hour.

Results: Compared with group 1, group 2 had higher neck circumference and waist-hip circumference (40.5 ± 3.2 cm vs. 38.0 ± 3.7 cm, p = 0.002, and 0.94 ± 0.05 vs. 0.89 ± 0.05, p = 0.001, respectively), higher systolic and diastolic blood pressure measured by the 24-h ABPM (122 ± 6 vs 118 ± 8 mmHg, p = 0.014, and 78 ± 6 vs 73 ± 7 mmHg, p = 0.008, respectively), and higher nocturnal diastolic pressure load (44.6 ± 25.9% vs 31.3 ± 27.3%, p = 0.041). Moreover, there was a positive correlation between nocturnal diastolic blood pressure and AHI (r = 0.43, p < 0.05).

Conclusions: Asymptomatic obese subjects with moderate-to-severe OSA have higher systolic and diastolic blood pressure at 24 hours compared with those with absent / mild OSA, despite normal casual blood pressure between the groups. These results indicate that ABPM may be useful in the evaluation of asymptomatic obese patients with moderate-to-severe OSA. (Arq Bras Cardiol. 2017; 109(4):313-320)

Keywords: Blood Pressure; Sleep Apnea, Obstructive; Hypertension; Blood Pressure Monitoring, Ambulatory.

Introduction

Obstructive sleep apnea (OSA) is the most common sleep respiratory disorder[1,2] characterized by repetitive collapse of the upper airway that causes pauses in respiration and intermittent hypoxia.[2] During these nocturnal episodes of obstruction, there is an increase in sympathetic tonus and in the release of vasoactive substances, leading to increased risk of cardiovascular injury.[3]

A recent systematic review estimated that the prevalence of OSA is higher among men, and ranges from 9 and 38% in the general population.[4] In the study by Tufik et al.,[5] performed in the city of Sao Paulo, Brazil, OSA was observed in 32,8% of the participants. However, according to the classic study Sleep Health Study, many OSA patients are asymptomatic, as 70% of patients with mild apnea and 9% of those with severe apnea were asymptomatic.[6]

OSA is mostly related to obesity and systemic arterial hypertension (SAH).[2] Obese patients have higher prevalence of OSA and SAH[7] and the association of obesity with SAH may cause target-organ injury and cardiovascular events.[8,9] Studies have demonstrated that OSA patients have less nocturnal blood pressure (BP) dipping and nocturnal hypertension.[10,11] Most of these reports have included hypertensive patients with previous diagnosis of OSA. A previous study suggested a higher prevalence of masked hypertension (MH) in patients with OSA.[8] However, little is known about the 24-hour BP behavior in obese individuals with OSA and normal casual BP. The aim of this study was to assess 24-hour BP circadian variation in obese, asymptomatic subjects with moderate-to-severe OSA compared with subjects with mild OSA or without OSA.

Methods

Subjects

In the period from January to December 2014, individuals attending the internal medicine outpatient clinic of Piquet Carneiro Polyclinic of Rio de Janeiro State University (UERJ)

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were invited to participate in the study. Inclusion criteria were age between 30 and 55 years, body mass index (BMI) between 30 and 39.9 kg/m^2, normal casual BP (BP < 140/90 mmHg), and absence of comorbidities, and regular follow-up. Exclusion criteria were history of arterial hypertension or treatment for this condition, diabetes mellitus, pulmonary disease, Parkinson disease, previous therapy with continuous positive airway pressure (CPAP), and previous diagnosis of OSA.

The study was approved by the local ethics committee (*Plataforma Brasil*/*CAAE*: 03489612.1.0000.52590), and informed consent was obtained from all participants.

Study design

This was a cross sectional, observational study. At the first visit, patients underwent clinical, anthropometrical, and laboratory assessments, and diagnostic test for OSA. At the second visit, ambulatory blood pressure monitoring (ABPM) was performed, with a maximum interval of one-week between the visits.

Anthropometric measures

Body weight was measured with participants standing at the center of the platform, wearing light clothes and barefoot, using a Filizola® digital scale with maximum capacity of 180 kg.[12] Height was measured using the vertical rod attached to the same scale, with patients standing straight and heels together. Body mass index (BMI) was then calculated, by dividing body weight (kg) by height (m^2). Circumferences were measured using an inextensible, graduated measuring tape.[13] Neck circumference (NC) was at the level of cricoid cartilage; waist circumference (WC) was measured at the midpoint between the lower rib and the iliac crest at the end of expiratory phase of respiration. Hip circumference was measured at the femoral trochanters.[14] All measures were taken in cm and at the nearest 0.5 cm.

Blood pressure

Casual BP was measured using an electronic device (HEM-705CP, Omron Healthcare Inc., Lake Forest, IL, USA) and a cuff with adequate size, according to patient's arm circumference, following the Brazilian Guidelines on Hypertension.[15] Before the measurement, participants remained seated for 30 minutes and refrained from coffee and smoking. Three measurements were taken with a one-minute interval between them, and the mean of these three measurements was defined as casual BP.

Blood tests

Venous blood samples were collected after an overnight fasting (12 hours) for determination of total cholesterol, HDL-cholesterol, triglycerides and glucose levels. HDL-cholesterol levels were calculated by the Friedewald formula.

Evaluation of obstructive sleep apnea

The diagnosis of OSA was determined by a home, portable monitoring device, the Watch-PAT, which indirectly detects apnea-hypopnea events by identifying sympathetic activities related to these events. After the test, results are automatically read and analyzed by a computer program.[16] Watch-PAT provides an algorithm able to differentiate between sleep and awake state every 30 seconds, and to calculate the respiratory disturbance index (RDI) using the total sleep time rather than the total recording time at rest. The actigraphy algorithm provides an accurate measure of sleep and wake states in normal subjects and patients with OSA. This simple method for evaluation of sleep total time is a useful tool to accurately quantify OSA in the home environment.[17]

The American Academy of Sleep Medicine recognizes the Watch-PAT device as a useful alternative for the diagnosis of OSA, since it allows a manual or automatic edition of the scores obtained. Besides, there are not many technical failures with the use of the Watch-PAT at home.[13,18] The analysis algorithm uses four functions to detect different parameters including the apnea-hypopnea index (AHI), RDI, oxygen desaturation index (ODI), the minimum, mean and maximum oxygen saturation and sleep stages.[16]

Patients were divided into two groups based on the AHI: group 1 with an AHI < 15 events/hour and group 2 with an AHI ≥ 15 events/hour, aiming to separate patients with moderate/severe OSA (group 2) from those without OSA (AHI < 5 events/hour) or mild OSA (AHI = 5-14 events/hour).

Ambulatory blood pressure monitoring

Twenty-four-hour ABPM was performed using the Spacelabs 90207 monitor (Spacelabs Inc., Redmond, WA, USA). The cuff, with a size appropriate for the patient's arm circumference, was placed on the non-dominant upper-arm. This monitor is validated by the British Hypertension Society and by the Brazilian Society of Cardiology.[19] The readings were taken every 20 minutes during the day and every 30 minutes at night. During the monitoring period, subjects recorded the awake and sleep periods to calculate mean BP during these periods. Patients were instructed to avoid sleeping for more than one hour during the day. The ABPM was considered adequate if 70% of the measures were successfully obtained. The percentage of nocturnal BP decrease for systolic and diastolic pressures was calculated as the mean of diurnal BP minus the mean nocturnal BP, multiplied by 100 and divided by the mean diurnal BP. BP load was considered abnormal when more than 30% of the valid BP readings in the ABPM were above the normal limits. MH was defined as a casual BP lower than 140/90 mmHg and 24-hour BP higher than 130/80 mmHg in the ABPM, and/or awake BP greater than 135/85 mmHg and or sleep BP greater than 120/70 mmHg.[11]

Statistical analysis

Data were analyzed by the Statistical Package for Social Sciences (SPSS) version 18.0 (SPSS Inc., Chicago, IL, USA), and the results expressed as mean ± standard deviation. Continuous variable showed a normal distribution according to the Kolmogorov–Smirnov test. The unpaired Student's t test was used to compare the mean between the groups. Categorical variables were compared using the chi-square test (χ^2) and expressed as percentage of frequency distribution.

Correlations were assessed by the Pearson correlation test. Sample size was estimated based on previous studies on 24-hour systolic BP in similar populations.[9] Assuming a level of significance of 5% and a standard deviation of 8 mmHg, 23 patients in each group would have a power of 80% to detect a difference of 5 mmHg in 24-hour systolic BP between the groups.

Results

A total of 86 participants were selected. However, 3 patients had arterial hypertension during the first visit, and 2 subjects refused to perform the ABPM. Therefore, full examination was performed in 81 patients. Mean age was 42 ± 6 years, and mean BMI was 33.8 ± 3.0 kg/m^2. Group 1 was composed of 55 individuals (68%), and group 2 was composed of 26 (32%) individuals.

Despite similar mean age in both groups, male sex was predominant in group 2 (Table 1). Also, although group 1 and 2 had similar BMI and WC, greater NC and greater waist-hip circumference (WHC) were observed in group 2 as compared with group 1 (Table 1). There were significant, positive correlations of AHI with NC ($r = 0.42$, $p < 0.001$) and WHC ($r = 0.35$, $p = 0.001$), and of NC with 24-hour systolic BP ($r = 0.25$, $p = 0.023$) and 24-hour diastolic BP ($r = 0.22$, $p = 0.048$) (Figure 1).

Systolic and diastolic casual BPs were similar between the groups. Nevertheless, group 2 had higher diurnal and nocturnal BP levels in the ABPM, and higher nocturnal diastolic BP load (Table 2). Also in group 2, nocturnal diastolic BP was positively correlated with AHI ($r = 0.43$, $p < 0.05$) (Figure 2), and the frequency of MH was slightly higher (50% vs. 33%, $p= 0.103$) than in group 1 (Table 2).

Discussion

The findings of the present study showed that asymptomatic, obese subjects with moderate/severe OSA had higher 24-hour BP than subjects without OSA and/or with mild OSA. In addition, nocturnal diastolic BP was correlated with AHI. The main mechanisms of increased BP in patients with OSA are increased sympathetic activity, renin-angiotensin system dysfunction, endothelial dysfunction, hypoxemia, and disruption of normal sleep. These changes lead to increased peripheral vascular resistance and a predominantly diastolic hypertension.[8,20]

In obese individuals, the prevalence of OSA is higher than in non-obese subjects.[7] In the present study, the percentage of patients with moderate/severe OSA was similar to those reported in previous reports.[21-23] In the Wisconsin study, approximately 9% of men and 4% of women aged between 30 and 60 years had AHI ≥ 15 events/hour.[24] In a similar study, approximately 13% of men and 9% of women had moderate/severe OSA (AHI ≥ 15 events/hour).[25] In this study, we also observed a higher number of men than women in the group of moderate/severe OSA.[26]

The relationship between BMI and OSA is controversial. Although such correlation was not found in two previous studies,[27,28] in the Sleep Heart Health Study,[6] which evaluated 6,120 individuals in a hospital population, BMI

Table 1 – Anthropometric, laboratory and Watch PAT data

Variables	Group 1 (n = 55) AHI < 15 events/h	Group 2 (n = 26) IAH ≥ 15 events/h	p value
Male sex, n (%)	10 (18.2)	12 (46.2)	0.008*
Age (years)	41 ± 7	44 ± 6	0.170
BMI (kg/m²)	33.8 ± 2.9	33.9 ± 3.2	0.850
Waist-hip ratio (cm)	0.89 ± 0.05	0.94 ± 0.05	0.001*
Neck circumference (cm)	38.0 ± 3.7	40.5 ± 3.2	0.002*
Waist circumference (cm)	104.3 ± 8.3	108.5 ± 7.6	0.030
Glucose (mg/dl)	87.5 ± 11.7	91.8 ± 30.3	0.375
Cholesterol Total (mg/dl)	202.7 ± 41.3	203.6 ± 39.9	0.926
LDL-cholesterol (mg/dl)	128.3 ± 35.5	127.5 ± 34.9	0.918
HDL-cholesterol (mg/dl)	50.4 ± 14.4	48.1 ± 9.5	0.453
Triglyceride (mg/dl)	119.7 ± 71.9	140.4 ± 83.6	0.257
AHI (events/h)	6.4 ± 4.1	24.4 ± 8.8	< 0.001*
RDI (events/h)	11.8 ± 5.1	28.6 ± 8.9	< 0.001*
ODI (events/h)	3.0 ± 2.4	14.5 ± 6.9	< 0.001*
Mean O_2 saturation (%)	95.8 ± 1.2	94.3 ± 1.4	< 0.001*
REM sleep (%)	24.0 ± 7.4	26.0 ± 8.2	0.249

*Data shown as mean ± standard deviation; BMI: body mass index; LDL: low-density lipoprotein; HDL: high-density lipoprotein; AHI: apnea-hypopnea index; RDI: respiratory disturbance index; ODI: oxygen desaturation index; REM: rapid eye movement. Continuous variables were analyzed by the unpaired Student t-test, and categorical variables by the chi-squared test (χ2).*p < 0.05.*

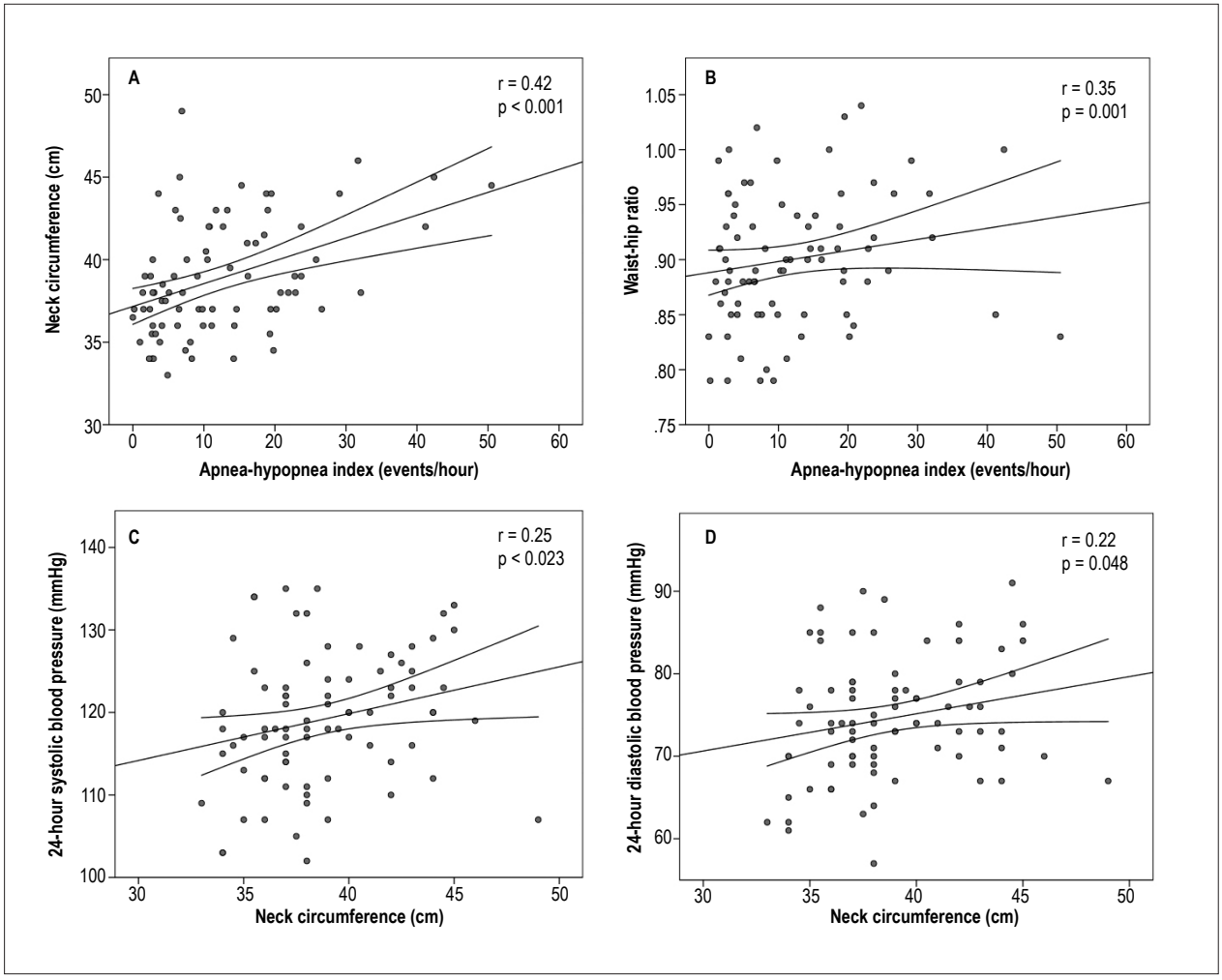

Figure 1 – *Positive correlations of apnea-hypopnea index with neck circumference (A) and waist-hip ratio (B), and of neck circumference with 24-hour systolic blood pressure (C) and 24-hour diastolic blood pressure (D).*

was an independent risk factor for OSA, with an odds ratio of 1.55-1.60. In the present study, we did not find an association between BMI and OSA, which may be explained by the small sample size and narrower range of BMI for the inclusion criteria (BMI ≥ 40 kg/m^2 was excluded). Besides, increased visceral adiposity may be more important in OSA physiopathology than overall obesity.

The anthropometric parameters NC and WHR could be used to identify individuals at high risk for OSA. In a study with 192 patients suspected of OSA, WHR was associated with moderate-to-severe OSA.[27] Similar results were found in a study comparing individuals with different degree of snoring, indicating a significant difference in WHR between the groups.[29]

With respect to NC, a study on 129 individuals suspected of OSA reported that this anthropometric parameter was an independent risk factor for OSA.[30] In the present study, both NC and WHR were significantly higher in patients with moderate/severe OSA, despite similar BMI and WC between the groups. This finding corroborates previous studies, suggesting that both NC and WHR could be routinely assessed in obese outpatients, to identify those patients at higher risk for OSA.

The current study also found that subjects with moderate-to-severe OSA had higher systolic and diastolic BP in the ABPM. According to cross-sectional studies on OSA, hypertension is more prevalent in OSA patients, even after controlling for confounding factors, such as age and obesity.[31] Besides, analysis of BP circadian rhythm by the ABPM may reveal other prognostic information, such as increased prevalence of MH and increased nocturnal BP. The identification of patients with MH is important in daily clinical practice, since previous studies suggested that these patients have more target-organ injuries, including microalbuminuria and left ventricular hypertrophy.[32,33] Furthermore, a meta-analysis of seven studies and 11,502 patients reported that MH patients have twice the risk of cardiovascular death than normal BP subjects.[34] The prevalence of MH in the general population varies from 16 to 24%.[33] However, in OSA patients, these values may

Table 2 – Casual blood pressure and 24-hour ambulatory blood pressure monitoring results

Variables	Group 1 (n = 55) AHI < 15 events/h	Group 2 (n = 26) AHI ≥ 15 events/h	p value
Casual SBP (mmHg)	121.4 ± 8.1	123.6 ± 7.7	0.321
Casual DBP (mmHg)	77.6 ± 7.6	79.1 ± 6.8	0.393
24h-SBP (mmHg)	117.6 ± 8.5	122.3 ± 6.2	0.014*
24h-DBP (mmHg)	73.1 ± 7.3	77.7 ± 6.2	0.008*
Awake SBP (mmHg)	120.5 ± 8.5	125.7 ± 6.1	0.007*
Awake DBP (mmHg)	76.1 ± 7.6	81.3 ± 5.7	0.003*
Sleep SBP (mmHg)	110.6 ± 9.9	115.3 ± 7.7	0.036*
Sleep DBP (mmHg)	65.9 ± 8.4	70.4 ± 7.7	0.025*
Dipping SBP, n (%)	19 (76)	6 (24)	0.297
Diurnal SBP load (%)	12.6 ± 16.7	16.8 ± 18.8	0.305
Diurnal DBP load (%)	21.6 ± 24.6	32.2 ± 24.7	0.074
Nocturnal SBP load (%)	22.8 ± 26.7	29.1 ± 26.2	0.322
Nocturnal DBP load (%)	31.3 ± 27.3	44.6 ± 25.9	0.041*
Nocturnal hypertension, n (%)	17 (30.9)	16 (61.5)	0.009*
Masked hypertension, n (%)	18 (33)	13 (50.0)	0.103

*Data shown as mean ± standard deviation; SBP: systolic blood pressure; DBP: diastolic blood pressure. Continuous variables were analyzed by the unpaired Student's t-test, and categorical variables were compared using the chi-squared test (χ2). *p < 0.05.*

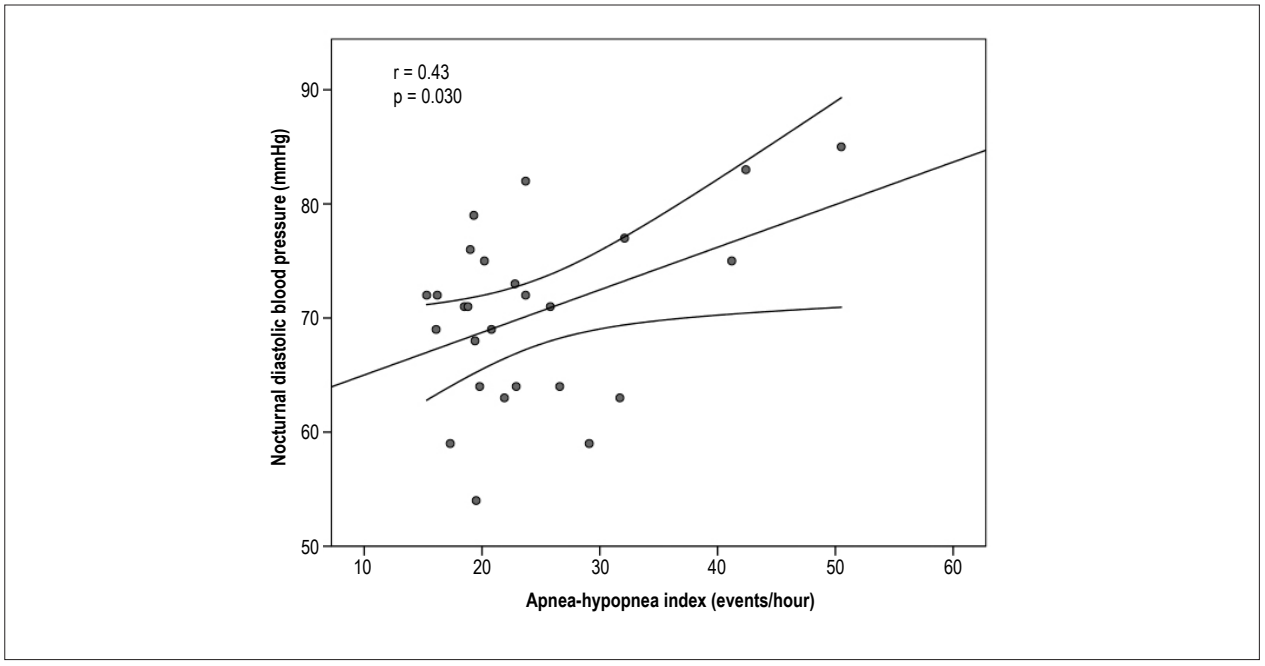

Figure 2 – *Positive correlation between apnea-hypopnea index and nocturnal diastolic blood pressure in the group of obese individuals with moderate-to-severe obstructive sleep apnea.*

be even higher: two previous studies reported a prevalence of nearly 30% of MH in OSA patients.[8,9] In accordance with these studies, the present study showed a slightly higher percentage of MH in the moderate/severe OSA group.

Previous studies have suggested a relationship between OSA and nocturnal hypertension. The authors suggest that increased adrenergic activity, hypoxemia, and sleep disruption could explain the increased nocturnal hypertension in patients with OSA.[32,35] Increased nocturnal BP may be associated with increased inflammatory markers, which may explain the increased risk for cardiovascular complications.[36]

Two studies showed a relationship between OSA and nocturnal diastolic hypertension.[37,38] In the first study, 84% of patients with mild to moderate OSA were considered "non-dippers" (without nocturnal dipping).[11] In the second study, the authors observed nocturnal arterial hypertension and absence of nocturnal BP dipping in OSA patients, in addition to a significant correlation between nocturnal arterial hypertension, absence of nocturnal dipping and AHI.[39] In our study, higher values of BP in the ABPM, and increased nocturnal diastolic pressure load were found in patients with moderate/severe OSA. Also, there was a correlation between nocturnal diastolic BP and AHI. However, no significant difference in nocturnal dipping was found between the groups.

This study has some limitations. First, OSA was diagnosed by a portable monitor rather than polissonography, which is the gold-standard diagnostic method. Nevertheless, studies on validation of the Watch-PAT equipment showed similar results between measures taken by this system and those obtained by polissonography.[17,18,40] Second, the higher prevalence of men in the group with higher AHI may have influenced the anthropometric results. Third, the cross sectional design of the study does not allow us to conclude a causal relationship between OSA and arterial hypertension. However, the use of ABPM permitted the measurements of nocturnal BP, and the identification of MH and nocturnal arterial hypertension.

Conclusions

Asymptomatic obese individuals with moderate/severe OSA have higher 24-hour systolic and diastolic BP in comparison with those with absent/mild OSA, despite normal casual BP. These results indicate that the ABPM may be useful in the assessment of asymptomatic obese patients with moderate-to-severe OSA. Prospective studies are needed to confirm this hypothesis.

Author contributions

Conception and design of the research: Neves MF, Oigman W; Acquisition of data and Writing of the manuscript: Correa CMN; Analysis and interpretation of the data, Statistical analysis and Critical revision of the manuscript for intellectual content: Correa CMN, Gismondi RA, Cunha AR, Neves MF, Oigman W.

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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Causes and Predictors of In-Hospital Mortality in Patients Admitted with or for Heart Failure at a Tertiary Hospital in Brazil

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Abstract

Background: Although heart failure (HF) has high morbidity and mortality, studies in Latin America on causes and predictors of in-hospital mortality are scarce. We also do not know the evolution of patients with compensated HF hospitalized for other reasons.

Objective: To identify causes and predictors of in-hospital mortality in patients hospitalized for acute decompensated HF (ADHF), compared to those with HF and admitted to the hospital for non-HF related causes (NDHF).

Methods: Historical cohort of patients hospitalized in a public tertiary hospital in Brazil with a diagnosis of HF identified by the Charlson Comorbidity Index (CCI).

Results: A total of 2056 patients hospitalized between January 2009 and December 2010 (51% men, median age of 71 years, length of stay of 15 days) were evaluated. There were 17.6% of deaths during hospitalization, of which 58.4% were non-cardiovascular (63.6% NDHF vs 47.4% ADHF, p = 0.004). Infectious causes were responsible for most of the deaths and only 21.6% of the deaths were attributed to HF. The independent predictors of in-hospital mortality were similar between the groups and included: age, length of stay, elevated potassium, clinical comorbidities, and CCI. Renal insufficiency was the most relevant predictor in both groups.

Conclusion: Patients hospitalized with HF have high in-hospital mortality, regardless of the primary reason for hospitalization. Few deaths are directly attributed to HF; Age, renal function and levels of serum potassium, length of stay, comorbid burden and CCI were independent predictors of in-hospital death in a Brazilian tertiary hospital. (Arq Bras Cardiol. 2017; 109(4):321-330)

Keywords: Cardiovascular Diseases; Heart Failure; Hospital Mortality; Demographic Aging; Hospitals, Public.

Introduction

Despite the decline in many cardiovascular diseases, there is a stable or increased prevalence of heart failure (HF) in the world and in Brazil, which is probably due to population aging associated with an increase in survival in patients with cardiovascular diseases.[1] Despite the great progress in its treatment, HF remains one of the main causes of hospitalization in several countries and is associated with high rates of morbidity and mortality.[2] Even with optimized therapy, estimates account for a 4-year mortality rate of 40%,[3] with a reduction in quality of life and prognosis when compared, for example, with various neoplasias.[2]

Observational studies in several countries have shown that after a hospitalization due to decompensated HF, significant changes occur in the natural history of the syndrome, implying a high risk of readmission and death.[4-6] These data have been partially reproduced in studies in Brazil and are observed in the Brazilian public system statistics.[2,7] The recent publication of the initial results of the BREATHE Registry, which included 52 centers in Brazil, clearly demonstrates the great impact of the syndrome, with in-hospital mortality of 12,6%.[8]

Despite the importance of the BREATHE Registry for Brazil, the majority of existing cohorts of acute decompensated HF were performed in the United States or Europe, including patients with a clinical, etiological, social and economic profile different from that of Brazilian patients.[9] In addition, an aspect not explored in the scenario of hospitalized patients refers to the hospital and extra-hospital evolution of patients hospitalized for decompensated HF compared to the prognosis of patients hospitalized for other causes, but who present a previous diagnosis of HF. It is plausible to speculate that the presence of HF, even if this is not the primary cause of hospitalization, implies a reserved prognosis. In this context, it is still of great value to recognize prognostic predictors in order to identify patients requiring more intensive monitoring and treatment.[10] The objective of the present study is to identify the predictors and causes of in-hospital mortality in patients hospitalized for acute decompensated HF compared to those who have HF and hospitalize for other conditions in a Brazilian public tertiary hospital.

