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EDITORIAL

Continuous Aerobic and High-Intensity Interval Exercise: Which one Produces greater Post-Exercise Hypotension?

André L. Teixeira and Lauro C. Vianna

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Exercise training is a key recommendation for maintenance of a healthy life style. It is well established that regular physical exercise provides innumerous physiological and psychological benefits not only to young healthy subjects, but also individuals with diabetes, heart failure, Parkinson disease, multiple sclerosis, claudication, autonomic failure, hypertension, among others. A well-documented physiological response to exercise is called post-exercise hypotension (PEH), in which a single bout of exercise leads to a decrease in arterial blood pressure. The first study showing PEH was published in 1898 by Dr. L. Hill.[1] Thereafter, several authors confirmed these results showing that a single bout of exercise can reduce arterial blood pressure below pre-exercise values. However, one question that remains to be answered is which exercise modality produces greater PEH?

Previous studies have shown that continuous aerobic (CONT) exercise, high-intensity interval (HIIE) training, isometric exercise and resistance-based exercise can lead to a PEH.[2] Studies comparing CONT and HIIE showed that the magnitude of PEH was slightly superior following HIIE compared with CONT exercise.[3,4] However, in these studies, the exercise protocols were not matched by volume. This is important because longer exercise duration and higher-intensity exercise results in greater decreases in arterial blood pressure and longer PEH duration when compared with a short bout of low-intensity exercise.[5,6]

Keywords

Blood Pressure; Exercise Therapy; Hypertension/diagnosis; Hypertension/physiopathology; Hypertension/therapy, Physical Endurance; Time Factors; Treatment Outcome.

It is in this context that Boeno and colleagues,[7] in the current issue of the International Journal of Cardiovascular Sciences, take an important step forward in comparing CONT and HIIE in terms of the magnitude of PEH. The authors aimed to evaluate PEH following a single bout of CONT or HIIE running adjusted by equivalent volumes in healthy subjects. In a randomized cross-over design, thirteen young, sedentary and normotensive men were exposed to either CONT or HIIE treadmill running. Participants performed exercise until the completion of 5 km in CONT (at 70% of maximal heart rate previously obtained during maximal cardiopulmonary exercise test) or HIIE training (1-min running at 90% followed by 1-min at 60% maximum heart rate). Hemodynamic variables (heart rate and arterial blood pressure) were measured at rest, immediately after and 60-min following exercise (every 5-min of recovery). The main finding of the study was that both CONT and HIIE, matched by volume, promoted PEH in a similar magnitude. However, the onset of PEH was slightly different between exercise modalities. Indeed, PEH started 15-min following HIIE and remained throughout the 60-minute period, whereas PEH was initiated at the 30th minute following CONT running and remained throughout the testing period. Overall, Boeno et al.[7] provide exciting results on the effects of different running exercise modalities (i.e., CONT vs. HIIE) on acute blood pressure reduction following exercise.

The underlying mechanisms of PEH are not fully understood, but compelling evidence suggests that the central baroreflex pathway plays a key role in the development of PEH.[3,4] The arterial baroreflex represents a closed-loop, negative feedback control system involved in the regulation of arterial blood pressure. Mechanically-sensitive receptors located in the carotid

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body and aortic arch relay information to the brainstem regarding beat-to-beat changes in blood pressure.[8] In healthy individuals, arterial baroreflex remains functional during exercise by resetting to operate around the prevailing pressure elicited by exercise. However, some evidence suggests that arterial baroreflex function is impaired in hypertensive subjects and normalized by exercise training.[9] In this sense, although the work of Boeno et al.[7] suggests that PEH was similar between CONT and HIIE matched by volume, these results was observed in young sedentary normotensive men, limiting its extrapolation to other populations. Indeed, although PEH occurs in normotensive and hypertensive individuals, its occurrence is more prominent in hypertensive individuals.[10]

In conclusion, Boeno and colleagues should be commended for their approach equalizing exercise volume to examine PEH in response to CONT and HIIE. They demonstrated for the first time that exercise volume plays a critical role on the magnitude of PEH when comparing CONT and HIIE in young healthy subjects. We now await further studies examining the magnitude of PEH comparing CONT and HIIE matched by volume in older individuals and patients with hypertension to definitively answer that, if adjusted by equivalent volumes, both CONT and HIIE produce similar PEH.

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ORIGINAL ARTICLE

Endothelial Dysfunction and Pulse Wave Reflection in Women with Polycystic Ovarian Syndrome

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Abstract

Background: Patients with polycystic ovarian syndrome (PCOS) have an increased prevalence of metabolic syndrome and traditional atherosclerotic risk factors, such as dyslipidemia, diabetes and hypertension. Endothelial function and vascular stiffness are surrogate markers of early atherosclerosis, able to predict cardiovascular events.

Objective: To compare endothelial function and pulse wave reflection between women with PCOS and healthy controls.

Methods: Observational and cross-sectional study that included women with PCOS, age between 18 and 40 years-old and body mass index between 25.0 and 35.0 kg/m^2, and healthy controls. Rotterdan criteria was used to diagnose PCOS. Subjects underwent clinical and anthropometric evaluation, laboratory and hormonal assays and imaging tests to measure pulse wave velocity (PWV), augmentation index (AIx) and brachial artery flow-mediated vasodilation (FMD). Kolmogorov-Smirnov test showed normal distribution of most parameters. Unpaired Student t-test was used with significance level established at $p < 0.05$.

Results: A total of 52 patients were included, 29 (56%) in PCOS group and 23 (44%) in control group. Clinical and laboratory parameters were similar between the groups. Women with PCOS had lower FMD (8.8 ± 1.0 vs 12.8 ± 1.2%, p = 0.021); PWV and AIx were similar between the groups (7.5 ± 0.2 vs 7.5 ± 0.3 m/s, p = 0.671 and 21.0 ± 1 vs. 20 ± 2%, p = 0.716, respectively). In the PCOS group, women with higher testosterone levels had higher AIx (25 ± 2 vs. 17 ± 3%, p = 0.045).

Conclusions: PCOS women had endothelial dysfunction and those with higher testosterone levels had higher pulse wave reflection as compared with controls. (Int J Cardiovasc Sci. 2019;32(1)3-9)

Keywords: Endothelium, Vascular; Vascular,Stiffness; Metabolic Syndrome; Polycistic Ovary Syndrome; Insulin Resistance; Testosterone.

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common metabolic disorders in women, with an estimated prevalence of 5 to 15%.[1] The cardinal features of the syndrome encompass hyperandrogenism, ovulatory dysfunction, and/or polycystic ovaries on ultrasound. Obesity, insulin resistance and metabolic syndrome are closely related to PCOS. A recent meta-analysis observed a higher risk of metabolic syndrome in women with PCOS (OR 2.88, 95% CI 2.40-3.45), as well as glucose intolerance and diabetes mellitus (DM).[2] The occurrence of metabolic disorders is also elevated in non-obese PCOS patients, suggesting that the presence of the syndrome per se may favor the development of metabolic comorbidities.[3] In addition, women with PCOS have an increased prevalence of traditional atherosclerotic risk factors, such as dyslipidemia, DM and hypertension.[3,4] The present study aims to evaluate if parameters indicative of early atherosclerosis are also observed in patients with PCOS.

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Despite the association of PCOS with cardiovascular (CV) risk factors, recent studies showed controversial results regarding the incidence of CV events in women with PCOS.[5,6] A retrospective cohort study in United Kingdom showed a high incidence of DM, myocardial infarction (MI) and angina in women with PCOS, with over a quarter of the elderly individuals having had MI or angina.[5] However, a retrospective cohort study in the United States observed no increase in CV events in PCOS women,[6] which may be explained by different PCOS profiles, androgen levels, insulin resistance and body composition of the populations.[7] Thus, markers of atherosclerosis could be of help in improving CV risk stratification in PCOS women.

Endothelial function and vascular stiffness are surrogate markers of early atherosclerosis and can be easily measured by noninvasive methods, such as flow-mediated vasodilation (FMD) and carotid-femoral pulse wave velocity (PWV), respectively.[8,9] Moreover, both FMD and PWV have shown to be independent predictors of CV events in the general population.[10,11] A recent meta-analysis reported that PCOS women have approximately 4% lower FMD, irrespective of body mass index (BMI) and age.[12] However, there was significant heterogeneity across studies included in this meta-analysis.[12] Previous studies have shown an association between PCOS and PWV,[13,14] but these results could be influenced by age, BMI and comorbidity, in special the presence of hypertension. Other studies that controlled for these confounders did not find a correlation between PCOS and PWV.[15–18]

The aim of the present study was to compare endothelial function and pulse wave reflection between young, overweight women with PCOS and healthy controls.

Methods

Study population

This study recruited 52 consecutive women from the outpatient internal medicine and general gynecology clinics of our institution. We included patients with Rotterdam criteria for PCOS and age between 18-40 years. Exclusion criteria were evidence of secondary hypertension, BMI (calculated as weight divided by height squared) ≥ 35 kg/m², smoking, coronary artery disease, kidney or thyroid disease, hormone replacement therapy, DM or impaired tolerance glucose, severe dyslipidemia (LDL-cholesterol ≥ 4.14 mmol/L and/or triglycerides ≥ 3.39 mmol/L), use of lipid-lowering drugs, prolactin (PRL) > 25 ng/ml or pregnancy. Control group was composed by healthy female patients without PCOS criteria from the same institution. The protocol was approved by the local Ethics Committee Research (2795-CEP/HUPE), and all patients gave written informed consent.

PCOS was diagnosed according to the 2003 Rotterdam Criteria with at least two of the following features: oligomenorrhea (or amenorrhea) or hirsutism, clinical or biochemical hyperandrogenism, and polycystic ovaries on ultrasound. Patients with oligomenorrhea or hyperandrogenism caused by any other clinical conditions were excluded, such as nonclassical 21-hydroxylase deficiency, congenital adrenal hyperplasia, hypothyroidism, Cushing's syndrome, or significant elevation in serum PRL.

Laboratory evaluation

Venous blood samples were collected after 12 hours of fasting. Serum lipids (total cholesterol, high-density lipoprotein [HDL]-cholesterol, triglycerides), and blood glucose were measured using an auto analyzer technique (Technicon DAX 96; Miles Inc). Low-density lipoprotein (LDL)-cholesterol was calculated with the Friedewald formula when triglyceride values were < 400 mg/dL. Insulin was measured by radioimmunoassay, and serum C-reactive protein levels were measured by nephelometry using an immunochemistry system. Serum levels of testosterone and PRL were measured during the early follicular phase (days 2 to 5 of the menstrual cycle) and dehydroepiandrosterone sulphate (DHEAS) were measured using enzyme-linked immunosorbent assay (ELISAs).

Assessment of endothelial function

FMD was assessed as a measure of endothelial function.[19] The participant was positioned supine with the arm in a comfortable position, and the brachial artery was imaged above the antecubital fossa. After 10 minutes of rest, the right brachial artery was scanned in longitudinal section, 5 cm above the antecubital fossa, using a linear array transducer to acquire the baseline diameter of the brachial artery. A cuff was then inflated to at least 50 mmHg above systolic blood pressure and deflated after 5 minutes to induce reactive hyperemia. A pulse wave Doppler recording in the artery lumen documented the flow increase, and the maximal diameter 30, 60, and 90 seconds after cuff release was registered.

FMD was calculated as the percentage change of brachial artery diameter from baseline.

Pulse wave velocity

The same investigator measured the carotid-femoral PWV using a Complior device (Alam Medical, France) after the patients had rested for 10 minutes in supine position in a quiet room with a stable temperature.[8] All measurements were performed between 8 a.m. and 11 a.m. During the measurements, speaking or sleeping was not allowed, and no meal, caffeine or smoking was allowed within 3h before measurement. Pulse waveforms were obtained transcutaneously from the right common carotid artery and femoral artery. Aortic PWV was calculated by dividing the distance traveled (DT) by the transit time (TT). TT was obtained by measuring the time difference between the arrival of the pulse wave at the femoral and at carotid arteries. DT was measured using a tape measure and estimated as 80% of the distance between carotid and femoral arteries. Carotid-femoral PWV was calculated as DT in meters divided by TT in seconds (PWV = DT/TT). The mean of two measurements was calculated and when the difference between them was more than 0.5 m/s, a third measurement was obtained. All PWV values were adjusted by mean arterial pressure (MAP) to obtain normalized PWV (PWV norm) as 100 x (PWV/MAP).

Central hemodynamic parameters

Applanation tonometry was performed with the SphygmoCor system (Atcor Medical, Sydney, Australia) with the patient in the sitting position, resting the arm on a rigid surface, and a sensor in the radial artery.[20] Central aortic pressure was calculated from the radial pulse wave analysis with the use of a validated transfer function. Wave reflection parameters, such as augmentation pressure (AP) and augmentation index (AIx), were also obtained by this method.

Statistical analysis

Continuous variables were expressed as mean ± standard error and categorical variables were described as absolute numbers and/or percentages. Kolmogorov-Smirnov test showed normal distribution of the variables. Differences between the two study groups were evaluated with unpaired Student's t-tests for continuous variables. All tests were performed considering a significance level of 5% and a two-tailed probability. Based on a recent study,[12] assuming a 5% level of significance and 85% power, we estimated 18 patients in each group to detect 4% difference in FMD between the groups and 4% standard deviation.12 Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 18.0 for Windows (SPSS, Chicago, IL).

Results

Fifty-two patients were included, 29 (56%) in PCOS group and 23 (44%) in control group. The demographics and clinical characteristics of study patients are presented in Table 1. Clinical and laboratorial parameters were similar between the groups. No cases of acne, alopecia,

Table 1 - Clinical and demographic characteristics of patients with polycystic ovarian syndrome (PCOS) (n = 52)

	Control (n = 29)	PCOS (n = 23)	p value
Age (years)	29 ± 1	28 ± 1	0.399
BMI (kg/m²)	28.6 ± 0.7	28.9 ± 0.7	0.809
Waist circumference (cm)	91 ± 1	95 ± 2	0.156
Systolic BP (mmHg)	116 ± 2	118 ± 2	0.640
Diastolic BP (mmHg)	72 ± 1	73 ± 2	0.633
Insulin (mcU/mL)	14.3 ± 1.7	14.1 ± 1.3	0.934
Glucose (mg/dL)	86 ± 2	87 ± 1	0.671
HOMA–IR	3.1 ± 0.4	3.0 ± 0.3	0.802
HOMA-Beta	241 ± 44	251 ± 34	0.866
Total cholesterol (mg/dL)	188 ± 10	178 ± 7	0.452
LDL-cholesterol (mg/dL)	120 ± 9	104 ± 6	0.150
HDL-cholesterol (mg/dL)	52 ± 3	49 ± 2	0.521
Triglycerides (mg/dL)	104 ± 10	122 ± 14	0.334
Testosterone (ng/dL)	28 ± 5	47 ± 7	0.052
DHEAS (mmol/liter)	190 ± 38	170 ± 21	0.623

BMI: body mass index; BP: blood pressure; HOMA: homeostatic model assessment; LDL: low-density lipoprotein; HDL: high density lipoprotein; DHEAS: dehydroepiandrosterone sulphate. Between-group differences were analyzed using unpaired Student's t-test, considering a significance level of 5% and a two-tailed probability. Values expressed as mean ± standard error.

seborrheic dermatitis and acanthosis nigricans were observed in PCOS patients.

Brachial artery diameter was similar between the groups (3.13 ± 0.38 vs. 3.23 ± 0.37, p = 0.49). PCOS group had significant lower FMD than control group (Figure 1). PWV, AIx and aortic pressures were similar between the groups (Table 2).

When PCOS individuals were divided into two groups according to the median of serum testosterone (46.4 ng/dL), those with higher and lower testosterone levels had similar baseline clinical and laboratorial characteristics. PWV, FMD and aortic pressures were also similar between the groups. However, AIx was significantly higher in patients with higher testosterone levels (25 ± 2 vs. 17 ± 3%, p = 0.045; Figure 2).

Table 2. Vascular parameters of patients with polycystic ovarian syndrome (PCOS) (n = 52)

	Control (n = 29)	PCOS (n = 23)	p value
Flow mediated vasodilation (%)	12.8 ± 1.2	8.8 ± 1.0	0.021
CR PWV (m/s)	9.1 ± 0.3	8.8 ± 0.2	0.930
CF PWV (m/s)	7.5 ± 0.3	7.5 ± 0.2	0.671
Augmentation pressure (mmHg)	6 ± 1	8 ± 2	0.337
Augmentation index (%)	20 ± 2	21 ± 1	0.716
Aortic systolic pressure (mmHg)	106 ± 2	116 ± 5	0.320
Aortic pulse pressure (mmHg)	31± 1	35 ± 4	0.335

Values expressed as mean ± standard error; CF- PWV: carotid-femoral pulse wave velocity; CR-PWV: carotid-radial pulse wave velocity. Between-group differences were analyzed using unpaired Student's t-test, considering a significance level of 5% and a two-tailed probability.

Discussion

In the present study, young overweight women with PCOS had endothelial dysfunction. In addition, women with PCOS and higher testosterone levels had higher

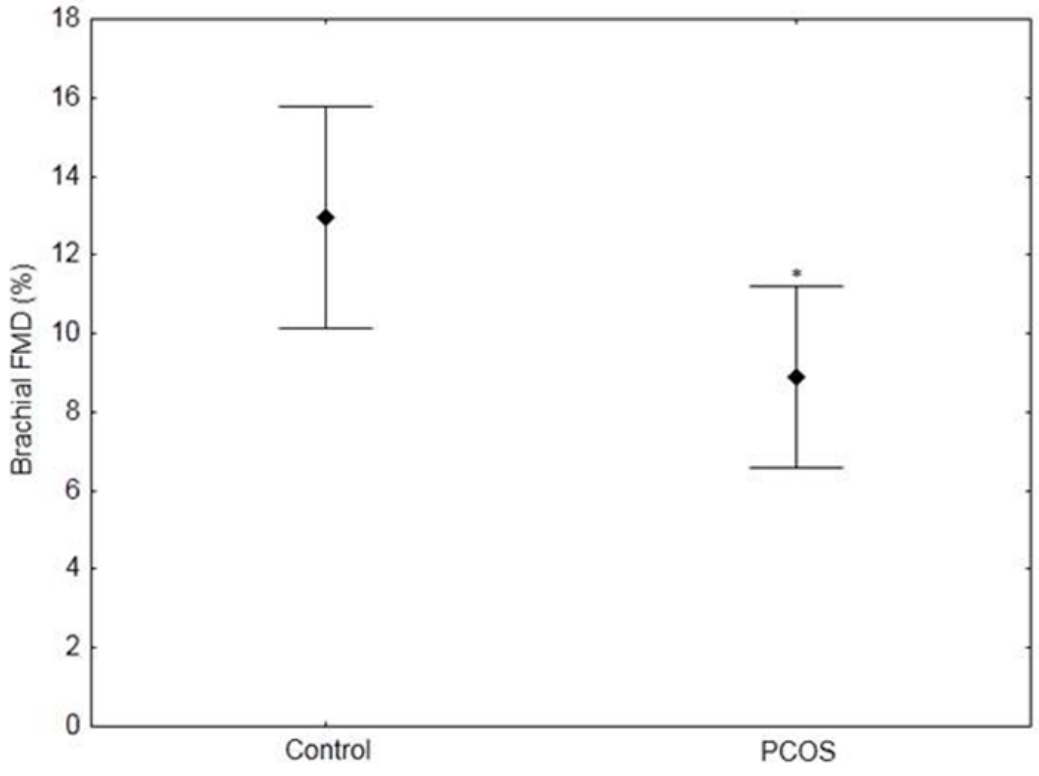

Figure 1 - Lower brachial flow-mediated dilation values in polycystic ovarian syndrome (PCOS) group (n = 29) compared with control group (n = 23). P value = 0.021 by Student's t-test.

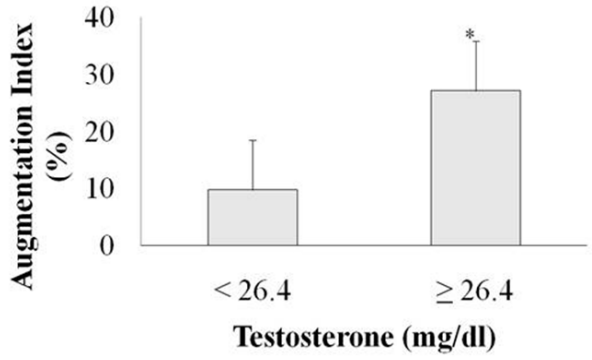

Figure 2 - Bar graph comparing augmentation index (mean ± standard error) by testosterone levels in polycystic ovarian syndrome (POS) women after division by the median; *P = 0.045 by Student's t-test.

pulse wave reflection than those with PCOS and lower testosterone levels. Previous studies have shown that women with PCOS have high prevalence of CV risk factors, in addition to besides the clinical features of menstrual irregularity, hyperandrogenism and infertility. Thus, some studies have suggested an association between PCOS and accelerated CV disease.[7,21,22] Recent cohort studies had controversial results regarding CV events in PCOS patients.[5,6] Both endothelial dysfunction and arterial stiffness have been associated to worse CV outcomes in the general population and are proposed as complementary CV risk evaluation.[10,11]

Vascular endothelium plays a crucial role in maintaining vascular homeostasis and endothelial dysfunction is an important early step in the development of atherosclerosis and CV diseases.[21] There are many pathophysiological mechanisms that explain the relationship between PCOS and endothelial dysfunction.[7,21] Insulin resistance impairs intracellular signaling, which in endothelium may cause lower production of nitric oxide and increased secretion of endothelin-1, leading to vasoconstriction and decreased blood flow.[23] Moreover, hyperinsulinemia exerts a direct hypertrophic effect on the vascular wall, which deteriorates endothelial function and may lead to vascular stiffening.[7,21,23] Other proposed mechanisms involve atherogenic dyslipidemia, lipo-oxidative stress, products of glycation and glycoxidation, and inflammatory cytokines.[7]

One of the first studies relating PCOS and endothelial dysfunction was published in 2001 and enrolled 12 patients with PCOS and 13 age- and weight-matched controls.[24] They observed that PCOS subjects had endothelial dysfunction that was related to hyperandrogenism and insulin resistance.[24] These results have been confirmed by subsequent studies and a recent meta-analysis, which showed that PCOS women had a pooled mean FMD 3.4% lower than controls.[12,18,25] However, there are controversies if endothelial dysfunction is a consequence of high androgen levels, hyperinsulinemia-obesity syndrome or both.[18,24,26]

A previous study compared PCOS women and controls, both groups with BMI < 30 kg/m^2, and observed that PCOS subjects had lower FMD and higher androgen levels despite no biochemical evidence of insulin resistance.[18] A similar study involving overweight young women with PCOS also observed endothelial dysfunction, but FMD was statistically correlated not only to high androgen levels but also to inflammatory markers and insulin resistance.[26] In contrast, a previous small study of PCOS women with high testosterone levels and normal insulin resistance did not observe endothelial dysfunction.[27] A study of PCOS subjects with high androgen levels also did not observe lower FMD when compared to age- and BMI- matched controls; in that study, the PCOS group had hyperinsulinemia.[28] In addition, a study comparing non-obese PCOS women and age- and BMI-matched controls showed similar FMD despite higher androgen levels in PCOS subjects; insulin levels and HOMA-IR indices were similar between the groups.[29] In the present study, women with PCOS had endothelial dysfunction, and our sample consisted essentially of young and overweight women. Furthermore, insulin levels and both HOMA-IR and HOMA-Beta were within normal range for their BMI, suggesting a non-significant insulin resistance. Thus, our results reinforce that PCOS women may have endothelial dysfunction due to mechanisms other than insulin resistance.

Changes in the arterial wall, with loss of elastin fibers and increase in collagen proteins, leads to vascular stiffening.[30] Age and hypertension are two of the most important factors that trigger these modifications.[30] Endothelial dysfunction and arterial stiffening are related to each other. Carotid-femoral PWV is the gold-standard method to evaluate arterial stiffness and is a powerful and independent predictor of CV events.[11,31]

A previous study enrolled overweight women and demonstrated that subjects with PCOS had higher PWV and lower FMD than controls.[32] However, other studies did not confirm the hypothesis of stiffer vessels in PCOS

women. In a young and non-obese sample of PCOS subjects, PWV and AIx were similar to healthy controls.[18] A recent study of 84 women with PCOS and 95 healthy volunteers, aged 16-45 years, also reported similar PWV between groups.[15] However, a small study showed that PCOS non-obese women had higher AIx than healthy controls, although not measuring PWV.[33] Our study showed that PWV and AIx were similar between PCOS subjects and controls. On the other hand, those PCOS women with higher testosterone levels had higher AIx, indicating greater reflected pulse wave, which might represent an initial process of arterial stiffness. As PWV is largely influenced by age, young patients, including those with PCOS, tend to have normal values. AIx may be a better parameter in this population, as it reflects the influence, at the aortic level, of an increased stiffness of the arterial tree.[30]

This study has some limitations. First, sample size was small, so that we could have missed a small difference between PWV in PCOS and control groups. Second, as a cross-sectional study, we could not evaluate the occurrence of CV events, but merely suggest an association between FMD, AIx and PCOS. An important consideration of the study was to hypothesize a relationship between hyperandrogenism and an increased pulse wave reflection, maybe associated with arterial stiffness.

Conclusion

In summary, these PCOS women demonstrated endothelial dysfunction when compared to those young overweight women without the syndrome. Moreover, higher testosterone levels, even in the normal range, were associated with an increase in pulse wave reflection. Large prospective studies are needed to evaluate the prognostic value of FMD, PWV and AIx in this population. In addition, large trials can analyze if measurement of endothelial function and arterial stiffness would improve CV risk stratification beyond traditional atherosclerotic risk factors.

Author contributions

Conception and design of the research: Burlá M, Oigman W, Neves MF, Medeiros F. Acquisition of data: Burlá M. Analysis and interpretation of the data: Burlá M, Cunha AR, Gismondi R, Oigman W, Neves MF, Medeiros F. Statistical analysis: Cunha AR, Gismondi R, Neves MF. Obtaining financing: Neves MF. Writing of the manuscript: Burlá M, Cunha AR, Gismondi R, Oigman W, Neves MF, Medeiros F. Critical revision of the manuscript for intellectual content: Burlá M, Cunha AR, Gismondi R, Oigman W, Neves MF, Medeiros F.

Potential conflict of interest

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

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Study association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital Universitário Pedro Ernesto under the protocol number 2795. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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ORIGINAL ARTICLE

Cardiovascular Disease in Patients with Ankylosing Spondylitis from the Rheumatology Outpatient Clinic of the UFMS-affiliated Hospital

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Abstract

Background: Cardiovascular diseases are a major cause of morbidity and mortality today. Despite its wide distribution, it presents particularly prevalent in certain groups of individuals, particularly when exposed to a higher degree of inflammation, giving increased cardiovascular risk. Rheumatic diseases expose their holders to this increased cardiovascular risk condition; however only recently have been associated with spondyloarthritis, particularly ankylosing spondylitis (AS). For being a classically autoimmune disease related to HLA histocompatibility system, AS may present phenotypic variations in different ethnic groups with possible diverse cardiovascular consequences.

Objectives: To estimate the prevalence of cardiovascular disease (CVD) and the cardiovascular risk profile, correlating the time since diagnosis and activity of ankylosing spondylitis (AS) in patients from the rheumatology outpatient clinic of the UFMS-affiliated hospital.

Methods: Of 55 patients with AS, 42 were selected consecutively and compared to a control group (CG) in a cross-sectional study. Patients with diabetes, indigenous background and pregnant women were excluded. Quantitative variables were assessed by use of Student t test, while qualitative variables, by chi-square test. The patients underwent electrocardiography, echocardiography and carotid Doppler examination, measurement of serum lipid levels and inflammatory markers, and were stratified according to global cardiovascular risk. The AS activity and impairment were evaluated by use of the BASMI, BASDAI, BASFI and ASDAS.

Results: Mean age, 42.87 ± 12.37 years; time since AS diagnosis, 10.76 ± 8.74 years. There was no difference in cardiovascular risk stratification between the groups, most of the patients being at high or moderate risk (AS: 64.3%, and CG: 52%, p = 0.134). The prevalence of manifest CVD (2%) showed no difference between the groups, except for right bundle-branch block (AS: 14%, and CG: 2%, p = 0.027). The prevalence of subclinical CVD showed no difference between the groups, except for higher carotid medial-intimal thickness (CIMT) in the AS group (AS: 1.82 ± 2.63, and CG: 0.67 ± 0.16, p = 0.018). There was no correlation between AS activity or inflammatory markers and CVD, but with time since AS diagnosis and CIMT (p = 0.039, r = 0.328).

Conclusions: Prevalence of CVD and risk factors was similar in the groups. Subclinical atherosclerosis degree was higher in the AS group, related to the time since diagnosis, but was independent of the cardiovascular risk factors or inflammation. Most patients with AS are at high cardiovascular risk. (Int J Cardiovasc Sci. 2019;32(1)10-18)

Keywords: Cardiovascular Diseases; Risk Factors; Cross-Sectional Studies; Spondylitis, Ankylosing / complications; Spondylitis, Ankylosing / diagnosis.

Introduction

Cardiovascular diseases (CVD) are currently a major cause of morbidity and mortality. Recent data from the World Health Organization have shown that 30% of the total of deaths worldwide in past decades result from CVD, approximately 17 million individuals.[1,2] The traditional risk factors for CVD, such as diabetes,

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metabolic syndrome, dyslipidemia, hypertension, smoking and family history, have been well established as predictors of cardiovascular events, and measures for their control and monitoring are recommended to reduce and fight CVD.[3]

However, in certain clinical conditions, such as rheumatic diseases, the traditional risk factors do not seem to contribute to the total incidence of CVD.[4] Despite the well described higher incidence of CVD in rheumatic diseases, especially rheumatoid arthritis, systemic sclerosis, systemic vasculitis, antiphospholipid syndrome and systemic lupus erythematosus, it was only recently that the association of CVD and ankylosing spondylitis (AS) gained attention.[5,6]

The greater mortality of individuals with AS compared to that of the general population seems to be related to CVD.[7,8] Early atherosclerosis has been reported in association with chronic inflammation and with AS.[9] Some studies have shown that CVD and their traditional risk factors are more prevalent in patients with AS,[10,11] which is still controversial when interpreting inflammation as the major responsible for the higher cardiovascular impairment.

Despite the international publications, Brazilian studies correlating CVD and AS are scarce and more recent, especially those assessing their various presentation forms (clinically manifest or subclinical CVD).[12-14]

The characteristic racial miscegenation of the Brazilian population increases the interest for such studies, because it can lead to differences in the prevalence of CVD in that population, considering the association between AS and the HLA system.

This study was aimed at estimating the prevalence of CVD in individuals with AS from the Spondyloarthritis Outpatient Clinic of the Rheumatology Service of the Mato Grosso do Sul Federal University hospital (HU-UFMS), in addition to correlating the traditional risk factors and the inflammatory process of CVD.

Patients and methods

This is a quantitative descriptive study carried out from March to October 2015 with individuals with AS selected by convenience and consecutively from the patients regularly cared for at the Spondyloarthritis Outpatient Clinic of the Rheumatology Service of the HU-UFMS, which has records of 170 patients diagnosed with spondyloarthritis (psoriatic arthritis, AS, reactive arthritis, and enteropathic arthritis). Of those 170 patients, 55 were diagnosed with AS. A control group (CG) was formed by convenience sampling with employees of the UFMS without rheumatic disease and was similar to the AS group regarding age and sex. The inclusion and exclusion criteria allowed the selection of 42 individuals for the AS group and 50 for the CG.

Before data collection, all individuals provided written informed consent, duly registered in the Ethics Committee in Research of the UFMS (CAAE: 34043614.8.0000.0021).

Individuals with the following characteristics were excluded: diabetes, indigenous background, hypothyroidism or neoplasia, illiteracy, and pregnant women. All participants were screened for CVD and cardiovascular risk factors.

All individuals underwent cardiology clinical examination, laboratory tests, electrocardiography, echocardiography and carotid doppler examination on the same day, and within 20 days from the initial interview, which collected data from medical history and AS. The laboratory tests, performed after a 10-12-hour fasting, comprised the following measurements: total cholesterol and fractions, glycemia, glycated hemoglobin, uric acid, microalbuminuria, erythrocyte sedimentation rate (ESR), high-sensitivity C-reactive protein (hs-CRP) and interleukin 6 (IL-6).

The criteria to assess cardiovascular risk according to the V Brazilian Guideline on Dyslipidemia and Atherosclerosis Prevention comprised the presence of dyslipidemia, metabolic syndrome, arterial hypertension, current smoking, family history of early CVD, cardiac hypertrophy, and elevated levels of glycated hemoglobin, uric acid and hs-CRP.[15]

Cardiovascular disease was classified as clinically manifest or subclinical. Individuals with manifest CVD were those with history of myocardial infarction, stroke, coronary artery bypass graft surgery (CABG), peripheral revascularization surgery or procedure (PRV), or peripheral obstructive arterial disease (POAD), echocardiographic evidence of segmental, systolic, diastolic (over grade I) or hypertrophic cardiomyopathy, arrhythmias or bundle-branch and atrioventricular blocks on the electrocardiogram, and presence of carotid plaque obstruction > 50% of the lumen on Doppler.

Subclinical CVD was identified by an ankle-brachial index (ABI) < 0.9 or > 1.3, a carotid intima-media thickness (CIMT) >1 mm, but without significant plaque obstruction (> 50%) or microalbuminuria > 30 mg/g.[3]

Disease activity was assessed by using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score (ASDAS). The ASDAS-CRP and ASDAS-ESR indices16 were calculated after blood collection, using the information obtained when assessing the Bath Ankylosing Spondylitis Metrology Index (BASMI) and the Bath Ankylosing Spondylitis Functional Index (BASFI). In addition, the disease activity indices were correlated with the serum levels of IL-6, hs-CRP and uric acid, and compared to the occurrence of clinically manifest or subclinical CVD.

The AS group individuals were also assessed regarding the occurrence of CVD up to the age of 40 years and after 40 years.

Statistical analysis[17]

The results referring to the quantitative variables are presented as mean ± standard deviation, while the results of the categorical variables are presented as relative frequency followed by absolute frequency. The quantitative variables were compared between individuals with and without spondyloarthritis by use of parametric Student t test for independent samples (nonpaired) because most of the samples were normally distributed (Shapiro-Wilk test; $p > 0.05$). Student t test was used to compare quantitative variables between age groups. The association between the qualitative variables and the presence or absence of spondyloarthritis was assessed by use of chi-square test, which was also used to assess the association between the qualitative variables and the patients' age groups. The linear correlation between some quantitative variables was assessed by use of Pearson's linear correlation test. The results of the other variables were presented as descriptive statistics or tables and graphs. The SPSS statistical program, version 22.0, was used for statistical analysis, considering a 5% significance level.

