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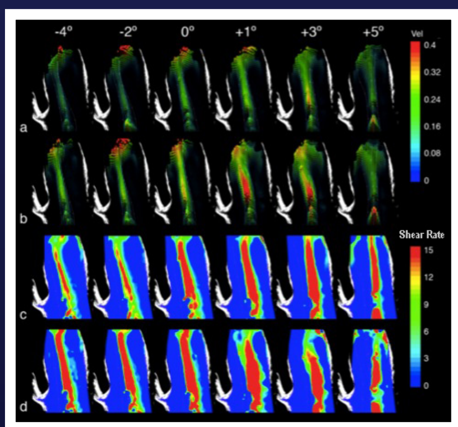

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20020-907 • Centro • Rio de Janeiro, RJ • Brasil
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When to Operate on Pediatric Patients with Congenital Heart Disease and Pulmonary Hypertension

Antonio Augusto Lopes and Ana Maria Thomaz
Instituto do Coração (InCor) - Faculdade de Medicina - Universidade de São Paulo, São Paulo, SP – Brazil

In pediatric patients with congenital heart disease associated with pulmonary arterial hypertension (PAH-CHD), deciding about surgery may be difficult depending on the diagnostic scenario. Most patients with communications between the cardiac chambers or the great arteries can now be operated on quite safely, with excellent results. Pulmonary hypertension accounts for complications in less than 10% of cases. In general, it has been considered that early assignment to surgery is the best strategy to avoid complications. This is unquestionable. However, late referral is still a problem in developing countries and underserved areas. Furthermore, it must be acknowledged that severe pulmonary vasculopathy may be present early in life, leading to the speculation that vascular lesions may develop from birth, or even before. Moderate to severe pulmonary vascular abnormalities limit the success of the repair of cardiac anomalies. First, the so-called postoperative pulmonary hypertensive crises are relatively infrequent in the present era, but still associated with high mortality rates (>20%).[1] Patient management requires sophisticated armamentarium for life support, sometimes extracorporeal membrane oxygenation (ECMO). Second, patients surviving the immediate postoperative period may remain at risk of persistent postoperative PAH, which is associated with poor outcome compared to other etiologies of pediatric PAH.[2] Therefore, while becoming aware of these complications, clinicians and surgeons need to get together and plan the best therapeutic strategy on an individual basis.

For a long time, cardiac catheterization (with the acute pulmonary vasodilation test, AVT) has been considered as a gold-standard assessment of PAH-CHD. In most tertiary centers indeed, catheterization data occupy a high hierarchical position in the decision to operate on PAH-CHD patients. Also, subclassifications of PAH-CHD according to disease severity are based on hemodynamic parameters. However, obtainment and interpretation of catheterization data are not easy tasks, especially in the pediatric population, for several reasons: 1- the procedure is generally performed under general anesthesia, mechanical ventilation and muscle relaxation, therefore, far from the physiological conditions; 2- even mild systemic hypotension (for example, due to inadequate hydration in regard to the effects of anesthetic drugs) makes results impossible to analyze in subjects with systemic-to-pulmonary shunts; 3- direct measurement of oxygen consumption, which is essential for calculations of pulmonary and systemic blood flow, is not done in many institutions; 4- inhaled nitric oxide is expensive and, therefore, unavailable in many centers, limiting the performance of the AVT; it is widely known that challenging the pulmonary circulation with ~100% oxygen is not adequate to test for vasoreactivity, leading to inaccurate results; and 5- there has been no consensus about the protocol for the AVT in the pediatric population, and the magnitude of the response does not correlate with outcomes in CHD.[3] In view of all these difficulties, cardiac catheterization remains as an important step in the evaluation of PAH-CHD,[4] but data are now taken into consideration as part of the whole diagnostic scenario.

In the era of the so-called specific drugs for the management of PAH, there have been attempts to treat inoperable patients (older subjects with elevated pulmonary vascular resistance and sometimes bidirectional shunting across the communications) aiming at making them operable. This approach has been referred to as "treat-and-repair strategy". However, there has not been sufficient evidence to support such recommendation in a generalized way.[5] On one hand, there is no guarantee that drugs will remain effective over the long term. On the other, persistence of severe PAH is a stormy complication after repair of congenital cardiac shunts, with significantly reduced survival.[2] Reopening of the communication frequently requires reoperation under cardiopulmonary bypass, a high-risk procedure in PAH patients. In selected cases, repairing an extracardiac lesion while leaving an intracardiac communication unrepaired, or considering partial closure of the defect may be an option.

Choosing the best therapeutic strategy in PAH-CHD, especially in the pediatric population, is something to be done on an individual basis. Sometimes, surgery must be considered even without expectation of complete hemodynamic normalization. This may be the case, for example, of a child with unrestrictive ventricular septal defect and PAH, with severe mitral regurgitation and nearly failing left ventricle. In this case, left heart disease will probably be more life limiting than PAH itself. Therefore, one could attempt to define operability in a general sense, not linking it to any single specific index of parameter cut-off. A patient should be deemed operable, if on the basis of all diagnostic data, the multiprofessional team is convinced that surgery can be offered with acceptable risk, with significant benefits envisioned over the medium and long term.

We would like to complement this view on the problem by presenting a summary of clinical features and diagnostic parameters that have been used for decision making about surgery in PAH-CHD, with emphasis on the pediatric

Keywords

Heart Defects, Congenital/surgery; Heart Defects/complications; Hypertension, Pulmonary/congenital; Postoperative Care/complications.

Mailing Address: Antonio Augusto Lopes •
Heart Institute, University of São Paulo School of Medicine. Av. Dr. Eneas de Carvalho Aguiar, 44, CEP: 05403-000. São Paulo, SP – Brazil
E-mail: aablopes@cardiol.b, aablopes@usp.br

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population (Table 1). Age and complexity of the cardiac anomaly must be considered. For example, while *truncus arteriosus* is now successfully repaired early in life, it is associated with development of severe pulmonary vasculopathy with increasing age. Echocardiography is useful for assessing the severity of PAH and right ventricular adaptation or dysfunction, provided that numeric parameters can be obtained in addition to anatomic information. Echocardiography is particularly useful when repeated measurements are needed in pediatric patients, before and after operation. Finally, cardiac catheterization with direct measurement of pulmonary vascular resistance should be considered in all patients with unrestrictive cardiac septal defects with no history of congestive heart failure and failure to thrive. Rather than looking at a single parameter, the best policy is to use a holistic diagnostic approach in these delicate patients.[6] In terms of decision making about surgery, "benign neglect" is probably the best humanistic attitude when risk overcomes benefits. Otherwise, decision to operate must be based on multiple diagnostic aspects and the opinion of an expert multiprofessional team.

Table 1 – Clinical features and noninvasive and invasive parameters considered for decision making about surgery in pediatric PAH-CHD

Favorable scenario	Parameters	Unfavorable scenario
< 9 months	Age	> 2 years
Pre-tricuspid or simple post-tricuspid defects	Complexity of cardiac anomaly	Complex defects Truncus arteriosus Transposition of the great arteries Atrioventricular septal defect in Down syndrome
Present in clinical history / physical examination	Congestive heart failure Pulmonary congestion Failure to thrive	Absent
> 93%, no gradient	Systemic oxygen saturation, gradient right arm vs. lower extremities	< 90%, presence of gradient
	Echocardiographic parameters	
> 2.5	Pulmonary-to-systemic blood flow ratio (Qp/Qs)	< 2.0
> 24 cm	Velocity-time integral of blood flow in pulmonary veins	< 20 cm
Left to right	Direction of flow across the cardiac communication	Bidirectional
	Cardiac catheterization	
≥ 20%	% decrease in pulmonary-to-systemic vascular resistance ratio (Rp/Rs) from baseline, during nitric oxide (NO) inhalation	< 20%
< 5.0 Wood units•m^2	Level of pulmonary vascular resistance achieved on NO	> 8.0 Wood units•m^2
< 0.27	Lowest Rp/Rs achieved during NO inhalation	> 0.33

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Minute-Ventilation Variability during Cardiopulmonary Exercise Test is Higher in Sedentary Men Than in Athletes

Renata Rodrigues Teixeira de Castro,[1,2] Sabrina Pedrosa Lima,[2] Allan Robson Kluser Sales,[1] Antonio Claudio Lucas da Nóbrega[1]

Laboratório de Ciências do Exercício (LACE) - Universidade Federal Fluminense (UFF)[1], Niterói, RJ; Hospital Naval Marcílio Dias - Marinha do Brazil,[2] Rio de Janeiro, RJ – Brazil

Abstract

Background: **The occurrence of minute-ventilation oscillations during exercise, named periodic breathing, exhibits important prognostic information in heart failure. Considering that exercise training could influence the fluctuation of ventilatory components during exercise, we hypothesized that ventilatory variability during exercise would be greater in sedentary men than athletes.**

Objective: **To compare time-domain variability of ventilatory components of sedentary healthy men and athletes during a progressive maximal exercise test, evaluating their relationship to other variables usually obtained during a cardiopulmonary exercise test.**

Methods: **Analysis of time-domain variability (SD/n and RMSSD/n) of minute-ventilation (Ve), respiratory rate (RR) and tidal volume (Vt) during a maximal cardiopulmonary exercise test of 9 athletes and 9 sedentary men was performed. Data was compared by two-tailed Student T test and Pearson´s correlations test.**

Results: **Sedentary men exhibited greater Vt (SD/n: 1.6 ± 0.3 vs. 0.9 ± 0.3 mL/breaths; p < 0.001) and Ve (SD/n: 97.5 ± 23.1 vs. 71.6 ± 4.8 mL/min x breaths; p = 0.038) variabilities than athletes. VE/VCO_2 correlated to Vt variability (RMSSD/n) in both groups.**

Conclusions: **Time-domain variability of Vt and Ve during exercise is greater in sedentary than athletes, with a positive relationship between VE/VCO_2 pointing to a possible influence of ventilation-perfusion ratio on ventilatory variability during exercise in healthy volunteers. (Arq Bras Cardiol. 2017; 109(3):185-190)**

Keywords: **Breathing; Respiratory Function Tests; Sedentary Lifestyle; Athletes; Pulmonary Ventilation; Exercise.**

Introduction

During a progressively increasing work rate exercise test, ventilation is expected to exhibit a curvilinear behavior when plotted against time, as work rate is increased above anaerobic threshold.[1] Some heart failure patients' ventilation versus time plot does not comply with this physiological pattern and exhibits oscillations, with sequenced ups and downs in their ventilation versus time graphics during a cardiopulmonary exercise test. The presence of abnormal ventilatory oscillations in exercise test, named periodic breathing, is a powerful predictor of adverse outcome which prevalence varies from 25 to 31% of heart failure patients, depending on the criteria used to define it[2] and regardless of the presence of other classic prognostic parameters.[3,4]

Recently, the prognostic value of oscillatory ventilation has been described in patients with heart failure with preserved ejection fraction[5,6] and its occurrence has been described in apparently healthy people.[7] Despite the prognostic value of this ventilatory parameter, there is still disagreement about the criteria that should be used to detect this phenomenon.[2,8] Noteworthy, many variables that indicate prognosis in cardiopulmonary exercise tests are analyzed in a dichotomized approach. This means that a cut-off point categorize patients regarding their risk. Although this is convenient, there may be loss of important information.[9] In fact, we have previously shown that some patients' ventilation versus time plot exhibits modest oscillations that although are not normal neither comply to any established criteria of periodic breathing.[10] Thus there is a grey area of ventilation variability pattern that is usually neglected by a binary approach. This is probably indicating that periodic breathing is the abnormal extreme of a more insidious process characterized by the inability to keep minute ventilation varying around an accepted set point. Thus, a method capable of quantifying the ventilation variability may not only add to the understanding of ventilatory patterns during exercise, but also to analyze prognosis in a leveled approach that could be more detailed than a binary one.

Time-domain variability techniques are used in cardiology for the analysis of heart rate variability. We have previously replicated this technique to analyze ventilatory variability in heart failure patients during a maximal exercise test.[10,11]

Mailing Address: Renata Rodrigues Teixeira de Castro •
LACE-UFF - Rua Professor Hernani Pires de Melo, 101 / Sala 106.
Postal Code 24210-130, São Domingos, Niterói, RJ – Brasil
E-mail: castrorrt@gmail.com, rrcastro@cardiol.br
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Original Article

Exercise training confers adaptations capable of modifying not only resting ventilatory parameters, but also their acute responses to a single exercise section.[12] The adaptability of ventilatory variability to physical training is still unknown, but we have previously reported the reversal of periodic breathing, and reduction of ventilatory variability, after 14 weeks of cardiac rehabilitation in a patient with heart failure.[10]

Considering that exercise training could influence the fluctuation of ventilation during a progressive exercise test, we hypothesized that time-domain ventilatory variability during exercise would be greater in sedentary men than in athletes. Thus, the present study was designed to compare time-domain minute-ventilation variability of sedentary healthy men and athletes during a progressive maximal exercise test.

Methods

Volunteers

Eighteen male volunteers (9 sedentary and 9 athletes) were invited to participate in the study. All of them were considered healthy after clinical history and physical examination. None of them was a smoker or had been in regular use of any medication. Sedentary men were not involved in any regular physical activity during the last three months and have never been considered as athletes before. Athletes were professional soccer players from the same soccer team, playing first division in Rio de Janeiro, Brazil.

Study protocol

All volunteers provided written informed consent to participate in the study after full explanation of the procedures and their potential risks. The investigation conformed to the principles outlined in the Declaration of Helsinki and have been approved by the Institutional Research Ethics Committee on Human Research.

All volunteers performed a maximal cardiopulmonary treadmill (Trackmaster 30x30, USA) exercise test following an individualized ramp protocol up to exhaustion. All tests achieved at least three of the following criteria to be considered maximum:[13] achievement of oxygen consumption (VO_2) plateau; perceived exertion (modified BORG scale) = 10; achievement of maximal predicted heart rate (220-age); respiratory exchange ratio ≥ 1,10.

Cardiopulmonary exercise tests were performed with gas exchange and ventilatory variables being analyzed breath-by-breath using a calibrated computer-based exercise system (*Ultima CardiO$_2$ System*, Medical Graphics Corporation, USA). The O_2 and CO_2 analyzers were calibrated before each test using a reference gas (12% O_2; 5% CO_2; nitrogen balance). The pneumotachograph used was also calibrated, with a 3L syringe using different flow profiles. During each cardiopulmonary exercise test, a 12-lead electrocardiogram was continuously recorded (*Cardioperfect*, Welch Allin, USA) and heart rate automatically derived. Carbon dioxide production (CO_2), VO_2, tidal volume (Vt) and respiratory rate (RR), were registered breath-by-breath. Minute ventilation (VE), O_2 and CO_2 ventilatory equivalents (VE/VO_2 and VE/VCO_2) were automatically calculated (*Breeze Software* 6.4.1, Medical Graphics, USA). All breath-by-breath results were exported to an Excel spreadsheet (*Microsoft Corporation*, USA), where standard deviation (SD) and root mean square successive difference (RMSSD) of VE during exercise test were calculated for each patient. Considering that the number of observations has a direct influence on variability measurement, results (SD and RMSSD) were normalized to the number of respiratory cycles during the test, reducing the probability that a greater number of observations registered in longer tests would be the sole responsible for greater variability (SD/n and RMSSD/n, respectively).[14]

Statistical analysis

Statistical analysis was performed using the software Statistica 7.0 (*Statsoft Inc,* USA). Variables from the cardiopulmonary exercise tests showed normal distribution when analyzed by the *Shapiro Wilk*'s test. Exercise variables in both groups were compared by paired two-tailed Student T test. Significance was set at $p < 0.05$. Results are presented as mean ± standard deviation.

A sample size of twelve individuals (6 in each group) would be needed to provide an 80% power with a 2-sided alpha of 0.05 to detect a difference of 10 ± 5 ml/min x breaths in SD/n ventilation variability between the two groups. Considering that ventilatory variability is a new variable, and that there are no published data to guide us regarding expected values, we have decided to increase sample in 50% and that is why the presented study included 18 individuals. After finishing the study, the calculated power of ventilatory variability is 100%.

Results

The demographic and anthropometric characteristics of both groups are described in table 1. All tests achieved the oxygen consumption plateau and a respiratory quotient greater than 1.10, and thus were considered maximum testes. Peak cardiopulmonary exercise data of both groups are shown in table 2.

Sedentary men exhibited higher time-domain variability of minute-ventilation than athletes during cardiopulmonary exercise test, as showed in figure 1.

Discussion

The analysis of minute-ventilation curve during exercise has gained interest since the first reports of exercise oscillatory ventilation.[15,16] Although a lot of progress has been done regarding the prognosis value of this phenomenon since then,[4,6,17] there was almost no progress in the quantification of this phenomenon.[18] There are currently two major diagnostic definitions of exercise oscillatory ventilation.[3,17] Both definitions require the visualization of the ventilatory pattern during exercise to determine the presence or absence of exercise oscillatory ventilation, in a dichotomized way. We have previously shown that applying time-domain variability techniques can be easily performed and may help quantifying exercise

Table 1 – Demographic and anthropometric data of volunteers (n = 18)

Variable	Sedentary men (n = 9)			Athletes (n = 9)			p value*
Age (years)	26	±	6	22	±	2	0.128
Weight (kg)	77.7	±	11.0	70.6	±	1.3	0.134
Height (m)	1.75	±	0.06	1.75	±	0.03	0.866
BMI (kg/m^2)	25.4	±	3.04	23.05	±	1.14	0.064

**Comparison between groups by student T test. BMI: body mass index.*

Table 2 – Peak exercise data during graded maximal cardiopulmonary exercise test performed by athletes and sedentary men in a treadmill

	Athletes (n = 9)			Sedentary men (n = 9)			p value
VO_2 (mL/kg/min)	47.8	±	0.3	42.6	±	4.2	0.029
VCO_2 (mL/kg/min)	64.1	±	1.2	54.8	±	6.0	0.009
RER	1.3	±	0.3	1.29	±	0.3	0.380
Ve (L/min)	128.7	±	0.3	123.4	±	14.7	0.550
Respiratory rate (breaths/min)	57	±	3	54	±	6	0.540
Vt (L)	2.3	±	0.3	2.3	±	0.3	0.837
Heart rate (beats/min)	181	±	3	186	±	3	0.343
VE/VO_2	2.7	±	0.3	2.9	±	0.3	0.309
VE/VCO_2	2.0	±	0.3	2.3	±	0.3	0.106
RR/VO_2 (breaths/ml/Kg/min)	1.2	±	0.3	1.3	±	0.3	0.363
VO_2/HR (ml/ beat)	0.3	±	0.3	0.2	±	0.3	0.015

VO_2: peak oxygen consumption; VCO_2: peak carbon dioxide production; RER: respiratory exchange ratio; Ve: minute-ventilation; Vt: tidal volume. P value refers to the result of paired student's T test.

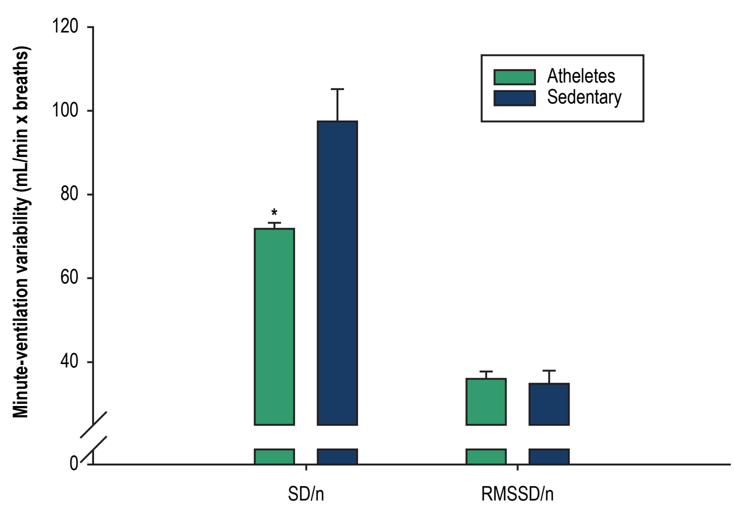

Figure 1 – *Minute-ventilation variability (SD/n and RMSSD/n) of athletes (green bars) and sedentary men (blue bars) during a graded maximal exercise test. * p < 0.05 vs. sedentary.*

ventilatory oscillations. Olson and Johnson[18] have also proposed a software application to quantify measures of exercise oscillatory ventilation in heart failure patients.

Considering that most ventilatory parameters exhibit some adaptation to physical training, it is conceivable to hypothesize that ventilatory variability would also be affected by chronic exposure to physical exercise. The present study compared ventilatory variability throughout exercise in athletes and sedentary men and concluded that untrained volunteers exhibited greater minute-ventilation variability than soccer athletes.

It is important to note that all volunteers were healthy and without any cardiovascular or respiratory disease. Therefore, some mechanisms involved in *Cheyne-Stokes* respiration and periodic breathing, such as hypocapnia, and pulmonary blood flow fluctuations,[19] which are considered key mechanisms of periodic breathing in heart failure, would probably not be useful in understanding physiological ventilatory variability during exercise in healthy subjects. Increased central and peripheral chemosensitivity[20] is also involved with *Cheyne-Stokes* respiration. Ohyabu et al showed that ventilatory sensitivity during hypoxia was attenuated in long-distance runners and sprinters compared to non-athletes.[21] In fact, endurance training reduces the ventilatory response to a given level of work due to an attenuated chemosensitivity.[22,23] So, it is possible that reduced chemosensitivity would explain the findings of the present study.

Although there was no statistical difference regarding weight or body mass index between groups, volunteers in the sedentary group exhibited near significantly higher weight and BMI. One could hypothesize that this slight and non-significant difference could have influenced the different breathing patterns found in the study. In fact, in morbid obese individuals, excessive body weight can induce chest wall restriction[24] and loosing body weight may improve lung function.[25] Nevertheless, although there was some overweight volunteers in both groups, there was not a single obese volunteer in this study. We could not found any study that compared ventilatory parameters in overweight and not overweight individuals during exercise. Regarding rest breathing patterns, it seems that body mass only influences lung function when obese individuals are in supine position. Our volunteers were non-obese and all tests were performed in the upright position. Thus, it seems unlikely that the slight and non significant difference in BMI between groups would have influenced the ventilatory variability results of the present study.

The analysis of table 2 shows maximal VO_2 that is not as high as expected for professional soccer players. There are several possible explanations for this finding. First of all, data was collected in the beginning of the season, just after holydays. So, athletes were not in their best shape. It is also important to note that there is clear VO_{2max} variation profiles between soccer players accordingly to their playing position and style.[26] We have included athletes from all playing positions, from the same team, in the athlete group. So, there were differences between their VO_{2max}. Finally, players in Brazil appear to be shorter in stature, similar in body mass and have a lower overall aerobic capacity when compared to their European equivalents.[26]

Study limitations

Some operational and technical aspects could have influenced the results of the present study. Subjects were not submitted to rest pulmonary function tests before entering the study. Considering none of them had any past history of pulmonary disease or smoking, the absence of rest pulmonary function tests, although desirable, does not seem to be a major issue influencing the present results.

The use of different interfaces to breath analysis may influence the depth and rate of breathing.[27] Although this effect appears to be restricted to lower levels of exercise,[28] it seems reasonable not to interchangeably compare ventilatory variability results recorded using mask, mouthpiece or canopy. All breath-by-breath data in this study was collected throughout a face mask. Thus, the selected interface could not have influenced the different results when both groups were compared.

This is a cross-sectional study where trained and untrained men were compared. A study that evaluates the effects of physical training would rather have a longitudinal than the present design. Nevertheless, the only difference between both studied groups was their peak VO_2, which was higher in athletes, as expected. Thus, although athletes were not longitudinally evaluated, it seems that the different exercise responses in both groups could be directly attributable to physical training.

Conclusions

The presence of periodic breathing is a powerful predictor of adverse outcome in heart failure.[2] This is an extreme presentation of a ventilatory variation that although unseen by our eyes can be mathematically calculated. The present study adds information regarding the quantification of exercise minute-ventilation variability, and points to the direction that this is a trainable exercise variable. The exact mechanisms that influence ventilatory variability during exercise remain to be studied.

Author contributions

Conception and design of the research: Castro RRT, Nóbrega ACL; Acquisition of data and Writing of the manuscript: Castro RRT, Lima SP, Sales ARK; Analysis and interpretation of the data, Statistical analysis and Critical revision of the manuscript for intellectual content: Castro RRT.

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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Relationship between Cardiometabolic Parameters and Elevated Resting and Effort Heart Rate in Schoolchildren

Cristiane Fernanda da Silva,[1] Miria Suzana Burgos,[1] Priscila Tatiana da Silva,[1] Leandro Tibiriçá Burgos,[1] Letícia Welser,[1] Ana Paula Sehn,[1] Jorge André Horta,[1] Elza Daniel de Mello,[2] Cézane Priscila Reuter[1]
Universidade de Santa Cruz do Sul (UNISC),[1] Santa Cruz do Sul, RS; Universidade Federal do Rio Grande do Sul,[2] Porto Alegre, RS – Brazil

Abstract

Background: Little has been studied on heart rate and its relationship with metabolic disorders.

Objective: To identify possible association between heart rate (HR) and metabolic disorders in children and adolescents.

Methods: This cross-sectional study evaluated 2.098 subjects, aged between 7 and 17 years. The variables evaluated were: HR, systolic (SBP) and diastolic blood pressure (DBP), pulse pressure (PP), double-product (DP), myocardial oxygen consumption (mVO_2), lipids, glucose and uric acid levels, body mass index (BMI) and waist circumference (WC). The values of HR at rest and effort were divided into quartiles. The association between continuous values of HR and cardiometabolic indicators was tested by linear regression.

Results: LDL cholesterol presented a significantly higher mean (p = 0.003) in schoolchildren with resting HR greater or equal to 91 bpm, compared to students with less than 75 bpm. Compared with the quartiles of effort HR, SBP, DBP, glucose and uric acid presented high values when HR was greater or equal than 185 bpm. SBP, glucose and HDL cholesterol demonstrated a significant association with resting HR. Uric acid was observed as a predictor of increased effort HR.

Conclusion: Schoolchildren with a higher resting HR have higher mean of LDL cholesterol. For effort HR, there was an increase in blood pressure, glucose and uric acid levels. Uric acid has been shown to be a predictor of elevated effort HR. (Arq Bras Cardiol. 2017; 109(3):191-198)

Keywords: Child Health; Adolescent Health; Metabolism Syndrome; Heart Rate; Physical Exertion; Rest.

Introduction

The search for new information that may contribute to the development of mechanisms for the prevention and treatment of cardiovascular and metabolic complications leads to different lines of research.[1] In childhood and adolescence, the focus of these studies has been the association between obesity,[2] cardiorespiratory fitness,[3] changes in the lipid profile[4] and non-communicable chronic diseases, such as diabetes and hypertension.[5] However, a variable that has received increasing attention is cardiac autonomic modulation in children and adolescents.[1,6]

Cardiac autonomic changes can be investigated by means of a change in heart rate (HR).[7] HR is a physiological variable that is easy to obtain and measure.[8] Because it is a parameter of low cost and associated with reliable variables of effort measurement, HR is often used to assess cardiovascular system response during exercise and recovery.[9] The association of HR with metabolic disorders has still been poorly studied, however, it is known that physical condition and the presence of pathologies may influence resting HR.[10]

A study carried out in Campinas-SP aimed to verify the existence of differences in the cardiovascular condition of obese and non-obese children under resting conditions. That study found that childhood obesity causes a greater overload on the resting heart due to a significant elevation of HR in obese children.[11] According to Freitas Junior et al.[12], a high amount of body fat leads to the release of inflammatory adipokines in the bloodstream which contributes to the development of chronic diseases, as well as the change in sympathetic and parasympathetic activities in children and adolescents, aspect which may cause an increase in resting heart rate.

Little has been studied about HR and its relationships with metabolic dysfunctions in childhood and adolescence.[8] At rest, low heart rate values may be associated with health, reflecting a lower risk of cardiovascular diseases.[13] A study by Fernandes et al.[14] analyzed the association between resting HR and blood pressure in male children and adolescents and identified a positive association between these variables, suggesting that elevated HR also causes an increase in blood pressure in the pediatric population. Bruneto et al.[6] have associated an increased morbidity rate and the onset

Mailing Address: Cézane Priscila Reuter •
Avenida Independência, 2293 - Bloco 42, sala 4206. Postal Code 96815-900, Universitário, Santa Cruz do Sul, RS – Brazil
E-mail: cpreuter@hotmail.com, cezanereuter@unisc.br
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of cardiovascular disease with the reduced practice of physical activity and low levels of conditioning in obese children and adolescents. In view of these perspectives, it is useful to investigate associations between heart rate and cardiometabolic indicators. In this way, we will be contributing to the construction of subsidies for the creation and implementation of health prevention and promotion policies aimed at improving the quality of life of the child and adolescent population. Thus, the present study aims to verify if there is an association between heart rate and metabolic dysfunctions in children and adolescents.

Methods

The participants of this cross-sectional study are 2.098 subjects, female and male, aged between 7 and 17 years, belonging to municipal, state and private schools in the urban and rural area of the municipality of Santa Cruz do Sul, Rio Grande do Sul. The present study is part of a larger study entitled "Health of schoolchildren - Phase III", approved by the Committee of Ethics in Research (CEP) with Human Beings under protocol number 714.216 and CAAE: 31576714.6.0000.5343.

The variables used to evaluate this study were: resting and effort heart rate (HR), resting blood pressure (BP), pulse pressure (PP), double product (DP), myocardial oxygen consumption (mVO_2), biochemical indicators, evaluated by means of serum (lipid and glycemic profile), anthropometrics: body mass index (BMI) and waist circumference (WC). To measure the resting HR, the student should be seated, with 5 minutes at rest. HR was assessed using the FT1 model frequency meter (Polar, Finland), with the heart rate sensor attached on the pectoral line over the sternum with an elastic band. The lowest value stabilized by the frequency meter was considered for resting HR. The exercise heart rate was evaluated after performing the 6-minute run/walk test, applied on the athletics track at the University of Santa Cruz do Sul-UNISC. For the 6-minute run/walk test, the guidelines of the protocol recommended by the Brazilian Sport Project - PROESP-BR[15] were followed. The schoolchildren were previously instructed to wear light clothing and appropriate footwear (sneakers) and walk the longest distance possible throughout the test. The obtained results were collected immediately after the interruption of the test. Stress HR values were obtained through the frequency meter and expressed in beats per minute (bpm). For the evaluation of BP, the same procedure was applied to the resting HR, and the evaluation was performed in the left arm, with the student sitting. After 5 minutes at rest, two BP measurements were performed, using a sphygmomanometer, stethoscope and cuff suitable for the student's brachial perimeter. Only the lowest values of systolic (SBP) and diastolic (DBP) pressure were considered, and PP was obtained by the difference between SBP and DBP.[16] All evaluations were performed at the University.

The biochemical indicators evaluated included lipid profile and glucose and uric acid levels, through serum samples from the children, who were oriented to maintain a previous fast of 12 hours. For the lipid profile, the following markers were measured: total cholesterol (TC) and HDL fraction (HDL-C) (high-density lipoprotein) as well as triglycerides. LDL-C (LDL-C) cholesterol was calculated according to the Friedewald, Levy and Fredrickson equation.[17] Data obtained follow the recommendations of the National Heart, Lung, and Blood Institute[18] and the American Diabetes Association,[19] to assess the lipid and glycemic profile, respectively. All analysis were performed on automated equipment Miura One (I.S.E., Rome, Italy), using commercial kits.

BMI was obtained after weight and height were evaluated, using a balance and stadiometer, respectively. The BMI was calculated by dividing the weight by height, squared.[20] The WC was evaluated with an inelastic tape measure, and the smallest perimeter of the trunk between the ribs and the iliac crest was evaluated.[21] The values of DP were obtained by the calculation of the SBP x HR. The mVO_2 values were obtained using the DP conversion formula: $mVO_2 = (DP \times 0.0014) - 6.3$, as proposed by Hellerstein and Wenger.[22] The evaluation of the maturational stage was performed by Tanner's classification, considering the maturational development in 5 phases, for both sexes, being evaluated the development of pubic hairiness and genitalia. For the application of the test, each of the phases was shown to the student through drawings and he was oriented to choose the phase that most closely resembled his current stage of development.[23]

Statistical analysis

Statistical analysis of the data was performed in the statistical program SPSS v. 23.0 (IBM, Armonk, NY, USA). The descriptive characteristics were presented in frequency and percentage for categorical variables. For continuous variables, the Shapiro-Wilk test was used to test the normality of the data (HR at rest and effort, SBP, DBP, PP, glucose, TC, HDL-C, LDL-C, TG and uric acid). Data were presented on average (standard deviation), since they had a normal distribution. Subsequently, HR values of rest and effort were divided into quartiles. Comparison of the mean values of the cardiometabolic indicators, according to categorization with the resting HR quartiles (Q1: < 75 bpm, Q2: 75-82 bpm, Q3: 83-90 bpm and Q4: ≥ 91 bpm) and effort (Q1: < 152 bpm; Q2: 152-171 bpm, Q3: 172-184 bpm and Q4: ≥ 185 bpm), was performed using analysis of variance (ANOVA), with a Tukey Post Hoc test for comparison between groups. The association between the continuous values of rest and effort HR with the cardiometabolic indicators was tested by linear regression, adjusted for the variables gender, age, body mass index and maturational stage. For all analysis, the differences for $p < 0.05$ were considered significant.

Results

The characteristics of the evaluated students, with respect to sex, maturational stage, age and rest and effort HR, can be visualized in table 1. Of the 2.098 students evaluated, 903 (43%) were males and 1195 (57%) female, with a mean age of 11.50 ± 2.77 years.

Comparison of the mean values of cardiometabolic indicators, according to resting HR quartiles (Table 2), shows that there was a significant association between DP (0.678 $p < 0.001$) and mVO_2 (0.678 $p < 0.001$) with HR, in rest. For LDL-C values, there was also a significant difference (p = 0.003), with a higher mean in the fourth quartile (88.68 mg / dL) compared to the first quartile (82.66 mg/dL). In addition, a significant difference was observed in the values of DP and mVO_2 from one quartile to another and all quartiles differed from each other. There was no significant association between PP and HR.

When the cardiometabolic indicators were compared with the effort HR quartiles (Table 3), mean values were higher in the fourth quartile compared to the first quartile for SBP (108.71 mmHg); $p < 0.001$), DBP (66.43 mmHg, $p < 0.001$), glucose (90.58 mg/dL, p = 0.028) and uric acid (4.40 mg/dL, $p < 0.001$).

When the association between HR and cardiometabolic indicators is analyzed by means of linear regression (Table 4), SBP, glucose and HDL-C were associated with resting HR; however, this association, although significant, was weak. An association between resting HR and mVO_2 ($\beta = 3.46$; $p < 0.001$) was found. For exercise HR, only uric acid was associated ($\beta = 0.73$, p = 0.015), demonstrating that it was a predictor of increased exercise HR in the sample evaluated. On the other hand, when the Pearson correlation coefficient was evaluated, a moderate association was found only between resting HR with DP (r = 0.678, $p < 0.001$) and mVO_2 (r = 0.678, $p < 0.001$).

Table 1 – Descriptive characteristics of subjects. Santa Cruz do Sul, RS, 2014-2015

	n (%)
Sex	
Male	903 (43)
Female	1195 (57)
Maturational stage	
I	517 (25)
II	510 (24)
III	437 (21)
IV	478 (23)
V	156 (7)
	Mean (standard deviation)
Age (years)	11.50 (2.77)
Resting HR(bpm)	82.67 (10.40)
Effort HR (bpm)	168.40 (22.47)

Discussion

The present study sought to evaluate possible associations between heart rate and metabolic disorders. We found that high resting HR (equal to or greater than 91 bpm) was associated with higher LDL-C levels (88.68 mg/dL, $p < 0.001$). High HR was associated with high SBP values (108.71 mmHg, $p < 0.001$), DBP (66.43 mmHg, $p < 0.001$), glucose (90.58 mg/dL, p = 0.028) and uric acid (4.40 mg/dL, $p < 0.001$). A study in Presidente Prudente-SP found similar data and showed a positive association between resting HR and dyslipidemia, and students with higher values of HR had higher levels of TC and triglycerides. However, no association was found with LDL-C values.[12]

In our study, the analysis of the association between HR and cardiometabolic indicators found a significant association among SBP, glucose and HDL-C, with resting HR, but this association was weak. Only uric acid, related to exercise HR,

Table 2 – Comparison of mean values of cardiometabolic indicators according to resting HR quartiles

	Quartiles of resting HR				p
	Q1 (n = 513)	Q2 (n = 515)	Q3 (n = 540)	Q4 (n = 530)	
	< 75 bpm	75-82 bpm	83-90 bpm	≥ 91 bpm	
SBP (mmHg)	106.94 (14.61)	105.95 (13.85)	105.03 (14.28)	107.02 (14.94)	0.081
DBP (mmHg)	65.47 (10.60)	64.62 (10.75)	64.49 (11,01)	65.18 (11.19)	0.412
Glucose (mg/dL)	89.85 (9.52)	89.44 (9.29)	89.31 (9.49)	90.24 (9.14)	0.354
TC (mg/dL)	158.62 (30.93)	160.60 (30.20)	161.85 (30.32)	163.70 (31.22)	0.055
HDL-C (mg/dL)	62.16 (10.86)	60.95 (11.48)	60.77 (12.40)	60.49 (11.30)	0.098
LDL-C (mg/dL)	82.66 (28.45)	85.11 (25.93)	86.47 (26.03)	88.68 (26.61)	0.003[I]
TG (mg/dL)	69.82 (30.76)	71.80 (31.61)	72.75 (36.96)	71.73 (34.40)	0.552
UA (mg/dL)	4.30 (1.57)	4.14 (1.26)	4.16 (2.44)	4.16 (1.19)	0.381
DP (bpm/mmHg)	7354.33 (1073.25)	8364.62 (1136.90)	9087.20 (1253.50)	10257.53 (1522.47)	< 0.001[II]
mVO_2 (mlO_2/100.LV.min)	3.99 (1.50)	5.41 (1.59)	6.42 (1.75)	8.06 (2.13)	< 0.001[II]
PP (mmHg)	41.47 (9.69)	41.34 (9.22)	40.54 (9.56)	41.84 (10.68)	0.176

Analysis of variance (ANOVA); Data expressed as mean (standard deviation); Q1: quartile 1; Q2: quartile 2; Q3: quartile 3; Q4: quartile 4; Bpm: beats per minute; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; HDL-C: high-density lipoprotein; LDL-C: low-density lipoprotein; TG: triglycerides; UA: uric acid; DP: double-product; MVO_2: consumption of oxygen by the myocardium; PP: pulse pressure; Tukey Post Hoc: I Significant difference from Q1 to Q4 (p = 0.002); II significant difference from Q1 to Q2 ($p < 0.001$), for Q3 ($p < 0.001$) and for Q4 ($p < 0.001$); ($p < 0.001$), from Q2 to Q4 ($p < 0.001$) and from Q3 to Q4 ($p < 0.001$).

