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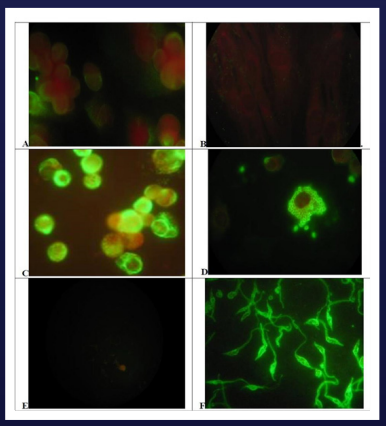

Figure 1 – *Distribution of Vimentin or Trypanosoma cruzi antigen on control or infected cells and parasites. A and B) Uninfected LLC MK2 cells reacted to antivimentin abs(A) or anti-T.cruzi abs(B). C and D) T.cruzi infected LLC MK2 cells reacted to antivimentin abs(C) or anti-T.cruzi abs(D). E and F) T.cruzi promastigote forms from in vitro culture reacted to antivimentin abs (E) or anti-T.cruzi abs(F). Cells, infected cells or parasites forms were reacted with Anti Vimentin mAb or chronic infection chagasic serum and revealed with adequate conjugate (x1000) (see Methods). Page 350*

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Catheter Ablation for Atrial Fibrillation in Patients with Heart Failure

Mauricio Scanavacca and Edimar Alcides Bocchi

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In the last years, atrial fibrillation (AF) and heart failure (HF) have been the two major epidemic syndromes in cardiology and they frequently coexist.[1] HF increases mean right and left atria pressures promoting their progressive dilation. Such mechanical electro-anatomic remodeling predisposes to atrial fibrosis and electrical heterogeneity, increases ectopic rhythm formation and ultimately induces AF.[2]

A new AF episode, in turn, immediately induces loss of atrial contraction, increases mean heart rate and provokes an important irregularity on ventricular contractions decreasing the heart's pump function performance. Therefore, around 50% of patients who present with new-onset congestive HF have atrial fibrillation and up to one-third of patients with new-onset AF have congestive heart failure.[2]

The Framingham study demonstrated that in AF patients, occurrence of HF was associated with significant increase in mortality, as well as in HF patients, a new AF development was associated with significant rise on mortality.[3] Therefore, there is a biological rationale for the prevention and treatment of AF associated with HF. The targets would be ventricular control, especially rhythm control.

Several pharmacological studies have failed to demonstrate clinical benefits in maintaining sinus rhythm compared to rate control in patients with normal or abnormal left ventricle function.[4-6] In the AFFIRM trial, the management of atrial fibrillation with rhythm-control strategy offered no survival advantage over the rate-control strategy, and patients had higher rate of hospitalization. The potential explanation for that was the antiarrhythmic drugs' adverse effects.[4] In patients with left ventricle dysfunction, the use of antiarrhythmic drugs safely recommended for this condition, such as dofetilide and amiodarone, also did not show any hard endpoint benefits.[5,6]

Catheter ablation for AF has emerged as the most effective strategy to maintain the sinus rhythm in patients with paroxysmal and persistent AF and has been used worldwide.[7,8] However, there is a paucity of studies investigating hard endpoints as mortality reduction in patients with HF with catheter ablation. The study "A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial)" was able to demonstrate an improvement in left ventricular ejection fraction (LVEF) with ablation in patients with persistent AF.[9] Additional advantages were observed in the *"Ablation versus Amiodarone for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure and an Implanted ICD (The AATAC) trial"*. Di Biase et al[10] showed that ablation was superior to amiodarone in maintaining sinus rhythm, improving LVEF, improving survival rates and decreasing hospitalization for HF.

More recently, an additional enthusiasm comes up with the report of *"Catheter ablation for atrial fibrillation with heart failure (Castle-AF) trial"*. Marrouche et al confirmed observations of the AATAC trial, showing that catheter ablation of AF significantly reduces mortality in patients with HF, as compared with medical therapy.[11]

CASTLE-AF is a multicenter study, conducted from January 2008 through January 2016, and involving a total 33 sites in Europe, Australia, and the United States. In this study, 263 patients with symptomatic paroxysmal or persistent AF were randomly assigned to undergo AF catheter ablation (179) or medical treatment (184), using rate or rhythm control strategies. All the patients had New York Heart Association (NYHA) class II, III, or IV HF, a LVEF of 35% or less, and an implanted defibrillator. The primary end point was notably hard, a composite of death from any cause and hospitalization for worsening HF. The final results were obtained after a median follow-up of 37.8 months and favored catheter ablation comparing to medical therapy. In the ablation group, 63% of patients were in sinus rhythm at 60 months versus 22% in the medical-therapy group. The primary composite end point occurred in 51 (28.5%) patients in the ablation group and in 82 (44.6%) patients in the medical therapy group (HR = 0.62; P = 0.007).

There was a significant reduction of all-cause mortality in the ablation group (13.4% vs. 25.0%), HR = 0.53, P = 0.01 and from cardiovascular causes (11.2% vs. 22.3%); HR = 0.49; P = 0.009. Additionally, patients undergoing catheter ablation showed reduced hospitalization rate in consequence of worsening heart failure (20.7%) comparing to medical treatment (35.9%), HR = 0.56, P = 0.004. Furthermore, catheter ablation reduced the burden of AF, increased the distance walked in 6 minutes, and improved the LVEF (8%). An important detail from this study was the observation that the mortality benefit of ablation emerged just after 3 years of follow-up.

These observations are unique since it is the first trial on catheter ablation field designed to show both, superiority in maintaining the sinus rhythm and mortality reduction comparing to medical therapy. However, CASTLE-AF trial has some important limitations as highly patient selection – from 3,013 patients assessed for eligibility, just 263 were finally included in the primary analysis. Investigators were not blinded treatment randomization, and a number of patients crossed over to the other treatment group. Additionally, the procedures were performed in high-volume medical centers

Keywords

Heart Failure; Atrial Fibrillation; Catheter Ablation / trends; Atrial Remodeling; Amiodarone

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with very experienced operators. Also, inclusion criteria of patients to the CASTLE-AF trial included absence of response to (45-47%), unacceptable side effects from (12-14%), and unwillingness to take antiarrhythmic drugs (40-43%). In fact, in the CASTLE-AF study the AF ablation was not tested in patients under acceptable rate control or rhythm control. So, new studies are needed to confirm such important observations.

Benefits of catheter ablation of AF have also been suggested in a recent retrospective study evaluating HF patients with preserved ejection fraction HFpEF.[12] Two hundred-thirty AF patients with HF, 133 HFpEF and 97 patients with reduced ejection fraction (HFrEF) underwent catheter ablation. After a mean follow-up of 12 months, postablation outcomes as in-hospital adverse events, symptoms according to the Mayo AF Symptom Inventory (MAFSI), NYHA functional class, and freedom from atrial arrhythmia] were recorded. Ablation procedure (pulmonary vein isolation, pulmonary vein isolation with roof line, complex fractionated atrial electrograms), procedural time, fluoroscopy duration, and radiofrequency time were comparable between these groups.

After ablation, the incidence of acute HF across these groups was similar. Both groups improved in MAFSI and NYHA functional class. Before ablation most of the patients were in NYHA functional class II, but after ablation the majority of patients shifted to class I from the more advanced classes. Preablation LVEF showed no correlation with freedom from atrial arrhythmia or repeat ablation rate. These results remained the same even after stratification based on AF phenotype. At 12 months postablation, all-cause hospitalization and cardiovascular hospitalization were similar for these patients. Also, previous study on AF ablation in HFpEF has suggested that AF can be effectively and safely treated with a composite of repeat procedures and pharmaceuticals. However, larger randomized controlled studies are also needed to confirm the benefits of AF ablation in HFpEF.[13]

In conclusion, HF and AF are widely distributed diseases and difficult-to-treat conditions due to their synergistic effect. Once installed, a vicious circle is established, which significantly worsens the patient's prognosis. No mortality or hard endpoint benefits have been demonstrated with the most commonly used antiarrhythmic drugs. Evidence has been generated in the last decade in favor of AF ablation in selected patients with AF with preserved or reduced LVEF.

Based on these new data, catheter ablation has already been considered as first-line therapy in patients with paroxysmal or persistent AF and HF.[14] Evident benefit can be obtained in patients in which AF is the main cause for HF (tachycardiomyopathy).[15] However, we still need to develop new markers and tools to better define ideal ablation techniques and candidates, especially for patients under acceptable rhythm or rate control.

References

1. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. Circulation 2003;107(23):2920–5.
2. Santhanakrishnan R, Wang N, Larson MG, Magnani JW, McManus DD, Lubitz SA, et al. Atrial fibrillation begets heart failure and vice versa: temporal associations and differences in preserved versus reduced ejection fraction. Circulation. 2016;133(5):484-92.
3. Luong C, Barnes ME, Tsang TS. Atrial fibrillation and heart failure: cause or effect ? Curr Heart Fail Rep. 2014;11(4):463-70.
4. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, et al; Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med. 2002;347(23):1825-33.
5. Torp-Pedersen C, Møller M, Bloch-Thomsen PE, Køber L, Sandøe E, Egstrup K, et al. Dofetilide in patients with congestive heart failure and left ventricular dysfunction. N Engl J Med. 1999;341(12):857-65.
6. Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, et al; Atrial Fibrillation and Congestive Heart Failure Investigators. Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med. 2008;358(25):2667-77.
7. Santos SN, Henz BD, Zanatta AR, Barreto JR, Loureiro KB, Novakoski C, et al. Impact of atrial fibrillation ablation on left ventricular filling pressure and left atrialremodeling. Arq Bras Cardiol. 2014;103(6):485-92.
8. Lobo TJ, Pachon CT, Pachon JC, Pachon EI, Pachon MZ, Pachon JC, et al. Atrial fibrillation ablation in systolic dysfunction: clinical and echocardiographic outcomes. Arq Bras Cardiol. 2015;104(1):45-52.
9. Hunter RJ, Berriman TJ, Diab I, Kamdar R, Richmond L, Baker V, et al. A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). Circ Arrhythm Electrophysiol. 2014;7(1):31-8.
10. Di Biase L, Mohanty P, Mohanty S, Santangeli P, Trivedi C, Lakkireddy D, et al. Ablation versus amiodarone for treatment of persistent atrial fibrillation in patients with congestive heart failure and an implanted device: results from the AATAC Multicenter Randomized Trial. Circulation. 2016;133(17):1637-44.
11. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, et al; CASTLE-AF Investigators. Catheter ablation for atrial fibrillation with heart failure. N Engl J Med. 2018;378(5):417-27.
12. Black-Maier E, Ren X, Steinberg BA, Green CL, Barnett AS, Rosa NS, et al. Catheter ablation of atrial fibrillation in patients with heart failure and preserved ejection fraction. Heart Rhythm. 2017 Dec 6. [Epub ahead of print].
13. Machino-Ohtsuka T, Seo Y, Ishizu T, Sugano A, Atsumi A, Yamamoto M, et al. Efficacy, safety, and outcomes of catheter ablation of atrial fibrillation in patients with heart failure with preserved ejection fraction. J Am Coll Cardiol. 2013;62(20):1857-65.
14. Kheirkhahan M, Marrouche NF. It is time for catheter ablation to be considered a first-line treatment option in patients with atrial fibrillation and heart failure. Heart Rhythm. 2018 Feb 8. [Epub ahead of print].
15. Calvo N, Bisbal F, Guiu E, Ramos P, Nadal M, Tolosana JM, et al. Impact of atrial fibrillation-induced tachycardiomyopathy in patients undergoing pulmonary vein isolation. Int J Cardiol. 2013;168(4):4093-7.

Heart Rate and its Variability Assessed by Spectral Analysis in Elderly Subjects with Orthostatic Hypotension: A Case-Control Study

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Abstract

Background: **The prevalence of orthostatic hypotension (OH) increases with age and is associated with changes in autonomic regulation of blood pressure (BP) and heart rate (HR).**

Objective: **to assess HR and HR variability (HRV) in elderly subjects with OH and determine OH predictors.**

Methods: **a total of 105 patients aged ≥ 60 years, 39 with OH (case group) and 66 without OH (control group) (age-matched) were studied. Patients underwent clinical assessment, electrocardiogram, biochemistry tests and Holter monitoring for spectral analysis of HRV (Fourier transform) in the supine and orthostatism positions to identify low frequency (LF) and high frequency (HF) components, as well as the LF/HF ratio.**

Results: **median age was 73.0 years, 64 patients were women. In all participants, there was a reduction in HF (133.0 versus 76.0 ms², p = 0.001) and increase in LF/HF (1.6 vs 2.1; p < 0.001) and no change in LF (233.0 versus 218.0 ms², p = 0.080). Between-group comparisons revealed significant differences in the median values of HR in the supine position (62.0 vs. 69.0 bpm, p = 0.001) and LF in the supine position (157.0 in case group vs. 275.0 ms² in the control group, p = 0.014). Spearman's correlation coefficient of 0.27 was found between the groups. Multivariate analysis revealed that HR in the supine position was an independent variable for OH (p = 0.001- 95%CI = -0.022 and -0.006). Using the operating characteristic curve, the best cutoff point was 61 bpm, with a sensitivity of 77.3% and specificity of 51.3%, positive predictive value of 61.3%, and negative predictive value 69.3%. Odds ratio was 3.23 for OH in patients with a HR lower than 61 bpm.**

Conclusions: **lower LF and HR in the supine position were found in patients with OH, regardless of age and gender. The independent predictor for OH was HR in the supine position, with an odds ratio of 3.23 for values lower than 61 bpm. (Arq Bras Cardiol. 2018; 110(4):303-311)**

Keywords: **Heart Rate; Hypotension, Orthostatic; Accidental Falls; Syncope; Aged; Dizziness.**

Introduction

Orthostatic hypotension (OH), also known as postural hypotension is defined as a sustained fall in blood pressure (of at least 20 mm Hg in systolic pressure and/or at least 10 mm Hg in diastolic pressure) occurring within 3 minutes of standing.[1,2] OH has been associated with falls, presyncope, syncope, functional impairment in the elderly, cardiovascular events, and increased mortality.[3-5] Its prevalence varies from 6 to 35%,[4] and can achieve 41% in individuals aged 80 years or older.[6]

With aging, there are changes in autonomic regulation of heart rate (HR) and blood pressure. Middle-aged women have a more dominant parasympathetic whereas men have a more sympathetic regulation of heart rate.[7] In addition, increased levels of norepinephrine and reduced sensitivity of beta-adrenergic receptors are found in elderly subjects. There is a decrease in vasomotor response mediated by alpha receptors, with decline in venous capacitance response of the lower limbs and in baroreflex response, which is also due to artery stiffness.[8,9] This altered regulation lead to autonomic dysfunction and may cause OH. Autonomic nervous system, involved in the physiopathology of OH, may be examined by measurements of the heart rate variability (HRV) by Holter monitoring,[10] a non-invasive, low-cost method.

Studies on the autonomic nervous system, including those on baroreflex sensitivity and head-up tilt test have been performed in hypertensive and normotensive elderly patients who were compared with young subjects. These studies included up to 80 elderly subjects, 64 with hypertension.[11-13] In the largest study, involving 362 volunteers, there were 38 men and 51 women aged between 57 and 88 years,[13] but the authors did not specify the exact number of older patients. In light of this, this study aimed to assess HR and HRV by spectral analysis during postural tilt in elderly patients, and evaluate OH predictors.

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Methods

This was an observational, prospective, cross-sectional study. Our sample was composed of 105 outpatients aged 60 years or older, included during the period from February 2013 to August 2014. Patients with dementia, autonomic dysfunction-related neurologic diseases, persistent or permanent atrial fibrillation, pacemakers, institutionalized patients, and those using antiarrhythmic agents (Class I, III or IV agents according to Vaughan Williams classification) or digoxin were excluded.

The study was approved by the local Research Ethics Committee and all participants signed the informed consent form.

For sample estimation, a one-tailed test was used, with significance level at 5%, power of 90%, two controls per case, frequency of OH of 30%. Two groups, age matched, were studied – a case group (n = 39) with OH, and a control group (n = 66) without OH.

Participants underwent clinical assessment, clinical pathology tests, 12-lead electrocardiography, measurements of blood pressure (BP) at supine position at the 5th minute of rest and at the 3rd minute of orthostatism or before, in case they had OH symptoms according to well-established conditions,[2] monitored by the Holter system. Measurements were performed at a temperature-controlled room, in the afternoon, at least two hours after lunch to exclude the possibility of post-prandial hypotension. Holter monitoring was performed using a three-channel digital recorder (Cardioflash) (modified V1 and V5 and DIII) version 1.0, at supine and orthostatic positions for 15 and 10 minutes, respectively, for analysis of HRV in the frequency domain by the fast Fourier transform method. Measurements of high-frequency (HF) and low-frequency (LF) components that indicate parasympathetic and sympathetic activities, respectively, as well as the LF/HF ratio[10] were calculated. This analysis was performed after manual edition of recordings to remove artifacts and correct arrhythmias. Measures were obtained during 5 minutes at 10th minute of supine position and 5th minute of orthostatic position. Results of the spectral analysis were expressed in ms^2.

The Framingham[14] and the PROCAM[15] risk scores were also calculated using clinical and laboratory data, which included plasma levels of cholesterol and its fractions, triglycerides, and fasting glucose levels.

Statistical analysis

For data analysis, we used the International Business Machines (IBM) Statistical Package for Social Sciences (SPSS) Statistics 19. Results were expressed as numbers and proportions for categorical variables and as central tendency (mean and median) and dispersion measures for continuous variables. Associations between categorical variables were assessed by the chi-square test or the Fisher's exact test, as appropriate. Data normality was not tested. The Mann-Whitney test was used for comparisons between continuous variables, and correlations between categorical variables were assessed by the Spearman's rank correlation test. The Wilcoxon test was used to compare the two periods HRV components in the spectral analysis (supine and orthostatic positions). Stepwise multivariate analysis was performed to evaluate predicting values of OH, considering the variables with a $p \leq 0.10$ in the univariate analysis. Receiver operating characteristic curve was analyzed for the stable variable postural response. The level of significance was set at 5%.

Results

General characteristics of the population

Mean and median age were 71.9 and 73.0 years, respectively; 64 (61%) were women. Clinical variables of the study population are described in Table 1.

With respect to cardiovascular risk factors, systemic arterial hypertension (SAH) and dyslipidemia were the most frequent, found in 80 (76.2%) and 42 (40%) patients, respectively. Diabetes was found in 17.1% of patients.

Thiazide diuretics were the most used antihypertensive drugs; 42 patients (40%) used them isolated or in combination with other antihypertensive agents. Following thiazide diuretics, angiotensin II receptor blockers (29.8%), angiotensin-converting enzyme (ACE inhibitor) (28.6%) and beta-blockers (27.6%) were the most common, with similar frequencies of use. Also, 14.3% of patients were using calcium antagonists (amlodipine or nifedipine).

Symptoms characterized by previous history of dizziness, falls, and presyncope and/or syncope were reported by 64 patients (61%).

Impaired conduction in the left bundle branch was detected at electrocardiography in 9.5% of patients, with mean PR and QT intervals of 166.9 ms (120-280) and 403.0 ms (320-520), respectively.

Comparison between case and control groups

No difference was found in age (mean of 73.5 ± 8.0 years; median of 74.0 in the case group and 71.0 ± 6.8 years and 72.0 years in the control group, $p = 0.119$), but a significant difference in sex was observed between the groups (56.4% of men in the case group and 27.8% of men in the control group, $p = 0.005$). No correlation was found between these two variables (Spearman's coefficient correlation of 0.274).

Results of other comparisons between the two groups are described in Table 2. No patient had dizziness, presyncope or syncope in orthostatism when BP was measured. No difference considered abnormal in BP between the upper limbs was detected in seated position.

Significant differences were found in the frequency of previous symptoms (dizziness, prepsyncope and syncope) – 77% in the case group *versus* 51.5% in the control group ($p < 0.001$). However, no difference between patients with and without previous symptoms were found in age (mean or median) – 71.4 ± 7.4 years; 72.0 years *versus* 72.7 ± 7.8 years, 74.0 years; respectively ($p = 0.38$) – nor in BP measured in the supine position.

With respect to hypertension, no difference was found between the case and control groups ($p = 0.54$). Forty-nine patients (74.2%) in the control group and 31 in the case group were hypertensive (79.4%). There was no difference

Table 1 – Anthropometric and clinical variables of studied patients

Variables	Median	Interquartile range Q1 - Q3	Minimum value	Maximum value
Age (years)	73.0	65.5 – 77.0	60.0	91.0
Weight (kg)	62.0	56.0 – 72.0	44.0	102.0
Height (m)	1.58	1.51 – 1.62	1.41	1.80
BMI (kg/m^2)	25.7	22.5 – 29.7	17.8	40.9
WC (cm)	87.3	80.3 – 96.0	68	116
HR supine position (bpm)	68.0	60.0 – 76.0	38.0	105.0
HR orthostatic (bpm)	72.0	64.0 – 80.0	44.0	109.0
SAP supine position (mmHg)	140.0	127.0 – 152.0	92.0	196.0
DAP supine position (mmHg)	80.0	75.0 – 87.0	60.0	104.0
SAP orthostatic position (mmHg)	130.0	120.0 – 142.0	60.0	220.0
DAP orthostatic position (mmHg)	80.0	70.0 – 90.0	30.0	100.0
SAP seated position (mmHg)	135.0	120.0 – 150.0	100.0	194.0
DAP seated position (mmHg)	80.0	70.0 – 90.0	60.0	106.0

BMI: body mass index; WC: waist circumference; HR: heart rate; bpm: beats per minute; SAP: systolic arterial pressure; DAP: diastolic arterial pressure; mmHg: millimeter of mercury; Q1: 25th percentile; Q3: 75th percentile

Table 2 – Between-group comparison of heart rate, blood pressure and cardiovascular risk scores

Variables	Case group Median (Q1 – Q3)	Control group Median (Q1 – Q3)	p-value
HR supine position (bpm)	62.0 (57.0 – 72.0)	69.0 (63.5 – 76.0)	0.001
HR orthostatism (bpm)	67.0 (60.0 – 76.0)	75.0 (68.0 – 80.0)	0.006
SAP supine position (mmHg)	140.0 (130.0 – 160.0)	135.0 (125.8 – 150.0)	0.189
DAP supine position (mmHg)	80.0 (70.0 – 90.00	80.0 (78.0 – 86.0)	0.543
SAP orthostatism (mmHg)	120.0 (110.0 – 135.0)	136.5 (120.0 – 146.2)	0.001
DAP orthostatism (mmHg)	72.0 (60.0 – 84.0)	80.0 (77.3 – 90.0)	0.001
Framingham score	15.5 (6.0 – 24.3)	12.0 (6.0 – 17.0)	0.063
PROCAM score	10.6 (5.01 – 21.4)	11.0 (5.0 – 16.8)	0.537

SD: standard deviation; HR: heart rate; bpm: beats per minute; SAP: systolic arterial pressure; DAP: diastolic arterial pressure; mmHg: millimeter of mercury. Mann-Whitney test; Q1: 25th percentile; Q3: 75th percentile

in the frequency of diabetes (7 patients in the case group and 11 in the control group; p = 0.86) or coronary arterial disease (5% in the case group and 9% in the control group) between the groups. All patients were stable, without chest pain.

Regarding the main groups of antihypertensives, higher percentage of users of ACE inhibitors was observed in the case group (41.0%) than in the control group (21.2%) (p = 0.030). No difference was found in other antihypertensive agents.

Heart rate variability

Medians and interquartile ranges of HRV components in supine position were – LF 233.0 ms^2 (130.5 – 422.5), HF 133.0 ms^2 (62.0 – 347.5), LF/HF 1.6 (0.8 – 3.0) – and in orthostatic position were – LF 218.0 ms^2 (110.5 – 359.7), HF 76.0 ms^2 (32.0 – 227.0) and LF/HF 2.1 (1.1 e 4.8). Comparisons of HRV components between supine and orthostatic positions performed by the Wilcoxon test showed no difference in LF (p = 0.080), but significant differences in HF (p = 0.01) and LF/HF (p < 0.001).

When HRV absolute values were compared between case and control groups by the Mann-Whitney test, significant difference was found in LF in supine position (Table 3). No difference between the groups was found in other components. Due to HRV data interval, a logarithmic transformation of HRV components was performed, and the same p-values were maintained. For analysis of HRV with change of position, median differences in LF component were compared between case and control groups (i.e. between the supine and the orthostatic position, median -0.27 ms^2) by the Mann Whitney test (p = 0.43). Median differences of HF and LF/HF components were 33.0 ms^2 and 0.53, respectively, and p-values of respective comparisons were 0.74 and 0.94.

Figures 1 and 2 depict the analysis of HRV components of a patient with OH in the supine and orthostatic positions, respectively. Figures 3 and 4 show the analysis of HRV components of a patient without OH in the supine and orthostatic positions, respectively.

Stepwise multivariate analysis

Variables with a $p \leq 0.10$ in the univariate analysis – sex, use of ACE inhibitors, presence of previous symptoms, HR, LF and LF/HF in supine and orthostatic positions, and Framingham score – were considered for the multivariate analysis. The independent variable with statistical significance was HR in the supine position, with $p = 0.001$, 95% confidence interval of -0.0022 – -0.006.

Analysis of the receiver operating characteristic curve

Using the receiver operating characteristic curve for the stable variable postural response without OH, and considering the variable HR in the supine position, an area under the curve of 0.70 was obtained (Figure 5), with a $p = 0.001$ (95% confidence interval of 0.595-0.796). The best cutoff point was 61 bpm, with a sensitivity of 77.3% and specificity of 51.3%. Positive predictive value was 61.3%, and negative predictive value 69.3%. Odds ratio was 3.23 for OH in patients with a HR lower than 61 bpm.

Discussion

The main finding of this study was that, in contrast to HRV components, HR in the supine position was an independent predictor for the occurrence of OH in the study population. Median HR in the supine position was significantly lower in the case group than in the control group in the same position. Although this variable was a predictor of OH, with an odds ratio of 3.23 for patients with HR < 61 bpm, it was not considered a good diagnostic test, as confirmed by the analysis of the receiver operating characteristic curve.