Results

General characteristics

There was no significant difference between individuals with or without AS regarding age, sex, skin color, educational level, weight, height, blood pressure and body mass index (Table 1).

Table 1 - Sociodemographic and physical data of the individuals with and without spondyloarthritis assessed in this study

Variables	Spondyloarthritis		p value
	No	Yes	
Age	40.60 ± 1.79	45.57 ± 1.78	0.054
Sex			
Female	28.0 (14)	23.8 (10)	0.648
Male	72.0 (36)	76.2 (32)	
Skin color			
White	73.5 (36)	76.2 (32)	0.766
Non-white	26.5 (13)	23.8 (10)	
No information	1	0	
Educational level			
Secondary education	71.4 (35)	83.3 (35)	0.179
Higher education	28.6 (14)	16.7 (7)	
No information	1	0	
Weight	79.99 ± 2.68	74.80 ± 2.70	0.179
Height	167.60 ± 1.54	164.74 ± 1.34	0.172
SBP	125.08 ± 1.77	129.05 ± 1.90	0.130
DBP	81.56 ± 1.12	84.86 ± 1.46	0.072
Abdominal circumference	92.28 ± 1.86	93.07 ± 2.22	0.783

SBP: systolic blood pressure; DBP: diastolic blood pressure. The results are expressed as mean ± standard error of the mean or relative frequency (absolute frequency). P value in the Student t test (quantitative variables) or the chi-square test (qualitative variables).

Risk factors for cardiovascular disease

Table 2 shows the results regarding the cardiovascular risk factors in the two groups. There was no significant difference between the groups regarding the variables family history, smoking habit, alcoholism, abdominal circumference, systemic arterial hypertension, total cholesterol, HDL-cholesterol, triglycerides, glycated hemoglobin, hs-CRP, microalbuminuria, metabolic syndrome, and IL-6. The LDL-cholesterol levels in the AS group, however, were higher than those in the CG ($p = 0.012$). The uric acid levels in the AS group were lower than those in the CG ($p = 0.019$).

All individuals were stratified into low, intermediate and high cardiovascular risk. Despite the higher frequency of high cardiovascular risk in the AS group, the difference was not significant; thus, there was no

Table 2 - Cardiovascular risk factors of the individuals with and without spondyloarthritis assessed in this study

Variables	Spondyloarthritis		p value
	No	Yes	
Family history			
No	76.0 (38)	73.2 (30)	0.757
Yes	24.0 (12)	26.8 (11)	
No information	0	1	
Smoking			
No	90.0 (45)	92.9 (39)	0.628
Yes	10.0 (5)	7.1 (3)	
Alcoholism			
No	60.0 (30)	71.4 (30)	0.252
Yes	40.0 (20)	28.6 (12)	
BMI	27.99 ± 0.76	27.33 ± 0.90	0.575
SAH			
No	64.0 (32)	57.1 (24)	0.502
Yes	36.0 (18)	42.9 (18)	
Total cholesterol	170.60 ± 5.36	180.67 ± 6.66	0.237
HDL	43.13 ± 2,45	45.81 ± 2.18	0.420
LDL	88.87 ± 6.36	110.79 ± 5.65	0.012
Triglycerides	137.58 ± 14.19	123.40 ± 11.76	0.455
Glycated hemoglobin	6.65 ± 1.41	5.59 ± 0.08	0.484
Uric acid	6.02 ± 0.26	5.22 ± 0.20	0.019
hs-CRP	2.35 ± 0.31	16.10 ± 8.88	0.130
Microalbuminuria	3.87 ± 0.95	8.31 ± 2.04	0.053
Metabolic syndrome			
No	62.0 (31)	69.0 (29)	0.480
Yes	38.0 (19)	31.0 (13)	
Interleukin-6	4.62 ± 0.48	4.84 ± 0.80	0.806

BMI: body mass index; SAH: systemic arterial hypertension; hs-CRP: high-sensitivity C-reactive protein. The results are expressed as mean ± standard error of the mean or relative frequency (absolute frequency). P value in the Student t test (quantitative variables) or the chi-square test (qualitative variables).

association between the presence or absence of AS and the cardiovascular risk classification.

To assess the cardiovascular risk of well-controlled patients, and thus with lower inflammation level, the global cardiovascular risk was calculated separately in patients with ASDAS-CRP < 2 and low disease activity level, but no significant statistical difference was found between the CG and the AS group patients with that characteristic.

Manifest cardiovascular disease

Most individuals assessed in this study had no clinically manifest CVD, with prevalence between 2% and 26%, and valvular dysfunctions were the most frequent change, although all of them were mild. The percentage of individuals with right bundle-branch block was higher in the AS group than in the CG. The following variables showed no association with the presence or absence of AS: stroke, acute myocardial infarction, CABG, angioplasty, PRV/POAD, presence of carotid plaques and other findings on echocardiogram and electrocardiogram. None of the individuals in the CG and AS group showed significant carotid obstruction (plaque obstruction ≥ 50% of the lumen) (Table 3).

Subclinical cardiovascular disease

None of the individuals achieved the cutoff values for the occurrence of microalbuminuria (> 30 mg/g) or altered ABI (< 0.9 and > 1.3); in addition, the mean values of ABI and microalbuminuria were similar in both groups. Carotid plaques without significant obstruction (< 50% of the lumen) were slightly more frequent in the AS group [CG: 12.2% (n = 6); AS: 21.4% (n = 9)], but with no significant statistical difference (p = 0.239). However, as shown in Figure 1, CIMT was higher in the AS group (p = 0.018), and the cutoff value to determine altered CIMT (> 1 mm) was more often observed in the AS group [CG: 2.3 (n = 1); AS: 24.2 (n = 8)] (p = 0.003). This difference was observed when individuals with carotid plaques were excluded. Considering only the individuals with carotid plaques, no significant difference regarding CIMT was observed between the groups (CG: 0.78 ± 0.13; AS: 1.45 ± 2.12) (p = 0.464).

Ankylosing spondylitis activity and specific data

Most individuals were HLA positive (64.3%, n = 27) and had exclusive (33.3%, n = 14) or predominantly (61.9%, n = 26) axial clinical manifestations and extra-

Table 3 - Results regarding manifest cardiovascular disease of the individuals with and without spondyloarthritis assessed in this study

Variables	Spondyloarthritis		p value
	No	Yes	
Stroke			
No	98.0 (49)	97.6 (41)	0.901
Yes	2.0 (1)	2.4 (1)	
AMI			
No	98.0 (49)	97.6 (41)	0.901
Yes	2.0 (1)	2.4 (1)	
CABG, angioplasty, or PRV/POAD			
No	98.0 (49)	100.0 (42)	0.357
Yes	2.0 (1)	0.0 (0)	
ECHO			
Normal	76.0 (38)	61.9 (26)	0.143
Valvular dysfunction	20.0 (10)	26.2 (11)	0.481
Aortic ectasia	6.0 (3)	14.3 (6)	0.183
Hypertrophy	4.0 (2)	4.8 (2)	0.858
Diastolic dysfunction	2.0 (1)	0.0 (0)	0.357
Chamber dilatation	0.0 (0)	4.8 (2)	0.119
Ejection fraction	0.0 (0)	0.0 (0)	-
Segmental change	0.0 (0)	0.0 (0)	-
ECG			
Normal	86.0 (43)	69.0 (29)	0.050
Right bundle-branch block	2.0 (1)	16.7 (7)	0.013
Ventricular repolarization change	8.0 (4)	2.4 (1)	0.236
Left hemiblock	2.0 (1)	4.8 (2)	0.458
Ventricular overload	2.0 (1)	7.1 (3)	0.228
Inactive area	0.0 (0)	2.4 (1)	0.273
Atrial fibrillation	0.0 (0)	0.0 (0)	-
Left bundle-branch block	0.0 (0)	0.0 (0)	-
Atrioventricular block	0.0 (0)	0.0 (0)	-

AMI: acute myocardial infarction; CABG: coronary artery bypass graft surgery; PRV: peripheral revascularization surgery or procedure; POAD: peripheral obstructive arterial disease; ECHO: echocardiography; ECG: electrocardiography. The results are expressed as relative frequency (absolute frequency). P value in the chi-square test.

articular symptoms (54.8%, n = 23), enthesitis being the most frequent (69.6%, n = 16).

Time since diagnosis ranged from 2 to 34 years (mean of 10.76 ± 8.74 years). The time since symptom onset ranged from 3 to 47 years (mean of 19.36 ± 11.02 years). The AS activity grade and impairment were: BASDAI = 2.84 ± 2.04, BASFI = 3.77 ± 2.82, BASMI = 4.59 ± 2.17, ASDAS-CRP = 2.17 ± 1.10 and ASDAS-ESR = 1.77 ± 0.81.

The hs-CRP and IL-6 levels were analyzed in both groups as one of the inflammation markers. The IL-6 showed no statistically significant difference (CG: 4.62 ± 3.41, AS: 4.84 ± 5.20; p = 0.806). Although more elevated in the AS group, the hs-CRP levels showed no significant difference as compared to those in the CG (CG: 2.35 ± 2.21, AS: 16.10 ± 56.85; p = 0.130).

There was moderate and positive significant linear correlation between the hs-CRP values obtained and those of ASDAS-CRP (Pearson, $p < 0.001$; $r = 0.657$), in addition to a positive significant, although weak, linear correlation between the hs-CRP values obtained and those of ASDAS-ESR ($p = 0.007$; $r = 0.418$). On the other hand, there was no significant linear correlation between the other inflammation markers and the disease activity indices assessed in this study (p-value between 0.177 and 0.875).

There was no linear correlation between the values obtained in ASDAS-CRP and the CIMT measures ($p = 0.932$, $r = -0.014$). In addition, there was no linear correlation between the values of hs-CRP and CIMT ($p = 0.625$, $r = -0.079$) or between time since diagnosis and CIMT ($p = 0.152$, $r = -0.225$). The lack of statistical significance in the linear correlation between CIMT and ASDAS-CRP, hs-CRP and time since diagnosis persisted even when individuals with and without plaque were separated.

In addition, the AS group patients were assessed according to age group (up to 40 years and over 40 years). There was no significant association between age group and manifest CVD. Regarding subclinical CVD, however, the percentage of patients older than 40 years with carotid plaques was significantly higher than that of those under 40 years. Microalbuminuria, ABI and CIMT showed no statistically significant difference according to age group (Table 4).

There was no linear correlation between time since diagnosis and CIMT in the age group under 40 years ($p = 0.688$, $r = -0.130$). However, there was a significant positive correlation between time since diagnosis and CIMT in individuals older than 40 years ($p = 0.049$,

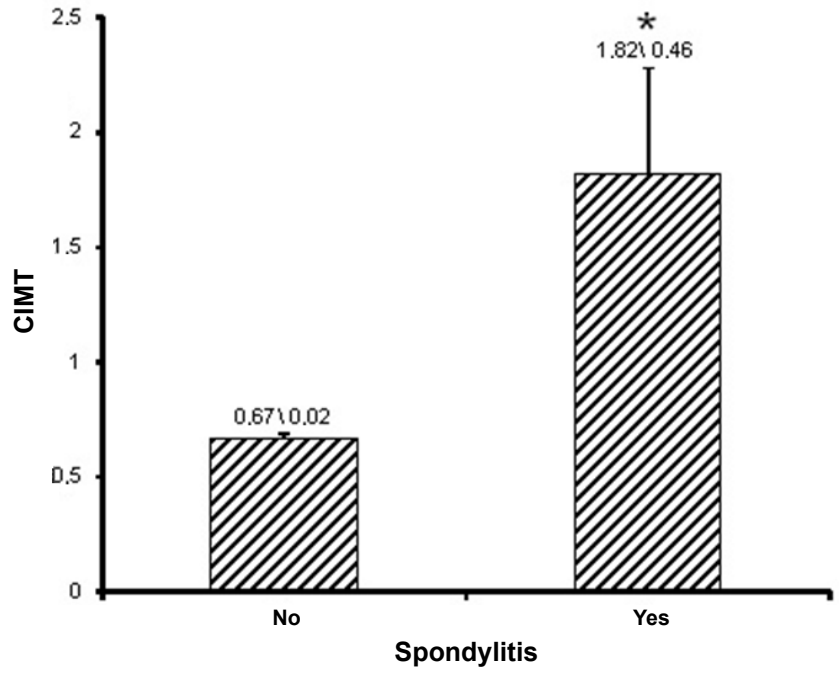

Figure 1 - Graph showing the carotid intima-media thickness (CIMT) of individuals with and without ankylosing spondylitis. Each column represents the mean, and the bar represents the standard error of the mean.
** Significant difference as compared to individuals without spondyloarthritis (Student t test, p = 0.018).*

r = -0.362). Among individuals with AS older than 40 years and no carotid plaque, the correlation between time since diagnosis and CIMT was also positive (Figure 2).

Medications

In the AS group, 34 patients (81%) used immune biologics, 26 (61.9%) used nonsteroidal anti-inflammatory drugs, 13 (31%) were on immunosuppressant drugs (methotrexate/sulfasalazine), and only 4 (9.5%) were using corticosteroids. There was no significant statistical difference between the CG and the AS group regarding the use of statin, angiotensin-converting-enzyme inhibitor/angiotensin-receptor-blocker, beta-blocker, calcium-channel blockers, and acetylsalicylic acid.

Discussion

The higher frequency of cardiovascular impairment in rheumatic diseases, whose major background is chronic inflammation, explains the higher cardiovascular morbidity and mortality of those patients.[18] However, the role of inflammation in the occurrence of CVD remains controversial in AS.

Although the prevalence of cardiovascular impairment in AS is not high,[12] there is consensus that the mortality rate of those patients is higher than that of the general population, mainly due to higher cardiovascular mortality.[7,8] In addition, the more accurate definition of the weight of each factor involved, such as chronic inflammation, traditional cardiovascular risk factors and genetics, still lacks. The cyclic characteristic of AS throughout life, the time of exposure to disease, the effect of treatment, and the variety of exposure to cardiovascular risk factors can interfere with the CVD occurrence in that population, hindering the better understanding of the correlation between AS and heart diseases.

Unlike rheumatoid arthritis, whose cardiovascular risk score is higher,[9] publications on AS are controversial. Some authors have explained the higher prevalence of subclinical atherosclerotic disease, such as a higher CIMT, in patients with AS because of the higher exposure to cardiovascular risk factors,[7] while others, have reported that the cardiovascular impairment was independent of the presence of the traditional risk factors for CVD.[19]

In our study, both groups were similarly exposed to the traditional risk factors for CVD, except for mean

Table 4 - Results regarding subclinical cardiovascular disease of the individuals up to 40 years of age and those older than 40 years assessed in this study

Variables	Age group		p value
	≤ 40 years	> 40 years	
Ankle-brachial index	1.11 ± 0.05	1.06 ± 0.02	0.375
Microalbuminuria	15.04 ± 6.35	5.62 ± 1.10	0.170
CIMT (excluding those with plaques)	1.97 ± 0.88	1.73 ± 0.53	0.811
Carotid plaque			
No	100.0 (12)	70.0 (21)	0.032
Yes	0.0 (0)	30.0 (9)	
CIMT (only those with plaques)	-	1.45 ± 0.71	-
Ankle-brachial index			
Not altered	75.0 (9)	93.3 (28)	0.097
Altered (< 0.9 or > 1.3)	25.0 (3)	6.7 (2)	
CIMT (excluding those with plaques) cutoff value			
Not altered (< 1 mm)	83.3 (10)	71.4 (15)	0.443
Altered (> 1 mm)	16.7 (2)	28.6 (6)	

CIMT: carotid intima-media thickness. The results are expressed as mean ± standard error of the mean or relative frequency (absolute frequency). P value in the Student t test (quantitative variables) or the chi-square test (qualitative variables).

LDL-cholesterol, higher in the AS group, which can be related to the use of immune biologics[20,21] or only to a more cautious diet in the CG.

No difference in the prevalence of manifest and subclinical CVD was found between the groups; however, most individuals were classified as intermediate and high risk. Considering that most individuals in both groups were young, the prevalence of risk factors for CVD at an early age is clear, which is especially relevant in patients with rheumatic diseases.

Excluding the limitations of a non-blinded study, the higher mean values of CIMT in the AS group indicate higher subclinical atherosclerosis. Despite the lack of consensus in the literature,[14,22] we believe that such finding reflects early subclinical atherosclerosis in a population with traditional risk factors for CVD similar to those of the general population, being an independent marker of risk. The presence of carotid plaques and the positive correlation between CIMT and the time since diagnosis of AS in individuals older than 40 years reinforces that hypothesis.

In addition, it is worth noting the considerably higher mean value of hs-CRP of the AS group individuals, indicating their higher cardiovascular risk. Furthermore, a good part of those with well-controlled rheumatic disease and low inflammation (ASDAS < 2) were at high cardiovascular risk and out of the recommended LDL-cholesterol target (< 70 mg/dL).

We do not know any Brazilian study using this cardiovascular risk stratification approach for those patients, but it is worth noting that some researchers have sought cardiovascular risk markers specific for AS,[23] according to the recommendations established for rheumatoid arthritis and systemic lupus erythematosus.[9]

The lack of correlation between markers of inflammation, activity and disease impairment in the AS group can be partially explained by the low mean age of the patients or the use of immune biologics in 80% of them. By being a cross-sectional study might have contributed to that, although other authors have found no correlation between inflammation and early atherosclerosis when cardiovascular risk factors were excluded.[13,21]

Conclusions

There is no difference in the prevalence of manifest CVD in patients with AS as compared to that of the CG. However, subclinical CVD is more prevalent in AS patients when assessed by use of CIMT, has no relation to the AS activity, but to the time since AS diagnosis and to more advanced ages. Most patients with AS are not only at higher cardiovascular risk, even when clinically controlled, but their CVD prevention is inadequate as well.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Universidade Federal do Mato Grosso do Sul* under the protocol number CAAE: 34043614.8.0000.0021. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

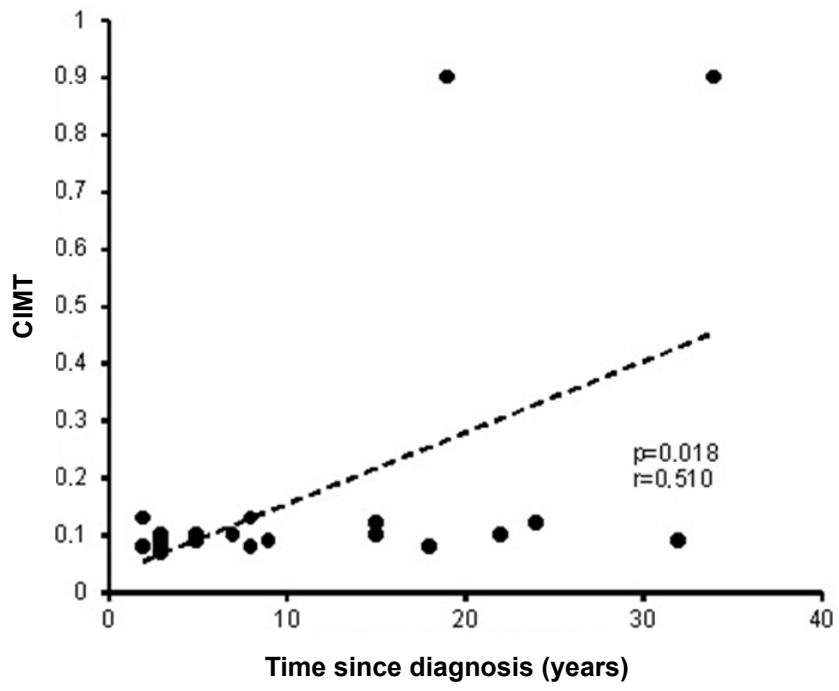

Figure 2 - Dispersion graph showing the moderate positive linear correlation between time since diagnosis and carotid intima-media thickness (CIMT), considering only patients with ankylosing spondylitis, without plaque, aged ≥ 40 years. Each symbol represents the value for both variables for a single individual. The dashed line represents the line of linear regression between those variables. The p value and r were obtained with Pearson's linear correlation test.

Author contributions

Conception and design of the research: Silva Junior DG. Acquisition of data: Silva Junior DG. Analysis and interpretation of the data: Silva Junior DG. Statistical analysis: Silva Junior DG. Writing of the manuscript: Silva Junior DG. Critical revision of the manuscript for intellectual content: Silva Junior DG, Costa IP.

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

Correlation between Exercise Stress Test and Echocardiographic Parameters in Elderly Individuals

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Abstract

Background: Maximum oxygen consumption (VO_2 max) in healthy individuals decreases approximately 10% per decade of life, and such decrease is more pronounced after the seventh decade.

Objectives: To assess functional capacity of individuals aged 75 years or older, submitted to ergometric test and transthoracic echocardiogram exam, by means of metabolic equivalent (MET) and VO_2 max measurements.

Methods: A total of 381 patients (205 women; 79 ± 3.7 years) were evaluated. Exclusion criteria were: presence of left ventricular (LV) systolic dysfunction, LV diastolic dysfunction grade II and III, significant valve disease, or coronary artery disease with systolic LV dysfunction or dilatation. Associations between quantitative variables were analyzed by Pearson and Spearman correlation coefficients, and comparisons of quantitative data by Student's t-test for independent samples.

Results: Increasing age was associated with a progressive decrease in the distance covered ($p = 0.021$), in the expected increase in HR ($p < 0.001$), in VO_2 max ($p < 0.001$), and METs ($p < 0.001$) in both genders. There was no correlation of exercise test parameters with the echocardiographic parameters.

Conclusions: Relatively healthy older individuals, with global systolic and diastolic functions of the left ventricle preserved, presented a progressive decrease in their functional capacity due to their natural aging process, comorbidities related to their age range and physical deconditioning. (Int J Cardiovasc Sci. 2019;32(1)19-27)

Keywords: Cardiovascular Diseases; Risk Factors; Aging; Oxygen Consumption; Exercise Test; Echocardiography / methods; Exercise.

Introduction

Priebe[1] provided a sensible description of the difficulties in defining "aged patients", since there is no clinical definition that precisely classifies elder or advanced-aged individuals. Aging is a continuous process rather than an abrupt event. As age advances, maximal aerobic capacity decreases 8 to 10% per decade in sedentary men and women, and exercise capacity decreases approximately 50% between ages 30 and 80. In addition, comorbidities such as obstructive pulmonary disease, peripheral vascular disease, obesity, arthritis, neuromuscular disease, and generalized deconditioning are more prevalent in elderly patients and should be considered before evaluating their clinical conditions, especially in relation to cardiovascular risk.[2-4]

The prevalence of coronary artery disease (CAD) is high in the elderly. Although it was detected in only 1.8% of men and 1.5% of women above the age of 75, an autopsy study of 5,558 patients revealed significant CAD in 54% of women and in 72% of men above the age of 70.[5-7]

Older patients require a special and careful approach. Functional capacity is evaluated by exercise tolerance in daily life and reflects the quality of biological age. Lower exercise tolerance may reflect the severity of

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an underlying disease such as significant CAD or just poor functional capacity in a sedentary old person. An individual's functional capability may be assessed by means of the maximum oxygen uptake (VO_2 max) that represents the maximum amount of oxygen an individual can take in with incremental exercise. The amount of exercise can be measured using the metabolic equivalent (MET); 1 MET is the amount of oxygen consumption at rest and is equivalent to approximately 3.5 ml $kg^{-1}min^{-1}$ (measured in a healthy, 40-year old man, 70 kg). VO_2 max decreases about 10% per decade in healthy individuals, and such decrease is even more pronounced in individuals older than 70 years. With the increase in life expectancy, many patients aged 75 years or older seek medical care for chest pain and presurgical evaluation for several elective surgeries. Individuals that feel fit enough to perform a physical stress test are submitted to treadmill or bicycle ergometric tests. However, although sensitivity to noninvasive stress testing increases with aging, specificity tends to decline.[5]

The objective of the current study is to correlate exercise test variables with echocardiographic parameters in patients over 75 years old, including functional capacity, measured in MET and VO_2 max (with or without myocardial ischemia at the physical stress test), left ventricular ejection fraction (LVEF), left ventricular mass and left ventricle mass index, left atrial volume and presence of pulmonary arterial hypertension.

Methods

We assessed 381 patients (205 women; 53.8%), mean age of 79 ± 3.7 years, who underwent exercise test and bidimensional transthoracic echocardiography (2DEcho) in a private cardiologic clinic. Subjects were selected by convenience. Each patient had results of blood tests and imaging tests to be analyzed before the exercise test.

Before the study, data on demographic characteristics and risk factors were collected from the private cardiologist's records and blood test results. Body mass index (BMI) was calculated by dividing the subjects' weight (kg) by the square of their height (m). Patients were queried about the presence of hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, and current smoking habit. Hypertension was defined as a history of treated hypertension or the presence of systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, measured by the private cardiologist. Smoking history was coded as never or current smoker.[8] Subjects were classified as having diabetes when treated for insulin-dependent or non-insulin-dependent diabetes or having elevated fasting glucose levels (≥ 126 mg/dL). The use of lipid-lowering drugs or the presence of total cholesterol > 200 mg/dL, HDL-cholesterol < 40 mg/dL, LDL - cholesterol > 100 mg/dL or triglycerides > 150 mg/dL was recorded.[9-10] A history of myocardial infarction, angioplasty, or coronary artery bypass surgery was recorded, and the presence of any of these conditions was considered a positive CAD history.

Indications for the 2DEcho included referral from a physician, information from close relatives, or patients' complaints. We analyzed echocardiographic and carotid ultrasonography data, including left ventricular ejection fraction, left ventricular diastolic function, left atrial volume, left ventricular mass and the presence of pulmonary arterial hypertension and carotid plaque. Exclusion criteria included the presence of left ventricular systolic dysfunction (ejection fraction < 50% on echocardiogram), left ventricular diastolic dysfunction grade II and III, significant valve disease such as mitral and aortic regurgitation or stenosis, CAD with left ventricular systolic dysfunction or dilatation, unstable cardiovascular or metabolic disease, and major orthopedic/neurological disability.

Subjects underwent treadmill electrocardiogram (ECG) testing (TET) or bike ECG testing (BET), according to the private physician request. Treadmill ECG test included Ellestad, Kattus, Naughton, Ramp, Bruce and modified Bruce protocols, and Balke and male Balke protocols, following standard recommendations.[11,12] The distance covered on the treadmill was automatically calculated by the protocol, according to the number of laps covered by each patient. Blood pressure and a 12-lead ECG were recorded before the test, during the test (during the last minute of each stage), and every 3 minutes in the recovery phase. During the test, three ECG leads were continuously monitored. The test was stopped in case of a) ST-segment elevation (> 1.0mm) in leads without preexisting Q waves due to prior myocardial infarction (other than aVR, aVL, and V1); b) drop in systolic blood pressure > 10 mmHg despite an increase in workload, when accompanied by any other evidence of ischemia; c) moderate to severe angina; d) central nervous system symptoms (e.g. ataxia, dizziness, near syncope); signs of poor perfusion (cyanosis or pallor); e) sustained ventricular tachycardia or other arrhythmias, including second- or third-degree atrioventricular block, which may affect cardiac output

during exercise; f) marked ST-segment depression (≥ 3mm); g) exercise-limiting symptoms such as angina, dyspnea, exhaustion, or the subjects' request to stop the test; and h) technical difficulties in monitoring the ECG or systolic blood pressure. An abnormal response of the ST-segment to exercise was defined as horizontal or downsloping ST-segment depression ≥ 1 mm measured at 80 ms after the J point or an elevated ST-segment ≥ 1 mm in leads without pathological Q-wave (excluding lead aVR). Measurements of left ventricular systolic and diastolic dysfunction, left atrial volume, valve disease, and systolic pulmonary artery pressure were performed according to recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[13-14] The study was approved by the local ethics committee and written informed consent was obtained from each participant to undergo the ergometric tests (treadmil ECG testing or bike ECG testing) , bidimensional transthoracic echocardiography and carotid ultrassonography, and to participate in the study.

Statistical analysis

Quantitative variables were described as means, medians, minimum and maximum values, quartiles and standard deviations, and categorical variables as frequency and percentiles. Associations between quantitative variables were analyzed by Pearson and Spearman correlation coefficients. Comparisons of quantitative variables between the two groups were made using the Student's t test for independent samples. Statistical testing of data normality was performed using the Kolmogorov-Smirnov test. Associations between categorical variables were assessed by the Fisher's exact test. A p-value ≤ 0.05 indicated statistical significance. Data were analyzed by means of the SPSS statistical software, version 20.

Results

Patients' baseline characteristics and echocardiographic and ergometric results are shown in Tables 1, 2 and 3. Only five patients (1.3%) performed cycle ergometer test, and then were excluded from the final analysis. Three hundred seventy-six patients performed treadmill test (Bruce protocol 203, 53.4%; Kattus 113, 29.7%; Ramp 28, 7.4%; modified Bruce 15, 3.9%; Naughton 12, 3.2%; Ellestad 5, 1.3%; Balke 3, 0.8%; Balke male 1, 0.3%). Nineteen (5%) patients did not achieve the submaximal heart rate (HR) expected for the age and 58 (15%) had previous ECG at resting conditions showing left bundle branch block and ST segment alterations. Forty (10.5%) of the patients tested positive for myocardial ischemia and 79 (21.8%) showed abnormal heart rate response in the first minute. As age increased, the distance covered by participants decreased ($p = 0.021$), as well the expected increase in HR ($p < 0.001$), VO_2 max ($p < 0.001$) and METs ($p < 0.001$) (Tables 3 and 4; Figure 1) in men and women. Women showed lower values of VO_2 max and METs when compared to men (Table 2). Inverse correlation was noted of the distance covered, VO_2 max and METs with the BMI (Table 3 and 4). Only 4 patients (1%) showed systolic pressure in the pulmonary artery above 40 mmHg in the echocardiogram at rest, which did not influence the distance covered by the subjects, HR at the first minute ($p = 1$), VO_2 max ($p = 0.5$), MET ($p = 0.5$) or ischemia ($p = 1.0$) (data not shown). The volume of the left atrium and left ventricular mass had no influence on the ergometric test variables (Table 5). Ischemia at stress test did not correlate with any echocardiographic variable (Table 5). In 198 patients (67.3%), atherosclerotic plaques in the extracranial carotid arteries were detected, which also did not correlate with any of the variables analyzed (data not shown). Severity of stenosis was not considered relevant, only the presence of the atherosclerotic plaque.

Discussion

The present study showed that relatively healthy patients aged 75-81 years, with similar demographic and echocardiographic characteristics, showed a progressive decrease in METs and VO_2 max, associated with a decrease in the distance covered during ergometric test with increasing age. These findings corroborate previous studies showing a marked decrease in VO_2 max with aging.[15-18] Considering that only individuals with preserved left ventricular systolic function was studied, we did not expect an influence of this parameter on the results. Similarly, no influence of left ventricular diastolic function was expected,[19] as individuals with grade II and III diastolic dysfunction were excluded from the study.