Table 3 – Comparison of the mean values of the cardiometabolic indicators according to the quartiles of the effort HR

	Quartiles of effort FC				p
	Q1 (n = 508)	Q2 (n = 537)	Q3 (n = 506)	Q4 (n = 547)	
	< 152 bpm	152-171 bpm	172-184 bpm	≥ 185 bpm	
SBP (mmHg)	103.72 (13.80)	105.44 (13.83)	106.89 (14.69)	108.71 (14.95)	< 0.001^I^
DBP (mmHg)	63.52 (10.59)	64.25 (10.28)	65.47 (10.81)	66.43 (11.63)	< 0.001^II^
Glucose (mg/dL)	89.23 (9.90)	89.93 (9.40)	89.02 (8.72)	90.58 (9.34)	0.028^III^
TC (mg/dL)	159,21 (30.31)	161.47 (27.42)	162.73 (33.54)	161.45 (31.34)	0.323
HDL-C (mg/dL)	60.80 (11.86)	61.42 (11.16)	60.62 (11.54)	61.45 (11.63)	0.544
LDL-C (mg/dL)	84.12 (26.79)	85.84 (24.29)	87.80 (28.78)	85.33 (27.33)	0.175
TG (mg/dL)	70.82 (31.96)	70.25 (31.88)	72.25 (36.33)	72.83 (34.00)	0.559
Uric acid (mg/dL)	3.91 (1.20)	4.28 (2.33)	4.16 (1.21)	4.40 (1.70)	< 0.001^IV^

Analysis of variance (ANOVA); Data expressed as mean (standard deviation); Q1: quartile 1; Q2: quartile 2; Q3: quartile 3; Q4: quartile 4; Bpm: beats per minute; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL-C: high-density lipoprotein; LDL-C: low density lipoprotein; Post Hoc of Tukey: I Significant difference of Q1 for Q3 (p = 0.002) and Q1 for Q4 (p < 0.001); II significant difference from Q1 to Q3 (p = 0.022) and Q1 to Q4 (p < 0.001); III significant difference from Q3 to Q4 (p = 0.035); IV significant difference from Q1 to Q2 (p = 0.002) and Q1 to Q4 (p < 0.001).

Table 4 – Association between heart rate and cardiometabolic indicators Rest HR Effort HR

	Rest HR					Effort HR				
	β	SE	p[1]	r	p[2]	β	EP	p[1]	r	p[2]
SBP	0.08	0.02	0.001	–0.00	0.967	0.08	0.05	0.096	0.13	< 0.001
DBP	0.02	0.03	0.500	–0.01	0.795	0.01	0.07	0.884	0.11	< 0.001
Glucose	0.05	0.02	0.034	0.01	0.684	0.01	0.05	0.911	0.05	0.030
Total cholesterol	0.16	0.08	0.060	0.07	0.001	-0.22	0.19	0.252	0.04	0.100
HDL-C	–0.20	0.09	0.022	–0.05	0.019	0.27	0.19	0.156	0.02	0.451
LDL-C	–0.14	0.08	0.096	0.09	< 0.001	0.26	0.19	0.168	0.03	0.122
Triglycerides	–0.02	0.02	0.285	0.04	0.062	0.02	0.04	0.631	0.01	0.546
Uric acid	–0.03	0,13	0.806	–0.03	0.132	0.73	0.30	0.015	0.09	< 0.001
DP	0.01	0.00	< 0.001	0.678	< 0.001	-	-	-	-	-
mVO_2	3.46	0.07	< 0.001	0.678	< 0.001	-	-	-	-	-
PP	0.07	0.02	0.003	0.005	0.820	-	-	-	-	-

Linear regression adjusted for sex, age, body mass index and maturational stage; SE: standard error; R: Pearson's correlation; [1]value of significance for the linear regression test; [2] significance value for the Pearson correlation test; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL-C: high-density lipoprotein; LDL-C: low-density lipoprotein; DP: double-product; MVO_2: consumption of oxygen by the myocardium; PP: pulse pressure.

showed a good association (β = 0.73, p = 0.015), which may be considered a predictor of increased cardiometabolic risks in the sample studied, considering that uric acid at high levels is associated with the occurrence of MS in adolescents.[24,25] The mechanism by which the relationship between uric acid and MS could be explained is in the fact that the hepatic consequence of MS is expressed through non-alcoholic fatty liver disease (NAFLD) .[26]

Thus, alterations in some specific components of MS, such as BP, glucose metabolism and lipids, suggest to be indicators of the aggravating installation of MS, including initial manifestations of NAFLD, an aspect that in this study already seems to have an impact on lower cardiovascular conditions for activities with high respiratory demands, thus reflecting a change in effort HR values. Likewise, uric acid, as an isolated component, would also be a more sensitive variable to capture these alterations. This hypothesis would be justified by the finding of NAFLD in the evaluated students. However, this relationship was not tested in the present study. On the other hand, a study carried out in Campina Grande, Brazil, with 129 children and adolescents aged 2 to 18 years, evaluated the relationship between uric acid concentration according to the presence of NAFLD and / or MS in children and adolescents with excess weight. The study identified that high levels of uric acid are associated with MS, SBP and adolescence, but this association was not observed with NAFLD.[27]

However, the low age range used in the study might have hampered the finding of NAFLD, since the condition would take time to set up. There is evidence that uric acid levels are significantly lower in children than in adolescents (4.74 ± 1.05 vs. 5.52 ± 1.49 mg/dL, $p < 0.001$), with boys tending to reach higher peak of uric acid between 12-14 years of age and girls between 10-12 years.[28] In addition, the study pointed out that individuals with elevated SBP were four times more likely to have hyperuricemia and that high levels of uric acid were associated with individual components of MS, such as BMI, WC and BP, which is similar to the findings pointed out in this study.[27]

Likewise, although the association of SBP, glucose and HDL-C with HR was weak, these data suggest to be indicative of the establishment of an early stage of MS, considering that recent studies have indicated positive associations between MS and changes in these metabolic indicators.[29,30] Recent data from the Cardiovascular Risk Study in Adolescents-ERICA, performed with 37.504 Brazilian adolescents from 27 capitals, showed that the combinations between high BP, high triglycerides and low HDL-C are the most frequently responsible for the diagnosis of MS in schoolchildren.[29] Thus, the data presented in this research point to elevated levels of HR as independent factor for the risk of dyslipidemias and cardiovascular disorders.[31,32]

On the other hand, a study carried out in 27 European cities evaluated 769 adolescents to verify the ability of HR to screen for metabolic risk factors and found that resting HR is not a good predictor for cardiometabolic risks. According to the study, the resting HR provides an underestimated value, so positive associations in studies between chronic degenerative diseases and resting HR would have been found due to the use of the percentiles scale, which would be a limited parameter, as it did not present the accuracy and precision of the HR rates; Thus, the study, using a better analysis, called the ROC curve, could consider the results presented by the study as more reliable. However, the same study pointed out that the isolated analysis of the risk factors identified that the male adolescents presented higher values of SBP (124.4 mmHg, 95% CI: 123.1-125.8) and TC/HDL (3.02; 95% CI: 2.96-3.09) compared to female adolescents (BP: 116.2 mmHg, 95% CI: 115.3-117.1, TC/HDL 2.99; 95% CI: 2.93-3.04). In addition, when compared with their female counterparts, the boys also presented higher resting HR, an aspect that suggests that higher resting HR levels are associated with an increase in BP and TC/HDL.[31]

In addition, changes in the behavior of HR of adolescents seem to be related to MS, both regarding changes to higher values and to reduced values. Studies with adolescents with obesity and alterations in the metabolic profile have shown that those with higher glucose levels, levels of TG, LDL-C and BP associated with obesity, in response to increased insulin resistance, alter the functions sympathetic and parasympathetic and results in a decrease in cardiac function and perhaps a reduction in HR values. This long-term fact would explain, in part, the increased risk for cardiovascular events and sudden death in obese individuals.[33,34]

Positive associations between resting HR and cardiovascular risk factors in adolescents were also found in a study carried out in 48 municipalities in the state of Pernambuco, (Northeastern Brazil), in which 4619 adolescents aged 14 to 19 years were evaluated. The study evaluated a set of risk factors and found that resting HR was associated with abdominal obesity ($b = 0.106$, $p = 0.003$), sedentary behavior ($b = 0.099$, $p < 0.001$), high BP ($b = 0.160$; $p < 0.001$) and physical inactivity ($b = 0.049$, $p = 0.034$) in boys, and in girls showed association with high BP ($b = 0.259$, $p < 0.001$). Moreover, the presence of five risk factors in schoolchildren resulted in significantly higher values of resting HR ($p < 0.05$), compared to schoolchildren with no cardiovascular risk factors. Thus, study data suggested that resting HR at or above 82.5 bpm ($\pm$ 13.9 bpm) in boys and 89.8 bpm ($\pm$ 10.9 bpm) in girls could be considered as a risk factor for CVD.[35]

In relation to the other cardiometabolic components evaluated, our study found a significant association between DP (0.678, $p < 0.001$) and mVO_2 (0.678, $p < 0.001$) with HR at rest. In addition, the comparison of mean values of cardiometabolic indicators, according to the resting HR quartiles, showed a significant difference in the values of DP and mVO_2 from one quartile to another and all quartiles differed from each other. These findings provide new perspectives for the use and approach of resting HR, since it is known that elevated HR values at rest are associated with worse functional conditions at more advanced ages.[36] However, there is scarce information available in the literature for analysis of these variables in the child and adolescent population. Due to the fact that both DP and mVO_2 express the conditions and demands of cardiac work, it is assumed that for the population evaluated, high resting HR can be considered as indicative of the occurrence of health problems or other compromises related to cardiac function, considering the high level of effort expended by the myocardium to develop the vital functions at rest.[37]

Thus, the hypothesis raised by the data found in our study indicates that the higher the resting HR, the greater the cardiac overload of the students. Therefore, elevated HR could be used as a predictor, in the first analysis, of altered physiological responses in children and adolescents, and the use of DP and mVO_2 values contributes to a better vision of the cardiac outcome. Moreover, associations among HR, obesity and cardiometabolic variables have indicated that overweight in children and adolescents cause greater impairment in cardiorespiratory fitness and pulmonary function, both at maximum and submaximal level, when compared to adolescents with normal weight, mainly By the commitment of oxygen consumption.[38,39]

Thus, in providing data demonstrating homeostatic changes in the child and adolescent population, our study supports the evidence that elevated cardiac responses indicate greater physiological fragility. Likewise, this study provides support for the development of new research aimed at better investigating this association, considering that no data were found in the literature regarding studies on possible interactions among HR, DP and mVO_2 with metabolic variables in children and adolescents.

At the same time, it should be noted that this study, however, has some limitations. The infeasibility of evaluating DP and mVO_2 values of effort prevents a broader view of cardiac function and the approach of this variable for the population surveyed. Simultaneously, the unavailability of studies relating such components to this public, restricts the understanding of the data and the formulation of hypotheses. Likewise, the lack of reference values for DP and mVO_2 variables for the pediatric population makes it difficult to interpret the results. However, the analysis presented here were adjusted to the characteristics of the study population and the associations found deserve to be further explored in future studies related to the health of schoolchildren, considering that changes in resting HR, SBP and DP, similar to those found in our analysis, have also been predictive of mortality from coronary events and increased risk of functional decline over the years.[35,40] DP is also known to be a stronger predictor of cardiac events than PA, HR and mVO_2, an aspect that demonstrates the importance of including these variables in the analysis of cardiac function.[40]

In this sense, the data found in this study can be seen as a small cut of an association that needs to be further investigated, since HR indicates to be a potential measure for the diagnosis of metabolic and cardiovascular diseases. However, future research is needed to determine whether these measures may be useful for screening for physiological changes related to HR dynamics in children and adolescents.

Final considerations

Schoolchildren with resting heart rate equal to or greater than 91 beats per minute present higher mean LDL cholesterol. For exercise heart rate, schoolchildren with 185 or more beats per minute had elevated systolic and diastolic blood pressure and glucose and uric acid levels. In addition, uric acid has been shown to be a predictor of elevated effort heart rate.

Author contributions

Conception and design of the research: Silva CF, Burgos MS, Burgos LT, Mello ED, Reuter CP; Acquisition of data: Silva CF, Burgos MS, Silva PT, Burgos LT, Welser L, Sehn AP, Horta JA, Reuter CP; Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Silva CF, Burgos MS, Silva PT, Burgos LT, Welser L, Sehn AP, Horta JA, Mello ED, Reuter CP; Statistical analysis: Reuter CP.

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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Playful Interventions Increase Knowledge about Healthy Habits and Cardiovascular Risk Factors in Children: The CARDIOKIDS Randomized Study

Fátima H. Cecchetto,[1] Daniela B. Pena,[2] Lucia C. Pellanda[1,2]

Pós-Graduação em Ciências da Saúde: Cardiologia - Instituto de Cardiologia/Fundação Universitária de Cardiologia;[1] Universidade Federal de Ciências da Saúde de Porto Alegre,[2] Porto Alegre, Brazil

Abstract

Background: **Childhood obesity is an important health problem worldwide. In this context, there is a need for the development and evaluation of innovative educational interventions targeting prevention and formation of health habits.**

Objectives: **To ascertain the impact of ludic workshops on children's knowledge, self-care, and body weight.**

Methods: **This was a randomized, clinical study with 79 students aged 7-11 years, conducted from March to November 2012. Anthropometric measurements were collected and two questionnaires (Typical Day of Physical Activities and Food Intake, in Portuguese, and the CARDIOKIDS, a questionnaire of knowledge about cardiovascular risk factors) were applied at baseline, at the end of intervention, and three months thereafter. The intervention consisted of eight playful workshops, which involved the presentation of a play.**

Results: **Seventy-nine students were randomized to the intervention ($n = 40$) or the control group ($n = 39$). Mean age was 10.0 ± 1.1 years. After eight weeks, the intervention group showed significant improvement in the knowledge score ($p < 0.001$). There was an increase in physical activity scores in both groups, but with no difference between the groups at the end of intervention ($p = 0.209$). A reduction in the BMI percentile was observed in the intervention group, but there was no significant statistical difference between the two groups after the intervention.**

Conclusions: **Playful interventions may improve knowledge and physical activity levels in children and, when combined with other strategies, may be beneficial to prevent child obesity and improve self-care. (Arq Bras Cardiol. 2017; 109(3):199-206)**

Keywords: **Child; Pediatric Obesity; Motor Activity; Games, Recreational; Knowledge; Randomized Controlled Trial as Topic.**

Introduction

Childhood obesity is an important health problem worldwide.[1,2] A study including 144 countries projected an increase of excess weight from 4.2% in 2010 to 9.1% in 2020, representing 60 million children; of those, 35 million will be from developing countries.[3,4]

Although genetic factors can influence the susceptibility to weight gain, the consensus is that a sedentary lifestyle, inadequate dietary practices and changes in family structure all contribute to this epidemic.[2] Urbanization and other environmental factors bring profound habits changes, especially regarding eating habits and physical activity.[5,6] In Brazil, economic and media globalization contributed to significant changes regarding diet (with more spread use of processed and ultraprocessed foods in detriment to more traditional preparations) and family habits, such as having all the meals together.[3]

The number of children between 5 and 9 years with excess weight more than doubled in the country from 1989 to 2009[3], escalating from 15% to 34.8%, while the number of obese children of the same age increased 30%, from 4.1% to 16.6%.[4]

Studies have shown an association between childhood obesity and risk factors for the development of chronic illnesses such as diabetes mellitus, hypertension, dyslipidemia and other cardiovascular diseases.[7-11] Therefore, there is an urgent need to focus on early prevention. Early health promotion strategies with comprehensive nutritional and physical activity guidance have shown to increase knowledge and improve self-care among patients with chronic conditions.[1,12,13] However, studies regarding educational interventions for obesity prevention in children are heterogeneous and yield different results.[14-20] Recent meta-analysis of educational interventions for obese and non-obese children showed positive results regarding blood pressure and waist circumference reduction, but a less clear effect on body mass index (BMI).[18,19]

Mailing Address: Lucia Campos Pellanda •
Av. Princesa Isabel, 370. Postal Code 90620-000, Santana, Porto Alegre, RS – Brazil
E-mail: luciapell.pesquisa@cardiologia.org.br, editoracao-pc@cardiologia.org.br
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In this context, there is a need for development and evaluation of innovative educational interventions targeting prevention and health habit formation. We designed a low-cost educational intervention based on playful workshops for children, in a low resource setting, that could be useful in many contexts worldwide. The objective of the present study is to ascertain the impact of this intervention on children's knowledge, physical activity levels and BMI in a low resource community in a developing country.

Methods

This was a cluster randomized, controlled study, carried out from March to November 2012. Seventy-nine students in four classes participated in the study and were randomly divided into two groups with two classes each, 40 participants in the intervention group and 39 students in the control group. The study was registered in the Brazilian Clinical Trials Registry under the code RBR-8f6wr7 (http://www.ensaiosclinicos.gov.br/rg/RBR-8f6wr7/). All parents signed the informed consent.

Participants

Inclusion criteria were children from seven to eleven years of age, who attended a philanthropic program during non-school hours for children with low socio-economic conditions in the city of Porto Alegre in the southern Brazilian state of Rio Grande do Sul. All children were healthy and were also enrolled in regular schools.

Exclusion criteria were clinical diseases that would prevent participation in the program or anthropometric evaluation. No children had any of these conditions, and therefore there were no exclusions after the signing of the consent form.

After randomization, 6 children in the intervention group and 5 in the control group were lost to follow up, because they moved to other schools or refused to continue in the study, thus resulting in 40 children in the intervention group and 39 in the control group. All other children attended to all sessions and completed the study. For those children that could not attend in a specific day, another day was scheduled.

Randomization

A table with random numbers representing each class was created by an investigator who was not related to the study, with the aid of the randomization tool available at www.randomization.com. These numbers were placed and sealed in brown envelopes. After inclusion of all participants, an investigator who was not related to the study opened the envelopes and the classes were assigned to the arms of intervention or control (cluster randomization).

Interventions

Intervention consisted of eight weekly Playful workshops lasting between 30 and 60 minutes during 60 to 90 minutes each. The workshops included collage, painting, games creation, physical activity, music and dance, and simulations of real life situations, all involving the importance of healthy habits for heart health, especially relating to healthy foods and physical activity. The same investigator (FHC, a Registered Nurse) performed all the activities in the classroom or in the school patio. The workshops are described in box 1.

The control group maintained their usual activities in math, language and music with their teacher in their class in the same period. They also had their usual physical education classes, including soccer, capoeira and tennis.

Outcomes

The primary outcome considered was increased knowledge about healthy habits and risk factors for cardiovascular disease, measured by the CARDIOKIDS questionnaire (Portuguese validated version, see below) immediately after and four weeks after intervention.

Secondary outcomes were change in physical activity levels and body mass index immediately after intervention.

Instruments

Two structured questionnaires were used in this study.

The Portuguese version of the "typical day of physical activity and food intake" (DAFA, *Dia Típico de Atividades*

Box 1 – The workshops.

Workshop 1	Students were divided in small groups of four. The task proposed to the groups was to make collages depicting healthy and unhealthy foods using old magazines, always with the guidance of the tutor. After completing the tasks, all groups discussed on the subject.
Workshop 2	Children played the role of a healthy heart and “all the things a happy heart enjoys” in a play developed by the group.
Workshop 3	The students discussed the importance of physical activity and with drawings and other materials, represented the activities that they liked most.
Workshop 4	Drawing and collages about healthy and unhealthy foods
Workshop 5	Dance class with music.
Workshop 6	Students showed some of the physical activities they liked and discussed in groups ways to perform them more frequently.
Workshop 7	Children built a “memory game” from recycled materials. The game contained pictures of healthy foods and different physical activities. This material was later used every day by the teacher in classes, for about 10 minutes.
Workshop 8	The investigator brought to class foods such as fruits, chocolate, vegetables, oil, eggs, salt and sugar. For each food, the group discussed its properties and if it was healthy or unhealthy. The students drew little happy or unhappy hearts accordingly. In all cases, it was discussed that all foods have good and “not so good” characteristics, and it is important to be aware of the quantities and frequency of consumption.

Source: Cecchetto,Pellanda 2013

Físicas e de Alimentação) is an illustrated and structured questionnaire developed by a group of Brazilian researchers with the objective to obtain information about weekly habits of physical activity in children aged seven to eleven years[21]. The instrument contains 36 illustrations of physical activities in different intensities, and a score system was developed to summarize the answers. Of a total of 141 points, values below 36 are classified as "less active," 37 to 58 as "intermediate," and 59 to 141 as "more active".

The questionnaire regarding knowledge of healthy habits and risk factors for cardiovascular disease (CARDIOKIDS) was also developed in Brazil and validated for children from 7 to 11 years. It contains twelve illustrated questions, divided in two dimensions: healthy habits (healthy eating and physical activity) and risk factors for cardiovascular diseases. Response options consist of three faces: "happy" (good for the heart), "unhappy" (bad for the heart), and "neutral" (do not know). Scores of 11-12 correct answers were considered as "excellent knowledge," 8-10 correct answers were considered "good knowledge," and scores below 7 correct answers were considered "insufficient knowledge".[22]

Data collection

Data collection took place at three moments between March and November of 2012, beginning soon after obtaining the informed consent from their parents.

At baseline, anthropometric measurements (weight and height) were performed and two questionnaires (DAFA and CARDIOKIDS) were applied. The same parameters were measured just after the intervention. Twelve weeks after completion of the program, the CARDIOKIDS questionnaire was repeated to evaluate knowledge retention.

Anthropometric measurements were obtained according to the recommendations of the World Health Organization.[23] For weight measurement, the participants were asked to remove their shoes and heavy clothing. A Plenna Wind digital scale was used, with a maximum capacity of 150 kg, accuracy of 100 g, and a stadiometer with a measuring range of 192 cm. Weight and height were measured twice by one of the investigators. Children above the 85th BMI percentile were considered overweight, and above the 95th were considered obese.[24]

Statistical analysis

The sample size was based on previous results from a pilot study on 38 individuals, in which an average of eight correct answers in the CARDIOKIDS questionnaire was observed, with standard deviation of 2.0. We estimated a 30% increase in the knowledge scores in the intervention group with a power of 95% and 0.05 level of significance, yielding a minimum sample of 44 participants (22 in each group). Considering possible losses during the study and the cluster effect, a total sample of 40 participants for each group was planned. Data analysis and processing was performed using the IBM SPSS Statistics software, version 14.0. Continuous variables are expressed by means and standard deviations and categorical variables are expressed by absolute and relative frequencies. Normality of data was evaluated with histograms and the Kolmogorov-Smirnof test. For comparisons between groups after the intervention we used the paired Student t test for continuous variables and the chi-squared test for categorical variables. GEE (generalized estimating equations) were used for comparisons between groups and within groups across different periods (baseline, immediately after and 12 weeks after intervention) adjusting for age and gender. The Bonferroni adjustment was used to identify differences in paired analysis. Repeated measures ANOVA was used to compare different points in time between groups. In all comparisons, a $p < 0.05$ was considered significant.

Results

The institution receives a total of 185 students from 7 to 11 years old. Parents or guardians of 25 children did not sign the consent form, and 70 children did not meet the inclusion criteria, thus resulting in a total sample of 90 children, 46 randomized in the intervention group and 44 in the control group.

Figure 1 presents the flow chart according to consort recommendations (www.consort-statement.org.). Table 1 contains baseline characteristics of the intervention and control groups. Students in the control group were older ($p = 0.007$) and more likely to be in grades 5-6 ($p < 0.001$) than students in the intervention group. Most children were classified as less active.

Table 2 presents the results for knowledge scores before and after the educational intervention. The results demonstrate that both groups had good knowledge before the intervention period, according to both dimensions of the questionnaire. However, there was a significant difference between the groups after intervention due to an increase in the scores of the intervention group. In the 12th week of evaluation, the results showed a reduction in the intervention group's knowledge scores, but still a significant difference in relation to the control group (Figure 2).

Table 3 shows the results for BMI percentiles and physical activity pre- and post-intervention. There were no differences for BMI percentiles. After the intervention, both groups showed a significant increase in physical activity level from baseline ($p < 0.001$), but there was no significant difference between groups after intervention ($p = 0.804$).

Discussion

This randomized controlled trial showed that an educational intervention based on playful activities was effective in increasing physical activity scores and knowledge about healthy habits and risk factors for cardiovascular disease.

The school environment is considered to be a good setting for health promotion because it allows reaching children and adolescents.[11] Playful activities focusing on health themes are an opportunity to create a bond to facilitate the sharing of experiences and knowledge, empowering a child to take care of the own health.

This is increasingly important in a context of rising prevalence of chronic diseases and unhealthy habits very early in life. In accordance with this context, approximately 38% of this sample of school children was overweight.[7,25] In south Brazil, 28% of children aged 11-18 years were overweight and 10% were obese.[6]

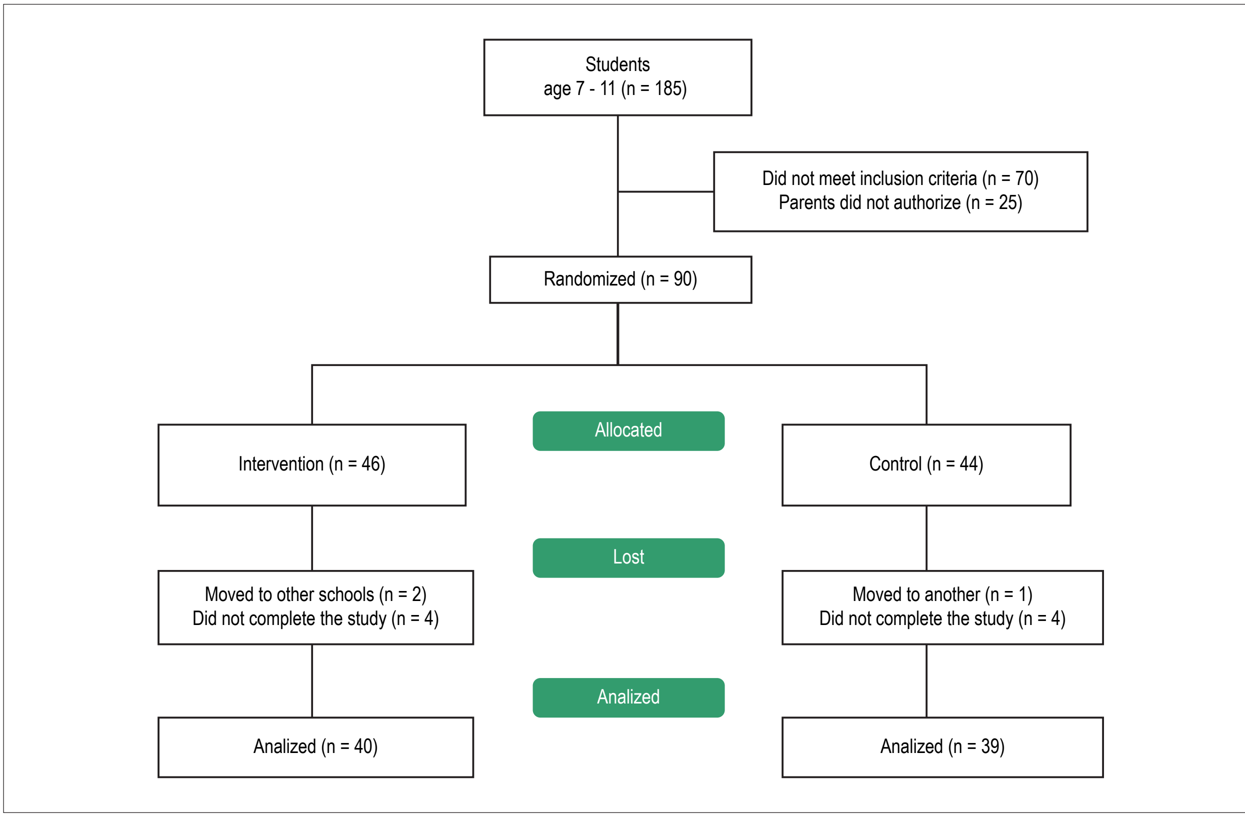

Figure 1 – *CONSORT flow chart depicting recruitment and randomization of the children into the study groups.*

In our study, both groups had previous knowledge of healthy habits and cardiovascular risk factors before the educational interventions, with no significant difference between groups at baseline. One possible explanation for these results is the fact that schools and the media have recently become more concerned about providing guidance on nutrition and the importance of physical activity for improved quality of life and prevention of cardiovascular diseases and obesity. However, these data suggest that playful activities may be a good educational strategy for students, and that knowledge about healthy habits and risk factors for cardiovascular diseases is present among students in this age group.

One recent study carried out with teachers and students aged 5 to 10 years in the Brazilian capital city of Brasília showed that, after nutritional interventions, there was an increase of knowledge from 61% to 74% in children, and a similar increase among the teachers.[26] One study carried on students with higher BMIs out in the southern region of Brazil in 2005 showed that these students have less knowledge and less healthy dietary practices than those observed in the present study.[27] Another recently-published study performed with 464 students in northern Portugal from November 2008 to March 2009, using interventions based on the Model of Health Promotion and cognitive theory, showed satisfactory results in relation to changes in dietary habits of the children in the intervention group.[28] Thus, it is believed that an increased knowledge can improve self-care related to weight control and dietary habit changes.

The evaluation of BMI percentiles did not show a statistically significant difference between the groups at the end of the intervention period, but a slight reduction in percentile was observed in the intervention group, along with a small increase in the control group. Studies involving interventions in schools for prevention and treatment of obesity have shown controversial results,[19] especially in non-selected populations composed of normal weight and overweight children. In these conditions, it is more difficult to observe changes in BMI, since a large part of the population does not need to lose weight. The heterogeneity of the interventions regarding type, duration and number of activities included must also be considered.[19,29] It is also possible that more prolonged and comprehensive interventions show more positive results regarding BMI changes.[30] Analysis of baseline data showed that the two groups were homogenous in regards to sex, ethnicity, weight, physical activity and knowledge, but the intervention group was older than the control group.[31]

It is also important to emphasize that BMI is a controversial measure to be pursued as an outcome in children. It is insensitive to changes in body composition (for example, gain of lean mass) and does not account for possible ethnic or body type differences. Additionally, the most important outcomes in children may be permanent habit change, and not BMI.

In regard to physical activity, our results are similar to various other studies, in which the majority of this population is considered to have low levels of physical

Table 1 – Baseline characteristics of students in the intervention and control groups

Participants (n = 79)	Intervention (n = 40)	Control (n = 39)	p
Age mean ± SD	*9.3 ± (1.4)	10.03 ± (1.1)	0.007
Gender n (%)			0.730
Female	*20 (50%)	22 (56.4%)	
Male	20 (50%)	17 (43.6%)	
Ethnicity n (%)			**1.000
Caucasian	30(75%)	29(74.4%)	
African	10(25%)	10(25.6%)	
Current school grade n (%)			0.001
Grades 2-4	23 (57.5%)	10 (25.7%)	
Grades 5-6	17 (42.5%)	29 (74.4%)	
Height (cm) mean ± SD	136.9±(11.5)	141.7 ± (8.7)	***0.041
Weight (kg) mean ± SD	36.7 ± (12.5)	38.1 ± (10.6)	0.571
BMI (km/m²) mean ± SD	19.1±(3.8)	19.2 ± (4.5)	0.875
Nutritional status n (%)			0.952
< 85th percentile	25(62.5%)	24(61.5%)	
≥ 85th percentile (overweight)	6(15%)	7(18%)	
> 95th percentile (obese)	9(22.5%)	8(20.5%)	
Physical activity (DAFA classification) n (%)			0.209
Less active	30(75%)	28(71.8%)	
Intermediate	8(20%)	10 (25.6%)	
More Active	1(5%)	1(2.7%)	

*Continuous variables are expressed by means and standard deviations and categorical variables are expressed by absolute and relative frequencies. **chi-squared test. ***paired t test. Source: Cecchetto, Pellanda 2014[22]*

Table 2 – Knowledge dimension before, immediately after and after 12 weeks of intervention or control activities

		Before intervention	After intervention	12 weeks after intervention	p *	Variation before-immediately after (95%CI)	Variation before-12 weeks after (95% CI)
		Mean(SE)**	Mean(SE)**	Mean(SE)**			
Dimension: Health habits	Intervention(n = 40)	4.2(0.3)	5.6(0.2)	5.2(0.2)	< 0.001	1.4(0.9 – 2.0)	1.0(0.3 – 1.6)
	Control(n = 39)	4.1(0.3)	4.1(0.2)	4.1(0.2)		0.02(–0.6 – 0.6)	0.04(–0.6 – 0.7)
Dimension: Risk factors	Intervention(n = 40)	5.2(0.2)	5.6(0.1)	5.7(0.1)	0.129	0.5(–0.01 – 1.0)	0.5(0.03 – 1.0)
	Control(n = 39)	5.3(0.2)	5.4(0.1)	5.4(0.1)		0.04(–0.5 – 0.5)	0.04(–0.5 – 0.5)

** Interaction between group and time - Anova –repeated measures. ** Adjusted means (age and gender) and standard errors (SE). Source: Cecchetto,Pellanda 2014[22]*

activity. Others studies carried out in 2004 in others regions Brazil, showed that 40% to 67% of children and 61% of the adolescents were sedentary.[29,32] Lifestyle changes of families and students, in which television, videogames and the computer have become the greatest source of entertainment among children and youth contribute to these numbers. Additionally, urban violence, especially in low-income settings, has been described as a barrier for children to become involved in sports and other outdoor activities.[32]

After intervention, we observed an increase in physical activity in both groups. This might be due to contamination (children in the intervention group who became more active may have influenced children in the control group) or to climate changes. While the intervention started during the winter, which is rainy and with temperatures around 10°C in Porto Alegre, and the second evaluation was performed during warmer weather.

Programs implemented with students to increase their physical activity level and provide dietary guidance have

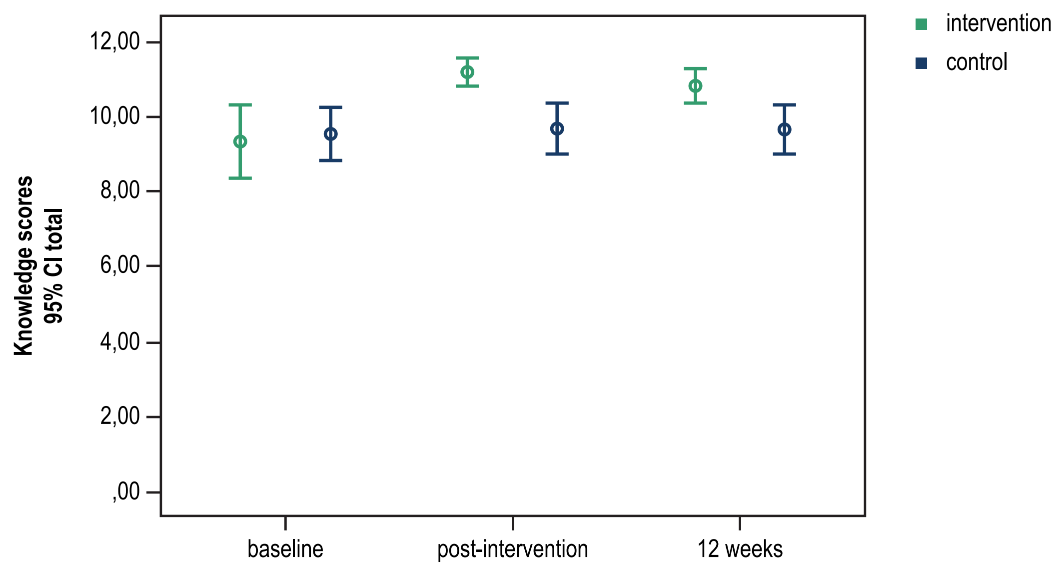

Figure 2 – *Intra- and between-group comparisons of knowledge at baseline, immediately after and at 12 weeks after the intervention. P-value for differences between the groups: 0.016; P-value for differences immediately after and 12 weeks after the intervention as compared with baseline in the intervention group: < 0.001; P for differences immediately after and 12 weeks after the intervention as compared with baseline in the control group group: 0.337; P-value for interaction between group and time: 0.002*

Table 3 – Comparison between groups before and after the intervention period: BMI and Physical activity score, n = 79

Variables	Intervention (n = 40) Mean (95% CI)	Control (n = 39) Mean (95% CI)
BMI (kg/m²)		
Before	70.9 (62.5; 79.3)	62(52.0; 72.0)
After	69.9 (61.9; 77.9)	63.8 (54.5; 73.1)
Mean difference (CI 95%)	– 1.0 (-3.7; 1.6)	1.8 (–1.0; 4.8)
Difference between groups: p = 0.240** Interaction between group and time: p = 0.669		
Physical Activity (Score)		
Before	31.9 (26.7; 37.1)	27.3 (22.6; 32.0)
After	34.1 (29.2; 39.0)	29.7 (24.9; 34.5)
Mean difference (95 CI%)	2.2 (1.0; 3.4)	2.4 (1.5; 3.3)
Difference between groups: p = 0.201 Interaction between group and time: p = 0.804		

***chi-squared test.* BMI: body mass index. *Source: Cecchetto,Pellanda 2014*[2]

shown good results,[1,32] but controversies exist regarding the best intervention to be applied. This may be due to the fact that these programs are applied to various groups with many cultural and environmental differences and interventions need to be customized according to these factors.

It must also be emphasized that knowledge is fundamental to motivate change, but is not enough to provoke persistent change. Education and health strategies involving playful activities can improve self-care, but must be done in conjunction with other strategies. Improving knowledge is the first step in any comprehensive prevention strategy, empowering the child for taking care of the own health.