Aging is one of the main predicting factors for OH, which may be explained by changes in the autonomic regulation

Table 3 – Comparison of heart rate spectral analysis between case and control groups

Variables	Case group Median (Q1 – Q3)	Control group Median (Q1 – Q3)	p-value
LF supine position (ms^2)	157.0 (83.6 – 323.3)	275.0 (164.0 – 439.5)	0.014
HF supine position (ms^2)	111.0 (50.5 – 368.5)	141.0 (65.0 – 342.5)	0.873
LF/HF supine position (ms^2)	1.5 (0.7 – 2.4)	1.8 (0.9 – 4.1)	0.054
LF orthostatism (ms^2)	161.5 (71.5 – 333.6)	242.0 (128.5 – 375.0)	0.075
HF orthostatism (ms^2)	66.0 (29.0 – 229.5)	91.0 (33.5 – 247.1)	0.898
LF/HF orthostatism (ms^2)	1.8 (1.0 – 3.3)	2.4 (1.2 – 6.1)	0.096

SD: standard deviation; LH: low frequency; HF: high frequency; LH/HF: low frequency/high frequency ratio; ms: milliseconds. Mann-Whitney test; Q1: 25th percentile; Q3: 75th percentile

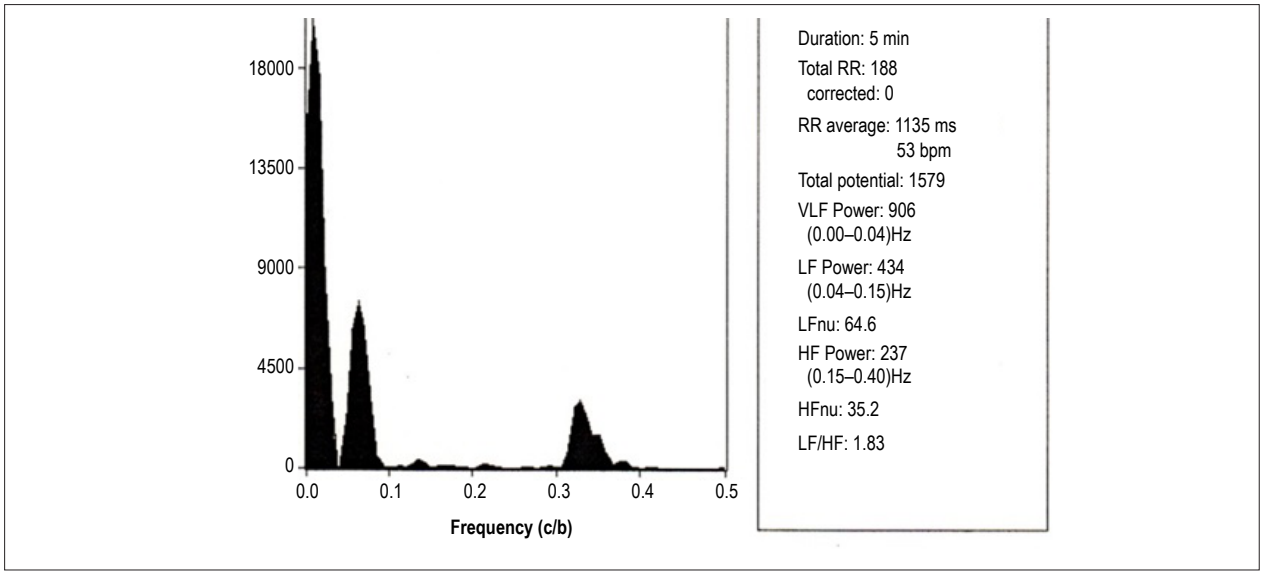

Figure 1 – *Spectral analysis of a male patient (67 years of age) with orthostatic hypotension in supine position. RR: number of QRS in sinus rhythm; VLF: very low frequency; LF: low frequency; HF: high frequency; HFnu: HF normalized unit.*

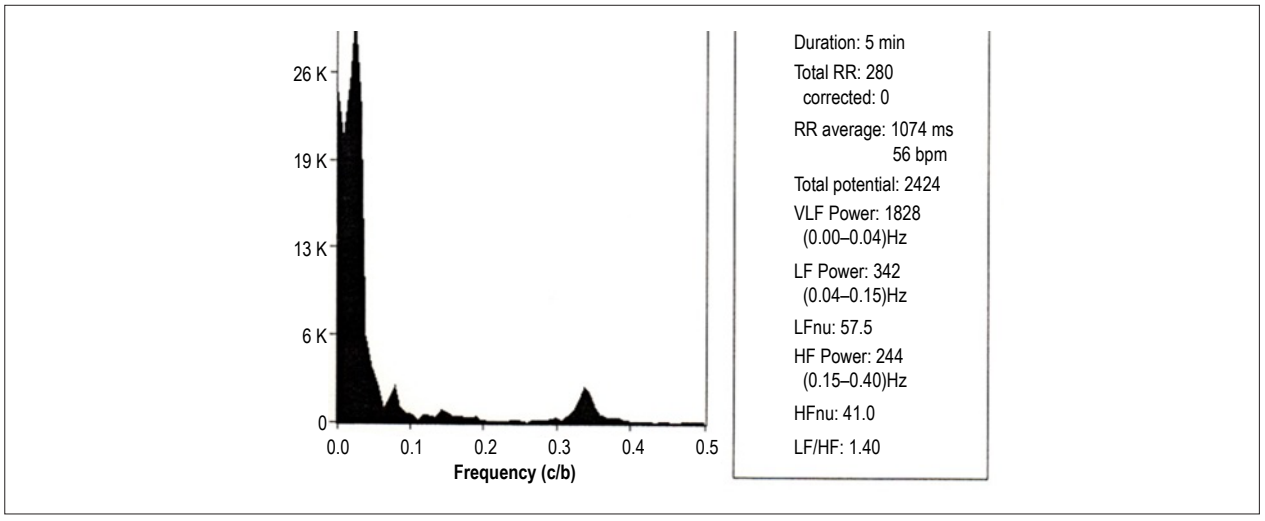

Figure 2 – *Spectral analysis of a male patient (67 years of age) with orthostatic hypotension (same of Figure 1) in orthostatic position, showing a decrease in low frequency (LF) component and in the LF/high frequency (HF) ratio, in relation to supine position. RR: number of QRS in sinus rhythm; VLF: very low frequency; HFnu: HF normalized unit.*

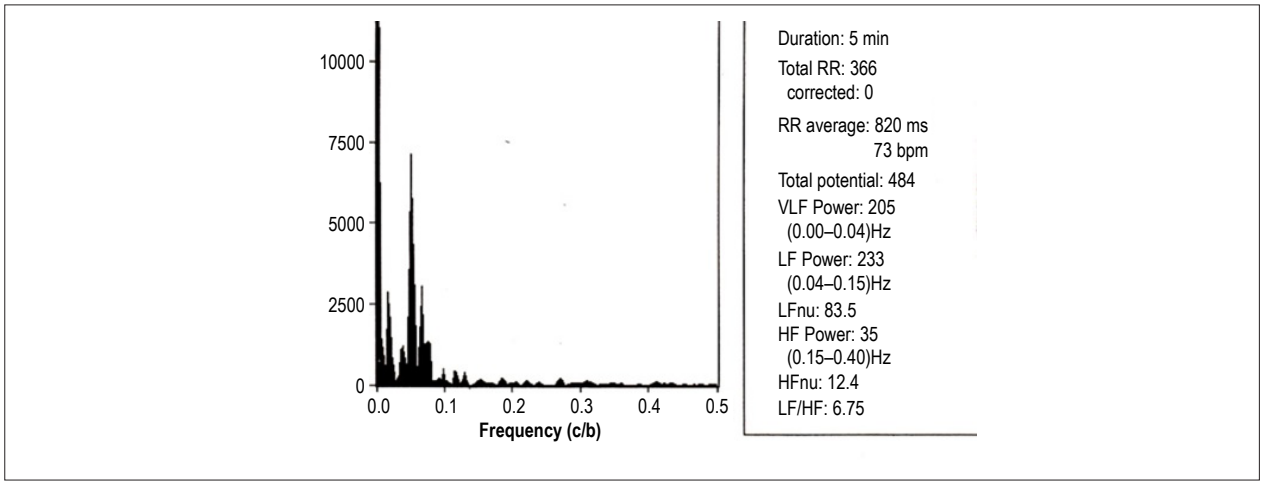

Figure 3 – *Spectral analysis of a female patient (62 years of age) without orthostatic hypotension in supine position. RR: number of QRS in sinus rhythm; VLF: very low frequency; LF: low frequency; HF: high frequency; HFnu: HF normalized unit.*

of BP and HR. Increases in norepinephrine plasma levels, decreased sensitivity of beta-adrenergic receptors, decreased vasomotor response mediated by alpha receptors, and reduced baroreflex response and parasympathetic tone contribute to the occurrence of OH in the elderly.[8,9] Therefore, while approximately 5% of middle-aged adults have OH,[16] the prevalence increases to nearly 41% in those aged 80 years or older.[6] In the present study, patients with and without OH were age-matched and all of them were younger than 60 years, and hence results were not affected by age.

Previous studies have shown different results in the prevalence of OH and its association with gender, according to age and study setting. In a study conducted in the 90's decade, Rutan et al.[17] evaluated a population of 5,201 elderly subjects (≥65 years), with an OH prevalence of 18.2% and no difference between the sexes. In patients hospitalized for OH, the prevalence was higher in men (55.3% in the age range of 65 – 74 years), although 54% of patients aged 75 years or older were women, with a total of 15,858 admissions for OH in a year.[18] In our population, there was a predominance of men in the group of patients with OH; however, Spearman's correlation coefficient was 0.27, i.e., of small magnitude, which suggest that there was no statistical difference in sex between the groups. Also, sex was not an OH predictor in multivariate analysis.

Studies have demonstrated the importance of rises in HR in the orthostatic position, its association with increased sympathetic activity and higher orthostatic tolerance.[19] Nevertheless, the role of HR in the supine position in OH patients has not been well established yet. Changes in autonomic tone[13] and sinus node

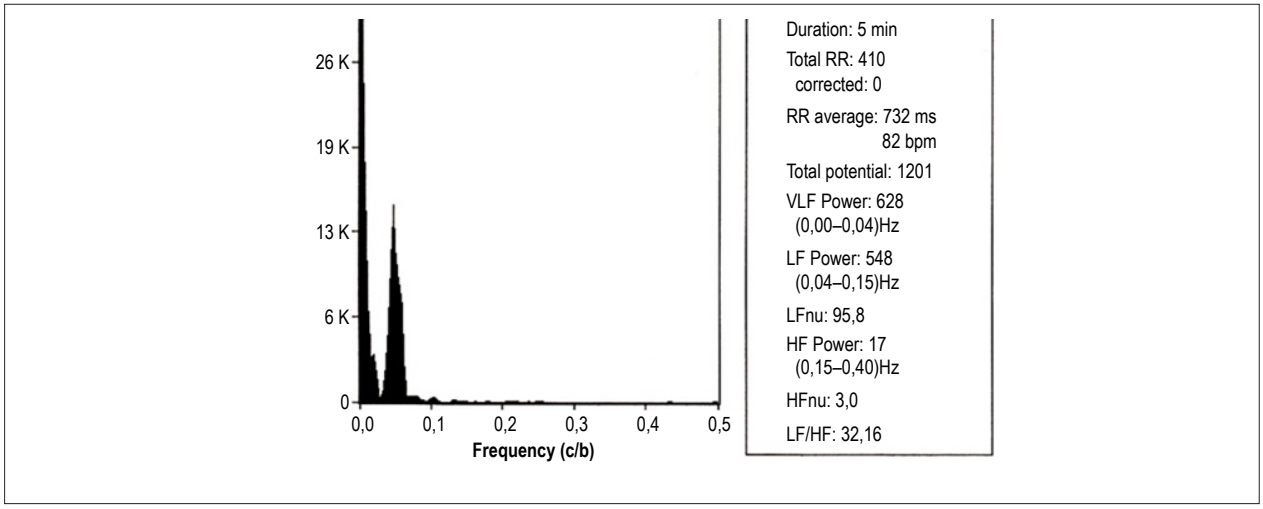

Figure 4 – *Spectral analysis of a female patient (62 years of age) without orthostatic hypotension (the same of Figure 3) in orthostatic position, showing an increase in low frequency (LF) component and in the LF/high frequency (HF) ratio, in relation to supine position. VLF: very low frequency; RR: number of QRS in sinus rhythm; VLF: very low frequency; HFnu: HF normalized unit.*

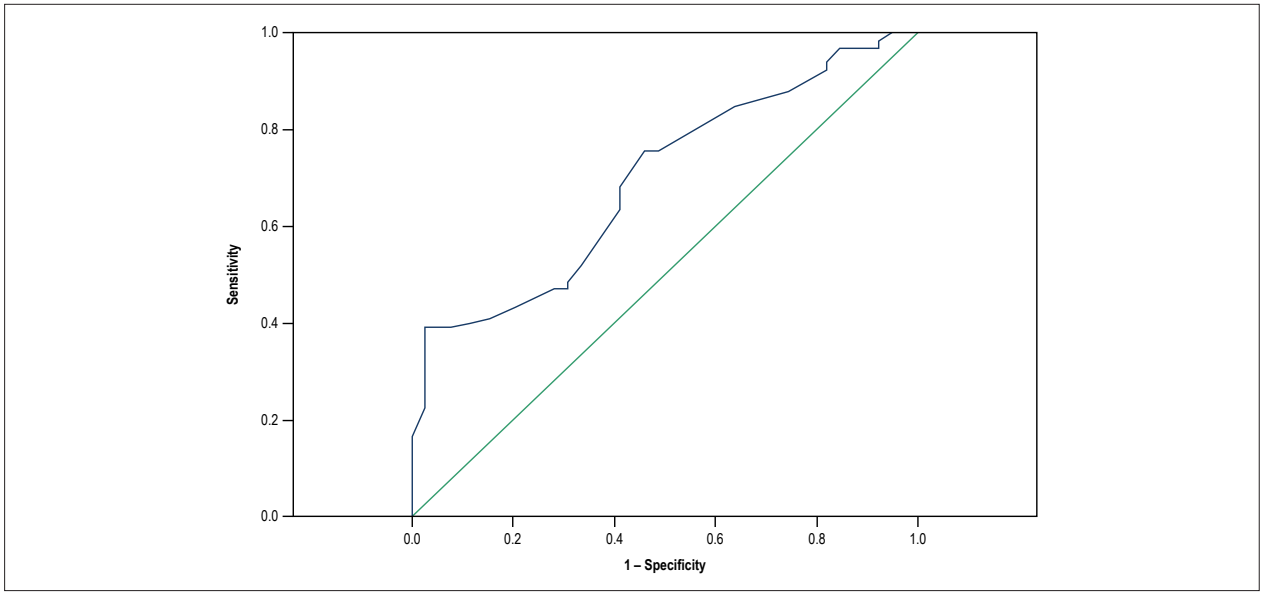

Figure 5 – *Receiver operating characteristic curve of heart rate in the supine position (blue line), considering the stable variable postural response without orthostatic hypotension.*

dysfunction[20] may be associated with reduced HR in supine position in elderly patients, regardless of OH. In the study population, when this variable was analyzed, median HR in supine position in the case group was significantly lower than in control group. In addition to the changes already described, another factor that may be associated with differences between the groups would be the use of beta-blockers. These medications have a negative chronotropic effect on HR.[21] However, in the present study, no difference was found in the use of most of these drugs between the groups. Significant difference was found in the use of ACE inhibitors, which decrease vascular resistance but have no substantial effect on HR, despite restoration of parasympathetic tone with the use of the drug in hypertensive patients.[22]

In light of this, analysis of HRV was important for the study of HR profile in elderly subjects with OH in supine position. With change of position, as expected,[10] there was a decrease in HF and increase in LF/HF in all patients, without an increase in the LF component. There is a decline in baroreflex and HRV with age in both sexes, resulting in autonomic dysfunction.[6,8,13] A U-curve has been used to describe the progressive decrease of HRV with aging, which reaches its nadir in the sixth or seventh decade of life, followed by progressive increase, which is determinant for longevity from those decades on.[23-26] Therefore, to avoid age bias, the case and control groups were matched by age. Although previous studies on OH and HRV[11-13,27] have shown different results, it is possible to

infer from their results that autonomic system and baroreflex dysfunction are associated with OH. Harrington et al.[11] evaluated baroreflex sensitivity by digital plethysmography in the elderly – 75 normotensive and 64 hypertensive patients, without medications. The authors reported reduced baroreflex, with impairment of HF component. Kawaguchi et al.[12] shown a decrease in the LF/HF ratio and decreased cerebral perfusion measured by infrared spectroscopy in a group of 80 elderly subjects after passive standing. A more recent study on hypertensive patients,[27] 18 with OH and 64 without OH (mean age of 74.2 years), demonstrated that, despite lower systolic volume in those with OH, no significant differences in change in the LF/HF ratio after orthostatism were found, which is in agreement with our results. Barantke et al.[13] demonstrated a decline in all components of HRV with age, and an association between LF and baroreflex sensitivity in orthostatic position. This evidence that LF reflects baroreflex function rather than sympathetic innervation measured by 6-[18F] fluorodopamine has also been demonstrated by other authors.[28,29] Consequently, our findings suggest the hypothesis that the lack of increase in HR and LF with orthostatism may be related to baroreflex dysfuntion,[27,30] which predisposes to OH.

Blood pressure may also influence the prevalence of OH. Studies on hypertensive elderly patients demonstrated higher prevalence of OH in those with higher BP levels. Gangavati et al.[31] followed 722 elderly patients and found a prevalence of OH of 19% in participants with uncontrolled hypertension (BP ≥ 140/90 mmHg) and of 5% in those with controlled hypertension (BP < 140/90 mmHg). Mean age was 78 years in both groups. Valbusa et al.[32] reported similar findings but with different OH prevalence – the authors evaluated 994 patients with mean age of 88 years; the prevalence of OH was 13% in hypertensive patients with BP ≤ 140/90 mmHg and 23% in those with BP > 140 mmHg. In the present study, no difference between the groups was found in baseline BP in the supine position or in the prevalence of hypertension.

Regarding the association of OH with the use of medications, in a study with 189 patients aged 75 or older with OH, the prevalence of OH was of 35%, 58%, 60% and 65% in those patients using none, one, two, three or more medications, respectively. Although the study included medications other than anti-hypertensive agents, hydrochlorothiazide was associated with higher prevalence of OH (65%).[33] Analysis of a cohort of 3,775 women aged between 60 and 80 years demonstrated that the use of three or more anti-hypertensive agents had a 2.2 greater chance of developing OH in comparison with patients taking no medications.[34] In the present study, although the use of ACE inhibitors was significantly higher in patients with OH, this drug was not a predictor of this condition, which may be explained by its role on autonomic modulation.[22]

Diabetes mellitus may also result in autonomic dysfunction.[4] In our study, its prevalence was 17.1% in the population, with no difference between the groups and, thereby, had no influence on the results.

As previously reported, clinical manifestations of OH that may lead to falls, fractures, presyncope and syncope cause functional impairment in the elderly, which is known as frailty syndrome.[3-5] In the current study, previous symptoms including dizziness, presyncope and syncope were more frequent in patients in the case group and, according to the literature, these symptoms may be associated with frailty syndrome and lower BP values after orthostatism.[4,35]

Data in the literature on the association between frailty and risk for cardiovascular disease are scarce. A study on 1,622 elderly men aged between 71 and 92 years showed an association between frailty and increased risk factors, including waist circumference, lipid profile and SAH, despite similar prevalence of these factors between frail and non-frail elderly persons. Cardiovascular risk scores were not calculated, but this association was independent of established cardiovascular disease.[36] In the present study, patients were assessed for cardiovascular risk using the Framingham[14] and PROCAM scores,[15] with no difference between the groups. It is worth mentioning that 75 years is the age limit for the use of these scores.

Limitations

The main limitations of this study were the number of patients and the fact that they were assessed only once, which made the evaluation of reproducibility of results impossible. The use of digital plethysmography for measurement of BP levels in orthostatic position would enable the early detection of OH. Besides, we did not evaluate the very low frequency (VLF) component of HRV, associated with renin-angiotensin-aldosterone system, thermoregulation and peripheral vasomotor tone.

Conclusions

In the study population, lower LF and HR in the supine position was found in patients with OH, regardless of gender, BP in supine position and use of beta-blockers. HR in the supine position was an independent predictor for OH with an odds ratio of 3.23 for values lower than 61 bpm.

Author contributions

Conception and design of the research and Statistical analysis: Silva RMFL; Acquisition of data and Analysis and interpretation of the data: Silva RMFL, Miranda CES, Barbosa MT, Bicalho MAC; Writing of the manuscript: Silva RMFL, Miranda CES; Critical revision of the manuscript for intellectual content: Silva RMFL, Miranda CES, Barbosa MT.

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 master submitted by Carlos Eduardo de Souza Miranda, from Universidade Federal de Minas Gerais.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Federal University of Minas Gerais under the protocol number 01933812.0.0000.5149. 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.

References

1. Moya A, Sutton R, Ammirati F, Blanc JJ, Brignole M, Dahm JB, et al; Task Force for the Diagnosis and Management of Syncope; European Society of Cardiology (ESC); European Heart Rhythm Association (EHRA); Heart Failure Association (HFA); Heart Rhythm Society (HRS). Guidelines for diagnosis and management of syncope (version 2009). Eur Heart J. 2009;30(21):2631-71. doi: 10.1093/eurheartj/ehp298.
2. Freeman R, Wieling W, Axelrod FB, Benditt E, Benarroch E, Biaggioni I, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Clin Auton Res. 2011;21(2):69-72. doi: 10.1007/s10286-011-0119-5.
3. Ricci F, Fedorowski A, Radico F, Romanello M, Tatasciore A, Di Nicola M, et al. Cardiovascular morbidity and mortality related to orthostatic hypotension: a meta-analysis of prospective observational studies. Eur Heart J. 2015;36(25):1609-17. doi: 10.1093/eurheartj/ehv093.
4. Ricci F, De Caterina R, Fedorowski A. Orthostatic hypotension: epidemiology, prognosis, and treatment. J Am Coll Cardiol. 2015;66(7):848-60. doi: 10.1016/j.jacc.2015.06.1084.
5. Finucane C, Kenny RA. Falls risk, orthostatic hypotension, and optimum blood pressure management: is it all in our heads? Am J Hypertens. 2017;30(2):115-7. doi: 10.1093/ajh/hpw129.
6. Finucane C, O'Connell MD, Fan CW, Savva GM, Soraghan CJ, Nolan H, et al. Age-related normative changes in phasic orthostatic blood pressure in a large population study: findings from The Irish Longitudinal Study on Ageing (TILDA). Circulation. 2014;130(20):1780-9. doi: 10.1161/CIRCULATIONAHA.114.009831.
7. Kuo TB, Lin T, Yang CC, Li CL, Chen CF, Chou P. Effect of aging on gender differences in neural control of heart rate. Am J Physiol. 1999;277(6 Pt 2):H2233-9. PMID: 10600841.
8. Monahan KD. Effect of aging on baroreflex function in humans. Am J Physiol Regul Integr Comp Physiol. 2007;293(1):R3-R12. doi: 10.1152/ajpregu.00031.2007.
9. Mattace-Raso FU, van den Meiracker AH, Bos WJ, van der Cammen TJ, Westerhof BE, Elias-Smale S, et al. Arterial stiffness, cardiovagal baroreflex sensitivity and postural blood pressure changes in older adults: the Rotterdam Study. J Hypertens. 2007; 25(7):1421-6. doi: 10.1097/HJH.0b013e32811d6a07.
10. Task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Circulation. 1996;93(5):1043-65. doi: https://doi.org/10.1161/01.CIR.93.5.1043.
11. Harrington F, Murray A, Ford GA. Relationship of baroreflex sensitivity and blood pressure in an older population. J Hypertens. 2000;18(11):1629-33. PMID: 11081776.
12. Kawaguchi T, Uyama O, Konishi M, Nishiyama T, Iida T. Orthostatic hypotension in elderly persons during passive standing: a comparison with young persons. J Gerontol A Biol Sci Med Sci. 2001;56(5):M273-80. PMID: 11320106.
13. Barantke M, Krauss T, Ortak J, Lieb W, Reppel M, Burdorf C, et al. Effects of gender and aging on differential autonomic responses to orthostatic maneuvers. J Cardiovasc Electrophysiol. 2008;19(12):1296-303. doi: 10.1111/j.1540-8167.2008.01257.x.
14. Wilson PW, D`Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation. 1998;97(18):1837-47. doi: https://doi.org/10.1161/01.CIR.97.18.1837.
15. Assmann G, Cullen P, Schulte H. Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the Prospective Cardiovascular Munster (PROCAM) study. Circulation. 2002;105(3):310-5. doi: https://doi.org/10.1161/hc0302.102575. Erratum in: Circulation. 2002;105(7):900.
16. Rose KM, Eigenbrodt ML, Biga RL, Couper DJ, Light KC, Sharrett AR, et al. Orthostatic hypotension predicts mortality in middle-aged adults: the Atherosclerosis Risk In Communities (ARIC) Study. Circulation. 2006;114(7):630-6. doi: 10.1161/CIRCULATIONAHA.105.598722.
17. Rutan GH, Hermanson B, Bild DE, Kittner SJ, LaBaw F, Tell GS. Orthostatic hypotension in older adults. The Cardiovascular Health Study. CHS Collaborative Research Group. Hypertension. 1992;19(6 Pt 1):508-19. doi: https://doi.org/10.1161/01.HYP.19.6.508.
18. Shibao C, Grijalva CG, Raj SR, Biaggioni I, Griffin MR. Orthostatic hypotension-related hospitalizations in the United States. Am J Med. 2007;120(11):975-80. doi: 10.1016/j.amjmed.2007.05.009.
19. Convertino VA. Neurohumoral mechanisms associated with orthostasis: reaffirmation of the significant contribution of the heart rate response. Front Physiol. 2014 Jun 30;5:236. doi: 10.3389/fphys.2014.00236.
20. Jensen PN, Gronroos NN, Chen LY, Folsom AR, deFilippi C, Heckbert SR, et al. Incidence of and risk factors for sick sinus syndrome in the general population. J Am Coll Cardiol. 2014;64(6):531-8. doi: 10.1016/j.jacc.2014.03.056.
21. Ram CV. Beta-blockers in hypertension. Am J Cardiol. 2010;106(12):1819-25. doi: 10.1016/j.amjcard.2010.08.023.
22. Menezes Ada S Jr, Moreira HG, Daher MT. Analysis of heart rate variability in hypertensive patients before and after treatment with angiotensin II-converting enzyme inhibitors. Arq Bras Cardiol. 2004;83(2):169-72; 165-8. doi: http://dx.doi.org/10.1590/S0066-782X2004001400008.
23. Piccirillo G, Bucca C, Bauco C, Cinti AM, Michele D, Fimognari FL, et al. Power spectral analysis of heart rate in subjects over a hundred years old. Int J Cardiol. 1998;63(1):53-61. doi: https://doi.org/10.1016/S0167-5273(97)00282-9.
24. Zulfiqar U, Jurivich DA, Gao W, Singer DH. Relation of high heart rate variability to healthy longevity. Am J Cardiol. 2010;105(8):1181-5. doi: 10.1016/j.amjcard.2009.12.022. Erratum in: Am J Cardiol. 2010;106(1):142.
25. Nicolini P, Ciulla MM, De Asmundis C, Magrini F, Brugada P. The prognostic value of heart rate variability in the elderly, changing the perspective: from sympathovagal balance to chaos theory. Pacing Clin Electrophysiol. 2012;35(5):622-38. doi: 10.1111/j.1540-8159.2012.03335.x.
26. Almeida-Santos MA, Barreto-Filho JA, Oliveira JL, Reis FP, da Cunha Oliveira CC, Sousa AC. Aging, heart rate variability and patterns of autonomic regulation of the heart. Arch Gerontol Geriatr. 2016 Mar-Apr;63:1-8. doi: 10.1016/j.archger.2015.11.011.
27. Toba A, Ishikawa J, Harada K. Orthostatic hypotension and association of arterial compliance in elderly patients with hypertension: a pilot study. Blood Press Monit. 2017;22(5):274-8. doi: 10.1097/MBP.0000000000000274.
28. Moak JP, Goldstein DS, Eldadah BA, Saleem A, Holmes C, Pechnik S, et al. Supine low-frequency power of heart rate variability reflects baroreflex function, not cardiac sympathetic innervation. Heart Rhythm. 2007;4(12):1523-9. doi: 10.1016/j.hrthm.2007.07.019.

29. Rahman F, Pechnik S, Gross D, Sewell L, Goldstein DS. Low frequency power of heart rate variability reflects baroreflex function, not cardiac sympathetic innervations. Clin Auton Res. 2011;21(3):133-41. doi: 10.1007/s10286-010-0098-y.

30. Joseph A, Wanono R, Flamant M, Vidal-Petiot E. Orthostatic hypotension: a review. Nephrol Ther. 2017 Apr;13 Suppl 1:S55-S67. doi: 10.1016/j.nephro.2017.01.003.

31. Gangavati A, Hajjar I, Quach L, Jones RN, Kiely DK, Gagnon P, et al. Hypertension, orthostatic hypotension, and the risk of falls in a community-dwelling elderly population: the maintenance of balance, independent living, intellect, and zest in the elderly of Boston Study. J Am Geriatr Soc. 2011;59(3):383-9. doi: 10.1111/j.1532-5415.2011.03317.x. Erratum in: J Am Geriatr Soc. 2011;59(5):960.

32. Valbusa F, Labat C, Salvi P, Vivian ME, Hanon O, Benetos A; PARTAGE investigators. Orthostatic hypotension in very old individuals living in nursing homes: the PARTAGE study. J Hypertens. 2012;30(1):53-60. doi: 10.1097/HJH.0b013e32834d3d73.

33. Poon O, Braun U. High prevalence of orthostatic hypotension and its correlation with potentially causative medications among elderly veterans. J Clin Pharm Ther. 2005;30(2):173-8. doi: 10.1111/j.1365-2710.2005.00629.x.

34. Kamaruzzaman S, Watt H, Carson C, Ebrahim S. The association between orthostatic hypotension and medication use in the British Women's Heart and Health Study. Age Ageing. 2010;39(1):51-6. doi: 10.1093/ageing/afp192.

35. O'Connell MD, Savva GM, Fan CW, Kenny RA. Orthostatic hypotension, orthostatic intolerance and frailty: the Irish Longitudinal Study on Aging-TILDA. Arch Gerontol Geriatr. 2015;60(3):507-13. doi: 10.1016/j.archger.2015.01.008.

36. Ramsay SE, Arianayagam DS, Whincup PH, Lennon LT, Cryer J, Papacosta AO, et al. Cardiovascular risk profile and frailty in a population-based study of older British men. Heart. 2015; 101(8):616-22. doi: 10.1136/heartjnl-2014-306472.

Mid-Term Results of Surgical Treatment of Atrial Fibrillation in Valvular Heart Disease Assesed by Speckle Tracking Echocardiography

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Abstract

Background: Atrial fibrillation frequently affects patients with valvular heart disease. Ablation of atrial fibrillation during valvular surgery is an alternative for restoring sinus rhythm.

Objectives: This study aimed to evaluate mid-term results of successful atrial fibrillation surgical ablation during valvular heart disease surgery, to explore left atrium post-ablation mechanics and to identify predictors of recurrence.

Methods: Fifty-three consecutive candidates were included. Eligibility criteria for ablation included persistent atrial fibrillation <10 years and left atrium diameter < 6.0 cm. Three months after surgery, echocardiogram, 24-hour Holter monitoring and electrocardiograms were performed in all candidates who maintained sinus rhythm (44 patients). Echo-study included left atrial deformation parameters (strain and strain rate), using 2-dimensional speckle-tracking echocardiography. Simultaneously, 30 healthy individuals (controls) were analyzed with the same protocol for left atrial performance. Significance was considered with a P value of < 0.05.

Results: After a mean follow up of 17 ± 2 months, 13 new post-operative cases of recurrent atrial fibrillation were identified. A total of 1,245 left atrial segments were analysed. Left atrium was severely dilated in the post-surgery group and, mechanical properties of left atrium did not recover after surgery when compared with normal values. Left atrial volume (≥ 64 mL/m^2) was the only independent predictor of atrial fibrillation recurrence (p = 0.03).

Conclusions: Left atrial volume was larger in patients with atrial fibrillation recurrence and emerges as the main predictor of recurrences, thereby improving the selection of candidates for this therapy; however, no differences were found regarding myocardial deformation parameters. Despite electrical maintenance of sinus rhythm, left atrium mechanics did not recover after atrial fibrillation ablation performed during valvular heart disease surgery. (Arq Bras Cardiol. 2018; 110(4):312-320)

Keywords: Ablation Techniques; Atrial Fibrillation; Heart Valve Diseases; Cryosurgery; Echocardiography.

Introduction

Atrial fibrillation (AF) is a serious and frequent problem in valvular heart disease (VHD) affecting more than 30% of these patients. VHD leads to pressure and/or volume overload of the atria, especially in the left atrium (LA) in left-sided disease. AF is associated with higher morbidity and mortality in general population, but even more in VHD patients, requiring low threshold of anticoagulation because of higher risk of thromboembolism. AF also affects the decision making for selection of prosthesis type.[1,2]

AF ablation during cardiac surgery has been demonstrated as a safe and effective procedure restoring sinus rhythm (SR). Although the original Cox-Maze procedure was described in patients with lone AF, its use has expanded to patients with associated organic heart disease.[3] According to some authors, success rates of the procedure can exceed 80%. However, there are few data on the results of this technique in valvular patients with persistent AF.[4,5]

Myocardial strain and strain rate (strainR) represent the magnitude and rate, respectively, of myocardial deformation. Both atrial strain and strainR, obtained using either Doppler tissue imaging (DTI) or two-dimensional speckle-tracking echocardiography, have proved to be feasible and reproducible techniques to evaluate LA mechanics.[6]

The aims of this study were to evaluate mid-term results after successful surgical ablation (SA) of AF in VHD patients, to explore LA mechanics using ultrasound strain and strainR imaging after SA of AF during VHD surgery and to identify clinical and echocardiographic predictors of recurrence during follow-up.