Regarding the left atrial volume, since there was no significant variation in its values among the patients, its influence on the ergometric parameters was not expected either, unlike previous studies that reported a worsening of functional capacity due to the increase in left atrial volume.[20-23] The same was observed with left ventricular mass and left ventricular mass index.[24]

Therefore, no correlation between ergometric and echocardiographic variables was found, which

Table 1 - Patients' baseline characteristics

Variable	N	Mean	Median	1st quartile	3rd quartile	Standard deviation
Age	381	79.0	78	76	81	3.7
Weight (kg)	381	70.4	70	60	79	13.9
Height (cm)	381	163.8	164	157	170	9.5
Body mass index (kg/m²)	380	26.2	25,6	23.4	28.5	4.2
Sex						
Female (N/%)	205/53.8					
Male (N/%)	176/46.2					
Hypertension						
Yes (N/%)	258/67.7					
No (N/%)	123/32.3					
Diabetes						
Yes (N/%)	91/23.9					
No (N/%)	290/76.1					
Dyslipidemia						
Yes (N/%)	178/46.7					
No (N/%)	203/53.3					
Coronary artery disease						
Yes (N/%)	43/11.3					
No (N/%)	338/88.7					
Carotid plaque						
Yes (N/%)	198/67.3					
No (N/%)	93/32.7					

indicates that, in relatively healthy individuals older than 75 years old, the decrease in functional capacity is associated with age, progressive physical deconditioning and comorbidities, which will negatively affect their independence and daily physical activity.[25-28] Nevertheless, comorbidities such as previous stroke, bone and articular diseases, and chronic obstructive pulmonary disease were not analyzed in the present study. In regard to HR at the first minute after the test, it is known that its restoration to baseline values reflects the integrity of the vagal system, which is compromised in older ages, in patients with diabetes, cardiac failures, and increased BMI.[29-31] In this regard, in the present study, only 21.8% of the individuals showed an abnormal HR response at the first minute after the exercise test. Also, there was no correlation of this variable with echocardiographic parameters, age, sex or BMI. This finding was expected, as the studied cohort comprised an aged population with similar clinical and echocardiographic characteristics. Another relevant finding was the fact that only 10% of the individuals in the present study showed positive for myocardial ischemia. Sensitivity of the ergometric test was similar to that documented by Vacanti et al.,[6] using myocardial perfusion scan with dipyridamole in individuals older than 75. However, it is known that elderly patients have a high prevalence of severe CAD, with low tolerance to exercise. Thus, results of exercise stress testing in

Table 2 - Echocardiographic and ergometric results

Variable	n	Mean	Median	Q1	Q3	SD	*p value
Maximum heart rate	381	128.2	129	118	140	20.7	
Distance	377	0.418	0.410	0.290	0.530	0.198	
VO_2 max	381	23.7	23.4	16.9	29.1	8.1	
MET	381	6.80	6.76	4.84	8.35	2.36	
Left ventricle mass	381	159.4	152	123	181	50.2	
Left ventricle/SA	381	91.1	85	74	103	33.1	
Left ventricle EF	381	69.5	70	67	73	6.3	
Left atrium	381	37.1	36	34	40	5.6	
VO_2 max female	205	21.0	20.9	16.7	25.1	7.3	
VO_2 max male	176	26.7	25.9	20.9	32.2	8.0	< 0.001
METs female	205	6.1	6.0	4.8	7.2	2.1	
METs male	176	7.7	7.5	6.0	9.2	2.3	< 0.001

** Student's t- test for independent samples, p < 0.05. VO_2 max: maximum oxygen consumption; MET: metabolic equivalent; SA: surface area; EF: ejection fraction.*

Table 3 - Correlation of heart rate (HR) and distance covered in exercise stress ECG test with echocardiographic data, age, surface area (SA) and body mass index (BMI) of patients

Variable	n	Spearman coefficient	p value
HR max x left ventricle mass	381	-0.09	0.082
HR max x left ventricle mass/SA	381	-0.03	0.556
HR max x age	381	-0.23	< 0.001
HR max x BMI	380	-0.06	0.249
HR max x left ventricle ejection fraction	381	0.13	0.010
HR max x left atrium	381	-0.05	0.325
Distance x left ventricle mass	377	0.03	0.520
Distance x left ventricle mass/SA	377	0.08	0.101
Distance x age	377	-0.12	0.021
Distance x BMI	376	-0.17	0.001
Distance x left ventricle ejection fraction	377	0.04	0.450
Distance x left atrium	377	0.01	0.833

Table 4 - Correlation of metabolic equivalent (MET) and maximum oxygen consumption (VO_2 max) with echocardiographic data, age, body mass index (BMI) and surface area (SA) of patients

Variable	N	Spearman coefficient	p value
MET x left ventricle	381	0.03	0.581
MET x left ventricle/SA	381	0.06	0.217
MET x age	381	-0.21	< 0.001
MET x BMI	380	-0.13	0.011
MET x ejection fraction	381	0.05	0.327
MET x left atrium	381	0.00	0.959
VO_2 max x left ventricular mass	381	0.04	0.488
VO_2 max x left ventricular mass/SA	381	0.07	0.167
VO_2 max x age	381	-0.19	< 0.001
VO_2 max x BMI	381	-0.16	0.002

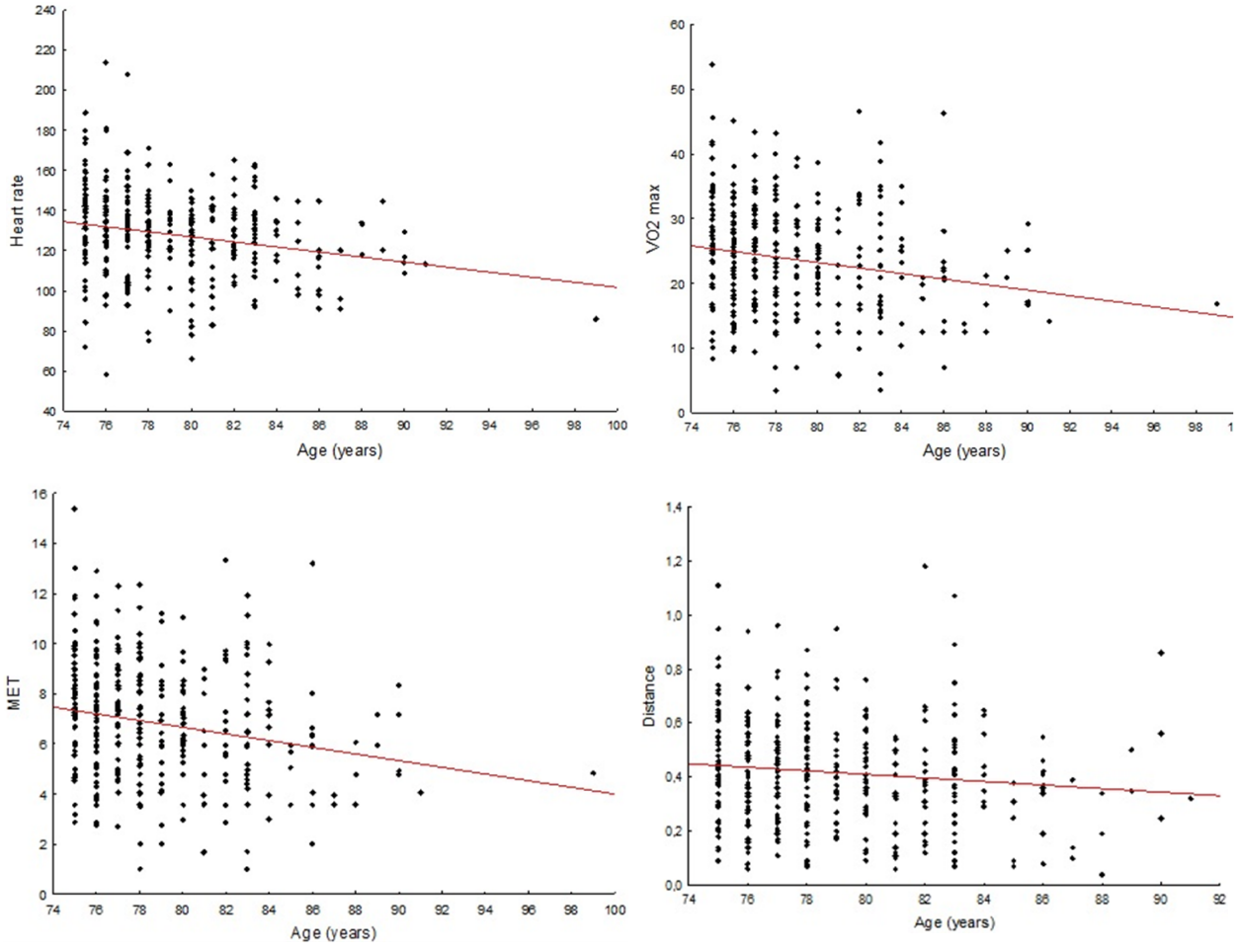

Figure 1 - Correlation of age with heart rate, VO_2 max, metabolic equivalent (MET), and distance (m) covered in exercise stress ECG test.

this population must be interpreted differently than in younger individuals, since even in patients classified as low risk by risk stratification scores, an annual cardiac mortality rate of 2% was found in patients aged 75 years or older.[32,33] These findings confirm the need for specific protocols and instruments for elderly patients,[34] considering the great heterogeneity in aging process and its biological consequences.[33]

In addition, considering the presence of atherosclerotic plaques in the extracranial carotid arteries in our patients, we expected its correlation with the other variables analyzed, which did not happen. In fact, its presence was previously shown to be correlated with systolic functions and left filling ventricular pressures,which revealed to be similar in all patients of this study.

An additional important finding was the inverse correlation of the distance covered, functional capacity (METs) and VO_2 max with BMI. There is a progressive BMI increase as age advances and the prevalence of obesity has considerably increased in the elderly.[36] This has a direct impact on individuals' health and life quality, since weight gain is associated with a decrease in functional capacity and vitality, body pain, emotional and physical problems, and increased risk for morbidity and disability.[37,38]

Some limitations of the present study should be mentioned. First, the choice of the exercise protocols was made by the physician who examined the patients, based on the physical limitations of each patient. This led to the use of different ergometric protocols, making

Table 5 - Echocardiographic variables, presence of ischemia and heart rate in the first minute of the exercise stress ECG test (HR 1st min) of the patients

Variable	Ischemia	n	Mean	Median	1st quartile	3rd quartile	SD	p* value
LV mass	No	341	160.1	152	123	185	51.5	
	Yes	40	153.6	146.5	122.5	181	36.9	0.315
LV mass/SA	No	341	91.9	87	75	103	34.5	
	Yes	40	84.2	81	74	94	16.7	0.018
Age	No	341	79.1	78	76	81	3.7	
	Yes	40	78.3	77	76	79	4.1	0.188
BMI	No	340	26.0	25.6	23.4	28.4	3.9	
	Yes	40	27.4	26.7	23.3	28.9	6.2	0.166
LVEF	No	341	69.5	70	67	73	6.4	
	Yes	40	69.0	70	66.5	72.5	5.4	0.628
Left atrium	No	341	36.9	36	33	40	5.6	
	Yes	40	38.5	37	35	41.5	5.0	0.107
Variable	**HR 1st min**	**n**	**Mean**	**Median**	**Qst**	**Qth**	**SD**	**p* value**
LV mass	Normal	283	157.6	148	122	181	48.9	
	Abnormal	79	163.3	158	132	181	47.0	0.354
LV mass/SA	Normal	283	90.8	85	73	103	35.5	
	Abnormal	79	91.1	88	77	104	21.7	0.928
Age	Normal	283	78.9	78	76	81	3.7	
	Abnormal	79	79.1	79	76	81	3.7	0.566
BMI	Normal	282	26.0	25.5	23.1	28.4	4.3	
	Abnormal	79	26.7	26.4	23.9	29.3	4.3	0.241
LVEF	Normal	283	69.5	70	67	73	6.3	
	Abnormal	79	69.5	70	67	73	6.7	0.975
Left atrium	Normal	283	37.1	36	34	40	5.6	
	Abnormal	79	36.4	36	33	40	5.4	0.269

** Student's t- test for independent samples, $p < 0.05$. LV: left ventricular; SA: surface area; EF: ejection fraction; BMI: body mass index.*

it difficult to accurately analyze and compare the ergometric variables between the subjects. Second, since only patients with preserved left ventricular systolic and diastolic functions were selected, no significant difference was expected in VO_2 max, METs, HR, and distance covered. Thus, further studies including patients with different degrees of left ventricular dysfunction in the elderly are necessary.

Conclusions

Individuals aged 75 years or older, of both genders, relatively healthy, with preserved left ventricular systolic and diastolic functions, showed progressive decrease in the distance covered, VO_2 max, METS and at the expected increase in HR in exercise stress ECG test, due to aging and related comorbidities and physical deconditioning.

Author contributions

Conception and design of the research: Baroncini LAV, Baroncini CV, Leal JF. Acquisition of data: Baroncini LAV, Baroncini CV, Leal JF. Analysis and interpretation of the data: Baroncini LAV, Baroncini CV, Leal JF. Statistical analysis: Baroncini LAV. Writing of the manuscript: Baroncini LAV. Critical revision of the manuscript for intellectual content: Baroncini LAV, Baroncini CV, Leal JF. Supervision / as the major investigador: Baroncini LAV.

Potential Conflict of Interest

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

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital do Trabalhador / SES / PR under the protocol number 57759416.5.000.5225. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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ORIGINAL ARTICLE

Impact of Complications of Myocardial Revascularization Surgery on Expenses During Hospital Stay

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Abstract

Background: Coronary artery bypass grafting (CABG) is an important treatment option for obstructive coronary artery disease, but it represents a high expense for paying sources. The complications of CABG impose an additional expense to the procedure that is not yet clearly established.

Objective: To determine the economic impact of postoperative complications of CABG during hospitalization in a hospital of the unified health system (SUS).

Methods: This is an observational study involving 240 patients undergoing isolated CABG in a reference hospital in cardiology in 2013. Patients aged over 30 years with proven coronary artery disease and indication to perform CRVM were included. Patients who performed CRVM associated with other procedures were excluded.

Results: The average cost of hospitalization was R$ 22,647.24 (SD = R$ 28,105.66). In 97 patients who presented some complication the average cost was R$ 35,400.28 (SD = R$ 40,509.47), and in the 143 patients without complications the average cost was R$ 13,996.57 (SD = R$ 5,800.61) ($p < 0.001$). Expenditures ranged from R$ 17,344.37 in patients with one complication up to R$ 104,596.52 in patients with five complications ($p < 0.001$).

Conclusions: The occurrence of complications during hospitalization for CABG significantly increases the costs of the procedure, but the magnitude of this increase depends on the type of complication developed, and higher expenses related to cardiovascular complications, infections and bleeding. With this information, managers can improve the allocation of resources to health. (Int J Cardiovasc Sci. 2019;32(1)28-34)

Keywords: Myocardial Revascularization/economy; Myocardial Revascularization/complications; Hospital Costs/trends; Hospitalization; Cardiovascular Diseases/economy.

Introduction

Cardiovascular diseases are the main cause of mortality worldwide[1], and ischemic heart disease accounts for about 7,500,000 deaths per year.[1] In Brazil, ischemic heart disease causes 107,916 deaths per year.[2]

Hospital stays and diagnostic and therapeutic procedures related with coronary artery disease (CAD) have a meaningful economic impact on paying sources, as wells as treatment-related complications. Complications of surgical myocardial revascularization (CABG) impose additional expenses on the procedure; however, different types of complications determine a varying increase in hospital expenses with CABG. This study aims at determining the economic impact of CABG postoperative complications during stay in a hospital of the Brazilian Unified Health System (SUS).

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Methods

This is a single-center observational retrospective study.

We selected 240 patients undergoing CABG at the National Institute of Cardiology (INC) in the period from 01 January to 31 December, 2013.

We included patients aged over 30 years, of both genders, with coronary artery disease confirmed by coronary angiography and indication for surgical myocardial revascularization after evaluation by the medical staff, composed of a clinical cardiologist, a hemodynamicist and a cardiac surgeon. We excluded patients who had undergone surgical myocardial revascularization combined with other surgical procedures, such as valve surgeries and vascular surgeries.

Hospitalization costs related to medications, laboratory tests, complementary imaging tests, materials, healthcare professionals and other indirect costs, collected from patients' medical records, were counted in accordance with the data provided by the cost centers. Indirect costs data were obtained from the Transparency Portal of the Brazilian Federal Government. Service agreements and expenses with security, food, information technology, contracting of general services, engineering companies, and maintenance of medical equipment were counted. The consolidated results allowed for the apportionment of the indirect costs per patient day. The costs with healthcare professionals were calculated according with the number of clinical doctors, surgeons, anesthetists, nurses, nursing technicians, physiotherapists, nutritionists and speech therapists who worked in the care of each patient. Subsequently, data related to the wages and workload of each professional were obtained from the Transparency Portal of the Brazilian Federal Government and, with this information, it was possible to estimate the value per hour worked by each professional involved in the healthcare of each patient, in each hospital sector where this patient remained hospitalized. We used the micro-costing method, in which the interventions performed on the patients are individually counted, finally leading to the total hospitalization costs. The values used as basis of cost estimation were obtained from the Table of Procedures and Medications of SUS Managing System (SIGTAP).

Statistical analysis

The statistical analysis of the continuous quantitative variables was carried out by the Student's t-test, or the Mann-Whitney's U test, to compare both samples, and the ANOVA test or the Kruskal-Wallis test to compare more than two samples. The results of these analyses were expressed as media and standard deviation. The categorical variables were assessed using the qui-square test or the exact Fisher's test. The results of the analysis of the categorical variables were expressed as percentage. The assessment of normality was performed using the Kolmogorov-Smirnov test, and the equality of the variances was assessed using the Levene's test. An α value of 0.05 was determined. The analysis was performed using the IBM SPSS (Statistical Package for the Social Science) software (version 20.0.0).

The research project was approved by the Ethics Committee in Research of the National Institute of Cardiology (approval number 648.089; CAAE: 30460013.4.0000.5257). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Results

A total of 240 patients, 169 males and 71 females, who had undergone isolated myocardial revascularization at the National Institute of Cardiology, in 2013, were observed as shown in Table 1.

Mean age was 61.7 years, 60.9 for men and 63.4 for women ($p = 0.054$). Twenty-four patients were over 75 years of age (10.0%).

The mean time of hospital stay was 32.3 days with standard deviation of 22.7 days. The patients waited, on average, 14.2 days for the surgery, with standard deviation of 8.4. The average recovery period after surgery was 18.4 days, with standard deviation of 20.9 days.

In total, 97 patients incurred complications of some type during hospitalization, corresponding to 40.4% of patients. Complications were grouped into categories related to infectious complications, cardiovascular complications, arrhythmia, bleeding and others, which could not be classified in the other groups, as shown in Table 2.

Direct costs were analyzed by the micro-costing approach and organized into groups relating to medications, laboratory and complementary imaging tests, material and professional costs.

Table 3 shows the average costs per intervention category during hospitalization, and the next sections will demonstrate the costs per category.

Table 1 - Patients' data

Demographic profile	n	%
Age, mean	61.7	
Male	169	70.4
Anthropometric data, mean		
Weight (kg)	76.2	
Height (m)	1.64	
Creatinine clearance (mL/min)	81.3	
Body mass index	28.2	
Cause of hospitalization		
Stable CAD without angina	11	4.6
Stable angina	130	54.2
CCS I	8	3.3
CCS II	43	17.9
CCS III	65	27.1
CCS IV	14	5.8
Unstable angina	40	16.7
NSTEMI	32	13.3
STEMI	23	9.6
Others	4	1.7
Clinical history		
Systemic arterial hypertension	229	95.4
Diabetes mellitus	110	46.0
Dyslipidemia	183	76.6
Current smoking	67	28.2
Previous smoking	83	34.7
Sedentary lifestyle	51	21.4
Previous MI	127	53.4
Previous PTCA	23	9.7
Arrhythmia	6	2.5
Family history of CAD	39	16.4
Peripheral artery disease	20	8.4
Carotid artery disease	6	2.5
Chronic kidney disease	19	8.0
Chronic obstructive pulmonar disease	11	4.6
Alcoholism	12	5.0
Previous stroke	9	3.8
Hypothyroidism	8	3.4
Obesity	73	30.7
Left ventricular function		
Normal	139	57.9
Mild dysfunction	33	13.8
Moderate dysfunction	31	12.9
Severe dysfunction	36	15.0
Ejection fraction, mean	55.7	
Angiographic data		
Left main lesions		30.8
Single-vessel disease		8.7
Two-vessel disease		226
Three-vessel disease		67.8
EuroSCORE II, mean	1.12	

CAD: Coronary Artery Disease; CCS: Canadian Cardiovascular Society (angina pectoris grading system); NSTEMI: non-ST-segment elevation myocardial infarction; STEMI: ST-elevation myocardial infarction.

The mean expenditure of hospitalization was R$ 22,647.24, with a median of R$ 14,772.98 and standard deviation of R$ 28,105.66.

In patients with any complication, corresponding to 97 individuals (40.4%), the mean expenditure was R$ 35,400.28, with standard deviation of R$ 40,509.47, and in those without complications, corresponding to 143 individuals (59.6%), the average expenditure was R$ 13,996.57, with standard deviation of R$ 5,800.61 ($p < 0.001$).

However, the complications and their associated costs may vary according to each category.

The 17 patients who evolved to bleeding, had a mean hospital expenditure of R$ 37,196.45 (SD = R$ 25,855.71), whereas the 223 patients without bleeding showed an expenditure of R$ 21,538.10 (SD = R$ 28,014.13) ($p < 0.021$).

The 27 patients with arrhythmia had an average expenditure of R$ 31,760.52 (SD = R$ 22.416,23), whereas the 213 patients without arrhythmia showed an average expenditure of R$ 21,492.03 (SD = R$ 28,583.01) ($p < 0.074$).

The 37 patients who developed cardiovascular complications showed an expenditure of R$ 45,899.94

Table 2 - Complications in patients undergoing CABG surgery

Complication	N	%
Infectious		
Pneumonia	16	9.7
Mediastinitis	9	5.5
Surgical wound infection	9	5.5
Urinary tract infection	2	1.2
Empiema	1	0.6
Sepsis	6	3.6
Cardiovascular		
Cardiogenic shock	10	6.1
Perioperative myocardial infarction	6	3.6
Stroke	6	3.6
Pulmonary thromboembolism	1	0.6
Cardiac tamponade	2	1.2
Pericarditis	1	0.6
Acute arterial insufficiency of amputated segments	3	1.8
Arrhythmia		
Atrial fibrillation	20	12.2
Atrial flutter	3	1.8
Supraventricular tachycardia	2	1.2
Ventricular Tachycardia	2	1.2
Symptomatic Bradycardia or advanced blocks	5	3.0
Bleeding	15	9.1
Others		
Acute kidney failure (demanding dialysis)	14	8.3
Pleural effusion	8	4.8
Acute abdomen	7	4.2
Systemic inflammatory response syndrome	6	3.6
Pneumothorax	4	2.4
Reversed cardiorespiratory arrest	3	1.8
Digestive bleeding	2	1.2
Phrenic paralysis	2	1.2
Bronchospasm	1	0.6
Convulsion	1	0.6
Deaths	27	11.3

Table 3 - Average costs during hospitalization

Cost	R$	%
Medications	4,673.29	20.6
Laboratory tests	592.46	2.6
Imaging tests	584.83	2.6
Materials	2,494.02	11.0
Profissionals	8,551.77	37.8
Indirect costs	5,750.87	25.4
Total	22,647.24	100.0

(SD = R$ 56,287.27), and the patients without cardiovascular complications showed an average expenditure of R$ 18,409.06 (SD = R$ 15,902.53) ($p < 0.005$).

The patients with infectious complications, corresponding to 37 individuals, showed a mean expenditure of hospitalization of R$ 53,949.79 (SD = R$ 56,814.94), whereas the patients without infectious complications showed an expenditure of R$ 16,941.84 (SD = R$ 12,130.63) ($p < 0.001$).

The additional expenditures for complications, as well as the additional mean length of stay are demonstrated in Table 4.

The occurrence of multiple complications during hospital stay are associated with increased hospitalization costs, as shown in Table 5.

With regard to the intra-hospital mortality, 27 deaths (11.3%) were observed. The mean age of the patients who died was 68.2 years, whereas those who survived had a mean age of 60.9 years ($p = 0.001$). Mortality in patients who presented with at least one complication was 27.8%.

The patients who died had an average hospitalization cost of R$ 40,497.63, with standard deviation of R$ 44,819.92, whereas those who survived had a mean cost of R$ 20,384.51, with standard deviation of R$ 24,463.07 ($p = 0.036$).

Table 6 shows the comparisons between the patients who died and those who survived.

Discussion

An understanding of the hospital costs due to CABG-related complications is important because this

Table 4 - Additional expenditures for complications

Complications	Average costs (± standard deviation)	Additional costs due to complications	Mean length of hospitalization (± standard deviation)	Additional time of hospitalization due to complications
All patients	22,647.24 (±28,105.66)	-	32.3 (±22.7)	-
Patients without complications	13,996.57 (±5,800.61)	-	25.3 (±11.6)	-
Patients with any complication	35,400.28 (±40,509.47)	21,403.71	42.8 (±29.9)	17.5
Patients with any specific complication compared to all the other patients				
Infectious complications	53,949.79 (±56,814.94)	37,007.95	58.0 (±38.6)	30.3
Cardiovascular complications	45,899.94 (±56,287.27)	27,490.88	50.1 (±39.2)	21.0
Arrhythmia	31,760.52 (±22,416.23)	10,268.49	39.8 (±15.9)	8.4
Bleeding	37,196.45 (±25,855.71)	15,658.35	43.6 (±18.1)	12.1

Table 5 - Mean expenditures according with the number of complications

Number of complications	N	Mean
0	141	13,996.57
1	39	17,344.37
2	26	38,109.85
3	13	68,789.86
4	7	59,340.00
5	2	104,596.52
Unspecified	12	
Total	228	

p < 0.001 (Kruskal-Wallis test).

is a procedure of high complexity and cost, and it is performed in a large number of patients during the treatment of ischemic cardiac disease, allowing for a rational and evidence-based use of healthcare resources.

In this study, the average cost of hospitalization was higher than that found in other studies carried out in Brazil. A prospective study performed with 103 coronary patients submitted to isolated elective CABG, observed that the average cost of hospitalization was R$ 6,990.30.[3]

The occurrence of complications is associated with increased hospitalization costs, but this increase depends on the type of complication observed. The most frequent were infectious and cardiovascular complications, followed by arrhythmia and bleeding.

The patients who presented cardiovascular complications, infectious complications and bleeding in the CABG postoperative period had a higher average hospitalization cost than the patients without these complications, because they consumed more material and human resources. In addition, they demanded a longer length of hospital stay.

Twenty-seven patients were diagnosed with arrhythmia-related complications during the postoperative period. The occurrence of atrial fibrillation (AF) was 12.2%, corresponding to 20 patients, a lower percentage compared to the percentage observed in another study, in which 33.6% of the patients presented atrial fibrillation.[4] This result is in accordance with a study that observed that atrial fibrillation occurred in 15.2% of the patients analysed[5] and another study that observed that atrial fibrillation occurred in 17.2% of patients, being the most frequent complication.[6] Another study demonstrated that patients who evolved with atrial fibrillation during the CABG postoperative period had a higher average hospitalization cost compared to the patients without arrhythmia,[7] which cannot be confirmed by this study.

Patients who evolved with infectious complications had a higher cost compared to the patients who evolved without nosocomial infections. HILLIS LD et al.,[8] demonstrated that nosocomial infections during CABG hospitalization are frequent events, occurring in 10 to 20% of cardiac surgery patients, with superficial wound infection occurring in 2% to 6% of patients after cardiac

Table 6 - Comparison of costs between patients who died and patients who survived

	Deaths		Survivors		*p**
	Mean	SD	Mean	SD	
Days of hospitalization	31.1	28.3	32.5	21.9	0.816
Age	68.2	8.8	60.9	8.6	0.000
Body mass index	27.4	5.3	28.3	4.4	0.322
Days in intensive care unit	19.6	26.6	6.8	12.7	0.020
Mechanical ventilation time	178.5	349.1	29.2	93.5	0.000
Left ventricle ejection fraction	54.4	14.3	55.9	14.6	0.637
Creatinine clearance	63.6	37.2	83.5	30.7	0.002
Costs of medications	11,717.50	18,120.39	3,780.36	9,721.33	0.034
Costs of laboratory tests	871.80	726.64	557.05	457.81	0.036
Costs of imaging tests	935.24	756.39	540.42	541.19	0.001
Material costs	4,477.27	3,833.72	2,242.62	1,318.88	0.006
Daily rate costs	10,737.76	13,509.94	5,118.73	6,680.65	0.042
Healthcare professional costs	11,758.06	12,386.86	8,145.34	6,788.84	0.148
Total costs	40,497.63	44,819.92	20,384.51	24,463.07	0.036

** Statistical Analysis performed with the Student's t test.*

surgery and deep sternal wound infection in 0.45% to 5% of cases. A study conducted in the state of Rio Grande do Sul with 717 patients observed an incidence of infections in the postoperative period of CABG of 19.1%, a higher percentage compared to the percentage found in this study (15.4%).[9] Surgical wound infections after CABG extend the length of hospital stay and increase hospitalization costs. The increase in hospitalization costs was attributed to more frequent use of antimicrobial agents in patients who had nosocomial infection.[10]

Patients with cardiovascular complications also had increased hospitalization cost. A study carried out identified that cardiovascular complications, such as stroke and postoperative shock following CABG increased hospitalization costs, because greater material and human resources were necessary due to extended length of hospital stay.[11]

Patients who had bleeding during the CABG postoperative period had a higher average hospitalization cost compared to patients without bleeding. Other studies also report the impact of this complication on the increase of hospital costs.[11,12]

The mortality rate observed in this study is similar to the one found in other Brazilian studies,[13] which showed a mortality rate of 13%. Another study carried out in Brazil,[14] in the city of Rio de Janeiro, showed that in-hospital CABG mortality in four hospitals ranged from 7.0% to 14.3%, with a joint mortality rate of 10.9%.

The patients who died had a higher cost compared to the survivors. This result is in accordance with another study[5] performed with 14,780 patients submitted to isolated CABG, which demonstrated that the patients who died had higher hospital costs, with an average cost of US$ 49,242, currently corresponding to R$ 178,748.46.

Among the limitations of this study, we can highlight that it is an observational and retrospective study. Consequently, we depended greatly on the accuracy of the information contained in the medical files to carry out this research. The undertaking of the study in a single reference center may generate questions about the validity of its findings in other hospitals of the SUS where the procedure is performed. Few patients underwent off-pump CABG, which limits the application of this study's results to this type of surgery.

Another limitation of this study is related with the non-inclusion of patients who were readmitted precociously due to late surgical complications, since the discharge from hospital can happen before the occurrence of any clinical manifestation.

Conclusions

We conclude that the occurrence of complications during CABG hospitalization significantly increases the expenditures with the procedure, but the magnitude of this increase will depend on the type of complication developed, with the highest costs being related to cardiovascular complications, infectious complications and bleeding.

Author contributions

Conception and design of the research: Barbosa JL. Acquisition of data: Barbosa JL, Silva AFR, Vianna MM, Gedeon POPR, Martins Neto L, Moreira MBUD, Faria LF. Analysis and interpretation of the data: Barbosa JL, Thiers CA, Tura BR. Statistical analysis: Barbosa JL. Writing of the manuscript: Barbosa JL. Critical revision of the manuscript for intellectual content: Barbosa JL, Thiers CA, Tura BR.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the UFRJ/*Plataforma Brasil* under the protocol number 648.089, CAAE: 30460013.4.0000.5257 . All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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ORIGINAL ARTICLE

Impact of Periodontal Disease on Late Morbimortality (10 Years) of Pacientes with Acute Coronary Syndrome

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Abstract

Background: It is known that predisposing factors for periodontal disease (PD) and cardiovascular diseases are similar, just as dissemination of oral flora pathogens can induce the development of cardiovascular diseases, which play a direct role on the morbimortality of patients.

Objective: To assess the impact of periodontal disease in the presence of acute coronary syndrome on late morbimortality after long-term follow-up of patients (10 years).

Methods: The historical prospective study of continuous assessment was based on the evaluation of 345 medical records of patients hospitalized for acute coronary syndrome, divided into 3 groups: edentulous, with periodontal disease and without periodontal disease. The patients studied were in the ICU, in 2006, with a clinical picture of acute coronary syndrome submitted to invasive stratification with coronary angiography on the basis of clinical indication and were reassessed over the next 10 years. The qualitative variables were compared using the Chi-square test. Long-term mortality was assessed using the Kaplan-Meier curves, quantified with the hazard ratio (HR) and a confidence interval of 95% and compared through Cox regression. P values of less than or equal to 0.05 were regarded as statistically significant.

Results: Of the 345 patients, 233 had at least one coronary obstruction greater than or equal to 50%, being the main group for comparison according to the different status of periodontal disease (without periodontal disease, with periodontal disease and edentulous). In this cardiovascular condition, we found a difference in mortality among edentulous patients compared to those free of periodontal disease, with a p = 0.004 and a hazard ratio of 10.496 (95% CI: 4.988-22.089). A significant difference was also noted between edentulous patients and patients with periodontal disease, with a p = 0.0017 and a hazard ratio of 2.512 (95% CI: 1.491-4.234).

Conclusion: A significant increase in mortality was found according with the progression of periodontal disease, which justifies its classification as an important risk factor for the development of cardiovascular diseases, as well as the need for prevention and treatment of oral diseases. (Int J Cardiovasc Sci. 2019;32(1)35-40)

Keywords: Periodontal Diseases / complications; Acute Coronary Syndrome / mortality; Dental Plaque; Gengivitis, Plaque Atherosclerotic.

Introduction

Cardiovascular diseases (CVD) are characterized as chronic or acute changes in the heart and blood vessels, such as angina, acute myocardial infarction and stroke, being responsible for 24.9% of the deaths registered in Brazil, according to data from the Health Ministry (MS, 2011).[1]

The main theory regarding the etiology of CVDs is the atherosclerotic plaque formation within arterial territory due to an inflammatory process associated with the deposition of toxins and organic materials. Thus, the direct presence of bacteria in the atheroma plaque and / or its toxins affect synergistically the integrity of the endothelium,[2] and diseases that cause bacteremia, such as the periodontal disease (PD), can promote this process.

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The groups of PD include periodontitis, whose main causal agent is the bacterial plaque, which causes a chronic inflammatory process that affects the tissues of tooth support, including the periodontal ligament and alveolar bone.[3]

It is worthy of note that both diseases share common risk factors, including obesity, smoking, diabetes mellitus and low educational level.[4] PD bacteria can disseminate hematogenously during dental procedures or as a result of inflammatory processes and dental loss in patients with low oral health.[5]

The proximity of the oral biofilm to the periodontal vasculature facilitates the spread of bacteria to different histological sites[6] promoting changes in the lungs, kidneys and in the cardiovascular system. In general, the presence of lipopolysaccharide (LPS) from anaerobic gram-negative bacteria, associated with the release of pro-inflammatory cytokines (IL-1, IL-6, TNF-α and prostaglandin E2), increased fibrinogen levels and C-reactive protein (CRP), promotes the activation of polymorphonuclear and macrophages with immunological response in the intima layer, which speeds the formation of foam cells, basic structures of the atherosclerotic plaque.[7] Furthermore, LPS can promote lipogenesis through direct action on the hepatocytes, also intensifying the formation of atheroma plaques.[8]

The aim of this study is to demonstrate and understand the relations established between PD and CVD in patients with acute coronary syndrome and proven diagnosis of PD, in terms of morbimortality, and who were followed during 10 years.

Methods

The research was designed as a historical prospective study of continuous evaluation of 361 patient medical files assessed for the first time around 10 years ago in Accarini's study, 20069. The access to the files was granted and monitored by the Research Ethics Committee (CAAE 44588915.9.0000.5415).

After the 10-year period, out of the 361 initial medical files, 345 (95,6%) were found for the current assessment. The lack of 16 medical files may be a result of the computerization process of the hospital management system, with a possible loss during the replacement of the paper medical records by the electronic medical records in the hospital.

The assessment and classification of the patients in 2006, in relation to periodontal disease, were performed by one single odontologist, specialized in periodontics, through clinical analysis carried out in the doctor's office or in hospital (patients in ICU). All six surfaces of the teeth were inspected, with assessment of the following parameters: level of pocket depth, level of clinical insertion, gingival index and plaque index. Out of the 345 medical files assessed, it was possible to keep the classification in relation to the PD: edentulous (182), with periodontal disease (113) and without periodontal disease (50).

In relation to CVD, in 2006, the diagnosis of unstable angina or acute myocardial infarction was established according to clinical, electrocardiographic and enzymatic criteria and coronary cineangiography. Therefore, the 345 patients were classified in relation to the CVDs into: without coronary disease (66), at least one coronary obstruction, always < 50% (12), at least one coronary obstruction, ≥ 50% (233) and those who did not undergo catheterization (34).

Statistical analysis

The qualitative variables were compared using the Chi-square test. Long-term mortality was assessed using the Kaplan-Meier curves, quantified with the hazard ratio (HR) and a confidence interval of 95% and compared through Cox regression. P values of less than or equal to 0.05 were regarded as statistically significant.