Limitations of the study

Some limitations of the study deserve mention. First of all, the study was carried out in an institution with low socioeconomic resources, making it difficult to apply these data to other student populations. The second limitation is related to the non-participation of students' parents in the study, as recent studies report success with strategies that include family members. Also, the intervention period of eight weeks may be too short to observe a significant change in habits resulting in weight loss. Finally, there was a difference of schooling between groups, with more children in the control group belonging to more advanced grades. However, this difference would reduce the differences between groups after intervention, thus altering the results to an opposite direction than that of our hypothesis.

Conclusion

Our results show that a simple, low-cost intervention consisting of playful educational activities performed with low-income children in a school may help improving knowledge about healthy habits and risk factors for cardiovascular disease, and may be useful for the planning of preventive strategies in similar settings.

Acknowledgments

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Author contributions

Conception and design of the research, Statistical analysis e Writing of the manuscript: Cecchetto FH, Pena DB; Acquisition of data, Analysis and interpretation of the data e Obtaining funding: Cecchetto FH, Pena DB, Pellanda LC; Critical revision of the manuscript for intellectual content: Pena DB.

Potential Conflict of Interest

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

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Study Association

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Original Article

Predictors of Mediastinitis Risk after Coronary Artery Bypass Surgery: Applicability of Score in 1.322 Cases

Fabiana dos Santos Oliveira, Letícia Delfino Oliveira de Freitas, Eneida Rejane Rabelo-Silva, Laura Maggi da Costa, Renato Abdala Karam Kalil, Maria Antonieta Pereira de Moraes
Instituto de Cardiologia / Fundação Universitária de Cardiologia (IC/FUC), Porto Alegre, RS – Brazil

Abstract

Background: **Mediastinitis is a severe surgical complication of low incidence, but high lethality. Scores used in the preoperative period to stratify the risk of postoperative mediastinitis may contribute to improve the results.**

Objective: **To test the applicability of the MagedanzSCORE in predicting the risk factors for mediastinitis in patients undergoing coronary artery bypass grafting at a cardiology reference hospital.**

Methods: **Historical cohort study with adult patients who underwent coronary artery bypass grafting. The analyzed variables were contemplated in the MagedanzSCORE: reoperation, chronic obstructive pulmonary disease (COPD), obesity, class IV unstable angina, polytransfusion therapy, mediastinitis and death as outcome variables.**

Results: **Of the 1.322 patients examined, 56 (4.2%) developed mediastinitis. Of these, 26 (46.4%) were classified as high risk for mediastinitis and 15 (26.8%) at very high risk for mediastinitis. Three of the five variables of the Magendanz Score showed statistically significant differences: reoperation, COPD and obesity. Class IV unstable angina and postoperative polytransfusion were not associated with mediastinitis after coronary artery by-pass grafting. The area under the ROC curve was 0.80 (CI 95% 0.73 – 0.86), indicating the model's satisfactory ability to predict the occurrence of mediastinitis.**

Conclusion: **The tool was useful in the preoperative assessment demonstrating the risk for mediastinitis in this population of intensive care patients. (Arq Bras Cardiol. 2017; 109(3):207-212)**

Keywords: **Mediastinitis; Myocardial Revascularization / complications; Risk Management; Cohort Studies.**

Introduction

Mediastinitis is characterized as a deep infection of the surgical wound of heart surgery, with involvement of the retrosternal space, associated or not with sternal instability/osteomyelitis. The literature data suggest an incidence of 0.6 to 5.6% of this complication, with mortality rates between 14 and 32%, resulting in high rates of morbidity and mortality, extended duration of hospitalization, delayed postoperative recovery and increased hospital costs.[1-4] In addition, it may be associated with a number of factors, including smoking, prolonged cardiopulmonary bypass (CPB) and the use of two mammary artery bypass.[5,6]

Estimating mediastinitis risks may contribute to the identification of potential complications in the preoperative period (PP), predicting in an individualized way which patients will need more intensive care, in order to develop preventive strategies.[6,7] Previous studies point to tissue hypoperfusion, polytransfusion, impaired asepsis, surgical reintervention, infections and the use of antibiotic therapy as risk factors associated with a higher prevalence of mediastinitis during cardiac surgery.[8,9]

The use in clinical practice of tools that help decision making in the face of possible complications will certainly bring benefits to this population at greater risk. National authors developed a scoring model to predict the risk of mediastinitis in patients undergoing myocardial revascularization (CABG) surgery. Among the 2,809 patients evaluated, five variables were identified as independent predictors for the occurrence of mediastinitis: stable angina class IV/unstable angina (UA), chronic obstructive pulmonary disease (COPD), obesity, surgical reintervention and polytransfusion at the PP. The risk score proved to be easy to apply and directed to clinical practice.[10]

Careful clinical examination, associated with such instruments, allows health professionals to improve the identification of infection predictors during clinical evaluation. In view of the increasing number of cardiac surgeries, the high mortality rate in the occurrence of mediastinitis and the absence of data in our professional environment, it was developed this study with the objective of testing the applicability of MagedanzSCORE to predict the risk of mediastinitis in patients submitted to CABG in a reference hospital in cardiology in RS.

Mailing Address: Maria Antonieta Pereira de Moraes •
Av. Princesa Isabel, 370. Postal Code 90620-000, Santana, Porto Alegre, RS – Brazil
E-mail: antonieta_moraes@uol.com.br, editoracao-pc@cardiologia.org.br
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Methods

Design

Observational study of historical cohort.

Population and sample

Study conducted with patients of both sexes, aged 18 years or older, submitted to isolated CABG, with or without CPB. Exclusion criteria were patients who had not recorded all the variables requested by the score. The convenience sample was estimated for variables predictors of infection. Considering a previous incidence of 1.0% in the institution, with OR of 3.5 of the surgical reintervention variable of the MagedanzSCORE, for a power of 80% and a level of statistical significance of 0.05, 1.322 patients were required.

Study variables and outcomes

Data were collected through the review of medical records in the medical histories and entered in the database of the postoperative unit of cardiac surgery of the institution.

Demographic data, pre and trans-operative clinical data, antibiotic therapy and length of stay were analyzed. Score-related variables, such as surgical reoperation; COPD, clinically diagnosed and/or radiological study of the thorax and/or spirometry and/or drug treatment with corticosteroids and/or bronchodilator in the preoperative period; obesity (BMI ≥ 30 kg/m^2); stable angina class IV or UA; polytransfusion (> 3 units of adult red cell concentrate at postoperative period). Outcomes analyzed included in-hospital mediastinitis (up to 30 days after surgery) and death from any cause, considered when it was after the date of diagnosis of Mediastinitis.

Mediastinitis was considered when it was diagnosed clinically or according to the criteria of the Centers for Disease Control and Prevention (CDC/NHSN),[11] positive culture for pathogens of tissue or mediastinal fluid obtained during surgical intervention or needle aspiration; evidence of mediastinitis observed during surgical intervention or histopathological examination; patient with at least one of the following signs or symptoms with no other known cause: fever (body temperature> 38°C), chest pain or sternal instability and at least one of the following: purulent discharge in the mediastinal area; organisms cultivated from blood or mediastinal area secretion; widening of the mediastinum on the X-ray. Superficial infection of the operative wound was not considered mediastinitis.

Tested score

The instrument used was the MagedanzSCORE,[10] prepared and validated previously.[12] This is a predictive risk score for mediastinitis in patients undergoing CABG, composed of five variables predictors independent. The sum was classified into four groups: low risk (zero points), medium risk (1 to 2 points), high risk (3 to 4 points) and very high risk (≥ 5 points), according to chart 1.

Chart 1 – MagedanzSCORE: prediction of risk for mediastinitis.

Clinical profile	Score
Surgical reoperation	3
COPD	2
Obesity	2
Class IV / unstable stable angina	1
Polytransfusion (post-operative)	1

Ethical considerations and statistical analysis

This study was approved by the Ethics Committee in Research of the Institute of Cardiology - University Foundation of Cardiology of RS, under the number 4705/12. The Term of Commitment for the Use of Medical History Data was used. Data were analyzed through the Statistical Package for the Social Sciences (SPSS), version 22.0.

Categorical variables were expressed as absolute (n) and relative (%) frequencies and compared by the chi-square test. Continuous variables were expressed as mean ± standard deviation for those with normal or median distribution and interquartile range.

The performance of the MagedanzSCORE was evaluated by comparing the rate of mediastinitis presumed by the score with the one observed. To measure the discriminant power of the score, the area under the ROC curve was estimated. We used the multivariate analysis of the categorical variables to obtain the odds ratio (OR) and confidence interval (CI) with a significance level $p < 0.05$.

Results

1.322 patients subjected to isolated CABG were included in this study, 84.5% performed a combined saphenous vein graft with two mammary artery grafts, and 97.4% used CPB. The mean age was 62.4 ± 9.8 years, and 72.6% of the patients were male.

The most prevalent independent predictors for mediastinitis were class IV/unstable angina (58.8%), followed by obesity (25.4%). The characteristics of the population are mentioned in Table 1.

Classification of risk and presence of mediastinitis according to MagedanzSCORE

The risk of mediastinitis according to the MagedanzSCORE and the classification of that risk identified that 384 (29.1%) patients presented low risk, 651 (49.3%) medium risk, 256 (19.4%) high risk and 30 (2.3%) patients were classified with very high risk of developing the outcome (Figure 1).

Fifty-six (4.2%) patients developed mediastinitis after CABG. Of these, 26 (46.4%) were classified as having high risk and 15 (26.8%) with very high risk. Table 2 shows the distribution of the patients who presented the outcome, according to the MagedanzSCORE.

It was evidenced that three of the five variables predictive of infection presented statistically significant associations among them, namely, surgical reoperation, COPD and obesity. Demographic variables gender and age, as well as class IV / unstable angina and postoperative polytransfusion were not associated with mediastinitis after CABG.

Table 1 – Characteristics of the population (n = 1322). Porto Alegre-RS

Characteristics	n (%)
Male	960 (72,6)
Age (years) *	62,4 ± 9,8
Body mass index (kg / m2) *	27,6 ± 4,2
Use of CPB 1.288	1.288 (97,4)
Three bypass grafting	696 (52,6)
Use of saphenous and double mammary artery bypass	1.117 (84,5)
Use of antibiotic therapy in the postoperative period	506 (38,3)
Preoperative hospitalization time (days) §	7 (0 – 69)
Total length of stay (days)§	41 (7 – 184)
MagedanzSCORE (predictor variables)	
Surgical reoperation	73 (5,5)
COPD	59 (4,5)
Obesity	336 (25,4)
Angina class IV / unstable	777 (58,8)
Polytransfusion (postoperative)	48 (3,6)
Mediastinitis	56 (4,2)
Death	7 (0,5)

** Data presented in mean ± standard deviation; § Data presented in median and intermediate. CPB: extracorporeal circulation; COPD: chronic obstructive pulmonary disease.*

The area under the ROC curve, used to measure the discriminant power of the score, was 0.80 (95% CI 0.73-0.87), demonstrating the model's satisfactory ability to predict the occurrence of mediastinitis at CABG isolated PP (Figure 2), compared to the validation study of the score[10] that had accuracy measured by the area under the ROC curve of 0.73 (95% CI 0.68-0.80).

Discussion

The results showed that the MagedanzSCORE is applicable and satisfactory to predict the risk of mediastinitis in this population of patients subjected to CABG. The applicability of risk scores in cardiac surgery is quite relevant, however it must be well evaluated, based on the real world population, so as not to underestimate or overestimate possible hospital events.[13,14]

The incidence of mediastinitis in this population was 4.2%, a value within the limits described in the literature, between 0.6 and 5.6%,[1,2] although higher than the 3.3% published in the study that originated the score.[10] An important result was that 73.2% of the patients who developed mediastinitis were classified in the high and very high risk groups. Similar results were found in the study that validated the instrument.[12] These findings reinforce the effectiveness of the score to predict the outcome.

Patients with Class IV or unstable angina and obese constituted a large proportion of the sample studied, and each of these variables contributed with 1 and 2 points, respectively, to the risk score. A German study evaluating 1.700 similar patients found a strong association of obesity with infection, reinforcing that each increase of one kilogram of body mass per square meter produces a 3% increase in the risk of developing mediastinitis.[7] The pathological mechanism involved in the association between obesity and mediastinitis is not yet well established. A previous study suggests that factors such as inadequate distribution of antibiotics due to increased body

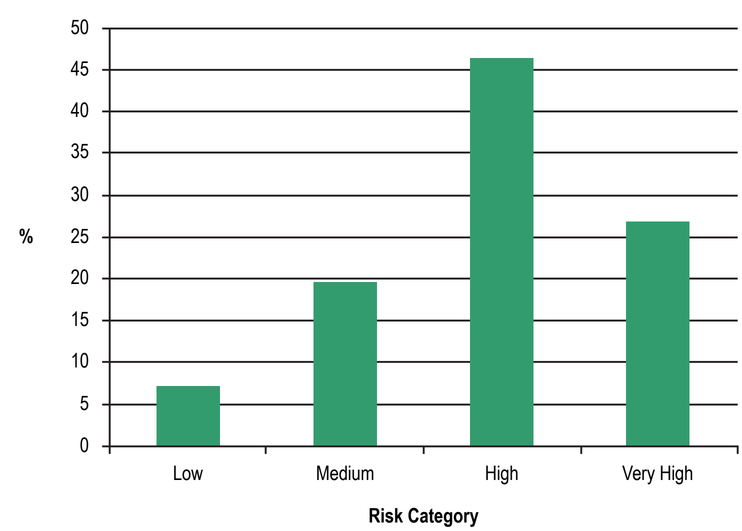

Figure 1 – *Presence of mediastinitis according to MagedanzSCORE. N = 56.*

Table 2 – Association between demographic variables and MagedanzSCORE in the occurrence of mediastinitis (multivariate analysis). Porto Alegre-RS

Variables	OR	IC 95%	p
Sex	1,76	0,92 – 3,31	0,085
Age	0,98	0,95 – 1,02	0,382
Surgical reoperation	37,76	18,75 – 77,92	< 0,001
COPD	3,83	1,23 – 10,46	< 0,001
Obesity	2,71	1,42 – 5,16	< 0,001
Angina class IV / unstable	1,88	0,95 – 3,96	0,072
Polytransfusion (postoperative)	0,51	0,15 – 1,52	0,236

COPD: chronic obstructive pulmonary disease; OR: odds ratio; 95% CI: 95% confidence interval

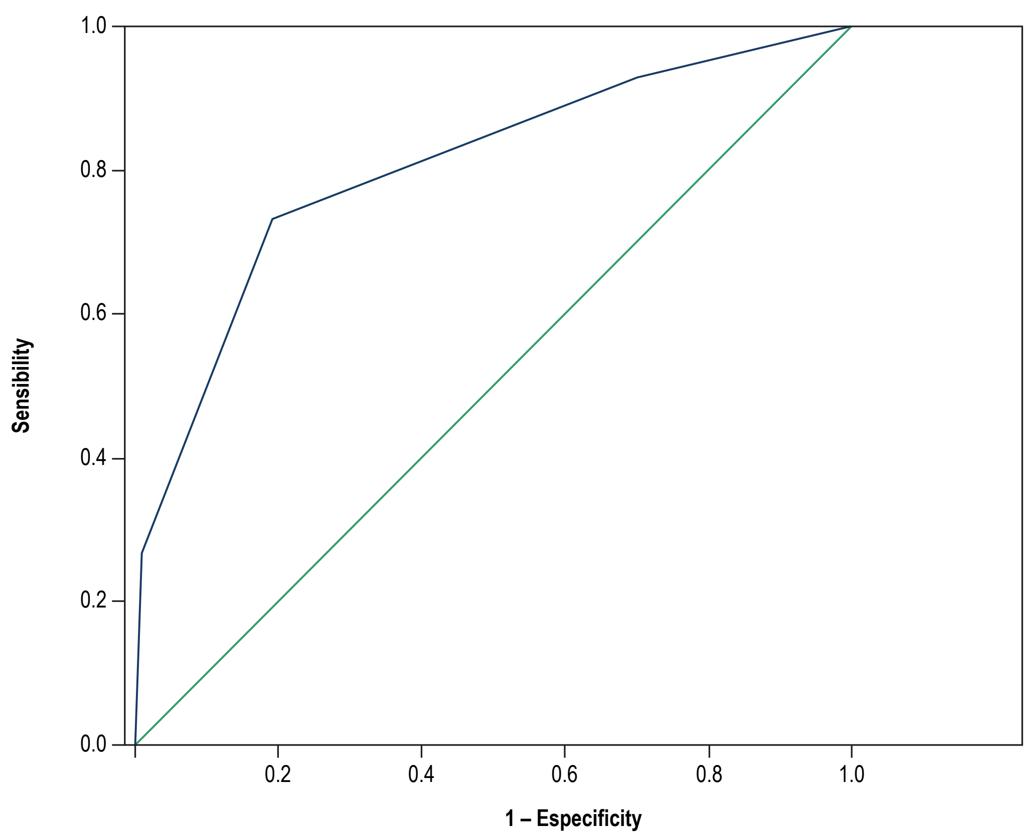

Figure 2 – *Area over the ROC curve in the measurement of the occurrence of mediastinitis. C: area under ROC curve; 95% CI: 95% confidence interval; 0.80 (95% CI 0.73-0.87).*

mass, difficult skin preparation, and large amounts of adipose tissue serving as a substrate for surgical wound infections may be involved in the mechanism of that association.[15]

Surgical reintervention is considered a predictor factor for the development of infections.[3,8,9] In the present study, 5.5% of patients required reoperation and presented statistical significance when associated with the occurrence of mediastinitis. In a study that sought to identify similar risk factors in diabetics undergoing CABG, surgical reintervention was also relevant as a variable associated with increased risk.[12]

Another equally important predictor of risk among the results of this investigation was the presence of COPD, which had a strong association with the occurrence of mediastinitis, presenting statistical significance. Similar findings were described in previous investigations.[2,6,9] Another study has cited COPD as a risk factor but not as an independent one. Patients with

COPD would be more vulnerable to surgical wound infection due to tissues hypoxemia, and the use of corticosteroids at the pre and / or postoperative period would be a factor that could facilitate the installation of infectious processes.[15]

Class IV stable angina / unstable angina and postoperative polytransfusion, although independent predictors for the development of mediastinitis, were less important when they were associated with the outcome in this casuistic, although previous studies have linked these variables with increased risk of infection and morbidity at PP.[16,17] In contrast to these findings, other authors found lower death rates in patients with UA undergoing isolated CA compared to those considered stable, attributing those results to possibly receiving better drug therapy, invasive monitoring and hemodynamic support with greater frequency.[18]

In this population studied, transfusion was not predictive of complication or worsening of results. However, data from the literature indicate that blood transfusions in the PP have been a constant concern, often reported as a contributing factor for infectious episodes, such as mediastinitis.[2,9,19] Previous studies corroborate these data and reinforce that the number of units of concentrate of red blood cells in the PP is directly associated with an increased risk of complications.[10,20]

It is known that diabetes mellitus (DM) may difficult the recovery of patients undergoing cardiovascular surgeries; however, in this study this was not evaluated, because DM was not an independent predictor of risk for mediastinitis among the population that originated the score. We assume that these findings, considering the rigorous glycemic control and the continuous insulin use, could have collaborated for a satisfactory prognosis.

Many factors have been associated with the development of mediastinitis following cardiovascular surgery; however, there is no consensus in the literature about which are the most important and how much each represents as an independent predictor of high risk for mediastinitis.[10] Other predictors cited in previous scores, such as age, sex and combined procedures, were evaluated and the five most important predictors for the development of MagedanzSCORE were defined.

Finally, the findings of this study allow us to infer that the instrument tested in the local population serves as a basis to aid in clinical practice. The limitations of the present study are those that are due to its retrospective nature and the search for medical records. Another factor worth highlighting is that the study has been developed in a single center specialized in cardiology, other studies are necessary to corroborate our observations, in order to disseminate the use of the score in clinical practice.

Conclusion

Results showed that the score tested was applicable and satisfactory to predict the risk of mediastinitis in patients undergoing CABG at this institution. It could be incorporated into clinical practice as a useful tool to help identify risk predictors for the development of nfection in this more intensive care population.

Author contributions

Conception and design of the research, Analysis and interpretation of the data and Writing of the manuscript: Oliveira FS, Freitas LDO, Silva ERR, Costa LM, Kalil RAK, Moraes MAP; Acquisition of data: Oliveira FS, Freitas LDO, Costa LM; Critical revision of the manuscript for intellectual content: Silva ERR, Kalil RAK, Moraes MAP.

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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Single Derivation Fragmented QRS Can Predict Poor Prognosis in Successfully Revascularized Acute STEMI Patients

Zulkif Tanriverdi,[1] Huseyin Dursun,[2] Tugce Colluoglu,[2] Dayimi Kaya[2]

Balikligol State Hospital – Clinic of Cardiology;[1] Dokuz Eylul University - Faculty of Medicine – Department of Cardiology[2], Turkey

Abstract

Background: QRS fragmentation (fQRS) is classically defined as the presence of slurred QRS morphology in at least two contiguous leads, and its prognostic importance has been shown in ST elevation myocardial infarction (STEMI). However, no study has investigated the significance of single lead fQRS (sl-fQRS) in surface electrocardiography (ECG).

Objectives: To evaluate whether sl-fQRS is as valuable as classical fQRS in patients with acute STEMI who had successful revascularization with primary percutaneous coronary intervention (pPCI).

Methods: We included 330 patients with a first STEMI who had been successfully revascularized with pPCI. The patient's electrocardiography was obtained in the first 48 hours, and the patients were divided into three groups according to the absence of fQRS (no-fQRS); fQRS presence in a single lead (sl-fQRS); and ≥2 leads with fQRS (classical fQRS).

Results: In-hospital mortality was significantly higher both in patients with sl-fQRS and in patients with ≥ 2 leads with fQRS compared to patients with no-fQRS. In ROC curve analysis, ≥ 1 leads with fQRS yielded a sensitivity of 75% and specificity of 57.4% for the prediction of in-hospital mortality. Multivariate analysis showed that sl-fQRS is an independent predictor of in-hospital mortality (OR: 3.989, 95% CI: 1.237-12.869, p = 0.021).

Conclusions: Although the concept of at least two derivations is mentioned for the classical definition of fQRS, our study showed that fQRS in only one lead is also associated with poor outcomes. Therefore, ≥1 leads with fQRS can be useful when describing the patients under high cardiac risk in acute STEMI. (Arq Bras Cardiol. 2017; 109(3):213-221)

Keywords: Myocardial Infarction/diagnosis; Percutaneous Coronary Intervention; Electrocardiography; Hospital Mortality; Myocardial Revascularization.

Introduction

The main therapeutic strategy for acute ST segment elevation myocardial infarction (STEMI) is the rapid restoration of epicardial blood flow in the infarct related artery (IRA). Primary percutaneous coronary intervention (pPCI) is the most effective and recommended therapeutic intervention for the reperfusion strategy.[1,2] Studies have shown that successful angiographic reperfusion, which is defined as Thrombolysis in Myocardial Infarction (TIMI) 3 flow in IRA, is associated with good outcomes.[3,4] Nevertheless, despite successful restoration of epicardial blood flow by pPCI, an important proportion of acute STEMI patients still continue to be at substantial risk because some amount of myocardial necrosis is inevitable. Therefore, there is a need for additional prognostic indicators.

The presence of slurred QRS morphology in at least two contiguous leads is accepted as the classical definition of fQRS on the 12-lead electrocardiogram (ECG).[5] This includes an additional R wave (R'), notching of the R wave, notching of the downstroke or upstroke of the S wave, or more than one R' (fragmentation).[6] It originates from inhomogeneous ventricular activation due to ischemic and/or injured myocardium and develops mostly within 48 hours during acute myocardial infarction.[5,7] The clinical significance of fQRS has been investigated in several studies, and the presence of fQRS was found to be associated with increased mortality, myocardial scarring, cardiac arrhythmias, and adverse cardiac events.[8-10]

Although the relationship between the presence of fQRS in at least two contiguous leads and adverse clinical outcomes is well known in patients with acute myocardial infarction,[10] the importance of fQRS in only one lead (single lead fQRS, sl-fQRS) in acute STEMI patients who underwent a successful pPCI has not been studied yet. The aim of our study is to investigate whether sl-fQRS is of prognostic importance in patients with acute STEMI who achieved TIMI 3 flow by pPCI.

Methods

Patient selection

This study was conducted at Dokuz Eylul University Hospital between January 1, 2009, and June 1, 2014. Patients who had been admitted to the coronary intensive care unit with the

Mailing Address: Zulkif Tanriverdi •
Balikligol State Hospital, Sanliurfa, Turkey
E-mail: ztverdi@gmail.com
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diagnosis of first acute STEMI and had undergone a successfully pPCI were retrospectively evaluated. Current guidelines were used for the diagnosis of acute STEMI.[2,11] Patients who were admitted with acute STEMI for the first time and successfully revascularized with pPCI in our clinic were included in this study. Successful revascularization was defined as post PCI TIMI 3 flow in the IRA, with a residual stenosis < 20%, and absence of stent thrombosis, repeat PCI, coronary dissection/rupture, or death. 24 patients with complete bundle branch block, 10 patients with incomplete right bundle branch block and 2 patients with pacemaker rhythm were excluded from the study. Also, patients who were known to have fQRS prior to STEMI, those with QRS duration ≥ 120 milliseconds, previous history of coronary artery bypass surgery, and patients who did not show TIMI 3 flow after pPCI were excluded from the study. As a result, 330 eligible patients were included in this study. The study was approved by the local ethics committee and study protocol complied with the Declaration of Helsinki.

Electrocardiography

Twelve-lead ECG was obtained at 25 mm/s paper speed, with a 0.16–100 Hz filter range and 10 mm/mV height from all patients in supine position, on admission, after pPCI, and at the 24th and 48th hours after admission to hospital. Routine ECG analyses were performed with the naked eye and without using any magnification by two independent clinicians. Pre-PCI sum of ST elevations and post-PCI sum of ST elevations were measured, and the percentage of total ST resolution (STR) calculated.[12] Fragmented QRS was defined by the presence of various RSR' patterns (QRS duration < 120 ms) with or without Q wave, which include an additional R wave (R' prime) or notching of the R wave or S wave, or the presence of more than one R' (fragmentation) without typical bundle branch block.[4] The presence of these criteria in two or more contiguous leads was required for the classical definition of fQRS. However, we also investigated the patients who had the criteria of a single derivation, and we divided the patients into three groups according to the fQRS derivation numbers at 48th hours: absence of fQRS in any lead (no-fQRS), its presence in a single lead (sl-fQRS) (Figure 1A), and its presence in two or more contiguous leads (classical fQRS) (Figure 1B).

Coronary angiography

Coronary angiography and PCI procedures were performed at the catheterization laboratory through the femoral/radial artery using the standard Judkins technique. Anticoagulant and antiplatelet therapies before PCI were given to all patients according to current guideline.[2] Angiographic data was assessed by two independent cardiologists. TIMI flow grading system was used to evaluate blood flow in the IRA.[13] Patients who achieved TIMI 3 flow after pPCI were included in this study. The presence of stenosis ≥ 50% in the left main coronary artery and ≥ 70% in the other major epicardial coronary arteries was considered critical stenosis.

Statistical analysis

Statistical analysis was performed using SPSS for Windows version 22.0 (SPSS Inc., Chicago, IL, USA). Kolmogorov-Smirnov test was used to determine normality of distribution. Continuous variables were tested for normal distribution using Kolmogorov-Smirnov test. Continuous variables were expressed as the mean ± standard deviation, and categorical variables were expressed as percentages. Continuous variables were compared with the one-way analysis of variance (ANOVA). A posteriori tests were performed after ANOVA to study differences between groups. Categorical variables were compared with chi-square or Fisher's exact tests. Correlation analysis between continuous variables was done by Pearson's method. A receiver operating characteristic (ROC) curve was used to determine the best cut-off number of the leads with fQRS in the prediction of in-hospital mortality. Multivariate logistic regression analysis was performed to determine the independent predictors of in-hospital mortality. A P value of < 0.05 was considered to be statistically significant.

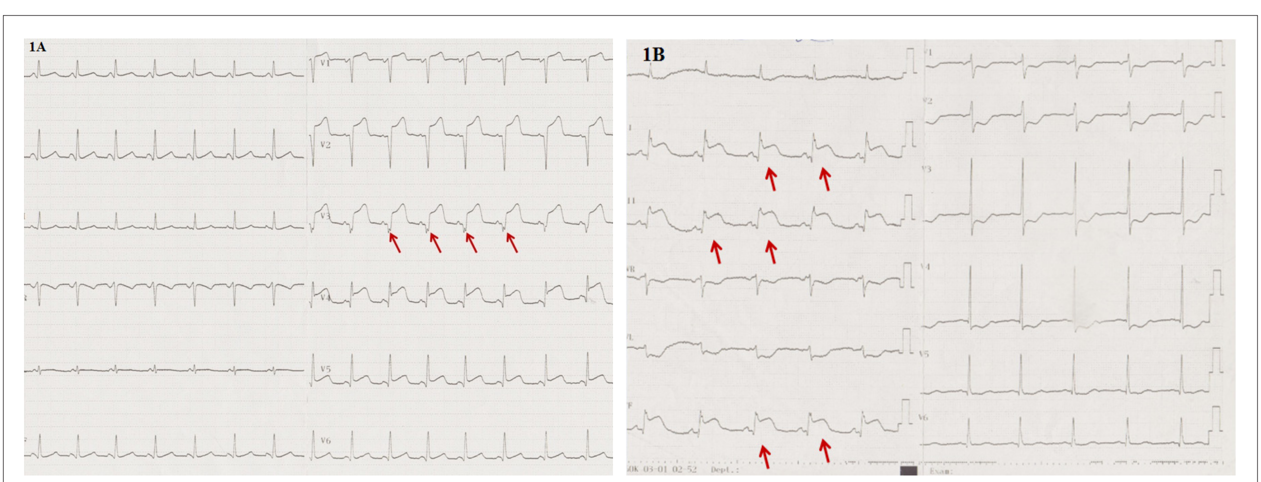

Figure 1 – *A) ECG example of single lead fQRS in a patient with anterior MI. B) ECG example of ≥ 2 leads with fQRS in a patient with inferior MI.*

Results

Three hundred-thirty patients who underwent a successful pPCI were included in this study. Baseline characteristics of patients are listed in Table 1.

Our study group was divided into three groups according to the number of leads with fQRS: no lead with fQRS; only one lead with fQRS; and ≥ 2 leads with fQRS. The higher number of leads with fQRS on surface ECG was significantly related with lower left ventricular ejection fraction (LVEF) ($p < 0.001$), lower STR ratio ($p < 0.001$), higher maximum CK-MB and troponin ($p < 0.001$ and $p< 0.001$), higher number of vessels with critical stenosis ($p < 0.001$), higher frequency of three-vessel disease ($p < 0.001$), and higher rate of in-hospital mortality ($p = 0.002$) (Table 2).

To better elucidate the importance of sl-fQRS, these patients were compared to those with no-fQRS and those with ≥ 2 leads with fQRS. Patients with sl-fQRS had a lower LVEF (41.0 ± 8.6 vs. 44.7 ± 7.5, $p = 0.007$), a lower ratio of STR (63.9 ± 28.3 vs. 74.9 ± 15.5, $p = 0.009$), higher maximum troponin levels (38.9 ± 24.0 vs. 29.2 ± 18.3, $p = 0.019$), and a higher rate of three-vessel disease (24.4% vs. 9.5%, $p = 0.007$) than patients with no-fQRS. Similarly, patients with ≥ 2 leads with fQRS also had a lower LVEF, a lower ratio of STR, higher maximum troponin levels, and a higher rate of three-vessel disease than patients with sl-fQRS (Figure 2). Hospital mortality was significantly higher in patients with sl-fQRS compared to patients with no-fQRS (13.3% vs 4.5%, $p = 0.039$), but it was not different between in patients with sl-fQRS and those with ≥ 2 leads with fQRS (Figure 3).

Correlation analysis showed that as the number of fQRS derivations increased, maximum troponin ($r = 0.389$, $p < 0.001$) and the number of vessels with critical stenosis ($r = 0.399$, $p < 0.001$) increased significantly; conversely, STR ($r = –0.506$, $p < 0.001$) and LVEF ($r = –0.520$, $p < 0.001$) decreased significantly.

In ROC curve analysis, ≥ 1 leads with fQRS yielded an area under curve (AUC) value of 0.707 (95% CI: 0.605-0.809, $p < 0.001$), which demonstrated a sensitivity of 75% and specificity of 57.4% for the prediction of in-hospital mortality (Figure 4A). When our study group was divided into two groups according to this cut-off value, in-hospital mortality was significantly higher for the group with ≥ 1 leads with fQRS (Figure 4B).

Multivariate logistic regression analyses were performed to determine the independent predictors of in-hospital mortality. Sl-fQRS (odds ratio [OR]: 3.989, 95% confidence interval [CI]: 1.237-12.869, $p = 0.021$), ≥ 2 leads with fQRS (OR: 4.298, 95% CI: 1.739-10.618, $p = 0.002$), and age (OR: 1.074, 95% CI: 1.039-1.110, $p < 0.001$) were found to be independent predictors of in-hospital mortality (Table 3). When patients were included as no-fQRS and ≥ 1 leads with fQRS in another model, age (OR: 1.076, 95% CI: 1.041-1.113, < 0.001) and ≥ 1 leads with fQRS (OR: 4.429, 95% CI: 1.851-10.595, $p = 0.001$) were found to be independent predictors of in-hospital mortality.

Discussion

The main finding of our study was that in-hospital mortality was significantly higher in patients with sl-fQRS compared to patients with no-fQRS. In addition, LVEF and STR ratio were significantly lower, whereas maximum troponin levels and frequency of three-vessel disease were significantly higher in patients with sl-fQRS than in those with no-fQRS. Our study showed that sl-fQRS and/or ≥ 1 leads with fQRS are independent predictors of in-hospital mortality even if TIMI grade 3 flow is achieved by primary PCI in acute STEMI patients.

Significant QRS fragmentation on surface ECG was defined as the presence of slurred QRS morphology in two or more contiguous leads, and only one lead with fQRS was not accepted as the presence of fQRS.[5] Therefore, the importance of the presence of fQRS at ≥ 2 lead has usually been investigated in studies, and it has been found to predict poor prognostic events in acute STEMI patients.[14,15] The importance of fQRS has also been investigated in coronary artery disease and non-ischaemic cardiomyopathy in a previous meta-analysis conducted by Rosengarten et al.[16] They also used the classical definiton for the presence of fQRS and excluded studies which used an alternative definition for fQRS. They found that fQRS was associated with all-cause mortality and the occurrence of sudden cardiac death. However, we think this classic definition may lead to overlook some patients who actually have high risk. That is because there is no study showing the importance of the presence of fQRS in a single derivation in patients with acute STEMI. To the best of our knowledge, ours is the first study that demonstrated the significance of sl-fQRS in acute STEMI patients who underwent a successful pPCI.

It is known that final TIMI ≤ 2 flow after pPCI is strongly associated with poor outcomes.[3] Therefore, these patients were not included in our study to avoid the effect of TIMI ≤ 2 flow on mortality. All patients in our study are the patients who underwent a successful pPCI, which means that these patients had lower necrotic myocardium so that angiographic TIMI 3 flow had been achieved. Despite successful revascularization with pPCI, in-hospital mortality rate of our study was 9.7%. This may be due to the small number of patients with respect to the current volume of pPCI and relatively higher rate of anterior MI (53.9%).

Clinical features, duration of chest pain, and MI localization were similar in the three groups. However, we found that in-hospital mortality was significantly higher in patients with sl-fQRS compared to patients with no-fQRS, and ≥ 1 leads with fQRS yielded a sensitivity of 75% and specificity of 57.4% for the prediction of in-hospital mortality. In addition, sl-fQRS was independent predictor of in-hospital mortality. As we showed that sl-fQRS was an independent predictor of in-hospital mortality, we constructed a new regression model, in which patients were included as no-fQRS and ≥ 1 leads with fQRS. We found that ≥ 1 lead with fQRS was independent predictor of mortality. More importantly, the odds ratio of ≥ 1 leads with

Table 1 – Baseline characteristics of patients

	(n = 330)
Age (years)	60.2 ± 13.2
Gender M/F	259/71
Hypertension (%)	151 (45.8)
Diabetes Mellitus (%)	77 (23.3)
Chest pain duration on admission (min.)	169.5 ± 184.3
Door to balloon time (min.)	21.5 ± 4.6
LVEF (%)	40.8 ± 8.7
Maximum CK-MB	145.2 ± 103.3
Maximum Troponin	38.2 ± 23.7
Number of STE derivations	5.0 ± 1.6
Number of STD derivations	3.1 ± 1.6
No leads with fQRS (%)	179 (54.2)
One lead with fQRS (%)	45 (13.6)
≥ 2 leads with fQRS (%)	106 (32.1)
Mean number of leads with fQRS	1.2 ± 1.8
MI localization	
Anterior (%)	178 (53.9)
Non-anterior (%)	152 (46.1)
Pre-PCI sum of STE	10.6 ± 7.0
Post-PCI sum of STE	3.7 ± 3.1
STR ratio (%)	65.1 ± 25.0
Infarct-related artery	
LAD (%)	178 (53.9)
CX (%)	53 (16.1)
RCA (%)	99 (30)
Stent type	
BMS (%)	94 (28.5)
DES (%)	236 (71.5)
Glycoprotein IIb-IIIa inhibitors (%)	29 (8.8)
Number of vessels with critical stenosis	1.8 ± 0.8
Three-vessel disease (%)	80 (24.2)
In-hospital mortality (%)	32 (9.7)

BMS: bare metal stent; CK-MB: creatinine kinase-MB; CX: circumflex artery; DES: drug-eluting stent; F: female; fQRS: Fragmented QRS; LAD: left anterior descending artery; LVEF: left ventricular ejection fraction; M, male; MI, myocardial infarction; min, minute; PCI, percutaneous coronary intervention; RCA, right coronary artery; STD, ST depression; STE: ST elevation; STR, ST resolution.

fQRS (4.429) was higher than odds ratio of ≥ 2 leads with fQRS (4.298). Although previous studies showed the presence of fQRS in two or more contiguous leads was associated with increased in-hospital mortality,[10] this is first study demonstrating the relationship between sl-fQRS, ≥ 1 leads with fQRS and in-hospital mortality. Celikyurt et al.,[17] found that the number of leads with fQRS was the only predictor of response to cardiac resynchronization therapy, and the best cut-off number of leads with fQRS to distinguish between responder and non-responder patients was one. These findings suggest that the presence of fQRS even in just one lead can be of prognostic significance. Furthermore, in-hospital mortality was similar between patients with sl-fQRS and those with ≥ 2 leads with fQRS in our study. This also suggests that sl-fQRS could be as significant a finding as classical fQRS in patients with acute STEMI.