Methods

Patient eligibility

We prospectively included candidates to surgical ablation, who underwent valvular heart surgery between May 2008 and May 2012 in our institution.

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Patient eligibility criteria for AF surgery included: persistent AF of less than ten years of evolution and left atrial anteroposterior (AP) diameter at preoperative transthoracic echocardiogram in long axis view of less than 6.0 cm.[3,7] All candidates were adequately informed and signed informed consent form for the procedure, according to the local ethics committee.

Fifty-three consecutive candidates who underwent valvular heart surgery were included to surgical ablation.

Success of AF ablation procedure was considered when patients maintained SR at the time of discharge. All these patients were selected for initial follow up. After rhythm stabilization, which is considered to occur at least 3 months after surgery,[8] an echocardiogram was scheduled, and ambulatory 24 hour Holter monitoring and electrocardiograms were systematically performed in all candidates who remained in SR (44 patients). Holter monitoring was programmed one month after the echocardiographic study, and electrocardiograms were made during clinical visits (at least two visits during the first year of follow up). Patients with persistent AF during the first 3 months after surgery were excluded from the follow-up.

Surgical technique

All the procedures were carried out by full sternotomy and extracorporeal circulation.

Surgical technique for cryoablation was the same as previously described.[9] After aortic clamping, LA was opened when needed and left atrial appendage was ligated from its inside using a 3.0 monofilament suture. The cryoablation probe was placed for 60 s at a temperature between –100°C and –160°C. Lines were created surrounding pulmonary veins and also joining between these circles. Three more lines were performed: between the left pulmonary veins and the left appendage, between the left pulmonary veins and the P3 portion of the mitral annulus and between the tricuspid septal valve and the inferior cava.

In cases where left atriotomy was not needed (in isolated aortic interventions), high-intensity-focused-ultrasound (HIFU - Epicor) cardiac ablation was used. Epicor Medical Cardiac Ablation System (St Jude) is designed to deliver HIFU via an entirely epicardial approach and consists of an array of transducers positioned after proper sizing around the LA wall of the pulmonary vein orifices.[4]

Echocardiographic study

A Vivid 7 Dimension ultrasound system (GE Healthcare) was used for the transthoracic echocardiographic examination. All images and measurements were acquired with a MS4 matrix probe using the standard views according to the standards of the European Association of Echocardiography and the American Society of Echocardiography.[10,11]

Strain parameters were obtained during ventricular systole (LASs – LA systolic strain) and diastole (LASa – LA diastolic strain), and strainR parameters were obtained during early (LASRe – LA strainR early) and late (LASRa – LA strainR late) ventricular diastole (Figure 1) in 2 standard echo-views (apical 4- and 2-chamber views), using speckle-tracking echocardiography to avoid the angle-dependence of DTI.[6,12]

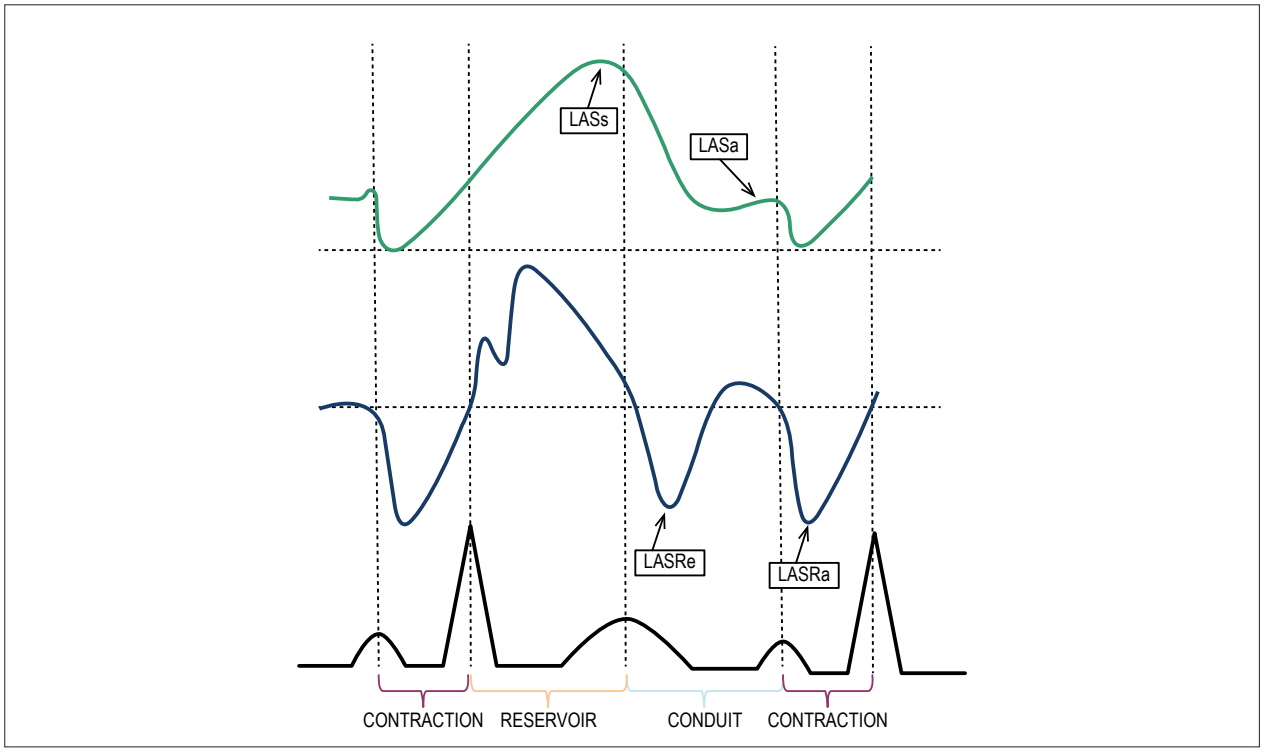

Figure 1 – *Left atrial phasic functions and their relationship with the cardiac cycle. Strain and strain rate curves are shown. During left ventricular (LV) systole and isovolumetric relaxation, left atrium (LA) works as a distensible reservoir accommodating blood flow from the pulmonary veins. During early LV diastole, LA behaves as a conduit that starts with mitral valve opening and terminates before LA contraction, allowing passive emptying during early ventricular diastole and diastasis. Finally, at end-diastole, LA acts as a muscular pump contributing to LV filling with active atrial contraction. (LASs: left atrial systolic strain; LASa: left atrial diastolic strain; LASRe: early left atrial strain rate; LASRa: late left atrial strain rate).*

In addition, 30 healthy individuals were analyzed following the same protocol in order to have a reference population for LA mechanics.

Two experienced observers carried out the measurements in both populations in different times, in order to determine intra- and inter-observer variability. Intra-observer variability was calculated with measurements of the same rater in different moments including random samples of either patients or healthy controls. The same 2D echocardiographic loops of random samples of both patients and healthy controls were used for inter-observer variability.

All images were digitally stored for offline analysis.

Definition of AF recurrence

AF recurrence was defined as presence of AF at any electrocardiogram or during at least 30 seconds in Holter monitoring.

Statistical analyses

Descriptive analyses were performed to explore study population characteristics. Categorical variables were reported as frequencies, and continuous variables with normal distribution were reported as mean ± SD. Median and interquartile range were used in cases of non-normality. Normal distribution of continuous variables was studied using Kolmogorv-Smirnov test.

Differences among cohorts were analyzed using Chi-square test for categorical variables (or Fisher´s exact test when the comparison group was < 30 individuals), and Student-*t*-test (or Mann-Whitney test if the comparison group was < 30 and in case of non-normal distribution) for the numerical ones.

Kaplan–Meier method was used for describing event free survival (AF) over time; the median was used as cutoff value to compare quantitative variables and differences between groups were investigated with the log-rank test. Those variables with p value < 0.15 were included for multivariate analyses using a Cox proportional hazard model.

Significance was considered with a p value of < 0.05.

Statistical analyses were performed using SPSS (Statistical Program for the Social Sciences [SPSS Inc., Chicago, USA]) version 15.0.

Intra- and inter-observer agreements in the speckle-tracking measurements were studied by regression analyses and calculation of the intraclass correlation coefficient. Bland Altman plots, combined with calculation of 95% limits of agreement were also generated. For this analysis MedCalc Statistical Software version 15.6.1 (MedCalc Software bvba, Ostend, Belgium) was employed.

Results

AF recurrence was identified in 9 out of 53 cases in the immediate post-surgery period (3 months). These 9 patients were excluded for subsequent follow-up.

The 44 patients with sustained SR after 3 months were included in the echocardiographic and rhythm follow-up. Baseline characteristics of this series are shown in Table 1.

Table 1 – Baseline characteristics of patients who maintained sinus rhythm in the immediate post-surgery period (3 months) (n = 44)

Characteristics	
Age (years)	69 ± 9
Female gender, n (%)	32 (73%)
Mitral surgery, n (%)	36 (82%)
Aortic surgery, n (%)	16 (37%)
Tricuspid intervention, n (%)	13 (29.5%)
Cryoablation, n (%)	36 (82%)
Antiarrhythmic treatment at discharge, n (%)	13 (29.5%)
ACE inhibitors at discharge, n (%)	21 (48%)
AF duration > 1 year before surgery, n (%)	26 (59%)
LA biplane volume (mL/m^2)	68 ± 22
AP LA diameter (mm/m^2)	28.9 ± 5
LVEF (%)	63 ± 12

ACE: angiotensin converting enzyme; AF: atrial fibrillation; AP: anteroposterior; LA: left atrium; LVEF: left ventricular ejection fraction.

The majority of the population underwent mitral surgery (28 patients, 63.6%), 8 (18.2%) mitral and aortic, and only 8 required exclusively aortic intervention. Mitral valve surgery included 34 prosthetic replacement procedures (26 mechanical and 8 biological), and two mitral valve repair surgeries. Valve replacement was the procedure employed in all patients with aortic disease (12 mechanical and 4 biological). There were 13 (29.5%) tricuspid annuloplasties using Carpentier-Edwards ring in all cases.

Overall, the study population showed preserved left ventricular ejection fraction (LVEF) and severely dilated LA. These patients were predominantly women with a mean age of 69 ± 9 years old (y.o.). Treatment at discharge included amiodarone in 30% of patients and angiotensin-converting-enzyme (ACE) inhibitors in 48% of patients.

After a mean follow up of 17 ± 2 months, 13 new post-operative cases of AF were identified.

Myocardial deformation parameters (strain and strainR) for assessing LA mechanical function after SA were obtained from 1,245 left atrial segments that were correctly analyzed (71% of possible). On average, 15.5% and 19.4% of 24 potential segments were analyzed per patient and per control, respectively. LA mechanical function (strain and strainR) was significantly worse in all patients than in normal population, independently of SR maintenance (Table 2, Figure 2).

As showed in Figure 3, intraclass correlation coefficient was always > 0.80, that represents good to excellent reliability and reproducibility of measurements.[13]

The univariate analyses showed a trend of AF recurrence related to age, mitral surgery, cryoablation and LA biplane volume (Table 3). Patients with mitral valve intervention and cryoablation were younger (66.6 ± 8.4 vs 73.6 ± 9.1 y.o.; p = 0.041). As patients treated with cryoablation were the same as those with mitral intervention, cryoablation was

Table 2 – Strain and strain rate parameters in the post-surgery group versus healthy individuals (Median and Interquatile Range were used because non-normal distribution of variables). P values were calculated with Mann-Whitney test

	LASs Median (P_{25}-P_{75})	LASa Median (P_{25}-P_{75})	LASRe Median (P_{25}-P_{75})	LASRa Median (P_{25}-P_{75})
Post-surgery group	16.9 (14.1-20.6)	5.9 (4.5-7)	-0.55 (-0.45- -0.67)	-0.41 (-0.56- -0.25)
Control group	42.5 (36.3-48.8)	13.1 (11.6-16.2)	-1.83 (-1.4- -2)	-1.6 (-1.8- -1.4)
p	< 0.001	< 0.001	< 0.001	< 0.001

LASe: LA systolic strain; LASa: LA diastolic strain; LASRe: LA early strain rate; LASRa: LA late strain rate

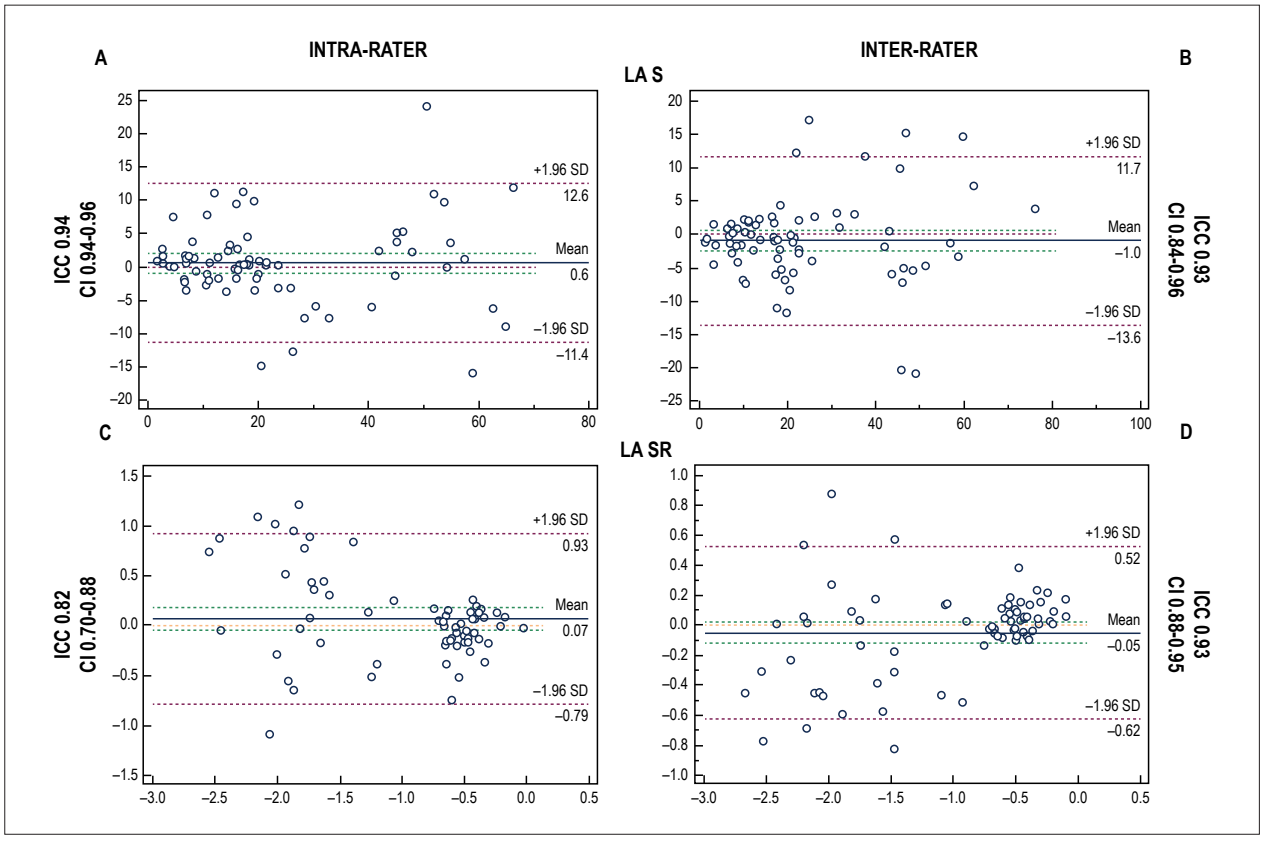

Figure 2 – *Intraclass correlation coefficient calculated (ICC) and Bland Altman difference plot combined with calculation of 95% limits of agreement (CI) of the intra-rater (A,C) and inter-rater (B,D) agreement of LA strain (LA S) and LA strain rate (LA SR)*

not included in further analyses to avoid collinearity in the multivariate analysis. No association was found between deformation parameters and AF recurrence.

As can be seen in Figure 4, employing the univariate log rank test, AF recurrence seems to be associated with: larger LA volume (p = 0.030), older age (p = 0.027), and inversely, with mitral valve intervention (p = 0.006).

A Cox proportional hazard model was built to explore potential sources of confusion and interactions. After SA of AF, LA volume was the only parameter associated with sustained SR (p = 0.028). Mitral surgery (p = 0.056) and age (p = 0.412) were not significantly associated with SR maintenance in the multivariate analyses.

Discussion

AF is the most common arrhythmia in general population and is even more common in VHD patients. This arrhythmia is cause of symptoms, hospital admissions, adverse events (systemic embolisms, side effects of antiarrhythmic drugs, etc.) and therefore, has a high impact in survival and quality of life. In addition, the presence of AF determines the necessity for antithrombotic therapy, and even the selection of the type of prosthesis.[1,2]

This study was conducted in patients who would otherwise have been chosen to heart rate control. Due to the scarcity of data about this treatment in "pure" VHD series, the current study may provide novel insights in this clinical

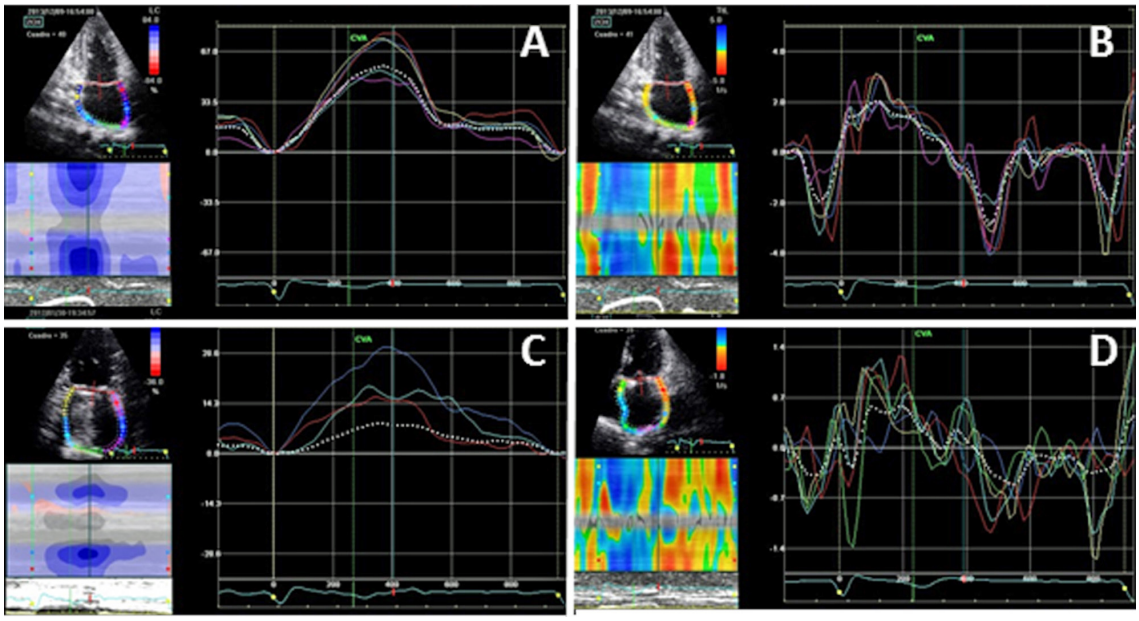

Figure 3 – *Strain and strain rate curves in a healthy individual (A and B, respectively) and in a post-surgery patient (C and D, respectively).*

Table 3 – Univariate analysis

	AF recurrence n = 13	SR maintenance n = 31	p (Univariate)
LA biplane volume (ml/m^2)	76.4 ± 25.5	63.7 ± 19.2	0.059
Age (years)	71.5 ± 7	66 ± 9	0.055
Mitral surgery	9 (25%)	27 (75%)	0.087
Antiarrhythmic treatment at discharge	3 (23%)	10 (77%)	0.498
ACE inhibitors at discharge	6 (28.6%)	15 (71.4%)	0.454
AF duration > 1 year before surgery	9 (34.6%)	17 (65.4%)	0.748
LASs*	14.1 (13.1-20.1)	17.2 (15.4-21.4)	0.961
LASa*	5.6 (3.3-6.3)	5.9 (4.7-7.4)	0.385
LASRe*	-0.5 (-0.45- -0.67)	-0.5 (-0.45- -0.67)	0.965
LASRa*	-0.4 (-0.25- -0.59)	-0.4 (-0.25- -0.58)	0.961

P values were calculated with the use of the Mann–Whitney or Fisher´s exact tests. (*) Variables with non-normal distribution (median and intercuartile range [P_{25}-P_{75}]). ACE: angiotensin converting enzyme; AF: atrial fibrillation; LA: left atrium; LASs: LA systolic strain; LASa: LA diastolic strain; LASRe: early LA strain rate; LASRa: late LA strain rate.

setting. We found that after 28 months, 50% of VHD patients with initial successful ablation remained in SR.

Veasey et al.[14] reported rates of SR of 74% in paroxysmal AF and 51% in persistent AF; nevertheless, the mean follow-up time was only 6 months, and, 39% of these patients had exclusively coronary artery bypass surgery. Similar results were found by Gaynor et al.[15] and Budera et al.;[16] 71% of patients had sustained SR after 6 months and 53.2% after one year respectively, but, these series included patients with lone AF surgery and revascularization for ischemic heart disease. Beukema et al.[17] reported one of the largest series including 285 patients with structural heart disease, finding that SR was present in 57.1% of patients after 5 years of follow- up; however, this study does not state the rate of patients with VHD.

The consensus statement of the American Society of Echocardiography and the European Association of Echocardiography suggests that LA mechanics can be assessed after AF to predict the maintenance of sinus rhythm and after percutaneous atrial septal defect repair. In addition, LA mechanics may offer suitable parameters to identify patients

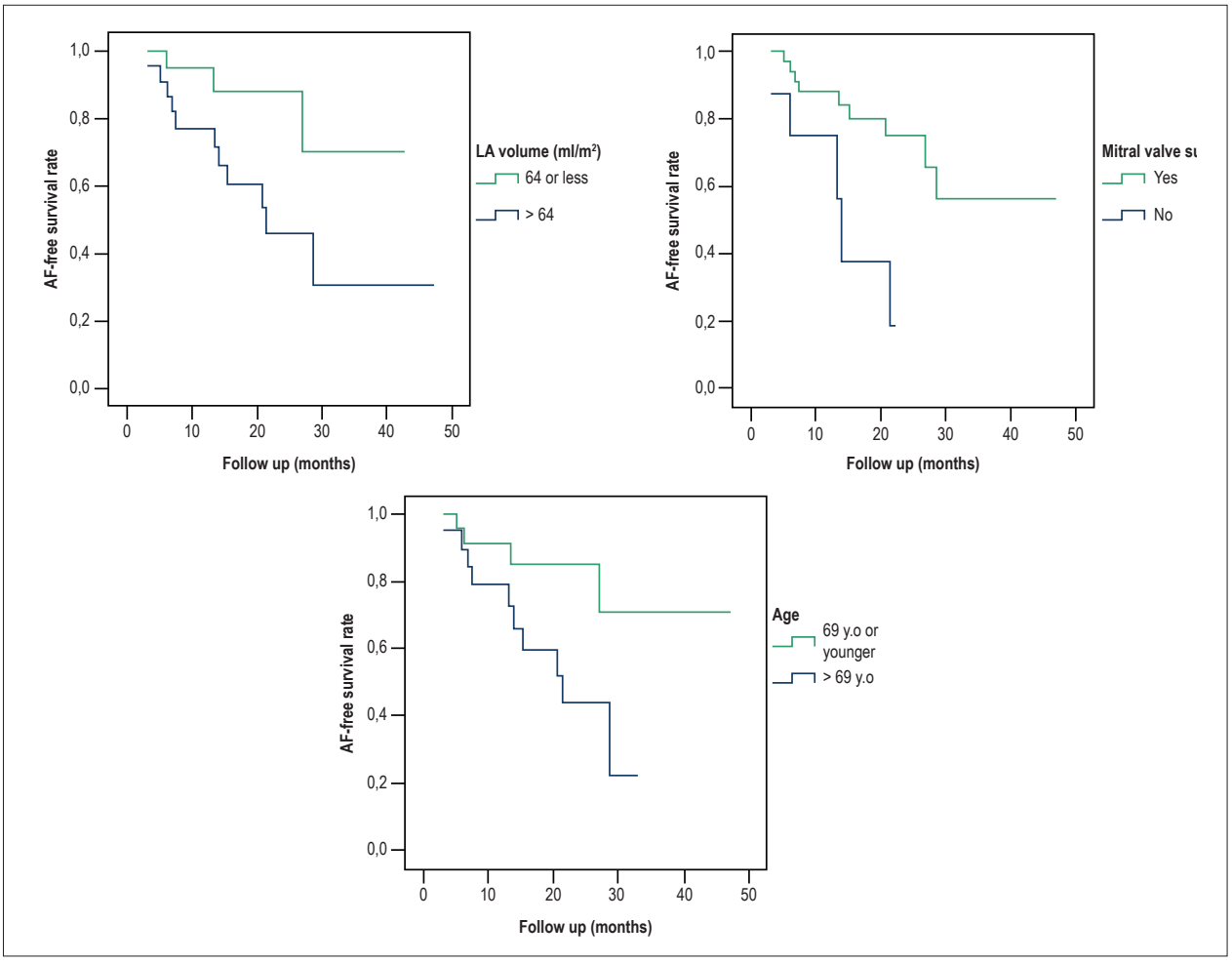

Figure 4 – *Log-rank test for comparison of Kaplan-Meier curves according to mitral valve surgery (p = 0.006), age > 69 years old (p = 0.027) and left atrial volume > 64 ml/m² (p = 0.030). AF: atrial fibrillation; LA: left atrial; y.o.: years old*

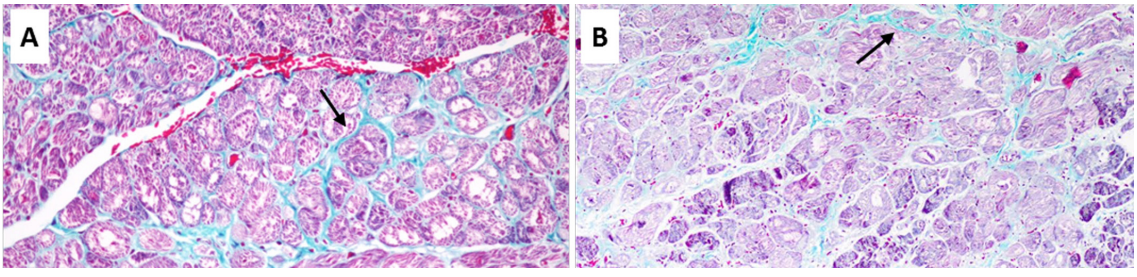

Figure 5 – *Masson´s Trichrome. Collagen fibers are stained blue. A) AF recurrence 6 days after ablation. Abundant atrial fibrosis (arrow) of perivascular predominance. B) Sinus rhythm maintenance during follow-up. Mild atrial fibrosis (arrow).*

at risk for LA regional failure or arrhythmias or to assess LA characteristics in patients with LA dilatation of undetermined cause.[18] LA strain has also been used to predict post-operative AF after mitral valve intervention.[19] However, there are no previous data describing LA mechanics after concomitant AF surgical ablation in VHD patients or series aiming to obtain the relationship between recurrence and atrial mechanics in this group of patients.

We speculate that the lack of association of LA strain and strainR parameters with AF postoperative recurrence may be explained by severe atrial dilation with extensive areas of fibrosis before surgery in both responders and non-responders to AF ablative techniques. Very large areas of atrial fibrosis may result in an important decrease in atrial mechanics, as shown by deformation parameters of patients included in this study in comparison with healthy individuals. Comparisons between responders and non-responders to AF are limited by the very low parameters of atrial deformation in all patients, which affects the sensitivity of deformation parameters to predict AF recurrences. However, the more fibrosis, the less likely it is to maintain SR. For illustrating this hypothesis, in Figure 5, we compare the anatomopathological characteristics of a patient with more extensive fibrosis and AF recurrence (Figure 5A) with another in SR during follow-up (Figure 5B). Larger studies and inclusion of LA tissue sampling should be necessary to demonstrate this hypothesis.

In accordance with prior reports,[20] in the current study, larger LA was associated with AF recurrence, suggesting that patients who could benefit more from this technique are those with LA volume < 64 ml/m^2. Another novel contribution of the series presented here, is that despite the fact that LA diameter has been traditionally considered one of the major inclusion criteria for candidate selection, only LA volume appears as a predictor of AF recurrence. To the best of our knowledge, the prognostic value of LA biplane volume to predict recurrences after AF cryoablation in VHD patients has not been previously reported and may contribute to better selection of candidates with VHD.

The suppression of AF was most successful in patients undergoing mitral valve surgery, patients in whom cryoablation was systematically used. Patients who underwent aortic valve surgery and AF ablation with HIFU-Epicor had significantly lower rate of SR maintenance. In prior publications, the success rate of Epicor system was also lower.[21] Endocardial approach (used in cryoablation) has shown higher success rates in comparison with the more superficial epicardial approach (HIFU-Epicor). However, according to other authors, this difference may not be due uniquely to the lower efficiency of the ablation system employed, and they speculate whether the underlying heart disease may also influence outcome, because it is well known, that isolated mitral valve surgery (without additional AF ablation) has a significant beneficial effect on spontaneous conversion to SR.[5,21]

Antiarrhythmic management is important in patients with recurrent AF in the post-operative period in improving results of SA.[4] However, in our study, no association was found between antiarrhythmic treatment and SR maintenance. We could not infer from our data whether this finding was due to the small number of patients was discharged with amiodarone, or if amiodarone is not effective for SR maintenance in these patients.