Results

Table 1 was structured based on the evaluation of the 345 medical records found, showing the number of patients according to the circumstances studied, both periodontal and cardiovascular, after ten-year evolution from the first analysis.[9]

Edentulous patients with at least one coronary obstruction ≥ 50% (Group A) were analyzed, with 125 elements in this intersection, and compared with the patients with no periodontal disease and no coronary disease (Group B), with 16 elements. During the 10-year-period of follow-up, the total death numbers observed in groups A and B were, respectively, 43 and 1. The Hazard Ratio for Group A versus Group B was equal to 6.853 (95% CI: 2.905-16.164). The chi-square test for equivalence of mortality rates indicated a p value of 0.0305. Thus, Chart 1 shows a comparison of patient survival in groups A and B during the follow-up period.

Another chart (Chart 2) was organized to compare Group A, with 125 elements, with the group of patients

Table 1 - Distribution of cases without coronary artery disease, with mild obstructive coronary disease (< 50%), with severe obstructive coronary disease (< 50%), and that did not undergo catheterization relative to the presence or not of periodontal disease or edentulous condition

	No periodontal disease [50]	Periodontal disease [113]	Edentulous [182]	Deaths / total
No coronary disease	16	19	31	11 / 66 (16.7%)
At least one coronary obstruction, always < 50%	3	5	4	2 / 12 (16.7%)
At least one coronary obstruction, ≥ 50%	28	80	125	58 / 233 (24.9%)
No catheterization	3	9	22	12 / 34 (35.3%)
Deaths / total	2/50 (4.0%)	17 / 113 (15.0%)	64 / 182 (35.2%)	83 / 345 (24.0%)

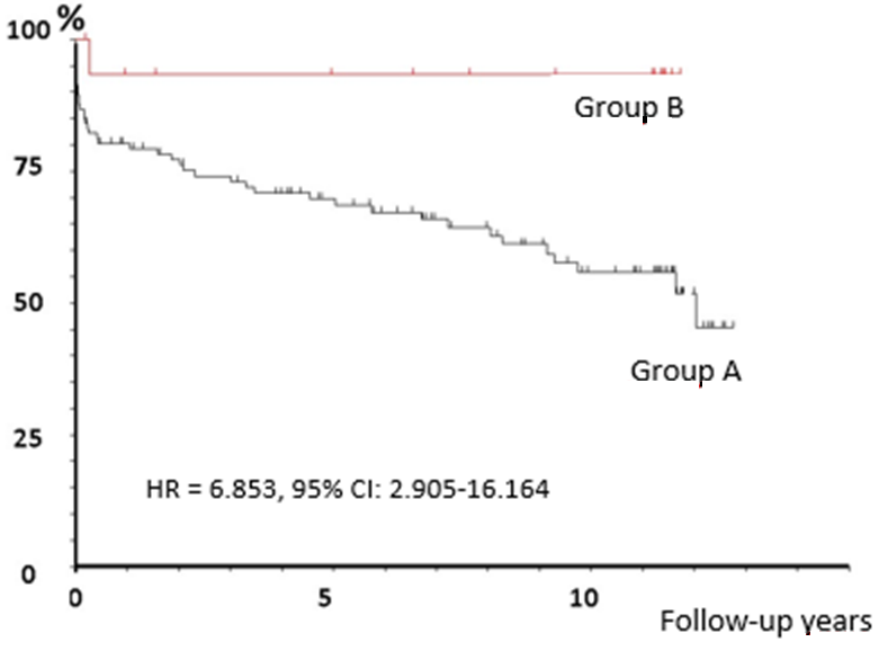

Chart 1 - Group A, formed by edentulous patients with at least one coronary obstruction ≥ 50%, compared with Group B, formed by patients with no periodontal disease and no coronary disease.

with active periodontal disease and at least one coronary obstruction, ≥ 50% (Group C), with 80 elements. During the time interval, the number of deaths in Group A was 43, while in Group C, only 14 deaths occurred. The Hazard Ratio Group A vs Group C was equal to 2.512 (95% CI: 1.491-4.234). The p-value found when comparing the curves was 0.0017.

Finally, it was possible to create Chart 3, by comparing Group A, with 125 elements, with the group of patients with no periodontal disease and at least one coronary obstruction ≥ 50% (Group D), with 28 elements. Within the 10-year-follow-up, 43 deaths occurred in Group A and only 1 death in Group D. In this comparison, the p value was 0.004 and the hazard ratio was 10.496 (4.988-22.089).

Discussion

This study, whose objective was to understand the relation, in terms of the morbimortality, between periodontal disease (PD) and acute coronary syndrome

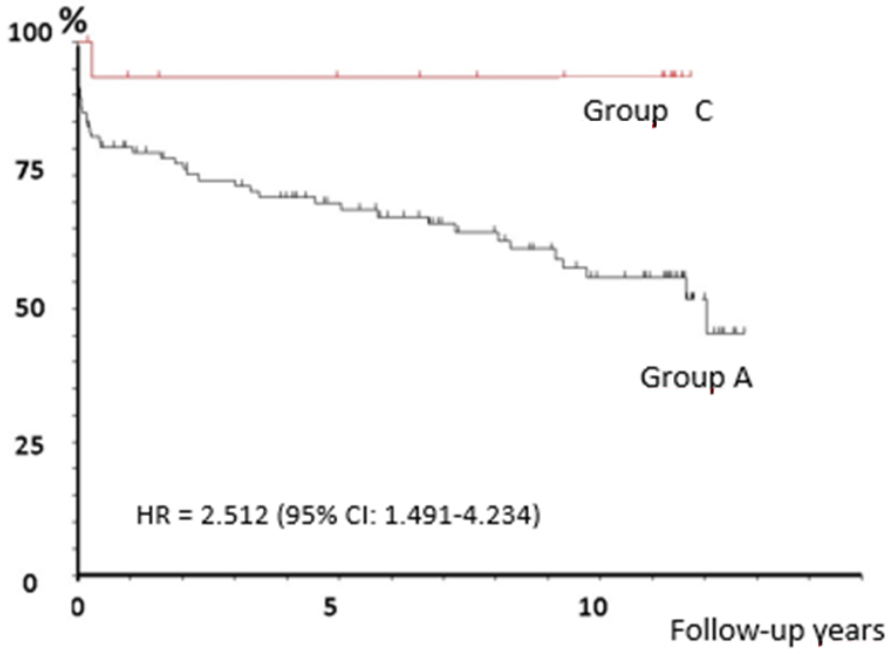

Chart 2 - Group A, formed by edentulous patients with at least one coronary obstruction ≥ 50%, compared with Group C, formed by patients with active periodontal disease and at least one coronary obstruction ≥ 50%.

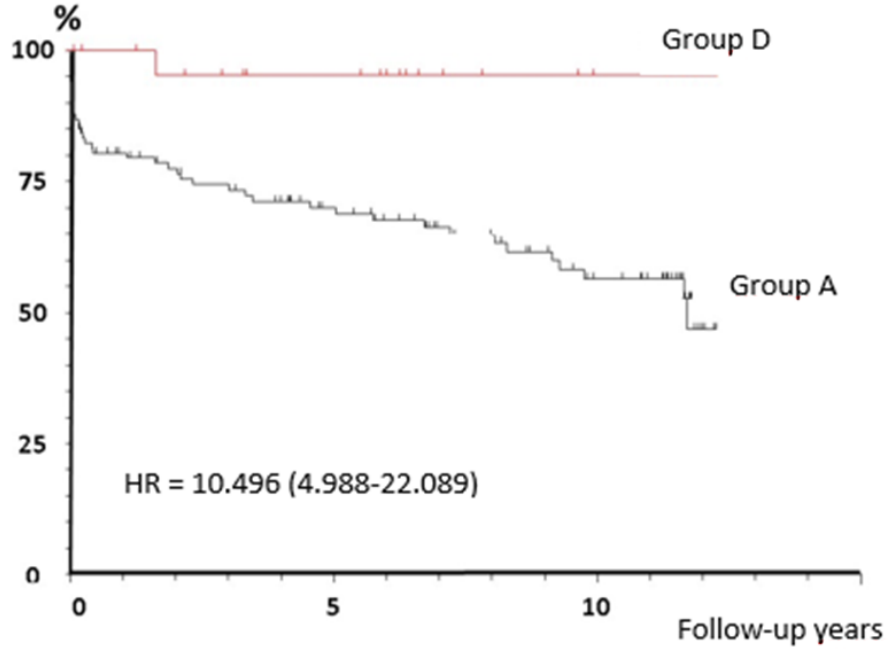

Chart 3 - Group A, formed by edentulous patients with at least one coronary obstruction ≥ 50%, compared with Group D, formed by patients with no periodontal disease and at least one coronary obstruction ≥ 50%.

(ACS) after long-term follow-up of patients (10 years), demonstrates that the presence of active periodontal disease or its sequel (edentulous patients) has a significant impact on late mortality over 10 years.

The most promising hypothesis to explain this association may lie in the analysis of inflammatory markers characteristic or predictive of cardiac ischemic events.[10] The inflamed and ulcerated periodontal pocket tissue acts as a route of entry for pathogens in the bloodstream, where it promotes bacteremia with dissemination throughout the host body. This pathway of infection is called transient metastatic bacteremia. The bacteremia caused by periodontal patogens interacts with the antibodies of the host and forms complexes that induce inflammatory reactions, a mechanism known as immunological metastatic lesion, responsible for the destructive process with the activation of defense cells, including macrophages and their precursors, monocytes, lymphocytes and polymorphonuclear leukocytes (PMNs).[11,12]

Monocytes respond to the bacterial endotoxin (LPS) with the liberation of inflammatory mediators, such as prostaglandin E2, and certain cytokines, including interleukin-1b and tumor necrosis factor-alpha (TNF-α).[13] These mediators promote vasodilation, increased vascular permeability, recruitment of inflammatory cells, connective tissue degradation and bone destruction.[14]

Data obtained in the extensive American study NHANES, with 32.000 participants, showed that the relative risk for CVD increased by 25% among patients with periodontitis. In addition to the pathophysiological process previously presented, it is worth mentioning that there is an indirect relation between periodontal and cardiovascular diseases.[15] Patients with poor hygiene habits present low consumption of low-GI foods, such as fruits and vegetables, which can result in obesity, hypertension and diabetes mellitus (precursors of CVD).[13] The statistically significant association between obstructive coronary disease and presence of periodontal disease strongly suggests that the latter should be inlcuded among the risk factors for the development of obstructive coronary disease and atherosclerotic plaque instability, culminating in an acute coronary syndrome.[9]

Conclusion

A significant increase was noted in the long-term mortality (10 years) according with the progression of periodontal disease, which justifies its classification as a major risk factor for the development of cardiovascular diseases, as well as the need for prevention and treatment of oral diseases.

Author contributions

Conception and design of the research: Godoy MF. Acquisition of data: Moras LL, Accarini R. Analysis and interpretation of the data: Carvalho TA. Statistical analysis: Godoy MF. Writing of the manuscript: Oliveira MB. Critical revision of the manuscript for intellectual content: Ricci GA.

Potential Conflict of Interest

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

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

Ethics approval and consent to participate

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

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ORIGINAL ARTICLE

Hemodynamic, Metabolic and Ventilatory Responses to Exercise in Adults with Congenital Heart Disease

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Abstract

Background: Congenital heart disease in adults shares some features with heart failure (HF), including exercise intolerance, ventilatory inefficiency, inflammatory and neurohormonal activation, cardiac arrhythmias and myocardial fibrosis. Over the last years, cardiopulmonary exercise test has gained importance in the diagnostic and prognostic evaluation of congenital heart diseases, as has already occurred in HF.

Objective: To describe the behavior of hemodynamic, metabolic and ventilatory parameters in response to exercise in adults with congenital heart disease.

Methods: Observational cross-sectional study evaluating 31 adults with congenital acyanotic or cyanotic heart disease, treated clinically, surgically or percutaneously, referred for cardiopulmonary exercise test. A descriptive analysis of the data was performed.

Results: Patients aged 35.7 ± 14.2 years were included. Oxygen consumption (VO_2) was 44.86 ± 18.01% of predicted at peak exercise and 36.92 ± 12.93% of predicted maximal VO_2 at anaerobic threshold. We found an oxygen uptake efficiency slope (OUES) of 1.49 ± 0.89 (61.43 ± 26.63% of predicted), oxygen pulse of 58.90 ± 22.24% and increment in systolic arterial pressure during exercise was 31.42 ± 21.60 mmHg.

Conclusion: Adults with congenital heart disease had similar responses to heart failure patients during exercise – reduced aerobic capacity, ventilatory inefficiency for oxygen consumption and limited inotropic response to exercise, characterized by reduced oxygen pulse and small increase in systolic arterial pressure. (Int J Cardiovasc Sci. 2019;32(1)41-47)

Keywords: Heart Defects, Congenital; Exercise; Adults; Exercise Test; Cyanosis; Hemodynamics; Metabolism.

Introduction

Congenital heart diseases are abnormalities in the structure of the heart at birth that may involve the interior surface of the walls of the heart, cardiac valves or blood vessels that carry blood to and from the heart to the body.[1] The incidence of congenital heart disease is eight cases per 1,000 live births and the estimated prevalence is more than 1,000,000 of adults in the USA.[1,2] The prevalence of congenital heart disease in adults has increased in the last five decades due to significant progression in the treatment of these conditions during childhood.[3] These patients, however, have decreased functional capacity[4-7] and higher morbidity and mortality rates as compared with healthy individuals.[8-14]

Congenital heart diseases in adults have characteristics similar to heart failure (HF) caused by other etiologies, such as exercise intolerance,[8-11] ventricular dysfunction (right or left),[15] cardiac arrhythmias,[16] myocardial fibrosis,[17] ventilatory inefficiency,[3,11,18] increased inflammatory cytokines,[19] and neurohormonal activation.[20]

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The most precise method to quantify aerobic capacity is the direct measure of peak exercise oxygen consumption (VO_2 max) obtained exclusively by cardiopulmonary exercise testing (CPET). Reduced values of VO_2 max not only indicate more accentuated functional impairment, but also imply an adverse prognosis especially in HF,[21] and also in other clinical conditions including congenital heart diseases in adults.[8-11]

The aim of the present study was to describe the level of functional limitation and hemodynamic, ventilatory and metabolic responses to exercise in adults with congenital heart disease referred for CPET in a tertiary cardiology hospital.

Methods

This was an observational, cross-sectional study that evaluated adults with congenital heart disease (cyanotic or acyanotic), under medical, surgical or percutaneous treatment. The study was approved by the local ethics committee (approval number 47563315.2.0000.5272). All patients were informed about the aim of the study and signed an informed consent form. The study was conducted in accordance with the World Health Organization recommendations and the Helsinki Declaration (October 2013) and the Brazilian National Health Council resolution number 466/2012.

Patients referred for CPET between April 2016 and August 2017 were included in this study. Exclusion criteria were: age younger than 18 years, unwillingness to sign the informed consent form, contraindications for CPET according to the Guidelines on Exercise Tests of the Brazilian Society of Cardiology.[22]

Cardiopulmonary exercise testing

A symptom-limited treadmill (Inbramed® - Porto Alegre - Brazil) exercise test was performed, using ramp protocol, with duration of approximately eight to 12 minutes. Patients were encouraged to continue exercise until exhaustion. Participants had a minimum of six minute-resting phase, with speed of 1.5 mph and slope of 2.5% in the first minute. For measurements of the gases, a clip was placed on patients' nose, a mouthpiece with saliva trap was connected to a pneumotachograph which, in turn, was connected to a VO2000® gas analyzer (MedGraphics® - St Paul - USA) coupled to a computer. Analysis was performed using the Ergo PC Elite® software (Micromed® - Brasília - Brazil). Every 20 seconds, the following parameters were analyzed in a breath-by-breath format: peak oxygen consumption (VO_2 max), expressed as percentage of the predicted value and related to body mass;[23] oxygen consumption at anaerobic threshold (AT), expressed as percentage of the predicted value and related to body mass; slope of the ratio of ventilation (VE) to CO_2 production (VCO_2) (VE/VCO_2 slope); oxygen uptake efficiency slope (OUES), expressed as absolute value and percentage of the predicted value;[24] respiratory exchange ratio (RER); changes in systolic arterial pressure (SAP) from resting to maximal exercise (ΔSAP); heart rate reserve (HRR) calculated as heart rate (HR) changes from resting to maximal exercise; chronotropic index (proportion between measured and predicted HRR); HR decrease during the first minute of recovery (HRrec); peak exercise oxygen pulse (O_2P); circulatory power (CP); ventilatory power (VP). Peak VO_2 was defined as the maximal value detected during the last 20 seconds of exercise or at the first measurement performed during the resting phase. AT was identified by the ventilatory equivalent method, and 40% of the predicted VO_2 max defined as the lower normal limit.[25] VE/VCO_2 slope was calculated during the whole test period.

Statistical analysis

A descriptive analysis of the data was performed. Categorical variables were described as frequency and percentage, whereas continuous variables as mean ± standard deviation (SD). Data were analyzed using Prism statistics software, version 5.0 (GraphPad Software Inc. La Jolla, CA, USA). Patients were selected by convenience.

Results

Thirty-one (17 female; 54.8%) adults with congenital heart disease, aged 35.7 ± 14.2 years participated in the study (Table 1). Twenty-seven (87.1%) patients had acyanotic heart disease and the most frequent disease was Tetralogy of Fallot (n = 9; 29.1%) (Table 1). Twenty-four patients had a history of surgery (77.4%), one patient (3.2%) had undergone percutaneous treatment, and six patients (19.4%) were under medical treatment with no history of interventional treatment. The most frequent comorbidities were – systemic arterial pressure (n = 3; 9.7%), dyslipidemia (n = 2; 6.4%), hyperuricemia (n = 2; 6.4%), coronary artery disease (n = 1; 3.2%) and hypothyroidism (n = 1; 3.2%). Medications used by the patients are listed in Table 2.

Table 1 - Clinical characteristics of the patients

Characteristics	n	%
Female/male sex	17/14	54.8/45.2
Age, mean ± SD	35.7 ± 14.2	-
Acyanotic /cyanotic	27/4	87.1/12.9
Primary diagnosis		
Tetralogy of Fallot	9	29.1
Single ventricle	4	12.9
Interventricular communication	3	9.7
Ebstein	2	6.4
Interatrial communication	2	6.4
TGA	2	6.4
Non-compacted myocardium	1	3.2
Tricuspid insufficiency	1	3.2
Tricuspid stenosis	1	3.2
Pulmonary stenosis	1	3.2
Aorta coarctation	1	3.2
Truncus arteriosus	1	3.2
TGA cc	1	3.2
cAVSD	1	3.2
ALCAPA syndrome	1	3.2

TGA: transposition of the great arteries; TGAcc: transposition of the great arteries congenitally corrected; cAVSD: complete atrioventricular septal defect, ALCAPA: Anomalous origin of the left coronary artery from the pulmonary artery.

Table 2 - Medications used by the study population

Drugs	n	%
Beta-blockers	19	61.3
Diuretics	15	48.4
ACEI	12	38.7
ARB	8	25.8
Warfarin	7	22.6
Sildenafil	5	16.1
Folic acid	4	12.9
Ferrous sulfate	4	12.9
Acetylsalicylic acid	3	9.7
Levothyroxine	3	9.7
Digoxin	2	6.5
Amiodarone	2	6.5
Amlodipine	2	6.5
Statin	2	6.5
Allopurinol	2	6.5
Prednisone	1	3.2
Trimetazidine	1	3.2
Metformin	1	3.2

ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin II receptor blockers.

CPET results are described in Table 3. Patients with congenital heart disease evaluated in the present study had reduced aerobic capacity, with a VO_2 max of 44.9% of predicted. AT could not be identified in 31 (25.8%) patients.

In addition, our study population showed ventilatory inefficiency for oxygen consumption, with OUES of 1.49 (61.4% of predicted) and limited SAP increment in response to exercise (ΔSAP: 31.4 mmHg). Also, patients showed reduced O_2P (8.7 mL/beat; 58.9% of the predicted value), even when only acyanotic subgroup was considered in the analysis (9.1 mL/beat; 60.9% of the predicted value).

Duration of the ramp exercise test was 9.2 ± 3.6 minutes, which was considered adequate. R value was 1.21 ± 0.26, indicating maximum efficiency of the test.

According to the Brazilian Society of Cardiology criteria,[22] the prevalence of parasympathetic autonomic dysfunction was 22.2%, and the small increase in SAP during incremental exercise indicated depressed response of this parameter. The prevalence of chronotropic incompetence was 44.4% based on different cut-off points for beta-blocker users[26] and non-users[22] (0.62 and 0.80, respectively).

Given the impossibility of HR measurement, patients with a permanent pacemaker (n = 3) and patients with atrial fibrillation (n = 1) were excluded from O_2P analysis, chronotropic response (HRR and chronotropic index) and parasympathetic autonomous modulation (HRrec).

Discussion

In the present study, we showed that adult patients with congenital heart disease have reduced aerobic

Table 3 - Results of the cardiopulmonary exercise test

Parameter	n	Mean ± SD
VO_2 max, mL.kg^{-1}.min^{-1}	31	19.1 ± 10.3
V'O_2 max, % of predicted	31	44.9 ± 18.0
AT, mL.kg^{-1}.min^{-1}	23	15.2 ± 6.8
AT, % do V'O_2 max predicted	23	36.9 ± 12.9
VE/VCO_2 slope	31	27.0 ± 9.8
OUES	30	1.49 ± 0.89
OUES, % of predicted	30	61.4 ± 26.6
O_2P, mL/beat	27	8.7 ± 3.8
O_2P, % of predicted	27	58.9 ± 22.2
O_2P in acyanotics, mL/beat	23	9.1 ± 3.8
O_2P in acyanotics, % of predicted	23	60.9 ± 23.3
ΔSAP, mmHg	31	31.4 ± 21.6
HRR, bpm	27	69.1 ± 33.5
Chronotropic index	27	0.64 ± 0.3
HRrec, bpm	27	23.5 ± 15.6
CP, mmHg.mLO_2.kg^{-1}.min^{-1}	31	2,890.4 ± 1,919.3
VP, mmHg	31	5.9 ± 2.0

VO_2 max: peak exercise oxygen consumption; AT: anaerobic threshold; VE/VCO_2 slope: ventilatory equivalent for carbon dioxide; OUES: oxygen uptake efficiency plateau; O_2P: peak exercise oxygen pulse; ΔSAP: changes in systolic arterial pressure, from resting to peak exercise; HRR: heart rate reserve; HRrec: heart rate recovery, from peak exercise to the first minute of recovery phase; CP: circulatory power; VP: ventilatory power.

capacity, with a decrease not only in maximum aerobic power (indicated by VO_2 max), but also in aerobic capacity for submaximal activities (indicated by the AT). In addition, results of the CPET revealed ventilatory inefficiency for oxygen consumption and limited inotropic response to exercise.

Previous studies have reported lower values of VO_2 max[4-6,9,27] and AT[5] in adults with congenital heart disease as compared with healthy adults.[5] Reduced aerobic capacity is a common condition in this population, and 80% of these patients have a VO_2 max lower than predicted for age and sex.[4] It is worth mentioning that many adults with congenital heart disease overestimate their own clinical conditions in light of the long period of exercise restriction. The level of exercise intolerance is more accurately assessed by measurement of the VO_2max, and even asymptomatic patients considered as New York Heart Association class 1 have lower VO_2max when compared with healthy individuals of the same age,[9] suggesting a discrepancy between a subjective and an objective approach of exercise capacity in this population.

The decrease in maximal aerobic capacity in congenital heart disease adults is so important that VO_2 max in these patients is comparable to that in patients with HF caused by other conditions.[9] VO_2 max is a traditional marker of an unfavorable prognosis of HF and has a central role in the evaluation of eligibility for heart transplantation in this group.[28] Similarly, a reduced VO_2 max is associated with higher morbidity and mortality in adults with congenital heart disease.[8,9]

We found a mean VO_2 max of 19.1 mL.kg^{-1}.min^{-1}. Diller et al.,[9] evaluating a large group of patients with congenital heart disease, suggested a VO_2 max of 15.5 mL.kg^{-1}.min^{-1} as a cut-off for predicting cardiac events. Patients with a VO_2 max lower than this had a three-time higher risk of death and hospitalization. Based on the studies by Diller et al.,[9,10] our patients had a good prognosis. However, this was a young population (< 35.7 years of age) and, in fact, VO_2 max found in these patients was only 44.9% of predicted, i.e., considerably lower than that expected for healthy individuals of the same sex and age. Inuzuka et al.,[8] also evaluated adults with congenital heart disease and suggested a cut-off value of 64% of predicted VO_2 max to identify patients with a low or high 5-year survival mortality risk.[8] Therefore, according to these authors, our study group could be, in fact, at risk of a poor prognosis.

Modern concepts of HF classify this syndrome in progressive stages. Patients with cardiac structural abnormalities but no signs of HF would be designated as stage B.[29,30] Although this classification did not include congenital heart disease, in a scientific statement published in 2016, the American Heart Association recommended that patients with congenital structural heart disease should be classified as being at least stage B of HF.[31] In agreement with this position, our results demonstrated a depressed response of SAP (ΔSAP: 31.4 mmHg) concomitantly with reduced O_2P in absolute (8.7 mL/beats) and relative (58.9% of predicted) values, suggesting a limited inotropism during exercise. Although O_2P response cannot be attributed only to the systolic volume behavior during incremental exercise (since it also depends on the arteriovenous oxygen difference, which in turn is altered in cyanotic and hypoxemic patients), the higher frequency of acyanotic

patients in our sample (87.1%) allow us to infer that the decreased O_2P was probably a consequence of a limited increase in systolic volume during exercise. We corroborate this hypothesis, as we found low O_2P values even when cyanotic patients (9.1mL/beat) were excluded from analysis. As previously mentioned, the decreased response of SAP reinforces the hypothesis of a modest inotropic response during exercise.

VO_2 max has been recognized as the most important marker of morbidity and mortality in HF. Recent evidences, however, have suggested other parameters related to ventilatory efficiency, notably VE/VCO_2 slope and OUES, as better prognostic predictors in HF.[32] Similar phenomenon was seen in congenial heart disease in adults. Dimopoulos et al.,[13] reported that adults with congenial heart disease had higher VE/VCO_2 slope than healthy individuals, and such difference was observed in all types of congenital heart diseases and was directly proportional to the functional class. According to the authors, cyanosis was the main predictor of an increased VE/VCO_2 slope. This parameter was the most important marker of mortality in adults with congenial heart disease in acyanotic patients (cut-off point of 38).[13] Similarly, Inuzuka et al.,[8] reported that a VE/VCO_2 slope > 39 was a predictor of mortality only in acyanotic congenital heart disease patients. In our study, mean VE/VCO_2 slope was 27, which is considered normal. This may be explained, at least in part, by the small frequency of cyanotic patients in our sample.

In addition to ventilatory inefficiency for carbon dioxide, adults with congenital heart disease commonly have a ventilatory inefficiency for oxygen consumption also, represented by low OUES values.[18] We found a mean OUES of 1.49, corresponding to only 61.4% of predicted. It is worth pointing out, for sake of comparison, that an OUES lower than 1.47 is associated with a poor prognosis of HF,[33] which indicates that our study population had a ventilatory efficiency for oxygen similar to that in patients with more severe HF.

HR responses during incremental exercise, particularly in the presence of chronotropic incompetence, were equally important for risk stratification of adults with congenital heart disease. Diller et al.,[14] reported that a HRR lower than 51 bpm was a predictor of lower survival in this population, especially when associated with a VO_2 max lower than 16.7 $mL.kg^{-1}.min^{-1}$, which increased the mortality risk by 3.8 times.[14] The authors also identified the chronotropic index and reduction in HRrec as parameters associated with unfavorable prognosis. Similarly, Inuzuka et al.,[8] identified the VO_2max combined with HRR as the main marker of mortality in cyanotic and acyanotic congenital heart disease. However, the cut-off point was 71 bpm.[8] Since we found a mean HRR of 69 bpm, our patients would be at increased risk according to these results reported by Inuzuka et al.,[8] but not according to those reported by Diller et al.[14]

The prevalence of chronotropic incompetence in our study was 44.4%, lower than that reported by Diller et al.,[14] (62%); chronotropic index, however, were similar in both studies (0.64 and 0.70, respectively). We found a mean HRrec of 23.5 bpm, which was considered normal and suggestive of adequate parasympathetic autonomous modulation. Only 22.2% of our population met criteria for parasympathetric dysautonomia.

Recently, CP and VP have emerged as important markers of adverse events in HF,[34] by using the product of SAP with VO_2 max, and the quotient of PAS by VE/VCO_2 slope, respectively. The cut-off points for CP and VP in HF were 1,750 $mmHg.mLO_2.kg^{-1}.min^{-1}$ and 3.5 mmHg, respectively.[34]

In adults with congenital heart disease, Giardini et al.,[12] found that low CP values (lower than 1,476 $mmHg.mLO_2.kg^{-1}.min^{-1}$) were associated with a 15.4-fold increase in the 4-year risk of death. The authors described that despite an inverse relationship between CP and functional class, even asymptomatic patients had a lower CP than healthy individuals. We found an adequate CP (2,890.4 $mmHg.mLO_2.kg^{-1}.min^{-1}$), as compared with that in HF patients and also with the findings by Giardini et al.,[12] In addition, we found adequate VP values taking into account HF patients, although we did not find other studies evaluating this parameter in adults with congenital heart disease in the literature.

Limitations

Limitations of this study included the relatively small sample size, which is common in studies involving low-prevalence conditions.

The lack of a control group could also be considered a limitation of our study. However, our results were compared with those obtained from well-established prediction equations based on age, sex and anthropometric indexes. Comparisons of our results with predicted values, previous studies on adults with congenital heart disease and especially on patients with HF, a recognized high severity condition, allow us to make important inferences about the cardiovascular conditions of the study population.

Conclusion

Adults with congenital heart disease had similar responses to HF patients during a cardiopulmonary exercise test, indicating an impaired aerobic capacity, ventilatory inefficiency for oxygen uptake and reduced inotropic response to exercise.

Author contributions

Conception and design of the research: Nascimento PMC, Kopiler DA, Cola MCT, Tibiriçá E. Acquisition of data: Nascimento PMC, Kopiler DA, Souza FCC, Cola MCT, Coelho MP, Lopes GO, Analysis and interpretation of the data: Nascimento PMC, Kopiler DA, Souza FCC, Tibiriçá E. Statistical analysis: Tibiriçá E. Writing of the manuscript: Nascimento PMC, Souza FCC, Tibiriçá E. Critical revision of the manuscript for intellectual content: Nascimento PMC, Kopiler DA, Souza FCC, Cola MCT, Coelho MP, Lopes GO, Tibiriçá E.

Potential Conflict of Interest

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

Sources of Funding

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Instituto Nacional de Cardiologia under the protocol number 47563315.2.0000.5272. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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ORIGINAL ARTICLE

Hypotensive Response to Continuous Aerobic and High-Intensity Interval Exercise Matched by Volume in Sedentary Subjects

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Abstract

Background: Systemic arterial hypertension (SAH) is one of the main risk factors for heart disease. Among the benefits linked to different modalities of physical exercise, post-exercise hypotension (PEH) is a key point for exercise prescription in this condition.

Objective: To investigate and compare PEH in response to continuous aerobic exercise (CONT) and high-intensity interval exercise (HIIE), matched by volume, in sedentary individuals.

Methods: A randomized cross-over study, composed of sedentary, healthy male subjects submitted to two acute physical exercise protocols matched by volume, HIIE and CONT, on a treadmill. Hemodynamic measures for the evaluation of PEH were performed pre, immediately after exercise and every five minutes thereafter, during one hour of recovery. Two-way ANOVA with repeated measurements was used for comparisons between groups and Bonferroni post hoc test as appropriate. $P < 0.05$ was considered significant.

Results: Both exercise protocols promoted significant PEH, with reductions in systolic blood pressure (SBP) and mean arterial pressure (MAP). HIIE promoted a reduction of SBP and MAP at the 15th minute, whereas the same effect was observed at the 30th following CONT.

Conclusion: Both HIIE and CONT, matched by volume, promote PEH of similar magnitude. However, PEH occurs earlier following HIIE, suggesting a better time / effectiveness ratio, and an additional beneficial effect of this modality. (Int J Cardiovasc Sci. 2019;32(1)48-54)

Keywords: Hypertensio/physiopathology; Cardiomegaly; Sedentarsm; Adherence Guidelines; Blood Pressure; Post –Exercise hypotension; Exercise; High-Intensity Interval Exercise.

Introduction

Systemic arterial hypertension (SAH) is a multifactorial chronic disease associated with metabolic and hormone dysfunctions, myocardial hypertrophy and lifestyle.[1] There is an exponential increase in the risk of cardiovascular events when systolic blood pressure (SBP) and diastolic blood pressure (DBP) are above 115 and 75 mmHg, respectively. Increments of 20 mmHg in SBP or 10 mmHg in DBP increase the risk for cardiovascular events by 100%.[2]

Nonpharmacological, low-cost strategies for prevention and treatment of SAH include regular physical exercise and interventions supported by national and international guidelines as primary strategy for the treatment of SAH.[3,4] Physical exercise cause physiological changes including post-exercise hypotension (PEH), which can effectively attenuate myocardial overload in SAH.[5]

Studies have demonstrated the occurrence of PEH in response to continuous aerobic exercise (CONT),[5] resistance exercise,[6] and more recently, to high-intensity

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interval exercise (HIIE).[7] In fact, both aerobic and resistance exercises have similar effects on PEH, with slightly stronger effects of CONT.[8] Besides, interval exercise protocols have drawn attention from scientific community, as they promote an increase in peak oxygen consumption, insulin sensitivity and mitochondrial enzymes, at the same proportion as observed with traditional continuous exercises in sedentary subjects, although these types of exercises require five-fold higher exercise volume as compared with HIIE.[9]

Regardless of the type of exercise, volume seems to be determinant for the magnitude of cardiovascular responses, influencing PEH. In this context, the effects of CONT and HIIE, adjusted for equivalent volumes, on hemodynamic variables are unknown. Therefore, the current study aims to investigate and compare PEH in response to HIIE and to CONT, matched by volume, in young sedentary individuals.

Methods

Subjects

Thirteen men aged 20-30 years, with sedentary lifestyle for at least six months[10] and no history of diseases, were recruited by convenience through print media and online social media. The following exclusion criteria were used: (1) individuals unable to exercise due to physical or psychological limitations; and (2) individuals using ergogenic aids or tobacco.

The study was approved by the local ethics committee (approval number 2.202.349) and performed according to the Helsinki Declaration.