Only one previous case report has assessed the association between fQRS in just one lead and myocardial scar.[18] In this case presentation, fQRS in lead V3 alone, without other electrocardiographic abnormalities, may be because myocardial infarction was limited to a narrow area of the

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Table 2 – Comparison of clinical, electrocardiographic, and angiographic characteristics of patients according to the number of leads with fQRS

	no-fQRS (n = 179)	sl-fQRS (n = 45)	Classical fQRS (n = 106)	p*
Age (years)	59.7 ± 13.1	57.9 ± 14.3	62.1 ± 12.8	0.149
Gender M/F	140/39	35/10	84/22	0.972
Hypertension (%)	77 (43)	20 (44.4)	54 (50.9)	0.423
Diabetes Mellitus (%)	34 (19)	12 (26.7)	31 (29.2)	0.120
Duration of chest pain on admission (min.)	159.9 ± 174.2	172.7 ± 155.7	184.4 ± 210.7	0.550
Door to balloon time (min.)	21.5 ± 4.7	21.6 ± 5.2	21.4 ± 4.2	0.986
LVEF (%)	44.7 ± 7.5	41.0 ± 8.6	34.2 ± 6.4	< 0.001
Max. CK-MB (ng/ml)	111.1 ± 84.9	122.4 ± 89.9	212.3 ± 105.3	< 0.001
Max. Troponin (ng/ml)	29.2 ± 18.3	38.9 ± 24.0	53.2 ± 24.1	< 0.001
Number of STE derivation	5.1 ± 1.6	4.9 ± 1.8	4.9 ± 1.6	0.785
Number of STD derivation	3.0 ± 1.7	3.0 ± 1.6	3.2 ± 1.6	0.632
Mean number of leads with fQRS	0.0 ± 0.0	1.0 ± 0.0	3.3 ± 1.6	< 0.001
MI localization (%)				
Anterior	103 (57.5)	21 (46.7)	54 (50.9)	0.320
Non-Anterior	76 (42.5)	24 (53.3)	52 (49.1)	
STR ratio (%)	74.9 ± 15.5	63.9 ± 28.3	49.1 ± 28.0	< 0.001
Stent type				
BMS (%)	59 (33)	12 (26.7)	23 (21.7)	0.121
DES (%)	120 (67)	33 (73.3)	83 (78.3)	
Glycoprotein IIb-IIIa inhibitors (%)	17 (9.5)	4 (8.9)	8 (7.5)	0.854
Number of vessels with critical stenosis (%)	1.5 ± 0.7	1.8 ± 0.8	2.2 ± 0.8	< 0.001
Three-vessel disease (%)	17 (9.5)	11 (24.4)	52 (49.1)	< 0.001
In-hospital mortality (%)	8 (4.5)	6 (13.3)	18 (17)	0.002

BMS: bare metal stent; Classical fQRS, ≥ 2 leads with fQRS; CK-MB: creatinine kinase-MB; DES: drug-eluting stent; F: female; fQRS: Fragmented QRS; LVEF: left ventricular ejection fraction; M: male; MI: myocardial infarction; min: minute; QRS; sl-fQRS, Single lead fragmented QRS; STD: ST depression; STE: ST elevation; STR: ST resolution

** ANOVA and Chi-square tests were performed to study differences among the three groups. A posteriori test (Tukey) was performed after ANOVA to study between group differences for no-fQRS vs. sl-fQRS, no-fQRS vs. classical fQRS and sl-fQRS vs. classical fQRS.*

left ventricular apex. However, there is no other information in literature about the importance of the fQRS in one lead alone in patients with acute STEMI. In this study, we detected that patients with sl-fQRS had a lower LVEF, higher maximum troponin levels, and a higher rate of three-vessel disease than patients with no-fQRS. Therefore, it can be suggested that the presence of fQRS even in one lead is also associated with the necrosis of certain amount of myocardial tissue. We think further studies with larger sample sizes are needed to better clarify the mechanism and clinical significance of fQRS in one lead alone.

It is known that the presence of fQRS is associated with lower STR in acute STEMI patients.[19,20] Coronary artery patency has been assessed with TIMI flow in clinical practices, but recent studies have shown that STR is a stronger marker than angiographic TIMI flow to evaluate tissue reperfusion and predict cardiac outcomes.[21,22] Although in this study TIMI 3 flow was provided in all patients after pPCI, we found that STR is lower in patients with sl-fQRS when compared to in patients with no lead with fQRS. Accordingly, we can conclude that acute STEMI patients who have only one lead with fQRS will also show poor reperfusion at the cellular level even if TIMI grade 3 flow is achieved by primary PCI.

Fragmented QRS is a novel ECG parameter that is used quite often in daily practice and that is gaining importance.[23] However, the number of fQRS derivations has recently attracted a greater interest. Even though there is no study showing the importance of the presence of fQRS in a single lead, the clinical significance of QRS distortion in only one lead, which is another important ECG finding in acute STEMI,[24] was investigated in a recently published study.[25] Similar to our study, this study first demonstrated that QRS distortion in only one lead was associated with larger infarct size. Based on these results, we suggest that the presence of fQRS in a single derivation also has prognostic importance. This cut-off number of leads with fQRS will need to be validated in larger prospective studies.

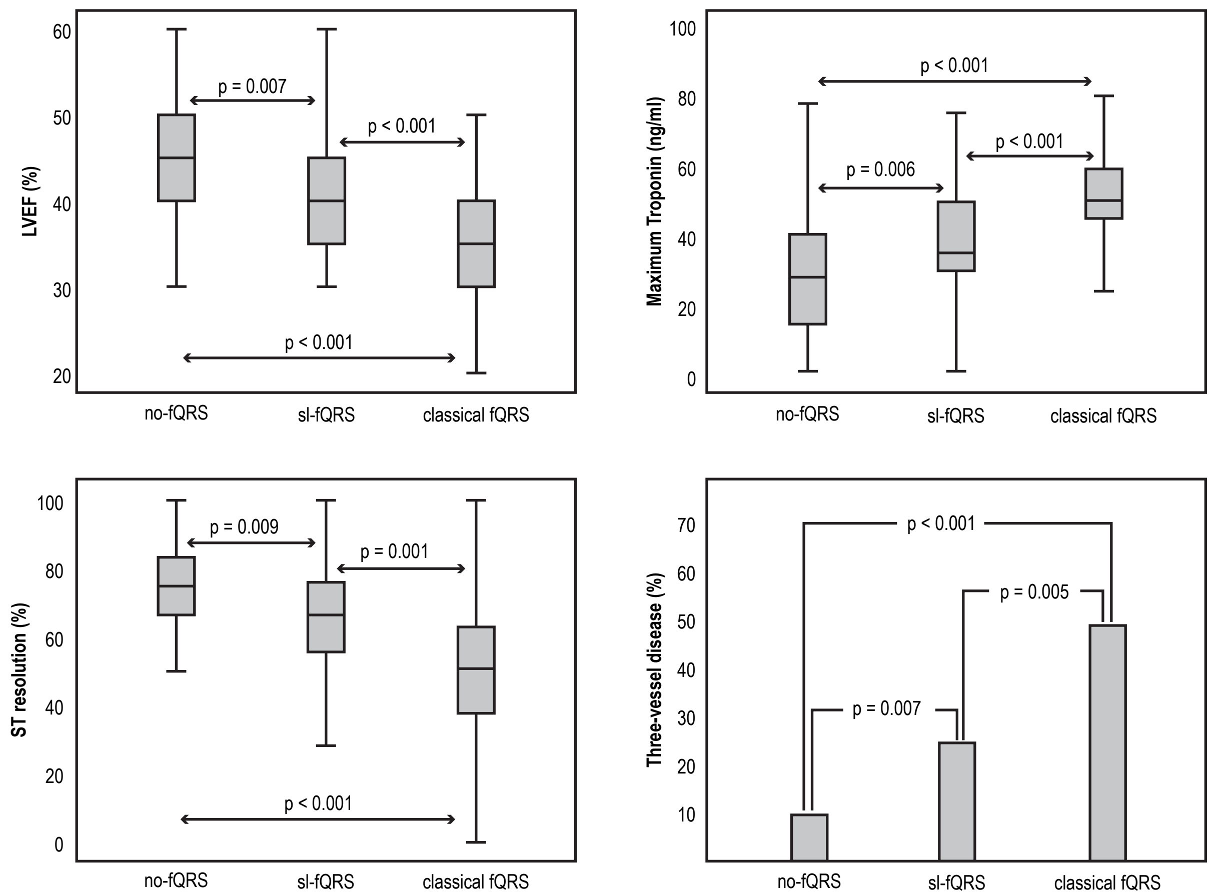

Figure 2 – *Comparisons among groups in terms of LVEF, maximum troponin, ST resolution, and the frequency of three-vessel disease. LVEF: left ventricular ejection fraction; fQRS: Fragmented QRS.*

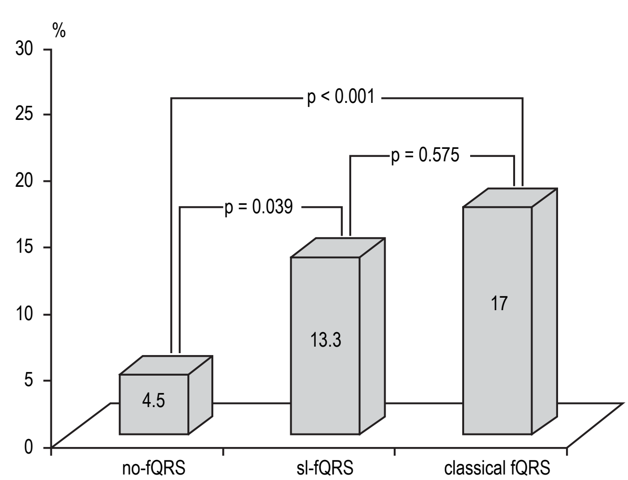

Figure 3 – *Comparisons among groups in terms of in-hospital mortality.*

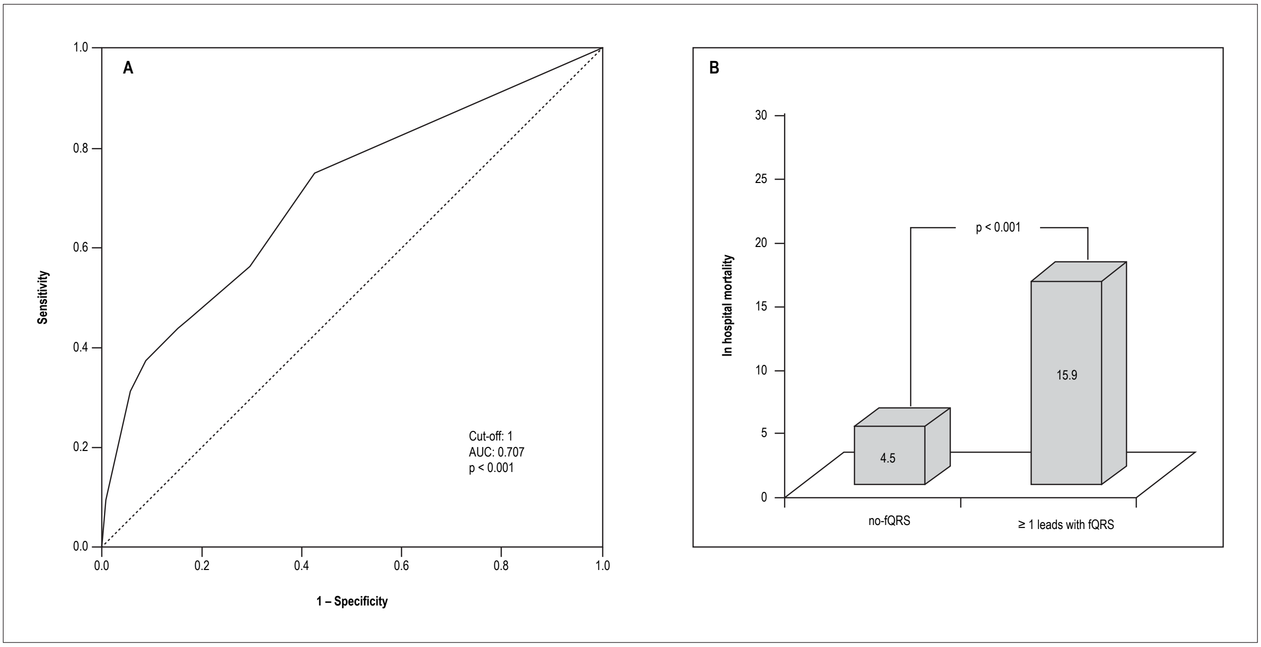

Figure 4 – *A) ROC curve to determine the best cut-off for number of leads with fQRS in the prediction of in-hospital mortality. B) In-hospital mortality rate in no-fQRS and ≥ 1 leads with fQRS groups.*

Table 3 – Multivariate logistic regression analysis showing the independent predictors of in-hospital mortality

	Predictors	OR	95% CI	p
	Age	1.074	1.039-1.110	< 0.001
Model 1*	sl-fQRS	3.989	1.237-12.869	0.021
	≥ 2 leads with fQRS	4.298	1.739-10.618	0.002
Model 2†	Age	1.076	1.041-1.113	< 0.001
	≥ 1 leads with fQRS	4.429	1.851-10.595	0.001

β, β coefficient; CI: confidence interval; OR: odds ratio; SE: Standard error.
** Entered variables: Age, Hypertension, Diabetes mellitus, Duration of chest pain on admission, Door to balloon time, Stent type, CK-MB, Troponin, Number of ST elevated and ST depressed derivations, MI localization, sl-fQRS, ≥ 2 leads with fQRS, Number of affected lesion narrowness >70%, ST segment resolution score.*
† Entered variables: Age, Hypertension, Diabetes Mellitus, Duration of chest pain on admission, Door to balloon time, Stent type, CK-MB, Troponin, Number of ST elevated and ST depressed derivations, MI localization, ≥ 1 leads with fQRS, Number of affected lesion narrowness >70%, ST segment resolution score.

One of the major limitations of this study is that we did not use the TIMI myocardial perfusion degree or myocardial blushing grade, which are the other parameters of angiographic reperfusion. These parameters could have provided additional benefits to our study. In addition, the findings of this study cannot be generalized to all acute STEMI patients since patients who underwent thrombolytic therapy, those with QRS duration ≥ 120 milliseconds, and those for whom it was not the first acute STEMI, were not included to the study.

Conclusion

The concept of at least two derivations is mentioned for the classical definition of fQRS, and only one lead with fQRS has not been accepted for the presence of fQRS. However, we showed for the first time that sl-fQRS is associated with greater extent of necrotic myocardium, increased in-hospital mortality and higher risk. Therefore, instead of the concept of at least two derivations, the presence of fQRS in only one lead and/or ≥1 leads with fQRS may also be enough when describing the patients under high cardiac risk. Further studies are needed to understand the importance of sl-fQRS.

Author contributions

Conception and design of the research, Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Tanriverdi Z, Dursun H, Colluoglu T, Kaya D; Acquisition of data: Tanriverdi Z, Colluoglu T, Kaya D; Statistical analysis: Tanriverdi Z, Dursun H; Writing of the manuscript: Tanriverdi Z, Kaya D.

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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Reproducibility and Reliability Of QTc and QTcd Measurements and Their Relationships with Left Ventricular Hypertrophy in Hemodialysis Patients

Maria Angélica Gonçalves Alonso,[1] Valentine de Almeida Costa de Castro Lima,[2] Maria Angela Magalhães de Queiroz Carreira,[2] Jocemir Ronaldo Lugon[2]

Universidade Federal Fluminense (UFF);[1] Hospital Universitário Antônio Pedro - Universidade Federal Fluminense (UFF),[2] Niterói, RJ – Brazil

Abstract

Background: Left ventricular hypertrophy (LVH) is very common in hemodialysis patients and an independent risk factor for mortality in this population. The myocardial remodeling underlying the LVH can affect ventricular repolarization causing abnormalities in QT interval.

Objective: to evaluate the reproducibility and reliability of measurements of corrected QT interval (QTc) and its dispersion (QTcd) and correlate these parameters with LVH in hemodialysis patients.

Methods: Case-control study involving hemodialysis patients and a control group. Clinical examination, blood sampling, transthoracic echocardiogram, and electrocardiogram were performed. Intra- and interobserver correlation and concordance tests were performed by Pearson´s correlation, Cohen's Kappa coefficient and Bland Altman diagram. Linear regression was used to analyze association of QTc or QTcd with HVE.

Results: Forty-one HD patients and 37 controls concluded the study. Hemodialysis patients tended to have higher values of QTc, QTcd and left ventricular mass index (LVMi) than controls but statistical significance was not found. Correlation and concordance tests depicted better results for QTc than for QTcd. In HD patients, a poor but significant correlation was found between QTc and LVMi ($R^2 = 0.12$; $p = 0.03$). No correlation was found between values of QTcd and LVMi ($R^2 = 0.00$; $p=0.940$). For the control group, the correspondent values were $R^2 = 0.00$; $p = 0.67$ and $R^2 = 0.00$; $p = 0.94$, respectively.

Conclusion: We found that QTc interval, in contrast to QTcd, is a reproducible and reliable measure and had a weak but positive correlation with LVMi in HD patients. (Arq Bras Cardiol. 2017; 109(3):222-230)

Keywords: Electrocardiography; Hypertrophy, Left Ventricular; Coronary Artery Disease; Cardiomyopathy, Hypertrophic; Renal Dialysis.

Introduction

Despite the improvement of the quality of dialysis over the years, patients with end-stage renal disease still have a high mortality rate. Heart disease remains the leading cause of death in these patients, with coronary artery disease and left ventricular hypertrophy (LVH) as the most frequent cardiovascular abnormalities. LVH is very common in hemodialysis (HD) patients, and an independent risk factor for mortality in this populaton.[1,2] Myocardial remodeling is not a homogeneous phenomenon and can affect ventricular repolarization causing non-uniform abnormalities in QT interval (QT).[3]

The QT interval (QT) represents the electrical ventricular systole, and QT dispersion (QTd), defined as the difference between the maximal and minimal QT on a 12-lead electrocardiogram (ECG), reflects the regional heterogeneity of the myocardial repolarization. Several studies have reported an association between increased values of any of these two parameters and all-cause mortality, sudden death, ventricular arrhythmias and coronary artery disease.[4,5] The measurement of QT is not an easy task and involves a number of pitfalls, as follows: recognizing the onset of the QRS complex and especially the end of the T wave may be difficult; the leads chosen to measure the QT interval varies among studies; there is more than one formula to adjust the QT interval for the cardiac rate; and finally, cut-off values for both QT and QTd are not well defined and the role of gender adjustment in this regard is disputable.[6,7]

While ECG is available in almost every dialysis center, the echocardiogram (ECO), considered the gold standard for the diagnosis of LVH, is not. In view of that we thought it would be of interest to investigate the reproducibility and reliability of corrected QT (QTc) and its dispersion (QTcd) measurements and their relationships with LVH in HD patients.

Mailing Address: Maria Angélica Gonçalves Alonso •
Rua Santos Dumont, 24/404. CEP 24220-280, Icaraí, Niterói, RJ – Brazil
E-mail: mangelica180@gmail.com
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Methods

Study population

This study used the database generated by a previous study.[8] The protocol was approved by the ethics committee of the university medical school under the number 0125.0258.000–10/2010 and a written informed consent was obtained from every patient. We conducted a case-control study with HD patients recruited from a single dialysis center and a control group matched by gender and age without overt kidney disease. HD patients should be on treatment for at least 3 months, in a schedule of 4-hour duration sessions, 3 times a week. The control group consisted of individuals referred for exercise testing at the university hospital. Participants should be aged between 18 and 70 years. Exclusion criteria were as follow: arrhythmias that prevent proper assessment of heart rate, presence of symptomatic heart disease, and, in the control group, an estimated glomerular filtration rate by the CKD-EPI equation[9] lower than 60 ml/min/1.73 m^2. Regular medications were not discontinued for the study. Cardiac evaluation was performed in the interval between dialysis sessions, in the middle of the week, and consisted of clinical examination, transthoracic ECO, and ECG. Blood samples were collected before the HD procedure for determination of ultrasensitive C-reactive protein and hemoglobin. The urea reduction ratio (URR) was calculated as the average of the last three determinations prior to enrollment. In the control group, blood sample collection (for determination of C-reactive protein, creatinine and hemoglobin levels) and cardiac evaluation were performed 30 min before the exercise test. C-reactive protein was analyzed by an immunoturbidimetric assay (Dimension RxLMax, Siemens, Berlin, Germany).

Echocardiography

A two-dimensional transthoracic ECO was performed with GE VIVID 7 System (General Electric Company, USA) by an experienced echocardiographist without prior knowledge of the results of other tests. Determination of internal chamber size, global and segmental ventricular systolic function, diastolic function and structural changes were performed. Patients and controls were considered to have LVH if left ventricular mass index (LVMi) were higher than 88 g/m^2 in women and 102 g/m^2 in men.[10]

Electrocardiogram and QT measurement

A 3-channel recorder was used for the electrocardiographic traces (Ergo 13, Heart Ware Co., Minas Gerais, Brazil). The twelve electrocardiographic leads were recorded on paper at a speed of 25 mm/s with patients at rest. Two observers (unaware of each other's results) manually measured the QT and its dispersion on the same electrocardiographic traces at two different times with an interval of one week between measurements. QTs were measured using the method of the tangent,[11] in which the end of the T wave is defined at the intersection point of the tangent line, drawn at the point of greatest slope of the last portion of the T wave, with the baseline. In the presence of the U wave, the tangent was drawn crossing the meeting point between the U and T waves. The chosen leads were DII or V5 (which had the highest value of QT) and the cutoff value for an enlarged QTc was ≥ 450 ms for men and ≥ 460 ms for women.[12] Leads in which a tangent could not be drawn because of unclear definition of T wave morphology were excluded from analysis. The correction of the QT for heart rate was performed by the method of Hodges[12] with the formula: QTc = QT + 1.75 (RR interval - 60). QT dispersion was obtained as usual, i.e. as the difference between the highest and the lowest QT value on a 12 lead ECG. Values of QTcd > 60 ms were considered abnormal.[13,14]

Statistical analysis

Results were expressed as mean and standard deviation for normally distributed data and median and range otherwise. Categorical variables were expressed as frequencies and compared using the Fisher Test. Comparisons between two continuous variables were accomplished by the non-paired T test (for normal distribution) or its nonparametric equivalent (Mann-Whitney test). For evaluation of the reproducibility and reliability of QTc and QTcd measures, intra and inter observer agreement, and concordance tests were performed employing Pearson´s correlation, Cohen's Kappa coefficient and Bland Altman diagram, respectively. Linear regression was used to analyze association of QTc and QTcd with LVH. $p < 0.05$ was considered significant. Analyses were performed using SPSS for Windows version 18.0 (SPSS Inc., Chicago, IL, USA) and MedCalcversion 16.4.3 (Medcalcsoftware bvba, Belgium).

Results

From a total of 125 patients from a single dialysis center, after application of exclusion criteria, 51 agreed to participate and signed the consent form. Ten patients did not show up for the exams resulting in 41 HD patients that concluded the study. From 41 control patients initially selected, 4 were excluded: 2 due to incomplete data and 2 had estimated glomerular filtration rate below 60 mL/min/1.73 m^2. Data for LVMi were available in 38 HD patients and 30 controls. The general features of participants are in Table 1. The most common etiologies of the renal disease were: hypertensive nephrosclerosis (56%), chronic glomerulonephritis (17%), polycystic kidney disease (10%), and diabetic nephropathy (7%).

Systolic function of the left ventricle, as analyzed by the ejection fraction, was similar between groups (66.1 ± 10.1% *vs.* 68.6 ± 5.4% for HD patients and controls, respectively, p = 0.167). The mean LVMi and the prevalence of LVH tended to be higher in HD patients than in controls but statistical significance was not found (128 ± 52 g/m^2 *vs.* 107 ± 30 g/m^2, p = 0.054 and 71% *vs.* 46%, p = 0.165, respectively).

Observer 1 excluded for analysis 11 leads at the first measurement and 22 leads at the second one in HD group, and 36 leads and 44 leads at first and second measurement, respectively in the control group. Observer 2 excluded for analysis 13 leads at the first measurement and 18 at the second one in HD group, and 28 and 16 leads at first and second measurements, respectively in the control group.

In HD patients, mean QTc and QTcd measures were 416.6 ± 29.5 ms and 48.3 ± 17.4 ms, respectively by observer 1, and 420.1 ± 30.6 ms and 65.9 ± 30.2 ms for

Table 1 – General features of 41 patients and 37 controls and echocardiogram data available in 38 patients and 30 controls

	Hemodialysis patients	Controls	p value
Age, years	50 ± 14[a]	50 ± 12	0.975
Male gender (%)	21 (51.2)	18 (48.6)	0.145
Non-white (%)	27 (65.9)	18 (48.6)	0.402
Body mass index, kg/m^2	25.1 ± 5.1	27.6 ± 4.2	0.016
Dialysis vintage, months	67.2 ± 47.3	n.a	-
Diabetes, (%)	4 (9.8)	4 (10.8)	0.467
Smoking, (%)	3 (9.1)	7 (19)	0.104
Familial CAD, f (%)	15 (36.6)	16 (43.2)	0.669
Familial hypertension, (%)	26 (63.4)	20 (54.1)	0.106
Sedentary, (%)	33 (80.5)	22 (59.5)	0.082
Use of blood pressure drugs (%)	33 (80.5)	19 (51.4)	0.860
Beta-blocker	14 (34.1)	6 (16.2)	0.411
Diuretic	2 (4.9)	8 (21.6)	0.599
Calcium channel blocker	5 (12.2)	2 (5.4)	0.134
ACE inhibitor/ARB	12 (29.3)	15 (40.5)	0.433
Clonidine	8 (19.5)	0	< 0,001
Alfa-blocker	6 (14.6)	0	< 0.001
C-reactive protein, mg/dL	1.02 ± 1.20	0.5 ± 0.52	0.016
URR, %	68.7 ± 7.8	n.a.	-
Hemoglobin, g/dL	11.5±1.4	13.8 ± 1.2	< 0.001
Left ventricular mass index, g/m^2	128 ± 52	107 ± 30	0.054
Left ventricular hypertrophy, % [b]	71	46	0.118
QTc, ms	418 ± 29	407 ± 27	0.085
QTcd, ms	57 ± 22	50 ± 20	0.189
Enlarged QTc[c], %	15	5.4	0.268
QTcd > 60 ms, %	34	21	0.314

[a] Mean ± S.D.; [b] > 110 g/m^2 for male and >88 g/m^2 for female; [c] ≥ 450 msec for male and ≥ 460 msec for female; ACE: angiotensin-converting–enzyme; ARB - AT1: receptor blocker; CAD: coronary artery disease; URR: urea reduction ratio; QTc: corrected QT interval; QTcd: Dispersion of QTc. Differences between continuous variables were tested by non-paired T test; For categorical variables, the Fisher Test was employed.

observer 2. In controls, mean values for QTc and QTcd were 408 ± 30.0 ms and 47 ± 17.3 ms for observer 1 and 406.2 ± 27 ms and 54.6 ± 28.6msec for observer 2.

Frequency distributions of both QTc and QTcd measures for patients and controls are in Figure 1. Intra and inter observer linear correlation coefficients for QTc and QTcd of HD patients and controls are in Table 2. Intra and inter observer concordance (inter-rater agreement) of measures of QTc and QTcd for each group are in Table 3. The Bland Altman diagrams addressing intra and inter observer agreement for these variables are in Figures 2 and 3, respectively.

The association of QTc or QTcd with LVH was evaluated by linear regression analysis (Figure 3). In HD patients, a poor but significant correlation was found between values of QTc interval and LVMi ($R^2 = 0.12$; $p = 0.033$). In contrast, no correlation was present between values of QTcd and LVMi ($R^2 = 0.00$; $p = 0.940$). For the control group, the correspondent values were $R^2 = 0.00$; $p = 0.67$ and $R^2 = 0.00$; $p = 0.94$, respectively.

Discussion

LVH is a frequent abnormality and a marker of cardiovascular events and death in HD patients.[1,2] Although alterations in QT are also associated with overall mortality and cardiovascular events in the general population,[4,15] studies correlating LVH and changes in QT in HD patients are scarce. In the present study, we analyzed the reproducibility and reliability of QTc and QTcd measurements and their relationship with LVH as diagnosed by ECO in HD patients and in a control group. For this purpose, we resorted to a database derived from a study in which HD patients suitable to engage in an exercise treadmill test were enrolled.[8] Mean age, gender distribution, skin color, and body mass index of patients and controls were similar. Since some diabetic patients were judged as not apt to undergo an exercise treadmill test, this may in part explain why diabetic patients have a low representation in our sample when compared to national data[16] and to international series.[17] In agreement with the majority of reported series, a notable

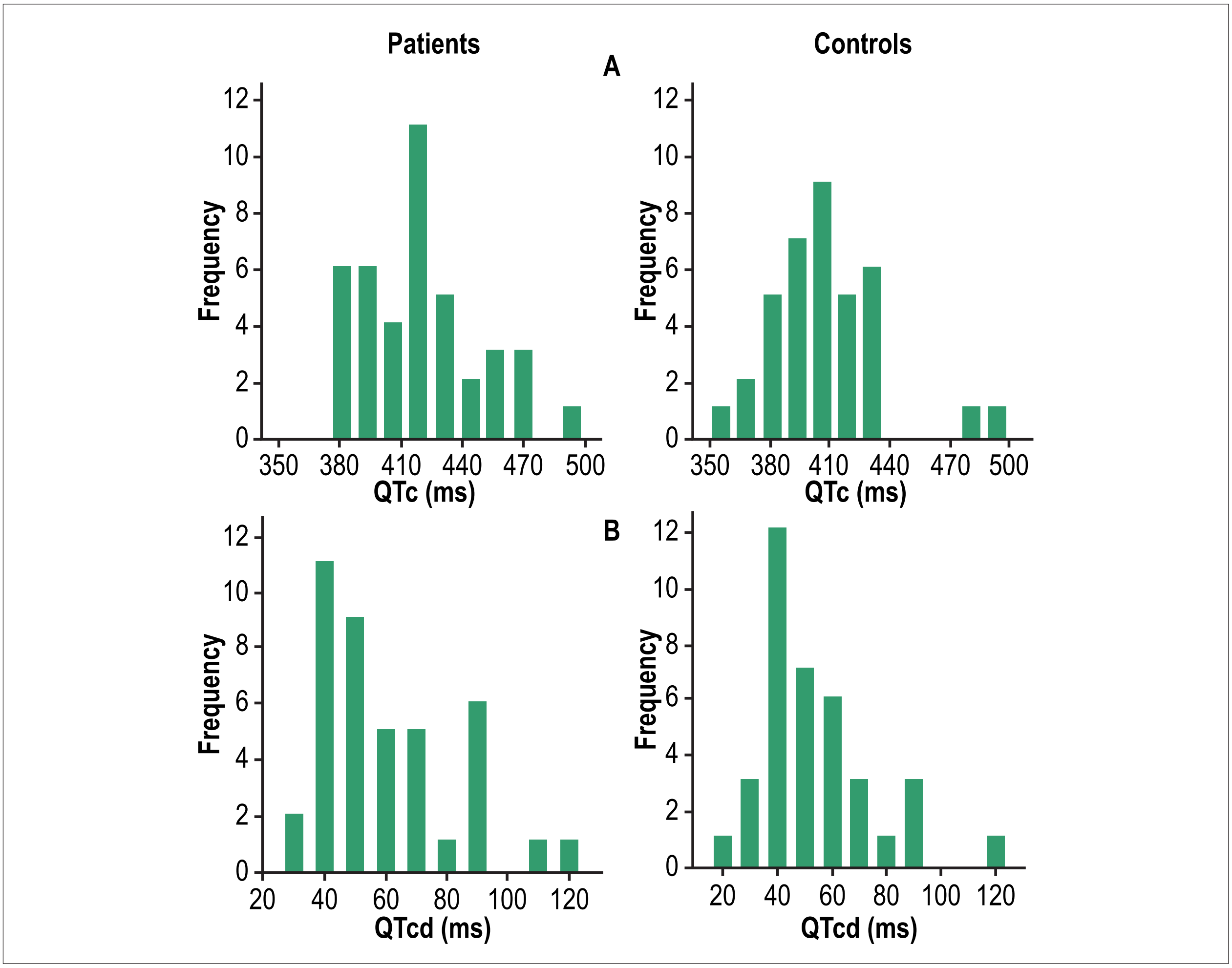

Figure 1 – *Frequency distribution of corrected QT interval, QTc (panel A) and dispersion of QTc, QTcd (panel B) in 41 hemodialysis patients and 37 controls. Data refer to the mean values of the two observers.*

number of the HD patients were in use of blood pressure drugs.[16,17] Serum levels of C-reactive protein were greater in HD patients, which are well recognized for their chronic inflammatory state.[18] It should be pointed out that HD patients had a standard dialysis treatment as evidenced by their mean URR and mean hemoglobin levels.[19]

The prevalence rate of LVH found in the ECO of HD patients (71%) is consistent with previous report[1] and tended to be higher than in controls (46%), also in accordance with a previous study[20]. In contrast, left ventricular systolic function was similar in both groups, perhaps due to our recruitment criteria that privileged healthier patients able to undergo an exercise test.

Mean QTc and QTcd in our sample were lower than the ones reported in major international studies on HD patients[21-26]. Again, one of the reasons that could account for this difference was our enrollment criteria, which excluded patients with overt heart failure who are more prone to QT alterations. In support of previous reports, the mean values for QTc and QTcd as well as the frequency of enlargement in each of these two parameters tended to be higher in HD patients than in controls.[27] Other possible explanation for the discrepancy of our results in comparison to literature may reside in the methodology chosen for the measurement of the QT and the moment the ECG was performed. We decided not to use the traditional Bazett formula to calculate heart-rate-corrected QT. The decision was taken to comply with the current recommendations of ECG interpretation[12] which explicitly discourage the use of Bazett formula because of its inability to properly correct the QT for heart rate.[7] It has long been known that the use of Bazett formula overestimate QT at fast heart rates and underestimate it at low heart rates[7]. A recent well designed study found that the Hodges formula is associated with lower QTc variability over the whole range of the investigated heart rates and seem to be the most accurate in determining the correct QTc.[28] For measuring the QT, we preferred to use the tangent technique rather than the conventional methodology[11]. A study conducted in a central ECG laboratory conclude that when ECGs are interpreted by trained readers using sophisticated on-screen tools and high quality digital ECGs recorders, the results are comparable for

Table 2 – Intra- and interobserver linear correlation coefficients of QTc and QTcd in 41 hemodialysis patients and 37 controls

		Intraobserver[a]		Interobserver	
		ρ (95% CI)	p	ρ (95% CI)	p
Patients	QTc	0.83 (0.69 – 0.90)	< 0.001	0.92 (0.85 – 0.96)	< 0.001
	QTcd	0.50 (0.22 – 0.70)	< 0.001	0.72 (0.53 – 0.84)	< 0.001
Controls	QTc	0.78 (0.62 – 0.88)	< 0.001	0.82 (0.68 – 0.90)	< 0.001
	QTcd	0.39 (0.07 – 0.63)	0.017	0.50 (0.22 – 0.71)	0.001

[a] observer 1; QTc: corrected QT interval; QTcd: dispersion of QTc; ρ: Pearson correlation coefficient.

Table 3 – Intra- and inter-observer concordance (inter-rater agreement) of measures of QTc and QTcd in 41 hemodialysis patients and 37 controls

		Intraobserver[a]	Interobserver
		κ (95% CI)	κ (95% CI)
Patients	QTc	0.66 (0.36 – 0.96)	0.83 (0.60 – 1.00)
	QTcd	0.14 (–0.21 – 0.49)	0.44 (0.17 – 0.70)
Controls	QTc	1.0 (1.0 – 1.0)	0.78 (0.38 – 1.00)
	QTcd	0.37 (–0.07 – 0.80)	0.32(–0.01 – 0.66)

[a] Observer 1; κ: Cohen's Kappa coefficient; QTc: corrected QT interval; QTcd: dispersion of QTc.

the tangent and the conventional method. However, the QT measured by the tangent method may be shorter than the conventional method by up to 10 milliseconds.[29] When QT measurements were manually evaluated by inexperienced readers on prints of 12-lead ECGs, the results were favorable to the method of tangent.[11] Furthermore, we chose to record the electrocardiogram in the interdialytic period, instead of during the HD procedure, in contrast to most of the studies that addressed the relationship between electrolyte disturbances and QT changes.[23,24,26]

When looking at the pattern of frequency distribution of QTc, it can be realized that baseline values of patients are higher than controls. Accordingly, mean values of QTc tended to be higher than in the control group. These findings are consistent with other studies and may be related to the higher prevalence of LVH and electrolyte imbalance in HD patients.[30] In contrast, distribution of QTcd looked frequencies very similar for patients and controls. It should be mentioned that many drugs, including some anti-hypertensive medications, are known to prolong the QT.[31,32] Of note, the frequency of use of clonidine and alpha-blockers was higher in HD patients than in the controls and could potentially account for the differences in QT between groups. However, when consulting a website that is thought to be an excellent source of information regarding drugs that may affect the QT interval,[31] such medications were not found in any of the four listed categories.[33]

The main purpose of our study was to address the reliability and reproducibility of QTc and QTcd measurements. A good correlation was found for the intraobserver measurements of QTc values in both, patients and controls. However, the intraobserver correlation of QTcd values for the two groups was poor. The interobserver values followed the same trend but, as a whole, correlation tended to be a little bit better than for the intraobserver measures probably because the mean of the two measures made by each observer was used for comparisons.