In the univariate analyses, age was associated with the recurrence of AF, however, this relationship was not observed after multivariate testing. It appears, therefore, that age is a confounding variable, since patients undergoing both mitral valve intervention and cryoablation are significantly younger.

It is well known that AF is associated with LA myocardial remodeling and ultra-structural changes, including fibrosis and accumulation of extracellular matrix – effects that may predispose to the formation of zones of slow conduction, which promote re-entry.[22] ACE-inhibitors are thought to reduce atrial dilatation, dysfunction, and fibrosis, which may reduce the propensity for developing AF.[23] In some studies, after catheter ablation, there is a trend towards fewer AF recurrences in patients treated with ACE-inhibitors, however, the efficacy of this treatment in routine clinical practice remains unknown.[24] In the present study, ACE-inhibitors were used in a substantial proportion of patients (48%), but they were not found to be effective enough for preventing AF recurrence.

As it has been demonstrated in previous studies,[25] AF surgical ablation is a safe procedure without increasing total surgical time, in comparison with the traditional Cox-Maze procedure, which has an elevated success rate but significantly increases intraoperative time. In our series we have not found major complications related to this technique.

Limitations of the study

Despite the systematic use of 24 hour Holter monitoring in the present series, silent AF remains an important issue in the post-operative follow-up of this type of patients. A major limitation of studies about AF treatment is that the burden of arrhythmia cannot be a reliable determinant unless an implantable device is used. It is also difficult to make a proper comparison with other studies in the absence of universal criteria for defining AF recurrences.

Results on the antiarrhythmic treatment should be interpreted with caution, since treatment with amiodarone (which was not uniformly employed across patients) could affect the success of the AF ablation technique. When antiarrhythmic drugs were forced into the multivariate model, recurrence predictors remained unchanged.

This study was carried out for a limited time period, with a relatively small sample size and in a single tertiary center. Multicenter studies and larger number of patients will be needed in the future to obtain more evidences about efficacy and safety of this technique in VHD patients.

Conclusions

Left atrial volume was larger in patients with AF recurrence, and emerges as the main predictor of recurrences improving candidate selection for this therapy; however, no differences were found regarding myocardial deformation parameters. Despite electrical maintenance of SR, left atrium mechanics did not recover after AF ablation performed during VHD surgery.

Author contributions

Conception and design of the research, Analysis and interpretation of the data, Statistical analysis and Critical revision of the manuscript for intellectual content: Lorenzo N, Aguilar R; Acquisition of data: Lorenzo N, Mendez I, Taibo M,

Martinis G, Badia S, Reyes G, Aguilar R; Writing of the manuscript: Lorenzo N.

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 La Princesa hospital. 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.

References

1. Nabauer M, Gerth A, Limbourg T, Schneider S, Oeff M, Kirchhof P, et al. The registry of the German competence NETwork on atrial fibrillation: patient characteristics and initial management. Europace. 2009;11(4):423-34. doi: 10.1093/europace/eun369.
2. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, et al; ESC Committee for Practice Guidelines. Guidelines for the management of atrial fibrillation: the task force for the management of atrial fibrillation of the European Society of Cardiology (ESC). Europace. 2010;12(10):1360-420. doi: 10.1093/europace/euq350. Erratum in: Europace. 2011 Jul;13(7):1058.
3. Halkos ME, Craver JM, Thourani VH, Kerendi F, Puskas JD, Cooper WA, et al. Intraoperative radiofrequency ablation of the treatment of atrial fibrillation during concomitant cardiac surgery. Ann Thorac Surg. 2005;80(1):210-5. doi: 10.1016/j.athoracsur.2005.01.051.
4. Feyrer R, Ballazhi F, Seitz T, Weyand M, Harig F. Impact of medical treatment on long-term results after surgical ablation of atrial fibrillation in cardiac surgical patients. Ann Thorac Cardiovasc Surg. 2014;20(3):207-12. doi: 10.5761/atcs.oa.12.02233.
5. Groh MA, Binns OA, Burton HG 3rd, Ely SW, Johnson AM. Ultrasonic cardiac ablation for atrial fibrillation during concomitant cardiac surgery: long-term clinical outcomes. Ann Thorac Surg. 2007;84(6):1978-83. doi: 10.1016/j.athoracsur.2007.06.081.
6. To AC, Flamm SD, Marwick TH, Klein AL. Clinical utility of multimodality LA imaging: assessment of size, function, and structure. JACC Cardiovasc Imaging. 2011;4(7):788-98. doi: 10.1016/j.jcmg.2011.02.018.
7. Myrdko T, Sniezek-Maciejewska M, Rudzinski P, Myc J, Lelakowski J, Majewski J. Efficacy of intra-operative radiofrequency ablation in patients with permanent atrial fibrillation undergoing concomitant mitral valve replacement. Kardiol Pol. 2008;66(9):932-8. PMID: 18924020.
8. Gillinov AM, Blackstone EH, McCarthy PM. Atrial fibrillation: current surgical options and their assessment. Ann Thorac Surg. 2002;74(6):2210-7. doi: https://doi.org/10.1016/S0003-4975(02)03977-2.
9. Reyes G, Benedicto A, Bustamante J, Sarraj A, Nuche JM, Alvarez P, et al. Restoration of atrial contractility after surgical cryoablation: clinical, electrical and mechanical results. Interact Cardiovasc Thorac Surg 2009;9(4):609-12. doi: 10.1510/icvts.2009.208173.
10. Lang RM, Bierig M, Devereux RB, Flachskamp FA, Foster E, Pellikka PA, et al; Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005;18(12):1440-63. doi: 10.1016/j.echo.2005.10.005.
11. Evangelista A, Flachskampf F, Lancellotti P, Badanao L, Aguilar R, Monaghan M, et al; European Association of Echocardiography. European Association of Echocardiography recommendations for standardization of performance, digital storage and reporting of echocardiographic studies. Eur J Echocardiogr. 2008;9(4):438-48. doi: 10.1093/ejechocard/jen174.
12. Aguilar-Torres R. Assesment of left atrial function. In: The EAE textbook of echocardiography. Oxford: European Society of Cardiology;/Oxford University Press; 2011. p.151-64.
13. Prieto L, Lamarca R, Casado A. [Assessment of the reliability of clinical findings: the intraclass correlation coefficient]. Med Clin (Barc). 1998;110(4):142-5. PMID: 9541905.
14. Veasey RA, Segal OR, Large JK, Lewis ME, Trivedi UH, Cohen AS, et al. The efficacy of intraoperative atrial radiofrequency ablation for atrial fibrillation during concomitant cardiac surgery-the Surgical Atrial Fibrillation Suppression (SAFS) Study. J Interv Card Electrophysiol. 2011;32(1):29-35. doi: 10.1007/s10840-011-9576-y.
15. Gaynor SL, Diodato MD, Prasad SM, Ishii Y, Schuessler RB, Bailey MS, et al. A prospective, single-center clinical trial of a modified Cox maze procedure with bipolar radiofrequency ablation. J Thorac Cardiovasc Surg. 2004;128(4):535-42. doi: 10.1016/j.jtcvs.2004.02.044. Erratum in: J Thorac Cardiovasc Surg. 2006;131(4):772.
16. Budera P, Straka Z, Osmančík P, Vaněk T, Jelínek Š, Hlavička J, et al. Comparison of cardiac surgery with left atrial surgical ablation vs. cardiac surgery without atrial ablation in patients with coronary and/or valvular heart disease plus atrial fibrillation: final results of the PRAGUE-12 randomized multicentre study. Eur Heart J. 2012;33(21):2644-52. doi: 10.1093/eurheartj/ehs290.
17. Beukema WP, Sie HT, Misier AR, Delnoy PP, Wellens HJ, Elvan A. Predictive factors of sustained sinus rhythm and recurrent atrial fibrillation after a radiofrequency modified Maze procedure. Eur J Cardiothorac Surg. 2008;34(4):771-5. doi: 10.1016/j.ejcts.2008.07.026.
18. Vieira MJ, Teixeira R, Gonçalves L, Gersh BJ. Left atrial mechanics: echocardiographic assessment and clinical implications. J Am Soc Echocardiogr. 2014;27(5):463-78. doi: 10.1016/j.echo.2014.01.021.
19. Candan O, Ozdemir N, Aung SM, Dogan C, Karabay CY, Gecmen C, et al. Left atrial longitudinal strain parameters predict postoperative persistent atrial fibrillation following mitral valve surgery: a speckle tracking echocardiography study. Echocardiography. 2013;30(9):1061-8. doi: 10.1111/echo.12222.
20. Williams MR, Steward JR, Bolling SF, Freeman S, Anderson JT, Argenziano M, et al. Surgical treatment of atrial fibrillation using radiofrequency energy. Ann Thorac Surg. 2001;71(6):1939-43. doi:http://dx.doi.org/10.1016/S0003-4975(01)02594-2

21. Schopka S, Schmid C, Keyser A, Kortner A, Tafelmeier J, Diez C, et al. Ablation of atrial fibrillation with the Epicor system: a prospective observational trial to evaluate safety and efficacy and predictors of success. J Cardiothorac Surg. 2010 May 5;5:34. doi: 10.1186/1749-8090-5-34.

22. Kourliouros A, Savelieva I, Kiotsekoglou A, Jahangiri M, Camm J. Current concepts in the pathogenesis of atrial fibrillation. Am Heart J. 2009;157(2):243-52. doi: 10.1016/j.ahj.2008.10.009.

23. Nakashima H, Kumagai K, Urata H, Gondo N, Ideishi M, Arakawa K. Angiotensin II antagonist prevents electrical remodeling in atrial fibrillation. Circulation. 2000;101(22):2612-7. doi: https://doi.org/10.1161/01.CIR.101.22.2612.

24. Tayebjee MH, Creta A, Moder S, Hunter RJ, Earley MJ, Dhinoja MB, et al. Impact of angiotensin-converting enzyme-inhibitors and angiotensin receptor blockers on long-term outcome of catheter ablation for atrial fibrillation. Europace. 2010;12(11):1537-42. doi: 10.1093/europace/euq284.

25. Ad N, Suri RM, Gammie JS, Sheng S, O'Brien SM, Henry L. Surgical ablation of atrial fibrillation trends and outcomes in North America. J Thorac Cardiovasc Surg. 2012;144(5):1051-60. doi: 10.1016/j.jtcvs.2012.07.065.

Short-Term and Mid-Term Clinical Outcomes Following Hybrid Coronary Revascularization Versus Off-Pump Coronary Artery Bypass: A Meta-Analysis

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Abstract

Background: Off-pump coronary artery bypass grafting (OPCAB) is one of the standard treatments for coronary artery disease (CAD) while hybrid coronary revascularization (HCR) represents an evolving revascularization strategy. However, the difference in outcomes between them remains unclear.

Objective: We performed a meta-analysis to compare the short-term and mid-term outcomes of HCR versus OPCAB for the treatment of multivessel or left main CAD.

Methods: We searched the PubMed, EMBASE, Web of Science and Cochrane databases to identify related studies and a routine meta-analysis was conducted.

Results: Nine studies with 6121 patients were included in the analysis. There was no significant difference in short-term major adverse cardiac and cerebrovascular event (MACCE) rate (RR: 0.55, 95% CI: 0.30–1.03, p = 0.06) or mortality (RR: 0.51, 95% CI: 0.17–1.48, p = 0.22). HCR required less ventilator time (SMD: -0.36, 95% CI: -0.55– -0.16, p < 0.001), ICU stay (SMD: -0.35, 95% CI: -0.58 – -0.13, p < 0.01), hospital stay (SMD: -0.29, 95% CI: -0.50– -0.07, p < 0.05) and blood transfusion rate (RR: 0.57, 95% CI: 0.49–0.67, p < 0.001), but needed more operation time (SMD: 1.29, 95% CI: 0.54–2.05, p < 0.001) and hospitalization costs (SMD: 1.06, 95% CI: 0.45–1.66, p < 0.001). The HCR group had lower mid-term MACCE rate (RR: 0.49, 95% CI: 0.26–0.92, p < 0.05) but higher rate in mid-term target vessel revascularization (TVR, RR: 2.20, 95% CI: 1.32–3.67, p < 0.01).

Conclusions: HCR had similar short-term mortality and morbidity comparing to OPCAB. HCR decreased the ventilator time, ICU stay, hospital stay, blood transfusion rate and increased operation time and hospitalization costs. HCR has a lower mid-term MACCE rate while OPCAB shows better in mid-term TVR. (Arq Bras Cardiol. 2018; 110(4):321-330)

Keywords: Coronary Artery Disease/surgery; Coronary Artery Bypass, Off-Pump; Myocardial Revascularization/trends; Meta-Analysis; Database Bibliographic.

Introduction

Surgical revascularization still plays an essential role in the treatment of coronary artery disease (CAD) even in the era of widely prevalent percutaneous coronary intervention (PCI). As the most classical and widespread procedure for revascularization, coronary artery bypass grafting (CABG) has been considered the gold standard therapy in the past decades.[1] In order to be safe and less disruptive, hybrid coronary revascularization (HCR) and off-pump coronary artery bypass grafting (OPCAB) which combines an off-pump technique with total arterial grafting. Recent years, more and more cardiac centers in the world have adopted OPCAB and HCR.[2,3]

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It has been intensively discussed whether OPCAB is superior for CAD compared with on-pump CABG, but it remains uncertain. A recent randomized controlled trial (RCT) including 4752 patients found that the outcomes of death, stroke, myocardial infarction, renal failure or repeat revascularization at 5-year follow-up were similar among patients who underwent OPCAB or on-pump CABG.[4] Another research investigated 3445 patents with a 13-year follow-up and drew conclusions that both OPCAB and on-pump CABG were safe and effective, and no significant difference was observed between them.[5] However, a meta-analysis including 12 studies detected a lower rate of death and adverse effects after OPCAB compared with conventional CABG.[6] Generally speaking, OPCAB is considered as lower incidence of neurological complications (including stroke, cognitive decline, etc.),[7] in addition to a comparable less mortality and morbidity, particularly in high-risk groups and elderly patients.[8,9]

HCR combines minimally invasive CABG and PCI, offering a relatively atraumatic therapy for multivessel CAD. HCR utilizes a left internal mammary artery (LIMA) graft to the left anterior

descending (LAD) coronary artery with drug-eluting stents (DES) to non-LAD target coronary arteries. Several studies have proved the excellent postoperative survival (higher than 99%) and LIMA patency rates (higher than 95%) of HCR, suggesting HCR should be considered as an alternative approach for patients with multivessel CAD.[10] A study in France confirmed the feasibility and safety of HCR and also detected that HCR compared favorably to those with traditional CABG alone.[11] In addition, both of simultaneous and staged HCR were indicated to be efficient and feasible with favorable outcomes at more than 12-month follow-up.[12,13] However, a 1-year clinical follow-up study angiographically showed a high rate of repeat revascularization after HCR.[14] In addition, a transient reduction in the antiplatelet effect of aspirin and clopidogrel was observed after HCR despite limited surgical trauma and off-pump technique.[15] Neither baseline platelet aggregation nor postoperatively increased platelet turnover and acute-phase response could explain it. Therefore, further research is badly needed.

Currently, several comparative studies about the clinical outcomes of OPCAB and HCR are available. Nonetheless, the optimal surgical strategy remains disputable. In the present analysis, we sought to compare the short-term and mid-term clinical outcomes of HCR versus OPCAB for the treatment of multivessel or left main CAD with a pooled data.

Methods

Search strategy and selection criteria

We searched four electronic bibliographic databases including PubMed, EMBASE, Web of Science and Cochrane by using following keywords with different combinations: "coronary artery disease", "multivessel coronary artery disease", "left main coronary artery disease", "no-touch coronary artery bypass", "off-pump coronary artery bypass", "hybrid coronary revascularization", "minimally invasive coronary artery bypass" and "percutaneous coronary intervention". The searches were limited to human studies and English-language literatures only. The last search date was March 1, 2017.

Inclusion criteria were: (1) RCTs, cohort studies or case-control trials (CCT) comparing the outcomes of HCR and OPCAB; (2) at least 15 participants in each group; (3) available to get complete data. In addition, exclusion criteria were: (1) duplicated papers that fail to provide supplementary information; (2) unfinished studies or unavailable data (3) studies with obvious defects in design or data statistics. Two researchers selected literatures and any disagreements were resolved through consensus.

Data extraction and quality assessment

For articles approved in the primary selection, two reviewers assessed the quality of studies and extract data independently. The CONSORT statement[16] and STROBE statement[17] were used to measure the quality of RCTs and observational studies, respectively. Low-quality studies should be excluded and any disagreements were resolved by consensus or judged by the senior author.

Extracted information included: (1) characteristics of studies and patients; (2) basic management of HCR and OPCAB; (3) short-term (in-hospital or 30-day) and mid-term (3 months to 36 months) mortality, stroke and major adverse cardiac and cerebrovascular event (MACCE) which was defined as the incidence of all-cause death, stroke, myocardial infarction (MI) and target vessel revascularization (TVR); (4) in-hospital outcomes: operation time, ventilator time, ICU stay, hospital stay, blood transfusion rate, incidence of atrial fibrillation (AF) and hospitalization costs.

Statistical analysis

We performed the analyses using RevMan 5.3 software (Cochrane Collaboration, Copenhagen, Denmark). Relative risk (RR) with 95% confidence interval (CI) was calculated for dichotomous variables and standardized mean difference (SMD) with 95% CI was calculated for continuous variables. Then *Forest plots* were presented graphically for all clinical outcomes. Statistical heterogeneity between studies was calculated using chi-squared test and the *I*-squared measure on a scale of 0-100% (less than 50% represented a low heterogeneity, 50%-75% indicated a moderate inconsistency and higher than 75% meant a large degree of heterogeneity). Fix-effect model was used in analysis with heterogeneity $< 50\%$ while random-effect model was conducted with heterogeneity $\geq 50\%$. In addition, publication bias of short-term (in-hospital or 30-day) MACCE rate was also assessed using funnel plot. Two-sided p value < 0.05 was considered statistically significant.

Results

Literature selection and characteristics of studies

The process of literature selection for potentially eligible studies and exclusion reasons is illustrated using a flow diagram in Figure 1. Initially, 1045 published articles were identified (455 from PubMed, 469 from EMBASE, 106 from Web of Science and 15 from Cochrane). Overall, 52 unduplicated English articles related to HCR and OPCAB were selected from these citations. Finally, nine observational studies with 6121 patients were included in the present analysis.[18-26]

The basic characteristics of these studies are presented in Table 1. Among 6121 patients, 5418 (88.5%) subjects got OPCAB while 290 (4.7%) patients received staged HCR and 398 (6.7%) patients received simultaneous HCR. For those who underwent HCR, minimal invasive techniques such as endoscopic atraumatic coronary artery bypass (endo-ACAB), mini-sternotomy and mini-thoracotomy were utilized. Most of them received DES and a combination of aspirin and clopidogrel was applied as a preventive antiplatelet therapy. Short-term (in-hospital or 30-day) and mid-term clinical outcomes are shown in Table 2.

Short-term outcomes

As illustrated in Table 3, there was no significant difference in short-term MACCE rate (relative risk (RR): 0.55, 95% confidence interval (CI): 0.30–1.03, $p = 0.06$; p

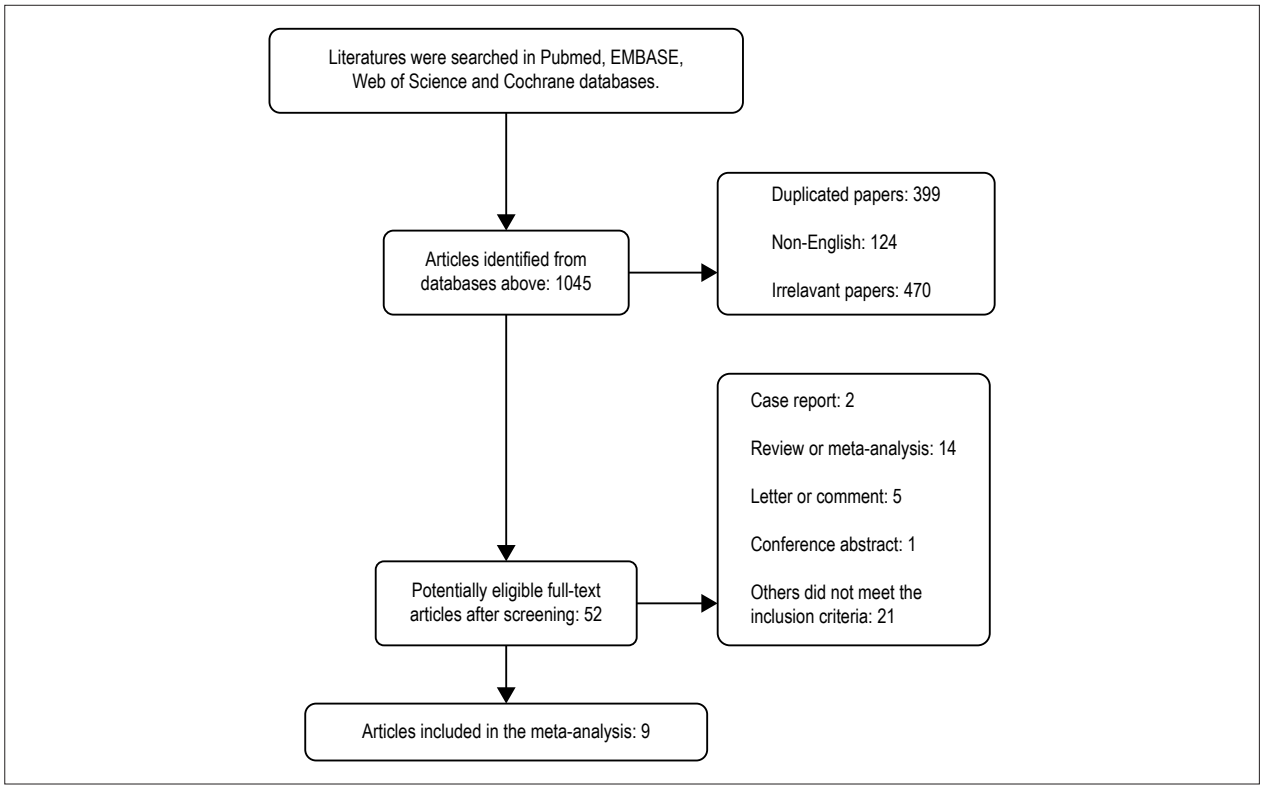

Figure 1 – *Flow diagram shows the process of literature selection.*

for heterogeneity = 0.85, I^2 = 0%) or mortality (RR: 0.51, 95% CI: 0.17–1.48, p = 0.22; p for heterogeneity = 0.99, I^2 = 0%) or stroke (RR: 0.93, 95% CI: 0.28–3.05, p = 0.90; p for heterogeneity = 1.00, I^2 = 0%) between the two groups. HCR required less ventilator time (standardized mean difference (SMD): -0.36, 95% CI: -0.55– -0.16, p < 0.001), ICU stay (SMD: -0.35, 95% CI: -0.58– -0.13, p < 0.01), hospital stay (SMD: -0.29, 95% CI: -0.50– -0.07, p < 0.05) and blood transfusion rate (relative risk (RR): 0.57, 95% CI: 0.49–0.67, p < 0.001), but needed more operation time (SMD: 1.29, 95% CI: 0.54–2.05, p < 0.001) and hospitalization costs (SMD: 1.06, 95% CI: 0.45–1.66, p < 0.001).

Subgroup analysis

Table 3 also showed the subgroup analysis, which was performed by dividing the studies into staged-HCR group and simultaneous-HCR group. No statistical difference was observed in short-term MACCE rate or mortality in the two subgroups (p value in both subgroups > 0.05).

Mid-term outcomes

The studies that contained mid-term outcomes were included in the analysis. As shown in Figure 2, the HCR group had lower MACCE rate (RR: 0.49, 95% CI: 0.26–0.92, p < 0.05, P for heterogeneity = 0.26, I^2 = 25%) but had higher rate in TVR (RR: 2.20, 95% CI: 1.32–3.67, p < 0.01, P for heterogeneity = 0.46, I^2 = 0%) in mid-term follow. No significant difference in mid-term mortality was detected between the two groups (RR: 0.47, 95% CI: 0.17–1.32, p < 0.01, P for heterogeneity = 0.34, I^2 = 7%).

Heterogeneity

In the current analysis, no obvious heterogeneity was found between studies in either short-term or mid-term MACCE rate and mortality (p for heterogeneity > 0.05, I^2 < 50%). And subgroup analysis showed no heterogeneity (p for heterogeneity = 0.95, I^2 = 0%).

Publication bias

The funnel graph of short-term MACCE rate was established in Figure 3, and there was no evident publication bias among all included studies by visual examination.

Discussion

The present meta-analysis shows that HCR, compared with OPCAB, seems not to significantly improve short-term mortality and morbidity of postoperative complications for patients with CAD. These results are similar to previews research. Hu[27] first systematically compared the short-term clinical outcomes after HCR versus OPCAB for the treatment of multivessel or left main CAD, and most of the results were consistent with the current analysis. However, some differences between the two analyses should be also mentioned. We excluded one study[28] due to small sample size(less than 15 patients), outdated

Table 1 – Characteristics of the included studies

References	Year	Primary endpoint	Follow-up	HCR							OPCAB		
				Number of patients	Mean age	Baseline LVEF (%)	Setting	Surgery type	Stents	Antiplatelet strategy	Number of patients	Mean age	Baseline LVEF (%)
Kon[18]	2008	In-hospital MACCE	1 year	15	61.0 ± 10.0	47.0 ± 14.0	Simultaneous	Small thoracotomy	DES	Aspirin 325 mg, clopidogrel 300 mg	30	65.0 ± 10.0	45.0 ± 14.0
Vassiliades[19]	2009	In-hospital mortality	1 year	91	64.7 ± 13.7	51.5 ± 9.4	Staged	Endo-ACAB	DES (85.8%)	Aspirin 81-162 mg, clopidogrel 75 mg	4175	62.8 ± 11.7	50.9 ± 12.7
Hu[20]	2010	In-hospital MACCE	Mean 18 months	104	61.8 ± 10.2	62.4 ± 6.9	Simultaneous	Ministernotomy	DES	Aspirin 100 mg, clopidogrel 300 mg	104	62.4 ± 8.0	63.4 ± 7.5
Halkos[21]	2011	In-hospital MACCE	Median 3.2 years	147	64.3 ± 12.8	54.6 ± 8.7	Staged	Endo-ACAB with robotic assistance	DES (mojority)	Clopidogrel 600 mg	588	64.3 ± 12.5	54.7 ± 8.7
Halkos[22]	2011	In-hospital and 30-day MACCE	Median 3.2 years	27	63.9 ± 13.7	56.6 ± 7.7	Staged	Mini-sternotomy, robotic assistance	DES (92.6%)	Clopidogrel 600 mg	81	63.9 ± 12.7	56.6 ± 7.6
Bachinsky[23]	2012	In-hospital and 30-day MACCE	30 days	25	63.2 ± 10.5	55.3 ± 10.4	Staged	Thoracotomy with robotic assistance	DES (71.0%)	Aspirin 325 mg, clopidogrel 600 mg	27	66.8 ± 10.7	51.5 ± 12.0
Zhou[24]	2013	In-hospital MACCE	30 days	141	62.0 ± 10.1	61.8 ± 6.9	Simultaneous	Mini-sternotomy	DES	Aspirin 100 mg, heparin 120 IU/kg	141	63.2 ± 8.5	60.1 ± 9.3
Harskamp[25]	2014	cTnI after 24h	1 year	33	65.0 ± 6.5	55.0 ± 7.5	Simultaneous	Mini-thoracotomy with robotic assistance	DES (75.8%)	Aspirin and clopidogrel	32	67.0 ± 7.0	55.0 ± 5.0
Song[26]	2016	In-hospital outcomes	Median 2.5 years	120	62.3 ± 9.4	63.9 ± 7.3	Simultaneous	Mini-sternotomy	DES (99.5%)	Aspirin 100 mg, clopidogrel 300 mg	240	62.8 ± 8.4	64.2 ± 6.9

MACCE: major adverse cardiac and cerebrovascular event, cTnI: cardiac troponin I, HCR: hybrid coronary revascularization, OPCAB: Off-pump coronary artery bypass grafting, LVEF: left ventricular ejection fraction, endo-ACAB: endoscopic atraumatic coronary artery bypass, DES: drug-eluting stent.

Table 2 – Short-term and mid-term clinical outcomes of the included studies

References	Time of outcomes	HCR						OPCAB					
		Number of patients	MACCE	Death	Stroke	MI	TVR	Number of patients	MACCE	Death	Stroke	MI	TVR
Kon[18]	Short-term	15	0	0	0	0	0	30	7	0	1	6	0
	Mid-term	15	1	0	0	0	1	30	7	0	0	0	0
Vassiliades[19]	Short-term	91	1	0	1	0	0	4175	126	74	47	20	12
	Mid-term	91	10	1	1	1	7	4175	--	230	--	--	--
Hu[20]	Short-term	104	0	0	0	0	0	104	0	0	0	0	0
	Mid-term	104	1	0	0	0	1	104	10	1	5	0	3
Halkos[21]	Short-term	147	3	1	1	1	0	588	12	5	4	3	0
	Mid-term	147	--	--	--	--	13	588	--	--	--	--	18
Halkos[22]	Short-term	27	0	0	0	0	0	81	4	3	0	2	0
	Mid-term	27	--	--	--	--	2	81	--	--	--	--	1
Bachinsky[23]	Short-term	25	0	0	0	0	0	27	1	1	0	0	0
Zhou[24]	Short-term	141	7	1	1	5	0	141	10	2	1	7	0
Harskamp[25]	Short-term	33	1	1	0	0	0	32	1	1	0	0	0
	Mid-term	33	1	1	0	0	2	32	2	1	0	1	1
Song[26]	Mid-term	120	8	3	0	0	5	237	19	6	8	2	6

HCR: hybrid coronary revascularization, OPCAB: Off-pump coronary artery bypass grafting, MACCE: major adverse cardiac and cerebrovascular event, MI: myocardial infarction, TVR: target vessel revascularization.