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Methods

Location, design and patients

This study was carried out in a public hospital of tertiary level in Porto Alegre, Rio Grande do Sul, Brazil, with approximately 850 beds. This is a prospective cohort study, in which adult patients (≥ 18 years) were admitted to any ward or intensive care unit (ICU) of this hospital and who were identified as having HF as indicated by the attending physician in the score of Charlson's comorbidity, or simply Charlson's index, via electronic medical records. Were excluded from the analisys pediatric patients (age <18 years), with permanence only in the emergency department (without admission to the infirmary or in the ICU), with hospital evasion or unavailable computerized discharge.

In this hospital, the Charlson index is filled out by the attending physician in the electronic medical record in a compulsory manner at the time of admission and at discharge. Failure to complete it prevents continuity of diagnostic and therapeutic procedures or hospital discharge. Although it was developed to predict risk in patients admitted to elective surgical procedures, the Charlson index has been described as an excellent tool for hospital use for clinical prediction of in-hospital mortality.[11] It is a score composed of several comorbidities that is widely used to classify the severity of patients, and it is possible to compare the burden of diseases of patients from different medical and hospital services. The comorbidities that make up the Charlson index are acute myocardial infarction (AMI), congestive heart failure, peripheral and aortic vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease (COPD), connective tissue disease, ulcer disease, moderate to severe kidney disease (creatinine > 3.0 mg/dL), hemiplegia, lymphoma/myeloma, leukemia/polycythemia vera, tumor, AIDS, and metastatic cancer.[12]

Logistics and data collection

For purposes of analysis, patients who had multiple hospitalizations had considered only their last hospitalization, so that all in-hospital deaths of the sample were included, avoiding that more severe patients with multiple readmissions had their characteristics analyzed multiple times and seeking to preserve independence of the data. Data collection was performed by internal medicine residents previously trained through the standardized review of electronic medical records, and a computerized collection protocol was created and fully integrated into the electronic medical record of the hospital. 10% of the sample was verified by two other researchers of the study, preceptors of the Internal Medicine Service, to measure the reliability of the data collected. The patients were selected through a computerized system that allowed the automatic identification of all those who fulfilled the inclusion criteria. The causes of in-hospital death were stratified into cardiovascular death (HF, acute coronary syndrome, stroke or other cardiovascular deaths) and non-cardiovascular death (from infection, neoplasia, respiratory origin or other non-cardiovascular death). When the collectors could not identify the cause of mortality, the case was evaluated by two experienced researchers. If they could not identify the cause of death, it was defined as "death for an indefinite cause."

The following variables and instruments were included in data collection: age; sex; geographical origin; (Porto Alegre, Metropolitan Region of Porto Alegre and interior); team in which the patient was hospitalized (Cardiology, Internal Medicine and Others); length of hospital stay; cause of hospitalization; Charlson index; laboratory values (urea, sodium, creatinine and potassium) in the first 24 hours of hospitalization; echocardiographic data up to 1 year before admission: left ventricular ejection fraction (LVEF); left ventricular hypertrophy; presence of diffuse hypokinesia or segmental alterations of contractility and valvular lesions; prescription of cardiovascular drugs at hospital discharge; non-pharmacological guidelines at hospital discharge; outpatient referral; hospitalization in ICU, intra-hospital death; reason for in-hospital death; emergency visit and rehospitalization within 30 days after hospitalization.

The sample was separated into two groups: patients who had heart failure and hospitalized for a reason other than acute decompensated HF (NDHF) and patients who had acute decompensated acute HF (ADHF) as the reason for hospitalization. The latter group consisted of patients who presented as the main diagnosis, defined by the attending physician, one of the International Codes of Disease (ICD) presented in Appendix 1. According to Steinberg et al.,[13] we stratified the patients into three subgroups of LVEF: preserved LEVF (> 50%), borderline LVEF (40-49%) or reduced LVEF (<40%).

Data analysis

Continuous variables were expressed as mean and standard deviation or median and interquartile range (IIQ 25% -75%) according to normality of data analyzed using the Shapiro-Wilk test. Categorical variables were expressed as frequency and percentages. Univariate analyzes were performed by unpaired Student's t test, Mann-Whitney test, Poisson's test and chi-square test. For the multivariate analyzes, the Poisson regression with estimation of robust variances was performed by the stepwise methodology, calculating the incidence ratios and the 95% confidence intervals. From the data collected from the patients, univariate analyzes of continuous and categorical variables were performed within each of the two pre-defined groups (ADHF and NDHF). The variables that had a value of $p < 0.20$ in the univariate analysis were selected for the multivariate analysis in order to identify the predictors of in-hospital mortality. A p value of 5% was considered statistically significant. Due to the potential multicollinearity effect, two models of statistical analysis were used, one with a Charlson index and urea (model 1), but without the items that make up the Charlson index (comorbidities and age) and the other without the Charlson index and urea (model 2). The accuracy of both methods was similar. The data collected in the computerized system customized for the research were exported to a Microsoft Excel version 18 spreadsheet (*Microsoft Inc*., Redmond, USA) and the statistical analyzes were conducted by the Statistical Package for the Social Sciences (SPSS) Basic version 19.0 (SPPS Inc., Chicago, USA).

The research project was approved by the Research Ethics Committee of the institution of the corresponding author. There were no sources of study funding.

Results

Patients

All patients admitted to the hospital from January 1, 2009 to December 31, 2010, and had congestive heart failure as one of the diseases fulfilled in the Charlson index (compulsory filling in the patient's hospitalization), totalizing 2056 patients and 2666 hospitalizations were included. The characteristics of the patients in the sample are listed in table 1. In the population studied, the distribution between the sexes was homogeneous, the median age of the patients was 71 years, and the majority of the patients came from Greater Porto Alegre (59.3%) and was admitted under the care of the Cardiology (37.8%) and Internal Medicine (29%) teams. The median length of hospital stay was 15 days (IIQ 25-75%: 10-23) and the Charlson index was 5 (IIQ 25-75%: 4-7). Only 590 patients (28.7%) were hospitalized for acute decompensated HF. We observed throughout our sample that 43.1% of the patients had reduced LVEF, 18.9% had borderline LVEF and 38% had preserved LVEF. When we analyzed, however, the two subgroups of patients, we found that the patients who hospitalized for ADHF had a higher prevalence of reduced LVEF compared to patients hospitalized for other reasons (58% X 36.3% respectively), similar prevalences of LVEF (17.4% X 19.6% respectively) and lower percentage of preserved LVEF (24.6% X 44.1% respectively).

Causes of death

During admission, 361 (17.6%) patients died, with a 19% mortality rate in the ADHF group and 17% mortality in the NDHF group. Table 2 shows the causes of death stratified by the two groups of analysis. It was found that approximately 60% of the cases of mortality were attributed to non-cardiovascular causes in the studied population, being higher in the group of patients with NDHF (63.6% versus 47.4%, p = 0.004). Of non-cardiovascular deaths, the most common cause in both groups was infection related, accounting for one-third of total deaths in the ADHF group and approximately half of all deaths in the NDHF group. On the other hand, death due to cardiovascular causes was more prevalent in the ADHF group (42.1% versus 28.7%, p = 0.016). Interestingly, in both groups, deaths attributed to heart failure occurred in only 21.6% of deaths in the study population, being more frequent in those patients with ADHF.

Table 1 – Baseline characteristics of ADHF and NDHF patients

	All (n = 2056)	ADHF (n = 590)	NDHF (n = 1466)	p value
Age (years)	71 (61 – 79)	70 (60 – 79)	71 (61 – 80)	0.11
Male	1041 (51%)	301 (51%)	740 (50%)	0.81
White Race	1736 (84%)	490 (83%)	1246 (85%)	0.25
Length of stay (days)	15 (10 – 23)	13 (9 – 20)	16 (10 – 24)	< 0.001
VE ejection fraction (%)	44 (36 – 59)	38 (31 – 49)	47 (40 – 64)	< 0.001
Charlson index	5 (4 – 7)	5 (4 – 7)	6 (4 – 7)	< 0.001
ICU hospitalization	362 (18%)	88 (15%)	274 (19%)	0.041
Cerebrovascular disease	361 (18%)	65 (11%)	296 (20%)	< 0.001
Previous AMI	503 (24.5%)	114 (19%)	389 (26.5%)	0.001
Diabetes mellitus	646 (31%)	171 (29%)	475 (32%)	0.13
Kidney disease*	287 (14%)	81 (14%)	206 (14%)	0.83
Peripheral vascular disease	307 (15%)	60 (10%)	247 (17%)	< 0.001
Neoplasia	49 (2 %)	6 (1%)	43 (3 %)	< 0.01
COPD	472 (23%)	106 (18%)	366 (25%)	0.001
Dementia	174 (8.5%)	41 (7%)	133 (9%)	0.12
Liver disease	86 (4%)	29 (5%)	57 (4%)	0.33
Urea (mg/dL) †	56 (42 – 78)	55 (42 – 79)	56 (42 – 78)	0.41
Creatinine (mg/dL)†	1.21 (0.94 – 1.59)	1.20 (0.98 – 1.56)	1.21 (0.92 – 1.60)	0.74
Sodium (mg/dL)†	138 (136 – 140)	139 (136 – 141)	138 (136 – 140)	< 0.001
Potassium (mEq/L)†	4.4 (4.0 – 4.8)	4.3 (4.0 – 4.8)	4.4 (4.1 – 4.8)	0.02

*Data expressed in absolute number and percentage, except if indicated. Continuous values expressed as median and interquartile range; Student's t test, Mann-Whitney test or chi-square test were used for statistical analysis as indicated. ADHF: acutely decompensated heart failure; NDHF: patients with non-decompensated heart failure admitted for non-HF conditions; LV: left ventricle; ICU: intensive care unit; AMI: acute myocardial infarction; COPD: chronic obstructive pulmonary disease; * Defined by creatinine > 3.0 mg/dL; † Laboratory values within the first 24 hours of admission.*

Table 2 – Causes of intra-hospital deaths in the groups of patients with ADHF and NDHF

	Todos (n = 361)	ADHF (n = 114)	NDHF (n = 247)	p value
CV death	119 (33%)	48 (42.1%)	71 (28.7%)	0.016
Heart failure	78 (21.6%)	39 (34.2%)	39 (15.8%)	< 0.001
Acute coronary syndrome	17 (4.7%)	4 (3.5%)	13 (5.3%)	0.60
Stroke	9 (2.5%)	3 (2.6%)	6 (2.4%)	1.000
Other CV causes	15 (4.2%)	2 (1.8%)	13 (5.3%)	0.16
Non-cardiac death	211 (58.4%)	54 (47.4%)	157 (63.6%)	0.004
Infection	159 (44%)	38 (33.3%)	121 (49.0%)	0.006
Neoplasia	6 (1.7%)	1 (0.9%)	5 (2%)	0.67
Respiratory Cause	18 (5%)	7 (6.1%)	11 (4.5%)	0.60
Other non-CV causes	28 (7.8%)	8 (7.0%)	20 (8.1%)	0.83
Undefined or ill-defined cause of death	31 (8.6%)	12 (10.5%)	19 (7.7%)	0.42

The chi-square test was used for statistical analysis. ADHF: acutely decompensated heart failure; NDHF: patients with non-decompensated heart failure admitted for non-HF conditions.

Univariate and multivariate analysis in the NDHF group

Table 3 describes clinical characteristics that were associated with in-hospital mortality in the group of patients with NDHF. On univariate analysis, the following variables were identified as predictors of risk: age, length of stay, Charlson index, serum potassium and urea levels, and presence of clinical comorbidities. Admission in a Cardiology team had a small protective effect. In the multivariate analysis, independent risk predictors were: age, length of stay, presence of renal disease and dementia (Table 4). When included in the analysis (model 1), the Charlson index was also an important predictor of risk of in-hospital mortality, with moderate-severe renal disease being the comorbidity with the greatest magnitude.

Univariate and multivariate analysis in the ADHF group

Table 5 describes clinical characteristics that were associated with in-hospital mortality in the group of ADHF patients. Mortality predictors were: age; length of stay; Charlson index; serum levels of sodium, potassium, urea and creatinine; And the presence of clinical comorbidities that make up the Charlson index. Admission in a cardiology team had a small protective effect. In the multivariate analysis, independent predictors of risk were: age, changes in urea and potassium levels, presence of renal disease, dementia, AMI and neoplasia (Table 6). When included in the analysis (model 1), the Charlson index was also a predictor of in-hospital mortality risk, with moderate-severe renal disease being the most relevant comorbidity, since the number of patients with neoplasia was very small (n = 6).

Discussion

Heart failure has been the subject of extensive research regarding the mortality and quality of in-hospital care. Most evidence evaluates patients with HF who hospitalizes for acute decompensation, identified by the primary diagnosis of discharge.[9] However, the literature demonstrates that most patients with HF is admitted due to other causes.[14-18] While quality measures of HF care are reported only in patients hospitalized for HF, some measures appear to be beneficial for all HF patients, regardless of the cause of hospitalization.[9,19,20] In this study, we identified that in-hospital mortality was extremely high in both the groups; (1) age, (2) renal function and potassium levels (3) length of stay, and (4) burden of comorbidities were independent predictors of risk of death within the hospital.

When comparing NDHF patients with ADHF patients, we found that the firsts had more comorbidities, with higher Charlson index and LVEF values, similar to those found in the scientific literature.[14,15] We found a prolonged lenght of stay when compared to hospitals in the USA[21] and in Brazil itself,[5] with the NDHF group having the highest median (16 days versus 13 days), which has already been described in other articles.[16,17,19] We found an association between longer lenght of stay and greater mortality in the NDHF group, a result that has also been reproduced in other scenarios.[19,21,22] One of the possible explanations for the above data is that the need for hospitalization due to causes not related to HF delimits patients with greater burden and severity of diseases, generating greater complexity of care. Another important issue is that exacerbation of comorbidities such as COPD and chronic renal failure may directly contribute to worsening severity of HF and compromising subsequent treatments and outcomes.[15]

Regarding mortality, the hospital death rate of the entire sample was 17.6%, considering the last hospitalization of the patients in the study period. This value is much higher than that found in other countries, and even in other Brazilian hospitals.[2,5-8,19] Although there were 19% deaths in the ADHF group and 17% in the NDHF group, this difference was not statistically significant. Blecker et al.[18] showed that there was a similar mortality rate at 1 year follow-up for ADHF and NDHF (25.6% versus 26.2%, respectively, p = 0.76). We believe that the differences found between our cohort and the international scenario may have been influenced by the organization of the Brazilian health system, by the patients' clinical characteristics and by cultural aspects related to end of life care. Thus, it would be hasty to attribute this result exclusively to the idiosyncrasies of the health system and variations in the management of the disease.

Table 3 – Univariate analysis of mortality predictors in the NDHF group

Predictors	RR (IC 95%)	p value
Age	1.028 (1.019 – 1.038)	< 0.0001
Lenght of stay	1.007 (1.004 – 1.010)	< 0.0001
Charlson index	1.185 (1.147 – 1.223)	< 0.0001
Creatinine	1.006 (0.974 – 1.040)	0.709
Potassium	1.209 (1.049 – 1.393)	0.009
Urea	1.004 (1.002 – 1.005)	< 0.0001
VE ejection fraction	0.993 (0.985 – 1.003)	0.126
Cardiology team	0.909 (0.868 – 0.952)	< 0.001
Ejection fraction VE ≤ 40%	1.157 (0.904 – 1.480)	0.248
Solid neoplasia	1.835 (1.148 – 2.932)	0.011
Dementia	2.412 (1.860 – 3.128)	< 0.001
Cerebrovascular disease	1.820 (1.437 – 2.304)	< 0.001
Kidney disease	2.610 (2.076 – 3.282)	< 0.001
Peripheral and aortic vascular disease	1.218 (0.920 – 1.614)	0.169
Liver disease	1.482 (0.926 – 2.371)	0.101

Poisson test was used for statistical analysis. NDHF: patients with non-decompensated heart failure admitted for non-HF conditions; RR: relative risk; 95% CI: 95% confidence interval; LV: left ventricle.

Table 4 – Multivariate analysis of mortality predictors in the NDHF group

Predictors	Model 1* (Including CCI)		Model 2† (Excluding CCI)	
	RR (IC 95%)	p value	RR (IC 95%)	p value
Age	NA	NA	1.003 (1.002 – 1.005)	< 0.001
Lenght of stay	1.002 (1.000 – 1.003)	0.036	1.002 (1.000 – 1.003)	0.018
Charlson index	1.030 (1.019 – 1.041)	< 0.0001	NA	NA
Cardiology team	0.994 (0.949 – 1.040)	0.780	0.999 (0.959 – 1.043)	0.988
Urea	1.000 (1.000 – 1.001)	0.113	NA	NA
Potassium	1.011 (0.980 – 1.043)	0.482	1.012 (0.981 – 1.045)	0.445
Neoplasia	NA	NA	1.111 (0.923 – 1.338)	0.267
Cerebrovascular disease	NA	NA	1.056 (0.995 – 1.121)	0.071
Peripheral and aortic vascular disease	NA	NA	1.060 (0.984 – 1.141)	0.126
Kidney disease	NA	NA	1.206 (1.115 – 1.304)	< 0.001
Dementia	NA	NA	1.176 (1.078 – 1.283)	< 0.001
Ejection Fraction VE ≤40%	1.028 (0.984 – 1.075)	0.219	1.032 (0.989 – 1.077)	0.151

*CCI: Charlson's comorbidity index; RR: relative risk; 95% CI: 95% confidence interval; NA: not applicable; LV: left ventricle; * Result after withdrawal of solid neoplasm. cerebrovascular disease. renal disease. peripheral and aortic vascular disease. dementia. liver disease. neo-hematological disease. pulmonary disease. acute myocardial infarction and age by potential multicollinearity effect with CCI; † Outcome after CCI withdrawal and urea due to potential multicollinearity effect with the above comorbidities.*

The analysis of the causes of death in the hospital environment showed that approximately 60% of the cases of mortality were attributed to non-cardiovascular causes, with a higher percentage in the group of patients with NDHF. Deaths attributed to HF occurred in only 21.6% of the sample, being more frequent in patients with ADHF. It is noteworthy that, even in the ADHF group, almost half of the patients died from non-cardiac causes - 33% from infectious causes - a similar number of HF-related death. Few studies have reported the causes of in-hospital deaths in patients with HF. In a study with 18 institutions in Thailand with ADHF patients (Thai ADHERE),[23] there was 5.5% of in-hospital deaths (29% from infection, 27% from HF and 13% from acute coronary syndrome). Finally, a CHARM[15]

Table 5 – Univariate analysis of the predictors of mortality in the ADHF group

Predictors	RR (CI 95%)	p value
Age	1.025 (1.01 – 1.04)	< 0.001
Lenght of stay	1.006 (1.001 – 1.011)	0.012
Charlson index	1.280 (1.215 – 1.348)	< 0.0001
Potassium	1.470 (1.235 – 1.751)	< 0.0001
Urea	1.010 (1.007 – 1.012)	< 0.0001
Creatinine	1.168 (1.047 – 1.302)	0.005
Sodium	0.955 (0.867 – 0.999)	0.048
Ejection fraction VE ≤ 40%	0.999 (0.712 – 1.402)	0.996
Cardiology team	0.931 (0.872 – 0.994)	0.033
Neoplasia	4.488 (3.021 – 6.668)	< 0.0001
Dementia	2.693 (1.847 – 3.925)	< 0.0001
Cerebrovascular disease	2.400 (1.685 – 3.418)	< 0.0001
Kidney disease	3.687 (2.732 – 4.976)	< 0.0001
Peripheral and aortic vascular disease	2.369 (1.648 – 3.404)	< 0.0001
Liver disease	1.667 (0.943 – 2.946)	0.079
AMI	1.786 (1.264 – 2.522)	0.001
COPD	1.550 (1.075 – 2.234)	0.019

Poisson test was used for statistical analysis. ADHF: acute compensated cardiac insufficiency; RR: relative risk; 95% CI: 95% confidence interval; LV: left ventricle; AMI: acute myocardial infarction; COPD: chronic obstructive pulmonary disease.

Table 6 – Multivariate analysis of the predictors of mortality in the group of patients hospitalized for acute HF (ADHF)

Predictors	Model 1* (Including CCI)		Model 2† (Excluding CCI)	
	RR (CI 95%)	p value	RR (CI 95%)	p value
Age	NA	NA	1.002 (1.000 –1.004)	0.004
Lenght of stay	0.996 (0.99 – 1.001)	0.99	0.999 (0.99 – 1.003)	0.821
Charlson index	1.034 (1.02 – 1.05)	< 0.0001	NA	NA
Urea	1.001 (1.000 –1.002)	0.014	NA	NA
Sodium	0.998 (0.992 – 1.005)	0.595	0.996 (0.990 –1.002)	0.238
Potassium	1.042 (1.006 –1.079)	0.021	1.036 (1.003 – 1.070)	0.032
Cardiology team	0.966 (0.912 – 1.023)	0.243	0.969 (0.92 – 1.02)	0.266
Kidney disease	NA	NA	1.22 (1.12 – 1.33)	< 0.001
Dementia	NA	NA	1.152 (1.03 – 1.29)	0.014
Neoplasia	NA	NA	1.373 (1.01 – 1.87)	0.044
Cerebrovascular disease	NA	NA	1.051 (0.96 – 1.15)	0.291
Peripheral and aortic vascular disease	NA	NA	1.074 (0.97 – 1.18)	0.143
AMI	NA	NA	1.081 (1.01 – 1.16)	0.021
COPD	NA	NA	1.022 (0.95 – 1.10)	0.552

*CCI: Charlson's comorbidity index; RR: relative risk; 95% CI: 95% confidence interval; NA: not applicable; AMI: acute myocardial infarction; * Outcome after withdrawal of solid neoplasm. cerebrovascular disease. renal disease. peripheral and aortic vascular disease. dementia. liver disease. neo-hematological disease. lung disease. AMI. creatinine and age by potential effect Multicollinearity with CCI; † Outcome after withdrawal of CCI. urea and creatinine due to the potential effect of multicollinearity with the comorbidities and exams above.*

sub-study evaluated the mortality rate according to the primary diagnosis of hospitalization and found that stroke, HF and AMI were the most relevant causes of death in patients hospitalized for cardiovascular conditions. Among the group admitted for non-cardiovascular disease, the leading causes of death were cancer, lung disease and kidney disease. We did not find research that investigated the causes of hospital deaths in the NDHF group.

Regarding the predictors of in-hospital mortality, moderate-severe renal disease (creatinine> 3.0 mg/dL) was the main predictor of mortality in both groups and elevated serum urea in the first 24 hours of hospitalization only in the ADHF group, as demonstrated in other studies.[6,21,24,25] In a North American study (ADHERE) with almost 120 thousand patients, there was a high prevalence of renal failure in patients with ADHF, with a great impact on hospital mortality.[25] Elevated potassium at hospital admission was also an independent predictor in the ADHF group and was used in a composite score (APACHE-HF) that was able to adequately predict adverse events in ADHF patients.[26] In a cohort of 122,630 patients from *Medicare*, the comorbidities most related to deaths in patients with HF were COPD, chronic renal failure, and acute renal failure.[27] Dementia was also a relevant independent predictor of mortality in both groups of our sample, a fact also described in a cohort of 282 elderly.[15,28] In our patients, age, as well as previous research,[6,10,29,30] also proved to be a marker of risk. The actual magnitude of the presence of neoplasia in the prediction of risk of in-hospital death should be better studied in other cohorts, because their sample had low statistical power (n = 6 in the ADHF group).

Although not originally developed and tested to describe a *mix* of clinical patients, the Charlson index has been widely used to describe and adjust inpatient populations.[31,32] In our study, with each increment of one point in the score, there was an increased risk of death in 3% in both groups. It should be noted that, although our patients are older than most of the individuals surveyed, this does not justify the higher burden of disease in our sample compared to the scientific literature. Similarly, in a cohort study in Canada of approximately 38,000 patients hospitalized for acute HF for the first time, the Charlson index was a good 30-day and 1-year mortality predictor, with values of 9.3% And 26% with a Charlson index of zero and 18.8% and 50.6% with a score ≥ 3.[33] We also observed, as in this Canadian study,[33] that previous MI was also a predictor of risk of death in patients with ADHF.

Although we have patients with characteristics different from those observed in the international literature, we found that most of the predictors of in-hospital mortality in our sample, which represents the Brazilian public real hospital world, are very similar to those previously published in other studies. In addition, although we assessed distinct populations, the predictors of in-hospital mortality found in both groups were very similar.

Hospitalization due to decompensated HF is an important variable related to mortality, although it accounts for less than a third of the total causes of hospitalization.[15,34] The few studies comparing HF populations have shown that patients with NDHF do not receive the care that modify the prognosis of the disease.[14,16,17] A study in which 4345 hospitalizations of patients with HF (39.6% ADHF) were evaluated, found that patients with NDHF had a 10% lower rate of prescription of angiotensin converting enzyme inhibitors and of angiotensin receptor blockers at hospital discharge in subjects with reduced LVEF and a 7% lower rate of LVEF assessment.[19] In our sample, we identified that a substantial portion of hospital morbidity and mortality was related to patients hospitalized for secondary causes, presenting causes and predictors of death of relevance similar to those with ADHF. To date, in most hospital settings, there is a priority focus on HF management, which may divert attention to the treatment of other diseases that significantly affect subsequent outcomes.[35] It is suggested that the evidenced based treatment for HF may improve the survival of patients with HF, regardless of the cause of hospitalization.[14,16,17,36] In this context, inadvertently neglecting other comorbidities in HF patients may represent a loss of opportunity to reduce admissions, improve the care of HF and reduce overall costs with HF.[37]

The findings of this research should be evaluated through some limitations of our study design. First, we analyzed only the latest hospital admission of each patient, which is likely to have overestimated in-hospital mortality. However, since the main objective of the study was to identify causes and predictors of mortality, this methodology allowed to have all the deaths of the sample. Second, data from a Brazilian tertiary hospital are not representative of the entire country, and there may be a limitation in its generalization. Finally, it should be emphasized that, the analyses are based on registry data. Study results might be influenced by differences in disease assessment. On the other hand, all these data require compulsory electronic filling by the attending physician both at admission and at hospital discharge.

Conclusion

Patients hospitalized with HF represent a high-risk group with high in-hospital mortality, regardless of the primary reason for hospitalization in a Brazilian tertiary hospital. Few deaths were attributed to HF and, in both groups, deaths from non-cardiovascular causes, mainly attributed to infections, prevailed. We identified that a substantial portion of hospital morbidity and mortality in HF patients was associated with hospitalizations due to secondary causes, and patients hospitalized for other reasons had similar predictors of death as those with ADHF. We observed that age, change in urea and potassium values, length of stay and comorbid burden were predictors of in-hospital mortality. These observations should call attention to opportunities to improve quality of care and reduce the costs associated with HF care, regardless of the cause of hospital admission, emphasizing the need for a more comprehensive management of both the HF and the associated comorbidities in patients with this pathology.

Author contributions

Conception and design of the research: Wajner A, Polanczyk CA, Rohde LE; Acquisition of data, Analysis and interpretation of the data, Statistical analysis and Critical

revision of the manuscript for intellectual content: Wajner A, Zuchinali P, Olsen V, Polanczyk CA, Rohde LE; Writing of the manuscript: Wajner A, Olsen V, Polanczyk CA, Rohde LE.

Potential Conflict of Interest

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

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Annex 1 – International Codes of Disease (ICD) to identify cases of heart failure

Code	Description
I11.0	Hypertensive heart disease with congestive heart failure
I13.0	Hypertensive cardiac and renal disease with congestive heart failure
I13.2	Cardiac and renal hypertensive disease with congestive heart failure and renal insufficiency
I42.0	Dilated cardiomyopathy
I42.6	Alcoholic cardiomyopathy
I42.8	Other cardiomyopathies
I42.9	Cardiomyopathy, unspecified
I50.0	Congestive heart failure
I.50.9	Unspecified heart failure
J.81	Pulmonary edema, unspecified and other

Minimally Invasive Epicardial Pacemaker Implantation in Neonates with Congenital Heart Block

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Abstract

Background: Few studies have characterized the surgical outcomes following epicardial pacemaker implantation in neonates with congenital complete atrioventricular block (CCAVB).

Objective: This study sought to assess the long-term outcomes of a minimally invasive epicardial approach using a subxiphoid access for pacemaker implantation in neonates.