Experimental design

This randomized crossover study consisted of three days of evaluations separated by 72 hours. On day 1, measurements of blood pressure (BP), heart rate (HR) and body mass index (BMI) using a scale and a stadiometer were obtained, and ergometric test was performed to determine maximal heart rate (maxHR). On days 2 and 3, patients underwent two exercise sessions – HIIE or CON in a random sequence. The website www.randomizer.org was used for randomization of the experimental conditions.

Hemodynamic measurements

BP measurements were taken using a digital sphygmomanometer (Omron, HEM-907, Japan) previously validated.[11] Measures were taken with individuals in sitting position at rest. Resting BP was measured on the first day of evaluation, following the VII guidelines for hypertension of the Brazilian Society of Cardiology.[4] BP measurements were taken on exercise test days before, immediately after and every five minutes thereafter during a 60-min resting period. HR was measured using a heart rate monitor (Polar Electro Oy, V800, Finland) every time BP was taken. Double product (DP) was calculated by the formula DP = SBP x HR at predetermined time points.

Ergometric test and peak oxygen consumption (peak VO_2)

Maximal effort ergometric test was performed on a treadmill (Imbramed, ATL 10200, Brazil), following the Conconi protocol.[12] Initial velocity was set at 5 km/h, with increments of 1 km/h/minute. The tests were interrupted when two of the following criteria were met – HR above that predicted for age (220-age), perceived exertion ≥ 20 on Borg's scale[13] or voluntary exertion. Peak oxygen consumption was predicted using a formula previously validated for the Brazilian population.[14] All volunteers were verbally encouraged to reach maximal exertion during the tests.

Exercise protocol

Exercise protocols were conducted using a treadmill (Imbramed, ATL 10200, Brazil). The protocols were equalized by volume, or distance covered, i.e., in both protocols, the distance covered was 5 km.[15]

Continuous aerobic exercise (CONT)

After a 5-minute warm-up, treadmill velocity was adjusted to 70% of the maximal heart rate reached during the ergometric test. This velocity was maintained until the volunteers ran a total of 5 km.[15]

High-intensity interval exercise (HIIE)

After a 5-minute warm-up, the volunteers performed an intermittent 5-km running test, consisting of a 1-minute running at 90% of maximal heart rate followed by a 1- minute resting period at 60% of maximal heart rate.[15]

Statistical analysis

Normality of data distribution was analyzed by the Shapiro-Wilk test. Two-way ANOVA (conditions

vs. time points) test for repeated measures was used for within-group and between-group comparisons, followed by post-hoc Bonferroni test as appropriate. A $p < 0.05$ was set as statistically significant. All data were analyzed using the Statistical Package for Social Sciences (SPSS) 20 software. Data were expressed as mean ± standard deviation.

Results

Characteristics of the sample are described in Table 1. No significant differences were found in SAP, DAP, mean arterial pressure (MAP) or HR between the exercise protocols at the pre-exercise moment. Higher HR was found in HIIE immediately after exercise as compared with CONT ($p = 0.02$). Exercise duration was shorter for HIIE compared with CONT ($p = 0.04$). Other descriptive variables of each experimental condition are described in Table 1.

Both conditions caused significant PEH. A significant reduction in SAP ($p = 0.01$) and MAP ($p < 0.01$) was observed at the 15th minute after HIIE, persisting until one hour thereafter. A significant reduction in SAP ($p = 0.04$) and MAP ($p = 0.01$) was observed at the 35th and 30th minute, respectively, after CONT, and hence the beneficial effect of PEH occurred later after CONT than HIIE. No significant changes in DAP were found during the exercise tests. Also, no significant differences were found between SAP, MAP and DAP between the conditions. Changes in BP in response to different exercise protocols are shown in Figure 1.

No differences were found in DP over the study period, except for the time immediately after the exercise, in which DP was higher in HIIE than in CONT ($p = 0.03$) (Figure 2).

Table 1 - Characteristics of the study group and exercise conditions

Variables	Mean ± standard deviation	
Age (years)	22.7 ± 2.6	
BMI (kg/m²)	25.3 ± 2.7	
Peak VO_2 (mL/kg/min)	35 ± 1.4	
Resting SBP (mmHg)	125.7 ± 7.8	
Resting DBP (mmHg)	80 ± 9.2	
Resting heart rate (bpm)	69.6 ± 5.6	
Maximal heart rate (bpm)	192.7 ± 6.3	
	HIIE	**CONT**
Pre SBP (mmHg)	127.9 ± 7.5	124.9 ± 7.2
Post SBP (mmHg)	141.8 ± 6.1	142 ± 8.1
Pre DBP (mmHg)	81.3 ± 7.4	82.7 ± 8.7
Post DBP (mmHg)	72.9 ± 6.8	78.8 ± 10.1
Minimum SBP (mmHg)	110 ± 6.7	111.5 ± 8
Minimum DBP (mmHg)	72.1 ± 10	73.5 ± 9.6
Pre-exercise heart rate (bpm)	84± 9.7	88.7 ± 12.3
Post-exercise heart rate (bpm)*	160.2 ± 17.7	139.2 ± 13.7
Session duration (min)#	35.4 ± 4.2	44.2 ± 2.1

*BMI: body mass index; peakVO_2: peak oxygen consumption; SBP: systolic blood pressure; DBP: diastolic blood pressure; CONT: continuous aerobic exercise; HIIE: high-intensity interval exercise; *: p = 0.02 between the groups; #: p = 0.04 between the groups.*

Discussion

In the present study, we evaluated blood pressure behavior after two exercise conditions, matched by volume – CONT and HIIE. The main findings were: 1) both conditions promoted PEH; 2) HIIE promoted PEH at the 15th minute and thereafter, while the onset of PEH occurred only at the 30th minute following CONT.

PEH has been systematically investigated, showing important effects on prevention and treatment of SAH.[5,7,8,16] The sum of the acute hypotensive effects in response to each exercise protocol promotes a long-term, protective effect on cardiovascular system, attenuating the risk for negative outcomes.[17,18] Therefore, manipulation of the type, volume and intensity of exercise is important for the selection of efficient and clinically applicable strategies.

Previous studies have suggested that the effects of HIIE on PEH were slightly superior than CONT. Angadi et al.,[7] have shown that PEH occurs in both exercise conditions (HIIE and CONT, not matched by volume) during the first post-exercise hour in normotensive subjects. Nevertheless, PEH persisted for three hours after HIIE.[7] In the study by Dantas et al.,[19] HIIE significantly reduced ambulatory BP in normotensive individuals. This effect persisted for 5 hours after the session, and no changes were found in asleep BP. Nevertheless, the study[19] did not include an aerobic condition, which made it impossible to compare both conditions. Carvalho et al.,[20] reported a significant PEH after HIIE and CONT

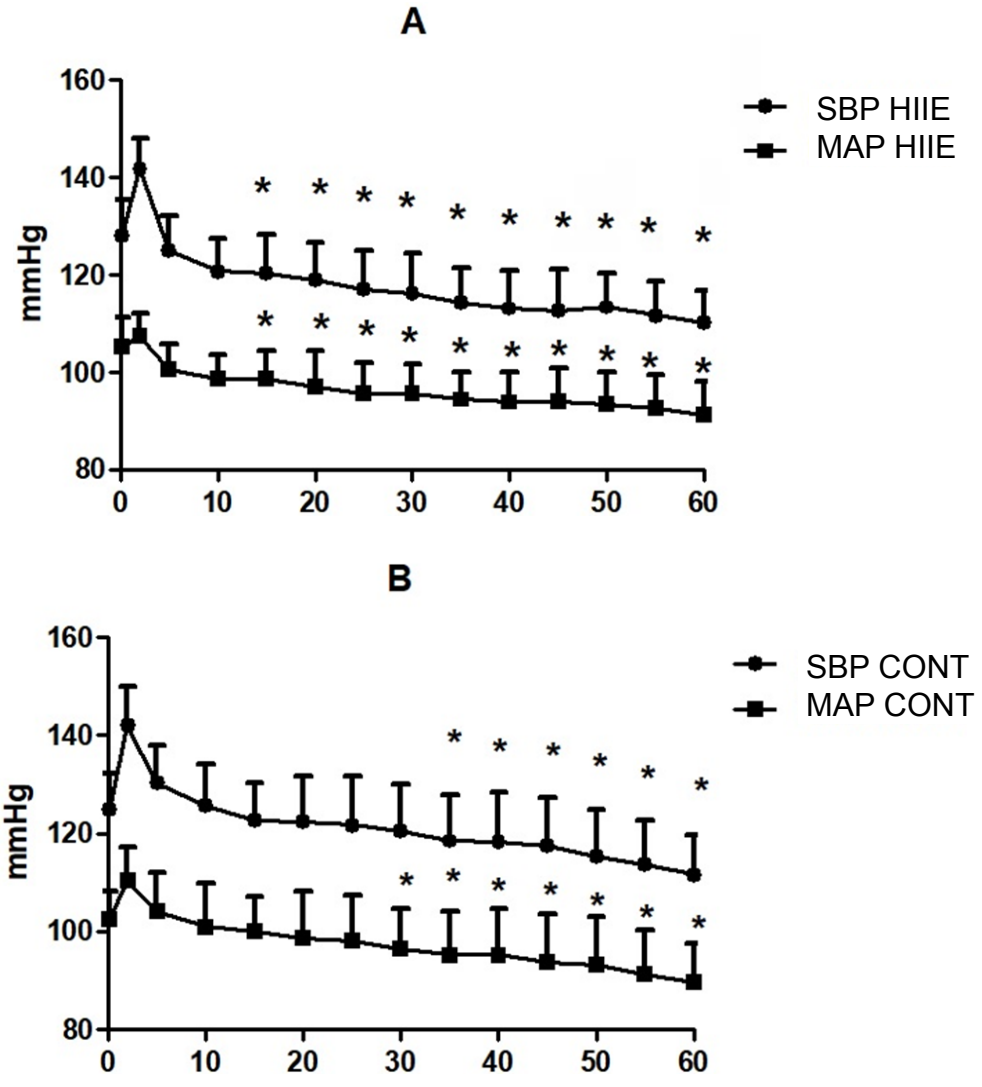

Figure 1 - Systolic blood pressure (SBP) behavior and mean arterial pressure (MAP) during the first hour following (A) high-intensity interval exercise (HIIE) and (B) continuous aerobic exercise (CONT); *p < 0.05 compared with pre-exercise, within- group comparisons.

in hypertensive, elderly subjects during a 24-hour period, with significantly lower BP levels in HIIE than CONT. According to the authors, these findings may be attributed to elevated BP levels in the study population, and the muscle mass involved in the exercise, since treadmill protocols seem to exert a higher effect on PEH.[20,21] It is worth pointing out that the protocols used in the studies cited above were not matched by volume.

Lacombe et al.,[22] compared the influence of equicaloric protocols of HIIE and CONT (not matched by volume) on PEH in prehypertensive subjects.[22] Reduced BP was seen one hour after the exercise sessions, with no significant differences between them.[22] These findings corroborate our results, since, as exercises sessions were equalized by volume (i.e., total distance covered) or by energy expenditure, the magnitude of PEH caused by the exercise tests was not different between the conditions. In addition, in the study by Lacombe et al.,[22] exercise duration was similar between HIIE and CONT (~20 vs. ~21 min, respectively),[22] whereas results of our study indicated a higher time/efficiency ratio, with shorter duration (~35 vs. ~44 min), for HIIE, compared with CONT.

The results of the present study showed that, compared with baseline BP values, there was an

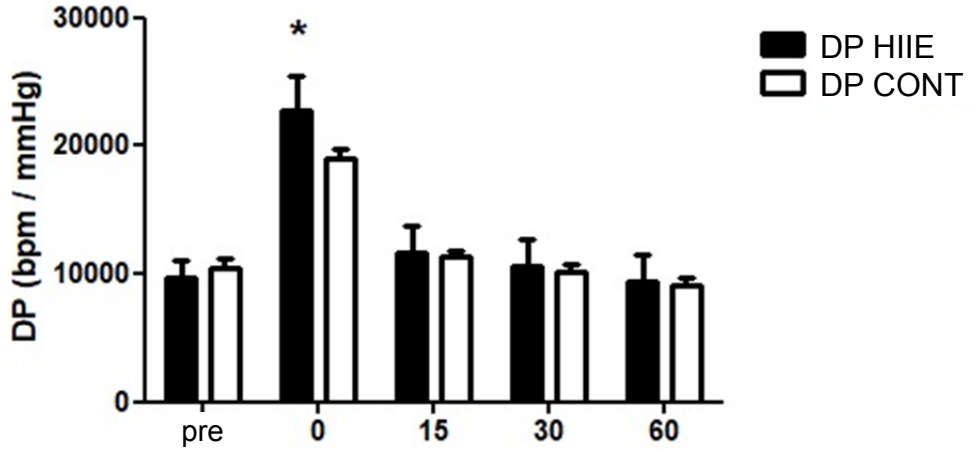

Figure 2 - Double product (DP) in response to high-intensity interval exercise (HIIE) and continuous aerobic exercise (CONT) before and during the first hour following the exercise sessions; * $p < 0.05$.

absolute reduction of 17.9 mmHg and 13.4 mmHg in SBP following HIIE and CONT, respectively. Such decrease is of clinical relevance, with a potential effect on cardiovascular risk reduction.[2] Similar effect has been reported in hypertensive individuals,[20,23,24] with increased resting BP. In this regard, PEH results from a decrease in peripheral vascular resistance by reduction in sympathetic activity.[18,25] In normotensive subjects, PEH seems to be lower than in hypertensive individuals.[7,19] However, in general the protocols of exercise of previous studies had a low volume and short duration (20 minutes) as compared with the protocol used in our study. Thus, higher volume protocols may be associated with higher sympathetic withdrawal and vasodilation after exercise.

In addition, we did not find any significant changes in DBP over time or between the exercise protocols. These findings are in accordance with those reported in the literature,[22] and was somehow expected, since the physiological response of DBP to dynamic exercise is to maintain baseline levels, which were normal in our sample.

As expected, myocardial work index, estimated by DP, was significantly higher following HIIE than CONT. This finding is related to the typical elevation in HR in high intensity exercises, with no major clinical impact in this population. In this sense, many strategies involving high intensity exercise and elevated HR have been shown to promote significant reductions in BP, not only in normotensive but also in hypertensive subjects.[1,16]

Besides, PEH at the 15th minute following HIIE and at the 30th minute following CONT may be associated with increased DP in the former, leading to increased cardiac output, shear stress and vasodilation induced by nitric oxide.[26] Based on the fact that endothelium-dependent vasodilation in response to exercise seems to be dependent on exercise intensity,[27] the high intensity of the HIIE protocol may be responsible for the earlier PEH in this condition.

Among the limitations of this study are the small sample size and the lack of a control condition.

Conclusion

Both HIIE and CONT, matched by volume, promote PEH of similar magnitude. In HIIE, PEH occurs earlier than CONT, suggesting an additional beneficial effect of this exercise modality on cardiovascular system, in addition to requiring a shorter exercise duration.

Further studies using ambulatorial BP monitoring could provide a more precise understanding of the mechanisms of BP behavior in response to HIIE and CONT equalized by volume. Also, studies to investigate the different biochemical and physiological mechanisms by which HIIE and CONT promote PEH are urgently needed.

Author contributions

Conception and design of the research: Boeno FP, Ramis TR, Farinha JB, Moritz C, Santos VP, Oliveira AR,

Teixeira BC. Acquisition of data: Boeno FP, Ramis TR, Farinha JB, Moritz C, Santos VP, Oliveira AR, Teixeira BC. Analysis and interpretation of the data: Boeno FP, Ramis TR, Farinha JB, Moritz C, Santos VP, Oliveira AR, Teixeira BC. Statistical analysis: Boeno FP, Ramis TR, Farinha JB, Moritz C, Santos VP, Oliveira AR, Teixeira BC. Writing of the manuscript: Boeno FP, Ramis TR, Farinha JB, Moritz C, Santos VP, Oliveira AR, Teixeira BC. Critical revision of the manuscript for intellectual content: Boeno FP, Ramis TR, Farinha JB, Moritz C, Santos VP, Oliveira AR, Teixeira BC.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade Regional Integrada do Alto Uruguai e das Missões (URI) under the protocol number 2.202.349. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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ORIGINAL ARTICLE

Influence of ACE Polymorphism on Echocardiographic Data of Patients with Heart Failure

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Abstract

Background: Angiotensin converting enzyme (ACE) polymorphism has been associated with different clinical and echocardiographic parameters in patients with heart failure (HF). However, no studies have been investigated such association with HF caused by Chagas disease.

Objectives: To perform a genetic study to evaluate the frequency of ACE polymorphism in patients with HF caused by Chagas disease attending a university hospital in the central-west region and its association with echocardiographic findings.

Methods: Descriptive study of ACE polymorphism (I/D) and echocardiographic data of 103 patients with HF caused by Chagas disease. Echocardiographic parameters were compared between the genotypes using the ANOVA test.

Results: Genotypic distribution of the ACE polymorphism was 16.5% DD, 57.3% DI and 26.2% II. There was no statistically significant difference in the distribution of genotypes between men and women. The echocardiographic findings were: left ventricular ejection fraction: 43.8 ± 14.8 (DD) vs. 42.3 ± 11.6 (ID) vs. 44.9 ± 13.0 (II), p = 0.664; left ventricular diastolic diameter: 59.2 ± 9.7 (DD) vs. 60.3 ± 7.6 (ID) vs. 59.7 ± 78.1 (II), p = 0.879; left ventricular systolic diameter: 48.6 ± 12.8 (DD) vs. 50.6 ± 9.7 (ID) vs. 49.3 ± 11.9 (II), p = 0.753; and left atrial volume: 44.9 ± 10.1 (DD) vs. 40.9 ± 9.6 (ID) vs. 38.2 ± 7.8 (II), p = 0.068. Significant correlation coefficients were found for gender, age, ethnicity, heart rate and dyslipidemia.

Conclusion: ACE polymorphism was not associated with echocardiographic findings in patients with HF caused by Chagas disease. (Int J Cardiovasc Sci. 2019;32(1)55-60)

Keywords: Heart Failure; Angiotensins; Polymorphism, Genetic; Chagas Disease; Echocardiography/methods.

Introduction

Chagas disease, described more than 100 years ago by Carlos Chagas, is considered one of the most neglected diseases in the world by the World Health Organization (WHO).[1] It is an important cause of heart failure (HF) in low socioeconomic regions, leading to high morbidity and mortality.[2] In the central-west region of Brazil, Chagas disease has been considered the main cause of HF.[3-5]

Most health problems, including HF, have a multifactorial etiology, that involves environmental, lifestyle, and genetic factors.[6] Multifactorial disorders are characterized by genotypic contributions from many genes that interact with each other and with environmental factors.[6] Genetic composition, associated with environmental factors, can predispose an individual to diseases and response to pharmacological interventions.[7]

Doppler echocardiography is a useful method for diagnostic confirmation, evaluation of etiology, pathophysiological and hemodynamic model, prognosis and indication of therapeutic alternatives for patients with HF.[8] Due to the importance and magnitude of this condition, clinical therapy of HF patients require a multidisciplinary approach, and search for new techniques.

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In this context, analysis of genetic polymorphisms is a non-invasive technique that may open new avenues and indicate potential preventive therapies for these patients.

Angiotensin converting enzyme (ACE) gene is located on chromosome 17q23 and consists of 24 introns.[9] Several approaches on ACE polymorphism in HF have been reported in the literature, including three clinical trials that did not find an association between ACE polymorphism and HF.[4,10,11] Other studies, however, have suggested the DD phenotype as a risk factor for cardiac hypertrophy and HF[12] and associated this phenotype with worse survival.[13] Figure 1 shows the localization of the gene that encodes ACE.[14]

In the last years, ACE polymorphism has drawn much attention due to conflicting results of the studies on HF. The present study aimed to identify ACE gene D/I (deletion/insertion) in patients with HF caused by Chagas disease and compare it with echocardiographic results.

Methods

This was an observational cohort study. Clinical data were collected from the medical records of patients seen at the Cardiology Unit of the Federal University of Goias, Brazil. Genetic analysis was performed at the Laboratory of Genetics and Molecular Cardiology (Incor/University of Sao Paulo, Brazil).

One hundred and three patients were evaluated from February 2014 to October 2015. All patients were on optimized drug therapy according to current guidelines.[8]

All patients included in the study underwent complete genotyping process for I/D alleles. Alleles were determined after the patients were included in the study. All clinical data were extracted from medical records by the first author of this article, before patients' visits, and ten patients were invited to participate in the study. Inclusion criteria were age older than 18 years, diagnosis of HF as established by the Framingham criteria, and doppler echocardiography using the Teichholz method (more recent and available tests were considered for analysis). Exclusion criteria were: unavailable or inadequate medical records, and HF caused by other than Chagas disease.

The study was analyzed and approved by the Ethics Committee of the General Hospital of the Federal University of Goias (approval number 908.870). All patients signed an informed consent form, and the study was conducted according to current ethical issues.

Echocardiographic variables

All patients had echocardiography results available in the medical records. The following echocardiographic parameters were evaluated (Table 1) – LAV: left atrial volume; EF: ejection fraction; LVDD: left ventricular diastolic diameter; LVSD: left ventricular systolic diameter (Teichholz method).

Echocardiographic measures of cavity diameter and muscle thickness were obtained following the American Echocardiography Society recommendations.[15]

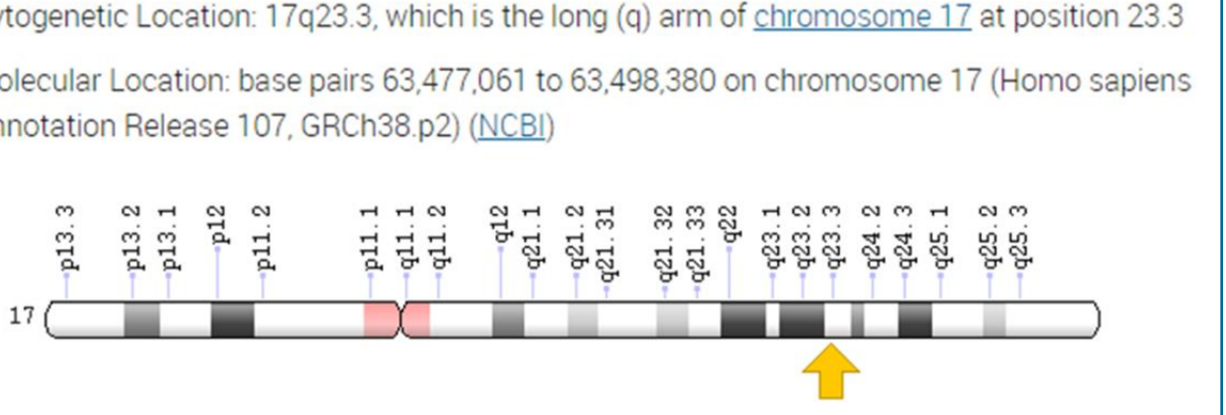

Figura 1 - Localization of the angiotensin converting enzyme (ACE) gene.

Table 1 - Echocardiographic parameters according to angiotensin-converting enzyme (ACE) (Deletion/Insertion, D/I)

	DD n (%)	DI n (%)	II n (%)	
N	17	59	27	
EF (%)				0.664
Mean	43.8	42.3	44.9	
Standard deviation	14.8	11.6	13.0	
LVDD				0.879
Mean	59.2	60.3	59.7	
Standard deviation	9.7	7.6	8.1	
LVSD				0.753
Mean	48.6	50.6	49.3	
Standard deviation	12.8	9.7	11.0	
LAV				0.068
Mean	44.9	40.9	38.2	
Standard deviation	10.1	9.6	7.8	

** ANOVA test. LAV: left atrial volume; DD: deletion/deletion; DI: deletion/insertion; LVDD: left ventricular diastolic diameter; LVSD: left ventricular systolic diameter; EF: ejection fraction; I/I: insertion/insertion.*

Genetic analysis

Blood (8 mL) was collected in tubes containing EDTA, and submitted to DNA extraction. Subsequently, polymorphism genotyping was performed by polymerase chain reaction (PCR) and classified as DD, DI or II. One pair of primers was used to amplify the D and I alleles, resulting in 319-bp (base pairs) and 597 bp amplicons.

Hace 3,5'GCCCTGCAGGTGTCTGCAGCATGT3'

Hace 3,5'GGATGGCTCTCCCCGCCTTGTCTC3'

The protocol of PCR using a thermal cycle consisted of a cycle of denaturation at 94ºC for 30 seconds, annealing at 56ºC for 45 minutes and extension at 72ºC for 7 minutes. Amplification products of the D and I alleles were identified using an ultraviolet transilluminator. Since the D allele in heterozygous samples is preferentially amplified, each sample initially found to have the DD genotype was equally subjected to a second, independent amplification with a primer pair that recognizes an insertion-specific sequence with identical PCR conditions except for an annealing temperature of 67ºC.[16]

Hace 5',5'TGGGACCACAGCGCCCGCCACTAC3'

Hace 5',5' TCGCCAGCCCTCCCATGCCCATAA3'

Statistical analysis

The Shapiro-Wilk test was used for testing normality of data. Mean and standard deviation of EF, LVDD, LVSD and LAV were calculated for patients grouped according to ACE polymorphism (DD, DI and II). Differences in echocardiographic parameters between these groups were compared by analysis of variance (ANOVA, F test). P-values lower than 0.05 were considered statistically significant. Analysis was performed using the SPSS software version 18.0.

Echocardiographic parameters (EF, LVDD, LVSD and LAV) were treated as continuous variables with normal distribution, and the DD. DI and II genotypes treated as categorical variables.

Results

A total of 103 patients with HF caused by Chagas disease, mean age of 62.4 years (36 – 95 years), 63% men, were included in the study. All patients were on optimized drug therapy according to current guidelines.

Genotypic distribution of the ACE polymorphism was 16.5% DD, 57.3% DI and 26.2% II. No statistically

significant difference was found in the distribution of genotypes between men and women, with a predominance of men with DI genotype (59.3%).

Functional class varied from II to IV; most patients were in NYHA functional class IV. Analysis of repeated measures for categorical data showed that there was no significant variation in functional class and D/I genotype ($p = 0.472$).

No difference was found in mean values of echocardiographic variables or genotypes. Patients with the DI genotype showed higher LVDD (60.3) as compared with the other genotypes.

Significant correlations were found for the variables sex, age, smoking, heart rate and dyslipidemia; male sex was associated with increased risk of HF ($p = 0.023$). Smoking was considered a risk factor for HF. Most patients did not consume alcohol, and thereby alcohol consumption was considered a protective factor ($p = 0.008$).

Dyslipidemia was associated with a five times higher risk for HF. DD, DI and II genotypes were not considered a risk factor or HF.

Discussion

Many researches involving ACE polymorphisms have been conducted to study the pathophysiology of HF and, so far, it is still controversial whether ACE polymorphism is associated with HF. Although ACE polymorphism has been associated with several pathophysiological events and with morbidity and mortality of cardiovascular diseases, in this study, we aimed to determine a relationship of this polymorphism with HF caused exclusively by Chagas disease.

Most of our patients were men (63%), similarly to other studies.[4,17,18] HF is an increasing epidemic that affects mostly older men, and its increasing incidence has been associated with higher survival.[4] No statistically significant difference in genotype distribution was found between men and women, which is in agreement with a previous study conducted in 2014.[19]

To evaluate an association of ACE polymorphism with HF severity, we investigated a possible association of D/I genotype with echocardiographic parameters, but no association was found. In contrast, a previous national study[20] reported an association of DD and ID genotype with worse and better echocardiographic profile, respectively.[20] We also did not find differences in EF values between the two genotypes ($p = 0.664$).

HF is a common clinical condition with high morbidity and mortality, affecting 1.5% - 2.0% of the general population. Its prevalence increases with age and affects approximately 10% of individuals older than 65 years.[21] Our findings corroborate this finding, since we found a statistically significant association of age with HF in the study population.

We did not find any difference in the frequency of genotypes after adjustment for gender, which agrees with the results of a study conducted in a Chinese population.[22]

A national study performed in 2005[23] reported augmented LVSD in patients with DD genotype, which was associated with higher morbidity and mortality in patients with different causes of HF. Our results differ from these findings, since we did not find any relationship between D/I genotypes and LVSD.

Similar occurrence of D/I genotypes was found in the study population, contradicting the hypothesis that D/I genotype is a risk factor for HF.[4,24]

We did not find any association of D/I genotypes with HF severity, differently from previous studies[25,26] reporting an association of the D allele with HF progression and higher mortality as compared with the I allele. Our study corroborates another Brazilian, clinical comparative study on 193 patients, that did not find any difference in the frequency of D/I genotype in patients with HF caused by Chagas disease without systolic dysfunction.[27]

Hospitalization for HF is an important public health problem.[28] Clinical treatment of this patients involves multidisciplinary approach, since they have many comorbidities that may have an impact on the clinical course of the disease. There is evidence that the risk for HF in the general population depends on a genetic predisposition characterized by a very complex genetic architecture. Predisposition to individual conditions and genetic variations modulate the pathophysiological responses.[29]

Possible limitations of this study include a small number of patients; however, there are available in the literature studies involving larger number of patients,[10,23] but also others with smaller samples.[27,30] Due to the lack of patients' follow-up in the study, we could not evaluate the natural course of the disease. Socioeconomical aspects can interact with genetic factors and influence HF outcomes. Our study included only patients attending public clinics and therefore our findings may not be reproduced to other populations.

Conclusions

This study suggests that ACE (D/I) polymorphism is not related with echocardiographic parameters of patients with HF caused by Chagas disease.

Further larger, prospective studies are needed to determine which factors may be associated with HF caused by Chagas disease and investigate the best intervention with minimal adverse effects in this population.

Author contributions

Conception and design of the research: Silva SJ, Rassi S. Acquisition of data: Silva SJ. Analysis and interpretation of the data: Silva SJ, Rassi S, Pereira AC. Statistical analysis: Silva SJ. Obtaining financing: Pereira AC. Writing of the manuscript: Silva SJ. Critical revision of the manuscript for intellectual content: Rassi S, Pereira AC.

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 article is part of the thesis of Doctoral submitted by Silene Jacinto da Silva, from Universidade Federal de Goiás (*Programa de Pós-graduação em Ciências da Saúde*).

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital das Clínicas (UFG) under the protocol number 908.870. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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REVIEW ARTICLE

Impedance Cardiography in the Evaluation of Patients with Arterial Hypertension

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Abstract

Arterial hypertension is responsible for high morbidity and mortality. Despite increasing awareness of the consequences of uncontrolled hypertension and the publication of several recommendations and guidelines, blood pressure control rates are suboptimal, and approximately half of the patients do not reach the targets. Defined as an increase in blood pressure, hypertension is characterized by hemodynamic abnormalities in cardiac output, systemic vascular resistance, or arterial compliance. Therefore, the approach to arterial hypertension can be improved by the knowledge of the hemodynamics underlying the blood pressure increase. Impedance Cardiography has emerged as a new strategy to customize therapy and monitor patients aiming to improve blood pressure control according to the hemodynamic profile, rather than a blind intensive care approach. This is a review of impedance cardiography evidence, its benefits, actual and future applications in the approach and management of arterial hypertension.

Introduction

Hypertension is a condition characterized by elevated blood pressure (BP). A comprehensive definition, published by the American Society of Hypertension in 2005, describes hypertension as "a progressive cardiovascular syndrome (CV) arising from complex and interrelated etiologies". Early markers of this syndrome are often present before blood-pressure (BP) elevation occurs; thus, hypertension cannot be solely classified by discreet blood-pressure thresholds. Disease progression is strongly associated with cardiac and vascular functional and structural abnormalities that damage the heart, kidneys, brain, vasculature and other organs, leading to early morbidity and mortality.[1]

It is estimated that hypertension affects approximately 1 billion individuals and causes more than 7 million deaths annually worldwide (13% of overall mortality). In Portugal, the prevalence of hypertension in the adult population aged 18 to 90 years is 42.2% (44.4% in men and 40.2% in women).[2] According to the World Health Organization (WHO), BP greater than 115 mmHg (systolic BP) is responsible for 62% of cerebrovascular diseases and 49% of ischemic cardiac pathologies, with little variation between the genders. These BP values are considered by the WHO as the main risk factor for mortality worldwide.[3,4]

Although BP control is a growing concern, with a consequent increase in the number of treated and controlled patients, there is still a large percentage of treated patients who do not reach their therapeutic targets. In Portugal, only 55.6% of treated hypertensive patients have controlled BP.[2,5,6]

To optimize BP control, new therapeutic strategies have been developed, namely the Plasma Renin Activity (PRA)-guided therapy, Impedance Cardiography (ICG)-guided therapy, and in some patients, renal denervation.[7-9] The choice of antihypertensive therapy based on hemodynamic systems is not new, but it has progressively become more accessible through the noninvasive hemodynamic parameters of the ICG. This is based on the knowledge that elevated BP results from changes in its hemodynamic components (cardiac output – CO, peripheral vascular resistance and/or blood volume). ICG is a non-invasive, operator-

Keywords

Hypertension / physiopathology; Blood Pressure; Cardiography, Impedance; Hemodynamics.

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independent and low-cost hemodynamic monitoring tool that allows defining the patients' hemodynamic profiles, leading to a more adequate selection of the antihypertensive therapy.[10]

Impedance cardiography

Biological tissues are complex anisotropic conductors with reactive and resistive components. The bioimpedance value depends on the type of tissue analyzed and can be altered by translocation of organs or tissues, by changes in shape or structure, by the volume or location of intracellular fluids, or by the frequency of the current used. The ICG consists in the evaluation of the electrical properties of the biological tissues of the chest.[11] The bioimpedance measures the way the tissues conduct the alternating electric current and varies according to the amount of body fluids. Thus, the chest impedance increases or decreases, depending on the changes in intrathoracic fluid with each heartbeat.[12,13]

The most common technique uses four electrodes, two of which are the current electrodes and the two that detect voltage changes. Since the current amplitude is constant, the detected voltage is proportional to the tissue impedance.[14] Figure 1 represents the four-pole impedance measurement scheme. The effective evaluation of the chest impedance during a cardiac cycle is hindered by several factors, such as chest size and shape, obesity, body weight, position and posture, thoracic circulation and respiratory rate. For this reason, although this method was published in 1940 by Nyboer et al.,[15] it took several years and many studies to reach a system that would correct them.[14,16-19] Current technology, with data processing and modeling techniques, has demonstrated that ICG has a high correlation, reproducibility and precision when compared to invasive hemodynamic monitoring techniques and echocardiography – which was considered more time-consuming, operator-dependent and technically demanding. Therefore, the ICG allows safe, non-invasive and low-cost hemodynamic and cardiac cycle monitoring.[20-25]

The ICG detects, analyzes, and records hemodynamic changes by measuring electrical resistance changes in the thorax, graphically translating them as impedance and electrocardiography waves (Figure 2). It allows the calculation of several hemodynamic parameters such as systolic volume (SV), cardiac output (CO), systemic vascular resistance (SVR), velocity and acceleration indexes, thoracic fluid content (TFC), pre-ejection period, left ventricular ejection time, systolic time ratio, left cardiac work, heart rate and mean BP.[26] The assessed parameters and respective formulas are shown in table 1.