Table 3 – Summary of results for short-term clinical outcomes of HCR versus OPCAB

Outcomes	Number of studies	Total numbers of patients	SMD or RR	95% CI	p value
Short-term MACCE rate	8	5761	0.55	[0.30, 1.03]	0.06
Staged HCR	4	5161	0.58	[0.23, 1.47]	0.25
Simultaneous HCR	4	600	0.54	[0.23, 1.23]	0.14
Short-term mortality	8	5761	0.51	[0.17, 1.48]	0.22
Staged HCR	4	5161	0.46	[0.12, 1.73]	0.25
Simultaneous HCR	4	600	0.66	[0.11, 3.88]	0.64
Short-term stroke	8	5761	0.93	[0.28, 3.05]	0.90
Operation time	3	542	1.29	[0.54, 2.05]	< 0.001
Ventilator time	6	1861	-0.36	[-0.55, -0.16]	< 0.001
ICU stay	7	1913	-0.35	[-0.58, -0.13]	0.002
Hospital stay	7	1538	-0.29	[-0.50, -0.07]	0.01
Blood transfusion rate	6	1361	0.57	[0.49, 0.67]	< 0.001
AF rate	7	1933	1.08	[0.83, 1.40]	0.56
Hospitalization costs	3	305	1.06	[0.45, 1.66]	< 0.001

HCR: hybrid coronary revascularization, OPCAB: Off-pump coronary artery bypass grafting, MACCE: major adverse cardiac and cerebrovascular event, AF: atrial fibrillation, SMD: standardized mean difference, RR: relative risk, CI: confidence interval.

surgical procedures (8-10 cm thoracotomy incisions), different kinds of DES (cypher or taxus), uncertainty of baseline LVEF (not reported) and high heterogeneity in analysis. We also put three recent high-quality studies into pooled data so that all outcomes are updated. In addition, in the present study, we focus on postoperative complications and take stroke as a primary endpoint. Therefore, the present analysis is needed for a better elucidation of HCR and OPCAB.

To our knowledge, this is the first meta-analysis comparing the mid-term clinical outcomes between HCR and OPCAB so far. Our data shows that HCR has a lower mid-term MACCE rate while OPCAB shows a better result in mid-term TVR. Moreover, no significant difference in mid-term mortality was detected between the two groups. Patients undergoing the hybrid procedure have relatively better mid-term clinical outcomes probably owing to reduced myocardial manipulation

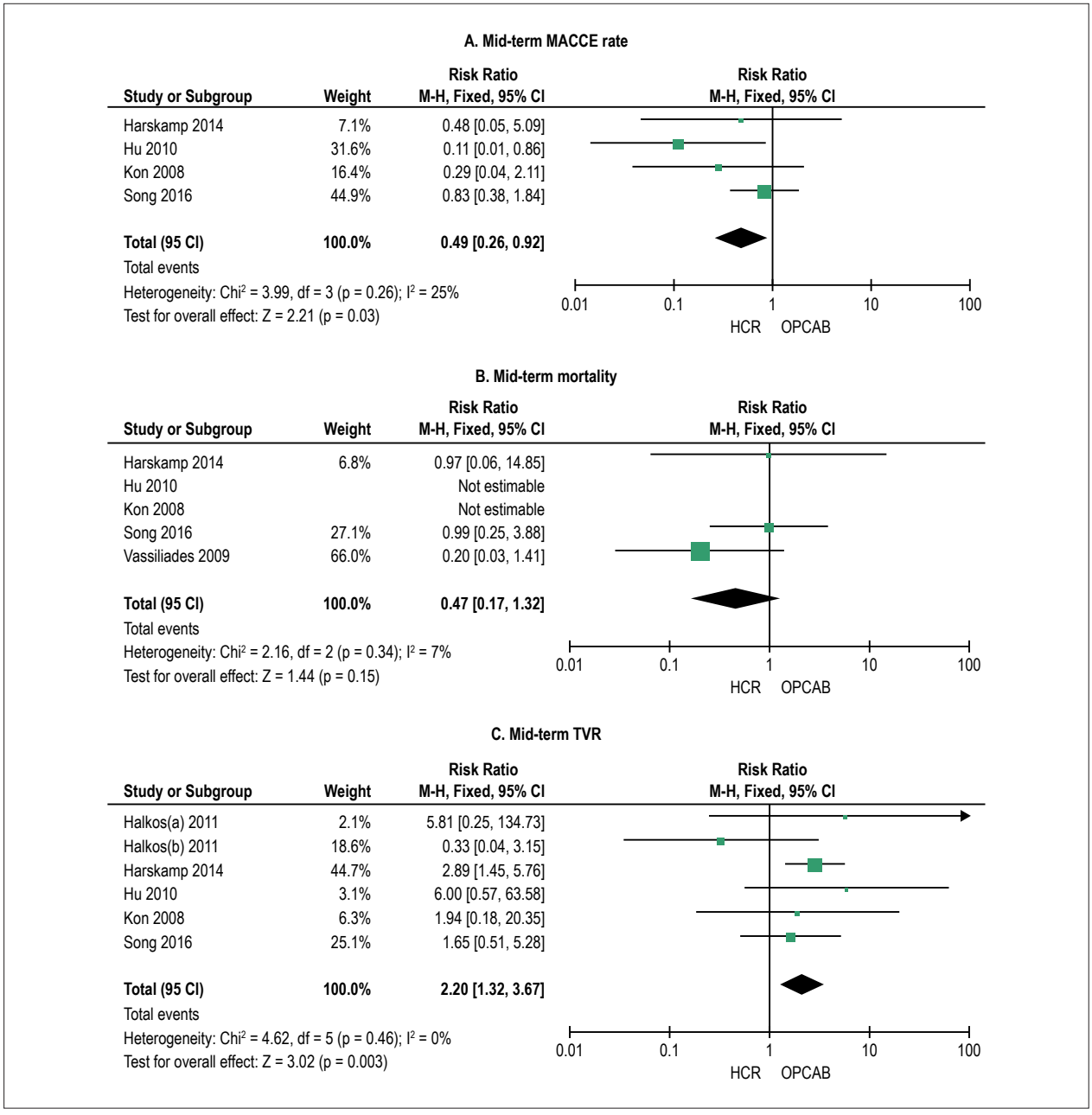

Figure 2 – *Meta-analysis shows the relative risk (RR) of mid-term MACCE rate, mortality and TVR. MACCE: major adverse cardiac and cerebrovascular event, TVR: target vessel revascularization, CI: confidence interval, HCR: hybrid coronary revascularization; OPCAB: off-pump coronary artery bypass grafting.*

and activation of coagulation[26]. It has been widely recognized that the dislodgement or rupture of atherosclerotic plaques during surgical aortic manipulation results in a major cause of stroke.[29] Since the aorta is more or less affected in the surgical procedure, it is still unclear whether OPCAB can decrease postoperative stroke rate compared with on-pump CABG. In contrast, grafting in HCR only involves LAD artery while other coronary arteries are treated by PCI. As a result, low rate of neurological complications becomes one of the main advantages of HCR. Although, in the present analysis we detect no significant difference of stroke rate between OPCAB and HCR in a short-term follow-up, which seems to be contradictory to some previous analyses.

However, Song et al.[26] reported that more patients in OPCAB group suffer from stroke than HCR group in a 30-month follow-up, which indicates that the differences may be well recognized in a long-term follow-up. In recent years, technical advances in OPCAB utilize a no-touch technique to avoid aortic manipulation during grafting. A retrospective study showed that the OPCAB with no-touch technique could improve prognosis by minimizing the neurological complications and the morbidity.[30] Emmert et al.[31] also reported that the aortic

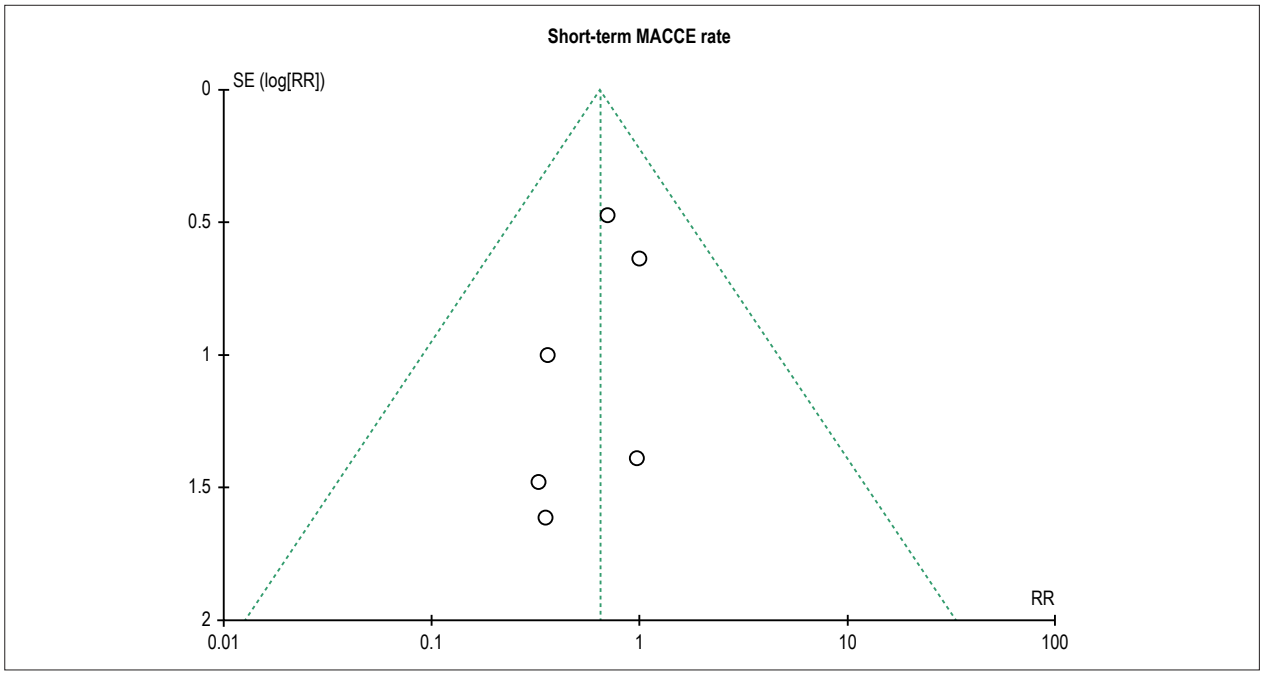

Figure 3 – *Funnel plot shows the test for publication bias of short-term (in-hospital or 30-day) mortality and MACCE rate. MACCE: major adverse cardiac and cerebrovascular event, RR: relative risk, SE: standard error.*

no-touch OPCAB provided superior neurological outcomes than on-pump CABG and no-touch technique should be properly applied. Halbersma et al.[32] investigated the four-year clinical outcomes after OPCAB with no-touch technique and concluded that it was a safe and efficient choice for patients with multivessel or left main CAD. Compelling data have indicated that the combination of OPCAB and clampless strategies can reduce stroke risk. However, the major shortcoming of no-touch OPCAB is its greater technical requirement so that it is not applicable for every surgical team or every patient.[33] Nevertheless, further investigations should be still carried out to compare no-touch OPCAB and HCR.

In the current analysis, neither staged HCR nor simultaneous HCR makes a difference to the short-term outcomes, which is consistent with former studies.[27] Commonly, there are three strategies for HCR: (1) performing LIMA-LAD grafting first and then followed by PCI, the interval varies from several hours to a few weeks; (2) vice versa; (3) combined LIMA-LAD grafting and PCI at the same time in a hybrid operative unit. The optimal sequence of LIMA-LAD grafting and PCI has been debated but still remains unclear. In fact, most centers choose their own surgical procedures mainly based on preferences of physicians, considerations of patients, economic issues and available resources. Although several studies have indicated that both simultaneous and staged HCR contribute to excellent results, most centers prefer to adopt the latter one with LIMA-LAD grafting performed first.[34] The CABG-first approach is recommended by the American College of Cardiology Foundation/American Heart Association[35] and it has some obvious advantages. It can reduce the overlapping from two different teams so that they can perform in their most familiar way and avoid to interacting with each other in operation room. Then antiplatelet and antithrombotic strategies can be well managed and adjusted according to physicians from different teams.[36] However, the disadvantages include that patients have to undergo at least two surgeries and need more time to recover. Moreover, hemorrhagic tendency and overload of kidneys also deserve significant attention. Currently, no study has compared the clinical outcomes of staged HCR and simultaneous HCR directly, so further research should be placed on it.

In the present analysis, we also confirm that HCR apparently decreases the ventilator time, ICU stay, hospital stay and blood transfusion rate comparing to OPCAB. Although these items may not directly influence the main outcomes, they are also important criteria to judge a surgical procedure. Several reasons may account for these advantages of HCR. With the development of surgical procedures, endoscopic technique and mini incision are widely utilized in HCR to help patients ease suffering and recover sooner.[37] And retractor-stabilizer, such as robot, provides access that LIMA-LAD grafting can be performed with accuracy and precision with minimally invasive thoracotomy or sternotomy.[38] Practically, with the assistance of a surgical robot, it offers an excellent visual field and reduces operation time. However, some drawbacks of HCR also deserve our attention. Our study detects that the hybrid procedure required longer operation time and incurred much higher in-hospital costs than OPCAB. In Bachinsky`s study,[23] despite lower postoperative costs, the HCR group still needs more overall hospital costs owning to its higher procedural costs. Consequently, pros and cons of HCR should be weighed and considered carefully before operation.

Some limitations of the present analysis should be also emphasized. Firstly, all included studies belong to observational studies and no single RCT has been conducted so far. Secondly, some included studies contain relatively small samples (fewer than 50 patients) and remain imbalance of patient number between groups so that deviation of results may inevitably exist. Thirdly, long-term patency is more convincing than short-term and mid-term outcomes, but very limited references were published with long-term follow-up so far. Finally, some uncontrolled factors may interfere with the current analysis. Variables like gender ratio and LVEF at baseline have not been adjusted. And diverse surgery procedures, stents (DES or bare stent) as well as antiplatelet strategies may disturb the accuracy of results too.

Conclusions

HCR shows similar results with OPCAB in short-term clinical outcomes. HCR decreases the ventilator time, ICU stay, hospital stay, blood transfusion rate and increases the operation time and hospitalization costs. Although repeated vessel revascularization is greater with HCR, it has a lower mid-term MACCE rate and could provide a safe and reproducible alternative for patients with multivessel CAD.

Author contributions

Conception and design of the research and Critical revision of the manuscript for intellectual content: Xiang-guang A; Acquisition of data, Analysis and interpretation of the data, Statistical analysis and Writing of the manuscript: Li D, Yi-kun K.

Potential Conflict of Interest

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Ethics approval and consent to participate

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

References

1. Ennker JC, Ennker IC. Coronary artery surgery: now and in the next decade. HSR Proc Intensive Care and Cardiovasc Anesth. 2012;4(4):217-23. PMID: 23439278.
2. Arom KV, Flavin TF, Emery RW, Kshettry VR, Petersen RJ, Janey PA. Is low ejection fraction safe for off-pump coronary artery bypass operation? Ann Thorac Surg. 2000;70(3):1021-5. Doi:http://dx.doi.org/10.1016/80003-4975(00)01761-6
3. Gao C, Yang M, Wu Y, Wang G, Xiao C, Liu H, et al. Hybrid coronary revascularization by endoscopic robotic coronary artery bypass grafting on beating heart and stent placement. Ann Thorac Surg. 2009;87(3):737-41. doi: 10.1016/j.athoracsur.2008.12.017.
4. Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Straka Z, et al; CORONARY Investigators. Five-year outcomes after off-pump or on-pump coronary-artery bypass grafting. N Engl J Med. 2016;375(24):2359-68. doi: 10.1056/NEJMoa1601564.
5. Riess FC, Heller S, Cramer E, Awwad N, Amin W, Hansen L, et al. On-pump versus off-pump complete arterial revascularization using bilateral internal mammary arteries and the t-graft technique: clinical and angiographic results for 3,445 patients in 13 years of follow-up. Cardiology. 2016;136(3):170-9. doi: 10.1159/000448428.
6. Sepehripour AH, Chaudhry UA, Suliman A, Kidher E, Sayani N, Ashrafian H, et al. How revascularization on the beating heart with cardiopulmonary bypass compares to off-pump? A meta-analysis of observational studies. Interact Cardiovasc Thorac Surg. 2016;22(1):63-71. doi: 10.1093/icvts/ivv291.
7. Vallely MP, Potger K, McMillan D, Hemli JM, Brady PW, Brereton RJ, et al. Anaortic techniques reduce neurological morbidity after off-pump coronary artery bypass surgery. Heart Lung Circ. 2008;17(4):299-304. doi: 10.1016/j.hlc.2007.11.138.
8. Lemma GM, Coscioni E, Centofanti P, Centofanti P, Fondacone C, Salica A, et al. On-pump versus off-pump coronary artery bypass surgery in high-risk patients: operative results of a prospective randomized trial (on-off study). J Thorac Cardiovasc Surg. 2012;143(3):625-31. doi: 10.1016/j.jtcvs.2011.11.011.
9. Falk V. Stay off-pump and do not touch the aorta! Eur Heart J. 2010;31(3):278-80. doi: 10.1093/eurheartj/ehp527.
10. Bonatti JO, Zimrin D, Lehr EJ, Vesely M, Kon ZN, Wehman B, et al. Hybrid coronary revascularization using robotic totally endoscopic surgery: perioperative outcomes and 5-year results. Ann Thorac Surg. 2012;94(6):1920-6. doi: 10.1016/j.athoracsur.2012.05.041.
11. Delhaye C, Sudre A, Lemesle G, Vanesson L, Koussa M, Fayad G, et al. Hybrid revascularization, comprising coronary artery bypass graft with exclusive arterial conduits followed by early drug-eluting stent implantation, in multivessel coronary artery disease. Arch Cardiovasc Dis. 2010;103(10):502-11. doi: 10.1016/j.acvd.2010.09.003.
12. Adams C, Burns DJ, Chu MW, Jones PM, Shridar K, Teefy P, et al. Single-stage hybrid coronary revascularization with long-term follow-up. Eur J Cardiothorac Surg. 2014;45(3):438-43. doi: 10.1093/ejcts/ezt390.
13. Versaci F, Reimers B, Del Giudice C, Schofer J, Giacomin A, Saccà S, et al. Simultaneous hybrid revascularization by carotid stenting and coronary artery bypass grafting: the SHARP study. JACC Cardiovasc Interv. 2009;2(5):393-401. doi: 10.1016/j.jcin.2009.02.010.
14. Modrau IS, Holm NR, Maeng M, Bøtker HE, Christiansen EH, Kristensen SD, et al. One-year clinical and angiographic results of hybrid coronary revascularization. J Thorac Cardiovasc Surg. 2015;150(5):1181-6. doi: 10.1016/j.jtcvs.2015.08.072.
15. Modrau IS, Wurtz M, Kristensen SD, Hvas AM. Reduced effect of aspirin and clopidogrel following hybrid coronary revascularization. Clin Appl Thromb Hemost. 2015;21(7):603-11. doi: 10.1177/1076029615573304.
16. Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. PLoS Med. 2010;7(3): e1000251. doi: 10.1371/journal.pmed.1000251.
17. Vandenbroucke JP, Von Elm E, Altman DG, Egger M, Gøtzsche PC, Mulrow CD, et al; STROBE Initiative. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. PLoS Med. 2007;4(10):e297. doi: 10.1371/journal.pmed.0040297.

18. Kon ZN, Brown EN, Tran R, Joshi A, Reicher B, Grant MC, et al. Simultaneous hybrid coronary revascularization reduces postoperative morbidity compared with results from conventional off-pump coronary artery bypass. J Thorac Cardiovasc Surg. 2008;135(2):367-75. doi: 10.1016/j.jtcvs.2007.09.025.

19. Vassiliades TA, Kilgo PD, Douglas JS, Babaliaros VC, Block PC, Samady H, et al. Clinical outcomes after hybrid coronary revascularization versus off pump coronary artery bypass. Innovations (Phila). 2009;4(6):299-306. doi: 10.1097/IMI.0b013e3181bbfa96.

20. Hu S, Li Q, Gao P, Xiong H, Zheng Z, Li L, et al. Simultaneous hybrid revascularization versus off-pump coronary artery bypass for multivessel coronary artery disease. Ann Thorac Surg. 2011;91(2):432-8. doi: 10.1016/j.athoracsur.2010.10.020.

21. Halkos ME, Vassiliades TA, Douglas JS, Morris DC, Rab ST, Liberman HA, et al. Hybrid coronary revascularization versus off-pump coronary artery bypass grafting for the treatment of multivessel coronary artery disease. Ann Thorac Surg. 2011;92(5):1695-701. doi: 10.1016/j.athoracsur.2011.05.090.

22. Halkos ME, Rab ST, Vassiliades TA, Morris DC, Douglas JS, Kilgo PD, et al. Hybrid coronary revascularization versus off-pump coronary artery bypass for the treatment of left main coronary stenosis. Ann Thorac Surg. 2011;92(6):2155-60. doi: 10.1016/j.athoracsur.2011.08.012.

23. Bachinsky WB, Abdelsalam M, Boga G, Kiljanek L, Mumtaz M, McCarty C. Comparative study of same sitting hybrid coronary artery revascularization versus off-pump coronary artery bypass in multivessel coronary artery disease. J Interv Cardiol. 2012;25(5):460-8. doi: 10.1111/j.1540-8183.2012.00752.x.

24. Zhou S, Fang Z, Xiong H, Hu S, Xu B, Chen L, Wang W. Effect of one-stop hybrid coronary revascularization on postoperative renal function and bleeding: a comparison study with off-pump coronary artery bypass grafting surgery. J Thorac Cardiovasc Surg. 2014;147(5):1511-6.e1. doi: 10.1016/j.jtcvs.2013.05.026.

25. Harskamp RE, Abdelsalam M, Lopes RD, Boga G, Hirji S, Krishnan M, et al. Cardiac troponin release following hybrid coronary revascularization versus off-pump coronary artery bypass surgery. Interact Cardiovasc Thorac Surg. 2014;19(6):1008-12. doi: 10.1093/icvts/ivu297.

26. Song Z, Shen L, Zheng Z, Xu B, Xiong H, Li L, et al. One-stop hybrid coronary revascularization versus off-pump coronary artery bypass in patients with diabetes mellitus. J Thorac Cardiovasc Surg. 2016;151(6):1695-701.e1. doi: 10.1016/j.jtcvs.2016.01.049.

27. Hu FB, Cui LQ. Short-term clinical outcomes after hybrid coronary revascularization versus off-pump coronary artery bypass for the treatment of multivessel or left main coronary artery disease: a meta-analysis. Coron Artery Dis. 2015;26(6):526-34. doi: 10.1097/MCA.0000000000000265.

28. Reicher B, Poston RS, Mehra MR, Joshi A, Odonkor P, Kon Z, et al. Simultaneous 'hybrid' percutaneous coronary intervention and minimally invasive surgical bypass grafting: feasibility, safety, and clinical outcomes. Am Heart J. 2008;155(4):661-7. doi: 10.1016/j.ahj.2007.12.032.

29. Lev-Ran O, Braunstein R, Sharony R, Kramer A, Paz Y, Mohr R, Uretzky G. No-touch aorta off-pump coronary surgery: the effect on stroke. J Thorac Cardiovasc Surg. 2005;129(2):307-13. doi: 10.1016/j.jtcvs.2004.06.013.

30. Arrigoni SC, Mecozzi G, Grandjean JG, Hillege JL, Kappetein AP, Mariani MA. Off-pump no-touch technique: 3-year results compared with the SYNTAX trial. Interact Cardiovasc Thorac Surg. 2015;20(5):601-4. doi: 10.1093/icvts/ivv012.

31. Emmert MY, Seifert B, Wilhelm M, Grünenfelder J, Falk V, Salzberg SP. Aortic no-touch technique makes the difference in off-pump coronary artery bypass grafting. J Thorac Cardiovasc Surg. 2011;142(6):1499-506. doi: 10.1016/j.jtcvs.2011.04.031. Erratum in: J Thorac Cardiovasc Surg. 2012;143(4):995.

32. Halbersma WB, Arrigoni SC, Mecozzi G, Grandjean JG, Kappetein AP, van der Palen J, et al. Four-year outcome of OPCAB no-touch with total arterial Y-graft: making the best treatment a daily practice. Ann Thorac Surg. 2009;88(3):796-801. doi: 10.1016/j.athoracsur.2009.04.104.

33. Yanagawa B, Nedadur R, Puskas JD. The future of off-pump coronary artery bypass grafting: a North American perspective. J Thorac Dis. 2016;8(Suppl 10):S832-8. doi: 10.21037/jtd.2016.10.07.

34. Zhang L, Cui Z, Song Z, Yang H, Fu Y, Gong Y, et al. Minimally invasive direct coronary artery bypass for left anterior descending artery revascularization - analysis of 300 cases. Wideochir Inne Tech Maloinwazyjne. 2016;10(4):548-54. doi: 10.5114/wiitm.2015.55842.

35. Hillis LD, Smith PK, Anderson JL, Bittl JA, Bridges CR, Byrne JG, et al; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2011 ACCF/AHA guideline for coronary artery bypass graft surgery: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Thorac Cardiovasc Surg. 2012;143(1):4-34. doi: 10.1016/j.jtcvs.2011.10.015. Erratum in: J Thorac Cardiovasc Surg. 2012;143(5):1235.

36. Halkos ME, Walker PF, Vassiliades TA, Douglas JS, Devireddy C, Guyton RA, et al. Clinical and angiographic results after hybrid coronary revascularization. Ann Thorac Surg. 2014;97(2):484-90. doi: 10.1016/j.athoracsur.2013.08.041.

37. Aubin H, Akhyari P, Lichtenberg A, Albert A. Additional right-sided upper "Half-Mini-Thoracotomy" for aortocoronary bypass grafting during minimally invasive multivessel revascularization. J Cardiothorac Surg. 2015 Oct 21;10:130. doi: 10.1186/s13019-015-0334-6.

38. Ejiofor JI, Leacche M, Byrne JG. Robotic CABG and hybrid approaches: the current landscape. Prog Cardiovasc Dis. 2015;58(3):356-64. doi: 10.1016/j.pcad.2015.08.012.

Better Technology, More Spending, Worse Outcomes

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Since its beginning, myocardial revascularization has suffered substantial technological changes. In fact, early techniques with no physiological basis were used to increase blood supply to the ischemic myocardium. These included pericardial talc insufflation, coronary sinus ligation, Beck surgical procedure, and the Vineberg procedure. Nevertheless, due to their frustrating results that did not meet the expectations, these techniques were abandoned.

The emergence of a new, more rational technique – the coronary artery bypass surgery using venous grafts (later substituted with arterial grafts) – enabled the provision of greater blood flow to the ischemic myocardium.

Due to surgical morbidity and high costs related to material and human resources, new percutaneous techniques for coronary artery obstruction were created, including percutaneous coronary angioplasty, initially performed with balloons and then by stent therapy. In this period, intra-arterial devices and techniques such as atherotomes, Rotablator™ and laser ablation have been developed, with unsatisfactory results though. In addition, drug-eluting stents (or other stents) have been the technique of choice by interventional cardiologists. However, technological advances of these devices were accompanied by higher costs.[1] Besides, recent studies have shown that percutaneous revascularization does not decrease cardiovascular events as compared with conventional procedures.[2,3]

In addition, with technological progresses including the use of robots and hybrid operating rooms, the number of surgery options for myocardial revascularization have increased. However, despite their refinement and safety, these techniques did not decrease the occurrence of events and cardiovascular mortality.[4] In fact, a recent meta-analysis of nine comparative studies of revascularization surgeries performed in conventional or hybrid rooms, robot-assisted or not, indicated a worse performance of the surgeries conducted in hybrid rooms regarding event and death rates.[5] Also, in this meta-analysis, there were disproportionate rates of reoperations (3.5%) and hemodynamic instability (9.5%) in surgeries performed in hybrid rooms, requiring the change of the surgical techniques to open procedures and extracorporeal circulation.[6] In addition, this study showed that conventional surgery had a better revascularization performance as compared with the technique performed in hybrid rooms. However, it is worth mentioning that the efficacy of complete and incomplete myocardial revascularization is still a matter of debate. Studies comparing the efficacy of complete, incomplete or no revascularization showed similar results between the procedures.[7]

Finally, 40 years has passed since the publication of the CASS Trial,[8] which pointed out that regardless of the number and extension of arteries involved, clinical and surgical therapy have comparable results in patients with preserved ventricular function and stable angina, with an annual mortality rate of approximately 2%. Therefore, in the CASS Trial,[8] considering that clinical therapy was based only in the use of beta-blockers and prolonged-action nitrates, one may consider that the surgery was compared with a control group (placebo).

Keywords

Myocardial Revascularization / economics; Myocardial Revascularization / mortality; Angioplasty, Balloon, Coronary; Robotic Surgical Procedures / trends; Drug-Eluting Stents / economics; Operating Rooms / trends.