Methods: Between July 2002 and February 2015, 16 consecutive neonates underwent epicardial pacemaker implantation due to CCAVB. Among these, 12 (75.0%) had congenital heart defects associated with CCAVB. The patients had a mean age of 4.7 ± 5.3 days and nine (56.3%) were female. Bipolar steroid-eluting epicardial leads were implanted in all patients through a minimally invasive subxiphoid approach and fixed on the diaphragmatic ventricular surface. The pulse generator was placed in an epigastric submuscular position.

Results: All procedures were successful, with no perioperative complications or early deaths. Mean operating time was 90.2 ± 16.8 minutes. None of the patients displayed pacing or sensing dysfunction, and all parameters remained stable throughout the follow-up period of 4.1 ± 3.9 years. Three children underwent pulse generator replacement due to normal battery depletion at 4.0, 7.2, and 9.0 years of age without the need of ventricular lead replacement. There were two deaths at 12 and 325 days after pacemaker implantation due to bleeding from thrombolytic use and progressive refractory heart failure, respectively.

Conclusion: Epicardial pacemaker implantation through a subxiphoid approach in neonates with CCAVB is technically feasible and associated with excellent surgical outcomes and pacing lead longevity. (Arq Bras Cardiol. 2017; 109(4):331-339)

Keywords: Heart Defects, Congenital; Infants, Newborns; Pacemaker, Artificial; Atrioventricular Block.

Introduction

Permanent pacemaker implantation in neonates with congenital complete atrioventricular block (CCAVB) is technically challenging due to the small size of the patients, presence of concomitant structural heart defects, and rapid child growth. This results in a high complication rate, including lead fracture and pacing/sensing dysfunction.[1-7] Fortunately, the number of children requiring pacemaker implantation in the first month of life is extremely low.[1-3] This is one reason why the surgical outcomes in this subset of patients remain poorly elucidated.

Several age-specific factors may contribute to the occurrence of pacemaker-related complications in pediatric patients. First, pulse generators and leads are primarily designed for adults. Second, small vessel size and associated intracardiac defects make transvenous implantation difficult or impossible. Third, there is a significant disproportion between the size of the permanent device and the child's body size. Furthermore, the effects of growth on the leads and on the lead-myocardial junction result in a high incidence of exit block and lead fractures.[1-16]

Deciding on the best surgical approach for pacemaker implantation in neonates requires a thorough assessment and a highly experienced cardiac surgery team, as evidence-based guidelines are still unavailable.[1-9,15-20] The purpose of this study was to assess the long-term outcomes of a minimally invasive epicardial approach using a subxiphoid access for pacemaker implantation in this patient population.

Methods

Patients

Between July 2002 and February 2015, a total of 16 consecutive neonates underwent epicardial pacemaker implantation in a cardiovascular referral center (Sao Paulo, Brazil). The Institutional Review Board of the institution approved this study. Device implantation was achieved through a minimally invasive subxiphoid incision.

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Among the 16 patients included in the study, nine (56.3%) were female. Mean patient age was 4.7 ± 5.3 days (range, 1 to 23 days). Indications for cardiac pacing included signs of low cardiac output in four (25%), heart rate < 55 beats/minute in three (18.7%), and both conditions in nine (56.3%) patients. Patent foramen ovale or patent ductus arteriosus were detected in 12 (75.0%) infants, and atrial septal defects were detected in four (25.0%) of them. In four (25.0%) neonates, congenital heart defects were not detected before pacemaker implantation. One child had moderate-to-severe tricuspid regurgitation, and another had pulmonary stenosis. Baseline characteristics of these patients are summarized in Table 1.

CCAVB was diagnosed prenatally in 15 (93.8%) patients and after birth in one. Fetal echocardiography, performed in 15 (93.8%) cases, confirmed the diagnosis of CCAVB and also detected structural heart defects in two (12.5%) fetuses. Maternal dexamethasone or beta-sympathomimetic agents were administered in six (37.5%) cases due to signs of fetal myocardial dysfunction and/or fetal hydrops.

Eight infants were delivered preterm (32-37 weeks gestational age). Cesarean section was carried out in all cases, except the one case in which there was no previous diagnosis of CCAVB. Gestational age, weight, and heart rate at birth are described in Table 1.

Clinical diagnosis of autoimmune disease was present in 12 (75.0%) mothers (Table 1). Among them, eight (50.0%) tested positive for systemic lupus erythematosus and four (25.0%) had Sjögren's syndrome. Neonatal lupus erythematosus was diagnosed in two infants. Increased levels of anti-Ro/SSA and anti-La/SSB antibodies were detected in 10 (62.5%) mothers, while in four (25.0%) mothers this test was not performed.

None of the neonates underwent temporary pacing. Two neonates had a pacemaker placed immediately after birth due to low cardiac output and severe bradycardia. The remaining cases were monitored closely in the neonatal intensive care unit. If the neonate had evidence of heart failure, low cardiac output, or heart rate < 55-beats/minute, infusion of dopamine was administered to postpone the time to pacemaker implantation.

Surgical technique

All procedures were performed with patients under general anesthesia in the operating room. A 3 cm longitudinal incision was made at the insertion of the xiphoid process and advanced inferiorly toward the umbilicus. After resection of the xiphoid process, an inverted T-shaped pericardiotomy was performed.

A bipolar steroid-eluting epicardial lead (CapSure Epi 4968-35; Medtronic Inc., Minnesota, USA) was implanted in all neonates. Each of the two poles of the lead was affixed to the visceral epicardium with 5-0 polypropylene sutures. One of the poles was positioned on the diaphragmatic wall of the right ventricle. The other pole was implanted either on the anterior wall of the right ventricle or the inferior wall of the left ventricle.

Measurements of sensing, impedance, and capture threshold were obtained for both unipolar and bipolar configurations. Once satisfactory pacing and sensing parameters were achieved, the ventricular lead and the pulse generator (VVIR) were connected and placed within a pocket located in the submuscular region of the epigastrium

Table 1 – Baseline characteristics of neonates with congenital complete atrioventricular block who underwent epicardial pacemaker implantation

Pt	Sex	Fetal diagnosis	GA at birth	Birth weight (g)	Heart rate at birth (bpm)	Cardiac defect	Age (days) at PM implant	Maternal lupus/ autoantibodies +	PM indication
1	F	Y	36	2630	40	N	4	Y	Bradycardia
2	F	Y	38	3046	50	PFO, PDA	3	Y	Bradycardia, HF
3	F	Y	36	1950	48	PFO, PDA, PS	2	N	Bradycardia
4	M	Y	37	3895	50	N	2	Y	HF
5	M	Y	32	2680	42	N	1	Y	Bradycardia, HF
6	F	Y	37	2720	45	ASD, PDA	9	Y	Bradycardia, HF
7	M	N	38	2700	40	PFO, PDA	23	N	Bradycardia, HF
8	F	Y	38	2655	42	N	2	Y	Bradycardia, HF
9	M	Y	39	3200	50	PFO, PDA	3	N	Bradycardia, HF
10	F	Y	36	2780	56	PFO, PDA	1	Y	Bradycardia, HF
11	F	Y	37	2340	42	ASD, PDA	5	Y	HF
12	F	Y	38	3340	40	PFO, PDA	2	Y	Bradycardia, HF
13	M	Y	38	3060	70	PFO, PDA	4	Y	HF
14	M	Y	38	2360	64	PFO, ASD	4	N	HF
15	M	Y	39	3500	49	PFO, PDA	4	Y	Bradycardia
16	F	Y	37	2600	50	ASD, PDA	6	Y	Bradycardia, HF

ASD: atrial septal defect; bpm: beats per minute; F: female; g: grams; GA: gestational age (in weeks); HF: heart failure; M: male; N: no/absence; PDA: patent ductus arteriosus; PFO: patent foramen ovale; PM: pacemaker; PS: pulmonary stenosis; Pt: patient; Y: yes/presence.

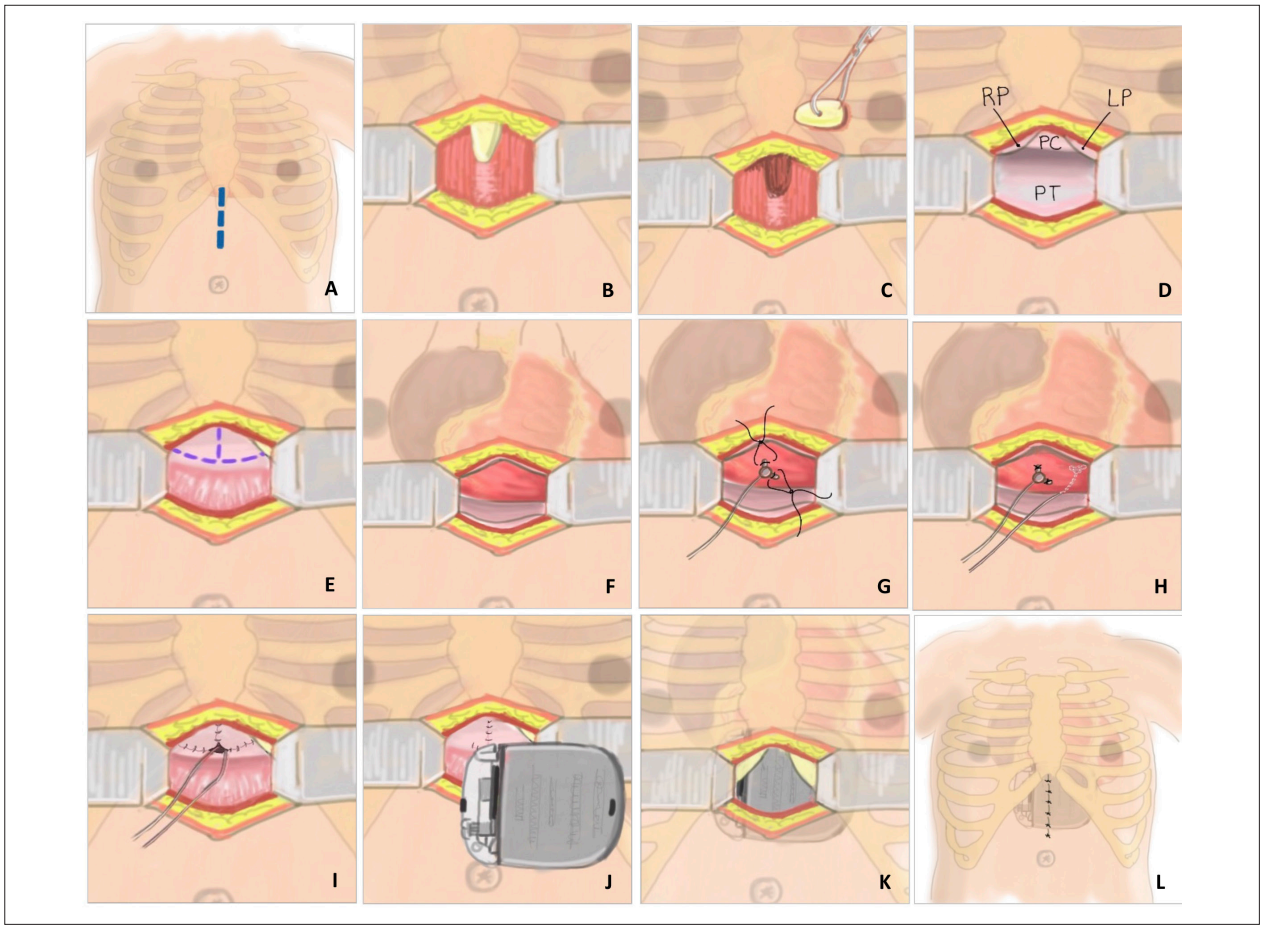

Figure 1 – *Epicardial pacemaker implantation in neonates through a subxiphoid approach. A: Midline incision in the skin, subcutaneous tissue, and aponeurosis of the rectus abdominis muscle; B: Xiphoid process view, which approximately occupies the upper half of the incision; C: Resection of the xiphoid process; D: Pericardial sac closed (PC), between the right pleura (RP), left pleura (LP) and the parietal peritoneum (PT); E: Inverted T-shaped pericardiotomy incision; F: Heart view after opening the pericardial sac and traction in the caudal direction; G: The bipolar steroid-eluting ventricular lead is directly affixed to the epicardium with two 5-0 polypropylene sutures; H: Position of the two poles of the lead: the cathode was positioned on the diaphragmatic wall of the right ventricle; the anode was implanted on the anterior wall of the right ventricle or on the inferior wall of the left ventricle; I: Pericardial sac already closed with the bipolar lead externalized in a rectilinear trajectory toward the epigastrium; J: Epigastric submuscular pulse generator pocket; K: Pulse generator positioned within the epigastric submuscular pocket and connected to the bipolar ventricular lead; L: Final aspect of the operation.*

(Figure 1). Lead excess was carefully accommodated under the pulse generator to leave its trajectory rectilinear to avoid excess in the pericardial sac or in the retrosternal space. The pulse generator was attached to the left rectus abdominis muscle. Pericardial drainage tubes were not used, and postoperative chest radiography confirmed proper lead location (Figure 2).

Patients' follow-up

All patients were followed up by a pediatric cardiology team and a cardiac pacing specialist. During follow-up, clinical assessment of all patients was performed, including careful evaluation of signs and symptoms related to heart failure. Patients with congenital heart defects were also evaluated regarding the optimal time for surgical repair.

Clinical follow-up and device interrogation visits were conducted every 6 months. In addition, subjects were periodically contacted by telephone and their medical records were regularly monitored.

Pacemaker programming was carried out according to individual patient clinical characteristics, and pacing energy was adjusted to allow for an optimal safety margin with respect to the ventricular pacing threshold. In the early follow-up period, the pacemaker was programmed at 110 to 120 beats per minute and this minimal heart rate was incrementally decreased in the chronic period, according to the individual characteristics and the childhood phase.

Data collection and outcome variables

Study data were collected and managed using Research Electronic Data Capture (REDCap) software hosted in our institution's server.[21,22]

The outcomes evaluated in the study included (1) intraoperative and immediate postoperative complications, or complications during the clinical follow-up period and (2) mortality from any cause. Quantitative variables are described as mean and standard deviation and qualitative variables as absolute and relative frequencies.

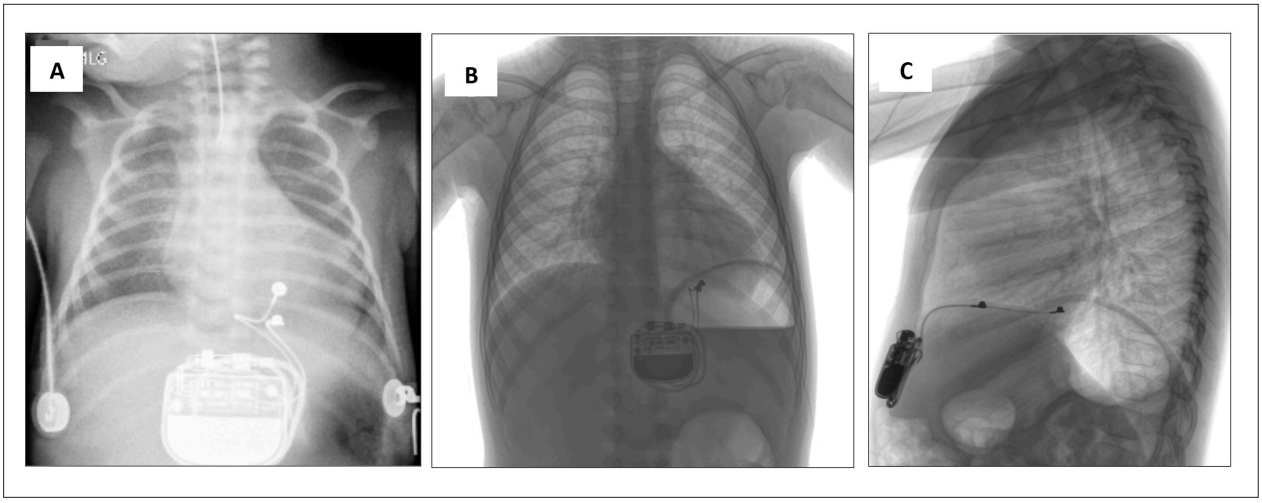

Figure 2 – *Chest radiographic projections displaying the radiologic appearance of epicardial pacemaker implantation immediately after the procedure (A) and 3 years later, in anteroposterior (B) and lateral projections (C).*

Results

All procedures were successful with no perioperative lead dislodgment, bleeding, arrhythmias, or early deaths. Mean operating time was 90.2 ± 16.8 minutes (range, 65 to 120 minutes; median, 89 minutes). Four patients had hemodynamic instability, which was treated by decreasing the pacing rate and intravenous infusion of epinephrine (0.01 μg/kg/min).

The cathode of the ventricular lead was implanted on the inferior wall of the left ventricle and the diaphragmatic wall of the right ventricle in 10 (62.5%) and six (37.5%) neonates, respectively. The anode was implanted on the diaphragmatic or anterior wall of the right ventricle in 13 (81.3%) and three (18.8%) patients, respectively. One neonate underwent concomitant surgical closure of the patent ductus arteriosus by an independent incision (extra-pleural posterolateral thoracotomy). Excellent intraoperative pacing and sensing thresholds were obtained in all patients, as described in Table 2.

A Microny II SR (St Jude Medical, California, USA) pulse generator was used in almost all patients. In only one case, an Altrua S601 SSIR (Boston Scientific, Minnesota, USA) pulse generator was chosen due to unavailability of the Microny device.

After pacemaker implantation, mechanical pulmonary ventilation was maintained for a minimum of 4 hours and a maximum of 30 days (mean, 117.2 ± 174.9 hours). One neonate was maintained on mechanical pulmonary ventilation for 30 days due to lung maturation problems. The length of stay in the neonatal intensive care unit ranged from 2 to 32 days (mean, 13.8 ± 7.0 days) and the total hospitalization length ranged from 7 to 49 days (mean, 23.4 ± 12.0 days).

Minimal superficial wound infection was the only procedure-related complication observed in our patients, occurring in three (18.8%) neonates. Other complications observed included pulmonary infection in two (12.5%), atelectasis in one (6.3%), urinary tract infection in one (6.3%), and renal failure in one (6.3%) neonate who also had superior vena cava thrombus treated with thrombolysis.

The patients were followed individually for 4.1 ± 3.9 years (range, 12 days - 12.7 years, median, 3.7 years). There were two deaths. One occurred 12 days after pacemaker implantation due to bleeding complications secondary to thrombolytic use. The other patient, who was being followed in another hospital, died of progressive refractory heart failure 325 days postoperatively.

Overall, 11 children remain without signs/symptoms of heart failure or need for cardiovascular medication. Two children underwent surgical repair of congenital heart defects. Percutaneous pulmonic valvuloplasty was performed in a 2-month-old girl with pulmonary valve stenosis. This resulted in rupture of a tricuspid valve papillary muscle and required urgent surgical repair of the pulmonic and tricuspid valve. A 4-year-old girl underwent surgical mitral valve repair and closure of an atrial septal defect. Concomitantly, this child was upgraded from a single-chamber to a dual-chamber pacemaker by using the previous ventricular lead and the same epigastric pulse generator pocket. Finally, a 5-year-old boy presented with refractory heart failure and was upgraded from a single-chamber device to a biventricular device for cardiac resynchronization therapy and 7 months later underwent heart transplantation (Table 3).

During follow-up, none of the subjects experienced loss of capture, lead dislodgement, or lead fracture. None of the patients displayed pacing or sensing dysfunction, and all pacemaker parameters remained stable throughout the follow-up period. Three children underwent pulse generator replacement due to normal battery depletion at 4.0, 7.2, and 9.0 years of age without the need for ventricular lead replacement (Table 3).

An echocardiogram confirmed normal cardiac anatomy and normal left ventricular function in five (31.3%) children. Among the cases with intracardiac defects, only two underwent surgical repair due to hemodynamic compromise. Of the 13 (81.3%) patients who remain in follow-up, only one was found to have reduced left ventricular ejection fraction (LVEF = 0.51).

Table 2 – Perioperative patient details

Pt	Total procedure time (minutes)	Pulse generator	Ventricular lead	Pacing site	R wave (mV) Uni/ Bi	Ventricular threshold at 0.5 ms (V) Uni/ Bi	Ventricular impedance (Ohms) Uni/ Bi	Endotracheal intubation (hours)	LOS in the ICU (days)
1	85	Altrua S601	4968-35	LV	12.5 / 12.5	0.5 / 0.5	695 / 896	28	16
2†	76	Microny	4968-35	LV	10.5 / 8.3	0.6 / 0.4	540 / 958	30	16
3	88	Microny	4968-35	LV	9.4 / 13.0	0.6 / 0.5	505 / 730	7	17
4	92	Microny	4968-35	RV	16.2 / 26.0	0.4 / 0.5	614 / 708	4	22
5	72	Microny	4968-35	RV	8.3 / 9.6	0.7 / 0.8	647 / 775	672	32
6	85	Microny	4968-35	LV	12.5 / 12.5	0.6 / 1.5	636 / 926	25	10
7	90	Microny	4968-35	LV	13.0 / 15.2	1.1 / 1.2	800 / 930	48	18
8	95	Microny	4968-35	RV	7.2 / 7.8	0.8 / 0.9	845 / 885	4	2
9	120	Microny	4968-35	RV	10.5 / 12.5	0.5 / 0.6	770 / 879	192	10
10	115	Microny	4968-35	LV	5.3 / 9.7	0.8 / 1.0	745 / 944	168	10
11	70	Microny	4968-35	LV	12.5 / 9.2	0.8 / 0.7	862 / 970	120	18
12	115	Microny	4968-35	RV	8.3 / 11.0	0.5 / 0.8	590 / 902	336	14
13	65	Microny	4968-35	LV	14.5 / 17.4	1.0 / 0.9	510 / 816	26	11
14	105	Microny	4968-35	LV	12.5/ 17.1	0.6 / 0.7	823 / 920	168	13
15	95	Microny	4968-35	RV	7.8 / 8.5	0.7 / 0.9	780 / 950	24	19
16	75	Microny	4968-35	LV	7.3 /9.6	0.6 /0.7	810 / 880	23	13

Bi: bipolar; LOS in the ICU: length of stay in the intensive care unit; LV: left ventricle; mV: millivolts; Pt: patient; RV: right ventricle; Uni: unipolar; V: volts. †: Neonate underwent concomitant surgical closure of the patent ductus arteriosus.

At the last follow-up, the electrocardiogram confirmed sinus rhythm with atrioventricular dissociation in all patients. Chest radiography revealed proper device location, lead integrity, and cardiac silhouettes within normal limits (Figure 3).

Discussion

The use of cardiac pacing in neonates is still an area of significant controversy. Opinions differ with respect to the ideal pacing mode, the best surgical approach to pace the heart of small infants, the optimal lead choice which provides the best short and long-term outcomes, and the appropriate strategy to accommodate the pulse generator in this subset of patients.[1-9,15-20]

Traditionally, an epicardial approach has been preferred, though access options (sternotomy, lateral thoracotomy, subxiphoid) may vary.[1-18] On the other hand, the feasibility of transvenous pacemaker implantation has been described in neonates, either by the tributaries of the superior vena cava or via the branches of the iliac veins.[3,10,13,14,20] The disproportion between the small body size and the device dimensions prevents placement of the pulse generator in the chest wall. Therefore, to prevent pocket-related problems in neonates, pulse generators are usually placed in the abdominal wall.[12-18]

The debate regarding the optimal pacing mode for neonates is still ongoing. In most experts' opinion, a single-chamber ventricular system is the first choice, reserving dual-chamber systems or even cardiac resynchronization therapy for children with impaired left ventricular function or poor adjustment to single-site ventricular pacing.[18-20] To date, few studies have recommended the use of more sophisticated pacing modes or cardiac resynchronization therapy as an initial strategy.[4,9,19]

Regardless of the surgical approach and pacing mode, device-related complications are common during follow-up. Although pocket-related complications, in particular, erosions or thinning of the skin are more frequent when the device is implanted in the chest wall, abdominal pockets may also be associated with complications.[15,17,18]

It is worth highlighting that lead fracture remains an important determinant of lead survival and is directly associated with the patient's growth.[3,4,7,10-16,20] Overall, standard epicardial penetrating leads have been associated with a high incidence of increased pacing thresholds following implantation, requiring early lead or pulse generator replacement. Recent studies have shown that steroid-eluting leads are associated with a lower rate of lead failure.[11,12]

The technique described in this article aims to increase the safety of pacemaker use in neonates in four main ways: (1) reduction in surgical trauma by not opening the sternum or intercostal spaces; (2) safe approach and good cosmetic result for pulse generator accommodation in the preperitoneal space submuscularly; (3) reduction in fibrosis at the lead-myocardial junction by the use of steroid-eluting leads; (4) reduction in the effect of the child's growth on the leads and on the lead-myocardial junction by using a rectilinear trajectory and by ensuring proximity between the lead and pulse generator.

Table 3 – Long-term outcomes after epicardial pacemaker implantation in neonates with congenital heart block

Pt	Follow-up time (years)	Surgical complications	Clinical complications	Medication use	NYHA FC	Generator replacement	Upgrade	LVEF	Surgical repair of intracardiac defect
1	4.2	N	N	N	I	N	N	0.51	N
2	1.1	N	N	N	I	N	N	0.67	N
3	0.8	N	N	Furosemide, spironolactone	I	N	N	0.61	Y
4	10.7	N	N	N	I	Y (7.2 years after PM implant)	N	0.66	N
5	5.0	N	N	N	I	N	N	0.71	N
6	4.2	Superficial wound infection	N	Furosemide, spironolactone	I	Y (4.0 years after PM implant)	DDD (4.0 years after PM implant)	0.67	Y
7	2.5	N	N	N	I	N	N	0.66	N
8	12.7	Superficial wound infection	N	N	I	Y (9.0 years after PM implant)	N	0.74	N
9	5.9	N	Heart transplant (5.9 years after PM implant)	Furosemide, spironolactone, carvedilol, captopril	III	Y (5.2 years after PM implant)	CRT-P (5.2 years after PM implant)	0.33	N
10	10.2	Superficial wound infection	N	N	I	Y (3.9 years after PM implant)	N	0.71	N
11	4.0	N	N	N	I	N	N	0.64	N
12	-	N	Death (12 days after PM implant)	Furosemide, amiodarone	IV	N	N	-	N
13	3.5	N	N	N	I	N	N	0.75	N
14	0.9	N	Death (325 days after PM implant)	N	I	N	N	0.65	N
15	0.4	N	N	Furosemide	I	N	N	0.75	N
16	0.8	N	N	N	I	N	N	0.68	N

CRT-P: cardiac resynchronization therapy; DDD: dual-chamber pacemaker; LVEF: left ventricular ejection fraction; N: no; NYHA FC: New York Heart Association Functional Class; PM: pacemaker; Pt: patient; Y: yes.

In our study, all operations were successful, and there were no perioperative complications. In addition, there were no complications related to surgical technique during the follow-up period (maximum of 12 years). In particular, there were no pocket-related complications (infection or skin erosion); lead-related complications (lead fracture), increases in pacing thresholds, or early battery depletion. Finally, measurements of sensing, pacing, and impedance remained satisfactory during the follow-up period.

Despite the use of single-site ventricular pacing, clinical signs of heart failure or echocardiographic abnormalities were not observed at last follow-up evaluation in 13 of the 16 neonates included in this study. In cases where hemodynamic compromise secondary to intracardiac defects was detected, surgical repair completely reversed this condition. Two patients developed severe ventricular dysfunction; one underwent a heart transplant and another died.

Within our study, there are several limitations. The main one is the small number of cases, inherent to the rarity of CCAVB and other causes of bradyarrhythmias requiring pacemaker implantation during the neonatal period. Second, the lack of a gold-standard surgical technique for pacemaker implantation in neonates does not allow for the formation of a control group with which to compare results. Even in larger centers, it is nearly impossible to conduct a study to compare outcomes between different techniques of pacemaker implantation in this subset of patients. Finally, all procedures were performed by the same surgeon. This lack of operator variability may have influenced surgical results.

Conclusion

Epicardial pacemaker implantation through a subxiphoid approach in neonates with CCAVB is technically feasible and results in excellent surgical outcomes and pacing lead longevity. In addition, this surgical approach solves two of the main challenges related to permanent cardiac pacing in neonates: pocket and lead-related complications.