The first derivative of the waveform (ΔZ) describes fluid velocity and is a smooth wave, which corresponds to the systole, called S wave. The initial slope of the S

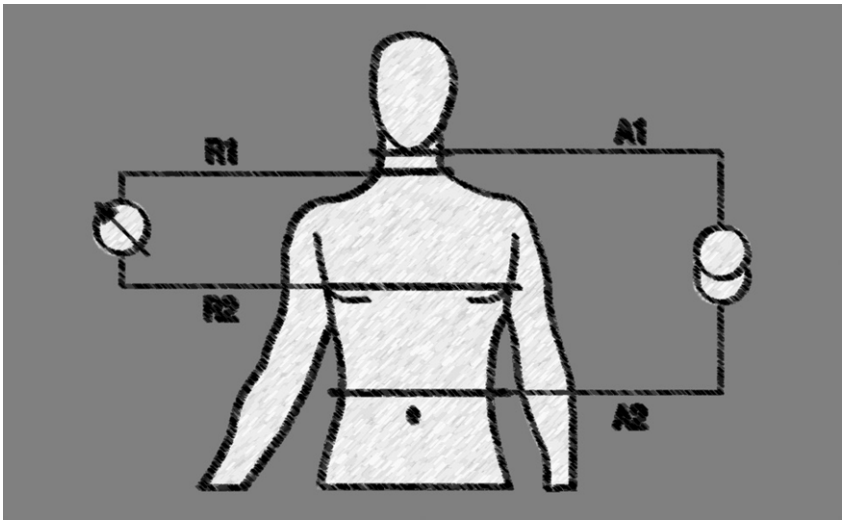

Figure 1 - Schematic illustration of impedance cardiography application, four-pole technique. A1 and A2 correspond to the current-applying electrodes; R1 and R2 to the current-receptor electrodes.
Source: adapted from Cybulski et al.[14]

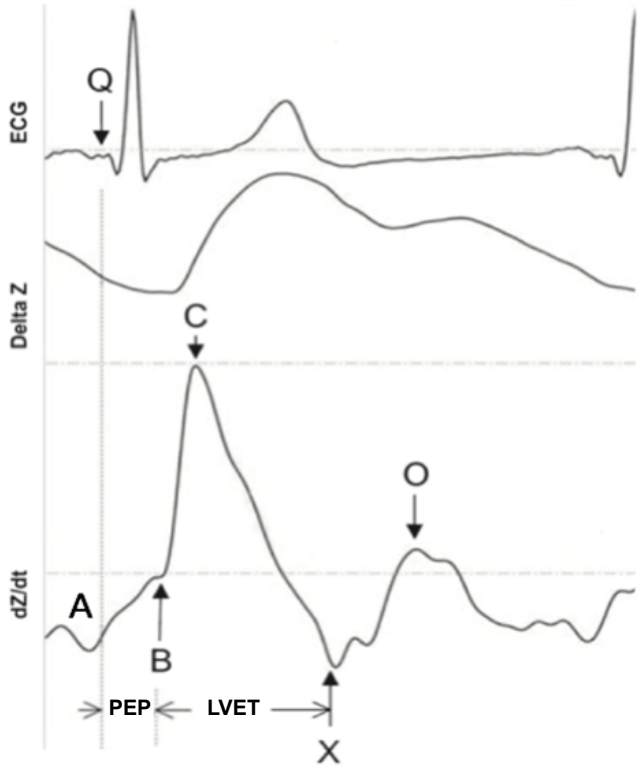

Figure 2 - Electrocardiography and impedance waves. PEP: pre-ejection period; LVET: left ventricular ejection time; ECG: electrocardiogram.
Source: adapted from Thompson et al.[27]

wave correlates with cardiac contractility, and its height and width, with systolic volume. Several indices, such as pre-ejection period, left ventricular ejection time, velocity index, acceleration index, left cardiac work index, and so on, can be obtained through the waveform, allowing non-invasive monitoring of CO and contractility, for instance. The second derivative of the waveform (dZ/dt), describes fluid acceleration and represents a more detailed wave, containing four reference points (A, B, C, and X) associated with both atrial and ventricular systole, and the point o, which is related to the onset of diastole.

Point A coincides with the electrocardiogram (ECG) p-wave and marks the beginning of the end of diastolic filling. The A wave only exists in the presence of an atrial contraction, being small and round, with its end clearly separated from the beginning of the S wave. The basal impedance corresponds to point B. Point C defines the maximum acceleration of blood output from the ventricles. The slope corresponding to the rise from point B to point C is associated with cardiac contractility: the steeper the upward curve, the greater the cardiac contractility. After reaching point C, there is a rapid deceleration to point X, which represents the inversion point of the intrathoracic fluid and corresponds to the closure of the aortic valve. After point X, the wave returns to the baseline and starts to form an early diastolic wave, associated with the opening of the mitral valve, the O wave. The moment of greatest opening of the mitral valve is represented by the peak of the S wave – point O. This interval between points X and O corresponds to the time of isovolumetric relaxation.[28]

This technology can be used, for instance, to evaluate postural cardiac rehabilitation, pacemaker optimization, sleep studies, hemodynamic monitoring in pregnant women and outpatients, and therapy and/or monitoring of hypertensive patients.[13,29-39]

ICG is a technique that has evolved in recent years and has become an attractive and cost-effective method of improving patients' clinical approach.

Table 1 - Parameters evaluated by impedance cardiography

Parameters	Definition	Normal values	Formula
HR	Number of beats per minute	58-96 bpm	RR interval measurement on the ECG and extrapolation to bpm
MAP	Mean pressure exerted by the blood on the arterial walls	84-100 mmHg	Manual = ((SBP-DBP) x KP) + DBP Automatic (oscillometric method) = MAP is measured directly through SBP and DBP
CO	Amount of blood pumped by the left ventricle per minute	4.5-8.5 L/min	CO = EjV x HR
CI	Standard CO for BSA	2.5-4.7 L/min/m2	CI = CO/BSA
SV	Amount of blood pumped by the left ventricle per heartbeat	60-130 mL/heartbeat	SV = VEPT x LVET x VI (Z MARC® Algorithm)
SI	Standard stroke volume for BSA	35-65 mL/heartbeat/m^2	SI = SV/BSA
SVR	Resistance of circulating blood to the arterial system	742-1,378 dynes sec/cm^5	SVR = 80 x ((MAP - CVP)/CO)
SVRI	Standard SVR for BSA	1,337-2,483 dynes.sec.m^2/cm^5	SVRI = 80 x ((MAP - CVP)/ CI)
AI	Initial acceleration of blood in the aorta that occurs within the first 10-20 milliseconds after opening of the aortic valve	Male: 70-150/100 sec^2 Female: 90-170/100 sec^2	AI = (d2Z/dt2Max)/ TFC
VI in the aorta	Peak velocity of blood flow in the aorta	33-65/1,000 sec	VI = (dZ/dtMax)/ TFC
TFC	Electrical conductivity of the thoracic cavity (determined by intravascular, interalveolar and interstitial fluid)	Male: 30-50/kohm Female: 21-37/kohm	TFC = 1/ TFI
LCW	Indicator of the amount of work exerted by the left ventricle in each minute to pump blood into the systemic circulation	5.4-10 kg.m	LCW = (MAP - PAOP) x CO
LCW index	Standard LCW for BSA	3.0-5.5 kg m/m^2	LCW index = (MAP - PAOP) x CI
PEP	The time interval from the beginning of electrical stimulation of the ventricles to the opening of the aortic valve (electrical systole)	Depends on HR, contractility and resistance to diastolic filling	Time interval between the beginning of the Q wave on the ECG and the B point on the dZ/dt wave (aortic valve opening)
LVET	Time interval from the opening to the closing of the aortic valve (mechanical systole)	Depends on HR, contractility and resistance to diastolic filling	Time interval between point B and point X of dZ/dt wave
STR	Ratio between the time of electrical and mechanical systole	0.3-0.5	STR = PEP / LVET

HR: heart rate; ECG: electrocardiogram; MAP: mean arterial pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure; KP: variable that depends on the pulse pressure ratio (usually varies between 0.25-0.33); CO: cardiac output; EjV: ejection volume; CI: cardiac index; BSA: body surface area; SV: stroke volume; VEPT: volume of electrically participating tissue (conductive volume for thorax size, affected by weight, height and gender); LVET: left ventricular ejection time; VI: Velocity index; SI: Stroke index; SVR: systemic vascular resistance; CVP: central venous pressure (pressure in the thoracic vena cava upon reaching the right atrium - the standard value of 7 mmHg is considered); SVRI: systemic vascular resistance index; AI: acceleration index; d2Z/ dt2Max: maximum of the second derivative of ΔZ; TFI: thoracic fluid index (baseline thoracic impedance, Z0); TFC: total fluid content; LCW: left cardiac work; PAOP: Pulmonary artery occluded pressure (the standard value is 10 mmHg); PEP: pre-ejection period; STR: systolic time ratio.

Arterial hypertension and impedance cardiography

Classically defined as an increase in BP, this parameter alone is an incomplete indicator of the cardiovascular system status, particularly in patients with resistance to drug therapy or hypervolemic ones.[7] The mean BP consists of the product of two hemodynamic parameters (CO and SVR), and arterial hypertension is the result of a disorder in one or both hemodynamic variables.[40] These findings, associated with the fact that the results obtained with empirical therapy based on current guidelines are suboptimal, have led some specialists to propose new approach pathways for the hypertensive patient, particularly a therapeutic approach guided by the patient's hemodynamic profile.[41-45] Historically, the use of BP as an indicator of cardiovascular status in hypertensive patients comes from the fact that hemodynamic parameters are assessed using invasive techniques.[46] More recently, echocardiography has been used to accurately estimate CO, but when compared with ICG, the latter was considered more time-consuming and technically demanding.[19] Thus, ICG emerges as a non-invasive, simple, accurate and inexpensive method to evaluate patients hemodynamically, characterizing the profile and guiding the therapeutic optimization in hypertensive patients.[44,45,47]

The use of ICG can improve our knowledge about arterial hypertension, especially regarding its hemodynamic characteristics and consequences. Hypertensive cardiopathy is a continuum, involving structural changes (myocardial fibrosis) and left ventricular geometry (hypertrophy and concentric remodeling), which progressively develop into systolic and/or diastolic function disorder.[48] Close to its end, the IMPEDDANS study (ClinicalTrials.gov; Identifier: NCT03209141) intends to verify the ability to screen for left ventricular diastolic dysfunction in its asymptomatic phase in hypertensive patients, which may allow an early diagnosis, as well as the study of the disease evolution and therapeutics. The growing interest in hemodynamic changes in arterial hypertension and orthostatic and emotional stress responses, led researchers to use ICG to study autonomic dysfunction in hypertension. The technological evolution of the ICG, with the development of monitors for the assessment of outpatients, is a new area of research in arterial hypertension. With this technique, one can assess cardiac performance for 24 to 48 hours, as well as the hemodynamic changes that occur during Daily Life Activities, and the hemodynamic responses to changes in body position and blood pressure control, for instance.[49-53]

Antihypertensive therapy guided by impedance cardiography

Hypertension management includes lifestyle measures such as sodium restriction and weight loss, and, in most cases, the use of one or more antihypertensive drugs. Considering this approach to arterial hypertension as a hemodynamic pathology, drugs are proposed according to the pathophysiological mechanism responsible for BP increase (Figure 3).

Drugs are selected according to elevated hemodynamic parameters. Therefore, it is first

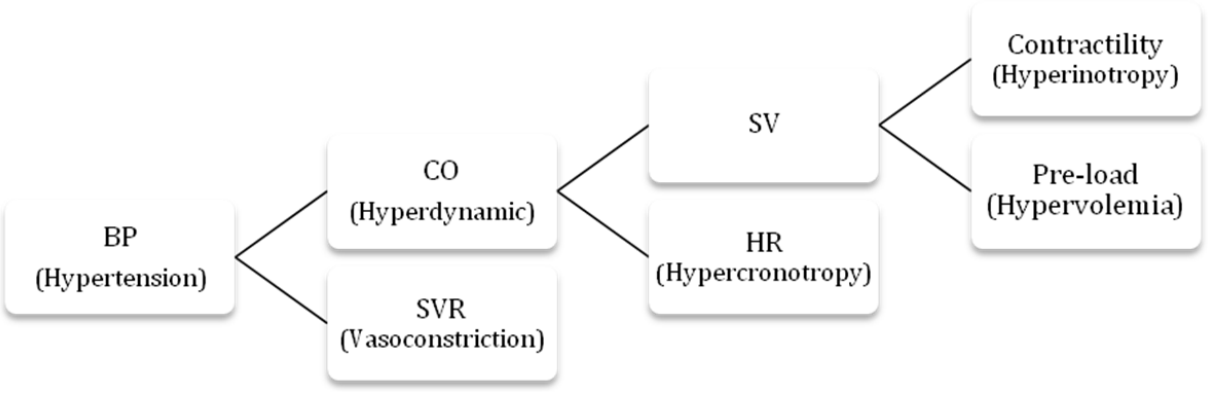

Figure 3 - Hemodynamic components of blood pressure. BP: blood pressure; CO: cardiac output; SVR: systemic vascular resistance; SV: stroke volume; HR: heart rate.

necessary to evaluate the hemodynamic variables to be able to target the therapy at a high cardiac or SVR index. Likewise, if any of these parameters is decreased, the drug responsible for the effect should be identified, its dose reduced, or the drug withdrawn (Figure 4).[10,25,44,45] Several studies have highlighted the apparent superiority – although never assessed in long-term studies – of the personalized therapeutic approach to the hemodynamic profile, both regarding its efficacy and cost-effectiveness (Table 2).

Conclusion

Hemodynamic-guided therapy can be valuable in the evaluation and management of hypertensive patients. Impedance cardiography is a cost-effective assessment that allows the diagnosis, therapeutic optimization, and follow-up of hypertensive patients, helping them to achieve therapeutic targets, even in those with resistant hypertension. This therapeutic approach, which focuses on the cause of blood pressure increase and its pathophysiological mechanism, allows better blood pressure control and a potential reduction in cardiovascular events, mortality and costs associated with arterial hypertension.

Future studies in the ICG area should broaden our understanding of the pathophysiology and hemodynamic changes of arterial hypertension and demonstrate that early diagnosis and treatment of hemodynamic characteristics have a positive impact on patient outcomes, reducing morbidity and mortality associated with high blood pressure.

Author contributions

Conception and design of the research: Leão RN, Silva PM. Acquisition of data: Leão RN, Silva PM. Analysis and interpretation of the data: Leão RN, Silva PM. Writing of the manuscript: Leão RN, Silva PM. Critical revision of the manuscript for intellectual content: Leão RN, Silva PM. Supervision / as the major investigador: Leão RN.

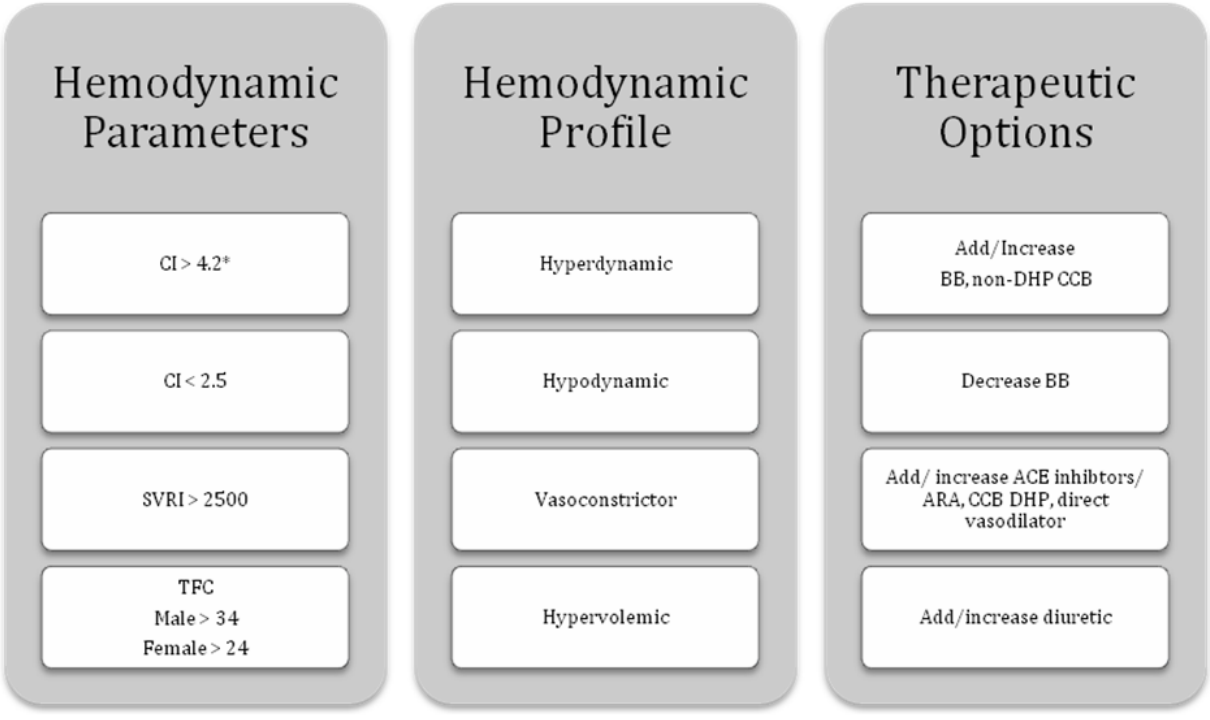

Figure 4 - Algorithm for choice of antihypertensive therapy guided by impedance cardiography. If the values do not correspond to the exposed criteria, the patient has a balanced profile. *If neither the cardiac index (CI) nor the systemic vascular resistance index (SVRI) are high, the therapy should be selected according to the highest parameter, within the normal range. TFC: total fluid content; BB: beta-blocker; DHP: dihydropyridine; CCB: calcium channel blocker; ACE inhibitors: angiotensin-converting enzyme inhibitor; ARA: angiotensin II receptor antagonist.

Table 2 - Main clinical trials on hemodynamically-guided antihypertensive therapy

Author	n	Study design	Results
Smith et al.[44]	164	Multicenter, randomized	After 3 months, a higher reduction in blood pressure was observed in the treatment group guided by ICG, 55% vs. 27%; OR 2.32 (1.27-5.35), p = 0.007
Taler et al.[45]	104	Single-center, randomized	After 3 months, 56% of the individuals in the ICG-based approach to hypertension achieved blood pressure < 140/90 mmHg vs. 18 (33%); OR 2.55 (1.15-5.64); p = 0.02
Sramek et al.[54]	322	Single-center prospective, non-randomized	After 3 weeks of ICG-based therapy, 63% of patients became normotensive; success rate of 58-68%
Sharman et al.[55]	21	Single-center, prospective, non-randomized	After 7 months, 57% of patients with resistant hypertension had BP control (blood pressure <140/90 mmHg); p < 0.001
Krzesinski et al.[56]	82	Single-center, randomized	After 3 months, more patients in the ICG-guided group achieved BP control in both ABPM (23.5 vs. 43.9%, p = 0.117) and OBPM (23.5 vs. 36.6%, p = 0.22)
Krzesinski et al.[57]	128	Single-center, randomized	After 3 months, all blood pressure values were lower in the ICG-guided treatment group, with statistical significance in OBPM and nocturnal blood pressure (p < 0.05)
Krzesinski et al.[58]	272	Single-center, randomized	After 3 months, final BP values were significantly lower in the ICG-guided treatment group for OBPM (p = 0.01), especially in patients with higher blood pressure (p = 0.003)
Krzesinski et al.[59]	144	Single-center, randomized	After 12 months, the final blood pressure values were lower in the ICG-guided treatment group, with a BP reduction of at least 20 mmHg in the office measurements of diastolic pressure (27.3% vs. 12.1%; = 0.034), 24-hour mean systolic blood pressure (49.1% vs. 27.3%, p = 0.013) and improvement in left ventricular diastolic dysfunction (delta E/A 0.34 vs. 0.12; = 0.017).

ICG: impedance cardiography; OR: odds ratio; ABPM, ambulatory blood pressure monitoring; OBPM, office blood pressure measurement.

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REVIEW ARTICLE

Myocardial Viability: From PARR-2 to IMAGE HF - Current Evidence and Future Directions

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Abstract

Ischemic heart failure is a growing disease with high morbidity and mortality. Several studies suggest the benefit of viability imaging to assist revascularization decision, but there is controversy. Multiple imaging modalities can be used to accurately define hibernating myocardium; however, the best approach remains uncertain. This review will highlight current evidence and future directions of viability imaging assessment.

Introduction

Ischemic heart failure (HF) is the leading cause of HF and an epidemic disease worldwide with growing prevalence and high mortality rate.[1,2] In 2011, 1 in 9 death certificates in the United States listed HF.[1] In 2015 in Brazil, 27,434 deaths occurred due to HF.[3] Medical treatment, cardiac rehabilitation, revascularization and the increased understanding of its pathophysiology have improved the overall prognosis and survival of patients with HF over the last years, but, despite that, around 50% of the patients diagnosed with HF will die 5 years after the initial diagnosis.[2]

Accumulated evidence of the past years has suggested that individualized-target therapy with viability imaging assessment may improve outcome.[4,14,15] This review will focus on the understanding of the viability concept and current evidence.

Keywords

Heart Failure; Myocardial Stunning; Positron Emission Tomography Computed Tomography; Hybernating.

What is viable myocardium?

A simplistic way to describe viable myocardium is all tissue that is not scar/fibrosis (non-viable myocardium). Naturally, normal myocardium is viable. Dysfunctional myocardium that is viable has the potential to recover from an injury.[4,14,15] Meanwhile, two concepts under the umbrella of "viable myocardium" can be often misunderstood. "Stunned" and "hibernating" myocardium are conditions in which function is impaired but is potentially reversible. Stunned myocardium is characterized by the persistent dysfunction that follows an episode of ischemia. Hence, there is normal rest flow and impaired function. The severity and duration of the stunning (post-ischemic dysfunction) depend on duration, extent and severity of the preceding ischemic insult. So long as there is no infarction during such ischemia, full recovery is expected, the timing of which also depends on the duration, extent and severity of the preceding ischemia. If stunning occurs repeatedly, the myocardium must adapt to the repetitive injury. It does so by reducing contractile function and flow in response to these events.[15] Repetitive stunning is believed to be the precursor to hibernating myocardium, where both measured perfusion and function are reduced but restorable in whole or in part if blood flow can be adequately restored before irreversible injury occurs. This is the area of focus for viability imaging (Table 1).[4,14,15]

Imaging modalities for viability assessment

Several imaging modalities can be used to assess hibernating myocardium, and each has different metabolic/cellular targets and findings to detect viable and hibernating myocardium. Cardiac positron emission tomography (PET) with ^{18}Fluorodeoxyglucose (^{18}FDG) uses a glucose analogue to measure myocardial

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Table 1 - Viable and non-viable myocardium

Myocardium	Flow	Glucose metabolism/ FDG	Function	Potential to recover
Non-Viable				
Scar/Fibrosis	Reduced	Reduced	Reduced	Unlikely
Viable				
Stunned	Preserved (has suffered an intermittent ischemic insult)[65,66]	Variable [can be normal, increased or reduced (reverse mismatch)][65–69,67–71,67–71]	Reduced	Likely to recover if ischemic injury does not persist or become repetitive;[4,14] may benefit from revascularization
Hibernation	Reduced	Preserved (flow-metabolism mismatch)	Reduced	Likely to have part or full recovery if adequate revascularization can be achieved[5,72]
Ischemia	Preserved at rest (impaired at stress)	Normal at rest, increased at stress[67]	Preserved	May benefit from revascularization

glucose uptake. Single-photon emission computed tomography (SPECT) with thallium-201 (^{201}Tl), a potassium analogue, has the sarcolemma membrane integrity as its target (sodium/potassium ATPase pump activity).[16] SPECT with technetium-99m (^{99m}Tc)-based tracers test the mitochondrial membrane integrity.[17,18] Dobutamine echocardiogram (ECHO) and dobutamine magnetic resonance imaging (MRI) measure myocardial contractile reserve. Delayed enhancement MRI and computed tomography target the amount of fibrotic tissue, and myocardial contrast ECHO targets the microvascular integrity.[19,20]

In a meta-analysis by Schinkel et al.[5] reviewing 24 studies (756 patients) comparing all available imaging modalities, ^{18}FDGPET was shown to be the most sensitive to predict regional function recovery, and dobutamine ECHO was the most specific (92%, 63%, 74% and 87% and 80%, 78%, 75% and 83% of sensitivity, specificity, positive and negative predictive value for PET and ECHO, respectively).[5] Cardiac MRI, which was underrepresented in this meta-analysis, had sensitivity, specificity, positive and negative predictive values of 74%, 82%, 78% and 78% for dobutamine stress MRI and 84%, 63%, 72% and 78% for delayed enhancement MRI.[5]

In this same meta-analysis, a total of 721 patients underwent ^{99m}Tc-tracer-based SPECT and 1,119 had ^{201}Tl SPECT to assess viability. ^{201}Tl was more sensitive and ^{99m}Tc-tracer-based SPECT more specific to predict recovery, with sensitivity, specificity, positive and negative predictive values of 87%, 54%, 67% and 79% and 83%, 65%, 74% and 76% for ^{201}Tl and ^{99m}Tc, respectively.[5] Comparisons between nuclear techniques suggest ^{18}FDG PET is the superior technique to detect the amount of hibernating myocardium,[21–25] except for one study directly comparing ^{201}Tl and ^{18}FDG PET, which suggested similar viability detection for both methods.[26]

More recent data analyzing MRI performance in detecting viable myocardium have supported its high sensitivity.[27–30] Romero et al.[27] have conducted a meta-analysis of MRI prospective trials including 24 studies (698 patients) and found a sensitivity of 95% for predicting functional recovery for MRI with delayed enhancement. Dobutamine MRI was the most specific (91%) when compared to delayed enhancement and end-diastolic wall thickness techniques.[27] Kühl et al.[29] have studied 29 patients with chronic ischemic HF and mean ejection fraction of 32% who had both MRI and PET/SPECT (^{18}FDG for metabolism and ^{99m}Tc SPECT for perfusion) performed at baseline and at 6-month follow-up after revascularization.[29] The group found MRI to have higher sensitivity and PET/SPECT to be more specific (97% *versus* 87% sensitivity and 68% *versus* 76% specificity for MRI and PET/SPECT, respectively).[29] A more recent study has analyzed the feasibility of PET/MRI scanners in evaluating segment functional recovery in 28 patients post-acute myocardial infarction (MI) and percutaneous revascularization.[30] All patients underwent PET/MRI with contrast for delayed enhancement and ^{18}FDG injection for uptake assessment 5-7 days after the acute event and had a follow-up MRI for contractility

assessment at 6 months.[30] The study has concluded that simultaneous assessment of glucose metabolism and scar assessment using a hybrid PET/MRI scanner is feasible. Moreover, the agreement between the techniques was high (82% of the segments were either non-viable or viable for both PET and MRI, k = 0.65). In only 18% of the segments was there disagreement, and, in all of them, PET suggested non-viability while MRI suggested viability.[30] The recovery was higher in the segments in which there was agreement between the techniques (78% *versus* 41% for PET viable/MRI viable and PET non-viable/MRI viable, respectively). Recovery was similar between PET non-viable/MRI viable and PET non-viable/MRI non-viable segments, suggesting PET better dichotomized the degree of recovery between viable and non-viable myocardium. In the PET non-viable/MRI viable segments, there was some recovery (41%), suggesting a lower threshold for % FDG uptake cutoff (40-45% instead of 50%) may have detected some viable segments identified by MRI. Overall the techniques appear complementary. Their combined use as PET/MR may offer comprehensive tissue characterization of metabolism, scar and function and may refine our ability to define viable myocardium. Further studies are warranted (Figures 1 and 2).[30]

Clinical relevance of viability assessment: PARR-2 and STICH

Several non-randomized studies have reported data that suggest a benefit of viability imaging in patients

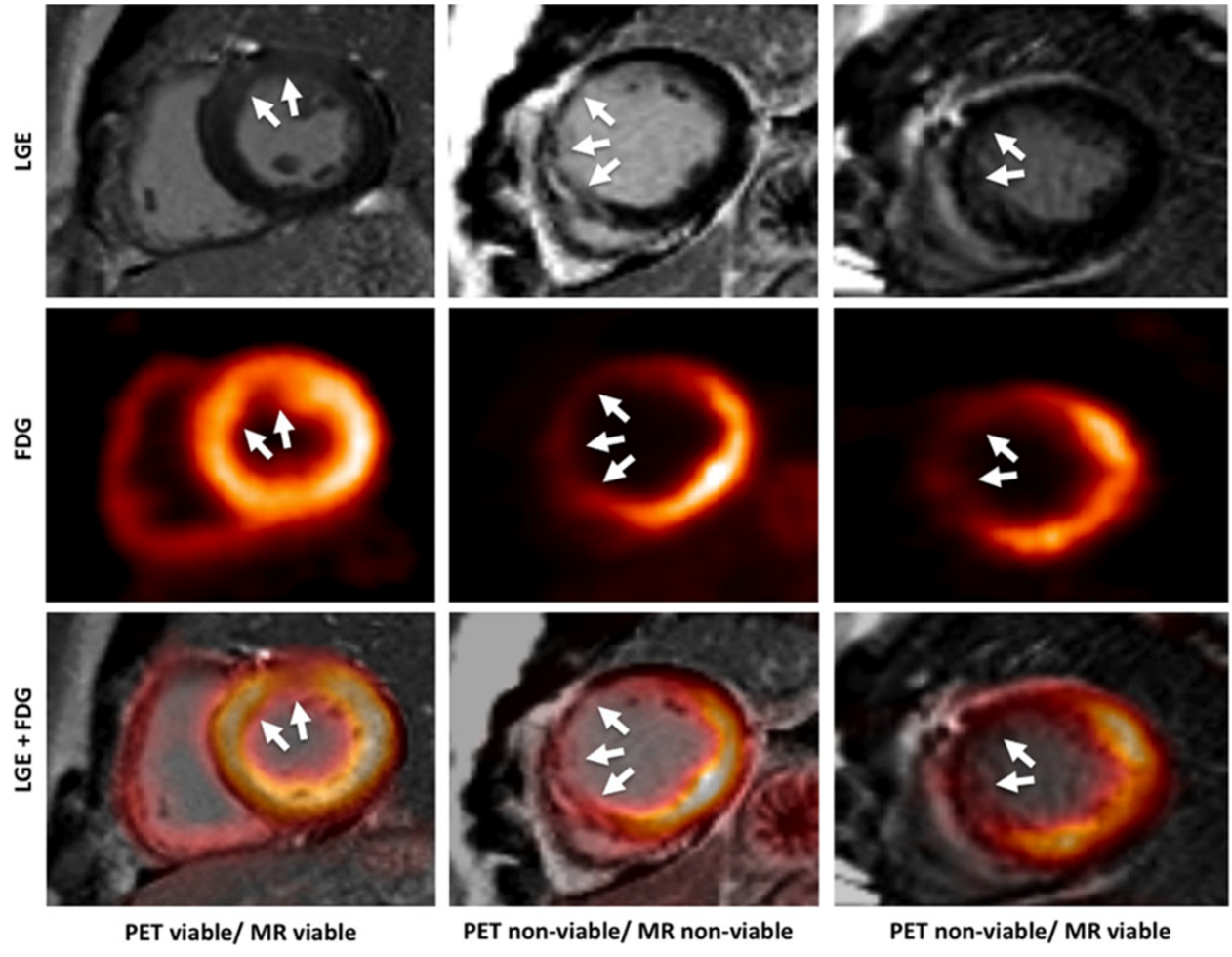

Figure 1 – "Images illustrating different combinations of FDG uptake and LGE transmurality. First column: FDG ≥ 50%/LGE non-transmural ('PET viable/MRI viable); second column: FDG < 50%/LGE transmural ('PET non-viable/MRI non-viable'); third column: FDG < 50%/LGE non-transmural ('PET non-viable/MRI viable'). White arrows indicate the respective area of ischaemically affected myocardium." – With permission from Rischpler et al, Eur Heart J Cardiovasc Imaging.[30]

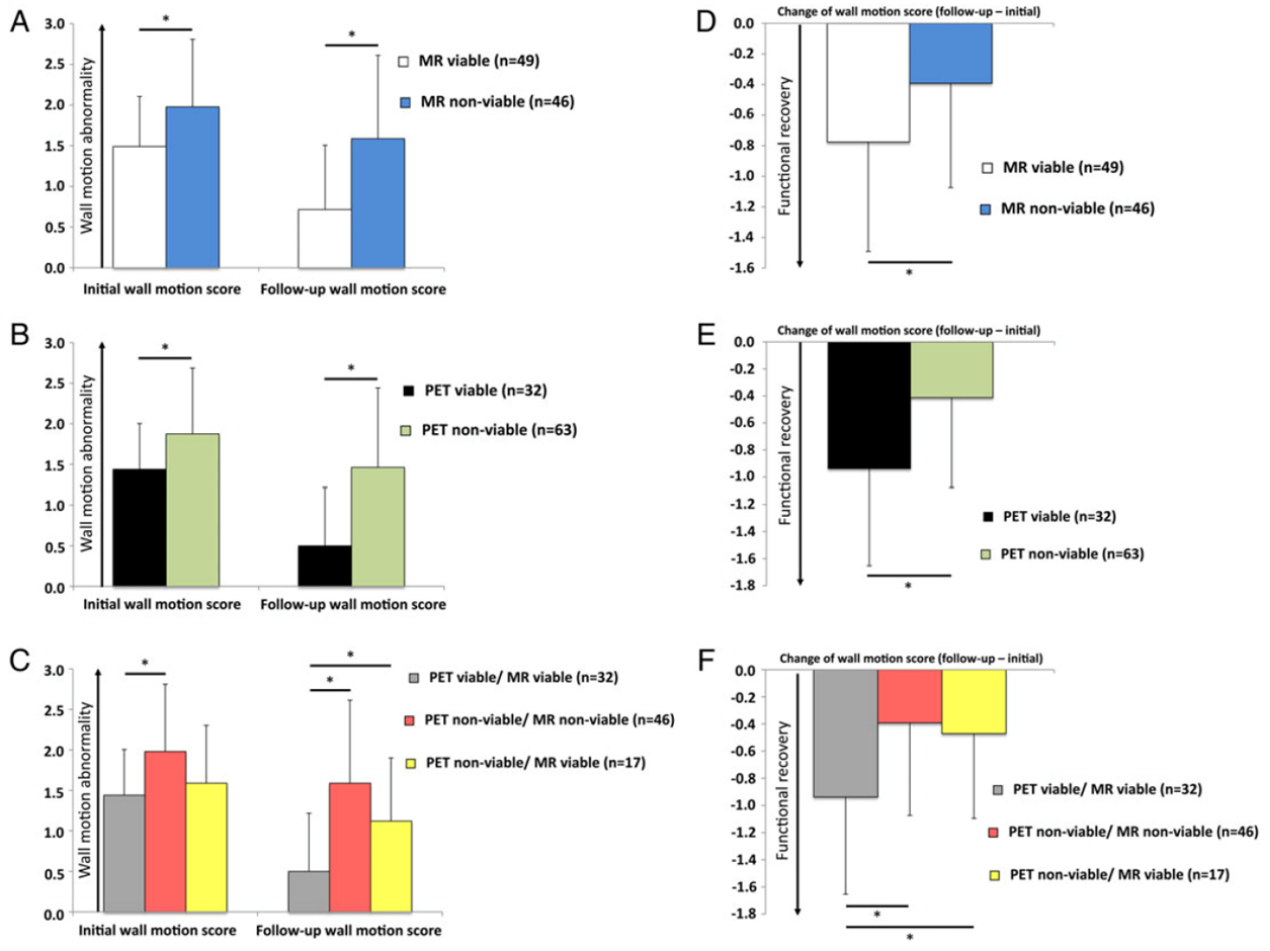

Figure 2 - "Regional wall motion abnormality and functional recovery in the long-term course. The wall motion abnormality early after AMI and at follow-up as well as the resulting functional recovery of the 95 dysfunctional segments were evaluated regarding different patterns of LGE transmurality and FDG uptake [LGE transmurality (A and D), FDG uptake (B and E), combination of LGE transmurality and FDG uptake (C and F)] "- With permission from Rischpler et al, Eur Heart J Cardiovasc Imaging.[30]
AMI: acute myocardial infarction; LGE: late gadolinium enhancement; PET: positron emission tomography; MR: magnetic resonance imaging.

with ischemic HF.[9,31–34] Allman et al.[9] have conducted a meta-analysis with 24 studies, and their analysis has shown the benefit of revascularization only in patients with viable myocardium as opposed to scar.[9] More recently, a meta-analysis including 29 studies by Inaba et al. has documented the benefit of revascularization over medical therapy in patients with dysfunctional viable myocardium.[31]

To date, there have been two major prospective randomized trials comparing outcome in patients with ischemic HF who underwent viability assessment: PARR-2 (Positron emission tomography And Recovery following Revascularization phase 2)[6] and STICH (Surgical Treatment for Ischemic Heart Failure) viability substudy[35] trials.