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References

1. Swaminathan M, Phillips-Bute BG, Patel UD, Shaw AD, Stafford-Smith M, Douglas PS, et al. Increasing healthcare resource utilization after coronary artery bypass graft surgery in the United States. Circ Cardiovasc Qual Outcomes. 2009;2(4):305-12.
2. Farkouh ME, Domanski M, Sleeper LA, Siami FS, Dangas G, Mack M, et al; FREEDOM Trial Investigators. Strategies for multivessel revascularization in patients with diabetes. N Engl J Med. 2012;367(25):2375-84.
3. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, et al; SYNTAX Investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med. 2009;360(10):961-72. Erratum in: N Engl J Med. 2013;368(6):584.
4. Zhao DX, Leacche M, Balaguer JM, Boudoulas KD, Damp JA, Greelish JP, et al; Writing Group of the Cardiac Surgery, Cardiac Anesthesiology, and Interventional Cardiology Groups at the Vanderbilt Heart and Vascular Institute. Routine intraoperative completion angiography after coronary artery bypass grafting and 1-stop hybrid revascularization results from a fully integrated hybrid catheterization laboratory/operating room. J Am Coll Cardiol. 2009;53(3):232-41.
5. Dong L, Kang YK, Xiang G Resultados clínicos de curto e médio prazo após revascularização coronariana híbrida versus revascularização miocárdica sem circulação extracorpórea: uma meta-análise. Arq Bras Cardiol. 2018; 110(4):321-330.
6. Hueb WA, Ramires JA. Complete, incomplete or no myocardial revascularization. Arq Bras Cardiol. 2006;87(4):e144-6.
7. Bonatti JO, Zimrin D, Lehr EJ, Vesely M, Kon ZN, Wehman B, et al. Hybrid coronary revascularization using robotic totally endoscopic surgery: perioperative outcomes and 5-year results. Ann Thorac Surg. 2012;94(6):1920-6.
8. Coronary Artery Surgery Study (CASS): a randomized trial of coronary artery bypass surgery: survival data. Circulation. 1983;68(5):939-50.

Association of Monocyte Count on Admission with the Angiographic Thrombus Burden in Patients with ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention

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Abstract

Background: **The intracoronary high-thrombus burden during the primary percutaneous coronary intervention in patients with ST-elevation myocardial infarction (STEMI) can lead to poor outcomes. Monocytes have been described to play an important role in thrombotic disorders.**

Objectives: **This study aimed to investigate the relationship between admission monocyte count and angiographic intracoronary thrombus burden in patients receiving primary percutaneous coronary intervention (PPCI).**

Methods: **A total of 273 patients with acute STEMI who underwent PPCI were enrolled. The patients were divided into two groups according to the thrombolysis in myocardial infarction (TIMI) thrombus grade: low-thrombus burden group with a grade of 0–2 and high-thrombus burden group with a grade of 3-4. The monocyte count and other laboratory parameters were measured on admission before PPCI. P-value < 0.05 was considered significant.**

Results: **There were 95 patients (34.8%) in the high-thrombus burden group, and 178 patients (65.2%) in the low-thrombus burden group. Patients with high-thrombus burden had significantly higher admission monocyte count ($0.61 \pm 0.29 \times 10^9$/L vs. $0.53 \pm 0.24 \times 10^9$/L, p = 0.021). In multivariate analysis, monocyte count was the independent predictor of angiographic high-thrombus burden (odds ratio 3.107, 95% confidence interval [CI] 1.199–7.052, p = 0.020). For the prediction of angiographic high-thrombus burden, admission monocyte count at a cut-off value of 0.48×10^9/L yielded 0.59 ROC-AUC (71.9% sensitivity, 46.9% specificity).**

Conclusions: **Monocyte count on admission was an independent clinical predictor of high-thrombus burden in patients with STEMI undergoing PPCI. Our findings suggest that admission monocyte count may be available for early risk stratification of high-thrombus burden in acute STEMI patients and might allow the optimization of antithrombotic therapy to improve the outcomes of PPCI. (Arq Bras Cardiol. 2018; 110(4):333-338)**

Keywords: **Myocardial Infarction; Percutaneous Coronary Intervention/methods; Coronary Thrombosis/diagnostic imaging; Monocytes.**

Introduction

Complete thrombotic occlusion of a major epicardial coronary artery is the common pathophysiological mechanism of acute ST-segment elevation myocardial infarction (STEMI). Primary percutaneous coronary intervention (PPCI) of the infarct-related artery in patients with STEMI is associated with prompt restoration of normal blood flow and improved clinical outcomes. However, clinical studies have shown that a high burden of peri-procedural intracoronary thrombus is an essential contributor of low thrombolysis in myocardial infarction (TIMI) flow grade and impaired myocardial perfusion. Identification of relationships between blood cell-related biomarkers and blood flow state during PPCI procedure is one of the current research focuses. Studies have revealed that monocytes may be involved in the pathogenesis of coronary artery disease[1] and elevated monocyte count is a risk factor for myocardial infarction.[2] Previous studies have shown that monocytes play an important role in thrombotic disorders, not only via the secretion of pro-coagulant factors, such as tissue factor, but also by promoting inflammation processes. In our previous reports, monocyte counts on admission independently predict no-reflow following primary PPCI.[3] In the current study, we aimed to investigate further the relationship between on admission monocyte count and angiographic intracoronary thrombus burden in patients receiving PPCI.

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Methods

Study population

We enrolled 273 consecutive patients with STEMI undergoing PPCI within 12h from symptom onset between

September 2013 and May 2016 at the Cardiology Department of Beijing Shijitan Hospital. STEMI was defined as: typical chest pain > 30 minutes with ST elevation of > 1 mm in at least two consecutive leads on the electrocardiogram, or new onset left bundle branch block and more than two-fold increase in serum cardiac markers. Exclusion criteria included cardiogenic shock on admission, active infections, systemic inflammatory disease history, known malignancy, liver disease, as well as renal failure. The study protocol was approved by the Beijing Shijitan Hospital Ethics Committee, Capital Medical University, and written informed consent was obtained from patients.

Coronary angiography and PCI procedure

Pharmacological treatment of all enrolled patients before PPCI included aspirin (300 mg loading dose), clopidogrel (600 mg loading dose) and an intravenous bolus of unfractionated heparin at a dose of 70 U/kg of body weight. PPCI was performed using the standard radial or femoral approach with a 6-or 7-French guiding catheter. The stent was deployed in all patients. The use of balloon pre-dilatation or post-dilatation, the type of stents (bare metal or drug-eluting), and the use of thrombus aspiration was left to the operator's decision. The glycoprotein IIb/IIIa receptor inhibitor tirofiban was given by judgment of the operator and initiated during PCI procedure with 10 μg/kg intracoronary bolus followed by 0.15 μg/kg/min intravenous infusion. Technically successful stent implantation was defined as the residual stenosis < 10% in the culprit lesion after the procedure as visually assessed by angiography, without occlusion of a significant side branch, flow-limiting dissection, distal embolization, or angiographic thrombus.

To evaluate the intracoronary thrombus burden we performed TIMI thrombus scale[4,5] in all patients after ante-grade flow achievement through guide wire crossing or small balloon dilatation (final TIMI thrombus grade). In TIMI thrombus grade 0, no cine-angiographic characteristics of thrombus are present; in TIMI thrombus grade 1, possible thrombus is present with such angiographic characteristics as decreased contrast density, haziness, irregular lesion contour, or a smooth convex "meniscus"at the site of total occlusion suggestive, but not diagnostic of thrombus; in TIMI thrombus grade 2, there is definite thrombus, with the largest dimensions ≤ 1/2 the vessel diameter; in TIMI thrombus grade 3, there is definite thrombus with the largest linear dimension > 1/2 but < 2 vessel diameters; in TIMI thrombus grade 4, there is definite thrombus, with the largest dimension ≥ 2 vessel diameters; and in TIMI thrombus grade 5, there is total occlusion. Patients were divided into two groups according to the final TIMI thrombus grade: low-thrombus burden group with a grade of 0–2, and high-thrombus burden group with a grade of 3–4.

Laboratory analysis and echocardiography

In all patients, blood samples for measurements were performed according to our previous work.[3] White blood cell (WBC) count, monocyte count, and other biochemical parameters were drawn into standard ethylenediaminetetraacetic acid (EDTA) containing tubes on admission in the emergency room before the administration of aspirin and clopidogrel. Common blood counting (CBC) parameters were measured by an automated blood cell counter (XS-1000i; Sysmex Co.). Creatinine and cardiac enzymes were also measured in all patients determined by the standard methods. Echocardiography investigation was routinely performed on admission before PPCI, using GE ViVidE7 ultrasound machine (GE Healthcare, America) with a 3.5-MHz transducer. Left ventricular ejection fraction (LVEF) was measured by Simpson's method in the 2-dimensional echocardiographic apical 4-chamber view.

Statistical analyses

Statistical analysis was performed by using the SPSS 22.0 Statistical Package Program for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables are presented as a mean ± standard deviation or as medians and interquartile ranges. The differences between groups of continuous variables with a normal distribution (age, LVEF, creatinine, stent parameters and hematological parameters) were tested by independent samples t-test, while skewed distribution variable (peak cardiac troponin I (cTnI)) were compared by the Mann-Whitney U test. Categorical variables were summarized as percentages and compared with the chi-square test. A univariate analysis was first performed to test for the association of the high-thrombus burden and several potentially impacting variables (age, sex, history of diabetes mellitus, prior myocardial infarction (MI), LVEF, creatine level, time from symptom onset to PPCI, monocyte count, neutrophil count, lymphocyte count and hemoglobin level). Multivariate logistic regression analysis was then used to identify independent predictors of high thrombus burden using variables (prior MI, time from symptom onset to PPCI and monocyte count) that reached a trend-level effect ($p < 0.1$) in the univariate analyses. The receiver operating characteristics (ROC) curve was used to determine the cut-off value of monocyte count to predict the high-thrombus burden. A two-sided p-value of < 0.05 was considered significant.

Results

A total of 273 patients (mean age 62.2 ± 13.6 years; 81.0% male) who underwent PPCI were enrolled in our analysis. Stent implantation was technically successful in all patients. The comparison of baseline clinical and laboratory characteristics between thrombus burden groups are presented in Table 1. There were no significant differences between the low thrombus group and the high thrombus group in the age, sex distribution, hypertension, diabetes mellitus, hyperlipidemia, current smoking, prior MI left ventricular ejection fraction and serum creatinine level. Compared with patients with low thrombus burden, patients with high-thrombus burden had higher peak cTnI.

Comparison of the baseline angiographic and procedural characteristics of the groups based on thrombus burden is shown in Table 2. Thrombus aspiration device and intracoronary tirofiban administration were used more frequently in the high thrombus burden group than low-thrombus burden group (62.1 vs. 10.1%, $p = 0.000$, 83.2 vs. 52.2%, $p = 0.000$, respectively). There were no significant differences of the time from pain to intervention, infarct-related coronary artery and other procedural characteristics between two groups.

Table 1 – Baseline clinical and laboratory characteristics of the study population divided according to thrombus burden

	Low thrombus burden (n = 178)	High thrombus burden (n = 95)	p value
Age (years)	62.3 ± 13.2	62.0 ± 14.7	0.866*
Male sex, n (%)	143 (80.3)	77 (81.1)	0.482†
Diabetes mellitus, n (%)	56 (31.5)	31 (32.6)	0.716†
Hypertension, n (%)	106 (59.6)	57 (60.0)	0.503†
Hyperlipidemia, n (%)	109 (61.2)	65 (68.4)	0.395†
Active smokers, n (%)	75 (42.1)	47 (49.5)	0.200†
Prior MI, n (%)	6 (3.4)	3 (3.2)	0.145†
LVEF (%)	53.4 ± 9.7	52.9 ± 8.5	0.699*
Creatinine, µmol/L	76.9 ± 24.5	81.4 ± 25.6	0.167*
Peak cTnI (ng/mL)	29.8 (1.2–86.6)	56.7 (16.4–100.6)	0.037‡

**: Independent samples t-test; †: Chi-square test; ‡: Mann-Whitney U test; MI: myocardial infarction; LVEF: left ventricular ejection fraction; cTnI: cardiac troponin I.*

Table 2 – Baseline angiographic and procedural characteristics according to thrombus burden

Variable	Low thrombus burden (n = 178)	High thrombus burden (n = 95)	p value
Time from symptom onset to PPCI			0.773†
< 3 h (%)	48 (26.9)	27 (28.4)	
3–6 h (%)	66 (37.1)	38 (40.0)	
6–12 h (%)	64 (36.0)	30 (31.6)	
Anterior infarct location, n (%)	95 (53.4)	48 (50.5)	0.918†
Infarct-related coronary artery, n (%)			**0.788†**
Left main	0 (0.0)	0 (0.0)	
Left anterior descending	95 (53.4)	49 (51.6)	
Left circumflex	22 (12.4)	12 (12.6)	
Right coronary artery	61 (34.2)	34 (35.8)	
Number of used stent, n	1.6 ± 0.7	1.4 ± 0.7	0.106*
Total stent length, (mm)	36.7 ± 19.1	36.6 ± 17.6	0.164*
Stent diameter, (mm)	3.1 ± 0.4	3.2 ± 0.5	0.164*
Use of thrombus aspiration, n (%)	18(10.1)	59 (62.1)	0.000†
Tirofiban use, n (%)	93 (52.2)	79 (83.2)	0.000†

**: Independent samples t-test; †: Chi-square test.*

The comparison of admission hematological parameters is presented in Table 3. WBC counts, neutrophil counts, platelet count, hemoglobin, hematocrit, mean platelet volume, and lymphocyte count were similar in both groups. The patients in the high-thrombus burden group had significantly higher monocyte count when compared with the patients of low-thrombus burden group (0.61 ± 0.29×109/L vs. 0.53 ± 0.24×109/L, p = 0.021.

Univariate and multivariate logistic regression analysis of the association between the angiographic high thrombus burden and multiple parameters are presented in Table 4.

In multivariate analyses, on admission monocyte count was an independent predictor of angiographic high thrombus burden (odds ratio 3.107, 95% confidence interval [CI] 1.199–7.052, p = 0.020). The most discriminative cut-off values of monocyte count were 0.48×10^9/L, with a sensitivity of 71.9% and a specificity of 46.9% (AUC: 0.59; 95% CI: 0.515–0.654; p = 0.035).

Discussion

Acute STEMI is characterized by complete thrombotic occlusion of a coronary artery. The goal of PPCI in STEMI is the rapid restoration of coronary blood flow, maximum salvage of myocardium and improving patients' outcomes after STEMI. Studies have shown that intracoronary thrombi can lead to

Table 3 – Hematological parameters of the study population

Variable	Low thrombus burden (n = 178)	High thrombus burden (n = 95)	p value
White blood cell count ×10^9/L	9.6 ± 3.0	9.9 ± 3.2	0.326*
Neutrophil count×10^9/L	6.8 ± 2.8	6.9 ± 3.3	0.774*
Hemoglobin g/dL	14.4 ± 1.9	14.4 ± 2.3	0.707*
Platelet count×10^9/L	214.3 ± 60.5	218.8 ± 53.8	0.551*
Hematocrit %	42.3 ± 4.7	42.2 ± 4.9	0.835*
Mean platelet volume fl	10.3 ± 0.8	10.2 ± 0.9	0.668*
Lymphocyte count×10^9/L	2.23 ± 1.94	2.32 ± 1.35	0.827*
Monocyte count ×10^9/L	0.53 ± 0.24	0.61 ± 0.29	0.021*

**: Independent samples t-test.*

Table 4 – Independent predictors of high-thrombus burden in patients with ST-elevation myocardial infarction in logistic regression analyses

Variable	Univariate		Multivariate	
	Odds ratio (95%CI)	p value	Odds ratio (95%CI)	p value
Age	0.998(0.980–1.016)	0.829		
Sex	1.033(0.549–1.943)	0.921		
Diabetes mellitus	0.932(0.547–1.588)	0.797		
Prior MI	1.869 (0.781–9.178)	0.092	1.745 (0.752–8.644)	0.495
LVEF	0.995 (0.968–1.022)	0.702		
Time from symptom onset to PPCI	1.021 (1.008–1.208)	0.094	1.002 (0.979–1.195)	0.553
Creatinine	1.007 (0.997–1.017)	0.194		
Neutrophil count	1.016 (0.935–1.104)	0.704		
Hemoglobin	0.998 (0.986–1.010)	0.780		
Lymphocyte count	1.019 (0.886–1.173)	0.790		
Monocyte count	2.429 (1.022–5.776)	0.045	3.107 (1.199–7.052)	0.020

MI: myocardial infarction; LVEF: left ventricular ejection fraction; PPCI: primary percutaneous coronary intervention.

micro- and macro-vasculature embolization and is associated with poor outcomes in patients who underwent PPCI of culprit lesion.[6-8] However, management of thrombotic burden is still challenging during PPCI for STEMI. Early risk stratification to detect patients at high risk of high thrombus burden is very important for the individualized prevention and treatment of this condition. In the current study, elevated admission monocyte counts were found as an independent predictor of high thrombus burden of infarct-related artery (IRA) during PPCI in patients with STEMI.

Inflammation and oxidative stress were found to play an important role in the pathogenesis of plaque rupture and subsequent thrombus formation.[9,10] Monocyte comprises 10% of human blood leukocytes and is one of the major players of systemic inflammatory response. They are associated with the inflammatory response at the vulnerable plaque in patients with STEMI.[11] Tissue factor (TF) is an essential component of the extrinsic coagulation cascade and is critical in arterial thrombosis. Recent data have suggested that monocytes appear to be the major source of blood TF.[12] Palmerini et al.,[13] conducted a histological evaluation of thrombi aspirated from coronary arteries of patients with STEMI and found that monocytes consistently stained strongly for tissue factor, while neutrophils had a weakly and irregular tissue factor staining. Another explanation for the relationship between monocytes and high thrombus burden may be the increased formation of monocyte-platelet aggregates (MPA). MPA is a useful marker of platelet activation in ACS patients[14] and was found to be a significant predictor of no-reflow in patients with STEMI undergoing primary PCI.[15]

Involvement of monocytes in the prothrombotic state is not restricted to the above-mentioned mechanisms. Aleman et al.,[16] showed that microparticles (MPs) from monocytes are associated with prothrombinase activity and faster fibrin formation. Furthermore, monocytes may induce thrombus generation by promoting inflammation processes. Mach et al.,[17] found that stimulation of human monocytes induced the expression of interstitial collagenase and stromelysin, which were associated with plaque destabilization and thrombotic events. Post-mortem investigation and histological studies of in

vivo-obtained thrombus specimens of STEMI patients revealed that approximately 50% of the aspirated thrombi were days to even weeks old,[18] which suggests that prothrombotic factors, such as elevated levels of circulating monocyte, may starts days or even weeks before symptom onset during STEMI.

In the current study, admission monocyte count was evaluated regarding its potency to differ between high thrombus burden and low thrombus burden in STEMI patients underwent PPCI. However, admission monocyte count at cut-off value of 0.48×10^9/L presented a low diagnostic performance with 71.9% sensitivity and 46.9% specificity. A combination of parameters, including monocyte count, may be needed to improve diagnostic abilities.

The main limitations of this study were the retrospective design and relatively small number of patients. Also, the prior antithrombotic therapeutic profiles of the study population, which might affect intracoronary thrombotic status during PPCI, were not routinely available in the present study and not included in the risk factor analysis. Further large prospective cohort study with assessment of detailed information of prior antithrombotic therapy might be more illuminating.

Conclusions

In conclusion, we found that monocyte count on admission, which is cheaply and easily measurable laboratory data, is a predictor of high intracoronary thrombus burden in patients with STEMI undergoing primary PCI.

Author contributions

Conception and design of the research and Critical revision of the manuscript for intellectual content: Wang Z, Peng J; Acquisition of data and Analysis and interpretation of the data: Wang Z, Liu N, Ren L, Lei L, Ye H; Statistical analysis and Writing of the manuscript: Wang Z.

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 Beijing Shijitan Hospital, Capital Medical University under the protocol number L08-002. 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.

References

1. Taleb S. Inflammation in atherosclerosis. Arch Cardiovasc Dis. 2016;109(12):708-15. doi: 10.1016/j.acvd.2016.04.002.
2. Dutta P, Nahrendorf M. Monocytes in myocardial infarction. Arterioscler Thromb Vasc Biol. 2015;35(5):1066-70. doi: 10.1161/ATVBAHA.114.304652.
3. Wang Z, Ren L, Liu N, Lei L, Ye H, Peng J. Association of monocyte count on admission with angiographic no-reflow after primary percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction. Kardiol Pol. 2016;74(10):1160-1166. doi: 10.5603/KP.a2016.0065.
4. Gibson CM, de Lemos JA, Murphy SA, Marble SJ, McCabe CH, Cannon CP, et al. Combination therapy with abciximab reduces angiographically evident thrombus in acute myocardial infarction: a TIMI 14 substudy. Circulation. 2001;103(21):2550-4. doi: https://doi.org/10.1161/01.CIR.103.21.2550.
5. Sianos G, Papafaklis MI, Serruys PW. Angiographic thrombus burden classification in patients with ST-segment elevation myocardial infarction treated with percutaneous coronary intervention. J Invasive Cardiol. 2010;22(10 Suppl B):6B-14B.
6. Higuma T, Soeda T, Yamada M, Yokota T, Yokoyama H, Izumiyama K, et al. Does residual thrombus after aspiration thrombectomy affect the outcome of primary PCI in patients with ST-segment elevation myocardial infarction?: An optical coherence tomography study. JACC Cardiovasc Interv. 2016;9(19):2002-11. doi: 10.1016/j.jcin.2016.06.050.
7. Piccolo R, Galasso G, Iversen AZ, Eitel I, Dominguez-Rodriguez A, Gu YL, et al.Effects of baseline coronary occlusion and diabetes mellitus in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. Am J Cardiol. 2014;114(8):1145-50. doi: 10.1016/j.amjcard.2014.07.030
8. Lee WC, Chen HC, Fang HY, Hsueh SK, Chen CJ, Yang CH, et al. Comparison of different strategies for acute ST-segment elevation myocardial infarction with high thrombus burden in clinical practice: Symptom-free outcome at one year. Heart Lung. 2015;44(6):487-93. doi: 10.1016/j.hrtlng.2015.08.003.
9. Teng N, Maghzal GJ, Talib J, Rashid I, Lau AK, Stocker R. The roles of myeloperoxidase in coronary artery disease and its potential implication in plaque rupture. Redox Rep. 2017;22(2):51-73. doi: 10.1080/13510002.2016.1256119.
10. Chistiakov DA, Orekhov AN, Bobryshev YV. Contribution of neovascularization and intraplaque haemorrhage to atherosclerotic plaque progression and instability. Acta Physiol (Oxf). 2015;213(3):539-53. doi: 10.1111/apha.12438.
11. Cimmino G, Loffredo FS, Morello A, D'Elia S, De Palma R, Cirillo P, et al. Immune-inflammatory activation in acute coronary syndromes: a look into the heart of unstable coronary plaque. Curr Cardiol Rev. 2017;13(2):1-8. doi: 10.2174/1573403X12666161014093812.
12. Hisada Y, Alexander W, Kasthuri R, Voorhees P, Mobarrez F, Taylor A, et al. Measurement of microparticle tissue factor activity in clinical samples: A summary of two tissue factor-dependent FXa generation assays. Thromb Res. 2016 Mar;139:90-7. doi: 10.1016/j.thromres.2016.01.011.

13. Palmerini T, Tomasi L, Barozzi C, Della Riva D, Mariani A, Taglieri N, et al. Detection of tissue factor antigen and coagulation activity in coronary artery thrombi isolated from patients with ST-segment elevation acute myocardial infarction. PLoS One. 2013;8(12):e81501. doi: 10.1371/journal.pone.0081501.

14. Zhang SZ, Jin YP, Qin GM, Wang JH. Association of platelet-monocyte aggregates with platelet activation, systemic inflammation, and myocardial injury in patients with non-ST elevation acute coronary syndromes. Clin Cardiol. 2007;30(1):26-31. doi: 10.1002/clc.2.

15. Ren F, Mu N, Zhang X, Tan J, Li L, Zhang C, et al. Increased platelet-leukocyte aggregates are associated with myocardial no-reflow in patients with ST elevation myocardial infarction. Am J Med Sci. 2016;352(3):261-6. doi: 10.1016/j.amjms.2016.05.034.

16. Aleman MM, Gardiner C, Harrison P, Wolberg AS. Differential contributions of monocyte- and platelet-derived microparticles towards thrombin generation and fibrin formation and stability. J Thromb Haemost. 2011;9(11):2251-61. doi: 10.1111/j.1538-7836.2011.04488.x.

17. Mach F, Schönbeck U, Bonnefoy JY, Pober JS, Libby P. Activation of monocyte/macrophage functions related to acute atheroma complication by ligation of CD40: induction of collagenase, stromelysin, and tissue factor. Circulation. 1997;96(2):396-9. doi: https://doi.org/10.1161/01.CIR.96.2.396.

18. Rittersma SZ, van der Wal AC, Koch KT, Piek JJ, Henriques JP, Mulder KJ, et al. Plaque instability frequently occurs days or weeks before occlusive coronary thrombosis: a pathological thrombectomy study in primary percutaneous coronary intervention. Circulation. 2005;111(9):1160-5. doi: 10.1161/01.CIR.0000157141.00778.AC.

Original Article

Is Lipid Accumulation Product Associated with an Atherogenic Lipoprotein Profile in Brazilian Subjects?

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Abstract

Background: Lipid accumulation product (LAP), a simple and low-cost tool, is a novel biomarker of central lipid accumulation and represents a potential surrogate marker for atherogenic lipoprotein profile. However, its association with lipoprotein subfractions has not been described in the literature.

Objective: To determine whether LAP index could be used as a marker of low- and high-density lipoprotein (LDL and HDL) size in Brazilian individuals.

Methods: This cross-sectional study included patients (n = 351) of both sexes and age between 30-74 years. Clinical and sociodemographic data and family history of diseases were evaluated. Lipoprotein size, and levels of total cholesterol (TC), lipoproteins, apolipoprotein AI and B (APO AI/APO B), glucose, insulin, insulin resistance index (HOMA-IR) and non-esterified fatty acids (NEFA) were assessed in blood samples. LAP was calculated by the formulas [(waist circumference$_{[cm]}$-58) × (triglycerides$_{[mmol/L]}$) for women and (waist circumference $_{[cm]}$-65) × (triglycerides $_{[mmol/L]}$) for men]. The association between LAP and metabolic parameters were tested by linear trend (general linear model, GLM test) before and after multiple adjustments for potential confounders (sex, age, smoking, statin, fibrate, and hypoglycemic drugs) at significant level $p < 0.05$.

Results: LAP was positively associated with TC, APO B, NEFA, glucose, insulin and HOMA-IR values, and negatively associated with HDL-C. Higher central lipid accumulation was corelated with higher percentage of intermediate HDL and of small LDL and HDL and less amount of large HDL. LDL size was also reduced in greater LAP index values. The negative impact of LAP was maintained after adjustment for multiple variables.

Conclusion: LAP was robustly associated with atherogenic profile of lipoprotein subfractions, independently of multiple confounders. (Arq Bras Cardiol. 2018; 110(4):339-347)

Keywords: Cardiovascular Diseases; Lipoproteins, HDL; Lipoproteins, LDL; Insulin Resistance; Dyslipidemias; Adults; Risk Factors.

Introduction

Cardiovascular disease (CVD) is the leading cause of premature morbidity and mortality worldwide, compromising significant private and government resources.[1] Public policy programs are focused on prevention and modification in traditional risk factors (hypertension, dyslipidemia, smoking, and diabetes *mellitus*), which are the basis of all models of cardiovascular risk prediction. Nevertheless, identification of new risk factors and/or markers for CVD is important to better understand some clinical events that cannot be explained by classical risk factors.

These new biomarkers involve measurable biochemical parameters in serum or plasma, however, cholesterol associated with high-density lipoprotein (HDL-C) and low-density lipoprotein (LDL-C) remain the main lipoproteins monitored to estimate cardiovascular risk in adults.[2] Currently, biomarkers associated with functionality and structure of lipoproteins – such as their size (small, intermediate, large and phenotypes A and B) – antioxidants (tocopherols, carotenoids), apolipoproteins (Apo B, AI, CII, J, F) and enzymes (Lp-PLA$_2$, ACAT) have been investigated.[3-5] Particularly, small dense LDL have been extensively described by its proatherogenic properties. This particle migrates to the subendothelial space more easily, recruits and activates macrophages, causing their transformation into foam cells and generating fatty streak, a hallmark of atherosclerosis.[4] Contrary to the well-established atherogenic mechanisms of LDL, functional role of HDL size remains controversial. Small HDL species are described as more antioxidant, anti-inflammatory and more capable to promote cellular cholesterol efflux.[6] In opposite, Woudberg et al. showed that obesity was associated with reduced large HDL subclasses.[7] Many of these biomarkers are expensive, require methods technically sophisticated and show limited use in primary health care and prevention of diseases.

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Lipid Accumulation Product (LAP) was proposed as a simple, inexpensive and accurate surrogate index to estimate cardiovascular risk[8] and all-cause mortality.[9] This index combines anthropometric (waist circumference, WC) and biochemical (fasting triglycerides, TG) parameters, connecting anatomical to physiological changes associated with increased central accumulation of lipids in adults. Kahn[10] observed in the Third National Health and Nutrition Examination Survey (NHANES III) that LAP index evidenced the negative effect of large WC possibly related with small dense LDL, although direct measurement of LDL size has not been done. The validity and superiority of LAP to identify cardiovascular risk, metabolic syndrome, diabetes *mellitus* and insulin resistance have been compared with body mass index (BMI), WC and waist-to-hip ratio.[9-13] Despite the negative impact of LAP on glucose metabolism, monitored principally in postmenopausal[13,14] and polycystic ovary syndrome women,[15,16] its association with the size of lipoproteins has not been directly evaluated and reported yet.

Previous studies based in LAP confirmed its association with classical risk factors for CVD.[17-20] Therefore, the aim of this study was to extend current knowledge of LAP, by evaluating the impact of this parameter on LDL and HDL size, considering the potential influence of confounders.