Author contributions

Conception and design of the research, Acquisition of data and Writing of the manuscript: Costa R, Silva KR; Analysis and interpretation of the data and Critical revision

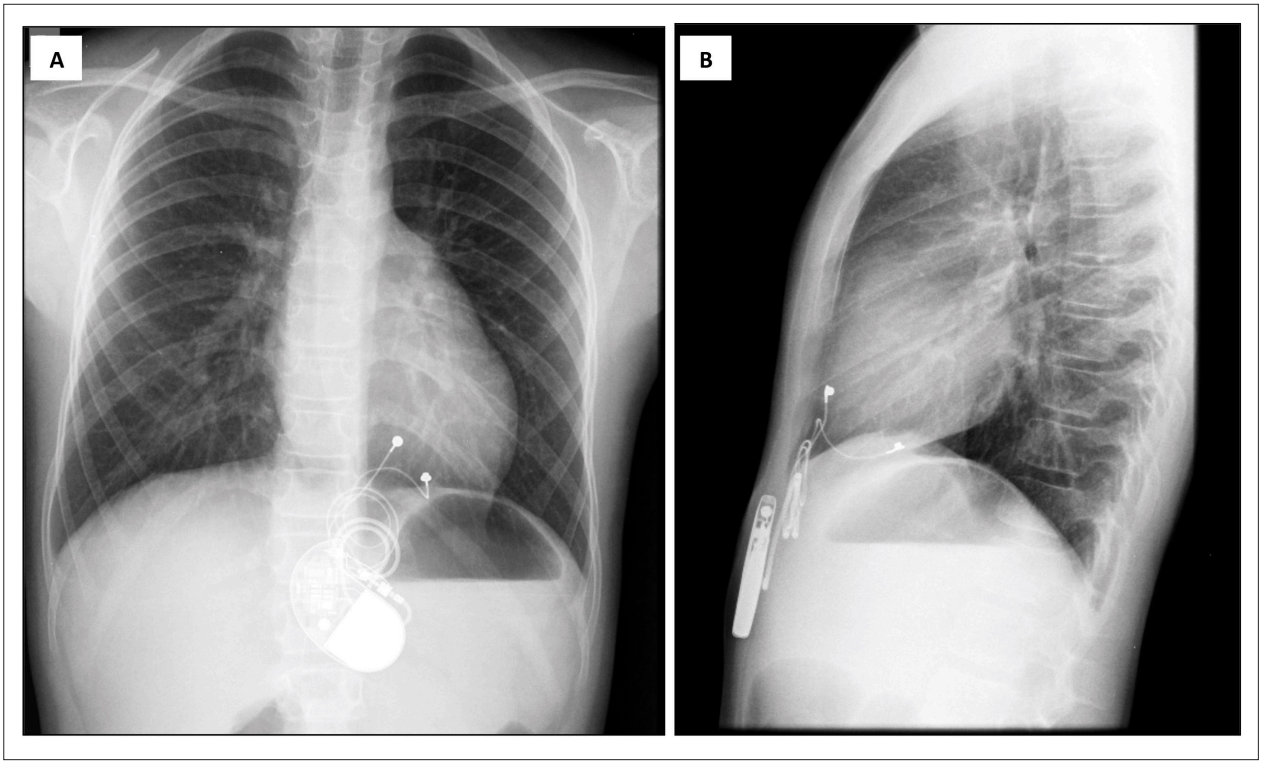

Figure 3 – *Chest radiographic projections displaying the appearance of epicardial pacemaker 10 years later, in anteroposterior (A) and lateral projections (B).*

of the manuscript for intellectual content: Costa R, Silva KR, Martinelli Filho M, Carrillo R.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

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Original Article

Pre-Participation Physical Fitness does not Influence Adherence to a Supervised Exercise Program

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Abstract

Background: **Exercise-based cardiac rehabilitation tends to reduce mortality. However, it requires medium/long-term adherence to regular physical exercise. It is relevant to identify the variables that affect adherence to an supervised exercise program (SEP).**

Objective: **To evaluate the influence of pre-participation levels of aerobic and non-aerobic physical fitness components in medium-term adherence to SEP.**

Methods: **A total of 567 SEP participants (65 ± 12 years) (68% men) were studied. Participants adherent to the program for less than 6 months (48%) (non-adherent - NAD) were compared with 52% of participants who were adherent for 6 months or more (adherents - AD). In the non-aerobic fitness, flexibility (FLX) (Flexitest) and muscle power (MPW)/body weight in standing rowing (watts/kg) were evaluated while aerobic fitness was obtained by direct measure of VO_2max/body weight (VO_2). These measurements were normatized for sex and age based on percentiles (P) (P-FLX/P-MPW) of reference data or percentages of predicted (P-VO_2). Additionally, AD and NAD with extreme results (tertiles) were simultaneously compared for the three variables.**

Results: **There was no difference between AD and NAD for non-aerobic results, in median [P25-P75], P-FLX: 30 [13-56] and 31 [9-52], respectively, (p = 0.69) and P-MPW: 34 [17-58] and 36 [16-62], respectively (p = 0.96), and for aerobic results (mean ± standard error) P-VO_2 (75.9 ± 1.3% and 75.0 ± 1.3%, respectively) (p = 0.83). When comparing extreme tertiles, a difference was found for P-MPW in the lower tertile only, with a slight advantage of AD over NAD- 9 [5-16] versus 4 [1-11] (p = 0.04).**

Conclusion: **Although awareness of the pre-participation levels of aerobic and non-aerobic physical fitness components is useful for individualized exercise prescription, these variables do not seem to influence medium-term adherence to SEP. (Arq Bras Cardiol. 2017; 109(4):340-347)**

Keywords: **Muscle Strength; Oxygen Consumption; Physical and Rehabilitation Medicine; Sports Medicine.**

Introduction

The beneficial effects of regular physical activities and physical exercises, exercises on health, even if in small doses, are widely known.[1] High levels of aerobic[2] and anaerobic[3] fitness are associated with reduced all-cause mortality in middle-aged and elderly individuals. In contrast, there is evidence that only three weeks of bed rest would result in a reduction of aerobic fitness by 30%.[4]

In fact, attention has been increasingly focused on physical exercise for secondary prevention of cardiovascular diseases (CVD) since the end of the 50s.[5-7] Currently, physical exercise is recommended by the guidelines of cardiology societies all over the world[8-12] as part of the so called cardiac rehabilitation (CR). CR encompasses several components, but classically, physical exercise in different forms are the single or the main component of which is characterized as exercise-based CR.[13,14] Although underused and frequently of short duration, exercise-based CR promotes several benefits to health, especially in the reduction of cardiovascular mortality.[13] However, despite these favorable evidence of the exercise-based CR, staying physically active throughout life, i.e., being adherent to habitual exercise is difficult for the majority of CVD patients,[15,16] reducing the potencial benefits of this intervention.

Therefore, it seems relevant to investigate the variables capable of influencing the adherence rate to adherence to an supervised exercise program (SEP).[17-21] To the best of our knowledge, the possible influence of the aerobic and non-aerobic[22] fitness component levels before SEP on its adherence has not been studied yet. If, on the one hand, it may be easier to increase initially low fitness levels, on the other hand, individuals with low physical fitness may feel unable to exercise regularly, which could compromise their

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adherence to a SEP. In this context, we aimed to investigate the influence of flexibility (FLX), muscle power (MPW) and aerobic fitness or maximum oxygen uptake (VO_2max) on medium-term adherence to a SPE.

Methods

Sample

We retrospectively analyzed data of 644 individuals who initiated their participation in a SEP in a private clinic located in the south of Rio de Janeiro city, Brazil, between January 2009 and March 2015. These individuals had been mostly referred by their assistant physicians. Before initiating the SEP, participants had undergone a comprehensive and detailed assessment, including anamnesis, physical exercise, anthropometry, electrocardiography, resting spirometry, 4-second exercise test, cardiopulmonary exercise test (CPET),[23,24] and evaluation of FLX[25] and MPW.[26]

For final characterization of the sample, individuals with one of the following conditions were excluded: 1- age younger than 30 years; 2- an interval longer than 120 days between pre-participation assessment and the start of participation in the SEP; 3- absent data on FLX, MPW or VO_2max in the pre-participation assessment. In the pre-participation assessment. After application of these criteria, 6 volunteers were excluded because of age, 14 for having started the SEP 120 days after pre-participation assessment, 41 for having incomplete non-aerobic fitness data, and 16 for not performing CPET or for having not achieved maximum strength. Therefore, 567 participants were included in the study.

For analysis if adherence, an 'appropriated participation was considerated as a continuos participation for more than six-months, that is, a medium-term participation without interruptions longer than one-month. There was a wide variation in the frequency of attendance of the SEP - one to six sessions a week - even though most were advised to attend the SEP three days a week. Thus, different from some other studies, the number of sessions that the volunteers effectively participated was not considered to characterize adherence. Participants were then separated in two groups according to the period of continuous participation in this SEP, as determined by registration in the attendance forms non-adherents (NAD) – less than six months – adherents (AD) – six months or more – regardless of the number of sessions attended in each month during the study period (January 2009 – September 2015).

All participants read and signed the informed consent form before the CPET and participation in the SEP. Both informed consent form and the retrospective analysis of the data for research purposes were approved by the Ethics Committee (report number 218/10).

Supervised exercise program

The SEP was conducted in a temperature- (21-24°C) and humidity-controlled (4-60%) room. Before initiating the exercise session, each participant was briefly seen by a physician, who prescribed the aerobic part of the session. The sessions included aerobic exercises – cycle ergometer tests of lower and upper limbs, treadmill, rowing ergometry, and ski ergometer test – and exercises for muscle strengthening, FLX, balance and motor coordination, each session with 60 to 75 minutes of duration. According to the patients clinical conditions and individual goals, some participants also underwent inspiratory muscle training and isometric handgrip test, whose clinical safety has been previously demonstrated.[27,28] Continuous heart rate monitoring and intermittent blood pressure and electrocardiohgram monitoring were performed during the exercise sessions, as clinically indicated.

One important characteristic of this SEP, and a variable that could positively contribute to adherence, was the complete freedom of choosing for exercising anytime – 15.5 hours/day during the weekdays and 9 hours/day on Saturdays - during the operation time of the clinic, a total of 86.5 hours per week.

Assessment of physical fitness components: FLX, MPW and aerobic conditioning

FLX was assessed by Flexiteste,[29,30] which evaluates the maximum passive mobility of twenty joint movements, including seven joints, using an increasing, ordinal scale of scores ranging from 0 to 4, by comparing the amplitude obtained by each patient with the specific evaluation maps. The sum of the scores of each of the 20 joint movements generated a global index of body flexibility named Flexindex. Aiming to control the influence of age and sex, Flexindex of each participant was expressed in percentile (P) (P-FLX), adjusted for age and sex, based on data from previous report.[25]

Assessment of relative MPW – MPW (watts)/body weight (kg) – was performed during the concentric phase in standing position, using a standardized method described in details in previous studies, showing the reliability of the evaluations.[26] Briefly, MPW was measured using the Fitrodyne (Fitronic, Slovakia), by the product of mean velocity (m/s) during concentric exercise and weight lifted (kg). The weight was gradually increased every five kilograms until maximum MPW was achieved.[26,31] Similarly to FLX, individual data were adjusted using laboratory reference data (unpublished data obtained from 4,567 adults in both sexes and age range compatible with the present study), and expressed as percentile (P-MPW), according to age and sex.

Aerobic fitness was evaluated by CPET using directly measured VO_2max relative to body weight and direct analysis of expired gases (VO2000; Medgraphics, USA), as previously described in details[24,32] and following a recent guidelines of Brazilian authors.[23] All tests were performed by only four physicians in a temperature-controlled room, which was properly equipped for potential clinical events. Tests were performed using individualized ramp protocols, aiming a duration of 8 to 12 minutes to achieve exhaustion.[33] Individual aerobic fitness, in mL/(kg.min), was then expressed as percentage of predicted VO_2max (P-VO_2), which was calculated by the formula 60-0.55 x age (years) for men and 48-0,37 x age (years) for women.[34]

Statistical analysis

Statistical analysis was performed based on the measuring scales and data distribution. The D'Agostinho & Pearson, Shapiro-Wilk and Kolmogorov-Smirnov tests were used to test the normality of data distribution. The Student's t-test was used for comparisons of continuous, normally distributed variables between groups and between subgroups. The Mann-Whitney test was used for analysis of continuous variables without normal distribution, and the chi-square statistics for categorical variables (clinical features and use of medications). Results are shown as mean and standard error for continuous, normally distributed variables, and as median and interquartile range (25th-75th percentile) or percentage (as appropriate) for the others.

As an additional analysis, we applied the Mann-Whitney test to identify, in NAD and AD groups, possible differences in adherence to SEP in those participants located in the lower (first tertile) and upper (third tertile) limits of physical fitness range of the three physical fitness components. Thus, new, smaller subgroups were defined – NAD1 and AD1, for NAD and AD individuals, respectively, located in the first tertile; and NAD3 and AD3, for non-adherent and adherent individuals, respectively, located in the third tertile – with results already adjusted for age and sex in flexibility, muscle power, and aerobic fitness. The GraphPad Prism 6.0 (GraphPad Software, USA) was used for analyses and figures, and a level of 5% was set as statistically significant.

Results

Among the 567 participants (68% men), mean age was 65 ± 12 years (31-92 years). Based on the criterion used to define adherence to SEP, i.e. continuous attendance in the program for six months, 52% were classified as AD and 48% as NAD. There were no differences in age (p = 0.29) or sex distribution (p = 0.27) between AD and NAD. Body mass index (BMI) varied from 17.5 to 52.4 kg/m^2 (median 27.1 kg/m^2, interquartile range of 24.6 – 30.5 kg/m^2), without difference between the groups (p = 0.25).

Based on clinical data obtained from patients' medical records, 61% of patients were hypertensive, 56% had coronary artery disease (CAD), 31% had previous acute myocardial infarction, 37% had a history of percutaneous angioplasty and 17% of coronary artery bypass surgery. In addition, 21% were obese, 30% had a diagnosis of diabetes mellitus, 46% were sedentary, 55% were former smokers, i.e., had not smoked for at least six months, and only 5% were active smokers. Considering all these variables, there was only a, slight difference in smoking history (mostly former smokers) between AD (55%) and NAD (65.8%) (p = 0.01). With respect to current and regular use of medications, 63% of patients used beta-blockers, 76% used hypolipidemic agents, 73% used antiplatelet gents, and 59% used psychotropics, with no difference between the groups (p > 0.05). A more detailed description of these results is found in Table 1.

The interval between pre-participation assessment and the first SEP session was between 1 and 9 days (median 4 days) for half of participants. During the study period, median duration of participation in the SEP was 6 months, with P25 and P75 of 3 months and 15 months, respectively. Median number of the SEP sessions attended by participants was 46, with P25 and P75 of 19 and 122 sessions, respectively, and minimum of one and maximum of 1,358 sessions. Most participants attended between 5 and 10 sessions per month, with a median of 7.6 sessions/month. Comparison of demographic and SEP's participation data between AD and NAD are shown in Table 2.

Table 1 – Clinical characteristics and use of medications in adherent and non-adherent patients (n = 567) to the supervised exercise program (SEP) and in the subgroups in the lower (n = 43) and upper (n = 50) extreme tertiles of aerobic and non-aerobic physical fitness

	Participants			1st (lower) tertile			3rd (upper) tertile		
	AD (n = 298)	NAD (n = 269)	p	AD1 (n = 18)	NAD1 (n = 25)	p	AD3 (n = 20)	NAD3 (n = 30)	p
Clinical features									
Coronary artery disease (%)	58	53	0.24	22	48	0.08	50	57	0.64
Systemic arterial hypertension (%)	64	58	0.16	67	80	0.32	65	57	0.56
Dyslipidemia (%)	69	68	0.78	50	76	0.08	80	70	0.43
Diabetes mellitus (%)	30	29	0.90	44	60	0.31	10	23	0.23
Smoking history (%)	55	66	0.01	44	64	0.20	50	70	0.15
Sedentary lifestyle (%)	44	48	0.30	72	72	0.99	25	33	0.53
Use of medications									
Beta-blockers (%)	66	60	0.17	72	72	0.99	65	63	0.90
Statins (%)	77	74	0.43	67	76	0.50	80	83	0.76
Antiplatelet agents (%)	73	72	0.64	50	68	0.23	60	77	0.21
Psychotropics (%)	58	60	0.79	56	64	0.58	30	50	0.16

NAD: non-adherents (<6 months of SEP); AD: adherents (≥6 months of SEP); NAD1: non-adherent 1st tertile; AD1: adherent 1st tertile; NAD3: non-adherent 3rd tertile; AD3: adherent 3rd tertile. Comparison of data distribution of the variables was carried out by chi-square test.

Table 2 – Results of demographic data and attendance data of adherent and non-adherent participants (n = 567) to the supervised exercise program (SEP) and in the subgroups in the lower (n = 43) and upper (n = 50) extreme tertiles

	Participants			1st (lower) tertile			3rd (upper) tertile		
	AD (n = 298)	NAD (n = 269)	p	AD1 (n = 18)	NAD1 (n = 25)	p	AD3 (n = 20)	NAD3 (n = 30)	p
Men (%)	66	70	0.26	64	56	0.57	83	90	0.51
Age (†)	66 ± 0.7	64 ± 0.7	0.29	60 ± 2.8	57 ± 2.1	0.34	69 ± 1.8	70 ± 2.4	0.76
Body mass index (kg/m^2) (†)	27 ± 0.2	28 ± 0.3	0.25	32 ± 1.5	34 ± 1.5	0.43	26 ± 0.74	25 ± 0.43	0.75
Interval between assessment and enrollment (days) (†)	9 ± 0.9	11 ± 1.2	0.44	7 ± 2.1	12 ± 4.9	0.73	14 ± 4.7	12 ± 4.6	0.28
Months of SEP (†)	22 ± 1.1	2.9 ± 0.1		19 ± 3.5	3 ± 0.3		22 ± 5.4	3 ± 0.2	
Number of sessions/month (*)	9 (7–10)	7 (4–9)	< 0.001	9 (9–13)	7 (5–9)	0.010	9 (7–10)	5 (3–8)	0.003

(*) median (percentile 25 – percentile 75); (†) mean ± standard error, t-test for age and Mann-Whitney test for the other variables. Comparison between men and women percentiles was performed by the chi-square test.
NAD: non-adherents (< 6 months of SEP); AD: adherents (≥ 6 months of SEP); NAD1: non-adherent 1st tertile; AD1: adherent 1st tertile; NAD3: non-adherent 3rd tertile; AD3: adherent 3rd tertile.

Regarding the results of physical fitness components in the pre-participation assessment, which are the main object of this study, we found that the values obtained in percentile and/or percentage of predicted value (adjusted for age and sex) for the 567 participants tended to be lower than those expected for the general population, i.e., percentiles equal to or greater than 50 (median) and percentage equal to or greater than 100%. For non-aerobic components the median and interquartile range were: P-FLX = 30[11-55] and P-MPW = 35[17-60], and for the aerobic component the mean ± standard error was P-VO_2 = 75.5 ± 0.91. Distribution of aerobic results, expressed as P (%) of VO_2max predicted, obtained by the CPET is shown in Figure 1. Comparison of the AD group with the NAD group showed no significant differences in the three components of aerobic and non-aerobic fitness, as described in Table 3.

In the other analysis, patients with worse (lower tertiles, n = 48) and better (upper tertiles, n = 50) physical fitness (the three components together) were compared for adherence to the SEP. In analysis of clinical data, current and regular use of medications, and results of physical fitness components, the only significant difference was found in P-MPW for individuals located in the lower tertile (in median and interquartile range): AD1 = 9 (5-16) and NAD1 = 4 (1-12) (p = 0.04). These results are described in Tables 1 and 2.

Discussion

The literature indicates that regular physical exercise is important for secondary prevention of CVD.[8,9] However, a very small proportion of patients is referred to, and an even smaller proportion of patients are actually enrolled in formal programs of CR or SEP. Despite cost-effectiveness of these programs,[21] the number of centers available in Brazil is known to be lower than the desired one. Among the individuals enrolled in the programs, a variable and unfortunately small number complete a reasonable number of exercise sessions, and an even smaller proportion effectively adopts the regular physical exercise as a healthy lifestyle practice. The present article contributes to the body of knowledge in the area, showing that pre-participation levels of the three components of both aerobic and non-aerobic physical fitness have no significant effect on medium-term (i.e., six months) adherence to a SEP.

Measurement and promotion of adherence to physical exercise is a big challenge that has been investigated for some decades, but there is still insufficient evidence towards desired clinical results.[35,36] Probably, adherence to a SEP is influenced by many factors including cognitive, behavioral, and environmental factors. By adopting different approaches and temporal criteria for characterization of adherence and non-adherence, we showed in previous studies with participants of this same SEP, the negative effect of obesity on adherence,[19] and that the distance from participants' home to the training center did not seem to be a determinant factor for adherence.[17]

Effective participation in SEPs normally results in significant improvement of physical fitness. A recent meta-analysis[37] indicates that mean gain in aerobic fitness was 6.6 mL/(kg.min), and 43 of the 48 original studies included showed significant aerobic gains from participation in an exercise-based CR. In this line of thought, it is of note that initial aerobic physical fitness seems to have a prognostic influence among CR participants. For example, in a study on 12,169 men with CVDs, Kavanagh et al.[38] observed that direct measurement of aerobic fitness before the CR had a strong, favorable influence on cardiovascular and all-cause mortality. Ross et al.[39] demonstrated in a recently published review that aerobic fitness is closely related to morbidity and mortality, and is a stronger predictor of cardiovascular risk than traditional risck factors such as diabetes mellitus, arterial hypertension and smoking.

Nevertheless, despite the rich literature about adherence to exercise, there seem to be very few data related to a possible influence of pre-participation aerobic and non-aerobic physical fitness levels on adherence to a SEP or to a more comprehensive CR program. Besides, the pre-participation

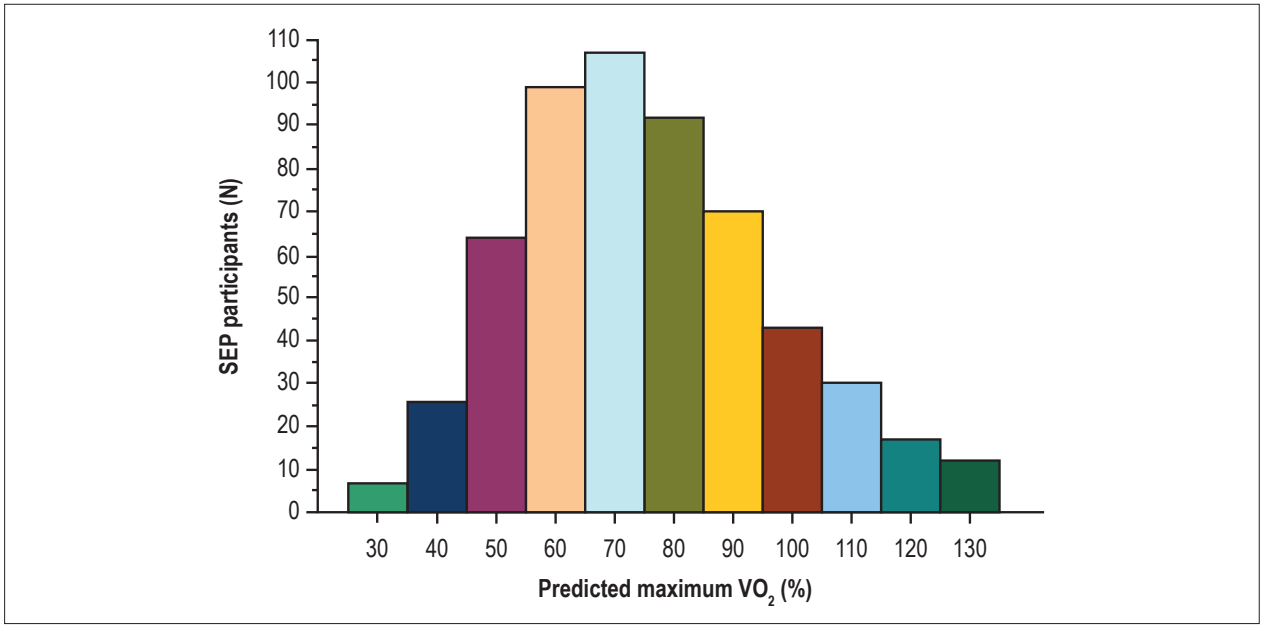

Figure 1 – *Distribution of aerobic fitness results (n = 567). SEP: supervised exercise program.*

Table 3 – Results of aerobic and non-aerobic physical fitness in adherent and non-adherent participants (n = 567) and in subgroups in the lower (n = 43) and upper (n = 50) tertiles

	Participants			1st (lower) tertile			3rd (upper) tertile		
	AD (n = 298)	NAD (n = 269)	p	AD1 (n = 18)	NAD1 (n = 25)	p	NAD3 (n = 20)	NAD3 (n = 30)	p
Flexindex*	30 (13–56)	31 (9–52)	0.69	6 (1–11)	4 (1–11)	0.70	70 (60–88)	74 (49–92)	0.85
Relative power *	34 (17–58)	36 (16–62)	0.96	9 (5–16)	4 (1–12)	0.039	78 (64–92)	73 (64–87)	0.42
Predicted relative maximum VO_2 (%)(†)	75.9 ± 1.27	75.0 ± 1.30	0.83	51.7 ± 2.65	52.1 ± 1.94	0.81	104.3 ± 3.54	103.0 ± 2.42	0.86

(*) age- and sex-percentile in median (25th percentile - 75th percentil); (†) percentile of predicted relative maximum VO_2 in mean ± standard error, Mann-Whitney test. NAD: non-adherents (< 6 months of SEP); AD: adherents (≥ 6 months of SEP); NAD1: non-adherent 1st tertile; AD1: adherent 1st tertile; NAD3: non-adherent 3rd tertile; AD3: adherent 3rd tertile; maximum VO_2: maximum oxygen consumption

levels of aerobic physical fitness were the object of studies about other relevant clinical outcomes. In light of this, it is worth mentioning the meta-analysis performed by Sandercook et al.,[37] which identified that initial aerobic levels may not predict the magnitude of absolute gain in VO_2max when participating on a CR,[37] although this seems to vary with the type of cardiovascular intervention and patient's clinical condition.[40] Unfortunately, this meta-analysis did not include adherence and hence its results cannot be compared with ours.

In fact, one should recognize the existence of many clinical, logistic and methodological difficulties for a careful, broad assessment of physical fitness components of all candidates for the CR programs and SEPs. Therefore, to our knowledge, this is the first study to obtain direct measurements of aerobic fitness and FLX and MPW data from a large group of participants before starting the SEP, and to evaluate the influence of these results on medium-term adherence (six months) to a SEP.

In the search of variables able to measure, in a practical, objective way, the chance of adherence, and to help physicians in the individualized approach of participants in the beginning of a SEP, we analyzed the possible influence of pre-participation levels of aerobic and non-aerobic components of physical fitness (FLX, MPW and aerobic fitness) on adherence to a SEP in a six-month period. Participants of the AD group and NAD group were not different in terms of sex, age, BMI, clinical profile and regular use of medications; the only exception was the different percentage of participants with history of smoking, which was higher in the NAD group. It is worth to mention that we opted to describe the variable 'smoking history' in the same way it has been usually described in clinical studies. However, in the present study, the percentage of active smokers among the SEP participants was very small, lower than 5%, with no relevant difference between the

groups and subgroups of the study. 'Active smoking' could have influenced the results if there was a clinically relevant difference in this variable between the groups. With respect to age, our data differ from a recent study that demonstrated that adherence in elderly patients is lower than in younger patients.[41] Demographic and clinical features, as well as different SEP may explain the discrepancy in these results.

In the general population, predicted VO_2max is expected to be 100%, and the mean percentile for age and sex is expected to be 50 (p50). However, our data indicated that pre-participation levels of physical fitness of the participants of a SEP, when normalized for age and sex based on reference data, tend to be lower than these values. This is in accordance with the perspective that CVDs and other chronic degenerative diseases tend to be more prevalent in sedentary or low active individuals or in those with low physical fitness.

Our most important finding was that low, isolated, pre-participation levels of aerobic fitness, global FLX and body weight-related MPW seem to not influence medium-term adherence to a SEP. Even using a combined analysis of the extreme tertiles, we did not find any marked influence of the pre-participation levels of physical fitness components on medium-term adherence to the SEP, except for a practically irrelevant, borderline statistically significant difference between median P-MPW of 9 and 4 for the AD and NAD groups, respectively. In this context, it is worth pointing out that recent data have shown beneficial effects of a four-week CR program even on individuals aged older than 75 years, with coronary or valve disease, with improvement of aerobic fitness and MPW.[42]

The present study has a number of positive features that deserve considerations. First, there is a new appreciation of CR and its application in non-hospital approaches, including community programs like the SEP of this study.[43] Second, our sample size of 567 participants was homogeneous regarding clinical features and regular use of medications after application of strict inclusion and exclusion criteria. Also, all measures were performed by only four physicians with wide experience in the protocols and measurement techniques, using routine assessment methods, which had been standardized in our lab. And since this was a retrospective study, the authors had no influence on the assessment and/or adherence to SEP results.