Values of kappa coefficient showed a strong intra- and interobserver agreement for QTc values and a weak one for QTcd for both patients and controls. In the Bland-Altman plots, our results showed concordance between measures of QTc, except in the intraobserver analysis of patients group. For QTcd we found a biased proportion in interobserver analysis of control group and absence of concordance in interobserver analysis of patients' group. In summary, we found that QTcd results for reproducibility and reliability were significantly poorer than QTc, in accordance to previous reports in healthy subjects,[34,35] patients with cardiovascular disease,[36] or undergoing HD[37] discouraging the use of QTcd routinely. In contrast, QTc seems to be a reliable and reproducible measure.

A linear regression was applied to assess the relationship of QTc and QTcd with LVH. In patients, a poor but significant correlation was found between values of QTc interval and LVMi and no correlation was found for QTcd. In the control group, there was no correlation between values of either QTc or QTcd interval and LVMi. The absence of correlation between LVH and QTc in the control group could be accounted for by the fact that we enrolled volunteers assigned to undergo an exercise treadmill test and had a high chance to have coronary artery disease. Predisposing risk factors for QTc prolongation include advanced age, left ventricular hypertrophy, heart failure, myocardial ischemia, hypertension, diabetes mellitus, elevated serum cholesterol, high body mass index, slow heart rate, electrolyte imbalance (including hypokalemia and hypomagnesemia) and drugs.[38] In the control group, in which the prevalence of LVH was not as high as in HD

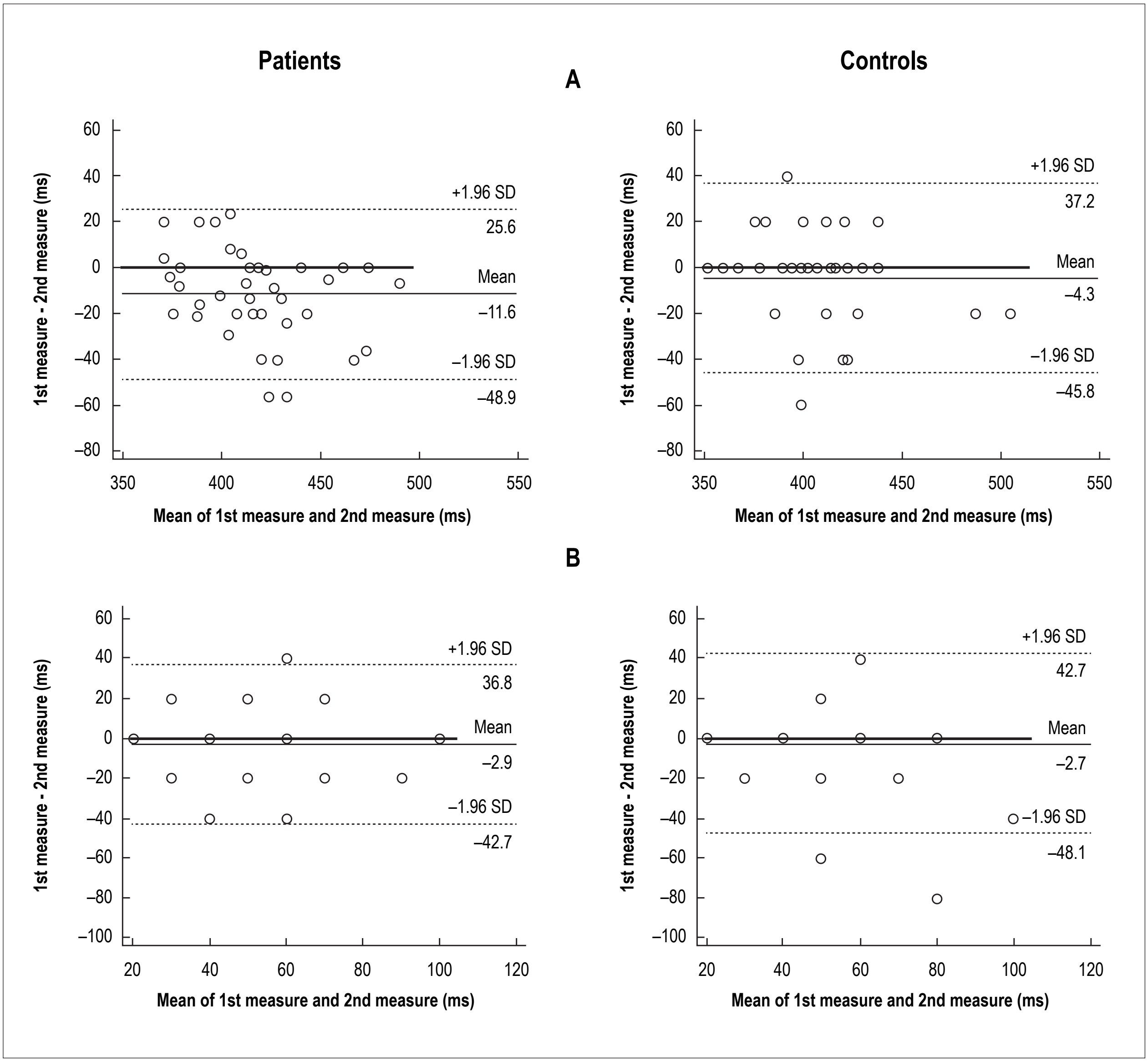

Figure 2 – *Intra-observer concordance (Bland Altman analysis of agreement) of measures of corrected QT interval, QTc (panel A) and dispersion of QTc, QTcd (panel B) in 41 hemodialysis patients and 37 controls of the study. Data refer to observer 1. Number of markers can be lower than the number of participants due to overlapping of markers.*

patients, ischemic alterations may have prevailed upon muscle hypertrophy as mechanism affecting repolarization.

The link between LVH and prolonged QT found in HD patients in the present study has previously been demonstrated by a number of authors in patients with hypertension and hypertrophic cardiomyopathy[13] and also in HD patients.[21,23,24] However, the correlation between QTcd and LVH in HD patients is uncertain with some studies reporting positive correlation[14,21,24] and others, corroborating our findings, absence of correlation between these variables.[22,30] The current review of literature on the electric heterogeneity in LVH allows us to conclude that electrical disturbances do indicate ventricular structural abnormalities.[39] The relationship between LVH and prolonged QTc has a rational biological basis although the cause of the phenomenon has not been completely defined. In the hypertrophic myocardium, multiple pathological changes occur, such as myocardial fibrosis, myocyte hypertrophy, cell death, and neurohormonal dysregulation that may have an important effect on QTc prolongation.[40] The reasons for the contradictory results of the link between QTcd and LVH in the literature can probably be explained by the poor reproducibility and reliability of QTcd.

The present study carries some limitations such as the relatively small number of patients and the exclusion criteria. Further studies involving larger patient populations are needed to determine associations between alterations in QTc interval or its dispersion and LVH, and to determine the optimal time to measure these parameters (pre-dialysis, during dialysis, or after dialysis), as well as the standardization of cut off points for these parameters, techniques of measurements and correction for heart rate.

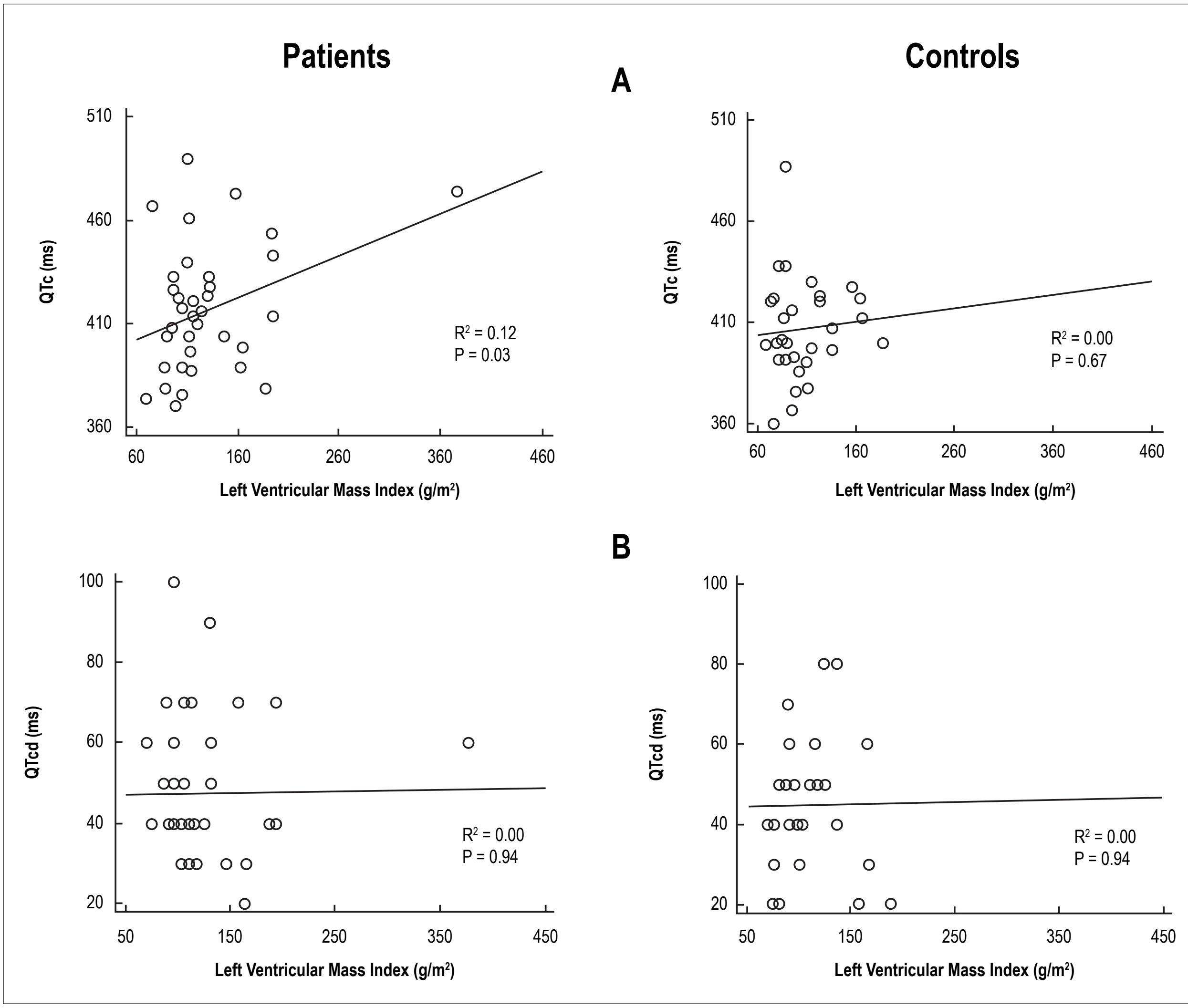

Figure 3 – *Linear regression of left ventricular mass index with corrected QT interval, QTc (panel A) and dispersion of QTc, QTcd (panel B) in 38 hemodialysis patients and thirty controls: data refer to observer 1.*

Conclusion

In conclusion, we found that QTc interval, in contrast to QTcd, is a reproducible and reliable measure and had a weak but positive correlation with LVMi in HD patients. Our findings suggest that precision of measurement can be improved if the mean of two measures are obtained using the tangent technique and by the application of Hodges formulae to correct QT interval.

Author contributions

Conception and design of the research: Alonso MAG, Carreira MAMQ, Lugon JR; Acquisition of data: Alonso MAG, Lima VACC, Carreira MAMQ; Analysis and interpretation of the data: Alonso MAG, Lima VACC, Carreira MAMQ, Lugon JR; Statistical analysis: Alonso MAG, Lima VACC, Lugon JR; Writing of the manuscript: Alonso MAG, Lugon JR; Critical revision of the manuscript for intellectual content: Alonso MAG, Carreira MAMQ, Lugon JR.

Potential Conflict of Interest

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

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Study Association

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Influence of the Tilt Angle of Percutaneous Aortic Prosthesis on Velocity and Shear Stress Fields

Bruno Alvares de Azevedo Gomes,[1,2,3] Gabriel Cordeiro Camargo,[1] Jorge Roberto Lopes dos Santos,[2] Luis Fernando Alzuguir Azevedo,[2] Ângela Ourivio Nieckele,[2] Aristarco Gonçalves Siqueira-Filho,[1] Glaucia Maria Moraes de Oliveira[1]
Programa de Pós Graduação em Cardiologia – Universidade Federal do Rio de Janeiro;[1] Pontifícia Universidade Católica do Rio de Janeiro (PUC-Rio);[2] Instituto Nacional de Cardiologia, INC/MS,[3] Rio de Janeiro, RJ – Brazil

Abstract

Background: **Due to the nature of the percutaneous prosthesis deployment process, a variation in its final position is expected. Prosthetic valve placement will define the spatial location of its effective orifice in relation to the aortic annulus. The blood flow pattern in the ascending aorta is related to the aortic remodeling process, and depends on the spatial location of the effective orifice. The hemodynamic effect of small variations in the angle of inclination of the effective orifice has not been studied in detail.**

Objective: **To implement an *in vitro* simulation to characterize the hydrodynamic blood flow pattern associated with small variations in the effective orifice inclination.**

Methods: **A three-dimensional aortic phantom was constructed, reproducing the anatomy of one patient submitted to percutaneous aortic valve implantation. Flow analysis was performed by use of the Particle Image Velocimetry technique. The flow pattern in the ascending aorta was characterized for six flow rate levels. In addition, six angles of inclination of the effective orifice were assessed.**

Results: **The effective orifice at the –4° and –2° angles directed the main flow towards the anterior wall of the aortic model, inducing asymmetric and high shear stress in that region. However, the effective orifice at the +3° and +5° angles mimics the physiological pattern, centralizing the main flow and promoting a symmetric distribution of shear stress.**

Conclusion: **The measurements performed suggest that small changes in the angle of inclination of the percutaneous prosthesis aid in the generation of a physiological hemodynamic pattern, and can contribute to reduce aortic remodeling. (Arq Bras Cardiol. 2017; 109(3):231-240)**

Keywords: **Heart Valve Prosthesis Implantation; Regional Blood Flow; Hemodynamics; Shear Stress.**

Introduction

Transcatheter Aortic Valve Implantation (TAVI) has been introduced by Cribier et al.[1] as an alternative to treat individuals with severe aortic valve stenosis at high surgical risk. With the development of new systems of percutaneous heart valve implantation, the use of TAVI for patients at intermediate surgical risk has been a worldwide trend.[2-4] Because of the nature of the implantation procedure, a variation in prosthetic valve placement is expected.[5] In addition, eccentric calcifications in the aortic annulus can influence the final orientation of the valve prosthesis. Valve placement will define the spatial location of its effective orifice in relation to the aortic annulus, and will determine the likelihood of generating eccentric flow in the vascular lumen.[6]

Mailing Address: Gláucia Maria Moraes de Oliveira •
Universidade Federal do Rio de Janeiro – R. Prof. Rodolpho P. Rocco, 255 – Prédio do HU 8º andar – sala 6, UFRJ. Postal Code 21941-913, Cidade Universitária, RJ – Brazil
E-mail: glauciam@cardiol.br, glauciamoraesoliveira@gmail.com
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Several studies have shown that the anatomical characteristics of the aortic root influence blood flow in the ascending aorta.[7] In addition, the changes in blood flow pattern after TAVI represent an important aspect that has not been studied in details.[5] Studies suggest that eccentric blood flow is related to the aortic remodeling process, such as dilatation and aneurysmal formations.[8-10]

In vitro simulations that preserve the anatomy of the aorta (patient-specific) can contribute to a better understanding of the blood flow changes produced by variations in the effective orifice inclination. Contrary to *in vivo* studies, *in vitro* simulations enable proper control of flow geometry and contour conditions, providing a systematic assessment of the blood flow response to valve placement variations.

So far, only one study[11] using flow-sensitive cardiovascular magnetic resonance imaging (4D flow MRI)[12] has reproduced the anatomy of the aorta of a patient and has assessed the changes in blood flow produced by variations in the effective orifice inclination. The objective of the present study was to implement an *in vitro* simulation to characterize the hydrodynamic pattern of blood flow associated with small variations in the effective orifice inclination.

Methods

This is a descriptive study of *in vitro* simulation of blood flow in a three-dimensional (3D) aortic model. For that purpose, a vascular phantom was constructed based on the tomographic angiography of the aorta of one patient submitted to TAVI. The present study was approved by the Research Ethics Committee of the institution. The patient was a 77-year-old male with severe degenerative aortic stenosis, mild ventricular dysfunction, and New York Heart Association functional class III.

Tomographic angiography of the aorta was performed with a Somatom Sensation 64-channel tomography device (Siemens, Germany). Tomographic slices from the aortic annulus to the distal segment of the thoracic aorta were selected. The DICOM images were transferred to the Mimics software (Materialise, Belgium) to implement the segmentation of the aortic region of interest. After the segmentation process, the digital file was exported to.*STL* (stereolithography) format to perform the 3D printing, with the Stratasys Fortus 400 mc Systems equipament (Stratasys, USA), using the ABS-M30 Affordable FDM thermoplastic material (Stratasys, USA). The 3D model was printed in a real scale, and its dimensions were confirmed via measurements taken on the tomographic angiography of the aorta (Figure 1).

The 3D aortic model was used to build a silicone phantom, with which the *in vitro* simulation of blood flow was implemented. The 3D model was positioned in a rectangular reservoire, built with plexiglass plaques. Liquid silicone elastomer was added to that reservoire, involving the aortic model. After 24 hours, the silicone elastomer was solid, allowing the extraction of the 3D model. A longitudinal cut was performed in the lateral walls of the elastomer block, dividing it into two halves. Then, the 3D model was removed from the silicone phantom, and the two halves were reconnected. To maintain proper alignment and to preserve the original anatomy of the aorta, five metallic rods, crossing the entire set, were used to guide the reassembly of the phantom. After reuniting the two halves of the phantom, connectors of the hydraulic circuit allowed the test solution to flow through the silicone model.

The Sylgard 184 silicone elastomer (Dow Corning, USA) was chosen because of its optical properties, and an image technique with laser was used to measure the flow patterns. That silicone has a refraction index (n = 1,417) close to that of the test solution chosen for the assays, an aqueous mixture of glycerine (60% glycerine, n = 1,420).[13] The test solution was drained into a closed circuit through the hydraulic instalation, boosted by a constant-volume pump, NEMO 4501140 (NETZSCH of BRASIL, Brazil). The flow rate was adjusted by controlling the frequency of pump rotation, using a frequency inversor CFW 08 (WEG, Brazil).

Figure 1 – *Three-dimensional aortic model. Model in ABS-M30 Affordable FDM thermoplastic material (Stratasys, USA).*

The flow was directed to the aortic phantom, with inflow in the vascular lumen occurring in the position equivalent to the aortic annulus, where a nozzle was connected to the phantom, representing the aortic prosthesis with full opening of its leaflets. The inner area of that nozzle measured 1.5 cm^2, based on the effective orifice of the patient's prosthesis, obtained via transthoracic echocardiography. The aortic phantom had the following outflow points: brachiocephalic trunk, left common carotid artery, left subclavian artery, and thoracic aorta.

The Particle Image Velocimetry (PIV) technique was chosen for flow analysis.[14] The particles that served as flow tracers were constituted by silver-coated hollow glass espheres of approximately 13 μm of diameter, and were addeded to the aqueous glycerine solution. A dual-cavity laser (BIG SKY Nd: YAG, 120 mJ, Quantel, USA) was the illumination source used, generating a 0.5-mm-thick light plane. A digital camera (PIVCAM 10-30, TSI, USA) captured synchronized images of the particles in the region between the aortic annulus and the middle ascending aortic segment. For each implemented hydrodynamic state, 3000 images of the tracers were captured, producing 1500 instantaneous velocity fields. The mean velocity and shear rate fields were calculated based on those instantaneous fields. Cross-correlation was the process used to determine the displacement of the tracers, by use of the INSIGHT 3G software (TSI, USA). Each velocity vector was obtained for an area of 32x32 pixels in the image, corresponding to a 2x2-mm resolution in the real flow.[14]

The PIV technique produced two-dimensional velocity fields. To have a 3D characterization of the aortic flow, the measurements were taken in four different planes. The central measuring plane was placed as to coincide with the central line of the effective orifice, crossing the right coronary ostium, and encompassing the main flow inside the aortic phantom. In addition, the velocity measurements were taken in three other planes, 4 mm apart from each other. Two of those planes were placed towards the dorsal region and one was placed towards the ventral region.

Because of the rapid blood flow acceleration at the beginning of the ventricular systole, it was hypothesized that significant changes in shear stress occur during that period.[15] Thus, the present study was designed to characterize the flow in the initial third of the ventricular systole. For that purpose, the following values of continuous flow were used: 0.8; 1.6; 2.6; 3.3; 4.0 and 5.3 liters per minute (L/min). Considering the properties of the test solution and the inner diameter of the effective orifice, the Reynolds numbers corresponding to each flow level were 195, 390, 630, 800, 970 and 1285, respectively.

The variation in the inclination of the effective orifice could be assessed by building a spindle inclination mechanism, comprising a threaded rod coupled to a 0-25-mm micrometer (Mitutoyo, Japan). In one extremity of that rod, a joint allowed coupling the spindle inclination mechanism to the entrance nozzle that was connected to the aortic phantom. When a translation movement was imposed to the spindle inclination mechanism, there would be a change in the effective orifice inclination. For flows of 2.6 and 3.3 L/min, the following angles of inclination were implemented: –4°, –2°, 0°, +1°, +3°, and +5°. The zero angle of inclination corresponded to the coincidence of the central line of the effective orifice with the central line of the aortic annulus. The negative angles tilted the main flow towards the right coronary ostium, while the positive angles tilted the main flow towards the posterior wall (Figure 2).

Results

The results of the analysis of the flow between the aortic annulus and the middle ascending aortic segment are now presented. Because the software used to implement the PIV technique provides no information on the physical boundaries limiting the flow, an image of the vascular model was overlapped with a typical velocity field. Figure 3 shows the anatomical structures close to the flow area in the aortic phantom.

The following results include the velocity and shear rate fields for the four measurement planes described. For each plane, the results are presented for six flow rate values, ranging from 0.8 to 5.3 L/min. Subsequently, for the central plane, the results will explore the effect of the variation in the effective orifice tilt angle.

Velocity field

Figure 4 shows the results for the mean velocity fields measured in the aortic phantom for four different planes. For each plane, six flow rate values are shown. The velocity vectors are colored according to their magnitude (meters per second – m/s), based on the scale at the right side of the figure.

The experimental tests represented the initial third of the ventricular systole, reaching maximum instantaneous velocities of approximately 1.2 m/s. For all velocity fields, the color scale of magnitude was maintained fixed, aiming at comparig between the different hydrodynamic states. Although the measures reached 1.2 m/s, the color scale was adjusted between 0 and 0.4 m/s, enabling the comparison between different cases, because, in the ventral plane, the low velocity values predominated. For each plane of measurement, one qualitative analysis of flow is shown.

4-mm ventral plane. For the flow rates of 2.6 and 3.3 L/min, the flow is directed towards the anterior wall. As the flow rate increases to 4.0 and 5.3 L/min, a larger part of the main jet acquires a centralized configuration, reaching a velocity of 0.4 m/s, at a flow rate of 5.3 L/min (Figure 4a).

Central plane. In this plane, the main jet is well defined to the flow rate of 1.6 L/min, and markedly inclined towards the anterior wall. As the flow rate increases, the main jet widens, showing a mild trend towards flow centralization (Figure 4b).

4-mm dorsal plane. In the first dorsal plane, the main jet is well defined as a dominant flow structure. From the flow rate of 3.3 L/min, maximum velocity is observed from the sinotubular junction to the middle ascending aortic segment. As the flow rate increases to 4.0 and 5.3 L/min, the maximum velocity region increases, seen as the dominance of the red color region (Figure 4c).

8-mm dorsal plane. In this plane, a continuous maximum velocity region is observed for the flow rate of 2.6 L/min, occupying the area from the sinotubular junction to the middle ascending aortic segment. In this plane, for all flow rate levels, left inclination towards the anterior wall is seen. The analysis of the

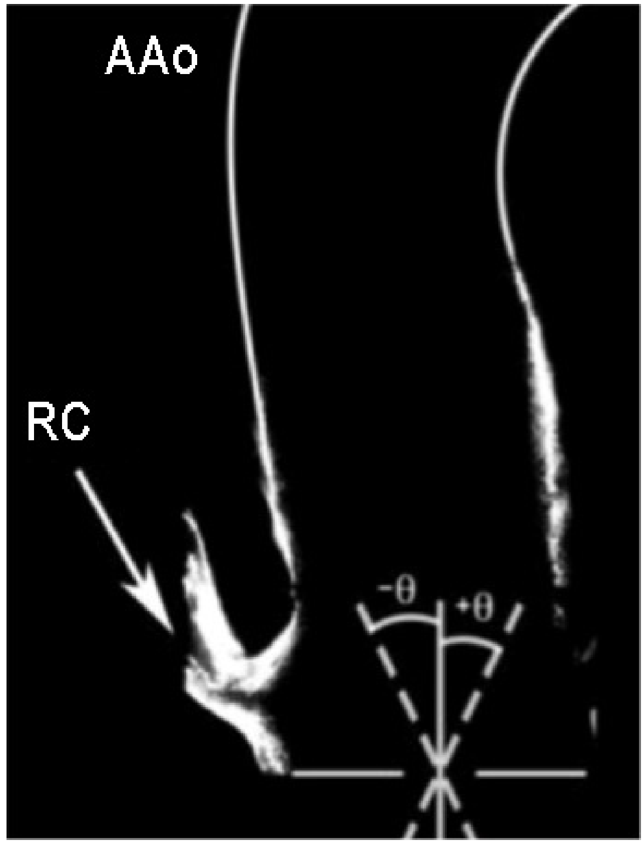

Figure 2 – *Angle of inclination of the effective orifice. AAo: ascending aorta; RC: right coronary artery; θ: angle of inclination.*

velocity field for the flow rate of 5.3 L/min clearly shows that the main jet falls on the anterior wall, as seen by the large maximum velocity area (Figure 4d).

Shear rate

The shear rate fields, calculated from the velocity fields shown in Figure 4, are now presented. As previously performed for the velocity fields, in Figure 5, an image of the vascular phantom was overlapped with a shear rate field to make the interpretation of results easier.

The results of shear rate are shown in Figure 6, being exhibited for the same planes and flow rates of the velocity fields. The color scale in the figure represents the shear rate magnitude, ranging from 0 to 15 s^{-1}.

4-mm ventral plane. In the ventral plane, a high shear rate region is identified at the flow rate of 2.6 L/min. At 3.3 L/min, maximum shear rate occurs, as indicated by the red band, which is elongated and leans towards the anterior wall. At higher flow rates, 4.0 and 5.3 L/min, the red band extends from the top to the bottom of the image. High shear rate regions are found close to the effective orifice, in the lower part of the figure (Figure 6a).

Central plane. In this plane, maximum shear is already identified, even in an incipient manner, at the flow rate of 0.8 L/min. From the flow rate of 1.6 L/min, the maximum shear stress band occupies the entire extension of the images. At subsequent flow rates, progressive widening of that area is seen (Figure 6b).

4-mm dorsal plane. From the flow rate of 2.6 L/min, maximum shear stress bends towards the anterior wall. In addition, expressive widening of that band is observed as the flow rate increases. Despite the pattern of inclination to the left, it is worth noting the presence of a small sector with maximum shear stress at the right upper part of the images, beginning at the flow rate of 2.6 L/min (Figure 6c).

8-mm dorsal plane. In this plane, widening of the maximum shear region is also seen from the flow rate of 2.6 L/min. The inclination of the high shear region towards the left upper part of the images remains, showing a preferential direction towards the anterior wall (Figure 6d).

Influence of the angle of inclination of the effective orifice

The influence of the inclination of the effective orifice on flow characteristics was assessed by use of measurements taken in the central plane, for the flow rates of 2.6 and 3.3 L/min. The angles of inclination ranged from –4° to +5°, as shown in Figure 2.

Velocity and shear rate fields

Figure 7 shows the influence of the angle of inclination of the effective orifice on the velocity and shear rate fields. For 2.6 L/min, at a zero angle of inclination, the main flow

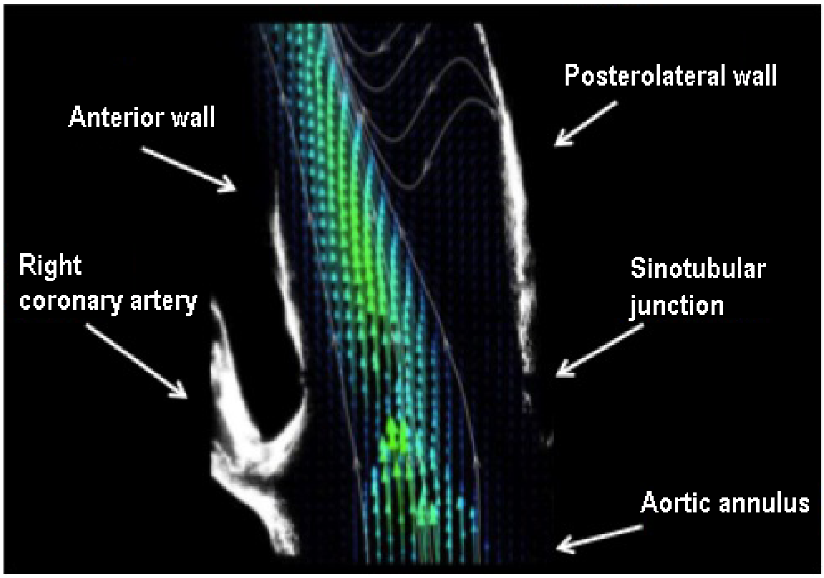

Figure 3 – *Velocity field measured inside the aortic phantom.*

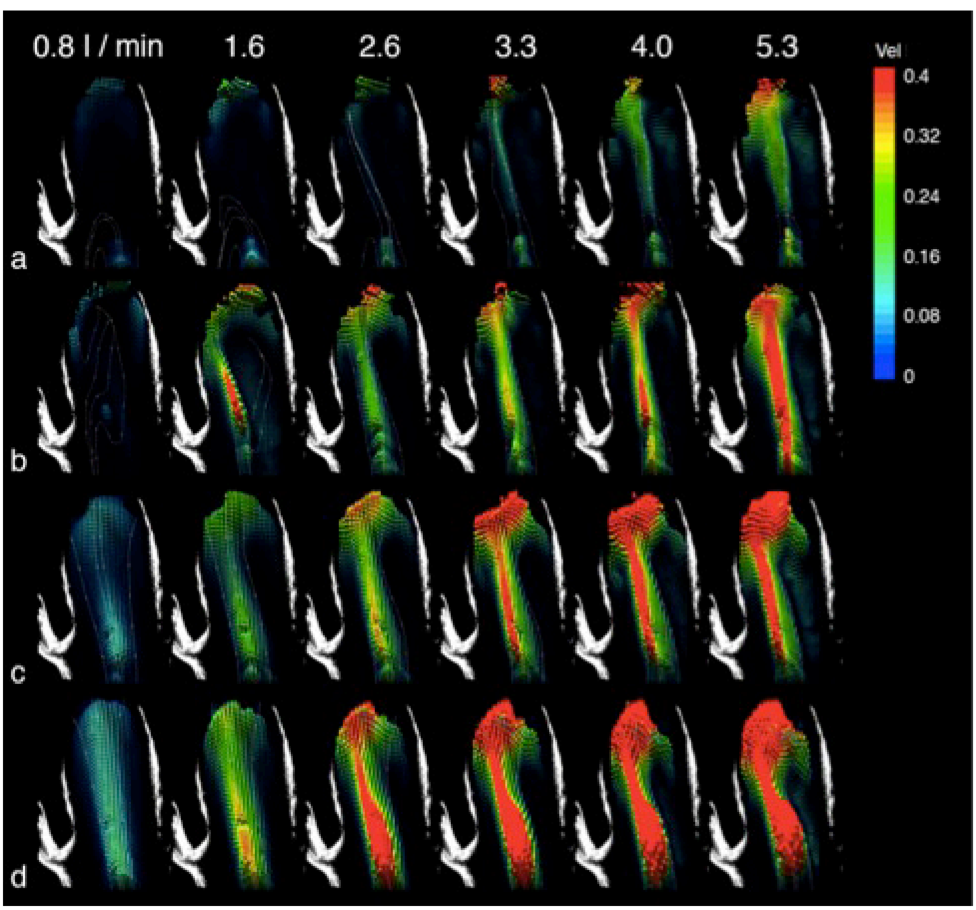

Figure 4 – *Velocity fields in the measurement planes. Velocity fields in the (a) 4-mm ventral, (b) central, (c) 4-mm dorsal, and (d) 8-mm dorsal planes. Velocity magnitude in meters per second.*

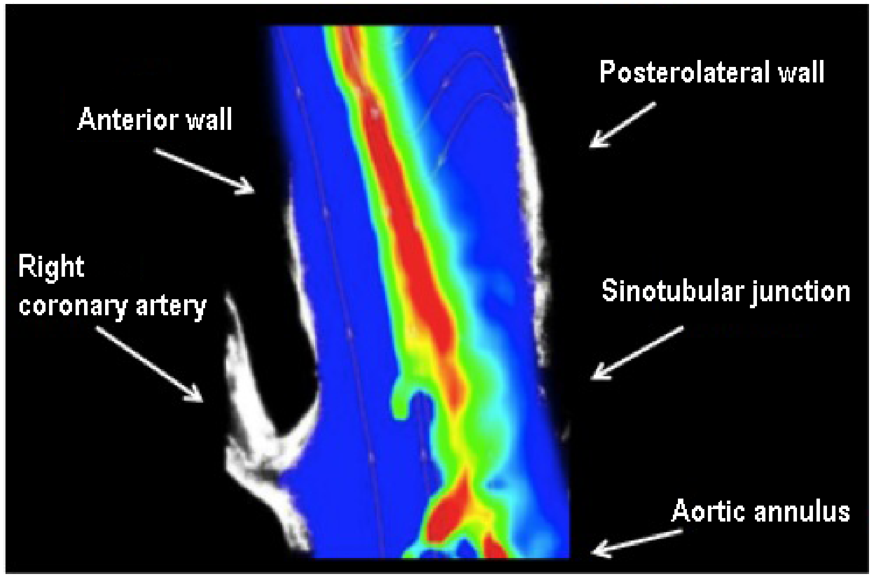

Figure 5 – *Shear rate inside the aortic phantom.*

was directed to the left, reaching the anterior wall in the middle ascending aortic segment. When the effective orifice was placed at negative inclinations (–4° and –2°), that flow eccentricity was exacerbated. For small positive inclinations (+1°, +3° and +5°), a trend towards flow centralization was observed. With that mild change in inclination, the main flow is directed to the posterolateral wall (Figure 7a).

At 3.3 L/min, the velocity fields show that, for the negative angles, the main jet decreased its width as compared to that at zero angle of inclination. The negative angles show similar velocity magnitudes, with a left inclination. When the inclination reaches positive values, a trend towards centralization of the main jet is observed. Thus, higher velocity values appear inside the jet, as seen by the red colored regions. The velocity patterns are similar at the angles +1° and +3°, maintaining a left inclination in the upper half of the image. The +5° angle of inclination shows a more significant centralization of the main jet (Figure 7b).

Figures 7c and 7d show the results for shear rate. At 2.6 L/min, for the negative inclinations, the red color bands are narrower as compared to those of other angle positions. For positive inclinations, maximum shear area widening and centralization are seen (+3° and +5°). For the +5° inclination, the maximum shear region is maintained close to the central line of the aortic model (Figure 7c).

The analysis of the shear rate results at the 3.3-L/min flow rate indicates that, for negative inclinations, maximum shear shows a left inclination. In the positive inclinations of +1° and +3°, maximum shear is located in the central region. Proximity of the high shear region to the posterolateral wall is observed at the +5° angle, because the red band occupies the right side of the image (Figure 7d).

Discussion

In the present study, an *in vitro* simulation was performed to characterize the hydrodynamic pattern of blood flow during ventricular systole in a 3D aortic model representing the anatomy of a patient submitted to TAVI. In addition, by use of velocity and shear rate fields, we identified flow changes due to six variations in the angle of inclination of the effective orifice.