Methods

Subjects

Three hundred fifty-one adults of both sexes and multiple cardiovascular risk factors were selected for this cross-sectional study after complete clinical evaluation and electrocardiogram (ECG). These subjects were recruited from the Research Center located at the University Hospital of the University of Sao Paulo. The non-probabilistic sampling was employed. According to inclusion criteria, the subjects included in the study were 30–74 years old and had at least one of the risk factors for CVD – dyslipidemia, diabetes *mellitus*, and/or hypertension. Pregnant or lactating women, individuals who participated in other studies, had severe hepatic or renal disease, type 1 diabetes mellitus, illicit drug users, alcoholics, and individuals under lipid-lowering drugs introduced or changed 30 days before blood collection were not enrolled in this protocol. This study was approved by the Research Ethics Committee of the University Hospital (n 1126/11) and the School of Public Health, University of Sao Paulo (n 2264) and all procedures followed the standards of the Declaration of Helsinki of 1975, revised in 2008. All subjects gave their written informed consent.

Demographic and clinical profile

Trained interviewers evaluated the demographic features of participants by a pre-structured questionnaire addressing sex, age, and ethnicity. The clinical evaluation consisted of current information on medical history, family history of chronic diseases (father and mother), and regular use of medication. Smoking was considered when the habit was reported by the subjects, regardless of the amount of cigarettes. Hypertension was confirmed by clinical history, use of antihypertensive medication and systolic (SBP) and diastolic (DBP) blood pressure monitored after at least five minutes at rest and mean of three measures was used for data analysis. Hypertension was defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg. Type 2 diabetes mellitus was defined by previous diagnosis of diabetes, use of oral hypoglycemic agents and plasma glucose levels higher 100 mg/dl. The Framingham Risk Score (FRS) was calculated as previously described.[21,22]

Anthropometric parameters

Weight (Kg) and height (cm) were measured to the nearest 0.1 kg and 0.1 cm, respectively, with standard methods and equipment. BMI was calculated as weight (Kg) divided by the square of the standing height (m^2). The WC was measured using flexible inelastic tape with an accuracy of 1.0-mm (TBW®; Sao Paulo, SP, Brazil) without tightening it against the body. Body composition was assessed by bioelectrical impedance (BIA) (Analyzer®, model Quantum II; RJL Systems; Michigan, USA). Body fat percentage was calculated using the Cyprus (Body Composition Analysis System, v. 2.5; RJL Systems®; Detroit, MI, USA) program, which considered sex, age, weight, height, level of physical activity, resistance and reactance. All measurements were performed in duplicate by trained staff.

Blood samples

After fasting (12 h), blood samples (20 mL) were collected. For analyses using plasma, blood was collected in vacutainer tubes containing ethylenediaminetetraacetic acid (EDTA; 1.0 μg/mL). The protease inhibitors aprotinin (10.0 μg/ml), benzamidine (10.0 μM), phenylmethylsulfonyl fluoride (PMSF; 5.0 μM) and the antioxidant butylated hydroxytoluene (BHT; 100.0 μM) were added to the samples. Plasma and serum were separated by centrifugation (3,000 rpm; 10 min; 4°C) and samples were kept frozen (−80 °C) until analysis.

Biochemical Analysis

Plasma TG, total cholesterol (TC), and HDL-C levels were measured using commercial kits (Labtest; Lagoa Santa, MG, Brazil). LDL-C levels were calculated using the Friedewald equation for subjects who had TG lower than 400 mg/dl.[23] Apolipoproteins B and AI (Apo B and Apo AI) were determined using standard methods (APO A1 and APO B Autokits, Randox; Kearneysville, WV, USA). Non-esterified fatty acids (NEFA) levels were determined using the Free Fatty Acid Quantification kit (Wako Chemicals – USA Inc.; Richmond, VA, USA). Glucose levels were determined using an enzymatic and colorimetric kit (Glucose PAP Liquiform; Labtest; Lagoa Santa, MG, Brazil). Plasma insulin was detected using the commercial Human Insulin Direct ELISA kit (Life Technologies; Grand Island, NY, USA). Insulin resistance was calculated using the homeostatic model assessment-insulin resistance (HOMA-IR) formula as follows: HOMA-IR = fasting insulin concentration (U/mL) x fasting glucose (mmol/L)/22.5.[24] These parameters were analyzed in duplicate in automatic Cobas system (Hitachi High Technology, Minato-ku, Tokyo, Japan).

The distribution of HDL and LDL subfractions was determined using the Lipoprint supplier system based on nondenaturing polyacrylamide gel. The LDL1 and LDL2 sub-fractions were classified as large LDL, and sub-fractions from LDL3 to LDL7 were classified as smaller and denser particles. The LDL size (nm) was determined and from that, phenotype A (> 25.6 nm, large and less dense LDL) and non-A (≤ 25.6 nm, small dense LDL) pattern were calculated. For HDL particle size, ten sub-fractions were identified, which were classified as large (HDL1 to HDL3), intermediate (HDL4 to HDL7), and small (HDL8 to HDL10) particles.

All analyses were conducted in duplicate and intra- (1-5.8%) and inter- (0.5-15%) assay coefficients of variance were calculated.

Lipid Accumulation Product (LAP)

LAP was calculated using different formulae for women ($WC_{[cm]}$-58) × ($TG_{[mmol/L]}$) and men ($WC_{[cm]}$-65) × ($TG_{[mmol/L]}$), which include the minimum sex-specific WC values.[8]

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS®; v. 20.0) software package. Two-sided P values < 0.05 were considered statistically significant. The Kolmogorov–Smirnov test (p > 0.05) was applied to assess normality of data. Normally distributed continuous variables are presented as mean values and standard deviations (SD), whereas non-normally distributed data are presented as median and 25th and 75th percentiles. Categorical variables are presented as absolute values (n) and percentages (%). Groups were compared using the unpaired Student's t-test for normally distributed data. Non-normally distributed data were analyzed using non-parametric Mann–Whitney U tests. Categorical variables were compared using the Pearson chi-square or Fisher's exact test. Subjects were divided into tertiles (T) of the LAP index: T1 ≤ 45.5; 45.5 < T2 ≤ 80.3; and T3 > 80.3. Association between tertiles of LAP index and atherogenic lipoprotein profile were tested in a linear trend test by raw and adjusted models: age and sex (Model A) and age, sex, smoking, use of statin, fibrate, and/or hypoglycemic drugs (Model B). In addition, comparison between groups was performed by analysis of variance (ANOVA or Kruskal-Wallis – with multiple comparisons by Tukey test) after all adjustments (Model B) with significance level at p < 0.05.

Results

The demographic and clinical characteristics of the 351 subjects grouped by sex are shown in Table 1. The mean age of the subjects was 49.4 years for men (range: 30–72 years) and 54.4 years for women (range: 30–74 years, p < 0.001). Women were older and reported greater use of drugs than men (83.6 *versus* 69.8, respectively, p = 0.001), whereas higher percentage of men were smokers (p = 0.026). More than 80% of the subjects had a prior disease at the time of screening. Hypertension was the most prevalence disease in both genders (56.9% in men and 57.1% in women), which was corroborated by the high percentage of antihypertensive drug users. This profile is in concordance with elevated frequency of hypertension in father, mother or both parents of individuals (62.9% in men and 66.2% in women).

Table 2 shows results of cardiovascular risk, assessed by FRS, and biochemical and anthropometric variables stratified by sex. The FRS was similar between men (13.6 points) and women (13.5 points), indicating a moderate cardiovascular risk in both groups. Men showed higher values of WC and TG, impacting directly on elevated values of LAP in comparison with women. In contrast, women had higher values of Apo AI, HDL-C and NEFAs. Both groups showed similar profile of BMI and glucose homeostasis evaluated by glucose, insulin and HOMA-IR parameters. The influence of gender on lipid metabolism was confirmed by elevated percentage of small HDL and LDL and reduced percentage of large HDL observed in men. This profile was reinforced by the increase of LDL size in men (26.9 in men *versus* 27.0 in women; p = 0.001) and phenotype A in women (52.3% in men *versus* 70.8% in women; p = 0.001).

Raw and adjusted associations between LAP and other parameters were tested by tertiles (Table 3). LAP was positively associated with TC, Apo B, NEFA, glucose, insulin, and HOMA-IR and, consequently, this association increased with FRS points. Surprisingly, LAP was not corelated with LDL-C. After multiple adjustments for potential confounders (A and B models), the associations between LAP and biochemical parameters were maintained, except for Apo AI.

Also, central lipid accumulation was positively associated with the percentage of intermediate and small HDL subfractions in both total (Figure 1A) and sex-stratified sample (Figures 1B, 1C) after adjustment for age, smoking, and use of statin, fibrate and hypoglycemic drugs. Similar results were found for small LDL, i.e., individuals in lowest, in the middle and in the highest tertile showed about 1.5%, 2.3% and 7.5% of small LDL, respectively (p < 0.001) (Figure 2Aii). Higher differences were seen in men (Figure 1Bi).

LDL size and percentage of large HDL were both negatively associated with LAP. In total sample, this difference was nearly 10 points for large HDL – 34.2% in T1 and 24.5% in T3 (Figures 1Ai, Bi, Ci). Associations between LAP index and large LDL were found in men (Figure 2Bi), but not in total sample nor in women, demonstrating a sex-dependent relationship for this subfraction.

Discussion

Based on this cross-sectional study, LAP has a significant association with classical and new cardiovascular biomarkers. These associations were especially important when LAP index was corelated to size of the LDL and HDL particles.

Previously, Kahn and Valdez[8] evaluated a cross-sectional sample from the NHANES III and reported that individuals with high WC and TG levels were more likely to show inadequate levels of HDL-C, Apo B, fasting insulin, and glucose. Later, Kahn[11] confirmed that the LAP was superior to BMI in indicating adults with diabetes mellitus and for predicting imbalance in glucometabolic variables (HOMA-IR, fasting glucose, and glycated hemoglobin). Similar results were found in studies conducted in other countries, in

Table 1 – Demographic and clinical characteristics of subjects by gender

Variables	Total (n = 351)		Men (n = 132)		Women (n = 219)		p
	n	%	n	%	n	%	
Age (years) **	52.5	(10.4)	49.4	(11.1)	54.4	(9.6)	< 0.001
Smoking No	282	80.3	98	74.2	184	84.0	0.026
Current illnesses	306	87.2	114	86.4	192	87.7	0.723
Diabetes mellitus	71	20.2	32	24.2	39	17.8	0.146
Hypertension	200	57.0	75	56.8	125	57.1	0.962
Dyslipidemia	192	54.7	72	54.5	120	54.8	0.964
Drugs	274	78.1	91	69.8	183	83.6	0.001
Statin	98	27.9	28	21.2	70	32.0	0.030
Antihypertensive	181	51.6	64	48.5	117	53.2	0.370
Hypoglycemic agents	73	20.8	29	22.0	44	20.1	0.674
Fibrate §	9	2.6	3	2.3	6	2.7	0.543
Family history of diseases	320	91.2	122	92.4	198	90.4	0.520
Obesity	64	18.2	28	21.2	36	16.4	0.262
Hypertension	228	65.0	83	62.9	145	66.2	0.526
Acute myocardial infarction	100	28.5	38	28.8	62	28.3	0.924
Stroke	67	19.1	25	18.9	42	19.2	0.956
Diabetes mellitus	134	38.2	49	37.1	85	38.8	0.752
Peripheral vascular disease	25	71	8	6.1	17	7.8	0.548

*Comparative analysis of categorical variables was performed by Pearson chi-square or Fisher's exact test (§) (p < 0.05). ** Data presented as mean and standard deviation. Comparative analysis of continuous variables was performed using the unpaired Student's t-test (p < 0.05)*

which LAP was a better marker of glucose imbalance and a stronger predictor of DM than BMI.[13-20] The present study confirms that LAP is sensitive to identify dysfunctions related to glucose metabolism, even after adjustment for drug use and multiple confounders.

The relevance of LDL-C in the development of atherosclerosis has been recognized. However, some individuals with normal LDL-C levels have cardiovascular events, indicating that other risk factors related or not with LDL exert a role in the atherosclerotic process. Epidemiological evidence shows that an increased proportion of small and dense LDL particles is strongly associated with the risk of coronary heart disease.[25] Individuals with elevated plasma concentrations of small and dense LDL are at 3–7 times greater risk to develop coronary artery disease (CAD), independent of the LDL-C level.[5] Smaller and denser LDL, known as phenotype B, has been proposed as a more atherogenic sub-fraction than large LDL. Smaller particles remain for a longer time in plasma and shows reduced affinity for the B/E receptor.[25] Phenotype-B LDL is highly recognized by scavenger receptor, and therefore is more susceptible to migration to the subendothelial layer and oxidation.[4,5] Despite that, the relationship between LAP and LDL size has not been described in the literature. Our results showed that small LDL particles and LDL size were positively and negatively associated with LAP, respectively, even if LDL-C was not related to LAP. Mirmiran et al.[26] also didn't find any correlation between LAP and LDL-C.

Reinforcing the negative role of small and dense LDL, Kwon et al.[27] described that this particle was independently associated with the incidence and extension of CAD in a Korean population, confirmed by subsequent studies.[28,29] Studies have also reported a negative correlation between LDL size and risk of acute myocardial infarction.[30,31] Similarly, small and dense LDL was associated with increased TG and decreased HDL-C levels.[32] Therefore, results presented in this study showed for the first time that the LAP was significantly and robustly associated with the more atherogenic small LDL particle in Brazilians subjects above 30 years of age and moderate cardiovascular risk.

Contrary to high LDL-C level, low HDL-C level is accepted as an independent risk factor for CVD.[22,23,32] Currently, it has been proposed that reverse cholesterol transport and other HDL properties such as antithrombotic action, endothelial function, and antioxidant and anti-inflammatory activities depend on HDL size.[33] Larger HDL particles have a higher content of Apo AI and are described as more effective in reverse cholesterol transport.[3] Asztalos et al.[32] showed that a predominance of small, rather than large HDL particles, increased the risk of coronary heart disease. It was also

Table 2 – Framingham risk score, biochemical and anthropometric characteristics of subjects by gender

Variables	Total (n = 351)	Men (n = 132)	Women (n=219)	p
FRS (points)	13.5 (4.8)	13.6 (5.0)	13.5 (4.5)	0.941
HDL-C (mg/dl)	37.0 (10.0)	32.0 (7.0)	40.0 (10.0)	< 0.001
LDL-C (mg/dl)	139.0 (38.0)	133.0 (22.0)	41.0 (40.0)	0.092
TG (mg/dl)*	128.0 (94.0 - 188.0)	145.0 (10.06 - 213.0)	121.0 (90.0 - 172.0)	0.001
Apo AI (mg/dl)	132.0 (25.0)	123.0 (33.0)	137.0 (26.0)	< 0.001
Apo B (mg/dl)	104.0 (25.0)	103.0 (23.0)	105.0 (26.0)	0.400
NEFA (mEq/dl)	0.6 (0.3)	0.6 (0.3)	0.7 (0.3)	0.016
Small LDL (%)*	1.6 (0.8 - 4.5)	2.1 (1.0 - 6.3)	1.4 (0.6 - 3.6)	0.003
Large LDL (%)	26.3 (5.4)	26.6 (4.9)	26.1 (5.6)	0.491
Small HDL (%)	19.8 (7.1)	21.1 (6.5)	19.1 (7.4)	0.022
Inter HDL (%)	50.3 (5.1)	51.1 (4.5)	49.8 (5.3)	0.039
Large HDL (%)	29.9 (8.6)	27.8 (7.8)	31.0 (8.8)	0.002
LDL size* (nm)	27.0 (26.5 - 27.2)	26.9 (26.4 - 27.1)	27.0 (26.7 - 27.2)	0.001
Phenotype A (%) **	63.8	52.3	70.8	0.001
Glucose (mg/dl)*	97 (91.0 - 108.0)	98 (91.0 - 113.0)	97 (91.0 - 105.0)	0.358
Insulin (µIU/ml)*	16.3 (12.6 - 22.1)	15.6 (12.7 - 22.5)	16.7 (12.4 - 22.0)	0.791
HOMA-IR *	4.0 (2.9 -5.9)	4.2 (3.1 - 5.9)	4.0 (2.9 - 5.8)	0.596
Weight (kg)	77.9 (68.8 - 93.9)	89.7 (75.8 - 101.7)	72.9 (64.1 - 86.5)	<0.001
WC (cm)	100.5 (13.5)	104.2 (12.7)	98.4 (13.5)	<0.001
Body fat (%)	37.8 (25.2 - 46.0)	23.4 (20.7 - 26.9)	43.4 (38.4 - 49.2)	<0.001
BMI (kg/m^2)	30.8 (5.9)	30.6 (5.4)	30.9 (6.2)	0.628
LAP *	57.7 (35.4 - 87.2)	68.4 (40.5 - 105.0)	53.2 (35.2 - 81.6)	0.026

Data presented as mean (SD) and median (p25-p75). Comparative analysis was performed by the unpaired Student's t test or Mann-Whitney test (*) and Pearson chi-square (**) (p < 0.05). FRS: Framingham Risk Score; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triacylglycerol; Apo AI: apolipoprotein AI; Apo B: apolipoprotein B; NEFA: non-esterified fatty acids; BMI: body mass index; LAP: lipid accumulation product; WC: waist circumference.

Table 3 – Linear trend analysis of Framingham risk score and biochemical variables in lipid accumulation product tertiles

	LAP			Raw data	Model A	Model B
	T1 ≤ 45.5 (n = 117)	45.5 < T2 ≤ 80.3 (n = 117)	T3 > 80.3 (n = 117)	p	p	p
FRS	12.3	13.6	14.6*§	< 0.001	< 0.001	< 0.001
TC (mg/dl)	198.2	201.0	216.0*§	0.001	< 0.001	< 0.001
HDL-C (mg/dl)	40.7	37.6	32.4*§	< 0.001	< 0.001	< 0.001
LDL-C (mg/dl)	139.6	136.1	136.2	0.514	0.660	0.770
Apo AI (mg/dl)	135.6	134.2	127.2	0.012	0.062	0.073
Apo B (mg/dl)	97.5	103.8*	111.9*§	< 0.001	< 0.001	< 0.001
NEFA (mEq/dl)	0.6	0.6	0.7*	0.012	0.002	0.006
Glucose (mg/dl)	96.4	101.8	122.1*§	< 0.001	< 0.001	< 0.001
Insulin (µIU/ml)	15.1	19.0*	21.0*	< 0.001	< 0.001	< 0.001
HOMA-IR	3.6	4.7	6.2*§	< 0.001	< 0.001	< 0.001

*Model A: adjusted by sex and age. Model B: adjusted by sex, age, smoking, statin, fibrate, and hypoglycemic drugs. FRS: Framingham Risk Score; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; Apo AI: apolipoprotein AI: Apo B: apolipoprotein B; NEFA: non-esterified fatty acids; LAP: lipid accumulation product. Comparison between groups was performed by ANOVA or Kruskal-Wallis and multiple comparisons by Tukey test. *versus T1, §versus T2. Significance level adopted for all analysis p < 0.05.*

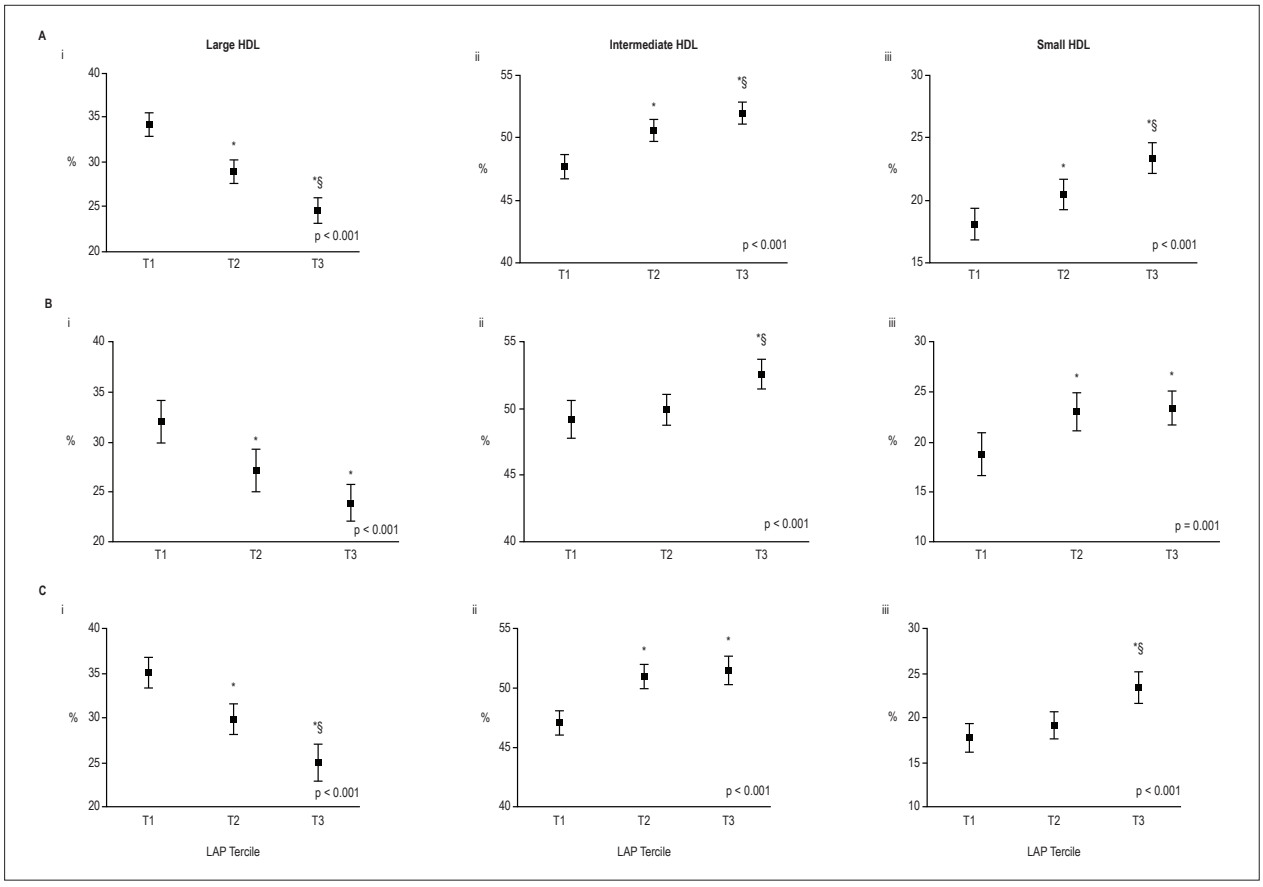

Figure 1 – *Percentages of large, intermediate, and small HDL (high density lipoprotein) particles, according to the LAP (lipid accumulation protein) tertiles. A) Adjusted by sex, age, smoking, statin, fibrate, and hypoglycemic drugs. B) Men, adjusted by age, smoking, statin, fibrate, and hypoglycemic drugs (n = 132). C) Women, adjusted by age, smoking, statin, fibrate, and hypoglycemic drugs (n = 219). i: Larger HDL. ii: Intermediate HDL. iii: Small HDL. Data are presented as mean and 95% confidence interval. Comparative analysis was performed using the linear trend test. LAP tertiles: T1 ≤ 45.5; 45.5 < T2 ≤ 80.3; T3 > 80.3. HDL – high-density lipoprotein, LAP: lipid accumulation product, % - percentage. Comparison between groups was performed by ANOVA or Kruskal-Wallis and multiple comparisons by Tukey test. *versus T1, §versus T2. Significance level adopted for all analysis p < 0.05.*

suggested that small HDL particle size is associated with several features of the metabolic syndrome and risk of CAD.[34] Our results showed a negative relationship of LAP with larger HDL and a positive relationship with smaller HDL particles. This profile is in agreement with the increased concentrations of HDL-C levels in subjects with lower LAP, although no correlation was found between LAP and Apo A1. Together with the LDL results, it reinforces the role of LAP as a surrogate marker for atherogenic lipoprotein subfractions.

In addition, our findings also showed a positive linear trend between NEFA values and LAP. Epidemiological studies have reported an association between NEFA and the risk of diabetes mellitus.[35,36] Increased concentrations of NEFA in individuals with visceral obesity contribute to the development of various disorders such as peripheral insulin resistance, dyslipidemia, and β-cell apoptosis.[37] Our data showed NEFA values similar to or higher than the values reported in the literature.[38,39] This is compatible with the increased values also observed for glucose, insulin and HOMA-IR, independent of sex in our study. Linear trends between LAP and fasting glucose, insulin and HOMA-IR confirm that this index is associated with multiple glucose- and cardiovascular-related dysfunctions. Previously, Sambataro et al.[40] showed that insulin sensitivity is not limited to dysfunction of fasting glucose and insulin and that lipid metabolism may affect this sensitivity. Therefore, the ability of LAP to simultaneously identify changes in glucose and lipid metabolism can expand the clinical relevance of this index.

This study had some limitations. The most significant one is that this study was conducted only in individuals with at least one cardiovascular risk factor, i.e., hypertension, diabetes mellitus or dyslipidemia. This suggests that the association found here might not be valid for health people. On the other hand, unfortunately, early diagnosis of dyslipidemia and changes in glucose metabolism are common events in young adults. Thus, more individuals would benefit from the inclusion of LAP in screening and monitoring of cardiovascular risk. Second limitation is the evaluation of previous cardiovascular events by clinical data and changes in the ECG. Although it is known that these data do not necessarily reflect the absence of coronary disease, in clinical practice, individuals are not submitted to complementary tests, such as provocation test to detect myocardial ischemia, if the initial evaluation indicates low cardiovascular risk. In screening protocols, ECG, in combination

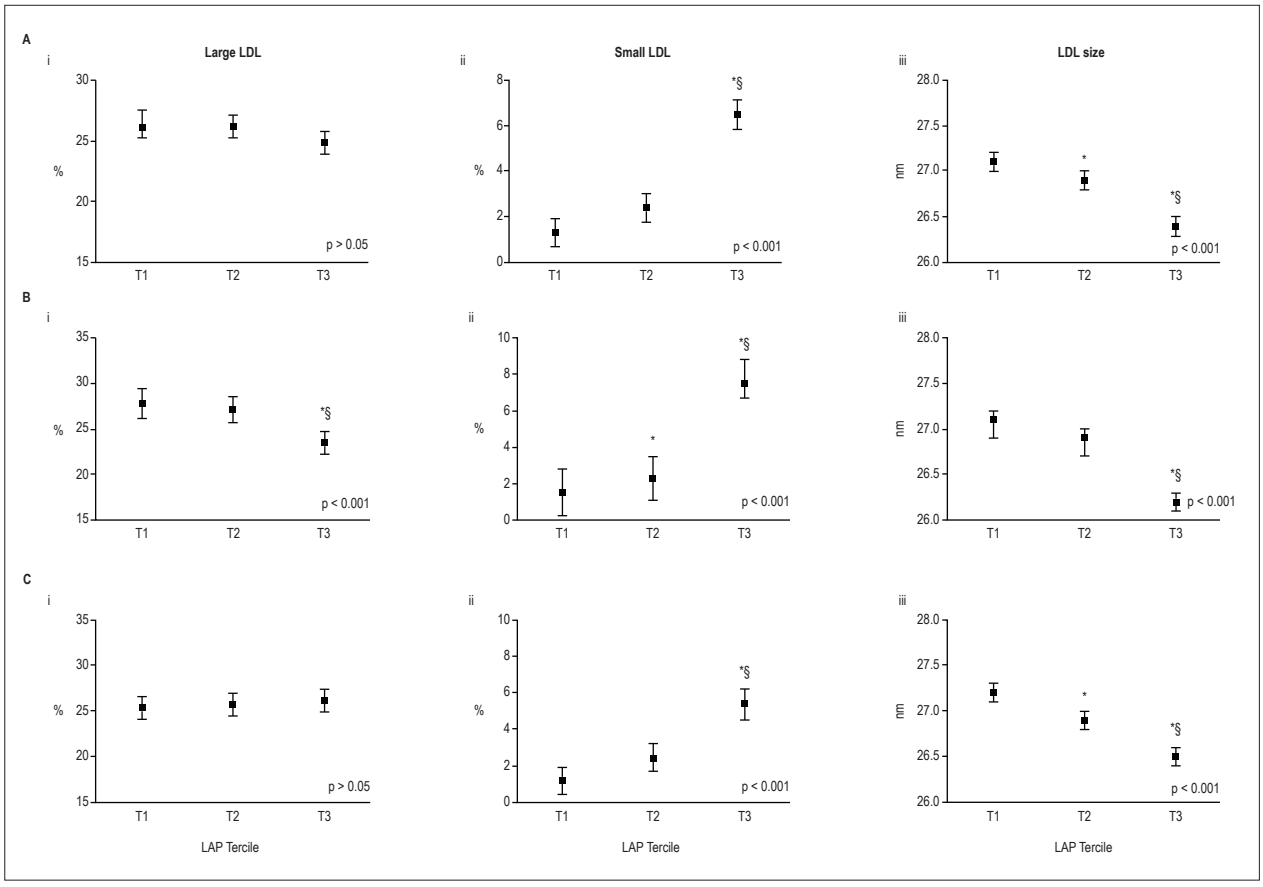

Figure 2 – *Percentages of large and small LDL particles and LDL size, according to the LAP tertiles. A) Adjusted by sex, age, smoking, statin, fibrate, and hypoglycemic drugs. B) Men, adjusted by age, smoking, statin, fibrate, and hypoglycemic drugs (n = 132). C) Women, adjusted by age, smoking, statin, fibrate, and hypoglycemic drugs (n = 219). i: Large LDL. ii: Small LDL. iii: LDL size. Data are presented as mean and 95% confidence interval. Comparative analysis was performed using the linear trend test. LAP tertiles: T1 ≤ 45.5; 45.5 < T2 ≤ 80.3; T3 > 80.3. HDL: high-density lipoprotein; LAP: lipid accumulation product; %: percentage Comparison between groups was performed by ANOVA or Kruskal-Wallis and multiple comparisons by Tukey test. *versus T1, §versus T2. Significance level adopted for all analysis p < 0.05.*

with complementary clinical and biochemical data, is the first instrument used because of its low cost. However, we admit that cardiovascular disease cannot be excluded in these individuals. And third, individuals included in this study were under statin (27.9%) and fibrate (2.6%). These drugs exert direct and indirect actions in lipid metabolism promoting changes in TG, a component of LAP. Despite that, these individuals were receiving the same drug treatment (in terms of type and posology) for at least 30 days prior to the study.