On the other hand, the study also has limitations that need to be addressed. Our sample included not only patients with coronary artery disease but also patients with many risk factors for CVD and other diseases. Unfortunately, we could not investigate objective indicators of the clinical reasons for SEP dropouts or mortality among participants of this study, which would be quite pertinent to the present study, and should be investigated in future studies. It is possible that the analysis of only some aspects of physical fitness lead to a limited and maybe biased view of the phenomenon of adherence to a SEP. However, the analysis of the extreme tertiles may corroborate our impression that pre-participation levels of the three physical fitness components, isolated or combined, do not affect medium-term adherence. Other aspects directly related to physical fitness, such as history of physical exercise and sports in different moments of life and magnitude of fitness gains during the SEP may have influenced adherence and should be object of future studies. In addition, racial, socioeconomic characteristics (most patients paid for participation in the SEP), and the higher proportion of men may have biased the present results and compromised their external validity. We could not assess the causes of SEP dropouts and whether participants who had dropped out the program before completing six months of participation continued or not to exercise by themselves and in different places such as clubs, gyms and even other SEPs. Further studies are needed to identify the influence of the components evaluated in this study, by comparing different programs and epidemiological profiles.

Conclusion

The levels of pre-participation aerobic and non-aerobic physical fitness do not affect medium-term adherence to a SEP, although the knowledge of these levels is not only important but recommended for an individualized prescription of aerobic and non-aerobic exercises. This information reinforces the idea that patients with optimal physical fitness, and even debilitated patients or with low physical fitness can be referred for enrollment in a SEP by their assistant physicians and be adherent to the program for at least six months.

Author contributions

Conception and design of the research and Acquisition of data: Nishijuka FA, Araújo CGS; Analysis and interpretation of the data, Statistical analysis, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Nishijuka FA, Silva CGS, Duarte CV, Araújo CGS; Obtaining funding: Araújo CGS.

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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Prevalence and Prediction of Obstructive Coronary Artery Disease in Patients Undergoing Primary Heart Valve Surgery

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Abstract

Background: The prevalence of coronary artery disease (CAD) in valvular patients is similar to that of the general population, with the usual association with traditional risk factors. Nevertheless, the search for obstructive CAD is more aggressive in the preoperative period of patients with valvular heart disease, resulting in the indication of invasive coronary angiography (ICA) to almost all adult patients, because it is believed that coronary artery bypass surgery should be associated with valve replacement.

Objectives: To evaluate the prevalence of obstructive CAD and factors associated with it in adult candidates for primary heart valve surgery between 2001 and 2014 at the National Institute of Cardiology (INC) and, thus, derive and validate a predictive obstructive CAD score.

Methods: Cross-sectional study evaluating 2898 patients with indication for heart surgery of any etiology. Of those, 712 patients, who had valvular heart disease and underwent ICA in the 12 months prior to surgery, were included. The P value < 0.05 was adopted as statistical significance.

Results: The prevalence of obstructive CAD was 20%. A predictive model of obstructive CAD was created from multivariate logistic regression, using the variables age, chest pain, family history of CAD, systemic arterial hypertension, diabetes mellitus, dyslipidemia, smoking, and male gender. The model showed excellent correlation and calibration (R^2 = 0.98), as well as excellent accuracy (ROC of 0.848; 95%CI: 0.817-0.879) and validation (ROC of 0.877; 95%CI: 0.830 - 0.923) in different valve populations.

Conclusions: Obstructive CAD can be estimated from clinical data of adult candidates for valve repair surgery, using a simple, accurate and validated score, easy to apply in clinical practice, which may contribute to changes in the preoperative strategy of acquired heart valve surgery in patients with a lower probability of obstructive disease. (Arq Bras Cardiol. 2017; 109(4):348-356)

Keywords: Coronary Artery Disease; Heart Valve Disease; Coronary Angiography; Computed Tomography Angiography.

Introduction

Coronary artery disease (CAD) in patients with valvular heart disease has the usual association with traditional risk factors. Nevertheless, the search for obstructive CAD is more aggressive in the preoperative period of patients with valvular heart disease, resulting in the indication of invasive coronary angiography (ICA) to almost all patients older than 35 years, because it is believed that coronary artery bypass surgery should be associated with valve replacement in the presence of obstructive CAD.

Angina is the major symptom, even though it can have other causes in valvular heart disease,[1] such as left ventricular hypertrophy or overload. Association of obstructive CAD with the impaired heart valve, mainly the aortic valve, is common; however, increasing age has been shown to accompany a higher prevalence of CAD, regardless of the valve.[2,3] Older patients tend to have degenerative aortic valve disease more often, but CAD does not differ between patients with aortic or mitral valve impairment in the same age group.[4]

The epidemiology of valvular heart disease is heterogeneous and has changed over the past decades in different countries. Rheumatic heart disease was the major cause of valvular heart disease until the mid-20th century, after which, with the widespread use of antibiotics and better access to health care, a substantial reduction in the incidence of that inflammatory valvular heart disease occurred in developed countries.[5] The current prevalence of rheumatic valvular disease is estimated to be 2.5% in the USA and Canada, and 22% in Europe.[6] Concomitantly, with the increase in life expectancy, the prevalence of age-related heart diseases increased, the degenerative etiology being the most common cause of valvular heart disease in developed countries.[7] In addition, the higher mean age and, consequently, the higher number of chronic diseases and associated atherosclerotic risk factors increase the

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prevalence of CAD, which, in North-American and Anglo-Saxon patients with valvular heart disease ranges from 20% to 40%.[8,9]

In developing countries, rheumatic heart disease is still the major cause of valvular heart disease.[10] In Brazil, its prevalence reaches 60.3%, with a mean age of 37 years.[7] It usually affects young individuals, who have less risk factors for atherosclerosis, and, thus, lower prevalence of obstructive CAD.[11,12]

The guidelines suggest that, because of the impact of non-treated CAD, its diagnosis is paramount.[1] Preoperative ICA is indicated to almost all patients older than 35 years, and non-invasive functional tests are not recommended because of their limited specificity. In the ACC/AHA guideline, coronary computed tomography angiography (CCTA) is suggested for patients with a low or intermediate pretest probability of CAD (class of recommendation IIa, level of evidence C), because of its high negative predictive value to exclude obstructive CAD.[13]

Stratification of obstructive CAD based on current indications does not seem to be the best strategy in our population. The ICA is a high-cost invasive procedure with widely documented morbidity and mortality. The development of tools to estimate the pretest probability of obstructive CAD, as performed in the general population, is urgent, to better select patients who will benefit from different preoperative strategies, therefore preventing the indiscriminate indication of unnecessary and invasive procedures, mainly in groups with a lower clinical probability of obstructive CAD.

This study was aimed at developing a predictive score for obstructive CAD in adult candidates for primary heart valve surgery, and at validating that score in an independent cohort of patients from another tertiary reference institution.

Methods

Selection of patients

The population studied comprises adults with primary acquired valvular heart disease from a tertiary reference hospital, submitted to heart valve replacement or repair surgery between 2001 and 2014.

Inclusion criteria

This study included patients older than 18 years with primary acquired valvular heart disease, submitted to heart valve surgery between 2001 and 2014, who underwent ICA within 12 months from surgery.

Data collection

Data were obtained retrospectively from medical record review and comprised the following variables: age, sex, chest pain, systemic arterial hypertension, diabetes *mellitus*, dyslipidemia, family history of CAD, smoking, surgery type, and impaired heart valve.

Obstructive CAD was defined as luminal obstruction greater than 50% in the left main coronary artery (LCA) and obstruction greater than 70% in the other major epicardial vessels, on preoperative ICA, according to the recommendations of the Brazilian Guidelines on Valvular Heart Diseases.[1]

In our study, we dichotomized the symptoms according to the presence or absence of chest pain. Chest pain was defined as the presence of atypical or typical angina, according to the classification of the Brazilian Guidelines on Chronic Coronary Artery Disease,[14] with two or three of the following characteristics: retrosternal discomfort or pain; triggered by exercise or emotional stress; relieved by rest or nitroglycerin use. Absence of chest pain was defined when the patient had none (asymptomatic) or only one of the above-cited characteristics (non-cardiac chest pain).

The risk factors were defined by the physicians in charge of filling out the patients' registration forms, according to their clinical judgement and the existing classifications at the time.

Exclusion criteria

Patients with incomplete clinical data were excluded from the study.

Statistical analysis

The categorical variables were described as frequency, being compared by use of chi-square test. The only continuous variable used in this study was age, which had a normal distribution confirmed by use of Kolmogorov-Smirnov test, was presented as mean and standard deviation and compared in the different groups by use of Student *t* test. Differences with p-value < 0.05 were considered statistically significant.

The variables associated with the outcome 'obstructive CAD' were assessed using univariate and multivariate logistic regression. The risk factors traditionally related to CAD and the variables that, on univariate analysis, showed association with obstructive CAD were included in multivariate analysis. The final model comprised the variables with statistically significant association in the multivariate model and those historically associated with CAD.

To test the calibration of the model in the derivation cohort, linear regression was used, correlating the mean estimated pretest probability (patients were divided into deciles of increasing probability of obstructive CAD) with the observed prevalence.

The predictive accuracy for obstructive CAD of the model, in both the derivation and validation cohorts, was tested by constructing the ROC curve and assessing the area under the curve.

The SPSS software (SPSS Inc., USA), version 22.0, was used for the statistical analysis.

Score validation

The score was validated in an independent sample (validation cohort) with 294 adult patients with primary valvular heart disease, candidates for heart valve surgery from 1999 to 2005, originating from another tertiary reference hospital for heart surgery, and whose preoperative clinical and angiographic data made them eligible for the study.

Results

From 2001 to 2014, a total of 2898 primary heart valve surgeries were recorded in adults, 1074 of whom with ICA

performed in the 12 months preceding surgery were included in the study, while 362 of whom were excluded due to incomplete clinical data in the hospital registry.

The prevalence of obstructive CAD in patients with valvular heart disease and ICA in the preoperative period was 20% (145 patients).

Of the 712 patients studied, 330 (46%) were of the male sex and 382 (54%) of the female sex. Their mean age was 58 (± 12.5) years, and 145 (20%) had obstructive CAD. Chest pain was reported by 165 (23%) patients. Aortic repair surgery was performed in 291 (41%) patients, while mitral repair surgery, in 302 (42%). Double aortic-mitral repair surgery was performed in 109 (15%) patients, while combined coronary artery bypass graft surgery and valvular heart repair surgery, in 139 (20%). The prevalences of cardiovascular risk factors, impaired heart valve and obstructive CAD are shown in Table 1.

Patients with obstructive CAD were older, had higher prevalence of chest pain and of traditional risk factors as compared to patients without obstructive CAD. The aortic valve, as compared to the mitral valve, was more often impaired in the former. The male sex showed a higher trend to obstructive CAD as compared to the female sex.

On univariate analysis, chest pain showed a strong association with obstructive CAD (odds ratio, 6.9; 95%CI: 4.67-10.4; $p < 0.001$), in addition to traditional risk factors and age. Mitral valve impairment showed no association with obstructive CAD.

The variables that associated with obstructive CAD on univariate analysis, such as traditional risk factors for atherosclerosis (age, sex, arterial hypertension, diabetes *mellitus*, dyslipidemia, family history and smoking), were entered into the multivariate analysis, in addition to aortic valve impairment, which had statistical significance. Age ($p < 0.001$), family history of CAD ($p < 0.001$) and angina ($p < 0.001$) were independent predictors of obstructive coronary lesion. Aortic valve impairment had no relevant association after adjusting for the other risk factors. Multivariate analysis is shown in Table 2.

A predictive logistic model for obstructive CAD was created based on the correlation degree between statistically significant independent predictive variables, in addition to the traditional risk factors, which, even though lacking statistical significance in the last analysis, comprised the model, because of their proven association with CAD. The logistic model is represented by the following equation:

Logit (CAD) = - 6.872 + (0.257 x male sex) + (0.066 x age) + (1.344 x chest pain) + (0.369 x hypertension) + (0.404 x diabetes) + (0.445 x dyslipidemia) + (0.297 x smoking) + (0.885 x family history of CAD)

To make clinical use easier, a score of point addition was developed, a simplification of logistic regression, where points are attributed to patients according to their clinical characteristics. One point should be added to every 5 complete yeas of life (from age zero), 1 point to each traditional risk factor (male sex, arterial hypertension, dyslipidemia, diabetes *mellitus* and smoking), 2 points to a family history of CAD, and 4 points to chest pain (Table 3).

Patients who scored 10 points or less (estimated pretest probability < 5%) were considered to have low pretest probability, while those who scored more than 17 points (estimated pretest probability > 30%) were considered to have high pretest probability. Those who scored between 11 and 16 points comprised the intermediate group (estimated pretest probability between 5% and 30%).

The model showed an excellent correlation between estimated pretest probability and the obstructive CAD prevalence found in our population (Table 4).

Table 1 – Clinical characteristics of the population and according to the subgroups without and with obstructive CAD

Variables	Cohort	Without obstructive CAD	With obstructive CAD	p value
	n = 712	n = 567 (80%)	n = 145 (20%)	-
Age	58 (± 12)	55 (± 12)	66 (± 8)	< 0.001
Male sex	330 (46%)	250 (44%)	80 (56%)	0.017
Diabetes *mellitus*	96 (13%)	55 (13%)	41 (28%)	< 0.001
Arterial hypertension	493 (69%)	366 (65%)	127 (88%)	< 0.001
Dyslipidemia	338 (47%)	239 (42%)	99 (68%)	< 0.001
Family history of CAD	122 (17%)	74 (13%)	48 (33%)	< 0.001
Smoking	240 (34%)	177 (31%)	63 (43%)	0.005
Chest pain	165 (23%)	85 (15%)	80 (55%)	< 0.001
Aortic valve impairment	291 (41%)	206 (36%)	85 (59%)	< 0.001
Mitral valve impairment	302 (42%)	249 (44%)	53 (37%)	0.109
Aortic and mitral valve impairment	109 (15%)	102 (18%)	7 (5%)	< 0.001
CABG	139 (20%)	17 (3%)	122 (84%)	< 0.001

Values expressed as mean ± SD or n (%). CAD: coronary artery disease; CABG: coronary artery bypass graft. Differences with p value < 0.05 were considered statistically significant. T test was used for the variable 'age', and chi-square test, for the other variables.

Table 2 – Univariate and multivariate analysis of risk factors for obstructive CAD

	Univariate analysis		Multivariate analysis	
Variables	**Odds ratio (95%CI)**	**p**	**Odds ratio (95%CI)**	**p**
Age	1.08 (1.06 - 1.10)	< 0.001	1.06 (1.04 - 1.09)	< 0.001
Chest pain	6.97 (4.67 - 10.41)	< 0.001	3.83 (2.44 - 6.01)	< 0.001
Family history	3.29 (2.15 - 5.03)	< 0.001	2.42 (1.46 - 3.99)	0.001
Male sex	1.56 (1.08 - 2.25)	0,17	1.29 (0.83 - 2.01)	0.255
Dyslipidemia	2.95 (2.0 - 4.35)	< 0.001	1.56 (0.99 - 2.44)	0.051
Smoking	1.69 (1.16 - 2.45)	0.006	1.34 (0.85 - 2.11)	0.198
Diabetes *mellitus*	3.67 (2.32 - 5.79)	< 0.001	1.49 (0.87 - 2.57)	0.142
Arterial hypertension	3.87 (2.29 - 6.53)	< 0.001	1.44 (0.79 - 2.62)	0.225
Aortic valve impairment	2.48 (1.71 - 2.60)	< 0.001	0.96 (0.60 - 1.53)	0.88
Mitral valve impairment	0.73 (0.50 - 1.07)	0.110	–	–

Univariate and multivariate logistic regression. Differences with p-value <0.05 were considered statistically significant.

Table 3 – Simplified score to predict obstructive CAD

Variable	Score
Age	1 point every 5 years
Male sex	1 point
Arterial hypertension	1 point
Diabetes *mellitus*	1 point
Dyslipidemia	1 point
Smoking	1 point
Family history of CAD	2 points
Chest pain	4 points

CAD: coronary artery disease.

To test the calibration of the predictive model, linear regression was applied correlating the estimated pretest probability (divided into deciles with increasing probability of obstructive CAD, and comprised by approximately 72 patients per decile) with the prevalence observed in the derivation cohort. A positive and significant correlation was observed between the estimated probability and the observed prevalence of obstructive CAD (R^2 = 0.98), proving the predictive capacity of the model, represented in the 0.9954 slope of the line (close to 1.0), confirming that there is neither underestimation nor overestimation of the model tested (Figure 1).

Both the logistic and the simple additive models had excellent accuracy to predict obstructive CAD in the derivation cohort, being represented by the areas under the ROC curve of 0.848 (95%CI: 0.817 – 0.879) and 0.844 (95%CI: 0.812 – 0.875), respectively (Figure 2).

To validate the models developed, we used data from a different population of 294 adult patients from another tertiary reference hospital for heart surgery, with primary valvular heart disease, candidates for heart valve surgery from 1999 to 2005. Their preoperative clinical and angiographic variables were eligible for the study.

In that validation cohort, similarly to our findings, the patients with obstructive CAD were older, mainly of the male sex and had a high prevalence of traditional risk factors. Angina occurred significantly more often in the group of patients with CAD (Table 5).

Both the logistic and simple additive models had excellent and similar accuracy to predict obstructive CAD in the validation cohort, represented by the areas under the ROC curve of 0.877 (95%CI: 0.830 – 0.923) and 0.882 (95%CI: 0.836 – 0.927), respectively (Figure 2).

Discussion

In our cohort, the observed prevalence of obstructive CAD was 20%, lower than that of the cohorts of developed countries,[8,9] and similar to that of the populations of developing countries.[15-19] The prevalence of obstructive CAD in individuals aged less than 50 years was 3.3%, similar to that of other Brazilian studies. Sampaio et al. have reported a prevalence of 3.42% in a sample of 3736 patients with a mean age of 43.7 years.[12] Kruczan et al.[11] have shown a global prevalence of obstructive CAD of 15.9%, 6% in patients aged less than 50 years.

The patients with obstructive CAD were older, mainly of the male sex and had a high prevalence of traditional risk factors and of chest pain.

There was a univariate association between atherosclerotic risk factors, chest pain, family history, and aortic valve impairment. However, on multivariate analysis, there was no independent association between dysfunctional valve and obstructive CAD, confirming reports in the literature.[3] Therefore, it was not entered in the logistic model. Similarly, the etiology of valvular heart disease has no independent association with CAD,[11] but with other aggregated risk factors.

Table 4 – Prevalence of obstructive CAD according to the category of estimated pretest probability

Categories	Score	Estimated pretest probability	Observed obstructive CAD prevalence
Low probability	0-10	< 5%	2%
Intermediate probability	11-16	5 - 30%	12%
High probability	≥ 17	> 30%	49%

CAD: coronary artery disease.

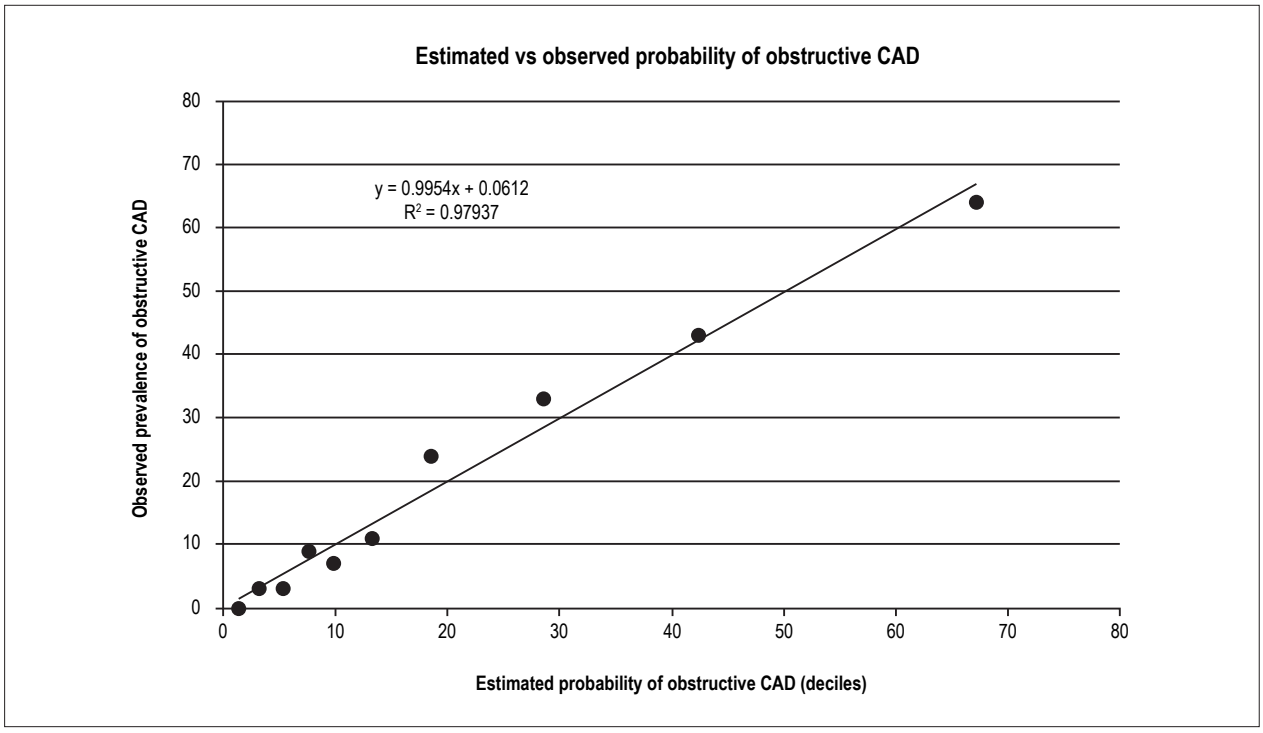

Figure 1 – *Calibration of the predictive model*

In the general population, calculators to predict and stratify CAD are widely used, and only patients with high probability and no response to clinical treatment or with tests with high-risk changes are referred for invasive stratification, while most patients with low or intermediate pretest probability being suitable for non-invasive stratification.[14]

The pretest probability of obstructive CAD is more often calculated by use of the score described in the 1970s by Diamond and Forrester,[20] who used estimates of postmortem studies and cross-sectional studies of the North-American population. Although limited and not contemplating other cardiovascular risk factors, that score is still widely used, and continues to be recommended by the guidelines. This currently used model has been shown to overestimate the probability of CAD, and, thus, could be updated.[21,22]

For patients with valvular heart disease, there is no specific calculator to estimate obstructive CAD and, thus, to guide the preoperative period according to the calculated probability.

The AHA/ACC guideline considers CCTA a way to exclude obstructive CAD without performing ICA for patients with low or intermediate pretest probability calculated according to the criteria by Diamond and Forrester, reserving invasive stratification for patients with higher probability of CAD.[13]

In the past years, with the widespread use of CCTA for CAD stratification in the general population, several studies have tested its performance. A meta-analysis that gathered 1107 patients and 12851 coronary artery segments, has validated CCTA as a safe alternative to ICA in the preoperative period of patients with valvular heart disease.[23] In another study assessing the preoperative period of valvular heart disease, the stratification strategy with CCTA to patients with low or intermediate pretest probability has predicted a significant cost reduction, because 28% of that study cohort would not require ICA.[4] In addition, in 2012, an European study emphasized the importance of having a preoperative strategy, not only because it is a more comfortable diagnostic alternative for the patient, but also more inexpensive than the conventional strategy.[24]

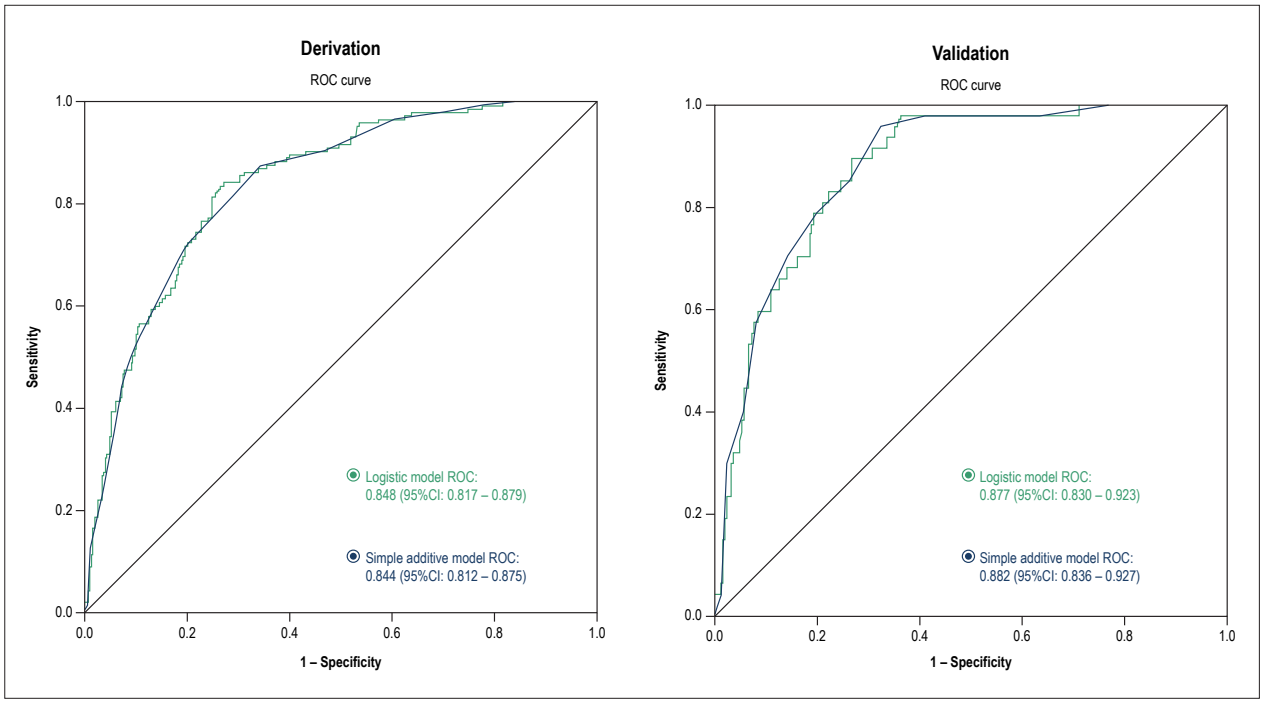

Figure 2 – *Comparison of the ROC curves of the logistic and simple additive models in the derivation and validation cohorts.*

Table 5 – Clinical characteristics of the validation cohort

Variables	Cohort	Without CAD	With CAD	p value
	n = 294	n = 247 (84%)	n = 47 (16%)	
Age	56 (± 11)	52 (± 10)	66 (± 10)	< 0.001
Male sex	139 (47%)	106 (43%)	33 (70%)	0.002
Diabetes *mellitus*	24 (8%)	11 (4%)	13 (28%)	< 0.001
Arterial hypertension	122 (41%)	90 (36%)	32 (68%)	< 0.001
Dyslipidemia	35 (12%)	22 (9%)	13 (28%)	0.003
Family history of CAD	142 (48%)	115 (46%)	27 (57%)	0.39
Smoking	145 (49%)	116 (47%)	29 (62%)	0.18
Chest pain	125 (42,5%)	85 (35%)	39 (83%)	< 0.001
Aortic valve repair	104 (35%)	61 (59%)	43 (41%)	-
Mitral valve repair	161 (55%)	149 (93%)	12 (7%)	-
Aortic and mitral valve repair	29 (10%)	25 (86%)	4 (14%)	-

Values expressed as mean ± SD or n (%). CAD: coronary artery disease. Differences with p value < 0.05 were considered statistically significant. T test was used for the variable 'age', and chi-square test, for the other variables.