PARR-2 has randomized 430 patients from 9 centers, to have either viability assessment with ^{18}FDG PET or standard care without ^{18}FDG PET, before decisions regarding revascularization.[6] A trend toward benefit for the primary outcome (cardiac death, MI and cardiac hospitalization at 1 year) has been observed in the arm that underwent FDG PET to assist with clinical decision-making [36% of events in the standard care arm and 30% in the PET arm, relative risk 0.82; p = 0.16 and hazard ratio (HR) 0.78; p = 0.15].[6] However, not all patients in the study followed the imaging recommendation. When analyzing only the patients who adhered to the recommendations from the imaging report, a significant reduction in outcome was observed in the PET arm *versus* standard care (HR 0.62; p = 0.019), indicating that

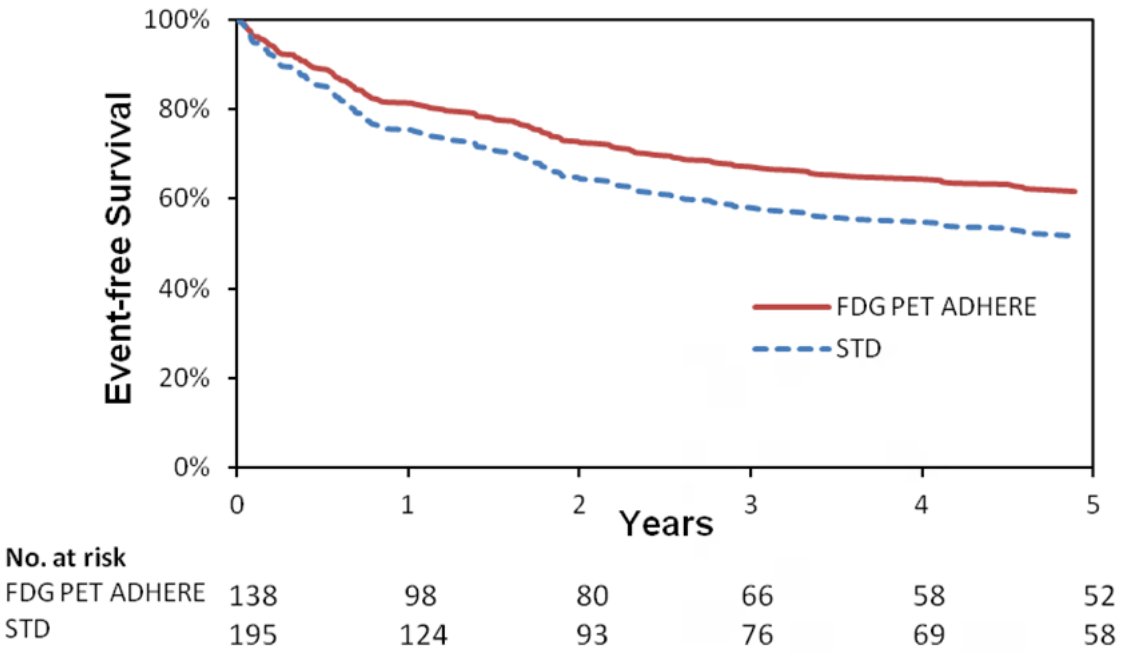

Figure 3 - "Risk-adjusted, event-free survival curves for time-to-composite event for patients who adhered to PET imaging recommendations (FDG PET Adhere) *versus* standard care (STD) in patients randomized at sites participating in long-term follow-up. Hazard ratio = 0.73 (95% CI 0.54–0.99; p = 0.042). No at risk = number of patients who had not died, not had transplant, not dropped out, and not had events. Seven patients whose last follow-up date was within 10 days of 1,825 days (5 years) were included in the 5-year total. CI indicates confidence interval; FDG PET, F-18-fluorodeoxyglucose positron emission tomography; and STD, standard care". – With permission from Mc Ardle et al, Circ Cardiovasc Imaging.[11]

management adhered to the imaging recommendations may have an impact on patient outcome.[6]

A PARR-2 substudy has supported the importance of adherence to PET findings and that of teamwork of: i) revascularization (surgeons, interventional cardiology); ii) HF; and iii) imaging specialists.[8] This along with iv) access to FDG and v) the cardiac PET imaging experience of a centre has the potential to impact outcome. The Ottawa-FIVE (i.e. i-v above) study has had 111 patients from an experienced center in which PET was easily available and physicians were comfortable with the technology and its interpretation. In this scenario, patients in the FDG PET arm had clear benefit when compared to standard care (19% of cumulative proportion of events in the PET arm *versus* 41% in the standard care group) and multivariable analysis showed benefit (HR 0.34; 95% confidence interval 0.16-0.72; p = 0.005).[8]

In long-term (5 years) follow-up, the PARR-2 population in which PET recommendations were followed had improved primary outcome (HR 0.73, 95% confidence interval 0.54-0.99, p = 0.042) (Figure 3).[11]

In addition, PARR-2 has shown that the amount of hibernating myocardium also plays an important role in patient outcome.[7] With increasing extent of mismatch (hibernating myocardium), the likelihood of benefit with revascularization also increases. In this substudy of the PARR-2 trial involving 182 patients in the PET arm, a cutoff of 7% was able to distinguish between patients who would or would not benefit from revascularization, which is in accordance with previous values reported by Di Carli el at.[10] (5%), Lee et al.[12] (7.6%) and Ling et al.[36] (10%) (Figure 4).

The STICH trial has observed conflicting results compared to previous studies regarding the benefit of revascularization for patients with viable myocardium.[35] A total of 1,212 patients were randomized to receive optimal medical therapy alone or medical therapy plus revascularization.[35,37] Of these, 601 patients underwent viability assessment independently of the randomization. The primary outcome was defined as all-cause mortality and there was no significant difference in the endpoint between the groups after

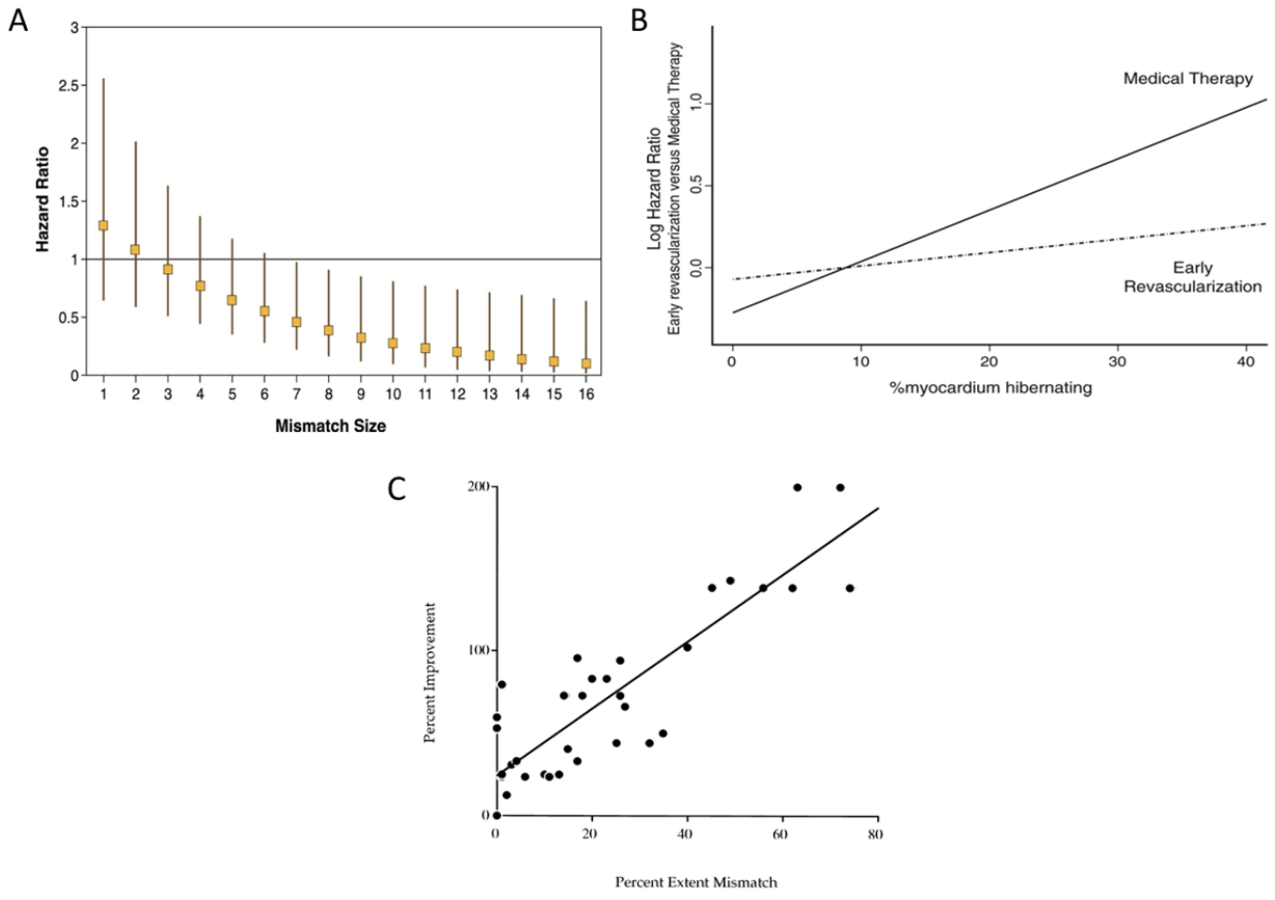

Figure 4 - Interaction between mismatch on ^{18}FDG PET (hibernating myocardium) and clinical outcome. A) Various levels of mismatch and its hazards ratios and 95% CI. For patients with mismatch > 7% there was improvement in the primary outcome (cardiac death, myocardial infarction and cardiac hospitalization at 1 year) (with permission from D'Egidio et al.[7]). B) Relationship between % of mismatch and adjusted HR for all cause of death in patients who received medical therapy or early revascularization. Greater amounts of hibernating myocardium related with increased risk of medical therapy (with permission from Ling et al.[12]). C) Relationship between amount of mismatch and improvement in functional status after revascularization (with permission from Di Carli et al., Circulation[10]).
CI: confidence interval; HR: hazard ratio.

adjustment for baseline characteristics.[35] More recently, the 10-year follow-up of the original trial, STICHES (STICH Extension Study)[37] has shown the benefit of revascularization for all-cause death, cardiovascular death and cardiovascular hospitalization over optimal medical therapy alone.[37]

In the STICH viability substudy, while viability did predict outcome, it was not independent of other parameters and did not predict outcome benefit from revascularization, leaving questions yet to be answered. The greater long-term benefit in the revascularization arm in the main trial indeed highlights the need for a careful assessment of patients with ischemic HF, balancing the risks and benefits in short and long term.

Although the ISCHEMIA trial (NCT01288560) does not specifically evaluate viability, its results may assist in understanding the role of ischemia imaging in guiding revascularization. Currently, more than 5,000 patients have been randomized worldwide to an invasive strategy +/- revascularization *versus* optimal medical management.

There was also a small randomized blinded study (total of 103 patients) comparing FDG PET to MIBI perfusion imaging to detect viability. While FDG PET appeared to have better outcomes, this did not reach statistically significance. The small sample size and the fact that < 1/3 of patients had significant left ventricular dysfunction limit conclusions from this study.[38,39]

Beyond clinical events, there is evidence that patients undergoing FDG PET have improved quality of life *versus* standard care (not undergoing FDG PET) at least in the short term.[40] Other studies have also reported revascularization directed by FDG PET improves HF symptoms and quality of life.[10,41] There is also evidence to support that viability imaging with PET is cost-effective when hibernation data are used to guide revascularization.[42]

Comparing PARR2 and STICH

It is important to understand the differences between PARR-2 and STICH in order to appreciate their respective significance.[6,35,40,43] First, in STICH, patients had to be acceptable for revascularization. While patients were randomized to coronary artery bypass graft surgery *versus* optimal medical therapy, imaging was not randomized nor did it direct the therapy decision. Conversely, in PARR-2, patients in whom decisions regarding revascularization was uncertain were randomized to FDG PET viability imaging *versus* standard care with no FDG PET imaging. The tests for viability assessment were also different: ^{18}FDG PET in PARR-2 and SPECT or dobutamine ECHO in STICH. Compared to the STICH population, PARR-2 patients had more renal dysfunction (7.5% *versus* 34%), had more prior coronary artery bypass graft surgery (3% *versus* 19%), more multivessel coronary artery disease (75% *versus* 90%) and less viable myocardium (81% *versus* 22%), suggesting these patient cohorts were not the same (Table 2).[40,43] From those studies, it is safe to conclude that viability imaging is not needed in all patients with ischemic heart disease and left ventricular dysfunction who are being considered for revascularization. However, there may be high-risk patients whose decisions are particularly difficult where viability imaging has a role.[40,43]

Table 2 - Comparison of the STICH Viability Substudy with PARR-2 - Adapted with permission from Mielniczuk et al., JACC Cardiovasc Imaging[43]

	STICH substudy	PARR-2
Patient population		
Randomized?	Not the substudy	Yes
Mean age, years	60.7	63
Male sex	85	84
Previous CABG	3	19
Diabetes mellitus	39	39
Estimated GFR < 60 mL/min/1.73m^2	7.5	34
Mean serum creatinine		108 μmol/L
Viability testing	SPECT or dobutamine echocardiography	PET
Prevalence of viability	81	22

Values are % unless otherwise indicated. CABG: coronary artery bypass grafting; GFR: glomerular filtration rate; SPECT: single-photon emission computed tomography.

Viability tests: when should we use it?

Current evidence and guidelines support the use of viability imaging to assist decision-making in patients with ischemic HF (Table 3).[44–50] The imaging modality of choice for viability assessment needs to be individualized according to each clinical scenario, technology availability and institution expertise.[14,40,41,49–52]

In our experience, viability imaging is appropriate in patients with known or strongly suspected ischemic HF, New York Heart Association (NYHA) ≥ II, moderate to severe left ventricular dysfunction (left ventricular ejection fraction < 40%), moderate to large perfusion defects and no significant ischemia, significant comorbities and/or poor vessel targets (Figure 5).[49,51,52] On the other hand, viability is not (or less) useful in patients with predominantly angina CCS > II, those with normal or mild left ventricular dysfunction, critical left main coronary artery disease, patients with good revascularization targets, those with already-demonstrated moderate to severe ischemia and those with minimal or no comorbidities.[51,52] Figure 6 illustrates two examples of viability imaging.

When viability imaging is needed, the choice of which test depends on specific advantages of the different modalities, availability and local expertise. Until comparative evidence is available (see "Future Directions"), the following is an approach to select which test for viability in which circumstance as suggested by the authors:[51,52]

1. Normal or mild left ventricular dysfunction – viability imaging is rarely needed.

2. Moderate left ventricular dysfunction – any method can be considered depending on availability and local expertise.

3. Very severe left ventricular dysfunction - consider nuclear methods (SPECT, FDG PET) or late

Table 3 - Guidelines, Appropriate Use Criteria and Position Statements for the use of viability imaging in patients with ischemic heart failure. With permission from Wiefels et al., Curr Cardiovasc Imaging Rep.[73]

Recommendation	Grade	Level	Organization
Nuclear imaging for assessment of myocardial viability for consideration of revascularization in patients with CAD and LV dysfunction who do not have angina	I	B	ACC/AHA/ASNC Radionuclide Imaging 2003[44]
Cardiac PET and CMR should be used in the evaluation and prognostication of patients with ICM and LV dysfunction	I	B	CCS/CAR/CANM/CNCS/ Can SCMR 2007[47]
Noninvasive imaging to detect myocardial ischemia /viability in HF and CAD	IIa	C	ACCF/AHA CHF 2013[48]
Viability assessment is reasonable before revascularization in HF patients with CAD	IIa	B	ACCF/AHA CHF 2013[48]
Non-invasive stress imaging (CMR, echo, SPECT, PET) may be considered for the assessment of myocardial ischemia and viability in patients with HF and CAD (considered suitable for coronary revascularization) before the decision on revascularization.	IIb	B	ESC CHF 2016[44]
Myocardial viability testing should be considered in patients with ischemic CM and reduced LV EF eligible for revascularization	Appropriate use score: 9		AACF/ASNC/ACR/ASE/ SCCT/SCMR/ SNM 2009[45]

gadolinium enhanced MRI which are more sensitive than contractile reserve.[5,27,53]

4. Renal failure (GFR < 30) or implanted devices – avoid MRI.

5. Left main coronary artery disease or severe proximal 3-vessel disease – avoid dobutamine.

6. Equivocal results on another viability test or negative results on another viability test, where certainty is needed to completely rule [in or] out viability – consider FDG PET or MRI as highly sensitive methods.[5,27,51,53]

Future directions

The IMAGE HF (Imaging Modalities to Assist with Guiding therapy in the Evaluation of patients with Heart Failure) project includes a group of clinical trials, one of which is the AIMI-HF trial (Alternative Imaging Modalities in Ischemic Heart Failure) (NCT01288560)[54] (Figure 7). AIMI-HF is a multicenter randomized trial and registry study involving centers from Canada, United States, Finland, Brazil and Argentina. It compares the impact of standard of care investigation (SPECT) *versus* advanced imaging (PET and MRI) for viability and ischemia assessment. Composite outcomes are cardiac death, resuscitated cardiac arrest, MI and cardiac hospitalization. In cases where the patient is not randomized to one or the other arm, they are included in a clinical registry.[54] This study will help us understand the impact of the advanced cardiac imaging modalities for the viability assessment and their impact on patient outcome.

PET and MRI viability targets are different and may be complementary. The availability of PET/MRI scanners is growing, and an initial study suggests the feasibility of simultaneous assessment of FDG uptake and delayed enhancement.[30] Indeed, analysis per segment showed increased accuracy for predicting wall motion recovery in segments of accordance between the modalities.[30] Further trials are needed to show its reproducibility.

Cardiac biomarkers (troponin T and brain natriuretic peptide) are used for patient assessment and as prognostic tools.[54–58] A recent study has demonstrated their correlation with hibernating myocardium independently of ejection fraction, age and kidney function (Figure 8).[58] Future paradigm shifts in the work-up of patients with ischemic HF could involve the use of biomarkers to optimize image-guided therapy or in some cases be independent of imaging to decide revascularization therapy, but this theoretical approach requires specific study.

Hibernating myocardium is a substrate for arrhythmia and increases the risk of sudden cardiac death, possibly due to the sympathetic innervation inhomogeneity.[58–62] The ADMIRE trial has used MIBG SPECT to define altered sympathetic neuronal (SN) function in patients with HF, demonstrating higher risk in patients with

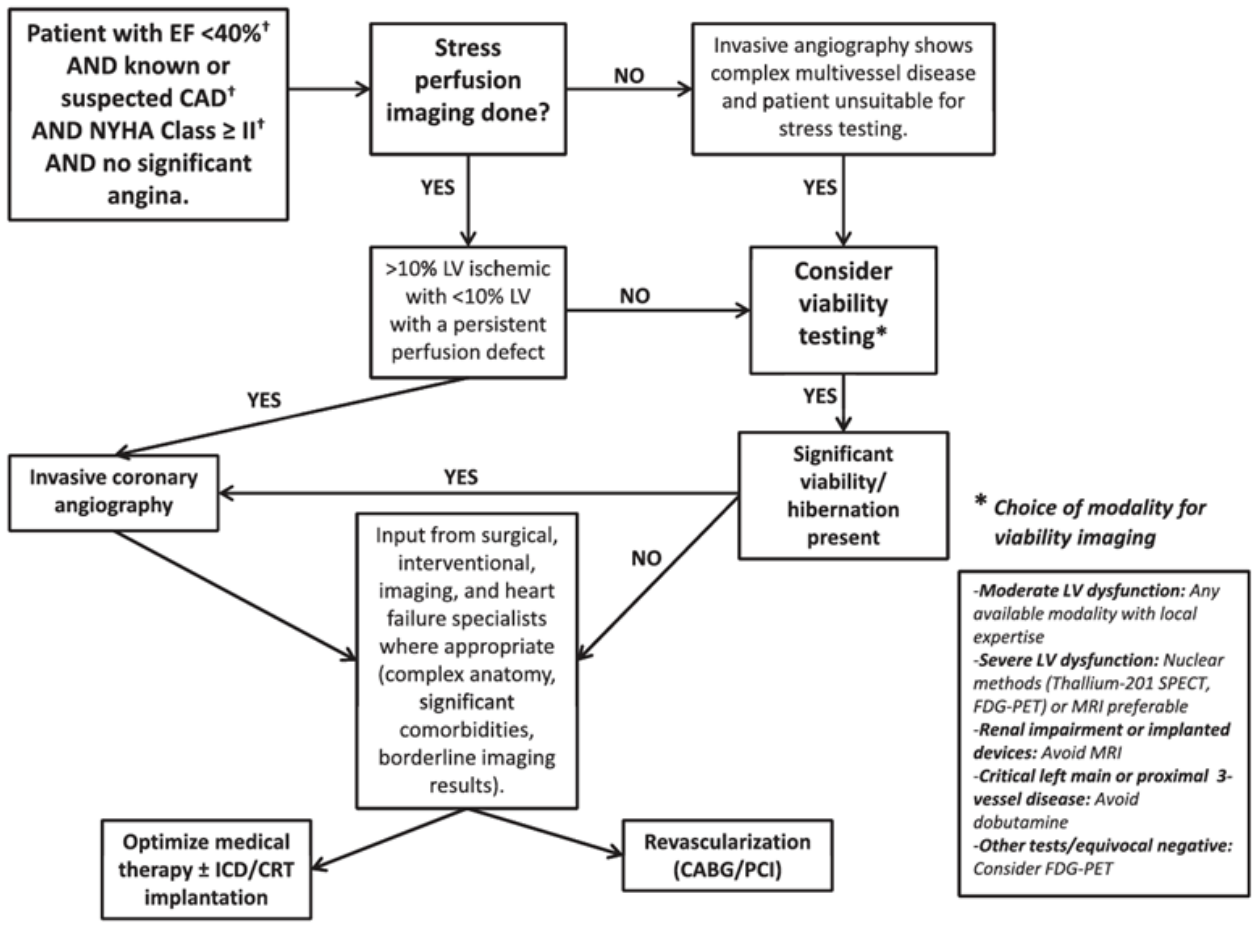

Figure 5 - Flow diagram illustrating a potential algorithm for use of viability imaging. – With permission from Mc Ardle et al., Can J Cardiol[52]

CABG: coronary artery bypass grafting; CAD: coronary artery disease; CRT: cardiac resynchronization therapy; EF: ejection fraction; ICD: implantable cardiac defibrillator; LV: left ventricle; MRI: magnetic resonance imaging; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; SPECT: single-photon emission computed tomography. †Denotes the required indications for 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) imaging in Ontario.

evidence of reduced MIBG uptake reflecting the high SN signal. The PARAPET study (Prediction of ARrhythmic Events with Positron Emission Tomography) has shown that sympathetic denervation measured by ^{11}C-meta-hydroxyephedrine (HED), a PET tracer able to quantify sympathetic denervation, could predict sudden cardiac death independently of ejection fraction and infarct size.[61] A novel F-18 PET tracer (LMI1195) is under initial evaluation and may be able to also measure myocardial innervation.[62–64] Its main advantage over HED is its longer half-life, which could enable wide distribution and hence potential for wider use of SN function imaging in the future.

Conclusion

Although the value of viability imaging may have been called into question by the STICH trial, several studies have reinforced the relationship between the extent of hibernating myocardium and improvement in patient outcome, left ventricular ejection fraction and quality of life if nutrient flow can be restored with revascularization. In general, there is accepted utility in using viability imaging in patient populations where decisions for revascularization are most difficult. Ongoing trials will further enable the identification of which patients most benefit from viability imaging and by which methods. Can biomarkers be used to guide

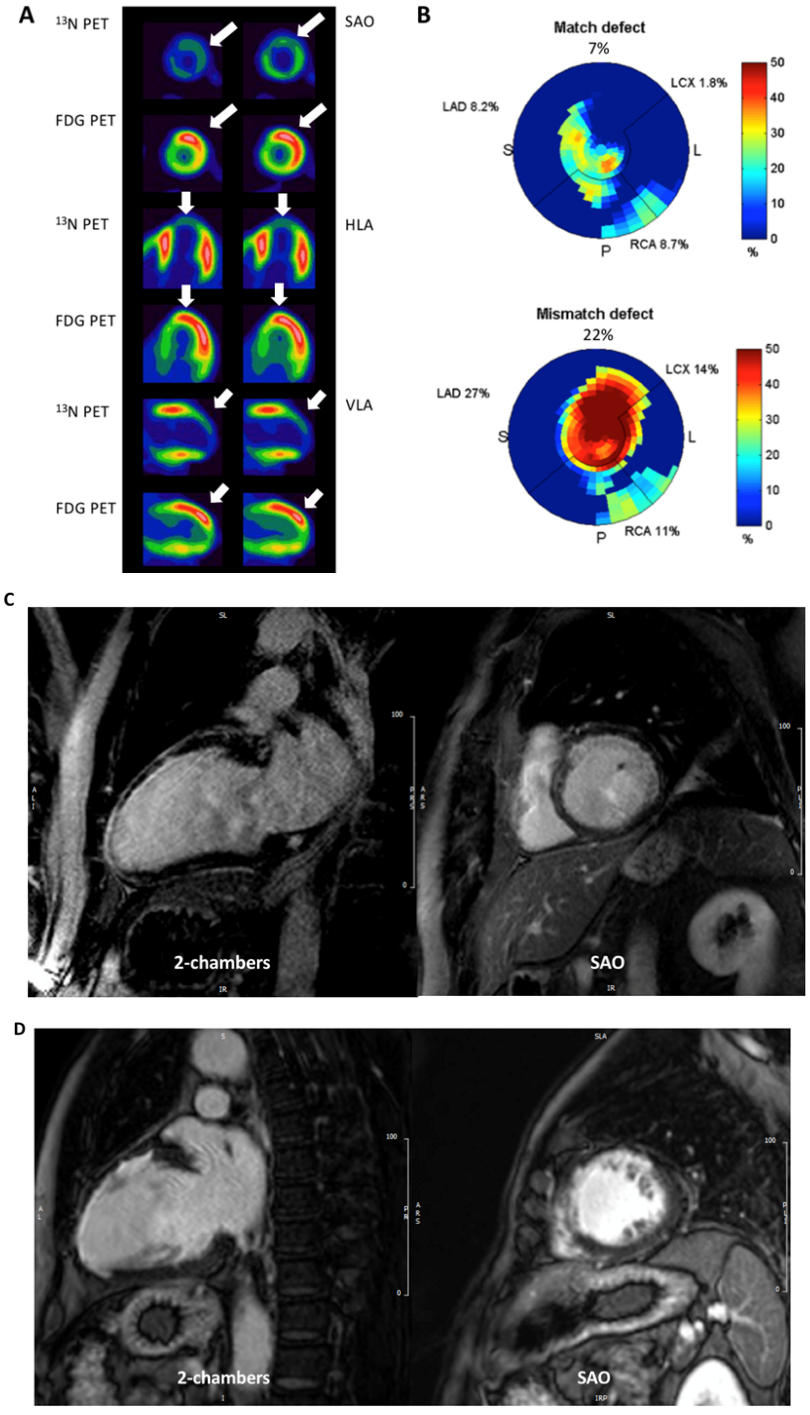

Figure 6 - (A) ^{13}N perfusion PET and ^{18}FDG metabolism PET in short axis (SAO), horizontal long axis (HLA) and vertical long axis (VLA) showing extensive area of mismatch in the mid to distal anterior wall and apex (white arrow). (B) Polar map with quantitative analysis of the scar amount (7%) on the top (match defect) and hibernating myocardium (22%) on the bottom (mismatch). "Given the significant amount of hibernating myocardium, it was recommended that the patient proceed with coronary artery bypass grafting." (adapted from Weifels et al., with permission).[73] (C) Cardiac MRI showing subendocardial scar involving > 75% of the myocardium from the basal to apical anteroseptal wall, mid to apical anterior wall and apex, suggesting no viability in the LAD territory in a patient with a history of previous anterior myocardial infarction and coronary angiogram showing occluded mid LAD. (D) Cardiac MRI of a patient with occluded proximal LAD with collaterals, 95% stenosis ostial LCx and occluded OM1 showing subendocardial scar from the basal to apical anterior wall, mid to apical anteroseptal wall, and basal to mid lateral wall involving < 50% myocardium, suggesting viability in the LAD and LCx territories. Given these findings, the patient went on to have CABG (LITA->LAD, left radial->OM1, SVG->right PIV). He is clinically doing well one year post-CABG.
LAD: left anterior descending artery; LCx: left circumflex artery; OM1: first marginal artery; SAO: short axis.

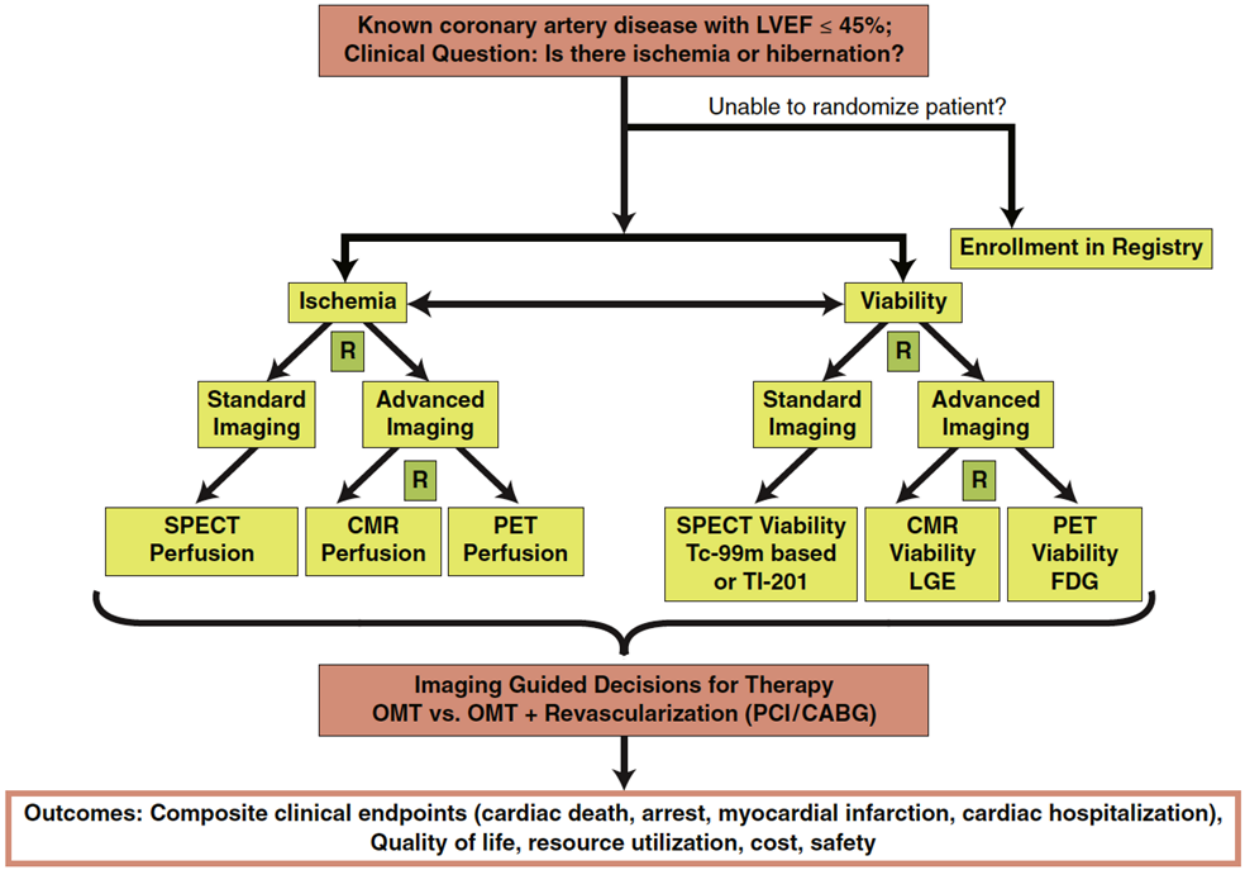

Figure 7 - "The AIMI-HF (Alternative Imaging Modalities in Ischemic Heart Failure) trial algorithm". "The primary endpoint is a composite of cardiac death, MI, resuscitated cardiac arrest, or cardiac rehospitalization." – With permission from Mielniczuk et al., JACC Cardiovasc Imaging[43]

CMR: cardiac magnetic resonance; LGE: late gadolinium enhancement; LVEF: left ventricular ejection fraction; SPECT: single-photon emission computed tomography; PET: positron emission tomography; R: randomization.

revascularization or at least to guide imaging to guide revascularization? Further research is needed here. In the meantime, clinicians, surgeons, interventional cardiologists and imaging specialists must work together as a team to enable the best decisions for each individualized patient in order to optimize the patient's desired outcomes.