The optimization of percutaneous valve prosthesis implantation, in addition to its placement according to the patient's native flow pattern, can be a means of ensuring its best performance after TAVI.[16,17] The generation of a blood flow with a hemodynamic pattern closer to the physiological one can have a beneficial impact on the patients' survival.[18,19]

The qualitative analysis of the velocity and shear rate fields for each plane analysed in the present study clearly shows the 3D nature of the flow inside the aortic model. These data stress the importance of using realistic models of aorta geometry, in addition to the limitations of *in vitro* studies that represent the aorta using circular and axisymmetric models.[5]

Groves et al.[5] have studied the effect of the variations in the axial placement of percutaneous prostheses. The aorta was represented with an plexiglass circular tube of 30-mm inner diameter. For a 4-L/min flow rate, only the 5-mm displacement below the aortic annulus resulted in low shear stress values, in addition to a symmetrical distribution.[5] In the present study, the effective orifice remained positioned less than 5 mm from the aortic annulus. However, because our model preserved the aorta anatomy, the results differed with respect to the planes assessed, which were not axisymmetric as in the study by Groves et al.[5]

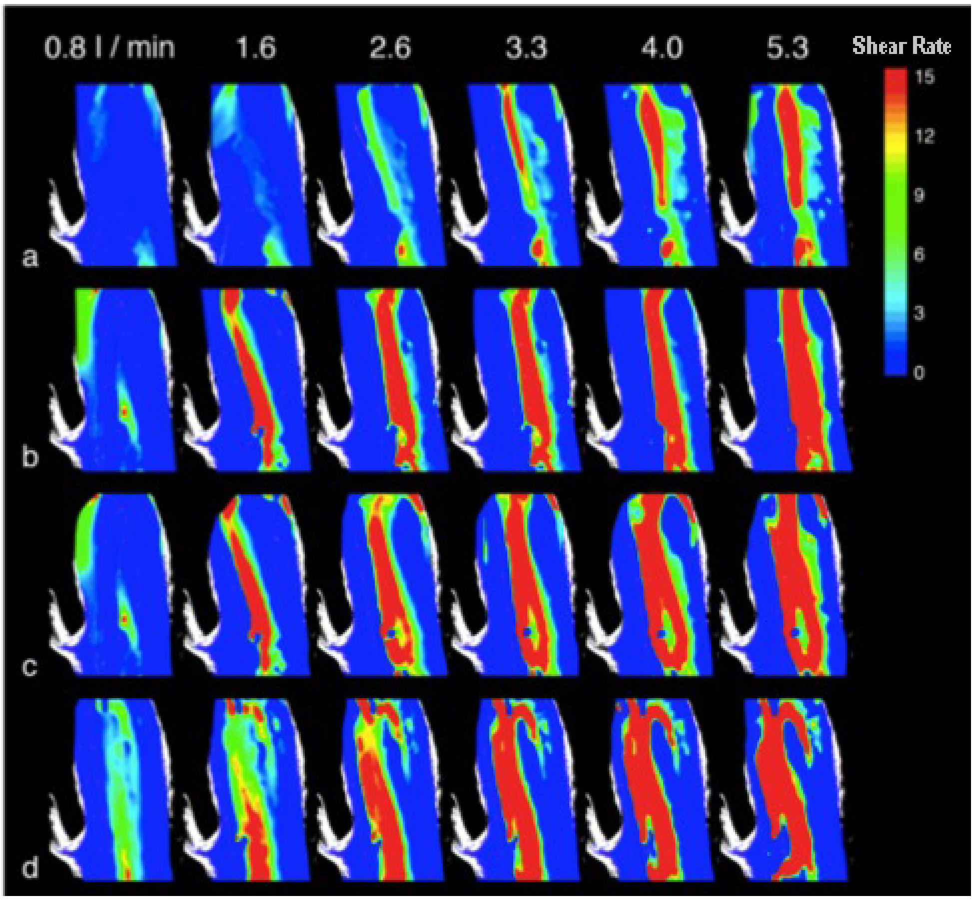

Figure 6 – *Shear rate in the measurement planes. Shear rate in the (a) 4-mm ventral, (b) central, (c) 4-mm dorsal, and (d) 8-mm dorsal planes. Shear rate magnitude in s^{-1}.*

Groves et al.[5] and Wilton et al.[20] have considered the hypothesis that high shear stress, in addition to its asymmetric distribution, would be related to aortic dilatation and a higher chance of dissection.[5,10,20,21] Based on that hypothesis, optimizing the axial placement and the effective orifice inclination would be desirable, so that symmetric and low-magnitude shear stress distribution would be obtained. An axial placement of less than 5 mm from the aortic annulus associated with positive angles of inclination would be suggested in this particular case. In addition, Groves et al.[5] have reiterated that high shear stress levels downstream the prosthesis could contribute to reduce its durability, because of higher mechanical stress, emphasizing the importance of optimizing the prosthesis placement.

Trauzeddel et al.[7] have assessed post-TAVI ascending aortic blood flow patterns, which were compared to those of patients submitted to conventional stented aortic valve replacement (AVR) and those of healthy individuals. That study showed that both TAVI and AVR resulted in maximum shear stress values in the right anterior wall, while minimum shear stress values were found in the left posterior wall. Healthy individuals, however, showed physiological central blood flow and a symmetric distribution of shear stress along the aortic circumference.[7] The maximum shear stress distribution in the anterior wall of patients submitted to TAVI and AVR coincides with the results of the *in vitro* simulation of the present study for the negative angles of inclination of the effective orifice. In the experimental model, that angle of inclination could be modified in the search for a configuration that produced a central blood flow pattern. As the results presented indicate, a decrease in shear stress in the anterior wall was obtained with small positive inclinations. For example, at the +3° angle, the maximum shear stress region remained restricted to the central portion of the aortic phantom. When the angle of inclination was increased to +5°, the maximum shear stress region approached the posterolateral wall.

The present analysis was limited to the anatomic findings of one patient. This simulation, however, represented a real 3D anatomy, providing a significant advance in relation to the circular and axisymmetric models used in previous studies.[5,6]

In the present study, only the initial third of the ventricular systole was represented. However, the highest prevalence of high shear stress values in the ascending aorta is known to occur during the systole. In addition, because that period of the cardiac cycle is characterized by sudden changes

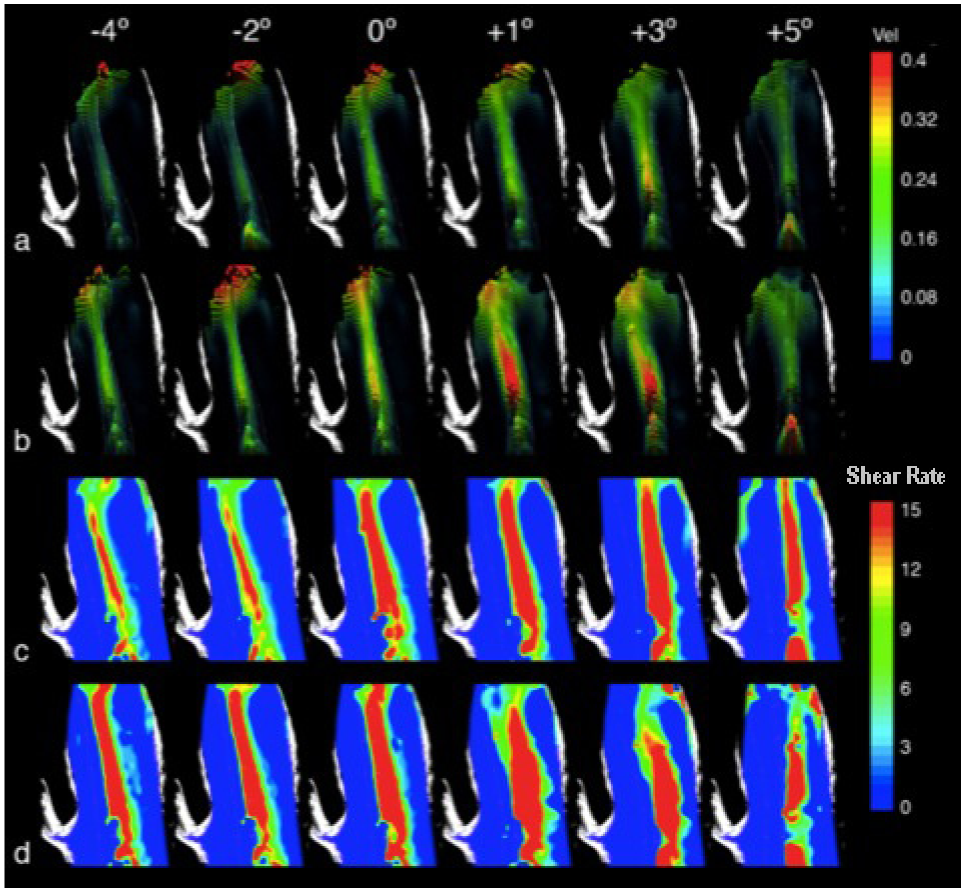

Figure 7 – *Velocity and shear rate fields for (a, c) 2.6 L/min and (b, d) 3.3 L/min. Inclination of the effective orifice: –4°, –2°, 0°, +1°, +3°, and +5°.*

in velocity, a rapid variation in shear stress values is also expected.[15] In this study, a segment of pulsatile blood flow, more precisely the initial third of the ventricular systole, was represented by six different continuous blood flow levels. With this approach, some structures of secondary blood flow might not have been captured. However, in cardiovascular science, the various stages of pulsatile blood flow are commonly modelled with an increasing sequence of continuous blood flow values.[11,22]

Based on these findings, projects of new prostheses, with the ability to change the angle of inclination of the effective orifice, can be proposed, enabling the generation of a centralized blood flow in the ascending aorta, mimicking a physiological hemodynamic pattern.

Conclusion

The present study evidenced the 3D character of the blood flow pattern inside the vascular phantom, and identified a range of optimized values for the angle of inclination of the effective orifice. For small positive inclinations, a physiological centralized blood flow was obtained in the middle ascending aortic segment, eliminating the high mechanical shear stress values in the anterior wall, which prevailed in the negative inclinations of the effective orifice (–4° and –2°). In the placements with positive inclinations, the regions with high shear stress levels were maintained close to the central line of the vascular phantom.

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Author contributions

Conception and design of the research: Gomes BAA, Camargo GC, Lopes J, Azevedo LFA, Oliveira GMM; Acquisition of data: Gomes BAA; Analysis and interpretation of the data: Gomes BAA, Camargo GC, Azevedo LFA, Nieckele AO, Oliveira GMM; Writing of the manuscript: Gomes BAA, Camargo GC; Critical revision of the manuscript for intellectual content: Gomes BAA, Azevedo LFA, Nieckele AO, Siqueira-Filho AG, Oliveira GMM.

Potential Conflict of Interest

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

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Study Association

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Home Blood Pressure Monitoring as an Alternative to Confirm Diagnoses of Hypertension in Adolescents with Elevated Office Blood Pressure from a Brazilian State Capital

Thaís Inacio Rolim Póvoa,[1,2] Thiago Veiga Jardim,[1] Carolina de Souza Carneiro,[1] Vanessa Roriz Ferreira,[1] Karla Lorena Mendonça,[1] Polyana Resende Silva de Morais,[1] Flávia Miquetichuc Nogueira Nascente,[1] Weimar Kunz Sebba Barroso de Souza,[1] Ana Luiza Lima Sousa,[1] Paulo César Brandão Veiga Jardim[1]

Liga de Hipertensão Arterial – Universidade Federal de Goiás;[1] Escola Superior de Educação Física e Fisioterapia de Goiás (ESEFFEGO) – Universidade Estadual de Goiás (UEG),[2] Goiânia, GO – Brazil

Abstract

Background: **Regional differences of using home blood pressure monitoring (HBPM) as an alternative to ambulatory blood pressure monitoring (ABPM) in hypertensive adolescents are unknown.**

Objectives: **Define if HBPM is an option to confirm diagnoses of hypertension in adolescents from a Brazilian capital with elevated office blood pressure (BP).**

Methods: **Adolescents (12-18years) from public and private schools with BP > 90th percentile were studied to compare and evaluate the agreement among office BP measurements, HBPM and ambulatory BP monitoring. Office BP measurements, HBPM and ABPM were performed according to guidelines recommendations. Semi-automatic devices were used for BP measurements. Values of p < 0.05 were considered significant.**

Results: **We included 133 predominantly males (63.2%) adolescents with a mean age of 15±1.6 years. HBPM systolic blood pressure and diastolic blood pressure mean values were similar to the daytime ABPM values (120.3 ± 12.6 mmHg x 121.5 ± 9.8 mmHg – p = 0.111 and 69.4 ± 7.7 mmHg x 70.2 ± 6.6 mmHg – p = 0.139) and lower than the office measurement values (127.3 ± 13.8 mmHg over 74.4 ± 9.5 mmHg – p < 0,001). The Bland-Altman plots showed good agreement between HBPM and ABPM.**

Conclusions: **HBPM is an option to confirm diagnoses of hypertension in adolescents from a Brazilian state capital with elevated office BP and can be used as an alternative to ABPM. (Arq Bras Cardiol. 2017; 109(3):241-247)**

Keywords: **Hypertension; Blood Pressure Monitoring, Ambulatory; Adolescent; Risk Factors.**

Introduction

Primary hypertension (HT) is no longer regarded as a rare phenomenon in childhood and adolescence.[1] It is strongly related to obesity, a condition that continues to increase in young population, therefore HT prevalence will continue to grow among them.[2] Blood pressure (BP) values are important markers in the evaluation of cardiovascular risk in adults,[3] however, for children and teenagers there is scarce information regarding different BP measurement methods, and only in the last decade[1] the interest in this subject has increased.

In Brazil, although many studies have assessed the prevalence of high blood pressure in adolescents in recent years, differences in measurement techniques and normalcy criteria according to regional differences make it difficult to know the actual prevalence. A systematic review of the literature found the prevalence ranging from 2.5 to 30.9%.[4] The national representative ERICA study,[5] evaluated 73.399 adolescents and identified a 9.6% prevalence of hypertension (values above the 95th percentile).

Investigate the viability and reliability of BP evaluation methods is necessary and contributes to clinical practice. For diagnosis, office BP measurements rank as the most common method and have a prognostic meaning for cardiovascular risk in adults. Nevertheless, BP values vary due to physiological and environmental stimulation, which indicates that a more accurate determination of BP values is needed. Identifying such variability may lead to more precise risk stratification, thus allowing early interventions initiatives.[6]

Taking multiple BP measurements within a short time period improves the reproducibility and increases the chances of obtaining accurate BP values. This repetition of measurements is possible with various BP monitoring methods, including ambulatory BP monitoring (ABPM), in which dozens of measurements are performed over a

Mailing Address: Thiago de Souza Veiga Jardim •
Rua B20 QD 13B LT 7. Postal Code 74885-614, Jardins Paris, Goiânia, GO – Brazil
E-mail: thiagoveiga@cardiol.br, thiagoloirin@hotmail.com
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24-hour period and is considered the gold standard,[7,8] or home BP monitoring (HBPM), in which some measurements are performed over a few days throughout the week. The use of ABPM has limitations due to its higher costs, on the other hand HBPM which may be a potential diagnostic alternative, needs more investigation when used in adolescents, particularly considering regional differences.[6,7,9,10] HBPM shows good viability if performed by the adolescents themselves or by a responsible adult with semi-automatic equipment and a specific protocol.[7]

The most common indication to use ABPM and HBPM in this particular subset of patients is for white coat hypertension (WCHT) diagnose, characterized by office BP measurement increased despite normal HBPM or ABPM values.[6,11] Another indication is to detect masked hypertension, in which normal office BP is identified in patients with elevated HBPM or ABPM values.[9,11]

To increase scientific knowledge regarding BP measurement methods for adolescents considering regional differences, the objective of this study was to compare BP values obtained from office measurements, HBPM and ABPM and to evaluate the agreement among these methods.

Methods

This was a cross-sectional study approved by the Research Ethics Committee of the institution (Register: 017/2010).

Subjects

Adolescents aged between 12 and 18 years with altered BP (> 90th percentile for the respective age, gender and height)[1] were identified by office measurement from a sample of 1025 young students from 26 schools. This was a representative sample of adolescents from a large city (1,302,001 inhabitants) in the Midwest of Brazil. Additionally, 33 normotensive adolescents were included. All subjects had an informed consent signed by their parents or legal guardians. The exclusion criteria were: physical handicap; pregnancy; chronic diseases (diabetes mellitus, kidney or heart disease); use of anti-hypertensive, antidepressants, anxiolytics, steroidal or non-steroidal anti-inflammatory drugs and contraceptives; and absence of sexual maturation (subjects with Tanner stages = 1).[12]

Anthropometric evaluation

The anthropometric evaluation was performed using the standardization suggested by the World Health Organization.[13] The measured variables were body weight, height and waist circumference. In addition, the body mass index (BMI) was calculated.

Blood pressure measurements

Office measurement

Office measurements were performed by trained health professionals, based on the 4th Task Force Technique.[1] The procedure took place at the schools, in two different moments (one-week interval) and with two measurements (with a three-minute interval) at each time point. For the analysis, the mean of the second measurements was considered. We utilized OMRON, model HEM-705CP semi-automatic equipment, which was validated for use with adolescents,[14] and cuffs in three different sizes (9x16 cm, 13x23 cm and 15x30 cm) were selected according to the adolescent's right arm circumference (80 to 100%).

Home Monitoring (HBPM)

The same equipment, cuffs and techniques that were used for the office measurements were used for HBPM. Adolescents received the device at school and were told to perform two measurements (with three-minute intervals) during the day (between 06:00 and 10:00 a.m.) and two at night (between 06:00 and 10:00 p.m.) over 6 days, for a total of 24 readings. The overall mean value was considered for analysis.

Ambulatory Monitoring (ABPM)

A *Spacelabs*® device model 90207 was used. The cuff size was the same of the office measurement and HBPM, and the exam was performed based on the American Heart Association technique.[15] The equipment was programmed to perform one measurement every 15 minutes during the day (07:00 to 23:00) and one measurement every 20 minutes at night (11:00 p.m. to 07:00 a.m.). The adolescents were instructed to keep their arms relaxed during inflation/deflation and to return after 24 hours of monitoring with a report containing their primary activities during that period. Records in which at least 70% of the measurements were valid were accepted, and for the analysis, the mean of daytime obtained values was considered.

Statistical analysis

Data were entered in duplicate and validated with Epi-Info (version 3.5.1), and the statistical analysis was performed with *SPSS* software (version 20.0; IBM Chicago, USA). The Kolmogorov-Smirnov test was used for data distribution evaluation and the paired Student's t test for the comparison of systolic and diastolic pressure values between the methods. The continuous variables with normal distribution are presented as means and standard deviations. Pearson`s correlation coefficient was used to evaluate the correlation between the blood pressure measurements. Values of $p < 0.05$ were considered significant. We generated Bland-Altman plots[16] to provide a visualization of the agreement between the measurements and a "mountain plot"[17] to provide information about the distribution of differences between the methods. The ABPM method (daytime measurement) was subtracted from the other methods to obtain the mountain plots. The Bland-Altman and mountain plots were produced using *Medcalc software* (Version 12.7.0).

Results

Among the 143 adolescents invited to participate the study, 133 (93%) accepted and 10 (7.0%) declined. No subject was excluded due to sexual maturation criteria. The final sample was composed of 133 adolescents, including 100 with altered BP and 33 normotensives. Overall, 63.2% were male with a mean age of 15 (± 1.6) years. Table 1 presents the sample characteristics.

HBPM presented mean SBP and DBP values that were similar to the daytime ABPM values and lower than the office measurement values. Office measurement presented higher mean values than those observed for daytime ABPM, and the correlation among the methods was moderate (Table 2).

The overall mean of 24-hour ABPM BP was 118.3 ± 9.1 mmHg for SBP and 66.4 ± 6.0 mmHg for DBP, which were significantly different than the overall mean of HBPM (SBP, $p = 0.009$; DBP, $p < 0.001$) and the office measurement ($p<0.001$ for SBP and DBP). A strong correlation ($r = 0.72$, $p < 0.001$) was found between SBP from 24-hour ABPM and HBPM, whereas a slight correlation ($r = 0.39$, $p = 0.005$) was found for DBP. There was also a correlation between the 24-hour ABPM and office measurement values ($r = 0.57$ for SBP and $r = 0.24$ for DBP; both with $p < 0.001$).

According to the Bland-Altman graphs, agreement was verified (and no systematic errors were identified) between HBPM and daytime ABPM for SBP and DBP (Figure 1-A); the means of the differences plotted in the central horizontal lines were close to zero (1.3 mmHg for SBP and 0.9 mmHg for DBP). Both daytime ABPM and HBPM agreed with the office measurement values; however, the magnitude was lower: daytime ABPM vs. office, difference in the means of 5.8 mmHg for SBP and 4.1 mmHg for DBP (Figure 1-B); HBPM vs. office, difference in the means of 7.0 mmHg for SBP and 5.0 mmHg for DBP (Figure 1-C).

From the mountain plots (Figure 2), with daytime ABPM as the reference (axis X), the differences between HBPM and ABPM were generally lower than those observed between the office measurement and daytime ABPM.

Discussion

This study provides initial information regarding the utilization of HBPM in a Brazilian sample composed exclusively of adolescents, mostly with BP levels higher than normal values. We have identified results similar to those in adults,[9,15,18-21] for whom office measurements present higher values than HBPM and ABPM for both SBP and DBP. The same phenomenon has already been identified in other studies,[22,-5] in hypertensive children and adolescents but only with SBP. In contrast to our results, office measurements were similar to HBPM for subjects over 12 years old according to Stergiou et al,[26] who examined a larger sample (n = 765); however, that study only observed normotensive children and adolescents. There is evidence[26,27] that the population type (hypertensive vs. normotensives) interferes with the results obtained by office measurement or HBPM.

Another important aspect of BP measurement is the equipment type, and in most studies, the oscillometric method was used. Moreover, analyzing the HBPM protocol is relevant because, currently, there is no consensus on the minimum number of measurements required for pediatric populations.

Table 1 – Sample characteristics (n = 133)

	Mean	Standard Deviation	Minimum	Maximum
Age (years)	15.0	±1.6	12	17
Body weight (kg)	65.5	±16.3	37.9	131.5
Height (cm)	167.0	±7.8	149.0	185.5
BMI (kg/m^2)	23.2	±4.8	15.9	42.5
WC (cm)	75.5	±10.9	58.0	120.0

BMI: body mass index; WC: waist circumference.

Table 2 – Comparison and correlation among office, home and ambulatory BP measurements (n = 133)

	Daytime ABPM	HBPM	p value*	r (p value)
SBP	121.5 ± 9.8	120.3 ± 12.6	0.111	0.70 (< 0.001)
DBP	70.2 ± 6.6	69.4 ± 7.7	0.139	0.60 (< 0.001)
	Daytime ABPM	**Office**		
SBP	121.5 ± 9.8	127.3 ± 13.8	< 0.001	0.60 (< 0.001)
DBP	70.2 ± 6.6	74.4 ± 9.5	< 0.001	0.45 (< 0.001)
	HBPM	**Office**		
SBP	120.3 ± 12.6	127.3 ± 13.8	< 0.001	0.75 (< 0.001)
DBP	69.4 ± 7.7	74.4 ± 9.5	< 0.001	0.53 (< 0.001)

*Values expressed as the mean ± standard deviation. SBP: systolic blood pressure (mmHg); DBP: diastolic blood pressure (mmHg). r- Pearson's correlation test. *paired Student's t test.*

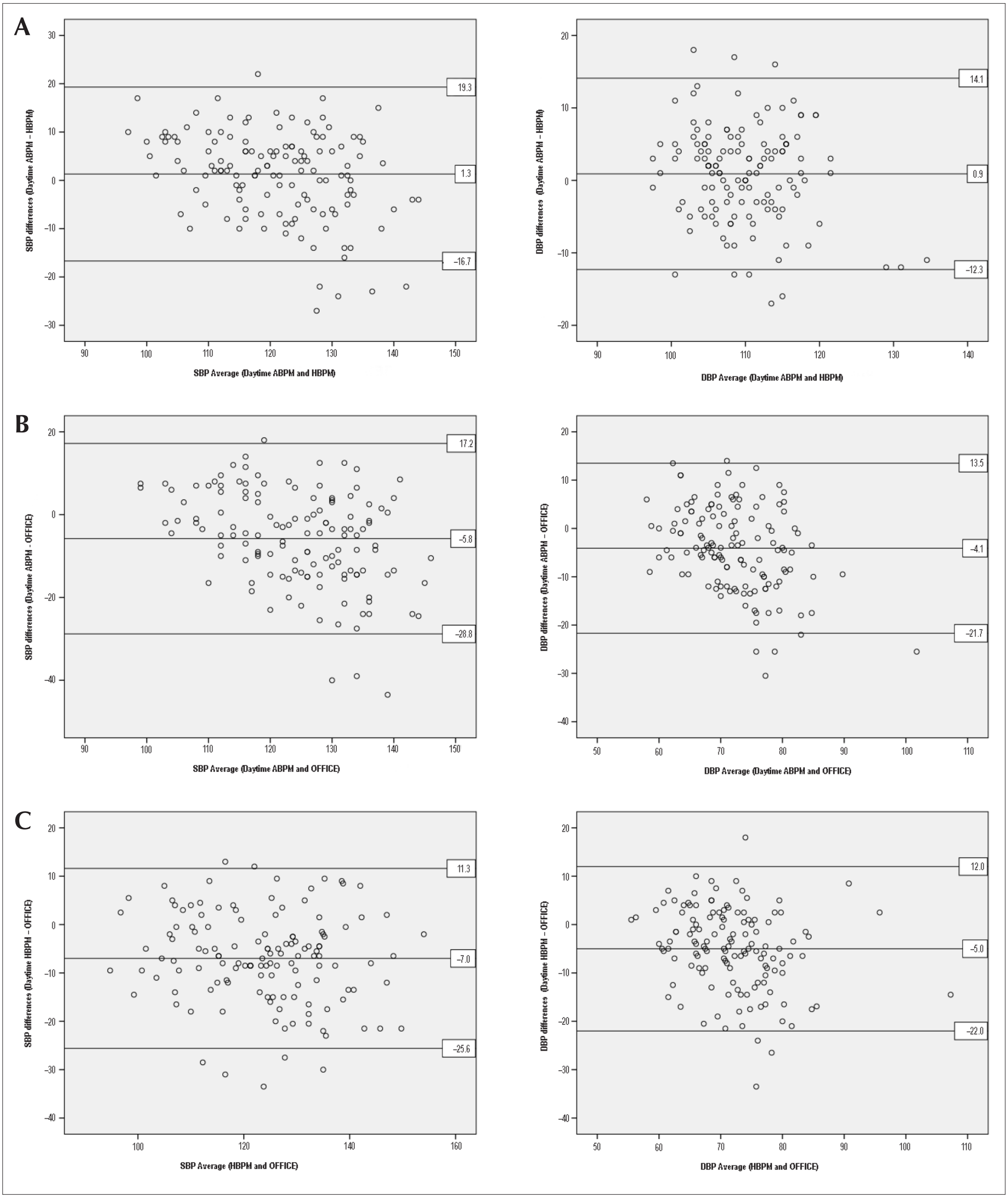

Figure 1 – *Bland-Altman plot agreement analysis between systolic and diastolic blood pressure (SBP and DBP) values (mmHg) determined by (A) HBPM and daytime ABPM, (B) daytime ABPM and office and (C) HBPM and office.*

In the present study, we used a total of 24 measurements (with a minimum of 12 measurements) over 6 days, whereas Stergiou et al[26] opted for a 12-measurement protocol (with a minimum of 2 measurements) over 3 days. This lower number of measurements in HBPM may have contributed to its agreement with the office measurements.

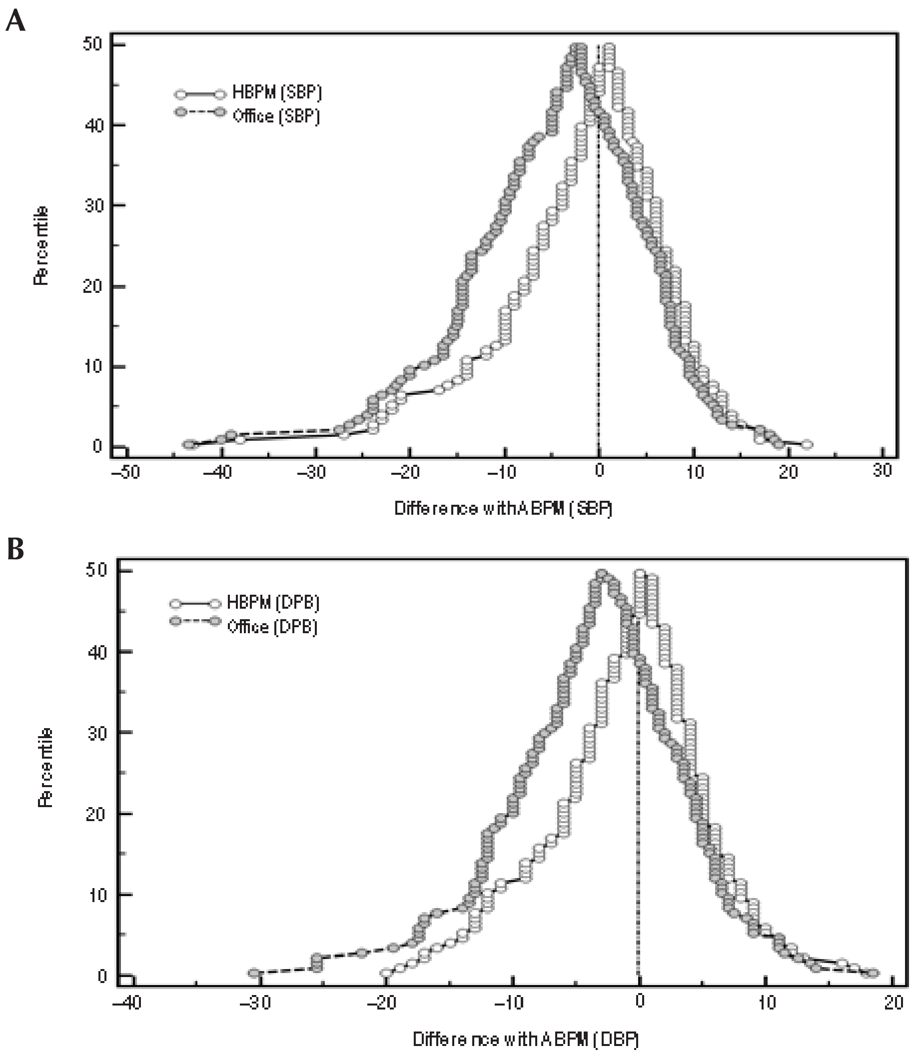

Figure 2 – *Mountain plots for agreement between (A) systolic blood pressure (SBP) and (B) diastolic blood pressure (DBP) determined by daytime ABPM (reference) and measured by HBPM and office measurement.*

Some studies[23,28-30] have shown lower HBPM values than daytime ABPM in children and adolescents, which may be explained by the high physical activity levels during childhood, which can increase BP values.

In this study, the result was different, as the BP values measured by HBPM were similar to those obtained by daytime ABPM, which is a commonly observed pattern for adults.[18,19] This finding is probably related to the fact that the sample consists only of adolescents, who have lower levels of physical activity during the day when compared to children.

Regarding the agreement among methods, a significant number of the studies used the correlation coefficient as an agreement indicator; however, the intrinsic variability of BP renders this index, by itself, inappropriate and requires a variability analysis among measures, such as that accomplished by Bland-Altman plots.[12] The strength of a correlation between two variables does not necessarily indicate agreement between them. In this study, we showed that the correlation among the three methods was moderate; however, using Bland-Altman plots,[16] we verified that there was no systematic error among the three methods, particularly between HBPM and daytime ABPM, which showed a difference of zero between the means of the systolic and diastolic pressures. This finding suggests that HBPM may be used as a substitute for ABPM when necessary. Nevertheless, because ABPM is the gold standard, it is still considered the first choice for confirming a diagnosis after detection of high BP by office measurements.

In adults, HBPM shows better reliability and agreement with ABPM than office measurement.[19,31] In adolescents, we observed a similar phenomenon, which has also been verified in other children and teenage populations, in which HBPM presents better reproducibility than office measurements.[25,32]

The differences between office measurements and the other methods may result in the overestimation of BP values and, consequently, label adolescents as hypertensive when they are actually normotensive. When there is no diagnostic confirmation with other types of evaluation such as HBPM or ABPM, adolescents may be misdiagnosed, with all its social and economic consequences, and even engage in unnecessary treatment by taking medicine. For example, in a study by Hornsby et al,[33] 44% of the children evaluated as hypertensive by office measurements were reclassified and considered as white coat hypertensive after ABPM.

It has been suggested that office measurements must be a screening method for adolescents and for those who present SBP or DBP values in the > 90th percentile an out-of-office blood pressure method must be performed to confirm the diagnosis. ABPM is the preferred option and HBPM an alternative.[1,27]

HBPM is more comfortable, easy to perform and has a lower cost than ABPM. In this study, daytime ABPM was similar to HBPM. Therefore, HBPM represents an acceptable alternative for a more accurate diagnosis. Nevertheless, when available and financially viable, ABPM should be the first option because it provides a more comprehensive evaluation.

This study was limited by the use of normal values of office measurements proposed for the American population,[1] as Brazilian studies proposing normal values for adolescents are lacking in the literature. A similar limitation for the HBPM use exists, since the normalcy data for adolescents is based in one study conducted with European students.[26]

Another potential limitation was the inclusion of adolescents enrolled in schools, which excluded adolescents who were out of school. Since the sample studied was obtained from both public and private schools, and since the education system coverage in Brazil is reported as almost universal, this limitation was attenuated.[34]

Longitudinal studies with adolescents that compare the three methods – office, home and ambulatory – and establish adequate normality criteria for different regions of the world are still required.

Conclusion

HBPM is an alternative option to confirm diagnosis of hypertension with results comparable to ABPM in adolescents from a Brazilian state capital with altered BP values.

Author contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Statistical analysis, Obtaining funding, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Jardim TSV, Povoa TIR, Carneiro CS, Roriz V, Mendonça KL, Morais PRS, Flávia Nascente MN, Souza WKSB, Sousa ALL, Jardim PCBV.

Potential Conflict of Interest

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

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Study Association

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Original Article

Evaluation of Quality of Life in Patients with and without Heart Failure in Primary Care

Antonio José Lagoeiro Jorge, Maria Luiza Garcia Rosa, Dayse Mary da Silva Correia, Wolney de Andrade Martins, Diana Maria Martinez Ceron, Leonardo Chaves Ferreira Coelho, William Shinji Nobre Soussume, Hye Chung Kang, Samuel Datum Moscavitch, Evandro Tinoco Mesquita

Curso de Pós-Graduação em Ciências Cardiovasculares – Universidade Federal Fluminense (UFF), Niterói, RJ – Brazil

Abstract

Background: **Heart failure (HF) is a major public health issue with implications on health-related quality of life (HRQL).**

Objective: **To compare HRQL, estimated by the Short-Form Health Survey (SF-36), in patients with and without HF in the community.**

Methods: **Cross-sectional study including 633 consecutive individuals aged 45 years or older, registered in primary care. The subjects were selected from a random sample representative of the population studied. They were divided into two groups: group I, HF patients (n = 59); and group II, patients without HF (n = 574). The HF group was divided into HF with preserved ejection fraction (HFpEF – n = 35) and HF with reduced ejection fraction (HFrEF – n = 24).**

Results: **Patients without HF had a mean SF-36 score significantly greater than those with HF (499.8 ± 139.1 vs 445.4 ± 123.8; p = 0.008). Functional capacity - ability and difficulty to perform common activities of everyday life - was significantly worse (p < 0.0001) in patients with HF independently of sex and age. There was no difference between HFpEF and HFrEF.**

Conclusion: **Patients with HF had low quality of life regardless of the syndrome presentation (HFpEF or HFrEF phenotype). Quality of life evaluation in primary care could help identify patients who would benefit from a proactive care program with more emphasis on multidisciplinary and social support. (Arq Bras Cardiol. 2017; 109(3):248-252)**

Keywords: **Heart Failure; Quality of Life; Primary Health Care.**

Introduction

Heart failure (HF) is a major public health issue with implications in health-related quality of life (HRQL).[1] Patients with HF present limitations on their usual activities, suffering impairment on social interaction, with a progressive loss of physical autonomy. Signs and symptoms of HF have a strong impact on HRQL regardless of the phenotype, affecting patients with either preserved ejection fraction (HFpEF) or reduced ejection fraction (HFrEF). Although HFrEF and HFpEF differ regarding mortality and hospitalization rates,[2-4] manifested signs and symptoms appear to have a similar impact on the well-being of those patients.[5]

To improve the HRQL of patients with HF is one of the major aims of the treatment. Additionally, many patients with HF usually attribute more importance to HRQL than to improvement in their survival.[6]

Mailing Address: Antonio José Lagoeiro Jorge •
Avenida Marques do Paraná, 303, 6º andar. Postal Code 24033-900, Centro, Niterói, RJ – Brazil
E-mail: lagoeiro@cardiol.br, lagoeiro@globo.com
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In the community setting, patients with HF are about a decade older, have multiple comorbidities and polypharmacy prescriptions, and are taking more medications than patients usually recruited for clinical trials.[7-9] These patients may benefit from measures that may improve their HRQL.

The objective of the present study was to compare the HRQL, estimated by the Short-Form Health Survey (SF-36), in patients with and without HF, and between the two phenotypes, HFrEF and HFpEF, in the community.

Methods

The Digitalis Study was a cross-sectional study including 633 volunteers, whose methodology is published elsewhere.[10] Briefly, individuals aged 45 to 99 years, registered in the Family Doctor Program (PMF) of the city of Niterói, Rio de Janeiro State, Brazil, were randomly selected to attend community visits for examination. Data were collected from July 2011 to December 2012. Initially, the healthcare units of the PMF were randomly selected, proportionally to the number of individuals enrolled. Then, in each unit, individuals aged 45 to 99 years were also randomly selected.

For the present study, individuals were divided into two groups: group I, formed by HF[11] patients (HF group – n = 59); and group II, formed by individuals without HF (n = 574). The HF group was divided into HFpEF (n = 35) and HFrEF (n = 24).

The Portuguese version of the SF-36 Questionnaire was used to classify HRQL.[12]

Statistical analysis

Statistical analysis was performed with the SPSS software, version 21.0 (Chicago, Illinois, USA). Categorical variables were expressed as absolute numbers and/or percentages. Quality of life and its domains presented non-Gaussian distribution, thus, the differences between categories were presented as median and interquartile range, and the differences were tested with the non-parametric Mann-Whitney test. All comparisons were assessed with bilateral tests. A 5% statistical significance level was considered.

Ethical considerations

This study was conducted in accordance with the principles of the Declaration of Helsinki, revised in 2000. The study protocol was approved by the Ethics Committee of the Institution under number 0077.0.258.000-10.

Results

We evaluated 633 subjects (59.6 ± 10.4 years; 62% female; 63% black or brown skin-color). The HF patients were older, had lower educational levels, consumed less alcohol, and showed a higher prevalence of former smokers. The average overall score, bodily pain and general health perception differed between patients without HF as compared to patients with HF. Two dimensions, physical and emotional aspects, showed no variation (Table 1).

Physical functioning was lower in patients with HF regardless of sex or age. Women, regardless of the presence of HF, scored lower for most of the dimensions than men did. The functional capacity - ability and difficulty to perform common everyday life activities -, general health perception and overall score were significantly worse in patients with HF independently of sex and age (Table 2).

Women had lower HRQL (vitality and general health perception) even in the absence of HF. Individuals younger than 60 years had a worse HRQL in the presence of HF, which was not observed in patients aged 60 years and older (Table 2).

Although the differences were not statistically significant (except for the vitality dimension), patients with HFpEF had lower mean values as compared to those with HFrEF (Table 3).

Discussion

Patients with HF had a lower mean overall SF-36 score than patients without HF (53.1 ± 29.6 vs. 76.2 ± 24.9; $p < 0.001$).