Although ICA is gold standard for the diagnosis of obstructive lesions, it an invasive method not free from complications, such as death, vascular events (bleedings, hematomas and arterial occlusions), neurological events (ischemic and hemorrhagic) and cardiac events (arrhythmias, perforations, dissections, revascularizations, infarctions, heat failure and cardiogenic shock).[25-27] A Brazilian study with 1916 patients has reported 190 (10.4%) complications in 175 patients.[27] In a registry comprising 85% of the catheterization laboratories in the USA and including 1,091,557 patients, 14,736 patients (1.35%) had complications, the in-hospital mortality related to the procedure being 0.72%.[28]

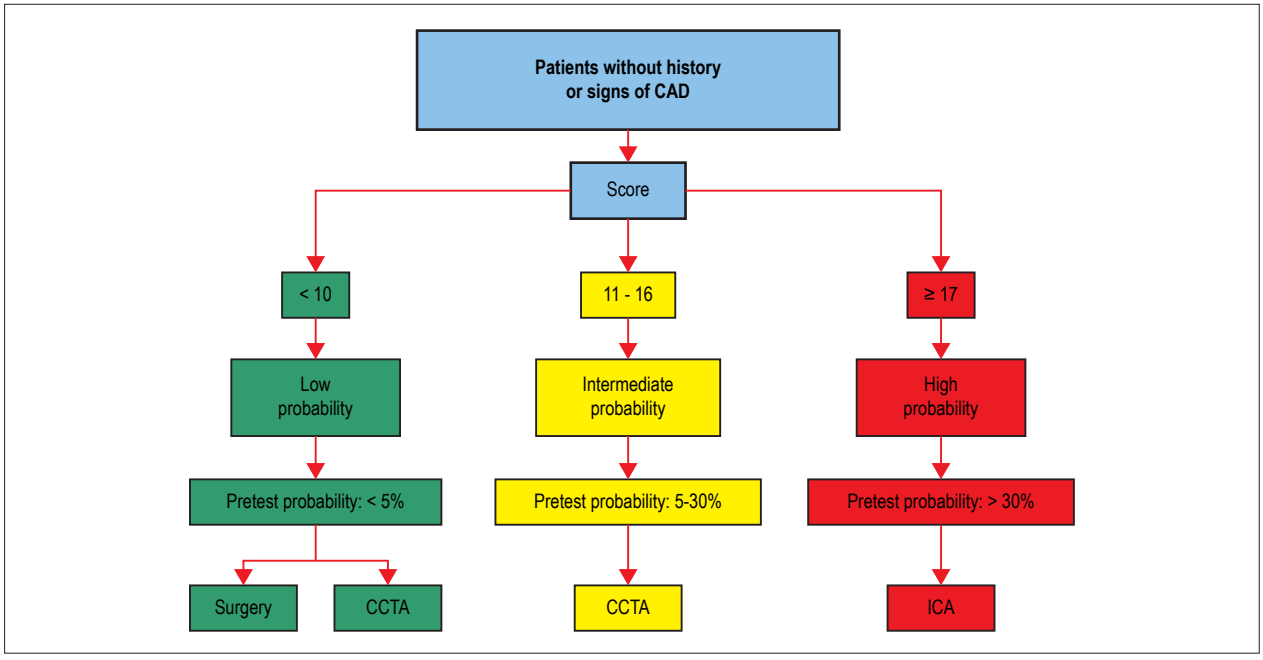

Figure 3 – *Preoperative strategy based on the use of the simple additive score and estimated pretest probability.*

To translate such data into future clinical tools, we elaborated a proposal for the preoperative assessment of patients referred for primary heart valve surgery, and applied it in the derivation cohort.

We developed a simplified easy-to-use score to stratify patients, and thus better guide the preoperative strategy. Using only clinical data, such as age, sex, chest pain and presence or absence of atherosclerotic risk factors, the pretest probability of obstructive CAD can be calculated at bedside with relative simplicity. The calculator developed in this study is available at https://connect.calcapp.net/?app=5tcj4a, and can be used in multifunctional devices.

To illustrate the use of that tool in the preoperative assessment of patients, we created arbitrarily three categories of estimated pretest probability of obstructive CAD: low, < 5%; intermediate, between 5% and 30%; and high, > 30%.

A patient with a score < 17 (low or intermediate probability) should be stratified conservatively, with CCTA, or even directed to heart valve surgery without additional stratification, if the probability is low, ICA being reserved for those with high pretest probability or positive CCTA for obstructive CAD (Figure 3).

In a simulation, applying the strategy proposed by the AHA/ACC guideline to our cohort, using CCTA to assess CAD in patients with low and intermediate pretest probability, we would reduce by 82% the ICA in those patients, with a total 57%reduction in the entire cohort. That strategy has a sensitivity of 99% and a specificity of 90%, using CCTA accuracy data in patients with valvular heart disease.[23] Considering the complication rate of ICA among us,[27,28] we would prevent 40 procedure-related complications (57% reduction).

Adopting an even more conservative strategy, with patients of low probability directed to surgery with no additional preoperative test and CCTA to assess CAD in patients of intermediate probability, we would have a 60% reduction in ICA, with sensitivity of 98% and specificity of 94%, in addition to a 61% reduction in ICA complications in our population.

That conservative strategy could result in a lack of diagnosis lower than 5% (< 2% in our cohort), which would not necessarily expose the patient to a higher risk, because cardiac catheterization itself is not free from severe complications, and it has not been clearly established that coronary artery bypass graft surgery combined with heart valve repair significantly influences patients' prognosis. In addition, ischemic complications in patients with CAD who undergo no revascularization during valve replacement are infrequent.[9,29] Among us, the mortality of coronary artery bypass graft surgery alone ranges from 4.8% to 8.3%,[30,31] and that rate can even triple when that surgery is combined with heart valve repair.[31]

It is worth noting that clinical predictive scores are secondary tools, and should not replace the current and previous clinical history, physical exam and previous complementary tests. Patients with a previous history of CAD, left ventricular dysfunction, evidence of myocardial ischemia on tests, or with atherosclerosis evidenced on any other exam or signs of it in other territories (such as reduced lower limb pulses, arterial stiffness and abdominal aneurysm), that increase the probability of CAD,[14] should be treated on an individual basis.

This study had limitations. It is a retrospective analysis based on a cohort from a single tertiary center of

reference, but validated in another independent cohort from another tertiary center of reference for heart surgery. Neither the previous history of CAD nor left ventricular dysfunction could be assessed, but the patients are already directed to ICA according to the recommendations of the guidelines.[1] In addition, neither the type of valvular dysfunction (stenosis *versus* regurgitation) nor its etiology (degenerative, infectious or inflammatory) could be determined, but none of those factors was an independent predictor of CAD in a review of studies on similar populations.

Conclusions

Obstructive CAD can be estimated based on clinical data of adult candidates for heart valve repair surgery by using a simple, accurate, calibrated, validated and easy-to-use score.

Establishing a preoperative flowchart beginning with the use of the predictive score of obstructive CAD and definition of the pretest probability group can be a more comfortable and safer strategy for the patient, preventing the indiscriminate indication of unnecessary and invasive procedures, mainly in the groups with higher probability of obstructive CAD.

Author contributions

Conception and design of the research, Analysis and interpretation of the data and Statistical analysis: Cazelli JG, Camargo GC, Gottlieb I; Acquisition of data: Cazelli JG, Kruczan DD, Weksler C, Felipe AR, Gottlieb I; Writing of the manuscript: Cazelli JG, Gottlieb I; Critical revision of the manuscript for intellectual content: Cazelli JG, Camargo GC, Kruczan DD, Weksler C, Gottlieb I.

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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Review Article

Functional Capacity in Congenital Heart Disease: A Systematic Review and Meta-Analysis

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Abstract

Background: **Children and adolescents with congenital heart disease often have alterations in their exercise capacity that can be evaluated by various functional testing.**

Objective: **To evaluate the functional capacity of children and adolescents with congenital heart disease (CHD) with systematic review and meta-analyses.**

Methods: **The review included observational studies, data from the first evaluation of randomized clinical trials or observational follow-up periods after clinical trials which evaluated functional capacity by cardiopulmonary exercise test, stress testing, six-minute walk test or step test, in children and adolescents with CHD, aged between six and 18 years, and comparisons with healthy controls in the same age group. The quantitative assessment was performed by meta-analysis, by comparing the maximal oxygen consumption (VO_2max) of children and adolescents with CHD and respective control groups.**

Results: **Twenty-five of 2.683 studies identified in the search met the inclusion criteria. The VO_2max measurement showed that patients with CHD have a decrease of 9.31 ml/Kg/min (95% CI. –12.48 to –6.13; I^2, 94.3%, P for heterogeneity < 0.001) compared with the control group. The meta-analysis of the data of maximum heart rate (HR) reached during cardiopulmonary test and stress testing, retrieved from 18 studies, showed a HR value of –15.14 bpm (95% CI. –20.97 to –9.31; I^2, 94.3%, P for heterogeneity < 0.001) compared with the control group.**

Conclusion: **Children and adolescents with CHD have lower VO_2max and HR compared to controls. (Arq Bras Cardiol. 2017; 109(4):357-367)**

Keywords: **Heart Defects, Congenital; Child; Adolescent; Exercise Tolerance; Review; Meta-Analysis.**

Introduction

Children with congenital heart disease (CHD) often have a sedentary lifestyle that may reflect both inherent physiological limitations in addition to overprotection of parents.[1] Such lifestyle pattern is likely to be maintained throughout adulthood, which can result in increased risk for cardiovascular diseases.[1] In children with restriction for physical activity practice, there is an increased risk for overweight and there is an increasing in overweight (RR, 2.51; 95% CI, 1.24-3.52) and obesity (RR, 6.14; 95% CI, 2.54-8.82) at follow-up.[2]

Functional capacity may indicate cardiovascular, pulmonary or motor dysfunction. In children with chronic disease, maximal oxygen consumption (VO_2max) can predict adverse outcomes as well as the greater aerobic fitness is associated with a nearly 10% risk reduction for hospitalization of children with cystic fibrosis.[3] The assessment of functional capacity in patients with heart disease is an important clinical tool for diagnosis, quantification of symptoms, prognosis and evaluation of response to treatment.[4] Several tests are available to assess functional capacity,[5] but their use in children and adolescents can give different information than those obtained from adults due to differences in physiological and metabolic responses to stress. Concerning differences in cardiovascular responses, healthy children showed higher chronotropic and lower inotropic responses during maximal effort.[5] Furthermore, the information of the tests is not standardized in terms of values, which limits the comparison of different studies.

Functional capacity varies according to the type of CHD, surgical outcome, age and gender of the patient. Patients with incomplete repair of heart defects present significant reductions in peak work rate and age-adjusted maximum ventilation as compared with their pairs who undergone complete repair.[6] Most of the published studies have a small sample size and include children, adolescents and adults, with a large range of age of subjects.[7] Thus, the present study aimed to systematically review the literature to summarize the functional capacity of children and adolescents diagnosed with CHD, through a meta-analysis of observational studies.

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Methods

Eligibility criteria

This review included observational studies (cohort, cross-sectional or case-control studies), data from the first evaluation of randomized or non-randomized clinical trials or observational follow-up periods after clinical trials, in which the sample consisted of children and adolescents with CHD, aged between six and 18 years. Other conditions for inclusion of the studies were evaluation of functional capacity by cardiopulmonary exercise test, stress testing, six-minute walk test (6MWT) or step test.

Studies published in English were included. Only studies published after 1980 were considered, since methods for evaluation of functional capacity were not standardized before that period.

Strategy of search and selection of studies

The following electronic databases were searched in June 2015: MEDLINE (accessed through Pubmed), *Cochrane Central Register of Controlled Trials* (Cochrane CENTRAL) and EMBASE. In addition, references from published studies were also searched manually. Duplicate reports were deleted in the first step of selection of articles. The MeSH terms and entry terms used are presented in Box 1 (Supplementary File).

The titles and abstracts of all articles identified in the search strategy were assessed in duplicate by independent investigators (C.W.S. and A.C.). All abstracts that did not provide sufficient information regarding the inclusion and exclusion criteria were selected for full-text evaluation. In the second phase, the same reviewers independently evaluated these full-text articles and made their selection in accordance with the eligibility criteria. Any disagreements between reviewers were resolved through consensus and, in cases of persistent disagreement, a third reviewer (G.S.) assessed the publications.

Data extraction

Data were extracted independently by two reviewers (C.W.S and A.C.), using standardized forms comprising methodological characteristics, description of interventions, and outcomes; disagreements were resolved by consensus or by a third reviewer (G.S.).

In order to quantify possible differences on the functional capacity, the primary outcomes were the VO_2max and the distance walked in the 6MWT. Additionally, maximum heart rate (HR) and other physiological variables taken from the cardiopulmonary exercise test (cardiovascular assessment and gas analyzes with direct measurement of oxygen consumption), 6MWT and stress testing (cardiovascular assessment, in which symptoms were observed, the behavior of heart rate, blood pressure and electrocardiogram) were also entered into the analyses. Variables extracted from the cardiopulmonary exercise test were the first and second ventilatory thresholds, and from the exercise stress testing we extracted the maximum systolic blood pressure (SBP).

Assessment of risk of bias

The methodological quality of the studies was assessed by two researchers (C.W.S and A.C.), previously trained and qualified. The *Newcastle-Ottawa Scale* was used for case-control and cohort studies, whereas cross-sectional studies were evaluated with an adaptation of the same scale. The quality score of cohort studies and case-control studies was calculated by the assessment of three components: selection of the study groups (0-4 points), quality of adjustment for confounding (0-2 points) and evaluation of exposure or outcome of interest. The cohort studies evaluation was used for quasi-experimental studies. In the case of cross-sectional studies, the score was calculated in two components: selection of the study groups (0-3 points) and assessment of the outcome of interest (0-4 points). The maximum score could be 9 points for case-control and cohort studies and seven points for cross-sectional studies, representing a high methodological quality.[8] Disagreement between reviewers were resolved by consensus, and, in cases of persistent disagreement, the assessment was made by a third reviewer (G.S).

Data analysis

The quantitative assessment of the included studies was performed by meta-analysis, by comparing the VO_2max in relation to body mass of children and adolescents with CHD and respective control groups without CHD. Combined estimates of effects were generated through the maximum values obtained in the studies reviewed, and are presented as weighted mean differences. Statistical heterogeneity among the results on functional capacity of the studies was assessed by the Cochran's Q test, with significance level of 0.1, and by the inconsistency I^2 test, in which values above 50% were considered as indicative of high heterogeneity.[9]

The heterogeneity among the studies was explored using two strategies. Initially, each study was individually removed from the meta-analysis in order to verify any particular influence on the results. Second, the influence of age and maximum HR during exercise testing was evaluated by univariate meta-regression, and a threshold of $p < 0.05$ was used to indicate statistical significance.

The analyses were performed using Stata software version 11.0.

Results

Twenty-five of the 2.683 studies identified in the search met the criteria of eligibility and were included in the analysis. Figure 1 shows the flow chart of studies of this review. The age of the participants ranged from six to 18 years. Seventeen cross-sectional studies, three quasi-experimental studies and five cross-sectional studies with follow-up were included, with a total of 770 patients with CHD and 754 healthy controls.

The characteristics of the studies are presented in Table 1. Most of the studies investigated children who underwent surgical correction for cyanotic CHD, such as tetralogy of Fallot (T4F), transposition of the great vessels (TGV) and univentricular hearts. Only one study evaluated children that were not submitted

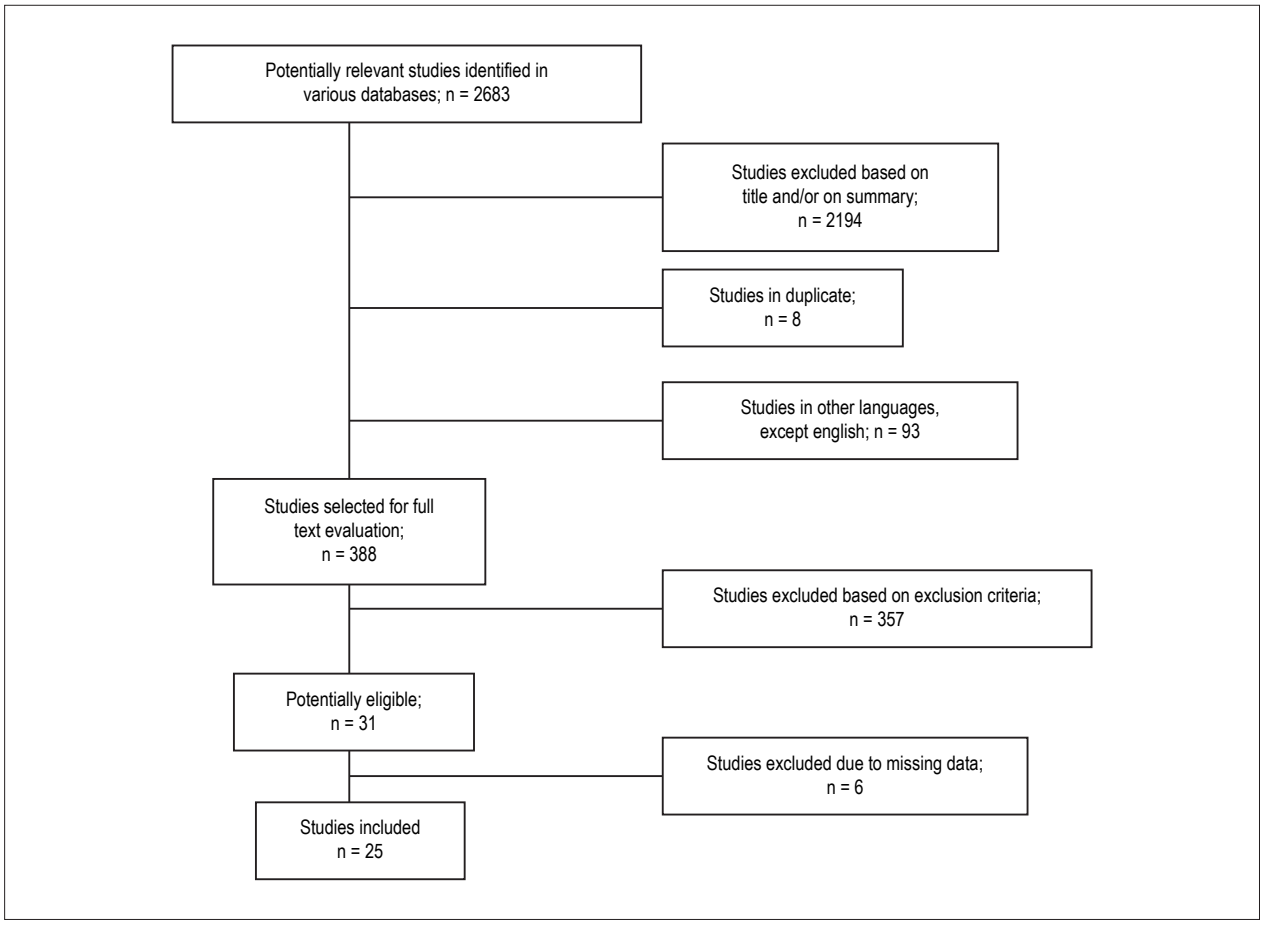

Figure 1 – *Flowchart of studies evaluated for the meta-analysis.*

previously to surgical correction. Considering the evaluation of functional capacity, 22 studies conducted maximal exercise testing (18 used cardiopulmonary exercise testing and four used the stress testing). In addition to maximal exercise testing, Moalla and collaborators[10] also performed submaximal test through the 6MWT. Three studies performed submaximal assessment: 1. Hjortdal and collaborators[11] used the stress test to evaluate the functional capacity up to 1 W/kg on the cycloergometer, and since the participants did not reach their maximal HR with this workload the test was considered as submaximal; 2. Reybrock and collaborators[12] conducted a cardiopulmonary exercise testing, considering it as a submaximal test, since the assessment was performed to a HR up to 170 bpm; 3. Marcuccio and collaborators[13] used the cardiopulmonary exercise test, but the maximum HR of the participants was not reached, and the test was therefore considered as submaximal.

The methodological quality of the cohort studies ranged from two to seven points, with an average of 6.0 ± 1.8 points. For cross-sectional studies, the score varied from three to seven points, with an average of 5.4 ± 1.0. The cohort study with lowest score (by Pfammater et al.[14]) did not describe the origin of the cohort, the methods for assessing the outcome of interest, and how losses were controlled. Among cross-sectional studies, the publication by Page et al.[15] had only three points, since it did not present non-response rates and did not inform on the representativeness of the sample, origin of the control group and situation of this group (whether it was disease-free). Among quasi-experimental studies, two had four points and one received five points.

In the meta-analysis including 17 studies that conducted cardiopulmonary exercise tests with measurement of VO_2max, it was 9.31 ml/kg/min lower in patients with CHD (95% CI, –12.48 to –6.13; I^2, 94.3%, P for heterogeneity < 0.001), as compared with the control group. As shown in Figure 2, studies were stratified according to the type of ergometer used for the maximal test. Eleven studies used the cycloergometer. In these studies, the difference between VO_2max in the CHD group and the control group was –9.71 ml/Kg/min (95% CI –14.06 to –5.36; I^2 = 94.2%, P for heterogeneity < 0.00001). Considering the six studies that used the treadmill, the difference between VO_2max in the CHD group and the control group was –8.58 ml/Kg/min (95% CI –12.73 to –4.44; I^2 91.5%, P for heterogeneity < 0.00001).

The meta-analysis on the anaerobic threshold included six studies, showing that the CHD group presented an anaerobic threshold of –4.27 mL/kg/minute (95% CI, –10.84 to 2.31; I^2, 97.6%, P for heterogeneity < 0.001) as compared with the control group.

Table 1 – Characteristics of studies included in the systematic review

Study year	Characteristics of participants	Participants (n)	Mean age (SD)	Female	Use of medication	Outcomes and evaluation methods	Values of functional capacity test
Cross-sectional studies							
Arvidsson, 2009[24]	Surgically corrected patients (54 patients had undergone biventricular repair), including: AoS, ASD, CoA, DORV, HLV, HRHS, MA, PA, PAPVC, TAPVC, PS, TGV, IVC. NYHA functional class II.	79	9 – 11 years 14 – 16 years	37	Not reported	Cardiopulmonary exercise test with cycloergometer; ramp protocol, duration 8-12 minutes and recovery. The patient was instructed to maintain a pedal rate of 60 rpm during the whole exercise test.	Mean and standard deviation of VO_2max = 42.28 ± 8.8 ml/Kg/min
Giordano, 2003[25]	Surgically corrected aortic coarctation patients. There were 3 end-to-end anastomoses, 10 patch angioplasties, and 7 left subclavian flap repairs.	20	13.7 ± 4.2	8	No antihypertensive medication.	Maximal stress test with treadmill; Bruce protocol. Mean of the time of exercise test = 10.5 ± 2 minutes.	Mean and standard deviation of heart rate = 171 ± 17 bpm
Goldstein, 2011[26]	Participants with Fontan's procedure, excluding patients with pacemaker dependence, severe hypoxemia (oxygen saturation <80% at rest), atrial arrhythmia or several ventricular dysfunction. NYHA functional class I (94%).	51	15 (10.9 -17.8)	20	Not reported	Cardiopulmonary exercise test with treadmill; Bruce protocol.	Median and range of VO_2max = 28.8 (25.6-33.2)
Grant, 1991[27]	Surgically corrected T4F patients NYHA functional class I.	13	14.1 ± 3	7	Not reported	Cardiopulmonary exercise test with cycloergometer; Godfrey protocol.	Mean and standard deviation of VO_2max = 28.7 ± 6.6 ml/Kg/min
Groen, 2009[28]	Surgically corrected T4F patients and Fontan's procedure.	13	14 ± 2.8	6	Not reported	Cardiopulmonary exercise test with cycloergometer; Godfrey protocol.	Mean and standard deviation of VO_2max = 33.7 ± 8.9 ml/Kg/min
Hjortdal, 2008[11]	Participants with Fontan's procedure. NYHA functional class I and II.	14	9.1 ± 5.2	6	Not reported	Submaximal stress test (up to 1 W/kg) with cycloergometer.	Mean and standard deviation of heart rate = 111.5 ± 64.2 bpm
Ishi, 2005[29]	Surgically corrected T4F patients.	26	9.6 ± 3.3	Nonspecific	Not reported	Maximal stress test with cycloergometer; ramp protocol.	Mean and standard deviation of heart rate = 143 ± 11 bpm
Marcuccio, 2012[13]	Surgically corrected T4F patients	21	15 (11-17)	Nonspecific	Not reported	Submaximal stress test with treadmill. Bruce protocol.	Median and range of VO_2max = 35.8 (23.8-47.8)
Moalla, 2008[30]	Surgically corrected patients including T4F, TGA, IAC, PA. NYHA functional class II and III.	12	13.0 ± 1.2	Nonspecific	Diuretics, cardiotonics, ACE inhibitors.	Cardiopulmonary exercise test with cycloergometer; Wasserman protocol.	Mean and standard deviation of VO_2max = 30.2 ± 6.1 ml/Kg/min
Mocelin, 1999[31]	Patients corrected for: TGA, IVC, PA, T4F.	35	10.8 ± 2.2	12	Not reported	Cardiopulmonary exercise test with treadmill, constant-load protocol.	Mean and standard deviation of VO_2max = 42.6 ± 8.6 ml/Kg/min

Continuation

Page, 1996[15]	Participants with corrected D-TGA.	7	10.4 ± 1.2	4	Not reported	Cardiopulmonary exercise test with treadmill; ramp protocol.	Mean and standard deviation of VO_2max = 37.6 ± 1.4 ml/Kg/min
Reybrouk, 2000 [12]	Participants corrected for TGA e T4F.	59	11.2 ± 7.6	24	Not reported	Submaximal exercise test (up to 170 bpm) with treadmill.	Mean of VO_2max = 40 ml/Kg/min
Sarubbi, 2000[32]	Surgically corrected T4F patients.	41	11.2 ± 3.9	12	No diuretic of cardiotonic medication.	Maximal stress test with cycloergometer.	Mean and standard deviation of heart rate = 167.5 ± 17.4 bpm
Tomassoni, 1991[33]	Surgically corrected T4F patients.	20	9.9 ± 2.8	9	Not reported	Cardiopulmonary exercise test with treadmill; Bruce protocol for >8 years-old and modified Bruce protocol for <8 years-old.	Mean and standard deviation of VO_2max = 34.1 ± 2.9 ml/Kg/min
Van Beck, 2009[34]	Participants with corrected TGV. NYHA functional class I.	17	12.2 ± 2	5	Not reported	Cardiopulmonary exercise test with cycloergometer; ramp protocol.	Mean and standard deviation of VO_2max = 41.1 ± 6.6 ml/Kg/min
Muller, 2012[35]	Participants with PS, IVC, IAC, T4F, aortic coarctation, valve stenosis/regurgitation after surgery, Ebstein anomaly, univentricular heart, TGV and TAC. NYHA functional class I and II.	88	12.7 (12.0-13.3)	36	Not reported	Cardiopulmonary exercise test and submaximal exercise test with cycloergometer.	Median and interquartil of VO_2max = 35.5 (31.3-41.0)
Su, 2013[36]	Participants corrected and non corrected IAC.	50	11.2 ± 3.5	31	Not reported	Cardiopulmonary exercise test with treadmill, Bruce protocol.	Mean and standard deviation of VO_2max = 31.8 ± 6.8ml/Kg/min
Quasi-experimental studies							
Amiard, 2008[37]	Surgically corrected patients including: single ventricle and PA, PA with intact sept, T4F, TGV, IAC.	23	15 ± 1.4	10	ACE inhibitor; diuretics, anticoagulants, cardiotonics, imunosuppressors.	Cardiopulmonary exercise test with cycloergometer; Wasserman protocol.	Mean and standard deviation of VO_2max = 34.4 ± 10.9ml/Kg/min
Moalla, 2005[10]	Participants surgically corrected for: T4F, TGA, IAC, PA. Functional class NYHA II and III.	17	12.9 ± 0.3	Nonspecific	Diuretics, cardiotonics, ACE inhibitor, except for beta-blocker.	Cardiopulmonary exercise test with cycloergometer; Wasserman protocol. Submaximal test with 6MWT.	Mean and standard deviation of VO_2max = 28.9 ± 1.7ml/Kg/min
Rutenberg, 1983[38]	Participants corrected for TGA, T4F, valve and aorta diseases.	24	12.8 ± 3.4	8	Not reported	Cardiopulmonary exercise test with treadmill; Bruce protocol.	Mean and standard deviation of VO_2max = 39.3 ± 8.8ml/Kg/min

Continuation

Cross-sectional studies with follow-up							
Binkhorst, 2008[39]	Participants with corrected and non-corrected IVC.	27 (13 post-correction IVC and 14 non-corrected), three were excluded from the analysis of functional capacity.	Corrected group = 13 ± 2.5 Non-corrected group = 12.5 ± 3	Corrected group = 6 Non-corrected group = 8	Not reported	Cardiopulmonary exercise test with cycloergometer, ramp protocol.	Mean and standard deviation of VO_2max = 45.5 ± 29.2 ml/Kg/min
Carvalho, 1992[40]	Surgically corrected T4F patients.	12	11.3 ± 2.7	Nonspecific	Not reported	Cardiopulmonary exercise test with treadmill; Bruce protocol.	Mean and standard deviation of VO_2max = 48.0 ± 8.8 ml/Kg/min
Hovels-Gurich, 2003[41]	Surgically corrected TGA patients. NYHA functional class I.	56	10.5 ± 1.6	13	Not reported	Maximal stress test with treadmill; Bruce protocol.	Mean and standard deviation of heart rate = 191.1 ± 10.0 bpm
Musewe, 1988[42]	Surgically corrected TGA patients. NYHA class I.	18	12.8 ± 1.6	7	Not reported	Cardiopulmonary exercise test with cycloergometer; Jones and Campbell protocol.	Mean and standard deviation of VO_2max = 31.0 ± 7.0 ml/Kg/min
Pfamatter, 2002 [14]	Participants with corrected IAC.	14	11.4 (6.8 – 16.1)	9	Not reported	Cardiopulmonary exercise test with treadmill; ramp protocol.	Mean and standard deviation of VO_2max = 37.8 ± 14.8 ml/Kg/min

AoS: aortic stenosis; ASD: atrioventricular septal defect; DORV: double outlet right ventricle; HLV: hypoplastic left ventricle; HRHS: hypoplastic right heart syndrome; MA: mitral atresia; PA: pulmonary atresia; PAPVC: partial anomalous pulmonary venous connection; TAPVC: total anomalous pulmonary venous connection; PS: pulmonary stenosis; TGA: transposition of the great arteries; IVC: interventricular communication; T4F: tetralogy of Fallot; IAC: interatrial communication; TAC: truncus arteriosus communis; ACE: angiotensin-converting-enzyme; HR: heart rate; NYHA: New York Heart Association; 6MWT: six minute walk test. VO_2max: maximum oxygen consumption

Figure 3 shows the meta-analysis of the maximum HR reached during cardiopulmonary exercise test and stress testing, retrieved from 18 studies. The CHD group presented HR of –15.14 bpm (95% CI, –20.97 to –9.31; I^2, 94.3%, P for heterogeneity < 0.001) as compared with the control group.