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Author contributions

Acquisition of data: Erthal F, Wiefels C, Promislow S. Analysis and interpretation of the data: Erthal F, Wiefels C, Promislow S. Writing of the manuscript: Erthal F, Wiefels C, Promislow S, Kandolin R, Stadnick E. Critical revision of the manuscript for intellectual content: Erthal F, Wiefels C, Promislow S, Stadnick E, Mielniczuk L, Ruddy T, Small G, Beanlands R.

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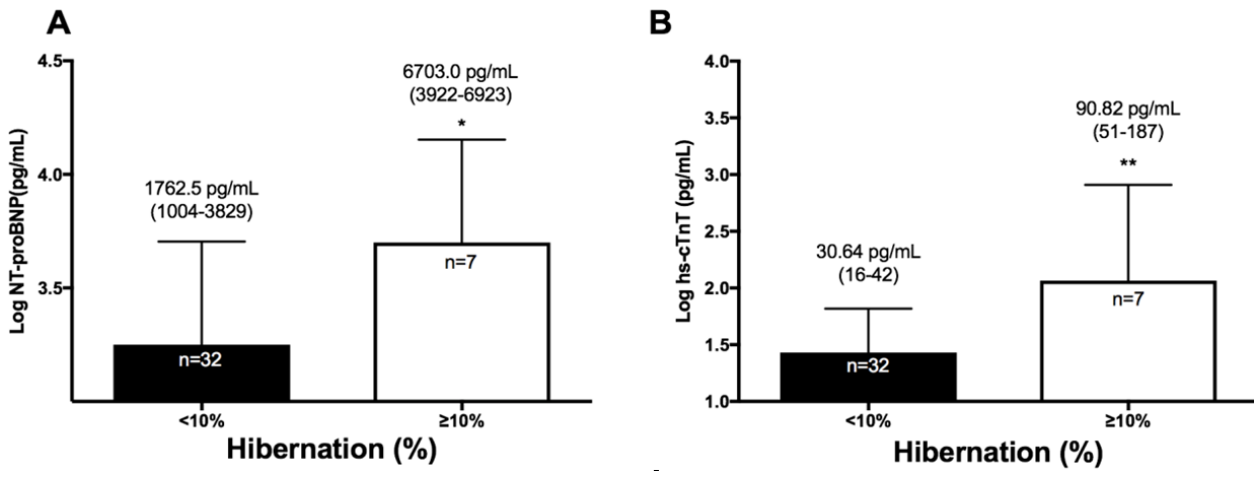

Figure 8 - NT-proBNP (A) and hs-cTnT (B) concentrations in "patients with and those without significant (> 10%) hibernation. Median (interquartile range) values of (A) serum NT-proBNP and (B) hs-cTnT levels are shown at the top of each corresponding bar." – Adapted with permission from Zelt et al., Can J Cardiol[58]
NT-proBNP (Log of serum N-terminal pro b-type natriuretic peptide), hs-cTnT (high-sensitivity cardiac troponin T).

Study Association

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

Ethics approval and consent to participate

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

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VIEWPOINT

Sudden Cardiac Death in Sports: Not a Fatality!

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Abstract

Sudden cardiac death in sports is still controversial. Despite being a rare event, the death of an apparently healthy young athlete causes a major impact on the media. On the other hand, for being a rare event, it is clearly undervalued. Sports preparticipation cardiological assessment is one of the most effective preventive medical actions for professional and amateur endurance athletes. The regular and supervised practice of physical exercise does not kill. We believe that deaths are triggered by excessive physical training and use of drugs, in individuals with not diagnosed or undervalued heart diseases. It is necessary to make health professionals and athletes aware of the athletes' physiological limits, in addition to preparing the athletes properly when they try to overcome human limits.

Introduction

Sudden death in sports is still a controversial topic among those who consider the death of an apparently healthy young individual a severe fact, with a strong media repercussion, and those who consider it a less relevant fact from the epidemiological viewpoint. That discussion is common among physicians and even among other health professionals.

We consider the sudden death of a young athlete a paradox: the symbol of health and physical vitality, experienced in a certain sports modality, suffers a cardiac arrest followed by sudden death when is not recovered.[1]

Keywords

Sports; Endurance Exercise; Risk Assessment; Sudden Death; Cardiac Arrest.

We cannot agree that it is a mere fatality, a condition mainly dependent on environmental factors such as accidents, lightening and floods, not on diseases.

In 2006, the International Olympic Committee, in Lausanne, Switzerland, reported data about sudden cardiac death in young athletes (< 35 years) from 1966 to 2004: 1,101 deaths were officially recorded worldwide, an incidence average of 29 athletes per year.[2]

At the beginning of 2018, the incidence of sudden death in professional and amateur athletes increased, taking everyone by surprise. Thirteen deaths were confirmed and 9 occurred in Brazil, including those of a 15-year-old soccer player and of a 37-year-old triathlete.

Among these deaths, only 3 had a definitive diagnosis after postmortem examination and DNA gene profile testing: 1 arrhythmogenic death syndrome (probable Brugada syndrome), 1 obstructive hypertrophic cardiomyopathy and 1 early coronary atherosclerotic disease. The other cases evidenced no macroscopic findings, but microscopy and laboratory tests to define the diagnosis are still pending. Some hypotheses are being analyzed and myocardial fibrosis due to high intensity and volume training leading to malignant arrhythmias may be a possible cause of death.

In order to prevent sudden cardiac death in athletes, in the 1970s-1980s the Medical Section of Sports Cardiology of the Instituto Dante Pazzanese de Cardiologia (IDPC-USP) initiated pre-participation evaluation of professional and amateur athletes of the major teams in São Paulo such as soccer, basketball and volleyball players, street runners and martial arts fighters, following a routine that is currently part of the Brazilian guidelines of Sports Cardiology for competitive athletes: personal and family history, physical examination, blood tests, exercise test and echocardiography.[3] Some Brazilian athletes resist

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undergoing that assessment because they are concerned about being excluded from sports competition.

The world scenario has changed after the tragic death of the African soccer player Foé, in June 2003 in Lyon, France, witnessed during the Confederations Cup, secondary to hypertrophic cardiomyopathy. In the following months, other deaths of soccer players occurred, such as the Polish player Fehér in January 2004 in Portugal, secondary to pulmonary thromboembolism, and the Brazilian player Serginho, of the São Paulo State premier league team, in October 2004, also secondary to hypertrophic cardiomyopathy. Because of such tragedies, the leaders began to investigate what should be done to prevent these events, in addition to enforcing the availability of emergency medical support with portable defibrillators in sports events in Brazil and worldwide.

Professional and amateur athletes of competitive sports should undergo preparticipation cardiovascular screening, an effective preventative strategy to avoid sudden death in sports, an event considered paradoxical because it occurs in a trained individual, a symbol of health, an example to the entire society. To corroborate our statement, we have statistical data from our Service of Sports Cardiology of the IDPC with approximately 14,000 athletes and ex-athletes cared for in the past 40 years, in addition to those from the Sports Medicine Clinic (ex-Sport Check-up HCor) of the Hospital do Coração (HCor), with approximately 1,000 athletes assessed in 10 years, mainly from 4 São Paulo State premier league teams.[4]

Sports cardiology of the IDPC and HCOR

1. Assessment of children and adolescents ("Soccer Sieve": a gateway for young individuals to play for a major league team):

Diagnostic results in 180 adolescents:

A. cleared for sports practice: 139 (77.3%)

B. comorbidities (anemia, asthma, type 1 diabetes mellitus, athlete's identified proteinuria syndrome): 9 (5%), 1 (0.5%) disqualified for sports competition

C. heart diseases: 32 (17.7%):

- disqualified for sports competition: 19 (10.5%), 1 death due to early coronary artery disease
- treated or recommended to change sports modality: 13 (7.2%)

D. Reason of the assessment:

- 110 (61%): preparticipation evaluation
- 70 (39%): presence of symptoms or abnormal tests

2. Preparticipation evaluation of Brazilian Olympic athletes

Diagnosis of 126 Brazilian Olympic athletes:

A. Normal results: 7.6%

B. Athlete's heart: 51%

C. Physiological arrhythmias: 2%

D. Mitral valve prolapse: 10%

E. Dyslipidemia: 25%

3. Assessment of 5,000 athletes by the IDPC

Cardiac abnormalities and/or heart diseases:

A. From 7 to 14 years of age: 21%

B. From 15 to 17 years of age: 17.7%

C. From 18 to 35 years of age: 8.2%

Sports practice is not a primary cause of sudden cardiac death. However, we believe that overtraining, use of licit (anabolic steroids, GH, amphetamines) and illicit drugs, and undiagnosed or undervalued heart diseases are the major causes of cardiac arrest and, consequently, sudden cardiac death.

Most of the common causes of sudden cardiac death can be identified by preparticipation evaluation of athletes performed by experienced doctors. Fatality is a death caused by an accident or a situation we couldn't avoid. Sudden cardiac death in athletes is a preventable event.

A recent study reported interesting data about triathlon competition, an endurance and high-intensity sport: "Deaths and cardiac arrests during triathlon are not rare as imagined, most of them occurring in middle-aged men and those older than 60 years". Most of the deaths occurred during swimming, a modality with difficult visual control of the possible events. The most important and surprising finding was the high incidence of silent cardiac abnormalities, particularly atherosclerotic coronary artery disease.[5]

In Brazil, sudden death in sports usually occurs in athletes who never underwent a preparticipation evaluation, mainly amateurs and those participating in intense physical activities at fitness centers. Many individuals presented arrhythmias, mostly secondary to viral myocarditis, the major cause of cardiac events in sports in Brazil.

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CASE REPORT

Acute Heart Failure Exacerbation in the Setting of Electrical Storm: Total Artificial Heart vs. Ventricle Assist Device

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Introduction

Total artificial heart (TAH) is a novel device with over a thousand implantations worldwide, being a suitable option for patients as a bridge to transplantation (BTT).[1] The following case was the second implantation of a TAH at our institution.

Case report

We report the case of a 64-year-old Caucasian male with past medical history of idiopathic dilated cardiomyopathy, reduced left ventricular ejection fraction (LVEF of 16%) reported during his last acute decompensation in 2012, sinus bradycardia with biventricular implantable cardioverter defibrillator (ICD) placement for secondary prevention of sudden cardiac death, in 2015, and atrial fibrillation. The patient was brought to the emergency department complaining of severe dyspnea and palpitations, preceded by multiple electrical shocking episodes (46 episodes). At admission, his electrocardiogram (ECG) showed a ventricular tachycardia (VT). He was monitored on telemetry, which evidenced a monomorphic VT with a mean heart rate of 188 beats per minute (bpm). The electrophysiology team was consulted; the device was interrogated and confirmed the above-mentioned number of shocks. Initial treatment with Lidocaine 2 mcg/kg/hr and Amiodarone 150 mg IV bolus achieved rate control. Initial laboratory testing showed hemoglobin of 16.2, WBC 12.1, platelets 186, Na 139, K 4.8, Cl 104, Cr 1.8 (GFR 38), BUN 36, glucose 169, AST 39, ALT 42, ALP 140, Ca 9.4, albumin 4.4. INR 4.2, digoxin 2.2.

The patient was transferred to the Coronary Care Unit (CCU), where physical examination revealed normal temperature, blood pressure of 94/65 mmHg, and heart rate of 91 bpm. His cardiovascular and lung exam was unremarkable. Chest X-ray showed small bilateral pleural effusions. Transthoracic Echocardiography showed markedly enlarged LV with severely decreased function (EF of 10-15%), severely generalized left ventricular hypokinesis, severely decreased right ventricular systolic function, right ventricular systolic pressure (RVSP) of 41 mmHg, right-to-left shunt at atrial level. At that point, no inotropic support was necessary.

The initial diagnosis was refractory VT (VT storm at presentation) in the setting of secondary acute systolic heart failure. Serial ECG strips were obtained, as shown in Figure 1. Unfortunately, his systolic blood pressure substantially decreased down to 60 mmHg, so he was placed on invasive monitoring, with a cardiac index of 1.81 L/min/m^2, estimated right atrial pressure (RAP) of 16 mmHg and mean pulmonary arterial pressure of 36 mmHg. At that point, cardiogenic shock required hemodynamic support therapies.

Electrophysiology staff attempted VT ablation, which showed possible endocardial and epicardial substrate. Consequently, EP performed epicardial VT ablation, with subsequent endocardial VT ablation, after an additional endocardial arrhythmic source was found during the procedure. Unfortunately, ablation was unsuccessful in controlling heart rhythm and his LVEF kept declining, this time to a LVEF of 5%.

Keywords

Dilated Cardiomyopathy; Heart Failure; Defibrillators, Implantable; Cardiac Resynchronization Therapy; Arrhythmias Cardiac.

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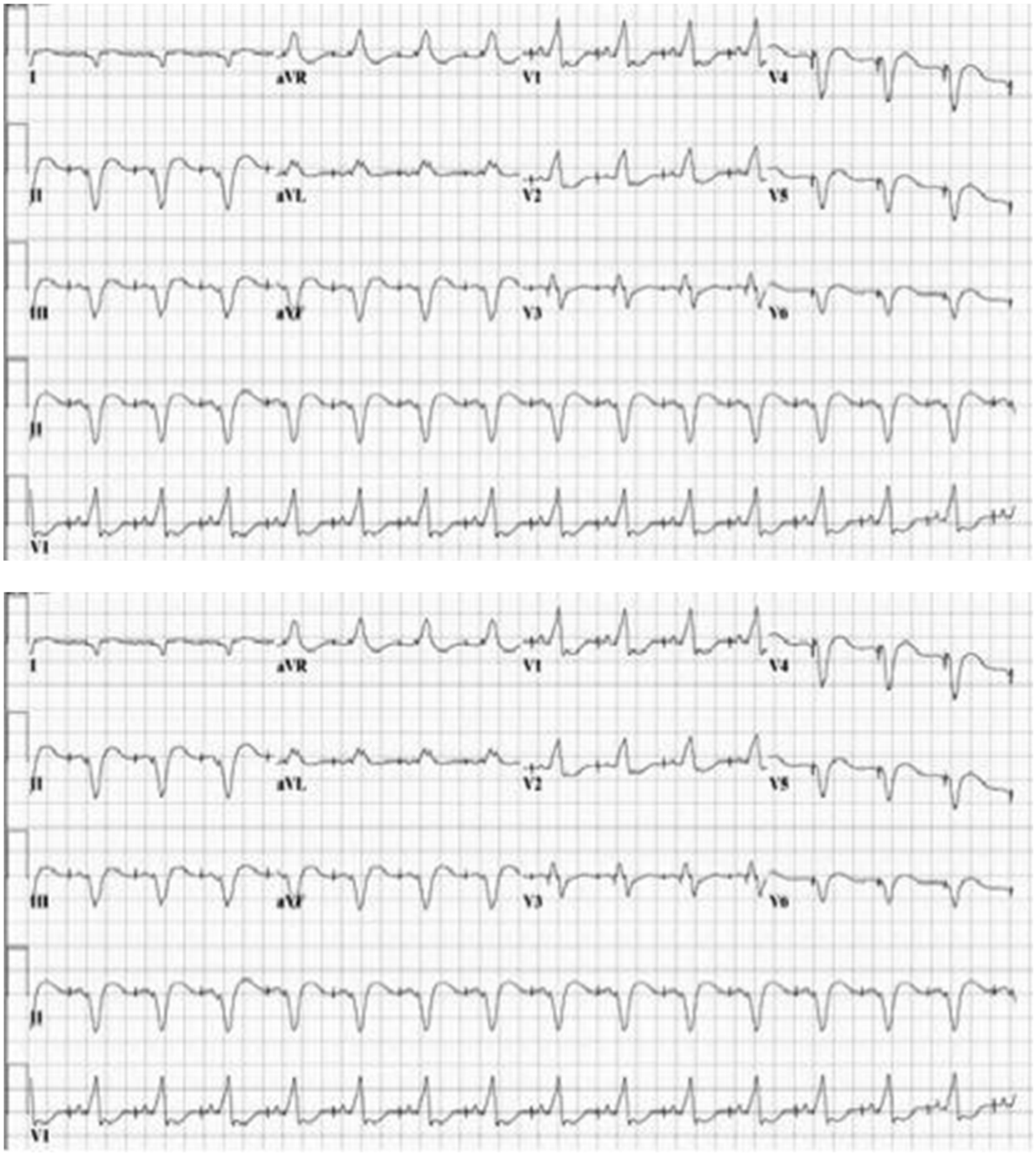

Figure 1 - ECG shows paced rhythm with right bundle branch block morphology.

The heart failure team considered temporary extracorporeal membrane oxygenation (ECMO) for short-term stabilization. Long-term hemodynamic support devices were discussed in detail in order to determine the best option (LVAD vs. TAH). If the patient had adequate right ventricular function and a controlled arrhythmia, left ventricular assist device (LVAD) would have been a suitable option. However, both these issues were a problem in this case; therefore, LVAD was not a suitable option. Biventricular assist device (BiVAD)

was also considered, but the arrhythmogenic ventricle was always a great concern. For that reason, a novel alternative therapy was pursued: the implantation of a total artificial heart (SynCardia) as a BTT. This was successfully done and the patient is now stable and on a waiting list for heart transplantation.

Discussion

Advanced heart failure with reduced ejection fraction remains a clinical dilemma in the medical world. Despite optimal medical therapy, cardiac resynchronization and ICD, there is a large population of patients that fail to compensate for the disease and demand heart transplantation. Due to low availability of heart transplantation, ventricular assist device (VAD) provides the mechanical circulatory support needed by these patients, as a bridge to transplant. In relation to our patient, decisions concerning the different types of VADs were made taking into account that right ventricular dysfunction and uncontrolled arrhythmias are a major limiting factor for LVAD use, making TAH a better option to maintain circulatory support in such case. A TAH was the most suitable option; LVAD limitations in this patient were right ventricular dysfunction and incessant ventricular refractory arrhythmias.[2,3]

Mechanical support therapies are alternative therapies for BTT patients who do not have an available heart donor. Nowadays, the industry provides several novel heart failure devices.[4] Most of them are intended to provide additional flow support, either continuous or pulsatile, for achieving temporary flow support. However, novel therapies, such as the TAH, have aimed to provide a long-term support even in the outpatient setting, with the great advantage of supplying the patient with fully autonomous ventricular function, making it a quite suitable option if no transplant is immediately available and for those patients with refractory, life-threatening malignant ventricular arrhythmias.[5] Interestingly, the patient described in our case report did not fit the guidelines, which made him a candidate for hemodynamic support with assist devices, but the main issue was to choose the most beneficial therapy.

The TAH, commonly known by the brand name "SynCardia", is a device option for patients with end-stage heart failure, particularly those with biventricular heart failure with no response to other assisted therapies. The FDA approved the device in 2004 as a BTT for biventricular failure. Table 1 shows all FDA-approved indications.[6] Therefore, its use has been slowly increasing due to the lack of implantation experience and clear guidelines supporting the indications, in addition to the absence of worldwide consensus and

Table 1 - FDA indications for Total Artificial Heart (Syncardia) inclusion and exclusion criteria[1]

Inclusion criteria:	Exclusion criteria:
Eligible for transplantation	Use of any vascular assist device
New York Heart Association (NYHA) class IV	Pulmonary vascular resistance ≥ 8 Wood units (640 dyne.sec.cm^{-5})
Body surface area 1.7–2.5 m^2, or T10 ≥ 10 cm (distance on computed tomographic scan from the anterior vertebral body to the sternum inner table at the level of the 10th thoracic vertebra)	Dialysis in previous 7 days
Hemodynamic insufficiency demonstrated by A or B:	Serum Creatinine level ≥ 5 mg/dL
A. Cardiac index ≤ 2 L/min/m^2 and one of the following: - Systolic arterial pressure ≤ 90 mmHg - Central venous pressure ≥ 18 mmHg	Cirrhosis and/or total bilirubin level ≥ 5 mg/dL
B. Two of the following: - Dopamine ≥ 10 μg/kg/min - Dobutamine ≥ 10 μg/kg/min - Epinephrine ≥ 2 μg/kg/min - Isoproterenol ≥ 2 μg/kg/min - Milrinone ≥ 0.5 μg/kg/min	Cytotoxic antibody ≥ 10%
Other drugs at toxic levels. Intra-aortic balloon pump, cardiopulmonary bypass.	

high costs for the patient, which are not usually covered by insurance companies.[7] The total artificial heart is a pneumatic, biventricular, orthotopic, pulsatile device that displaces 400 ml per cycle[7] (see Figure 1). Blood flow follows the normal physiology of the human heart, with flow rates of up to 9.5 L/min (barely turbulent). The device generated a Starling-like response by matching cardiac output with venous return and balancing blood flow between both ventricles.[8]

One of the main challenges facing the widespread use of TAH was the lack of clear indications. As far as we know, there are no clinical trials on course aiming to evaluate indications and outcomes of this device. The indications for TAH implantation are a matter of controversy. However, the FDA established inclusion and exclusion criteria, as shown in Table 1. Another important limiting factor is the short experience with TAH that makes this device a complex option for acute ill patients. Most surgeons would need proctor's help prior to implantation. Also the experience curve would have a slow-linear slope, making this device an option exclusively for highly specialized cardiovascular centers.[9]

Conclusion

Total artificial heart is a novel device that achieved more than expected benefits, particularly for BTT patients with right ventricle dysfunction and recalcitrant ventricular arrhythmias in need of mechanical support. However, no multicenter clinical trials have been conducted to assess its efficacy or safety in comparison with other assist devices. Short-experience still represents a hindrance for the device to be deployed. The lack of clear indications supported by international guidelines makes the use of these devices a skeptical decision that should only be made by experts.

Author contributions

Conception and design of the research: Rico JS, Prasad M. Acquisition of data: Rico JS, Prasad M. Analysis and interpretation of the data: Rico JS, Prasad M. Statistical analysis: Rico JS, Prasad M. Writing of the manuscript: Rico JS, Arango-Isaza D, Saldarriaga C. Critical revision of the manuscript for intellectual content: Rico JS, Arango-Isaza D, Prasad M, Saldarriaga C. Supervision / as the major investigador: Rico JS.

Potential Conflict of Interest

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

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CASE REPORT

Brugada Pattern, Brugada Phenocopy, What to Think?

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Introduction

Propafenone is a class 1 anti-arrhythmic medication with beta-adrenergic and calcium channel blocker properties.

Brugada syndrome (BrS) has a typical electrocardiographic pattern characterized by increased propensity for malignant ventricular arrhythmias and sudden death in patients with no structural heart disease.[1]

Brugada phenocopies (BrP) have electrocardiographic patterns that are identical to true type 1 and type 2 Br, despite the absence of a true congenital BrS. BrP are elicited by clinical conditions including ionic (or water and electrolyte) disturbances, myocardial ischemia and pulmonary embolism.[2-5]

We report a case of suicide attempt by an overdose of propafenone which yielded a type 1 Brugada pattern.

Case report

Seventeen-year-old adolescent admitted to the emergency department for voluntary intake of 40 tablets of propafenone 150 mg. The patient was hemodynamically stable at admission and conscious. There was no known family history of cardiovascular diseases, syncope or arrhythmias. Gastric lavage followed by activated charcoal (50 g) was performed, with emptying of food, but apparently not of medication. Ten minutes after admission, the patient had a generalized tonic clonic-seizure (with intravenous administration of midazolam 5 mg), followed by severe bradycardia that progressed to cardiac and respiratory arrest. Advanced life support (ALS) measures were started with return of spontaneous circulation (ROSC) after the fourth cycle. Electrocardiography (ECG) was performed and revealed a wide QRS and ST segment elevation in V1-V2 leads, consistent with a BS pattern (Figure 1). Arterial-blood gas test showed: pH 7.08; PCO_2: 51 mmHg; pO_2 45 mmHg; Na 145 mmol/L; K 3.6 mmol/L; Cl 113 mmol/L; Lact 9.4 mmol/L; HCO_3 14.8 mmol/L A second cardiorespiratory arrest occurred 20 minutes after ROSC, followed by three cycles of ALS and ROSC. For hemodynamic and rhythm stabilization, a temporary pacemaker was implanted by right femoral artery access. Norepinephrine at 0.1 mcg/kg/min and sodium bicarbonate 8.4% were administered for recovery of pulse rate. Complete reversal of the signs of toxicity was observed three hours after hospital admission. ECG then revealed sinus rhythm with no BrP features (Figure 2).

Discussion

BS is a rare, genetically determined condition with autosomal dominant transmission.[1]

Today, the diagnosis of BS is defined by the presence of type 1 ECG in at least two right precordial leads, combined with one of the following: documented ventricular fibrillation (VF) or ventricular tachycardia (VT), family history of cardiac sudden death (< 45 years), type 1 ECG in other members of the family, VF/VT in programmed electrical stimulation or syncope.[6]

Diagnosis may be difficult in cases of borderline or Brugada-like repolarization patterns with or without symptoms.[5]

Recent studies have reported cases of type 1 Brugada pattern at ECG caused by underlying causes, with normalization of ECG. Theses cases were classified as type 1 Brugada pattern.[2-5] BrP have been classified by

Keywords

Brugada syndrome/genetic; Propafenone; Anti-Arrhythmia Agents; Suicide; Death, Sudden, Cardiac; Arrhythmias, Cardiac; Electrocardiography.

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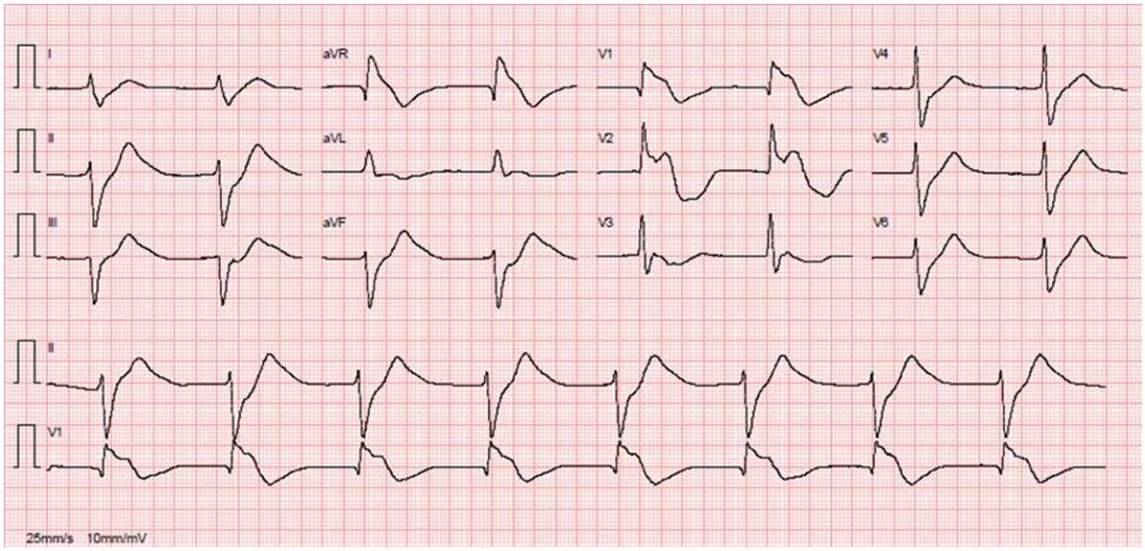

Figure 1 - Electrocardiogram performed after returning of spontaneous circulation showing widened complexes and ST-segment elevation in V1-V2 leads, consistent with the Brugada pattern.

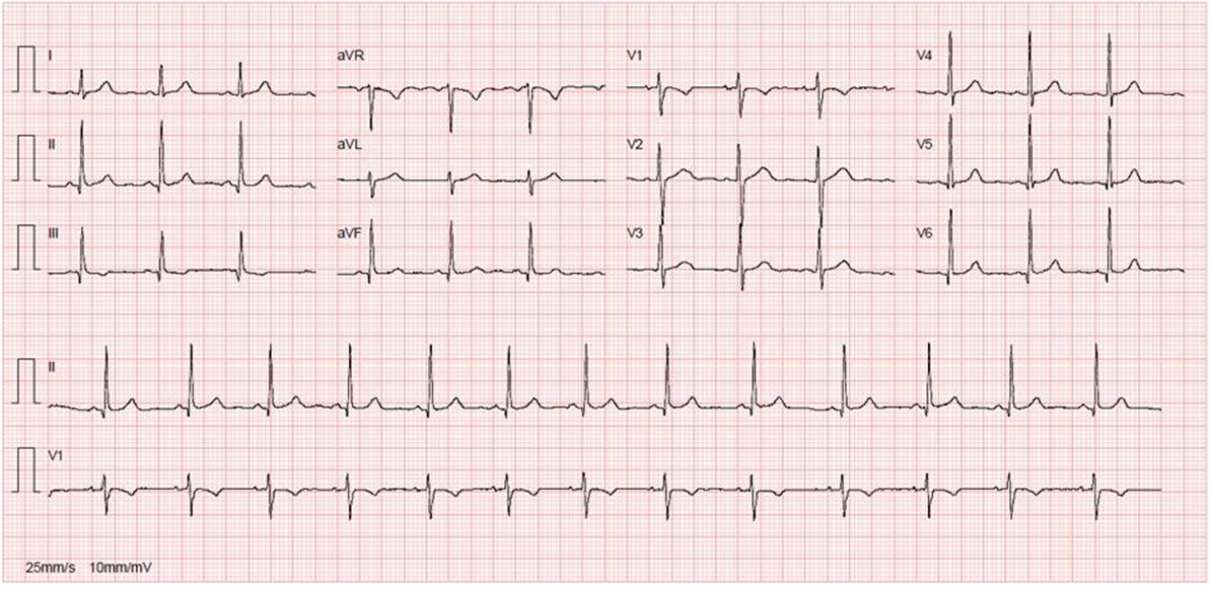

Figure 2 - Electrocardiogram with no signs of drug toxicity and without the Brugada pattern.

their etiologies, that include metabolic conditions such as hyperkalemia, mechanical compression, myocardial ischemia, pulmonary embolism, myocardial disease, pericardial disease and following catheter ablation.[6]

Electrocardiographic changes of BrP are identical to those of type 1 and type 2 Brugada pattern, with some different characteristics:[2-5]

1. Identifiable underlying condition;

2. Resolution of the ECGC pattern once the underlying condition has been treated;

3. Low pretest probability for BrS established by lack of symptoms and no family history of BrS;

4. Negative provocative testing with a sodium channel blocking agent;

5. Negative genetic testing

Propafenone has many known side effects, including increase of PR interval, widening of the QRS complex, bundle branch block, ventricular arrhythmias, bradycardia and hypotension. However, there are few reports on the effects of an overdose of propafenone, which have speculated the mechanisms of calcium channel inactivation even in the absence of a genetic mutation.[7-11]

"BrP" do not include type 1 Brugada pattern induced by calcium channel blockers and hence we could not find a correct classification of our case reported.

If on one hand some authors suggest provocative testing for patients with a "non-type 1" Brugada pattern to provide lifestyle counseling on fever management and use of provocative drugs, on the other hand, some advocate that there is no gain in performing this test in asymptomatic, "non-type 1" Brugada pattern patients for risk stratification. Thus, the role of provocative tests in patients with type 1 Brugada pattern in intoxication by propafenone has not been established.

In the case reported, we decided not to perform the provocative test; the adolescent is well, under no psychiatric treatment.[9]

Conclusion

Propafenone intoxication is a rare event and, to our knowledge, there is no detailed epidemiologic study on this in the literature.[8,11]

Despite the severity of the condition, successful stabilization of the individual was achieved by early resuscitation, invasive mechanical ventilation, transitory stimulation, and correct management of acidosis. This case emphasizes the importance of distinguishing the toxicological effect of BS from that of BrP.

Author contributions

Conception and design of the research: Martins JL, Ferreira R. Acquisition of data: Martins JL. Analysis and interpretation of the data: Martins JL. Writing of the manuscript: Martins JL, Ferreira R. Critical revision of the manuscript for intellectual content: Martins JL, Ferreira R, Viana J, Santos J.

Potential Conflict of Interest

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

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Study Association

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

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RETRACTION

Retraction

The editorial staff of the International Journal of Cardiovascular Sciences reports the formal publication of Retraction for extraction of the article:

SANTOS, Heitor Oliveira e IZIDORO, Luiz Fernando Moreira. Relação Neutrófilo-Linfócitos na Avaliação do Risco para Desenvolvimento de Doença Cardiovascular. Int. J. Cardiovasc. Sci. 2018;31(5)532-537. Epub 02-Jul-2018. ISSN 2359-4802. http://dx.doi.org/10.5935/2359-4802.20180038.

The article is being retracted because there will be no more Portuguese version, once the journal has publish from Volume 31, Nº 5, only articles in the English version.

Claudio Tinoco Mesquita

Chief Editor

DOI: 10.5935/2359-4802.20180096

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