Table 1 – Demographic characteristics and mean scores of the SF36 dimensions of individuals with and without heart failure

Variables	No HF (n = 574)	HF (n = 59)	p-value
Age (years)	58.4 ± 9.4	71.1 ± 12.4	< 0.001
Female (%)	61.8	61	0.901
Never studied (%)	5.4	17.2	0.020
Family income (mean in US $)	484.63 ± 461.71	406.85 ± 463.80	0.234
Black or brown skin-color (%)	63.2	63.8	0.929
Alcohol consumption (%)	9.9	3.4	0.100
Tobacco use			0.012
Never smoker (%)	48.6	50.8	-
Former smoker (%)	31.2	42.4	-
Smoker (%)	20.2	6.8	-
Private health insurance (%)	15.3	15.3	0.949
SF-36 dimensions			
Physical functioning	85 (60-90)	55(25-80)	< 0.0001
Physical health	100(100-100)	100(100-100)	--
Emotional health	100(100-100)	100(100-100)	--
Vitality	70(50-85)	65(40-80)	0.01
Mental Health	80(60-92)	78(57-96)	0.265
Social functioning	100(62-100)	87(53-100)	0.296
Bodily pain	70(45-100)	80(49-100)	0.865
General health perception	70(50-85)	67(45-80)	0.091
Overall SF-36	535(403-615)	447(356-537)	0.001

HF: heart failure; P value (associated with two-tailed t test for independent samples); Chi-square test with continuity correction; median (interquartile range) with Mann-Whitney test for non-parametric variables.

Table 2 – Mean SF-36 scores by sex and age in patients with and without heart failure

	Male (n = 242)			Female (n = 391)			Age (45 to 59 years) (n = 357)			Age (60 to 99 years) (n = 276)		
SF36 dimensions	No HF (n = 219)	HF (n = 23)	p-value	No HF (n = 355)	HF (n = 36)	p-value	No HF (n = 344)	HF (n = 13)	p-value	No HF (n = 230)	HF (n = 46)	p-value
Physical functioning	95 (75-100)	55 (23.7-81.2)	< 0.0001	80 (55-95)	55 (30-80)	< 0.0001	90 (65-95)	60 (22.5-77.5)	0.001	80 (55-95)	55 (25-80)	< 0.0001
Physical health	100 (100-100)	100 (100-100)	--	100 (100-100)	100 (100-100)	--	100 (100-100)	100 (100-100)	--	100 (100-100)	100 (100-100)	--
Emotional health	100 (100-100)	100 (100-100)	--	100 (100-100)	100 (100-100)	--	100 (100-100)	100 (100-100)	--	100 (100-100)	100 (100-100)	--
Vitality	80 (60-90)	67.5 (38.7-85)	0.05	60 (45-85)	60 (40-80)	0.571	70 (45-85)	50 (32.5-67.5)	0.037	75 (50-90)	70 (45-80)	0.215
Mental Health	84 (72-96)	80 (68-96)	0.455	76 (52-88)	68 (52-96)	0.987	76 (52-96)	70 (51-80)	0.086	80 (60-92)	80 (57-96)	0.891
Social functioning	100 (75-100)	93.7 (59.4-100)	0.228	100 (62-100)	88 (50-100)	0.419	100 (75-100)	87.5 (68.7-100)	0.582	100 (62.5-100)	88 (50-100)	0.260
Bodily pain	80 (57-100)	80 (61-100)	0.685	70 (45-90)	80 (42.5-100)	0.160	70 (45-90)	57.5 (27.5-80)	0.180	80 (47.5-100)	80 (57.5-100)	0.086
General health perception	70 (55-85)	67 (45-75)	0.058	70 (50-85)	68 (45-80)	0.568	70 (55-80)	50 (25-70)	0.027	70 (55-85)	70 (46.2-80)	0.265
Overall SF-36	585 (488.2-632)	500.2 (401.6-564.4)	0.003	497.7 (367.9-591.4)	425 (320.6-515.2)	0.056	537.5 (412-615)	388 (315-487.5)	0.005	529 (386-615)	475 (388.5-555)	0.058

HF: heart failure; median (interquartile range) with Mann-Whitney test for non-parametric variables.

Table 3 – SF-36 overall and dimension scores of individuals with heart failure with reduced or preserved ejection fraction (HFrEF and HFpEF, respectively)

SF36 dimensions	HFpEF (n = 35)	HFrEF (n = 24)	p-value
Physical functioning	55(25-77.5)	55(26.2-85)	0.582
Physical health	100(100-100)	100(100-100)	--
Emotional health	100(100-100)	100(100-100)	--
Vitality	55(36.2-70)	75(52.5-80)	0.024
Mental Health	68(44-96)	80(68-96)	0.143
Social functioning	93.7(50-100)	87.5(65.6-100)	0.951
Bodily pain	70(43.7-100)	100(58.7-100)	0.097
General health perception	62.5(45-80)	70(46.2-78.7)	0.420
Overall SF-36	441(314-520)	452(406-578)	0.126

Median (interquartile range) with Mann-Whitney test for non-parametric variables.

The HRQL worsening observed in this study was similar to data obtained in the literature.[13-15]

Age, vitality, pain and the overall SF-36 score were the four characteristics associated with worse HRQL in patients with HFrEF. On the other hand, only age was related to HRQL worsening in patients with HFpEF.

The CHARM study[16] has evaluated the HRQL in HF patients and has concluded that those with HFpEF had a similar HRQL when compared to patients with low left ventricular ejection fraction (LVEF). That study showed that the extent of HRQL worsening was independent of LVEF. Our data did not show a difference between the overall SF-36 scores in patients with HFpEF and HFrEF (418.9 ± 122.5 vs. 476.6 ± 120.5; p = 0.101).

In general, older HF patients reported better quality of life than younger ones, regardless of the LVEF value. Studies have shown a better HRQL among older patients than among younger patients with HFrEF, although older patients had a worse functional status and performed worse in the six-minute walk test.[17] Our data show that patients aged 45 to 59 years with HF have a more pronounced worsening of HRQL than those without HF (394.0 ± 106.4 vs. 501.3 ± 139.8; p = 0.012) when compared to patients aged ≥ 60 years (459.9 ± 125.7 vs. 497.7 ± 138.3; p = 0.113).

Patients with HF usually do not understand the cause and prognosis of their disease and rarely discuss the quality and end of life with the professionals involved in their care. Care for people with advanced progressive illnesses is currently prioritized by diagnosis rather than need. Patients with advanced HF should receive care that is proactive and designed to meet their specific needs.[18]

A chronic syndrome such as HF, which requires continuous treatment for an indeterminate period and is linked to aging and presence of comorbidities, is inexorably associated with worse quality of life.[13-15]

The present study had some limitations. This is a cross-sectional study where all evaluations were performed in a single day without follow-up of the population, leading to difficulty in establishing causal relationships between HF and loss of quality of life. Another limitation is related to the reduced number of HF cases assessed, which diminishes the power of the study, leading to the lack of statistical significance of some associations.

Conclusions

Patients with HF have low quality of life independent of the syndrome phenotype. The quality of life evaluation in primary care could help identify patients who would benefit from a proactive healthcare program with more emphasis on multidisciplinary and social support. Therefore, strategies that can improve the quality of life of those patients and bring them greater benefits than the prolongation of life without associated quality are needed.

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Author contributions

Conception and design of the research: Jorge AJL, Rosa MLG, Correia DMS, Mesquita ET; Acquisition of data: Jorge AJL, Rosa MLG, Kang HC; Analysis and interpretation of the data: Jorge AJL, Rosa MLG, Kang HC, Mesquita ET; Statistical analysis: Rosa MLG; Writing of the manuscript: Jorge AJL, Rosa MLG, Correia DMS, Martins WA, Ceron DMM, Coelho LCF, Soussume WSN, Mesquita ET; Critical revision of the manuscript for intellectual content: Jorge AJL, Rosa MLG, Correia DMS, Martins WA, Ceron DMM, Kang HC, Moscavitch SD, Mesquita ET.

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Review Article

Vascular Aging and Arterial Stiffness

Luana de Rezende Mikael,[1] Anelise Machado Gomes de Paiva,[2] Marco Mota Gomes,[2] Ana Luiza Lima Sousa,[1] Paulo César Brandão Veiga Jardim,[1] Priscila Valverde de Oliveira Vitorino,[3] Maicon Borges Euzébio,[1,3] Wátila de Moura Sousa,[1] Weimar Kunz Sebba Barroso[1]

Liga de Hipertensão Arterial - Faculdade de Medicina - UFG,[1] Goiânia, GO; Hospital do Coração,[2] Maceió, AL; Pontifícia Universidade Católica de Goiás,[3] Goiânia, GO – Brazil

Abstract

Cardiovascular diseases (CVD) account annually for almost one third of all deaths worldwide. Among the CVD, systemic arterial hypertension (SAH) is related to more than half of those outcomes. Type 2 diabetes mellitus is an independent risk factor for SAH because it causes functional and structural damage to the arterial wall, leading to stiffness. Several studies have related oxidative stress, production of free radicals, and neuroendocrine and genetic changes to the physiopathogenesis of vascular aging. Indirect ways to analyze that aging process have been widely studied, pulse wave velocity (PWV) being considered gold standard to assess arterial stiffness, because there is large epidemiological evidence of its predictive value for cardiovascular events, and it requires little technical knowledge to be performed. A pulse wave is generated during each cardiac contraction and travels along the arterial bed until finding peripheral resistance or any bifurcation point, determining the appearance of a reflected wave. In young individuals, arteries tend to be more elastic, therefore, the reflected wave occurs later in the cardiac cycle, reaching the heart during diastole. In older individuals, however, the reflected wave occurs earlier, reaching the heart during systole. Because PWV is an important biomarker of vascular damage, highly valuable in determining the patient's global cardiovascular risk, we chose to review the articles on vascular aging in the context of cardiovascular risk factors and the tools available to the early identification of that damage.

Keywords

Hypertension; Blood Pressure; Pulse Wave Analysis; Vascular Stiffness; Vascular Remodeling.

Mailing Address: Weimar Kunz Sebba Barroso de Souza •
Rua 70, n. 250, apt 1801, ed. Lyon. Postal Code 74810-350, Jardim Goiás, Goiânia, GO – Brazil
E-mail: weimarsb@cardiol.br, sebbabarroso@gmail.com
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Physiopathogenesis of vascular aging

Currently 17 million deaths per year are estimated to occur due to cardiovascular diseases (CVD), representing one third of all deaths worldwide. Of those CVD, 9.4 million are related to arterial hypertension (AH),[1] a highly relevant risk factor for stroke, coronary artery disease, heart failure and occlusive peripheral arterial disease.[2]

Arterial hypertension is often associated with other cardiovascular risk factors (CVRF), such as smoking, obesity, high cholesterol levels and type 2 diabetes mellitus (DM), and that association, mainly with DM, significantly increases the risk for micro- and macrovascular complications, as well as the incidence of CVD.[1,3]

Several studies have shown that DM is an independent and important risk factor for functional and structural damage to the arterial wall, resulting in early arterial stiffness.[4,5] The combination of those CVRF, mainly AH and DM, contributes to potentiate vascular damage and early arterial aging.[6]

Some theories explain the normal aging process, and, can be generally divided into evolution and physiological or structural theories. From the cardiovascular viewpoint, the major theories include oxidative stress, production of free radicals, neuroendocrine changes and genetic predisposition. The confluence of those factors, acting mainly on myocytes and arterial media-intima layer, increases ventricular and vascular stiffness, a phenomenon closely related to the cardiovascular aging process[7] (Figure 1).

In the arterial bed, the major structural and functional changes result from calcification, wall diameter increase and elasticity loss, leading to collagen deposition and elastin fragmentation in the media layer. That phenomenon is more evident in large arteries, but also occurs in the peripheral vascular bed.[8,9] All such changes contribute to reduce arterial compliance and its capacity to resist stress.[10]

The physiopathogenesis of that process is related to changes in the mechanical stretching of the arterial wall and its structural changes.[11] In addition, there is evidence on the association of inflammatory markers and biomarkers with proatherogenic phenomena, which participate in the pathogenesis of vascular damage. Increased levels of C-reactive protein (CRP), an inflammation marker, are present in hypertensive individuals and contribute to target-organ lesions. In addition, adiponectin, a plasma protein derived from adipocytes that is reduced in hypertensive individuals and related to the glucose metabolism, acts as an antiatherogenic endogenous factor, its reduction being associated with increased cardiovascular risk. Other inflammatory markers and biomarkers described are nuclear factor-kappa B (NF-KB) and insulin growth factor-1 (IGF-1).[9,12]

In addition, age-related changes are associated with the generation of oxygen-reactive species, inflammation, endothelial dysfunction, and calcium and phosphate metabolism disorders.[10] Those changes depend on genetic characteristics, and vary in different populations. They reflect differences in nutritional characteristics, physical activity, smoking habit, cholesterol and glucose blood levels, and other risk factors known to affect arterial stiffness.[13,14]

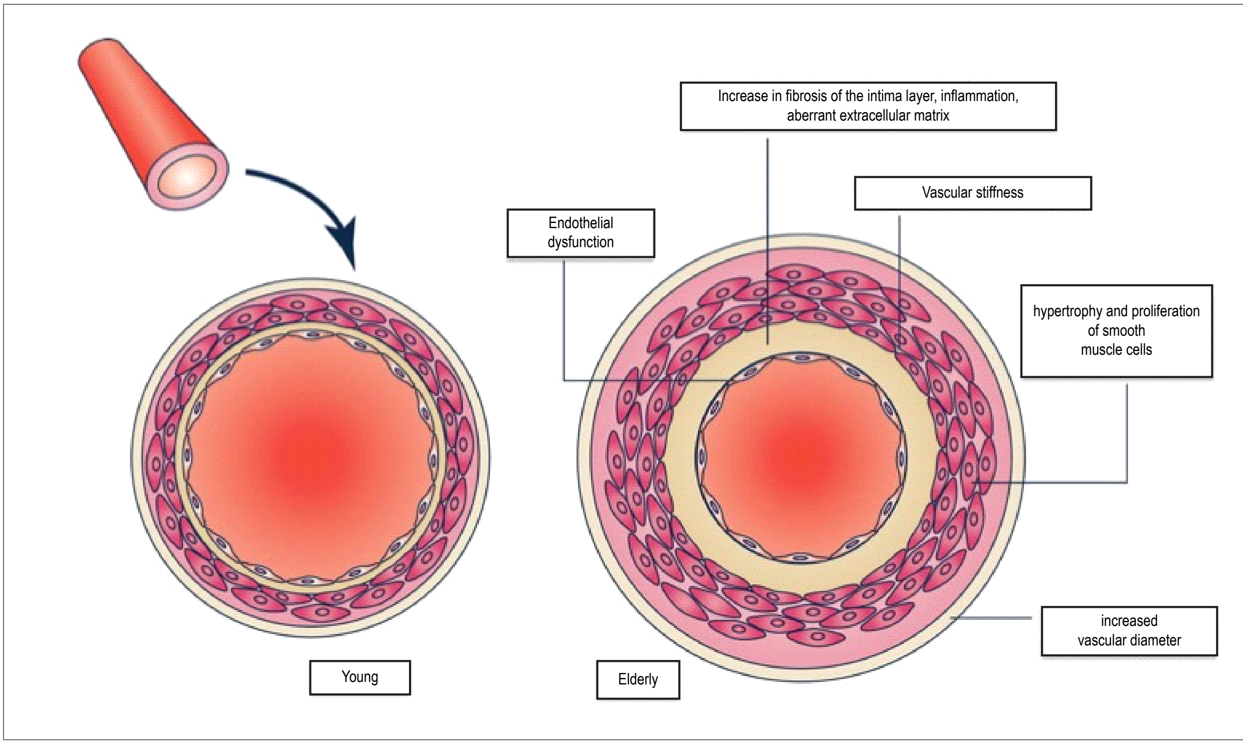

Figure 1 – *Pathophysiology of vascular aging.*[9]

Inflammatory mediators participate actively in mechanisms of vascular damage and atherosclerotic disease, their levels being increased in all AH stages. That association accelerates the vascular aging process. In addition, increased CRP levels can reduce the levels of endogenous nitric oxide, an important vasodilator related to the functional regulation of the compliance of large arteries *in vivo*.[12,15] Thus, the inflammatory and proatherogenic activation, mediated by several biomarkers in the presence of classical CVRF, contributes to worsen CV outcomes.[9,12,16]

The association of genetic, metabolic and inflammatory characteristics with cardiovascular risk phenotypes has been increasingly studied, and some genes that catalyze the process of early vascular aging have been identified.[9]

Finally, the aging phenomenon comprises changes related to a decrease in arterial elasticity and consequent increase in both arterial stiffness and systolic blood pressure (BP) levels. From the physiopathological viewpoint, the decrease in elastin amount, and the increase in collagen amount and in arterial intima-media thickness precede the endothelial damage, and can indirectly identify vascular damage at an initial phase.[7,9,17]

Arterial stiffness as a consequence of vascular aging

At each heartbeat, a pulse wave is generated and travels along the arterial bed until finding peripheral resistance or any bifurcation point, generating a new reflected wave back to the heart. The velocity of that reflected wave and the phase of the cardiac cycle in which it happens (systole or diastole) depend on peripheral vascular resistance, elasticity, mainly of large arteries, and central BP, being related to major cardiovascular outcomes.[16,17]

In young individuals, arteries are more elastic. Thus, the reflected wave is slow and reaches the heart during diastole, increasing the diastolic pressure and improving coronary perfusion.[18] In addition, the reflection of the wave returns part of the pulsatile energy to the central aorta, where it is dissipated, limiting the transmission of the pulsatile energy to the periphery and preventing damage to microcirculation.[19] With vascular aging, pulse wave velocity (PWV) increases, resulting in an early reflection of that wave, which reaches the heart during systole. This increases systolic BP, with a consequent increase in cardiac workload and a reduction in coronary perfusion.[18,19]

The arterial stiffness role in the development of CVD has been more emphatically studied in the past years, its use being recommended in guidelines to improve cardiovascular risk stratification.[20-22]

Assessment of vascular aging

Vascular aging can be assessed by use of arterial stiffness analysis. Several invasive and non-invasive methods have been described for that purpose. The most widely used and validated techniques involve PWV assessment.[23]

The PWV measurement is considered gold standard to evaluate arterial stiffness. Other methods, such as measuring central systolic BP (cSBP) and augmentation index (AI) (Figure 2), are under greater influence of pathophysiological conditions, medications, heart rate and age, which make them less reliable.[16,23]

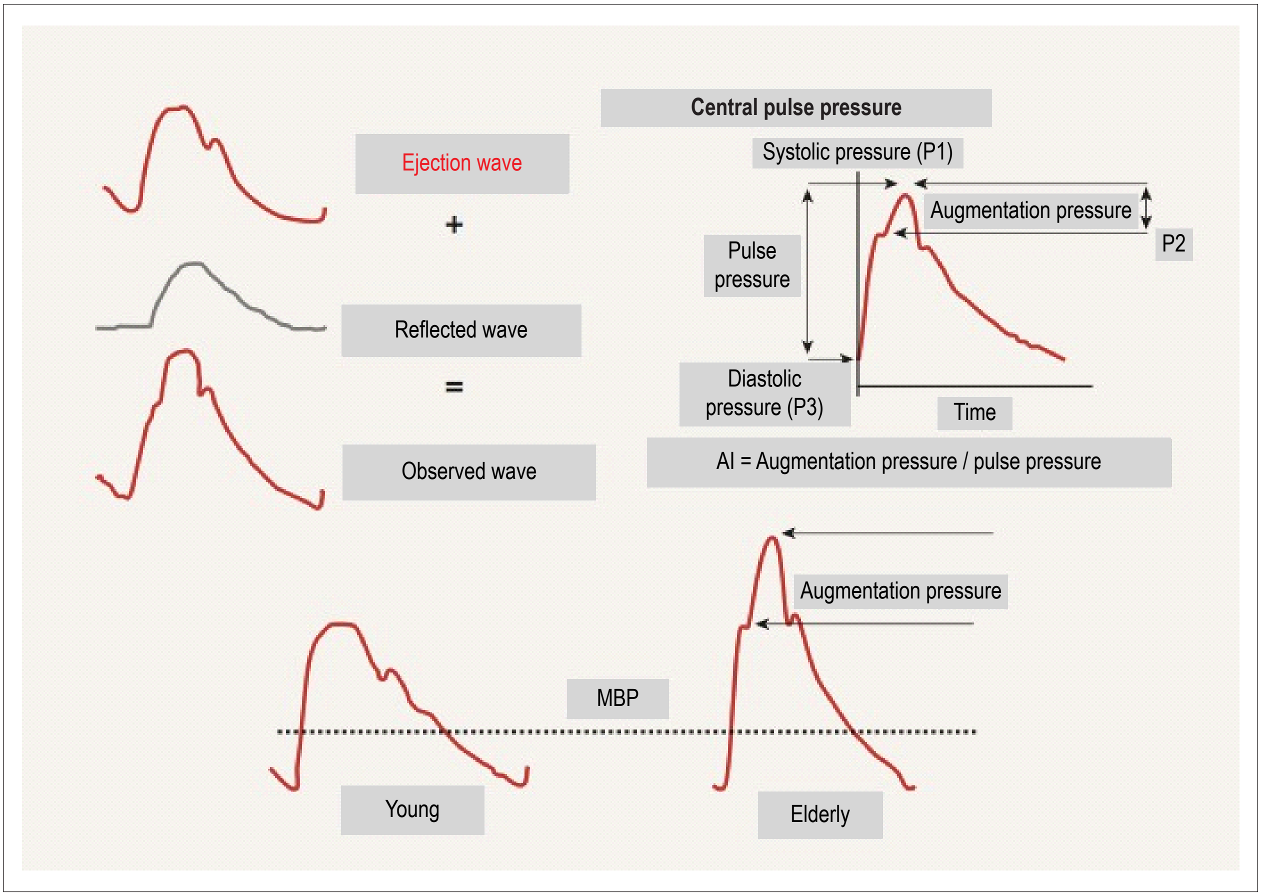

Figure 2 – *Blood pressure curve with description of its major components. AI: Augmentation Index; MBP: Mean Blood Pressure.*[28]

Carotid-femoral PWV is a clinically relevant measure of velocity along the aortoiliac trajectory, because the aorta and its first branches are closely related to the left ventricle, and correlate with most of the physiopathogenic effects of arterial stiffness.[16,24]

The carotid-femoral PWV analysis is gold standard for arterial stiffness assessment, because there is large epidemiological evidence of its predictive value for cardiovascular events, and it requires little technical knowledge to be performed. In addition, PWV can be measured in a point. The method for that has been validated, and consists in calculating, by use of transference with calibration, systolic BP/diastolic BP (SBP/DBP) with mean BP/DBP (MBP/DBP), being feasible and having better cost-benefit ratio for clinical practice.[16,21,25]

In addition, PWV bears a strong correlation to age and BP, in which the elastic properties of the arterial wall are reduced, with consequent increase in vascular stiffness.[7,26,27]

Clinical applicability of vascular aging assessment

Assessment of arterial elasticity (compliance) is clinically important as it correlates with the pathogenesis of a large spectrum of cardiovascular and non-cardiovascular outcomes, such as cerebral white matter lesions and several types of cognitive deficits, such as Alzheimer's disease, and kidney dysfunction.[28-32]

Vascular cognitive impairment (VCI), a term created to comprise a heterogeneous group of cognitive disorders that share a vascular etiology, including both dementia and cognitive impairment without dementia, has gained importance. This might result from its likely increasing prevalence in next decades, due to population aging and increase in life expectancy consequent to better CVD control.[32] In addition, VCI increases morbidity, disability and health costs for the elderly, reducing their quality of life and life expectancy.[7,33]

As compared to Alzheimer's disease, VCI is associated with 50% lower mean survival (6-7 years versus 3-4 years), higher health costs and comorbidity rates. Thus, its primary and secondary prevention is highly important, being usually approached as stroke prevention and changes in vascular risk factors, such as AH, dyslipidemia, DM, obesity and sedentary lifestyle. Better knowledge and early identification of the vascular aging process and of related biomarkers can contribute to improve prevention.[33,34]

The biological aging process is always associated with arterial stiffness, which is accelerated by arterial hypertension. The relationship between arterial stiffness and BP is more complex, being currently understood as bidirectional, because an increase in the vascular distension pressure causes an increase in arterial stiffness, and, conversely, an increase in stiffness can lead to SBP elevation. The relationship between arterial stiffness and BP can also be influenced by antihypertensive drugs, which, by reducing BP, can benefit vascular health. Thus, the interpretation of arterial stiffness data has to consider the patients' clinical characteristics, such as age, prevalence of comorbidities, use of medications, lifestyle and genetic factors.[35]

In addition to the dominant effect of aging, other physiological and pathophysiological conditions are associated with the increase in arterial stiffness and change in the behavior pattern of the reflected pulse wave: physiological conditions (low birth weight, menstrual cycle, menopause); genetic characteristics (family history of hypertension, DM or myocardial infarction, genetic polymorphisms); CVRF (sedentary lifestyle, obesity, smoking habit, AH, dyslipidemia, glucose intolerance, metabolic syndrome, types 1 and 2 DM); and CVD and non-cardiovascular diseases (different stages of kidney failure, rheumatoid arthritis, systemic vasculitis, systemic lupus erythematosus).[16,19]

Regarding DM and AH, the arterial wall undergoes several biomechanical changes that, from the theoretical viewpoint, can increase arterial stiffness.[36] In addition, adiponectin has been associated with aortic stiffness in patients with DM.[12] Another study comparing different procedures to measure PWV to evaluate arterial stiffness in patients with DM has concluded that further investigation is required to clarify its usefulness in those patients, reinforcing PWV as the gold-standard method in that population.[37] A systematic review assessing the relationship of PWV with several CVRF has shown that 52% of the studies found a positive association between increased PWV and DM.[38]

It is worth noting that arterial stiffness data provide direct evidence of damages in target organs, PWV being considered a biomarker of vascular damage,[17] which is important in determining the patient's global cardiovascular risk, considering that the classical risk scores, mainly in the intermediate risk stratum, perform badly to predict cardiovascular outcomes.[21,22] Traditionally used scores are based on well-established risk factors easily obtained; however, although at least one of those traditional risk factors is present in most patients who have a cardiovascular event, they can be found in patients who will not have an early event.[6,39]

Furthermore, CVD are preceded by an asymptomatic phase. Thus, patients with subclinical damages are at higher risk to develop symptomatic disease, reflecting a possible susceptibility to traditional risk factors. The most recent guidelines on AH have recommended the use of biomarkers to improve the accuracy of cardiovascular risk stratification, especially in patients at intermediate risk.[21,22]

Of the major biomarkers, PWV stands out, which, when added to the classical cardiovascular risk stratification, can reclassify individuals to higher strata, implicating in changes in the management aimed at higher cardiovascular protection.[40,41]

Thus, vascular aging analysis in the risk stratification context can improve the assessment and definition of the management of those patients, and can represent a useful strategy to reduce both absolute and residual risks, because it enables the identification of early damage and the proper treatment already in the cardiovascular *continuum* phase.[42]

Author contributions

Conception and design of the research and writing of the manuscript: Mikael LR, Paiva AMG, Barroso WKS; Acquisition of data: Mikael LR, Paiva AMG; Analysis and interpretation of the data: Mikael LR, Paiva AMG, Euzébio MB, Sousa WM, Barroso WKS; Critical revision of the manuscript for intellectual content: Gomes MM, Sousa ALL, Jardim PCBV, Vitorino PVO, Euzébio MB, Sousa WM, Barroso WKS.

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Percutaneous Management of Iatrogenic Aortocoronary Dissection Complicating Diagnostic Angiography or Percutaneous Coronary Intervention

Liang Tang, Xin-qun Hu, Jian-jun Tang, Sheng-hua Zhou, Zhen-fei Fang
Department of Cardiology – The Second Xiangya Hospital of Central South University, Changsha, China

Introduction

Aortocoronary dissection is an infrequent, yet potentially catastrophic complication of coronary angiography (CAG) or percutaneous coronary intervention (PCI) that can lead to emergency surgical aortic repair, coronary artery bypass graft surgery (CABG) or death.[1,2] According to the extent of aortic root involvement, Dunning et al.[3] proposed three classes of aortocoronary dissection: Class I for focal dissection limited to the sinus of Valsalva; Class II for dissection that propagated less than 40 mm to the ascending aorta; and Class III for dissection extending 40 mm or more to the ascending aorta. Management of this rare entity is still technically challenging and the optimal treatment of aortocoronary dissection complicating CAG or PCI had not been clearly established. In this article, we describe a case series of aortocoronary dissection among consecutive diagnostic CAG and PCI procedures, which were successfully treated by coronary ostial stenting.

Case 1

A 62-year-old woman with unstable angina pectoris was referred for diagnostic CAG at a local hospital. The left coronary system appeared normal. During the angiography of the right coronary artery (RCA), a coronary dissection progressing retrogradely more than 40 mm (Dunning dissection class III) from the proximal RCA into the Valsalva sinus and the ascending aorta occurred (Figure 1A and 1B). The patient suddenly complained of severe chest pain and developed hypotension and bradycardia. She was transferred immediately to our cath lab for the management of aortocoronary dissection. We decided to perform ostial stenting to seal the entry site of dissection and to stop blood flow into the false lumen. A Runthrough guidewire (Terumo, Japan) was rapidly advanced into the distal RCA. After pre-dilation with a Maverick 2.0×20 mm balloon (Boston Scientific, USA), a 3.0×24 mm stent (PROMUS Element, Boston Scientific, USA) was immediately deployed at the RCA ostium to cover the presumed entry-door of the dissection. Repeated angiography revealed no contrast leakage into the ascending aorta false lumen (Figure 1C). A computed tomography angiography (CTA) performed immediately after the PCI demonstrated complete halt of the dissection without progression. The patient had an uneventful hospital stay and repeated CTA performed two weeks later showed complete resolution of the aortic hematoma.

Keywords

Percutaneous Coronary Intervention; Aortocoronary Dissection; Coronary Artery Bypass; Complications.

Mailing Address: Zhen-fei Fang •
Department of Cardiology, The Second Xiangya Hospital of Central South University, N°.139, Middle Ren-min Road, Changsha, Hunan, 410011, China
E-mail: fangzhenfei2012@126.com
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Case 2

A 60-year-old man with hypertension and diabetes was admitted with effort angina for four months. CAG showed severe stenosis of the distal RCA. Transradial PCI was performed using a 5F JR4.0 guiding catheter (Cordis, USA) and Rinato guidewire (Terumo, Japan). The distal lesion was predilated using Maverick 2.0×15 mm balloon (Boston Scientific, USA). Immediately after removing the balloon, the patient complained of anterior chest pain and back pain. Angiography revealed a dissection at the RCA ostium, extending retrogradely into the sinus of Valsalva and ascending aorta (Dunning dissection class II) (Figure 1D). A 2.5×24 mm stent (EXCEL, JW Medical System, China) was immediately implanted at the RCA ostium to cover the entry point and RCA ostium, followed by post-dilatation (Figure 1E). After stenting, angiogram demonstrated no further extravasation of contrast medium (Figure 1F). An emergent CTA scan showed a limited intramural hematoma of ascending aorta. The clinical course was uneventful. At two-month follow-up, control CTA showing total resolution of the intramural hematoma.

Case 3

A 63-year-old woman with hypertension was admitted for effort angina of 2 week duration. CAG revealed proximal and mid-RCA diffused stenosis of approximately 90%. Transradial PCI was performed with a 6F JL 3.5 guiding catheter and a Runthrough guidewire. After pre-dilation with a 2.0 mm balloon, a 3.0 mm × 36 mm stent (Partner, Lepu Medical Technology, China) was successfully implanted in the mid-RCA. To prepare for stenting of the proximal RCA, we used the stent balloon of the mid-RCA to dilate the proximal portion at 14atm. However, after pre-dilation of the proximal lesion, a proximal RCA dissection occurred, which extended antegradely and also retrogradely into the Sinus of Valsalva (Dunning dissection class I) (Figure 2A). A 3.5×29 mm stent (Partner, Lepu Medical Technology, China) was immediately deployed at the proximal RCA, which was considered as the entry point of the aortic dissection. The final angiogram showed the aortic dissection

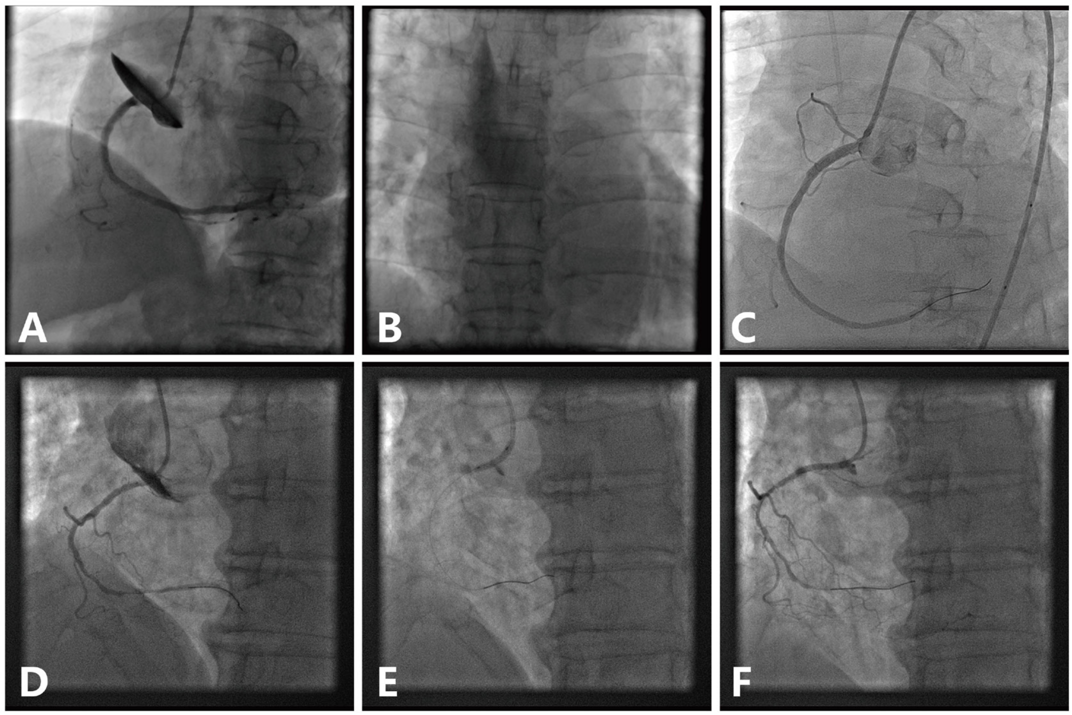

Figure 1 – *(A) Angiogram demonstrating proximal right coronary artery dissection, extending to sinus of Valsalva and ascending aorta. (B) Persistent contrast staining was observed along the aortic wall of the ascending aorta. (C) Stenting of the ostium of the right coronary artery to coverage the entry point of the dissection and final angiogram showed complete coverage of the aortocoronary dissection. (D) Angiogram showing a dissection ostium of the right coronary artery, extending retrogradely into the sinus of Valsalva and ascending aorta. (E) Stent deployment aiming at full sealing of the entry site of dissection and the RCA ostium. (F) Angiogram after ostial stenting revealed the dissection limited to the sinus of Valsalva*

was limited in the sinus of Valsalva (Figure 2B). A follow-up angiography was performed one week later and it revealed no residual contrast staining of the aortic wall (Figure 2C). The patient remained asymptomatic for one month without any clinical event.

Case 4

A 52-year-old woman with hypertension and hyperlipidemia presented with chest discomfort for one week. CAG demonstrated critical stenosis in the proximal and mid-portion of the RCA. During PCI, the RCA ostium was engaged with a 6F Amplatzer left1 (Cordis, USA) guiding catheter. Before attempting to advance the guidewire, contrast medium was injected. Immediately after the injection, a large proximal RCA dissection occurred, which quickly extended in a retrograde fashion into the ascending aorta (Figure 2D). Despite obliteration of the RCA dissection with a PROMUS Element 3.0×38 mm stent, persistent dye staining of the ascending aorta was present on final angiogram (Dunning dissection class III) (Figures 2E and 2F). A computed tomography scan performed 12 hours later showed an intramural hematoma ascending aorta without an intimal flap. The patient recovered well after stenting and was discharged 7 days later. At the one-month follow-up, the patient was asymptomatic and the CTA showing complete healing of the dissection.

Discussion

Iatrogenic aortocoronary dissection complicating coronary interventions is extremely rare and a few cases have been reported. The incidence of this complication was approximately 0.02% for diagnostic coronary angiography and 0.02-0.83% for PCI procedures.[2-5] The rapid propagation of aortocoronary dissection may become immediately life threatening via several mechanisms, including hemorrhage into the pericardium resulting in cardiac tamponade, occlusion of the contralateral coronary ostium, or propagation of the dissection into the descending aorta.[6,7] Most reported iatrogenic aortocoronary dissections have been related to procedures in the RCA, especially during PCI for chronic total occlusions.[2] The RCA is more easily dissected retrogradely into the coronary sinus than the left main coronary artery (LMCA). This may be because the periostial wall and sinotubular junction of the LMCA are formed by more smooth muscle cells and by a dense matrix of collagen type I fibers[8].