Considering the variable HR according to the type of test, 14 studies evaluated maximal HR though the exercise test. In these studies, the CHD group showed a difference of –17.70bpm (95% CI –24.37 to –11.03; I^2, 94.4%, P for heterogeneity < 0.00001) in relation to the control group. In the four studies that used stress test for evaluation, all presented data as maximal HR. Meta-analysis of these studies showed that the CHD group had a lower HR when compared to the control group (difference –4.68bpm (95% CI –9.32 to –0.04; I^2, 43.4%, P for heterogeneity = 0.15) (Figure 3).

The meta-regression showed that the age (n = 16) was not associated with the heterogeneity observed in VO_2max (R^2 = 18.43%. p = 0.09). Maximum HR (n = 13), however, had a significant influence on the heterogeneity observed in VO_2max (R^2 = 69.20%. p = 0.005), as shown in Figure 4. An inverse relationship is por was between the chronotropic deficit and VO_2max (β = –0.688; p = 0.005).

Since only one study evaluated functional capacity through the 6MWT, distance walked could not be analyzed. None of the included studies used the step test for evaluation of functional capacity.

Discussion

This systematic review with meta-analysis of observational studies showed that children and adolescents with CHD present a decrease in functional capacity and in the anaerobic threshold during an exercise maximal test as compared with healthy individuals of the same age group, even when treated. In addition, children and adolescents with CHD have a chronotropic deficit that explained 69.20% of the VO_2max variance observed among the 13 studies analyzed.

Maximal oxygen consumption (VO_2max) has been widely used as gold standard for evaluation of functional capacity in healthy or ill individuals. There is a difference in cardiorespiratory responses between adults and children.[5] The anatomically smaller heart size in children results in lower venous return, and therefore lower cardiac output, which in turn results in lower VO_2max when compared with adults. Therefore, the most important compensatory mechanism for children is through the increase in HR.[16] During exercise, the systolic volume increases around 20% in a normal heart, and the further increase in the cardiac output is due to an increase in HR.[17] Although expected, the information that children

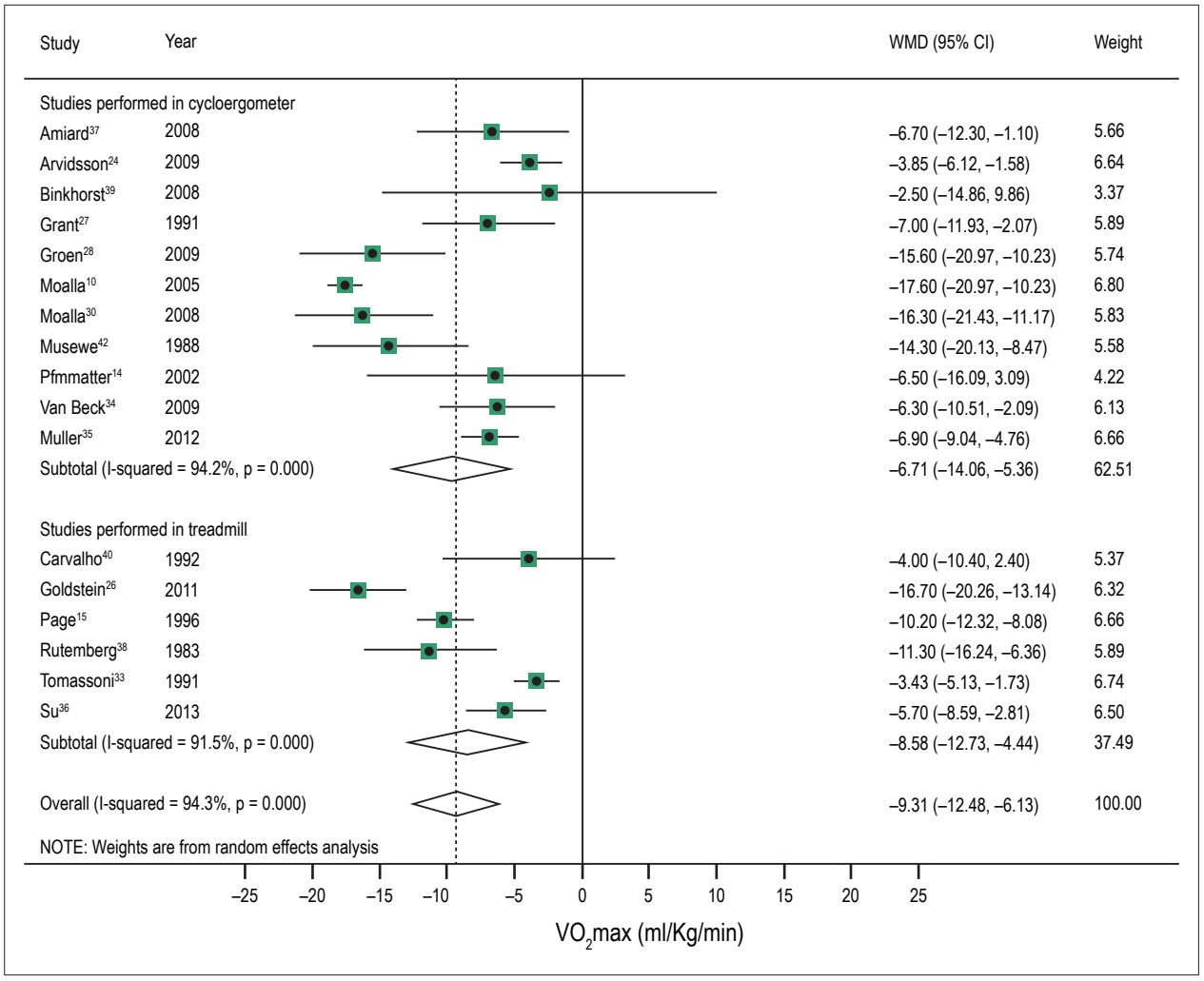

Figure 2 – *Meta-analysis of maximum oxygen consumption (VO_2max) in children and adolescents with CHD and in controls, as evaluated on cycloergometer or on treadmill.*

and adolescents with CHD in fact have lower functional capacity than their peers, even after corrective surgery, is first summarized in the present meta-analysis.

Individuals with CHD have insufficient chronotropic response, which leads to a decreased maximum HR, consequently reducing the VO_2max in this population.[17] Fedriksen et al.[7] investigated children between eight and 17 years of age with several types of CHD and observed that those aged 10 to 13 years with obstruction of the left ventricular output presented oxygen consumption values above that of those with TGV or T4F. Children with T4F had a natural development of the capacity for physical exercise, which was however lower than that of healthy children; children with TGV showed a decline of VO_2 between the ages of 12 and 13 years, probably due to a reduction of right ventricular function.[7] In the present meta-analysis, maximum HR was diminished in 15.14 bpm in the CHD group as compared to the control group. This chronotropic incompetence implies an inability to increase the HR in response to metabolic demand.[18] The activity of the sympathetic and parasympathetic nervous system, which plays an important role in the modulation of HR during exercise, can be affected by ischemia and/or denervation resulting from surgical procedure or, in cases of cyanotic CHD, by chronic hypoxemia.[19] Ohuchi et al.[20] observed that both SBP at rest or during peak exercise and HR variability were lower in the group of children with univentricular hearts compared with healthy controls,[20] which supports this hypothesis, that the HR directly influences the VO_2max.

The anaerobic threshold, defined as the maximum intensity of exercise performed by an individual using aerobic metabolism, is inversely related to age.[21] In a study with 17 children with complex CHD, evaluated by cardiopulmonary exercise testing, Ohuchi et al.[22] observed that the anaerobic threshold was lower in these children as compared with the control group.[22] In addition, Paridon et al.[23] also used cardiopulmonary exercise test to assess 411 children who undergone Fontan procedure showing normal maximal oxygen consumption in 28% of the sample. Maximal oxygen consumption (VO_2max) within the normal range was observed

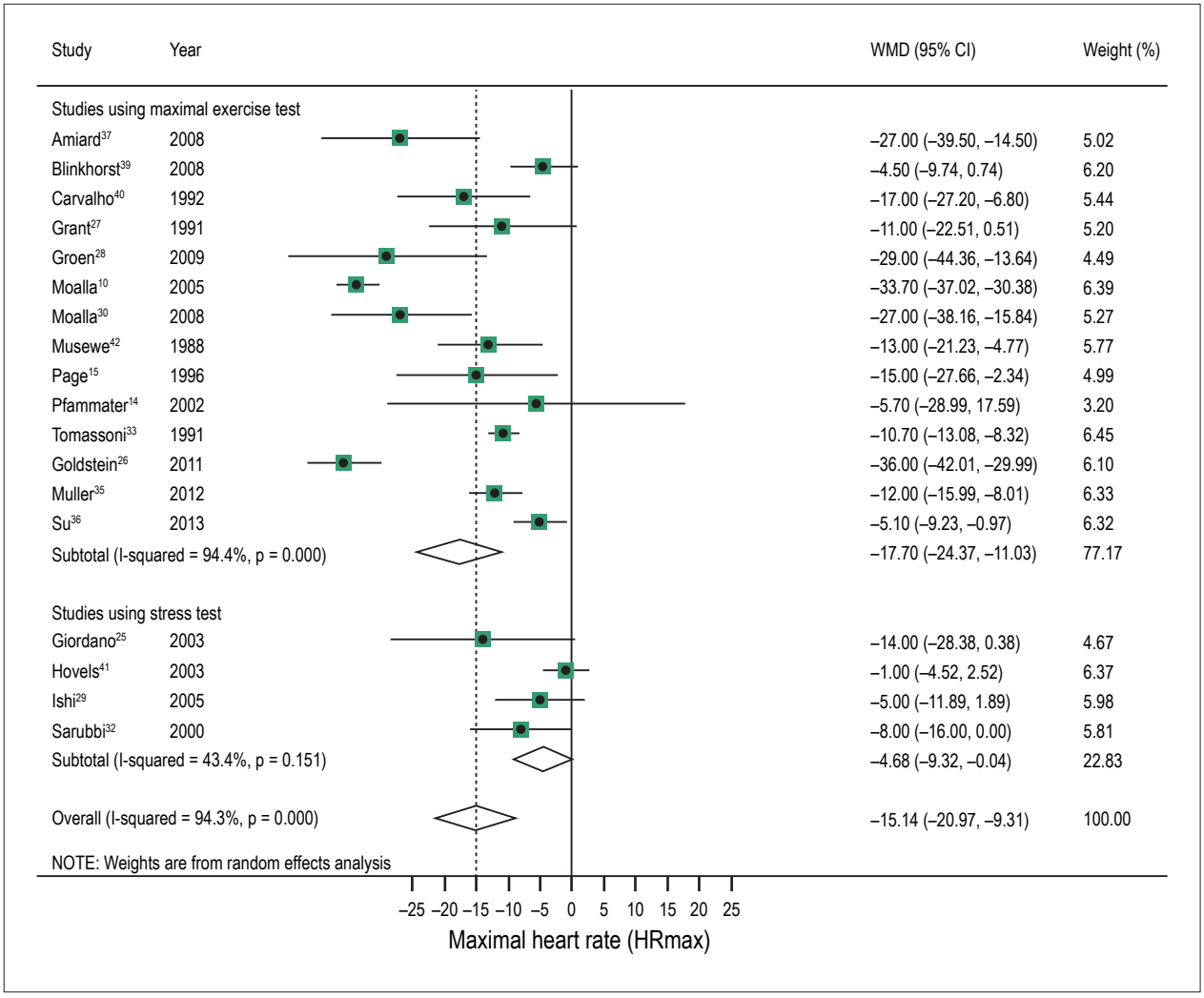

Figure 3 – *Meta-analysis of maximal heart rate (HRmax) in children and adolescents with CHD and in controls, as evaluated in studies using maximum stress testing and studies using stress test.*

in only 28% of the sample. However, the anaerobic threshold was in the normal predicted range in most individuals (63%), suggesting that this population with univentricular hearts could tolerate a high level of submaximal and non-maximal activity.[23]

Most studies showed high methodological quality in the evaluation of both exposure and outcome variables. Cross-sectional studies described more detailed evaluations regarding these variables when compared to cohort studies.

The main study limitation derive from that most studies included patients with different types of heart disease, and used different types of evaluation protocols with heterogeneity of ergometers for functional capacity evaluation, even if these are standardized in the literature. Thus, studies showed important differences in relation to these methodological aspects, although all have fulfilled the inclusion criteria for this meta-analysis. High heterogeneity observed in the meta-analyses partially reflects such methodological aspects, and we therefore explored it by using meta-regression analyses for factors of interest. In addition, the heterogeneous nature of the congenital heart lesions may also limit wide exploration of studies in this field, since many lesions have different pathophysiological behaviors and a broad spectrum of severity. In this context, it is important to systematically review all the available information in order to establish more detailed and useful evidence for this specific group.

Conclusion

The presence of CHD in children and adolescents is associated with lower functional capacity than in healthy controls, measured by VO_2max in cardiopulmonary exercise testing, being influenced by the impaired chronotropic response observed in this population, and not by age. In addition, a lower ventilatory threshold was observed in the same group, suggesting a lower ability to perform aerobic

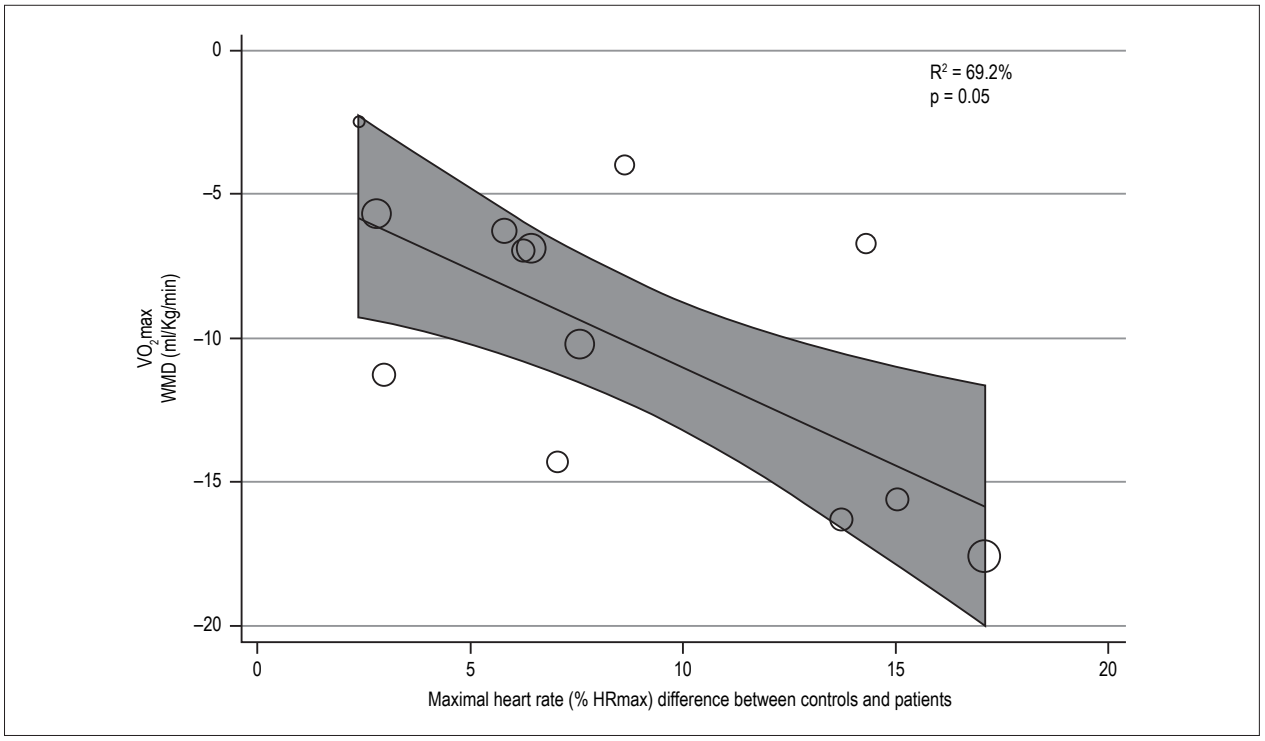

Figure 4 – *Association between maximum oxygen consumption (VO_2max) with maximal heart rate (% HR) difference between groups during the maximal exercise test. WMD: weighted mean differences.*

exercise and consequently tolerate lower exercise loads when comparing to healthy controls of the same age.

Author contributions

Conception and design of the research: Schaan CW, Macedo ACP, Sbruzzi G, Schaan BD, Pellanda LC; Acquisition of data and Writing of the manuscript: Schaan CW, Macedo ACP, Umpierre D; Analysis and interpretation of the data: Schaan CW, Macedo ACP, Sbruzzi G, Umpierre D, Schaan BD, Pellanda LC; Statistical analysis: Schaan CW, Macedo ACP, Sbruzzi G, Umpierre D; Critical revision of the manuscript for intellectual content: Schaan CW, Sbruzzi G, Umpierre D, Schaan BD, Pellanda LC.

Potential Conflict of Interest

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Review Article

Positions, Guidelines and Standardizations. Vehicles of Assistance to Medical Practice

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In a field as complex and rapidly changing as cardiology, Clinical Practice Guidelines are important tools for applying evidence-based medicine to patient care. It should be noted, however, that adherence to them varies widely, and that some doctors have concerns that these instruments characterize a rigid or simplified practice of medicine. Therefore, the appropriate implementation of health care guidelines is of great interest to national organizations, professional societies, health care providers, policy makers, legal field of medicine, patients and the public. Given the importance of the theme, several tools have been developed to assess the credibility of existing guidelines,[1] and guidances have been elaborated step-by-step for the implementation of a practical and reliable document.[2]

Since 1992, the Brazilian Society of Cardiology (SBC) has systematically published guidelines on the most relevant themes of the specialty.[3] However, there was a lack of discernment regarding three important concepts[4] in the intention of the departments that integrate the SBC to carry out guidelines: a) "Guideline" - a term that should be reserved for the document that formally summarizes the evidences in the areas of diagnosis and therapeutics of pathologies; b) "Communication" (or "Standardization") shall be used for manuscripts reporting the laboratory methodology and definitions of clinical outcome and, c) "Clinical Guidance" (or "Positioning") - which should be used for official printouts that provide expert advice on challenges in patient management.

It is imperative that the documents issued by SBC should be presented with adequate titration and background to avoid confusing the reader in the differentiation of terms and, consequently, disinterest in reading them. Therefore, the main objective of this publication is to establish in a simplified and objective way, the meaning of these terminologies, aiming to standardize the issuance of Guidelines, Communications and Guidances by SBC.

Keywords

Evidence-Based Practice; Delivery of Health Care; Practice Guidelines as Topic.

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Positioning document

These documents aim to address a particular topic (diagnostic, therapeutic or laboratory) of recognized clinical interest, for which there are no (or unlikely to exist) evidence of substantial quality or, especially, those from randomized clinical trials. These documents are complementary to the guidelines and are prepared by a team of professionals with established experience in the subject.

As an example, we could cite the use of direct anticoagulants in pregnant patients.[5] In general, the guidelines contained in these documents are anchored in the best evidence available; however, often incorporate the personal opinion of specialists.

Clinical Guideline

Clinical guideline consists of systematically developed assertions to assist health professionals and patients in making decisions about the most appropriate form of health care under specific conditions.[6] Unlike a guidance document, a guideline addresses a topic where there is evidence of moderate to high quality, usually from randomized trials with a satisfactory number of members, to convey the most appropriate clinical practices.

In its elaboration, a process is used to summarize the evidences (that is, systematic review) and to provide a standardized method to express the degrees of recommendations with their respective levels of evidences. To produce a guideline, it is recommended that a rigorous checklist of 146 items be followed.[2]

Therefore, these documents rarely address medical practice where evidence is scarce. They are designed to support decision-making processes in patient care; its content is based on a systematic review of clinical evidence.

Normative document

These devices differ from those listed above since they address topics primarily focused on the standardization of clinical, laboratory and research methodologies. As an example, we could cite the Subcommittee on Anticoagulation Control of the International Society of Thrombosis and Hemostasis to measure the anticoagulant activity of factor Xa inhibitors.[7] Therefore, it is a useful tool available to SBC departments.

The movement toward evidence-based health care has been rising rapidly in recent years, motivated by clinicians, policymakers and managers concerned about the quality, consistency, and cost of health care.

Thus, the above-mentioned documents, based on standardized best practices, provided they are written in a practical and objective manner, may be able to promote improvements in the quality and consistency of health care.

Author contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data and Statistical analysis: Sousa ACS, Cunha CP, Magalhães LBNC, Kaiser SE, Saraiva JFK; Obtaining financing: Sousa ACS, Cunha CP; Writing of the manuscript and Critical revision of the manuscript for intellectual content: Sousa ACS.

Potential Conflict of Interest

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Case 5/2017 – A 28-Year-Old Woman with Cor Pulmonale Due to Pulmonary Hypertension Secondary to Chronic Pulmonary Thromboembolism

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The patient is a 28-year-old female, who presented with dyspnea on minimum exertion and dry cough.

The patient reported being asymptomatic until one year ago, when she had an episode of retrosternal pain followed by syncope, requiring admission to the intensive care unit, being then diagnosed with pulmonary thromboembolism (PTE).

Her technetium-99m diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) radioaerosol inhalation lung scintigraphy (May 21, 2008) revealed marked hypoventilation of the left lung and retention of the radiotracer in the right peri-hilar region, suggestive of a parenchymal process. The use of ^{99m}TC human albumin macroaggregates (^{99m}TC MAA) revealed no perfusion in the left lung and perfusion defects in the right lung base.

Computed tomography (acute phase) with contrast suggested thrombosis of the left pulmonary artery.

The patient was referred for treatment at InCor.

On her first visit (Jul 8, 2008), she complained of dyspnea on milder than usual exertion and dry cough. She denied smoking, and reported being on oral contraception until the time of the PTE. Her obstetrical history revealed one gestation with normal delivery and no abortion.

Her physical examination showed heart rate (HR) of 80 bpm and blood pressure (BP) of 120/80 mm Hg. Her pulmonary auscultation showed reduced breath sound intensity in the left lung. Her cardiac auscultation was normal, as was her abdominal examination. There was edema (+/4+) in the left lower limb. Her pulses were palpable and symmetrical. Her peripheral capillary oxygen saturation (SpO_2) was 90%. She was on warfarin, and her INR was 2.4.

Her laboratory tests (Jul 17, 2008) were as follows: glycemia, 70 mg/dL; creatinine, 0.81 mg/dL; potassium, 5.4 mEq/L; sodium, 141 mEq/L; hemoglobin, 17 g/dL; hematocrit, 53%; MCV, 91 fL; leukocytes, 12900/mm^3 (65% neutrophils, 1% eosinophils, 29% lymphocytes and 5% monocytes); platelets, 341000/mm^3; PT (INR), 2.4; APTT (rel), 1.17; normal urinalysis; homocysteine, 7.5 μmol/L. The lupus anticoagulant test was negative, and mutant prothrombin, absent. The anticardiolipin antibody test was negative, as were the antinuclear factor (ANF HEp-2; Anti-SM) and ANCA antibody tests.

Her echocardiogram (Sept 16, 2008) revealed the following diameters: aorta, 29 mm; left atrium, 30 mm; right ventricle, 34 mm; left ventricle (D/S), 39/23 mm; septal and posterior wall thickness, 8 mm. Left ventricular ejection fraction (LVEF) was 73%, left ventricular relaxation was abnormal, and ventricular septal motion, atypical. The right ventricle was markedly hypokinetic, and the valves, normal. The systolic pulmonary artery pressure was estimated as 50 mm Hg.

Computed tomography angiography of the pulmonary arteries (24 Sept 2008) revealed chronic PTE with occlusion of the left branch of the pulmonary artery.

Selective pulmonary angiography (Dec 17, 2008) showed occlusion at the origin of the left pulmonary artery. The right pulmonary artery was dilated and patent, and there was contrast stop at the level of the anterior basal branches of the lower lobe and branches of the middle lobe.

Spirometry revealed forced expiratory volume in 1 second (FEV_1) of 71% of the predicted value, and forced vital capacity (FVC) of 68% of the predicted value, being the ventilatory disorder classified as mild.

Furosemide (40 mg) was prescribed, and warfarin, maintained. Surgical treatment of chronic thromboembolism by use of pulmonary endarterectomy was considered.

The dyspnea progressed to minimum exertion, being then accompanied by precordial pain and weight loss of 6 kg over 1 year. The patient was then hospitalized.

On physical examination (Mar 24, 2009), she was tachypneic (respiratory rate of 28 bpm), cyanotic and hydrated. Her HR was 100 bpm, and blood pressure, 110/80 mm Hg. Her weight was 69.7 kg, and height, 1.59 m. Her pulmonary auscultation revealed reduced breath sound intensity in the lung bases, worse at the right side. On cardiac auscultation, there was increased intensity of the pulmonary component of the second cardiac sound, and neither accessory sounds nor murmurs were heard. The abdomen was difficult to exam due to the patient's dyspnea. Her left lower limb showed hard edema. Her pulses were normal and symmetrical. Her SpO_2 was 84%, even with the use of an O_2 catheter (5 L/min).

Her laboratory tests (Mar 25, 2009) were as follows: hemoglobin, 16.5 g/dL; hematocrit, 50%; MCV, 100 fL;

Keywords

Pulmonary Heart Disease; Pulmonary, Hypertension; Pulmonary Embolism/complications; Risk Factors; Respiratory Insufficiency.

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leukocytes, 5000/mm^3 (5% band neutrophils, 47% segmented neutrophils, 1% eosinophils, 42% lymphocytes and 5% monocytes); platelets, 229000/mm^3; ESR, 1 mm; glucose, 68 mg/dL; urea, 26.1 mg/dL; creatinine, 0.94 mg/dL; sodium, 142 mEq/L; potassium, 4.7 mEq/L; AST, 21 U/L; ALT, 40 U/L; calcium, 4.4 mEq/L; phosphorus, 4.5 mg/dL; magnesium, 1.5 mEq/L; DHL, 238 u/L; CRP, 2.4 mg/L; BNP, 463 pg/mL; INR, 2.6; APTT (rel), 1.22.

Her ECG (Mar 29, 2009) revealed sinus rhythm, HR of 100 bpm, PR = 160 ms, dQRS = 80 ms, right atrial overload (P = 4 mV; SÂP = +60º) and right ventricular overload (SÂQRS = +120º forward, qR in V1).

Her echocardiogram (Mar 26 and 30, 2009) showed the following diameters: aorta, 29 mm; left atrium, 32; right ventricle, 40/45 mm; left ventricle, 40/26 mm. The ventricular septum and posterior wall thickness was 9 mm, and the LVEF, 65%. Left ventricular systole was normal, and the filling pattern showed relaxation impairment. The right ventricle was hypertrophic and severely hypokinetic. The valves had no changes. Systolic pulmonary artery pressure was estimated as 64 mm Hg.

The dyspnea and hypoxemia worsened, and the patient required orotracheal intubation. Nitric oxide, milrinone and cefepime were initiated (Mar 30, 2009).

Her laboratory tests (Mar 30, 2009) were as follows: urea, 39 mg/dL; creatinine, 0.92 mg/dL; glucose, 87 mg/dL; potassium, 4.2 mEq/L; sodium, 140 mEq/L; BNP, 510 pg/mL; INR, 1.8; TTPA (rel), 1.27; arterial lactate, 267 mg/dL. Arterial blood gas analysis revealed: pH, 7.41; pCO_2, 23.5 mm Hg; pO_2, 48.7 mm Hg; $SatO_2$, 82%; HCO_3, 17.2 mEq/L; and base excess (-) 3.2 mEq/L

Two hours after intubation, the patient had a cardiac arrest with pulseless electrical activity, which was initially reversed, but recurred few minutes later, and the patient died (Mar 31, 2009, 2h45min).

Clinical aspects

We report the case of a 28-year female patient denying any previous morbidity, who had acute PTE and progressively developed significant functional impairment and signs suggestive of chronic PTE during follow-up until death.

Venous thromboembolism (VTE) is the third most frequent cause of cardiovascular disease in the general population, with an annual incidence of 100 to 200 cases per 100000 inhabitants, acute PTE being its most severe clinical presentation.[1] The prevalence and incidence of spontaneous VTE in young adults are low, but increase significantly in the presence of risk factors, such as oral contraception use, obesity and thrombophilia, especially in associations. The use of oral contraceptives, such as estrogens/progestogens, increases by 2 to 4 times the risk of venous thromboembolic events.[2] Activated protein C resistance is attributed to a mechanism related to higher risk for VTE in patients on oral contraceptives. In our case, the patient had been on regular use of oral contraceptives until the first event, but there is no information on their formulation. Obesity is considered a risk factor, increasing by 2.4 times the risk for VTE in obese individuals as compared to non-obese individuals.[3] When associating obesity and oral contraceptive use simultaneously, the risk for VTE increases by 10 times.[4] Significant thrombophilias, such as deficiencies in protein C, protein S and antithrombin, homozygosity for factor V Leiden and prothrombin gene mutation increase in up to 7 times the risk for venous thromboembolic events in patients on oral contraceptives.[5] During the patient's follow-up, certain thrombophilias, such as prothrombin gene mutation, hyperhomocysteinemia and antiphospholipid syndrome, were excluded, but neither factor V Leiden nor deficiency in natural anticoagulants were investigated.

The incidence of chronic PTE is heterogeneous, ranging from 0.4% to 9.1% of the patients after an acute embolic event in different studies.[6] Its etiology is little known, being related to genetic and ethnic factors.[7] Hypercoagulable states, such as clotting factor VIII elevation and presence of antiphospholipid antibodies, are related to thromboembolic pulmonary hypertension.[8] Mortality related to recurrent PTE 3 to 6 months after anticoagulant therapy is approximately 0.4% per year, partially depending on the presence or absence of comorbidities. Patients with acute PTE, who develop systolic pulmonary hypertension (levels > 50 mm Hg), that is not solved in the first weeks, have worse prognosis. In addition, the incidence of death due to recurrent PTE or chronic pulmonary hypertension within the first 3 years after anticoagulant treatment discontinuation ranges from 1% to 3%.[9]

Our patient maintained significant pulmonary hypertension and right ventricular dysfunction according to the findings from both the echocardiography in September 2009, and the computed tomography angiography of the pulmonary arteries and the pulmonary angiography suggesting chronic occlusion of the left pulmonary artery despite the anticoagulant therapy instituted. During outpatient clinic follow-up, between September and December 2008, the possibility of surgical treatment was considered. Assessment for pulmonary thromboendarterectomy in patients with chronic PTE should be early, even in patients with non-limiting symptoms, because surgery can prevent irreversible vasculopathy. The decision to perform the procedure should consider whether the pulmonary artery anatomy is favorable, presence of hemodynamic and ventilatory abnormalities, comorbidities associated, and the patient's will. In specialized centers, the mortality related to pulmonary thromboendarterectomy in low-risk patients is around 1.3%.[10] In patients not eligible for surgical treatment and those maintaining pulmonary hypertension after the procedure, pharmacological treatment with the following pulmonary vasodilators should be considered: riociguat (soluble guanylate cyclase stimulator) and intravenous prostanoids, such as eprostinil and treprostinil, in critical patients. Phosphodiesterase inhibitors, such as sildenafil and tadalafil, and endothelin receptor antagonists, such as bosentan, can be alternatives to treatment.[11]

The patient developed progressive dyspnea with important functional impairment until hospitalization in March 2009. She had the following factors of poor prognosis: advanced functional class (III/IV, according to the WHO classification); right ventricular systolic dysfunction; signs of overload of the right chambers (Figure 1); and lack of specific treatment (pharmacological or surgical). Her echocardiogram revealed increased right ventricular dimensions and elevated systolic

pulmonary artery pressure as compared to previous measurements, in addition to persistence of important right ventricular dysfunction. It is worth noting the significant respiratory failure and hypoxemia even when using oxygen supplementation via catheter, which required orotracheal intubation for mechanical ventilation. Despite those measures, the patient had a cardiac arrest with pulseless electrical activity, probably related to refractory respiratory failure. Regarding the causes of decompensation and death, we considered the course of the underlying disease, with progressive aggravation of pulmonary arterial hypertension and right ventricular dysfunction, in addition to the likelihood of a new acute pulmonary thromboembolic event. **(Jussara de Almeida Bruno, MD, and Rafael Amorim Belo Nunes, MD)**

Diagnostic hypothesis: respiratory failure and hemodynamic collapse due to chronic thromboembolic pulmonary arterial hypertension and right ventricular dysfunction, and possible recurrence of acute pulmonary thromboembolism. **(Jussara de Almeida Bruno, MD, and Rafael Amorim Belo Nunes, MD)**

Postmortem examination

Not even the postmortem examination could clarify the major issues of this patient's disease. The major findings were: partial occlusion of the left pulmonary artery (Figure 2); *cor pulmonale* (Figure 3); phlebosclerosis of the left iliac vein (Figure 4); focal areas similar to pulmonary capillary hemangiomatosis (Figure 5); and severe pulmonary congestion, with blood in larger vessels and questionable recent thromboembolism (Figure 6). The causes of neither chronic thromboembolism nor phlebosclerosis could be determined, and it was not certain whether the pulmonary vessels really had thromboemboli that would explain the sudden worsening of the patient's condition and her death. The bone marrow pattern was normal to age. **(Prof. Paulo Sampaio Gutierrez, MD)**

Anatomopathological diagnoses: Major disease: chronic pulmonary thromboembolism.

Cause of death: undetermined (questionable recent thromboembolism). **(Prof. Paulo Sampaio Gutierrez, MD)**

Comments

Neither the underlying disease nor the cause of death were determined, but the anatomopathological findings confirmed the clinical, echocardiographic and imaging diagnoses: the patient had chronic pulmonary thromboembolism, and signs of organized peripheral venous thrombosis.

Therefore, her thrombophilic condition, whose nature was not clarified even with the postmortem examination, was evident. Some thrombophilic conditions are as follows: collagen diseases, such as lupus and antiphospholipid antibody syndrome; hematological disorders; and postsplenectomy state. Apparently, lupus was ruled out based on the laboratory tests, but there was no time for a comprehensive clinical investigation.

In chronic pulmonary thromboembolism, the histopathological findings usually differ between central and peripheral arteries. Thrombi in central elastic arteries usually organize as intimal thickenings of varied degrees, which extend to the hilar branches.[12] Surgical endarterectomy is aimed at resecting those thickenings, re-establishing local circulation. In smaller arteries, thromboses can organize as a re-channeling with multiple vascular lumens, named "colander lesion", which should not be mistaken for the classic plexiform lesion.

However, in peripheral pulmonary arteries, the changes are usually similar to those found in the idiopathic form of pulmonary arterial hypertension and in the Eisenmenger syndrome, reflecting vascular remodeling in response to increased flow and shear stress in the distal portions of the vascular bed of the central arterial branches that were not obstructed by thrombosis.[13] Those changes include mainly hypertrophy of the arterial tunica media and concentric proliferation of the intima.

In our case, it is worth noting the relatively mild remodeling of the peripheral pulmonary arteries, with mild hypertrophy of the tunica media and few foci of intimal thickening. In addition, the pattern known as pulmonary capillary hemangiomatosis was observed, a finding not usually described in the thromboembolic condition. That occurred in foci, being characterized by the presence

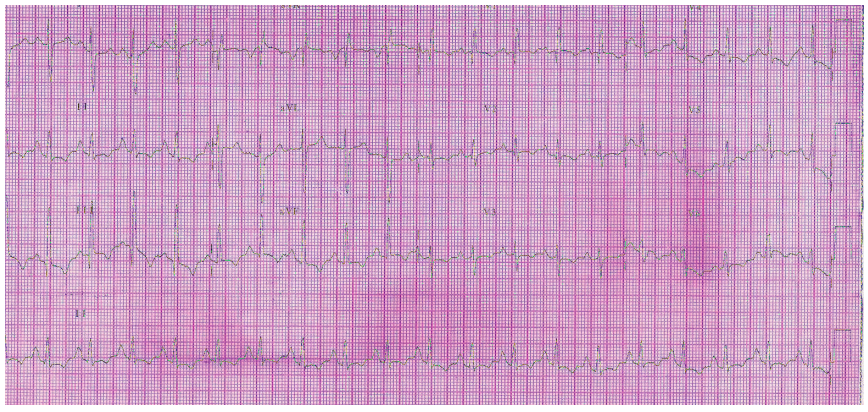

Figure 1 – *ECG: Sinus rhythm, right atrial overload, SÂQRS +120º, right ventricular overload.*

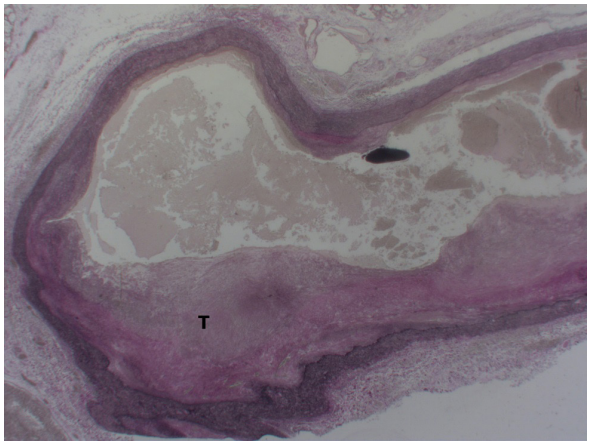

Figure 2 – *Microscopic section of o a central pulmonary artery showing partial occlusion by an organizing thrombus (T). Verhoeff stain; Objective magnification = 1X.*

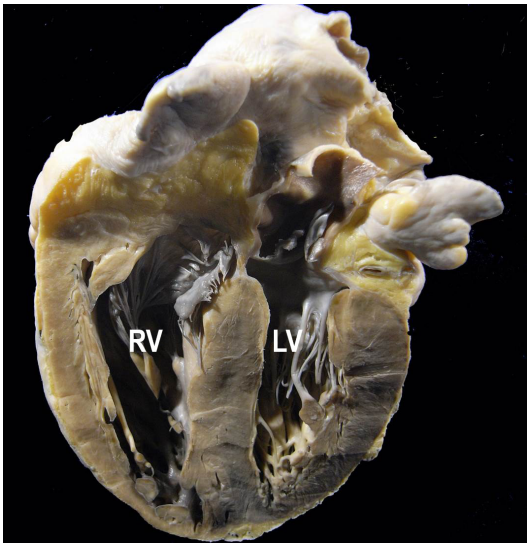

Figure 3 – *Gross aspect of the heart, frontal section, showing cor pulmonale, characterized by hypertrophy and dilatation of the right ventricle (RV), whose dimensions are close to those of the left ventricle (LV).*

of capillary proliferation in alveolar septa, in more than one layer, as opposed to the normal aspect of one single layer. That type of lesion has been mainly described in association with pulmonary veno-occlusive disease (absent in our case),[14] but also in some other forms of pulmonary vascular disease[15] or as an incidental necropsy finding.[16] Its meaning is uncertain, but seems more often related to pulmonary venous hypertensive conditions. **(Prof. Vera Demarchi Aiello, MD)**

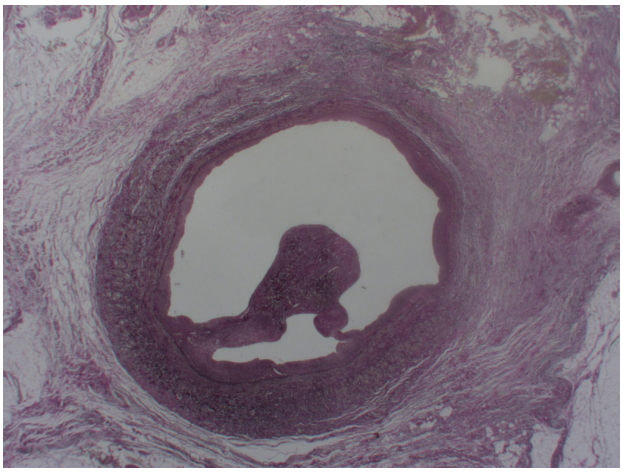

Figure 4 – *Microscopic section of the left iliac vein showing phlebosclerosis and organized thrombosis. Verhoeff stain; Objective magnification = 1X.*

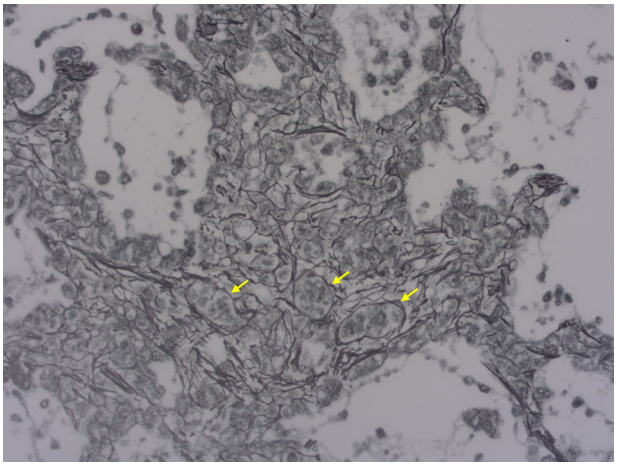

Figure 5 – *Microscopic section of the lung showing an area with capillary hemangiomatosis, characterized by the presence of more than one layer of capillaries (some indicated by the arrows) in alveolar septa. Reticulin stain; Objective magnification = 1X.*

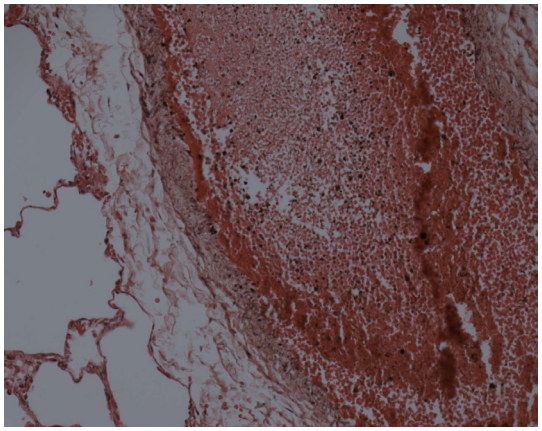

Figure 6 – *Microscopic section of an intrapulmonary arterial branch showing severe congestion, not conclusive of recent thromboembolism. Hematoxylin-Eosin; Objective magnification = 20X.*

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Spider-Like Coronary Anatomy; the True Spider!

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Introduction

Coronary anomalies are uncommon, affecting approximately 0.3–5.6% of the general population according to the literature. However, some cases can result in severe life-threatening events, such as myocardial ischemia, arrhythmia, and acute myocardial infarction.[1,2]

Case Report

A 55 year-old man was admitted to the hospital with typical chest pain; the ECG and cardiac biomarkers were normal. He had a history of hypertension and coronary angiography (CAG) a year ago due to unstable angina pectoris and a drug-eluting stent was implanted at the left anterior descending (LAD) coronary artery. CAG was performed at admission due to persistent chest pain and a single right coronary ostium was seen at the right coronary sinus, where LAD artery, left circumflex coronary (LCx) artery and right coronary artery (RCA) arose altogether. Non-significant plaques were seen at LAD and LCx, whereas RCA was obstructed from the middle segment and retrograde perfusion was observed (Figure 1A and 1B). The patient was treated conservatively and reported no chest pain 12 months later. The single coronary ostium is classified into 20 categories based on the ostium's location and our patient had characteristics of type IID[3] (Figure 1C). Although type IID coronary anomaly has been described before, it has been reported only once and this is the second case of literature showing a single coronary ostium originating from the right coronary ostium.

Discussion

Single coronary artery (SCA) from the right sinus of Valsalva was detected in 0.019% on coronary angiography[1]. Shirani and Roberts[2] reported 97 cases of SCA, 51 of which originated from the right sinus of Valsalva.

Lipton et al.[3] recommended a classification, which was modified by Yamanaka and Hobbs.[1] Depending on the sinus of origin, the anomalous artery is designated as R (right) or L (left). It is further classified as: Type I: normal course of left or RCA with a continuation into the absent artery's territory. Type II: Anomalous artery arises from the proximal part of the other normal artery and courses the base of the heart before taking the native course. Type III: The LAD and LCx arteries arise from the proximal part of the RCA. Type III anomalies are very rare. Single coronary ostium is classified into 20 categories, based on the ostium's location and our patient had characteristics of type IID.[3] Although type IID coronary anomaly has been described before, it has been reported only once and this is the second case in the literature showing single coronary ostium originating from the right coronary ostium.

CT angiography might be very useful in detecting the anatomical malformations, acute angle take-off, the transmural course, and compression between the great arteries, which would require surgery.[4] Canbay et al.[5] reported three cases of anomalous single coronary artery detected incidentally during routine coronary angiography.

The SCA anomaly is mostly asymptomatic. However, some cases can result in severe life-threatening events such as myocardial ischemia, arrhythmia, and acute myocardial infarction.[1,2] Recurrent chest pain without atherosclerosis in patients with SCA must be evaluated by computed tomography or pulmonary catheterization to determine the course of the artery.[6]

SCA is usually diagnosed incidentally during coronary angiographies or on postmortem evaluations. Multislice computed tomography is more effective than coronary angiography in determining coronary anomalies.[6,7]

The treatment strategy for single coronary artery has yet to be defined. Coronary artery bypass surgery might be useful in patients with anomalous coronary artery coursing between the aorta and main pulmonary artery or/and patients with atherosclerosis may benefit from revascularization procedures.

Keywords

Coronary Vessels / anatomy & histology; Coronary Vessels Anomalies; Tomography, X-Ray Computed.

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Author contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Cerit L, Duygu H, Gulsen K, Kemal H, Ozcem B.

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Study Association

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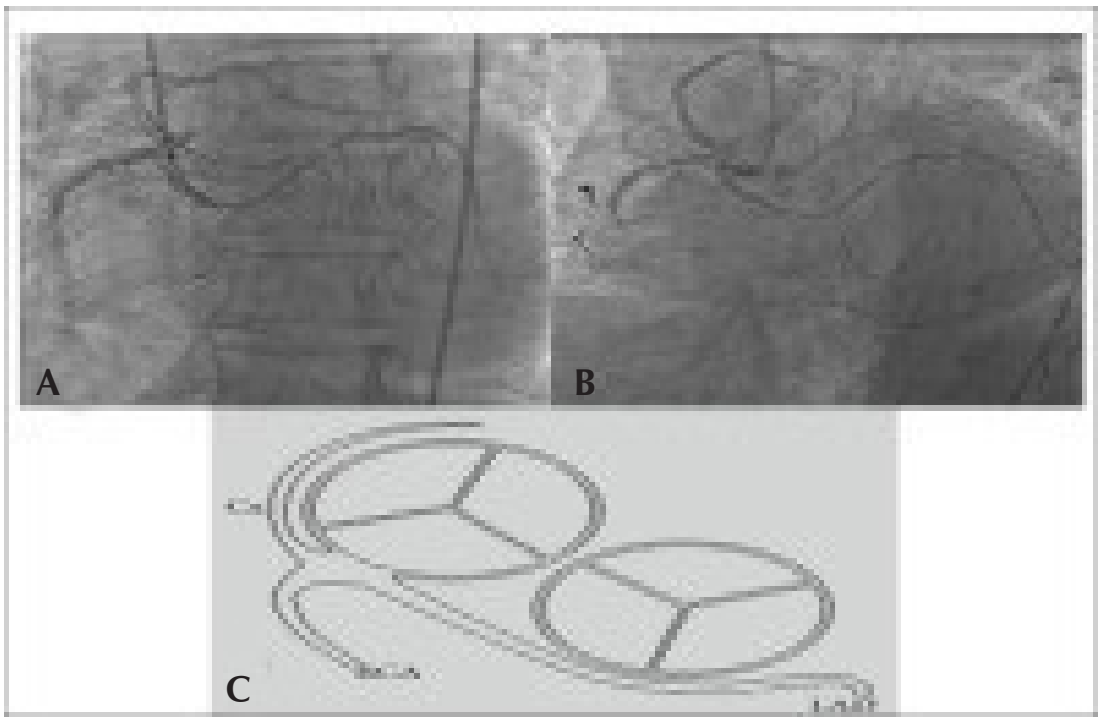

Figure 1 – *(A,B) Coronary angiographic imaging in the left anterior oblique projection showing three coronary arteries originating from right sinus of Valsalva. (C) Schematic drawing of the coronary anomaly.*

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Myocardial Edema without Fibrosis by Magnetic Resonance T2 Mapping in Acute Chagas' Myocarditis

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A 47-year old previously healthy male presented fever and malaise for 30 days. Chagas' disease was diagnosed by direct visualization of *Trypanosoma cruzi* parasites at thick blood smear (Figure 1A). Benznidazole was started and symptoms gradually subsided. At presentation, the patient had low QRS voltage and primary repolarization abnormalities on ECG, normal troponin level, moderate pericardial effusion and normal systolic function of both ventricles on echocardiogram. Cardiac magnetic resonance (CMR) using a 3T system (Verio, Siemens Healthcare) was performed five days after the treatment started and confirmed normal biventricular function and cavity sizes and moderate pericardial effusion. Late gadolinium enhancement (LGE) was normal (Figure 1B), but parametric T2 mapping of the myocardium (Siemens Healthcare) revealed myocardial T2 times of 70-72 ms (normal < 50 ms) compatible with edema in all myocardial segments (Figure 1C). A second CMR study, 26 days after treatment initiation, showed no pericardial effusion and partial regression of myocardial edema with T2 times of 50-54ms. A third study, 56 days after treatment initiation, showed complete regression of myocardial edema, with T2 times of 45-48 ms (Figure 1D). LGE was always negative. Direct detection of the parasite in the bloodstream was negative 13 days after treatment. This well documented acute Chagas' myocarditis case had no myocardial fibrosis. Nonetheless, exuberant myocardial edema was present that gradually subsided 56 days after specific treatment was started. T2 mapping was able to identify myocardial involvement beyond conventional CMR techniques as LGE, and it was demonstrated for the first time for acute Chagas disease.

Keywords

Acute Chagas' Myocarditis; Parametric Mapping.

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Conception and design of the research: Sousa AS, Xavier SS; Acquisition of data and Analysis and interpretation of the data: Derenne ME, Gottlieb I; Writing of the manuscript: Sousa AS, Derenne ME, Gottlieb I; Critical revision of the manuscript for intellectual content: Sousa AS, Hasslocher-Moreno AM, Xavier SS, Gottlieb I.

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Image

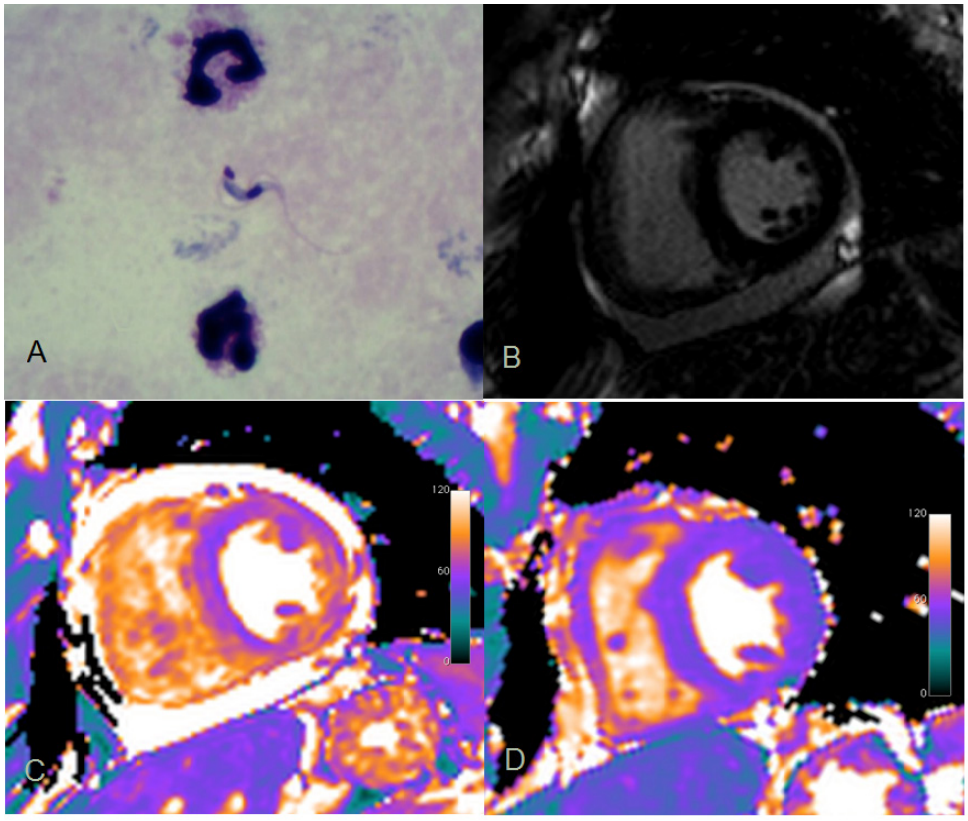

Figure 1 – *Trypanosoma cruzi parasite at thick blood smear in acute Chagas disease (A); first cardiac magnetic resonance with no myocardial fibrosis at late gadolinium enhancement (B), but with moderate pericardial effusion and myocardial T2 times of 70-72 ms compatible with edema in all myocardial segments (C); complete edema regression (T2 = 45-48 ms) and no pericardial effusion after specific treatment (D).*

Childhood Obesity, MMP-9 Levels, and Vitamin D

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Dear Editor,

I have read the article entitled "MMP-9 Levels and IMT of Carotid Arteries are Elevated in Obese Children and Adolescents Compared to Non-Obese" by Andrade et al.[1], recently published in journal, with great interest. The investigators reported that obese children and adolescents present higher mean intima-media thickness (IMT), plasma matrix metalloproteinase (MMP)-9 and MMP-9/tissue inhibitor of metalloproteinase-1 ratio compared to the non-obese. Thus, these findings indicate that this group presents a risk profile for early atherosclerosis.[1]

Keywords

Pediatric Obesity; Child; Adolescents; Cardiovascular Diseases; Overweight; Matrix Metaloproteinase 9.

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Childhood obesity is an international public health problem leading to an increased risk of adult obesity and associated with cardiovascular diseases such as hypertension, peripheral and coronary artery disease.[2] Vitamin D (vit D) may regulate adipose tissue mass, differentiation, and metabolism. Vit D deficiency might contribute with overweight and/or obesity, possibly by effects on lipogenesis and/or adipogenesis.[3] Coussens et al.[4] reported an inverse correlation between circulating vit D concentration and serum inflammatory biomarkers. Increased tumor necrosis factor-alpha (TNF-α) is associated with low vit D concentrations. Vit D down-regulates MMP-9 production by TNF-α and decreases production of MMP-9. Wang et al.[5] reported that vit D derivatives could significantly inhibit TNF-α induced MMP-2 and MMP-9 secretion in nasal polyp-derived fibroblasts.

In this context, considering a close association among childhood obesity, serum MMP-9 and vit D levels, the correlation of this study's result[1] with serum vit D levels might be beneficial.

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Letter to the Editor

Reply

We would like to thank you and agree with the considerations inserted in the letter about obesity and atherosclerosis. Indeed, we found a close association between obese children and adolescents with atherosclerosis, compared to non-obese ones.[1]

Besides, many authors have cited the important role of Vitamin D in these situations. Certainly, there is an inverse association between Vitamin and obesity. In this point, the Vitamin should regulate the adipose tissue metabolism, although its real role is still unknown, that is, whether it is cause or consequence.[2]

Indeed, obesity and Vitamin D deficiency represent an important health concern in the United States among children and adults.[2]

Because of the association between cardiovascular risk in obese children and adolescents, Atabeck et al.[3] suggest the prescription of Vitamin D as a way to prevent the premature onset of atherosclerosis. Gul at al.[4] reported that Vitamin D deficiency could contribute with morbidities associated to childhood obesity, such as increasing cardiovascular cardiometabolic risks, atherogenic dyslipidemia and hypertension.

In short, we think it would be important to promote more studies in order to prevent and treat atherosclerosis in obesity, as well to considerer the other diseases.

Sincerely,

Claudio Andrade
Adriana Bosco
Valeria Sandrim
Francisco Silva

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