Its mechanism involves disruption of the coronary intimal by mechanical trauma, followed by vigorous contrast injection, which, in turn, contributes to subsequent retrograde extension of the dissection. The entry port is usually created by direct trauma from the catheter tip, forceful balloon inflation, the dilation of a calcified plaque, from aggressive manipulation of

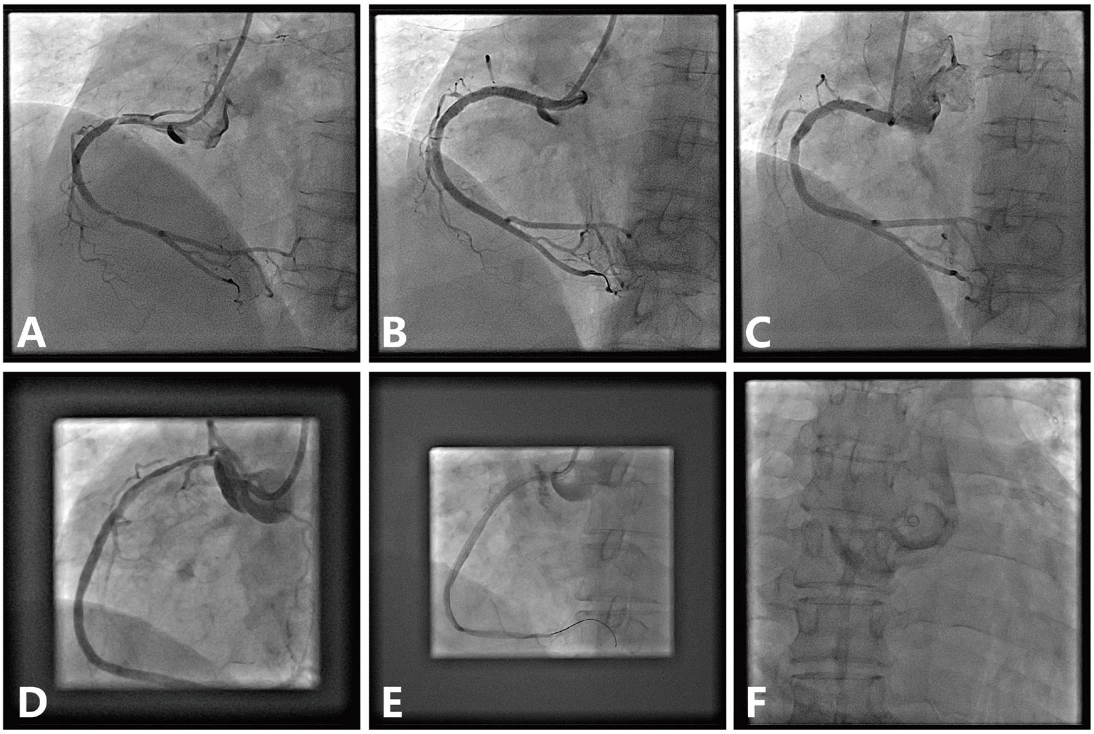

Figure 2 – *(A) After pre-dilation, a dissection of the proximal right coronary artery extending retrogradely into the sinus of Valsalva occurred. (B) Repeated angiogram after stenting demonstrating the aortic dissection was successfully sealed and limited in the sinus of Valsalva. (C) Follow-up angiogram showing complete resolution of the dissection. (D) After contrast injection, a dissection of the proximal right coronary artery with propagation into the aortic sinus and ascending aorta developed. (E) After right coronary artery ostium stenting, angiogram showed no further contrast leakage from the ostium entry point of the right coronary point to the false lumen of the ascending aorta. (F) Persistent contrast dye present in the wall of ascending aorta.*

rigid or hydrophilic guide wires, or vigorous contrast injection with a wedged catheter.[1,9,10] In the present cases, the cause of dissection in case 1 and case 4 was thought to be noncoaxial engagement of the catheter followed by continuous vigorous contrast injection. In case 2, the trigger for the dissection was thought to be direct trauma caused by the tip of the guiding catheter, whereas in case 3, the dissection may have been caused by dilation of the balloon in the proximal RCA, with its propagation into the ostium and the coronary sinus of Valsalva.

To date, the optimal treatment of this rare entity has not been well established. Several methods including emergent surgery, coronary artery stenting, or conservative medical treatment have been proposed to manage aortocoronary dissection.[11-13] Given that over 40% of the cases will spread rapidly to the ascending aorta if the entry-door is not sealed rapidly, a "wait and see" approach may be too risky for uncontrollable dissection and major complications.[9] Therefore, once aortocoronary dissection occurred, every effort should be undertaken to prevent rapid progression of the dissection. Dunning et al.[3] proposed that patients might be successfully managed by stenting of the entry point of the coronary dissection if the dissection extends < 40 mm from the coronary ostium and that surgical intervention might be required if the dissection extends > 40 mm from the ostium. However, Park et al.[13] reported a case of iatrogenic coronary dissection with extensive propagation into the entire ascending aorta complicating PCI for chronic total occlusion of the RCA, which was successfully managed by stenting of the RCA ostium with favorable outcome. Carstensen and Ward[9] reviewed 67 cases published in the literature and suggested that even rapidly propagating dissections can be successfully managed percutaneously and that attempting to halt propagation does not appear to compromise the chances of surgical success if the initial approach fails. Additionally, the surgical repair of catheter-related dissection may be more risky in the setting of coronary ischemia and following PCI with full anticoagulation and antiplatelet therapy. Boukhris et al.[2] recently assessed the management strategy and outcomes of such a complication among 956 cases of complicating PCI for chronic total occlusion, and found aortocoronary dissection occurred in eight patients for an overall frequency of 0.83%. In all these cases, rapid ostial stenting was performed and no emergency surgery was required. In Shorrock et al[1] study, four of six patients (67%) with aortocoronary dissection were treated with ostial stenting, one underwent emergency CABG, and the remaining one was treated conservatively without subsequent adverse clinical outcomes. Moreover, they performed a systematic literature review of 107 published cases of aortocoronary dissection during PCI, and showed that this complication were most commonly treated with stenting (49.5%) or conservative management (21.5%) although approximately 29% required surgery. Hence, Shorrock et al.[1] proposed that emergency surgery for aortocoronary dissection is not needed in the vast majority of cases and should only be considered in cases of occlusion of the dissected vessel with cessation of antegrade flow that cannot be restored percutaneously, and extension of the dissection to the descending aorta.

In our case series, rapid ostial stenting was performed in all of them, and all patients had uneventful recovery. Follow-up imaging with CTA or CAG showed complete resolution of the dissection in all patients. So, the outcome of coronary stenting for the management of aortocoronary dissection is relatively favorable.

It is worth noting that the best approach to management of aortocoronary dissection is to prevent its occurrence. During catheterization, there should be a coaxial alignment of the catheter with the coronary artery, and meticulous attention should be paid to the pressure waveform. Once the pressure waveform is dampened, the contrast should not be injected. Moreover, if aortocoronary dissection occurs, stopping antegrade contrast injections is critical to avoid propagation and enlargement of the dissection[12]. In addition, a careful and gentle handling of wires and guiding catheter probably would prevent some of the cases of this catastrophic complication.

Conclusion

Iatrogenic aortocoronary dissection is an infrequent but life-threatening complication of diagnostic CAG and PCI, necessitating a prompt diagnosis and appropriate treatment. Immediate coronary ostial stenting to seal off the entry point of the dissection is a feasible and reasonable initial management for this devastating complication.

Author contributions

Conception and design of the research: Tang L, Jian-jun T, Zhen-fei F; Acquisition of data: Tang L, Xin-qun H; Analysis and interpretation of the data: Tang L, Xin-qun H, Jian-jun T, Sheng-hua Z; Statistical analysis: Xin-qun H; Obtaining funding and Writing of the manuscript: Tang L; Critical revision of the manuscript for intellectual content: Sheng-hua Z, Zhen-fei F.

Potential Conflict of Interest

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

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Study Association

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

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Case 5 / 2017 – Scimitar Syndrome and Pulmonary Sequestration in Natural Progression in a 68-Year-Old Woman

Edmar Atik, Álvaro Francisco Gudiño, Marcelo Lopes Montemor
Instituto do Coração do Hospital das Clínicas da Universidade de São Paulo, São Paulo, SP – Brazil

Clinical data

Tiredness and palpitations during physical work for approximately 20 years, without progression. Some episodes of small-volume hemoptysis during this period. Taking enalapril for hypertension and metformin for diabetes.

Physical examination: good general condition, eupneic, acyanotic. Weight: 56 Kg, Height: 160 cm, blood pressure (right arm): 140/90 mm Hg, HR: 95 bpm, oxygen saturation = 99%.

Precordium: apex beat was not palpable, without systolic impulses. Normophonetic heart sounds, and no heart murmurs. Liver was not palpable and lungs were clear.

Complementary tests

Electrocardiography: sinus rhythm, HR 113 bpm, with no signs of chamber overload, PR: 0.12, QRS: 0.89; AP = +60º, AQRS = +40º, AT = +60º (Figure 1A).

Chest radiography: normal-sized heart, with deviation to the right due to pulmonary hypoplasia of the right lung, which was compensated by the left lung. In the right lower lobe, there was a vascular image with the shape of a scimitar (Figure 1B).

Echocardiography: normal cardiac chambers, except for mild biatrial enlargement, normal biventricular function. Aorta = 32 mm, LA = 34, RV = 28, LV = 53, septum = posterior wall = 10 mm, LVEF = 68%. There was a very low blood flow from the LA to the RA.

Chest computed tomography: *situs solitus* and levocardia, and heart in dextroposition. Anomalous pulmonary venous connection at right, with drainage of pulmonary veins through a venous collector (largest diameter 11 x 10 mm), that descended to the suprahepatic segment of the inferior vena cava (scimitar) (Figure 1C).

Normal pulmonary trunk (22 mm). Dilated left pulmonary artery (27 mm) with increased pulmonary artery-to-bronchus ratio, which may indicate either redirection of the flow or increased pulmonary pressure. Right pulmonary artery was tortuous and hypoplastic, measuring 10 mm in its proximal portion and 9mm in its medial third (Figure 1D).

Enlarged branch (13 x 13 mm) from the abdominal aorta at the level of the celiac trunk with ascending course to the posterior-inferior region of the right lung ("aneurysmatic" pulmonary sequestration).

Hypoplastic right lung with compensation by the left lung.

Posterolateral diaphragmatic discontinuity, suggestive of Bochdalek hernia.

Clinical diagnosis

Scimitar syndrome with right lung hypoplasia and pulmonary sequestration of the right inferior lobe.

Clinical reasoning

Patient with few symptoms, without a definite clinical diagnosis, due to absence of signs suggestive of congenital heart disease and normal ECG results. Chest radiography has become paramount in the diagnosis of scimitar syndrome, which is confirmed by angiotomography. The few clinical manifestations of the disease associated with its long natural progression resulted from the small interatrial communication and low pulmonary blood flow at right.

Differential diagnosis

Congenital heart diseases with few manifestations may have the same long term progress, including acyanogenic heart diseases with low blood flow from the left to the right, such as interatrial communication, interventricular communication, and patent ductus arteriosus (PDA).

Management

Due to few clinical and hemodynamic manifestations of the pulmonary venous abnormality, expectant management was performed.

Comments

Scimitar syndrome consists in an anomalous venous drainage of the right lung to the inferior vena cava associated with right lung hypoplasia, anomalies of the bronchial tree, dextrocardia, systemic arterial blood supply coming from the abdominal aorta. In one third of the cases, congenital heart diseases are concomitant, such as ventricular/atrial septal defect, PDA, coarctation of the aorta, and Tetralogy of Fallot. Other congenital disorders that may be associated with this syndrome are right diaphragmatic hernia, spinal abnormalities, hypospadias, duplicated ureter and double urethra.[1]

Scimitar syndrome was first described by Cooper and Chassinat in 1836 and its first surgical treatment was described by Kirkling et al.[1] in 1956.

Palavras-chave

Heart Defects, Congenital; Scimitar Syndrome; Heart Septal Defects, Atrial; Pulmonary Sequestration.

Mailing Address: Edmar Atik •
Rua Dona Adma Jafet, 74, conj.73, Bela Vista. Postal Code 01308-050, São Paulo, SP – Brazil
E-mail: conatik@incor.usp.br

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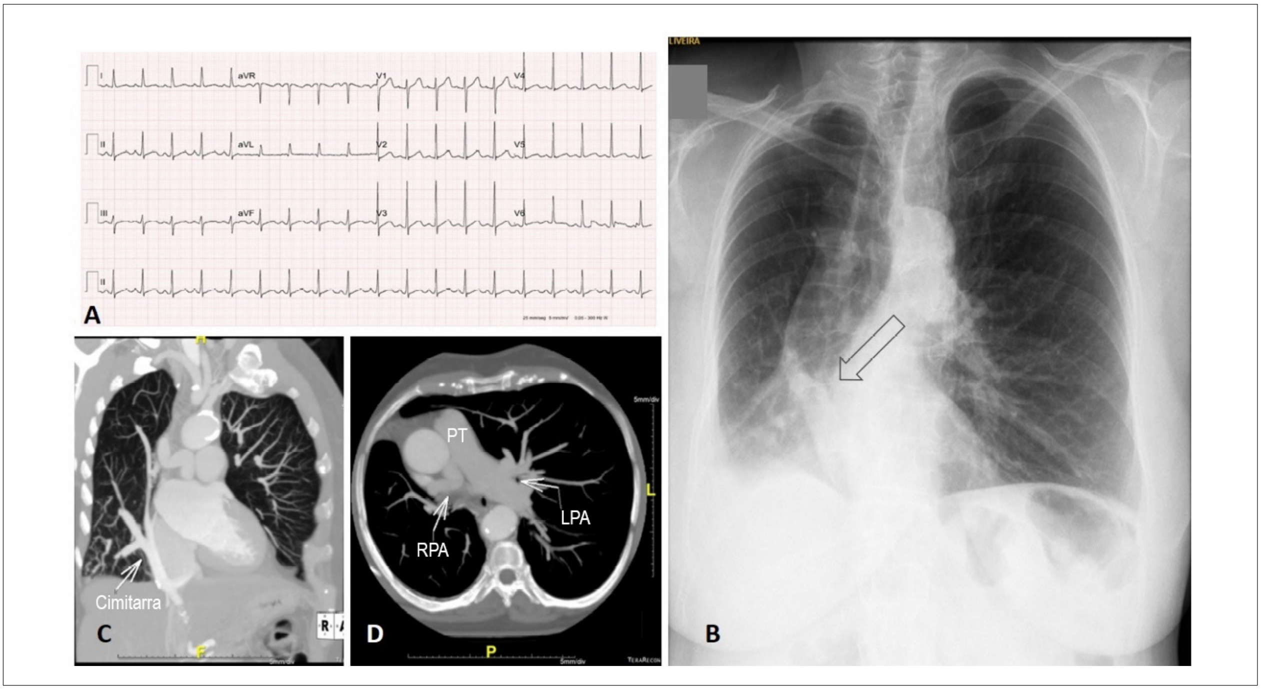

Figure 1 – *Normal electrocardiogram (A). Chest X-ray (B) In the posteroanterior view, normal-sized heart, right lung hypoplasia and scimitar-shaped vein (arrow). Computed tomography angiography shows right pulmonary vein in the shape of a scimitar (arrow) draining to inferior vena cava (C) and size contrast between the pulmonary arteries (D). PT: pulmonary trunk; RPA: right pulmonary artery; left pulmonary artery (LPA).*

The syndrome was classified by Depuis et al.[2] into two distinct presentations: infantile and adult. The infantile form affects children younger than one year; it usually progresses to heart failure and pulmonary hypertension, with a worse prognosis. The adult form affects both children and adults; it is usually asymptomatic and has a better prognosis.[1,2]

The name 'scimitar' (the Turkish sword) is symbolic, described by Neil et al. in 1960 due to the radiographic image showing the oriental sabre appearance of the anomalous, vertical descending pulmonary vein in the right lung.[1]

Most of the cases reported in the literature undergo surgical repair from early years to youth, and rarely in adult ages, as described in a 66-year-old patient.[3]

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Case Report

Balloon Cryoablation for the Treatment of Paroxysmal Atrial Fibrillation

Guilherme Fenelon,[1,2] Frederico Scuotto,[1,2] Claudio Fischer,[1,2] Marco Antonio Perin,[1] Marcia Makdisse,[1] Angelo Amato Vincenzo de Paola[1,2]

Hospital Israelita Albert Einstein,[1] São Paulo, SP; Universidade Federal de São Paulo (UNIFESP),[2] São Paulo, SP – Brazil

Introduction

Radiofrequency ablation (RFA) aiming at the electrical isolation of the pulmonary vein (PV) is more effective in controlling the rhythm than drugs, especially in young individuals with symptomatic paroxysmal atrial fibrillation (AF) without structural heart disease.[1-3] Electrical isolation is performed with point-by-point RFA around the PV, constituting a complex and lengthy procedure.[2,3] Recently, technologies have been developed aiming to simplify PV isolation, among them the balloon cryoablation.[2,4] In this approach, the cryoballoon is inflated in the PV ostium in order to completely occlude it. The release of cryoenergy cools the balloon surface, having the potential to isolate the vein with a single application. The efficacy and safety of cryoablation are similar to RFA, but the procedure is faster.[4-7]

Although used worldwide,[2-4] only recently cryoablation was made available in Brazil. The objective of this study was to report the first three cases performed in our country using this technology.

Case Reports

Patients were included in a study approved by the National Research Ethics Commission (Comissão Nacional de Ética em Pesquisa - CONEP), number 03094112.9.0000.0071, after signing the Free and Informed Consent form. All patients met the following inclusion criteria: (1) documented symptomatic paroxysmal AF; (2) at least two episodes in the last 3 months; (3) refractory to at least one antiarrhythmic drug.

Case 1

Male patient, 36 years old, hypertension controlled with losartan, with paroxysmal AF for the last 5 years, had used sotalol without success. He remained symptomatic (palpitations) with the use of propafenone, atenolol and dabigatran (CHA2DS2-VASc score 1).[8] The echocardiogram showed a slight increase in the left atrium (anteroposterior diameter of 44 mm) and normal ventricular function (left ventricular ejection fraction of 65%).

Keywords

Atrial Fibrillation / therapy; Catheter Ablation / methods; Cryosurgery / methods; Cryosurgery / trends.

Mailing Address: Guilherme Fenelon •
Rua Borba Gato, 331, Bouganville, 242, Santo Amaro.
Postal Code 04747-030, São Paulo, SP – Brazil
E-mail: guifenelon@cardiol.br
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Case 2

Female patient, 67 years old, with hypertension, dyslipidemia and hypothyroidism, controlled with enalapril, metoprolol, levothyroxine and rosuvastatin. She had paroxysmal AF crisis for the last 3 years and remained symptomatic (palpitations) while using propafenone and rivaroxaban (CHA2DS2-VASc score 3).[8] She used amiodarone, withdrawn due to hypothyroidism. Echocardiography showed normal left atrium (anteroposterior diameter of 39 mm) and ventricular function (left ventricular ejection fraction of 74%).

Case 3

Male patient, 50 years old, hypertension controlled with losartan and chronic bronchitis due to smoking, paroxysmal AF for the last 10 years, had used sotalol and amiodarone without success. He was symptomatic (palpitations) while using propafenone and dabigatran (CHA2DS2-VASc score 1).[8] The echocardiogram showed a slight increase in the left atrium (anteroposterior diameter of 44 mm), normal ventricular function (left ventricular ejection fraction of 63%) and mild mitral escape.

The procedures were performed on November 3, 2014, by the same team, with the help of an instructor, using standardized techniques.[9] Antiarrhythmic and anticoagulant drug use was suspended five days before and on the day before the procedure, respectively. Imaging methods for anatomical definition of the PV were not used. Transesophageal echocardiography was performed under general anesthesia, to exclude thrombi. Then, femoral venous access was obtained for allocation of decapolar and quadruple catheters in the coronary sinus and right atrium. With the aid of transesophageal echocardiography, a single transseptal puncture was performed and an 8F sheath (SL1, St. Jude Medical) was placed in the left atrium, which subsequently was replaced by a 15F deflectable sheath (Flexcath, Medtronic), through which the second-generation, 28-mm diameter 10.5F balloon catheter (Arctic Front Advance, Medtronic) was introduced. Selective catheterization of the PV was performed with the Achieve octapolar circular catheter (Medtronic), which was also used to measure real-time electrical insulation. After cryoballoon insufflation and occlusion of each vein (measured by contrast luminal retention), two applications of cryoenergy were performed, lasting 3 minutes, aiming at a temperature of -40°C in the catheter thermistor. The second application was a reinforcement one, for longer lasting of the lesion. To prevent injury to the phrenic nerve, applications in the right veins were performed under continuous phrenic stimulation through the decapolar catheter located in the upper right atrium (Figure 1). Esophageal temperature monitoring and full heparinization (ACT 300-350 seconds) were maintained.

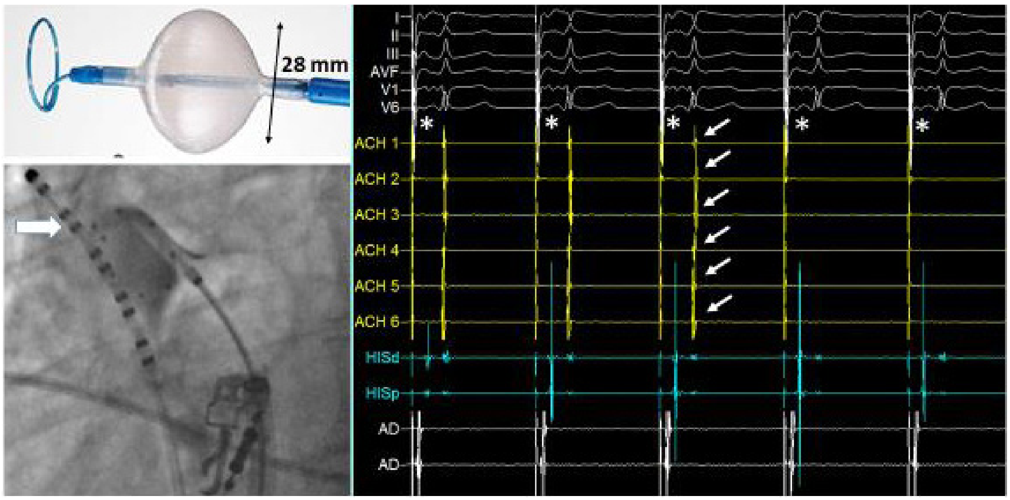

Figure 1 – *The upper left panel shows the 28-mm diameter cryoballoon and the octapolar circular catheter, used to measure real-time isolation of the pulmonary veins. In the lower left panel, fluoroscopic image showing the balloon catheter inflated in the ostium of the right superior pulmonary vein of the third case. Contrast retention inside the vein indicates vessel occlusion. Observe the circular catheter inside the vein and the decapolar catheter (arrow) placed in the upper right atrium for phrenic stimulation. In the right panel, intracavitary tracings showing the isolation of the same vein. From top to bottom, surface electrocardiogram (leads I, II, III, aVF, V1 and V6); electrograms recorded inside the vein by the circular catheter (ACH 1, 2 ACH, ACH 3, 4 ACH, ACH 5 and ACH 6); atrial and ventricular electrograms collected by the catheter positioned in the bundle of His (His D and His P); and electrograms of the two pairs of distal electrodes of the decapolar catheter in upper right atrium. Observe the sudden disappearance of the pulmonary vein potentials (arrows) 40 seconds after application of cryoenergy, indicating electrical isolation. The asterisks indicate the spicules of the continuous phrenic nerve stimulation by the catheter in the upper right atrium at 60 bpm cycles. Observe that the stimulation also commands the atria. Tracings at 50 mm/second.*

Twelve PV were treated (Figure 2), and electrical isolation was achieved in all (100%), with a mean of 2.3 adequate applications (-40°C) of cryoenergy per vein (mean of three applications per vein in the first patient and two per vein in the remaining). Applications with inadequate temperature were discontinued after approximately 30 seconds, and the balloon was repositioned. The mean procedure time (skin to skin) was 125 minutes (150, 150 and 75 minutes) and of fluoroscopy, 47 minutes (63, 47 and 33 minutes). The esophageal temperature did not change during the applications. At the end of the procedure, heparin was neutralized with protamine, hemostasis was obtained and a compressive dressing was performed. After recovery from anesthesia, the patients were sent to the infirmary, receiving enoxaparin (half the full dose – 0.5 mg/kg every 12 hours) during the first 24 hours. There were no complications, and all patients were discharged in the following morning, receiving the usual antiarrhythmic and anticoagulation drugs, in addition to omeprazole (for 30 days). The exams at hospital discharge (electrocardiogram and chest X-ray) were normal.

After a follow-up of 14 months, all patients remained asymptomatic and in sinus rhythm without antiarrhythmic drugs (withdrawn after 12 months), but receiving anticoagulants. There were no AF recurrences and the 24-hour Holter monitoring at 3, 6 and 12 months showed no arrhythmias.

Discussion

These were the first cases in the country that used the cryoballoon for treatment of paroxysmal AF. It was possible to safely isolate the PV, attaining adequate control of the arrhythmia in the 14-month follow-up. These observations support the literature.[4-6] In a multicenter randomized controlled trial comparing cryoablation with drugs, 70% (114/163) of the cryoablation group showed no recurrence after 1 year, compared with 7.3% (6/82) of the medication group. A systematic review reported 98% of immediate success with PV isolation, with maintenance of sinus rhythm of 72% after 1 year.[4] Considering these results, cryoablation and point-by-point RFA were classified as standard techniques for ablation of paroxysmal AF.[2]

Studies comparing RF ablation with cryoballoon indicated success and similar complications, but cryoablation is faster.[4,6,7] In this regard, one of our procedures was completed (skin to skin) in 75 minutes. While the overall rate of complications is similar, RFA tends to have a higher incidence of esophageal lesions and PV stenosis.[4] This is because, compared to the heat lesion in RFA, cryothermic cooling lesions show less tissue breakdown, are more homogeneous and less thrombogenic.[4] In contrast, cryoablation causes more phrenic lesions. Therefore, it is necessary to stimulate the phrenic nerve during the isolation of the right veins, immediately interrupting the application if there is any reduction in diaphragm contractions (Figure 1). With these measures, the incidence of permanent phrenic lesion is less than 0.3%.[4,7,9] We had no complications in our series. It is noteworthy the fact that a randomized controlled trial was recently published, demonstrating the non-inferiority of cryoablation in relation to RFA regarding safety and efficacy.[10]

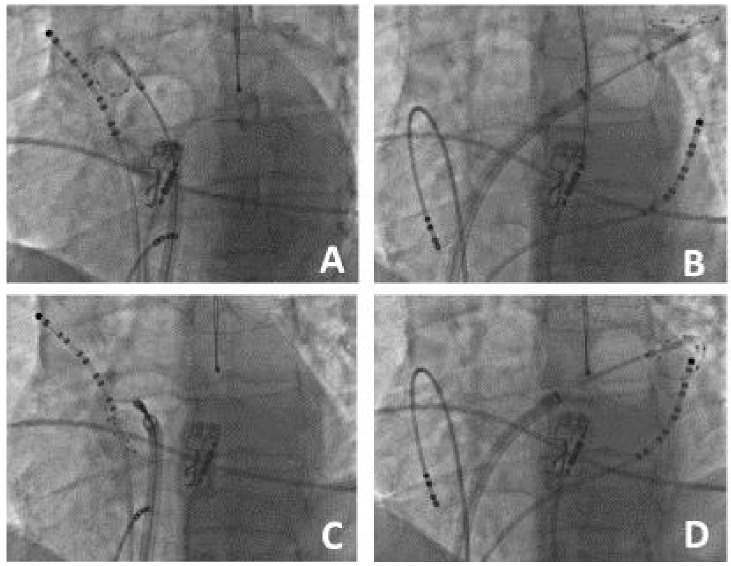

Figure 2 – *Fluoroscopic images in the left anterior oblique projection showing the position of the balloon catheter inflated in the ostium of the four pulmonary veins of the third case: (A) upper right; (B) upper left; (C) lower right; (D) lower left. In the B and C panels, observe the decapolar catheter positioned in the coronary sinus. This same catheter is subsequently used for phrenic stimulation in the upper right atrium during cryoablation of the right veins (A and D). Also, observe the esophageal thermometer (projecting on the spinal column).*

Cryoablation has a faster learning curve than the RFA.[4,5] However, it is currently indicated only in paroxysmal AF, as the cryoballoon lesions are restricted to the PV antrum.[4,9] The formation of linear lesions or the approach of other atrial regions require RF ablation.[1-3]

A limitation of this report is the sample size, which was small and obtained during the learning curve. The follow-up without antiarrhythmic drugs (two months) was short, but all patients were very symptomatic with frequent crises, despite the medication. The cost-effectiveness of the technique was not assessed.

This initial experience suggests that balloon cryoablation is effective and safe for fast PV isolation in patients with paroxysmal AF.

Author contributions

Conception and design of the research: Fenelon G, Perin MA, Makdisse M, Paola AAV; Acquisition of data: Fenelon G, Scuotto F, Fischer C, Paola AAV; Analysis and interpretation of the data: Fenelon G, Scuotto F, Paola AAV; Writing of the manuscript: Fenelon G.

Potential Conflict of Interest

Dr. Guilherme Fenelon received assistance from the manufacturer of the product for participation in congress. The rest have no conflicts.

Sources of Funding

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Study Association

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

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Cardiac Catheterization in a Patient with Obstructive Hypertrophic Cardiomyopathy and Syncope

Rafael Amorim Belo Nunes, Henrique Barbosa Ribeiro, Luiz Junya Kajita, Fábio Antônio Gaiotto

Instituto do Coração – Hospital das Clínicas – Faculdade de Medicina – Universidade de São Paulo (USP), São Paulo, SP – Brazil

A 35-year-old man sought medical care for recurrent syncope episodes related to moderate exertion in the past 2 months. Upon physical examination, the presence of a rude systolic murmur on the left sternal border was identified. The echocardiogram disclosed a moderate increase in the left atrium and significant hypertrophy of the interventricular septum with an estimated maximum diastolic diameter of 31 mmHg and a maximum left ventricular outflow tract gradient of 56 mmHg. The 24-hour Holter assessment showed the presence of frequent ventricular extrasystoles and an episode of nonsustained ventricular tachycardia. He was prescribed metoprolol 50 mg daily and, based on the high risk of sudden death, received an implantable cardioverter-defibrillator.

Despite the progressive increase in beta-blocker doses, the patient remained quite symptomatic with daily episodes of lipothymia and angina pectoris at minor exertion. Invasive strategy to reduce the intraventricular gradient was planned and the patient underwent a hemodynamic study to better assess the coronary and interventricular septum anatomy.

Keywords

Cardiomyopathy, Hypertrrophic; Cardiac Catheterization; Syncope.

Mailing Address: Rafael Amorim Belo Nunes •
Rua Luis Carlos gentile de Laet 1518 casa 58. Postal Code 02378-000, Horto Florestal, São Paulo, SP – Brazil
E-mail: rafael.amorim@hc.fm.usp.br, ra.nunes16@gmail.com
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The coronary angiography showed extrinsic compression of the first diagonal branch and septal arteries (Panel A). Simultaneous ventriculography of both ventricles disclosed significant hypertrophy of the medial and basal portions of the interventricular septum (Panel B) with left ventricular outflow tract obstruction (Panel C). The isoproterenol infusion during manometry resulted in increased intraventricular gradient from 30 mmHg to 130 mmHg, which revealed an important dynamic obstructive component. The patient was submitted to septal myectomy with no complications, with a significant reduction in the intraventricular gradient.

Author contributions

Conception and design of the research and Writing of the manuscript: Nunes RAB; Acquisition of data: Kajita LJ, Gaiotto FA; Analysis and interpretation of the data: Nunes RAB, Ribeiro HB, Kajita LJ, Gaiotto FA; Critical revision of the manuscript for intellectual content: Nunes RAB, Ribeiro HB.

Potential Conflict of Interest

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

Sources of Funding

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Study Association

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

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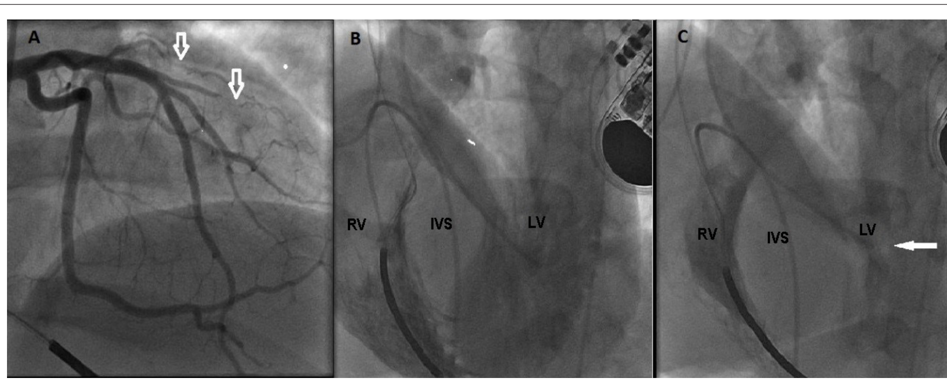

Figure 1 – *Panel A, extrinsic compression of the diagonal branch and septal branches (white arrows). Panel B, ventriculography of the right ventricle (RV) and left ventricle (LV), showing significant interventricular septal (IVS) hypertrophy during diastole and Panel C, LV outflow tract obstruction during end-systole.*

Major Depression as a Complicating Factor for Acute Coronary Syndrome

Levent Cerit
Near East University, Nicosia – Cyprus

Dear Editor,

I have read with great interest the article entitled "Major Depression and Acute Coronary Syndrome-Related Factors" by Figueiredo et al.,[1] recently published in journal. The investigators found a 23% prevalence of patients with acute coronary syndrome (ACS) meeting the diagnostic criteria for major depressive disorder (MDD). Women were more susceptible to develop MDD in the sample group of ACS patients, with a three-and-a-half-time greater likelihood than men.[1]

Almost half of patients with ACS are affected by depression,[2] many of them receiving antiplatelet therapy and often treated with a serotonin selective reuptake inhibitor (SSRI). Fluoxetine and fluvoxamine are potent inhibitors of CYP2C19.[3] Clopidogrel is a pro-drug that undergoes a two-stage activation process, which is mediated by several cytochrome P450 (CYP) hepatic enzymes. CYP2C19 is involved in both activation steps, raising concern that the drug that inhibit CYP2C19 may decrease clopidogrel's effectiveness.[4] Bykov et al.[5] reported that treatment with a CYP2C19-inhibiting SSRI such as fluoxetine and fluvoxamine when initiating clopidogrel might be associated with slight decrease in its effectiveness.

In this context, considering not only the concomitant disorder with ACS but also the complicating factor due to CYP2C19-inhibiting SSRI treatment, MDD should be evaluated meticulously.

Keywords

Acute Coronary Syndrome; Depression; Seorotin Uptake Inhibitors.

Mailing Address: Levent Cerit •
Near East University. 07100, Nicosia – Cyprus
E-mail: drcerit@hotmail.com, drcerit@yahoo.com
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Letter to the Editor

Reply

The authors are grateful for the comments made in a letter to the editor regarding the article Major Depression and Acute Coronary Syndrome-Related Factors, published in Arq Bras Cardiol. 2017; 108 (3): 217-227.

We agree with the relevant comments of the author of the letter, warning about the use of antidepressants in patients with acute coronary syndrome and their interaction with the antiplatelet Clopidogrel.

We complement the comments with the following considerations:

1) The effectiveness of Clopidogrel (a platelet P2Y12 receptor blocker), in its action as a platelet antiadhesive, among other known and unknown actions, is dependent on its conversion to an active metabolite by the cytochrome-dependent P450 (CYP- 450), mainly CYP2C19. Its effect as a platelet antiadhesive is lower in patients who are homozygous for non-functional alleles of CP2C19 genes, so-called "poor metabolizers". It is not recommended the use of Clopidogrel in these patients and, when possible, to identify these cases using genetic tests. Therefore, any other drug that interferes with the cytochrome dependent system altering the conversion of Clopidogrel to its active metabolite, mainly in the poor metabolizers, may reduce its effect.

Selective serotonin reuptake inhibitor antidepressants (such as fluoxetine, fluvoxamine, etc.) may interfere with the metabolism of clopidogrel, increasing the adverse effect of clopidogrel (by increasing the inhibition of the P2Y12 receptor) and, therefore, increasing the Risk of bleeding, decreasing the concentration of the active metabolite of Clopidogrel, mainly in the genetically "poor metabolizers", reducing its effectiveness.

2) Selective serotonin reuptake inhibitor antidepressants have multiple adverse cardiovascular effects such as: chest pain, angina pectoris, palpitation, arterial hypertension, prolonged *QT interval* on the *ECG*, ventricular arrhythmias, syndrome of inappropriate antidiuretic hormone secretion, increase of the risk of severe hyponatremias in patients already in use of diuretics, among innumerable adverse effects, which always more serious in patients with acute coronary syndrome.

3) Our article sought to initially verify the presence of the pattern (set of variables found in association) that is called "Major Depression" among patients with another pattern called Acute Coronary Syndrome and hospitalized in the hospital coronary units environment. In addition to this identification of variable patterns (diagnostics), we intend to study how and which, among the variables collected in these individuals, including sociodemographic variables, were associated. We do not intend to define causal associations, even because the design of the study would not allow such inferences. However, we intend to understand the interactions between variables present in a certain evolutionary state of patients' lives. This allows us a better clinical understanding of the person and, therefore, greater possibility of helping it during its evolution in this acute period and its subsequent evolution. We do not understand causality deterministically, that is, if the variable x is present then y will occur. We understand a person as a complex system that interacts with the environment in which he lives. Therefore, it is more important to understand the organization or interaction between component variables, which we can be identified in that complex system formed by people living in an environment (including the hospital environment), than to isolate possible "causal" variables, whether genetic or pharmacological and impute a direct causality that does not exist or that we only identify in simple or more stable systems. We believe that complex thinking is the basis of clinical judgment and that the important thing is to understand the biological system as a whole, due to its constant evolution or dynamics. For this, only observing the system in its continuous evolution.

We have chosen the linear log model to study these interactions as shown in Figures 1 and 2 of the article. The previous history of depression was one of the variables of that model. Certainly, these patients were already exposed to antidepressant drug use during their lifetime, but we cannot conclude, and it was not our goal, that these drugs "cause" coronary syndrome. However, from the clinical point of view, the associations found indicate that individuals and clinicians should be warned that antidepressants may be involved in the interactions of variables that make up the pattern Acute Coronary Syndrome and its complications (eg. arrhythmias), and that this type of drug also interacts with other drugs such as antiplatelet drugs, diuretics and others, composing other patterns such as hyponatremia syndrome of inappropriate secretion of antidiuretic hormone, and even opposing patterns such as bleeding or loss of the efficacy of Clopidogrel.

Clinical thinking needs to detach itself from the bonds in which deterministic and causal thinking placed it and return to what has always been clinical judgment, now with a strong theoretical basis, complex thinking and complex adaptive dynamic systems. To do this we have to observe the evolution of the person throughout his life and his relationship or interaction with the environment in which he lives, including his social and cultural relations and understand the interactions between infinite variables always with a degree of uncertainty and considering the appearance of emerging or unpredictable phenomena.

José Henrique Cunha Figueiredo
Nelson Albuquerque de Souza e Silva
Basilio de Bragança Pereira
Gláucia Maria Moraes de Oliveira