Methods for the measurement of emerging cardiovascular risk factors are generally complex and expensive, and hence could not be used in large-scale studies. LAP is a low-cost, easily measured variable that could be used to establish causal effects on clinical outcomes. So, the positive results from clinical trials and prospective cohort studies using this instrument are expected to encourage new approaches to estimate CVD risk.

Conclusions

In conclusion, our results showed that the LAP index was associated with an atherogenic lipoprotein profile in Brazilian subjects, such as TC, HDL-C, Apo B, small HDL, small LDL and LDL size. It is plausible to suggest that the LAP may be a useful and simple clinical marker for assessment of cardiometabolic risk factors.

Author contributions

Conception and design of the research: Cartolano FDC, Freitas MCP, Damasceno NRT; Acquisition of data: Cartolano FDC, Pappiani C, Freitas MCP; Analysis and interpretation of the data: Cartolano FDC, Pappiani C, Figueiredo Neto AM, Carioca AAF; Statistical analysis: Cartolano FDC, Carioca AAF; Obtaining financing: Figueiredo Neto AM; Writing of the manuscript: Cartolano FDC; Critical revision of the manuscript for intellectual content: Cartolano FDC, Freitas MCP.

Potential Conflict of Interest

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

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Study Association

This article is part of the thesis of master submitted by Flavia De Conti Cartolano, from Universidade de São Paulo.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital Universitário da Universidade de São Paulo under the protocol number 1126/11 and Faculdade de Saúde Pública da Universidade de São Paulo sob o número 2264. 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.

References

1. World Health Organization. (WHO). Prevention of cardiovascular disease – Guidelines for assessment and management of cardiovascular risk. Geneva; 2007. [Series of Technical Reports].
2. Upadhyay RK. Emerging risk biomarkers in cardiovascular diseases and disorders. J Lipids. 2015;2015:971453. doi: 10.1155/2015/971453.
3. Sviridov D, Nestel P. Dynamics of reverse cholesterol transport: protection against atherosclerosis. Atherosclerosis. 2002;161(12):245-54. doi: https://doi.org/10.1016/S0021-9150(01)00677-3.
4. Hirayama S, Miida T. Small dense LDL: an emerging risk factor for cardiovascular disease. Clin Chim Acta. 2012 Dec 24;414:215-24. doi: 10.1016/j.cca.2012.09.010.
5. Nikolic D, Katsiki N, Montalto G, Isenovic ER, Mikhailidis DP, Rizzo M. Lipoprotein subfractions in metabolic syndrome and obesity: clinical significance and therapeutic approaches. Nutrients. 2013;5(3):928-48. doi: 10.3390/nu5030928.
6. Camont L, Lhomme M, Rached F, Le Goff W, Negre-Salvayre A, Salvavrey R, et al. Small, dense high-density lipoprotein-3 particles are enriched in negatively charged phospholipids: relevance to cellular cholesterol efflux, antioxidative, antithrombotic, anti-inflammatory, and antiapoptotic functionalities. Arterioscler Thromb Vasc Biol. 2013;33(12):2715-23. doi: 10.1161/ATVBAHA.113.301468.
7. Woudberg NJ, Goedecke JH, Blackhurst D, Frias M, James R, Opie LH, et al. Association between ethnicity and obesity with high-density lipoprotein (HDL) function and subclass distribution. Lipids Health Dis. 2016 May 11;15:92. doi: 10.1186/s12944-016-0257-9.
8. Kahn HS, Valdez R. Metabolic risks identified by the combination of enlarged waist and elevated triacylglycerol concentration. Am J Clin Nutr. 2003;78(5):928-34. PMID: 14594778.
9. Ioachimescu AG, Brennan DM, Hoar BM, Hoogwerf BJ. The lipid accumulation product and all-cause mortality in patients at high cardiovascular risk: a PreCIS database study. Obesity (Silver Spring). 2010;18(9):1836-44. doi: 10.1038/oby.2009.453.
10. Kahn HS. The "lipid accumulation product" performs better than the body mass index for recognizing cardiovascular risk: a population-based comparison. BMC Cardiovasc Disord. 2005 Sep 8;5:26. doi: 10.1186/1471-2261-5-26.
11. Kahn HS. The lipid accumulation product is better than BMI for identifying diabetes: a population-based comparison. Diabetes Care. 2006;29(1):151-3. doi: https://doi.org/10.2337/diacare.29.01.06.dc05-1805.
12. Oh JY, Sung YA, Lee HJ. The lipid accumulation product as a useful index for identifying abnormal glucose regulation in young Korean women. Diabet Med. 2013;30(4):436-42. doi: 10.1111/dme.12052.
13. Tankó LB, Bagger YZ, Qin G, Alexandersen P, Larsen PJ, Christiansen C. Enlarged waist combined with elevated triglycerides is a strong predictor of accelerated atherogenesis and related cardiovascular mortality in postmenopausal women. Circulation. 2005;111(15):1883-90. doi: 10.1161/01.CIR.0000161801.65408.8D.
14. Lwow F, Jedrzejuk D, Milewicz A, Szmigiero L. Lipid accumulation product (LAP) as a criterion for the identification of the healthy obesity phenotype in postmenopausal women. Exp Gerontol. 2016 Sep;82:81-7. doi: 10.1016/j.exger.2016.06.007.
15. Nascimento JX, Chein MB, Sousa RM, Ferreira AS, Navarro PA, Brito LM. Importance of lipid accumulation product index as marker of CVD risk in PCOS women. Lipids Health Dis. 2015 Jun 24;14:62. doi: 10.1186/s12944-015-0061-y.
16. Macut D, Tziomalos K, Antic-Bozic I, Bjekic-Macut J, Katsikis I, Papadakis E, et al. Non-alcoholic fatty liver disease is associated with insulin resistance and lipid accumulation product in women with polycystic ovary syndrome. Hum Reprod. 2016 Jun;31(6):1347-53. doi: 10.1093/humrep/dew076.
17. Costa EC, Ferezini De Sá JC, Soares EM, Lemos TM, Maranhão TM, Azevedo GD. Evaluation of cardiovascular risk by the LAP index in non-obese patients with polycystic ovary syndrome. Arq Bras Endocrinol Metab. 2010;54(7):630-5. doi: http://dx.doi.org/10.1590/S0004-27302010000700007.
18. Wehr E, Pilz S, Boehm BO, März W, Obermayer-Pietsch B. The lipid accumulation product is associated with increased mortality in normal weight postmenopausal women. Obesity (Silver Spring). 2011;19(9):1873-80. doi: 10.1038/oby.2011.42.
19. Maturana MA, Moreira RM, Spritzer PM. Lipid accumulation product (LAP) is related to androgenicity and cardiovascular risk factors in postmenopausal women. Maturitas. 2011;70(4):395-9. doi: 10.1016/j.maturitas.2011.09.012.
20. Pontes AG, Rehme MF, Martins AM, Micussi MT, Maranhão TM, Pimenta WP, et al. Insulin resistance in women with polycystic ovary syndrome: relationship with anthropometric and biochemical variables. Rev Bras Ginecol Obstet. 2012;34(2):74-9. doi: http://dx.doi.org/10.1590/S0100-72032012000200006.
21. D´Agostino RB, Vasan RS, Pecina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care: The Framingham Heart Study. Circulation. 2008;117(6):743-53. doi: 10.1161/CIRCULATIONAHA.107.699579.
22. Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women 2011 update: a guideline from the American Heart Association. Circulation. 2011;123(11):1243-62. doi: 10.1161/CIR.0b013e31820faaf8. Erratum in: Circulation. 2011;123(22):e624; Circulation. 2011;124(16):e427.
23. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972;18(6):499-502. PMID: 4337382.
24. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentration in man. Diabetologia. 1985;28(7):412-9. PMID: 3899825.
25. Koba S, Hirano T, Kondo T, Shibata M, Suzuki H, Murakami M, et al. Significance of small dense low-density lipoproteins and other risk factors in patients with various types of coronary heart disease. Am Heart J. 2002;144(6):1026-35. doi: 10.1067/mhj.2002.126119.

26. Mirmiran P, Bahadoran Z, Azizi F. Lipid accumulation product is associated with insulin resistance, lipid peroxidation, and systemic inflammation in type 2 diabetic patients. Endocrinol Metab (Seoul). 2014;29(4):443-9. doi: 10.3803/EnM.2014.29.4.443.

27. Kwon SW, Yoon SJ, Kang TS, Kwon HM, Kim JH, Rhee J, et al. Significance of small dense low-density lipoprotein as a risk factor for coronary artery disease and acute coronary syndrome. Yonsei Med J. 2006; 47(3): 405-14. doi: 10.3349/ymj.2006.47.3.405.

28. Shen H, Xu L, Lu J, Hao T, Ma C, Yang H, et al. Correlation between small dense low-density lipoprotein cholesterol and carotid artery intima-media thickness in a healthy Chinese population. Lipids Health Dis. 2015 Oct 29;14:137. doi: 10.1186/s12944-015-0143-x.

29. Toth PP, Patti AM, Nikolic D, Giglio RV, Castellino G, Biancucci T, et al. Bergamot reduces plasma lipids, atherogenic small dense LDL, and subclinical atherosclerosis in subjects with moderate hypercholesterolemia: a 6 months prospective study. Front Pharmacol. 2016 Jan 6;6:299. doi: 10.3389/fphar.2015.00299.

30. Shen H, Zhou J, Shen G, Yang H, Lu Z, Wang H. Correlation between serum levels of small, dense low-density lipoprotein cholesterol and carotid stenosis in cerebral infarction patients >65 years of age. Ann Vasc Surg. 2014;28(2):375-80. doi: 10.1016/j.avsg.2013.01.029.

31. Eppinga RN, Hartman MH, van Veldhuisen DJ, Lexis CP, Connelly MP, Lipsic E, et al. Effect of metformin treatment on lipoprotein subfractions in non-diabetic patients with acute myocardial infarction: a glycometabolic intervention as adjunct to primary coronary intervention in ST elevation myocardial infarction (GIPS-III) trial. PLoS One. 2016;11(1):e0145719. doi: 10.1371/journal.pone.0145719.

32. Asztalos BF, Cupples LA, Demissie S, Horvath KV, Cox CE, Batista MC, et al. High-density lipoprotein subpopulation profile and coronary heart disease prevalence in male participants of the Framingham Offspring Study. Arterioscler Thromb Vasc Biol. 2004;24(11):2181-7. doi: 10.1161/01.ATV.0000146325.93749.a8.

33. O'Neill F, McLoughlin E, Riwanto M, Manz J, Adler A, Sutill E, et al. Reproducibility and biological variability of HDL's vascular functional assays. Atherosclerosis. 2015;241(2):588-94. doi: 10.1016/j.atherosclerosis.2015.06.005.

34. El Harchaoui K, Arsenault BJ, Franssen R, Despres JP, Hovingh GK, Stroes ES, et al. High-density lipoprotein particle size and concentration and coronary risk. Ann Intern Med. 2009;150(2):84-93. doi: 10.7326/0003-4819-150-2-200901200-00006.

35. Pankow JS, Duncan BB, Schmidt MI, Ballantyne CM, Couper DJ, Hoogeveen RC, et al. Fasting plasma free fatty acids and risk of type 2 diabetes: the atherosclerosis risk in communities study. Diabetes Care. 2004;27(1):77-82. doi: https://doi.org/10.2337/diacare.27.1.77.

36. Il'yasova D, Wang F, D'Agostino RB Jr, Hanley A, Wagenknecht LE. Prospective association between fasting NEFA and type 2 diabetes: impact of post-load glucose. Diabetologia. 2010;53(5):8668-74. doi: 10.1007/s00125-010-1657-4.

37. Sarafidis PA, Bakris GL. Non-esterified fatty acids and blood pressure elevation: a mechanism for hypertension in subjects with obesity/insulin resistance? J Hum Hypertens. 2007;21(1):12-9. doi: 10.1038/sj.jhh.1002103

38. Djoussé L, Biggs ML, Ix JH, Kizer JR, Lemaitre RN, Sotoodehnia N, et al. Nonesterified fatty acids and risk of sudden cardiac death in older adults. Circ Arrhythm Electrophysiol. 2012; 5(2): 273-8. doi: 10.1161/CIRCEP.111.967661.

39. Morita S, Shimajiri Y, Sakagashira S, Furuta M, Sanke T. Effect of exposure to non-esterified fatty acid on progressive deterioration of insulin secretion in patients with Type 2 diabetes: a long-term follow-up study. Diabet Med. 2012;29(8):980-5. doi: 10.1111/j.1464-5491.2011.03566.x.

40. Sambataro M, Perseghin G, Lattuada G, Beltramello G, Luzi L, Pacini G. Lipid accumulation in overweight type 2 diabetic subjects: relationships with insulin sensitivity and adipokines. Acta Diabetol. 2013; 50(3): 301-7. doi: 10.1007/s00592-011-0366-x.

Vimentin and Anti Vimentin Antibodies in Chagas' Disease

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Abstract

Background: Vimentin is a main structural protein of the cell, a component of intermediate cell filaments and immersed in cytoplasm. Vimentin is mimicked by some bacterial proteins and anti-vimentin antibodies occur in autoimmune cardiac disease, as rheumatic fever. In this work we studied vimentin distribution on LLC-MK2 cells infected with T. cruzi and anti-vimentin antibodies in sera from several clinical pictures of Chagas' disease or American Trypanosomiasis, in order to elucidate any vimentin involvement in the humoral response of this pathology.

Objective: We standardized an indirect immunofluorescence assay (IFI) to determine sub cellular expression in either parasites and host cells, and ELISA to evaluate anti-vimentin antibodies in sera fron chagasic patients.

Methods: We analyzed the distribution of vimentin in culture cells using indirect fluorescent assays, using as external controls anti-T. cruzi sera, derived from chronic infected patients for identification of the parasites in the same model. After infection and growth of T.cruzi amastigotes, those cells express larger amounts of vimentin, with heavy staining of cytoplasm outside the parasitophorous vacuole and some particle shadowing patterns, suggesting that vimentin are associated with cell cytoplasm. Anti-vimentin antibodies were present in most American trypanosomiasis samples, but notably, they are much more present in acute (76, 9%) or clinical defined syndromes, especially cardiac disease (87, 9%). Paradoxically, they were relatively infrequent in asymptomatic (25%) infected patients, which had a clearly positive serological reaction to parasite antigens, but had low frequency of anti-vimentin antibodies, similar to controls (2,5%).

Conclusion: Our current data revealed that anti-vimentin antibodies induced during T. cruzi infection could be a marker of active disease in the host and its levels could also justify drug therapy in American Trypanosomiasis chronic infection, as a large group of asymptomatic patients would be submitted to treatment with frequent adverse reactions of the available drugs. Anti-vimentin antibodies could be a marker of cardiac muscle cell damage, appearing in American Trypanosomiasis patients during active muscle cell damage. (Arq Bras Cardiol. 2018; 110(4):348-353)

Keywords: Chagas Disease; Heart Diseases; Trypanossoma Cruzi; Rheumatic Fever; Vimentin; Antibodies, Monoclonal.

Introduction

Chagas' disease or American Trypanosomiasis is a peculiar parasitic infection as *Trypanosoma cruzi* is a unique intracellular parasite which resulted in cytoplasmic presence of amastigotes forms, a rare cellular event in nature, as cytoplasm is usually free from parasites in almost all intracellular infections[1]. After its reproduction, the parasite had a set of enzymes, as sialidases, that transfers host cell molecules to their surface, allowing cell evasion without disruption[2]. All those processes could alter cell cytoskeleton and its proteins, probably generating in the host cell signals that alters the protein synthesis of structural proteins. Vimentin is a main structural protein of the cell, a component of intermediate cell filaments and immersed in cytoplasm[3]. Vimentin is expressed in normal cardiac muscle and their tumors, and autoantibodies against a vimentin re found in allograft rejection[4]. or cardiac models of allograft rejection[5].Vimentin is mimicked by some bacterial proteins and anti-vimentin antibodies occur in autoimmune cardiac disease, as rheumatic fever[6]. In this work we studied vimentin distribution on LLC-MK2 cells infected with *T.cruzi* and anti-vimentin antibodies in sera from several clinical pictures of American Trypanosomiasis, in order to elucidate any vimentin involvement in the humoral response of this pathology.

Methods

Parasites and serum samples

Trypanosoma cruzi epimastigotes were grown from Y strain routinely maintained in our lab on Liver Infusion Tryptose (LIT) culture media supplemented with 10% fetal calf serum. *T. cruzi* trypomastigotes were obtained from cell culture supernatants of LLC-MK2 cells previously infected. Monoclonal mouse Anti-Vimentin antibody (V6630) and

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vimentin from bovine lens was obtained commercially (Sigma Aldrich, Saint Louis, Missouri, USA). A serum from patient with cardiac chronic American Trypanosomiasis was used as anti *T.cruzi* antibody. Human sera from American Trypanosomiasis patients and controls were used from the biorepository of *T.cruzi* patients samples from E.S.Umezawa, Lab.Protozoology, IMTSP, serologically characterized in TESA specific serology tests and published previously in several articles, were recovered and comprising 26 sera from acute disease, 33 from isolated cardiac disease, 17 from isolated digestive disease, 20 without clinical disease (asymptomatic disease) and 40 sera from patients outside endemic area. All clinical data were maintained by the attendant physician and not available for this study.

Antigen expression and morphology

All morphological assays were performed in a Zeiss Axioplan epifluorescent microscope with fluorescein filters. For antigen detection, we fixed LLC-MK2 control cells, *T.cruzi* infected LLC-MK2 cells and *T.cruzi* epimastigotes and permeated cell surface with Triton X-100[7] with either anti-Vimentin mAb or anti-*T.cruzi* antibodies as elsewhere described. After this step, bound antibodies were revealed with adequate fluorescein conjugate, carefully washed and mounted in glycerin for observation. Representative Fields were digitalized at high power field using a Canon camera.

TESA and vimentin ELISA

T.cruzi trypomastigotes excreted secreted antigen was obtained as elsewhere described[8]. TESA (1/80) and Vimentin (0.06ug/ml) in carbonate 0.05 M pH9.6 were adsorbed overnight to wells of 96 wells high binding ELISA plates (Corning Inc. New York, USA). After washing and blocking with PBS Tween 20, 0,05% plus 5% milk or BSA 0.5%, adequate dilution of sera (1/50 vimentin and 1/200 TESA) were incubated for one hour. After new washings, adequate dilution of peroxidase conjugate were added for another hour, washed and bound conjugate revealed by 1 h with orto-phenylenediamine and hydrogen peroxide. After 30 min in 37°C, reaction was stopped with 4N HCl and 492 nm absorbance determined in a microplate reader (Multiskan-Titertek II).

Statistical analysis

All quantitative data, such as O.D. ELISA, were analyzed using ANOVA after the Levene test for variance check, with intragroup comparisons by the Bonferroni's test, if there are uniformity of variances. In the absence of this homogeneity, data were analyzed by Kruskal-Wallis tests with Dunns post-tests. We opt for graphical representation of individual data in dot plot with association of mean and SEM for comparison. Qualitative analysis, as frequency of positive sera in the group, was analyzed by Fisher exact tests in two group analysis. We also included 95% confidence interval of estimated proportion. Significant difference was considered when the probability of equality (H1 = H0) was less than 0.05($p \leq 0.05$), using two-tailed analysis and power greater than 90%. We used the statistical package GraphPad Prism 7.0 for all statistical analysis and plotting.

Results

We analyzed the distribution of Vimentin in culture cells using indirect fluorescent assays as described in Methods, using as external controls anti-*T.cruzi* sera, derived from chronic infected patients for identification of the parasites in the same model, as could be seen in figure 1. LLC-MK2 cells, the host cell used for intracellular growth of *T.cruzi*, showed a discrete and uniform cytoplasmic staining, uniform in most cells (Figure 1A). Those cells are no reactive to anti-*T-cruzi* antibodies, without any staining (Figure 1B). After infection and growth of *T.cruzi* amastigotes, those cells express larger amounts of vimentin, with heavy staining of cytoplasm outside the parasitophorous vacuole and some particle shadowing patterns, suggesting that vimentin are associated with cell cytoplasm (Figure 1C). Vimentin could involve unstained cytoplasmic parasites, but no specific staining of parasites was seen. Those parasites were easily identified by anti-*T.cruzi* antibodies showing a typical morular pattern in the cytoplasm of infected cells (Figure 1D). No staining of those parasites was observed with anti-vimentin mAbs, which demonstrate the absence of antigen mimicry, both for amastigotes (Figure 1C) or extracellular parasites (Figure 1E). Those extracellular parasites are heavily stained by anti *T.cruzi* antibodies as well as intracellular amastigotes (Figure 1F).

Anti-vimentin auto antibodies

We search for anti-vimentin antibodies in human sera from controls or American trypanosomiasis patients. Our sample was composed by patients with well-defined clinical forms as described in Methods. Vimentin ELISA was prepared with commercial protein and antibody binding was revealed by commercial conjugates. Standardization was easily as controls were adequately negative, allowing an adequate cut-off definition. We also tested all samples in a reported high specificity ELISA assay, TESA, which uses an excreted secreted antigen in solid phase, with high reactivity in all clinical forms of American trypanosomiasis. Those assays could be seen in Figure 2. We clearly demonstrate that all patients from our sample of American trypanosomiasis react very well in TESA assay, without any false positive or dubious sample in control groups. All clinical forms presented a similar reactivity for parasite antigens, including those with asymptomatic infection. Anti-vimentin antibodies were present in most American trypanosomiasis samples, but notably, they are much more present in acute or clinical defined syndromes (76,9%), especially cardiac disease (87,9%) and digestive form 70,5%. Paradoxically, they were relatively infrequent in asymptomatic infected patients (25%), which had a clearly positive serological reaction to parasite antigens, but had low frequency of anti-vimentin antibodies, similar to controls (2,5%), $p>0.05$, Bonferroni's ANOVA post-test) or frequency of positive samples (Table 1) with similar conclusions. The main reactivity of these autoantibodies appears to be more intense in active cardiac or acute disease, which were associated to large parasite burden and inflammatory response than digestive or asymptomatic disease. The proportion of reagent sera was also shown in Table 1 assuming cutoff value estimated as defined in methods. The anti-vimentin ELISA reactivity of

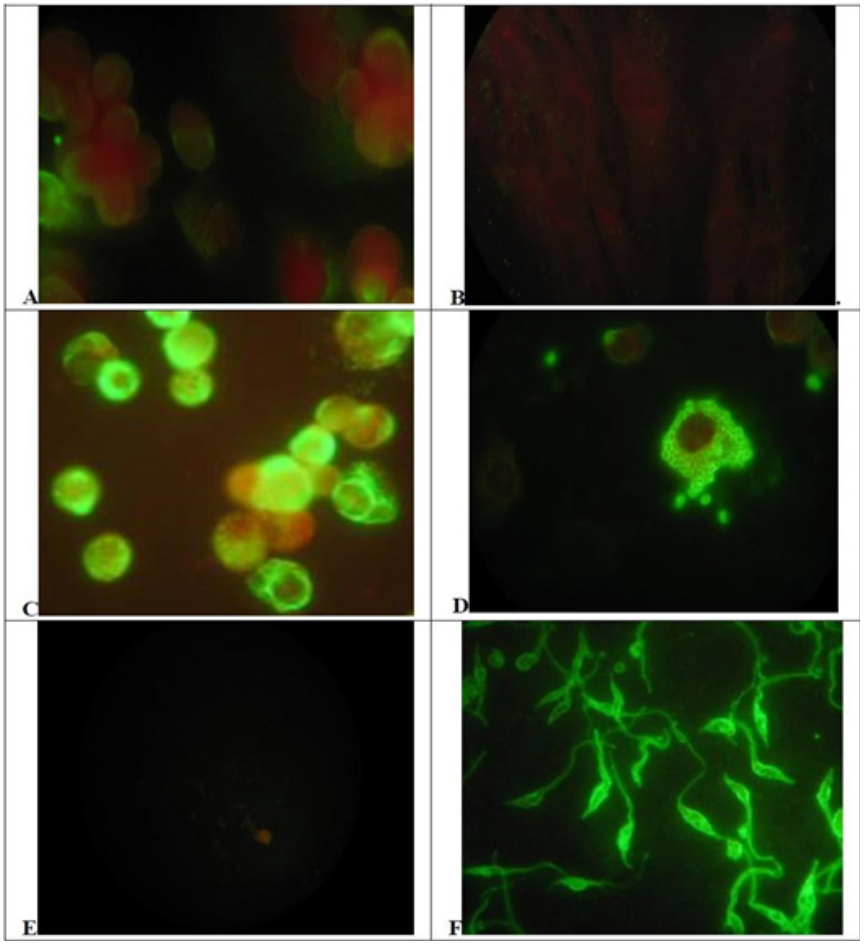

Figure 1 – *Distribution of Vimentin or Trypanosoma cruzi antigen on control or infected cells and parasites. A and B) Uninfected LLC MK2 cells reacted to antivimentin abs(A) or anti-T.cruzi abs(B). C and D) T.cruzi infected LLC MK2 cells reacted to antivimentin abs(C) or anti-T.cruzi abs(D). E and F) T.cruzi promastigote forms from in vitro culture reacted to antivimentin abs (E) or anti-T.cruzi abs(F). Cells, infected cells or parasites forms were reacted with Anti Vimentin mAb or chronic infection chagasic serum and revealed with adequate conjugate (x1000) (see Methods).*

sera from patients with clinical active disease for any origin was in higher frequency than in patients without active disease or non-infected controls. Data were compared mainly with active or undetermined without clinical forms of Chagas' disease shows greater difference as expected with high statistical difference ($p < 0.01$) and also demonstrated by 95% confidence interval of the proportion

The Table 1 Summarizes the data obtained in Figure 2 and provides ELISA positivity indexes with commercial Vimentin, showing that the percentage of positive sera from the groups of chronic patients with clinical manifestations of Chagas' disease and the group of patients from the acute phase was higher than that observed in the indeterminate group of chagasic patients.

The positivity index of sera from patients in the acute phase was 76.9% with 20 positive sera from the 26 analyzed. In the group of chronic digestive tract positive percentage was 70.5% with 12 positive in the 17 analyzed, the cardiac patients had a positive percentage of 87.9% with 29 positive sera from the 23 analyzed and in the group of indeterminate patients, the Index was 25% with 5 positive of the 20 analyzed. The positivity of the non-chagasic sera was 2.5% or only a positive serum in 40 analyzed.

Discussion

This intracytoplasmic infection resulted in altered expression of cell fibrillary proteins as vimentin, as we clearly show in immunofluorescence of infected cells. This altered vimentin production is devoid of association with the parasite, which has no reactivity with antivimentin antibodies in any form. Vimentin is important for specific virus entry, another possible cytoplasmic pathogen and are used by Foot-and-mouth disease virus (FMDV) for virus mounting inside the cells.[9]

This intracytoplasmic infection resulted in altered expression of cell fibrillary proteins as vimentin, as we clearly show in immunofluorescence of infected cells. This altered

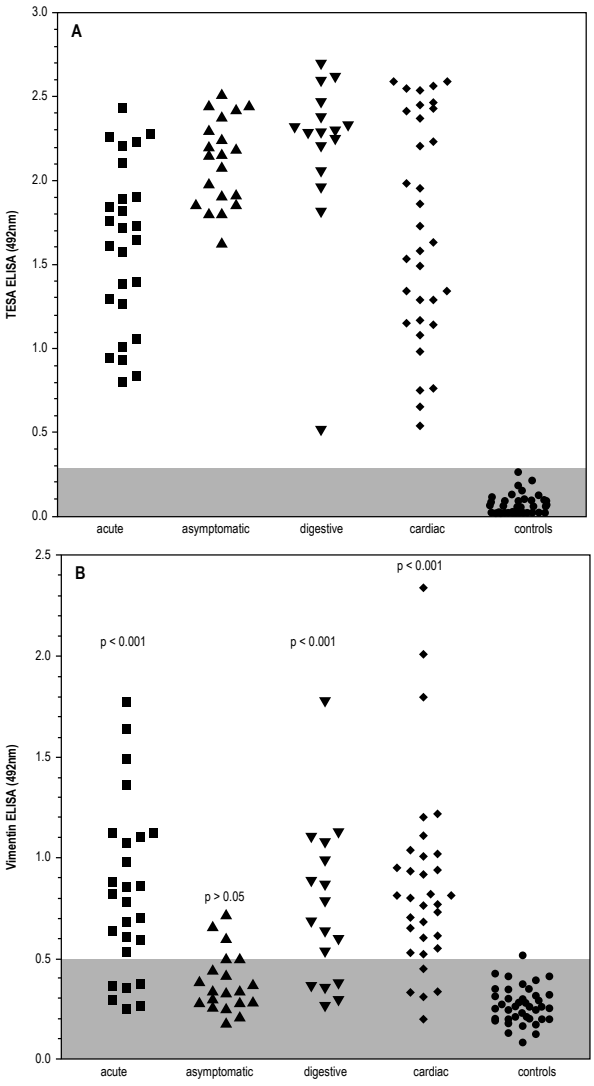

Figure 2 – *Sera reactivity profile of patients with different clinical forms of Chagas disease by ELISA with T. cruzi TESA antigens (A) and commercial vimentin (B). Groups were compare with ANOVA with Bonferronipost tests.*

Table 1 – Percentage of positivity of sera with different clinical forms of Chagas disease for Vimentin antigen in the ELISA reaction

Clinical form	Samples (n)	Positives (n)	Negatives (n)	Positivity (%)	95% C.I. (p vs w/o Chagas)	p VS undetermined
Acute	26	20	6	76.9	53-87 (p < 0.001)	p < 0.001
Cardiac	33	29	4	87.8	67-93 (p < 0.001)	p < 0.001
Digestive	17	12	5	25	42-84 (p < 0.001)	p < 0.01
Symptomatic	76	61	15	80,2	70-88 (p < 0.001)	p < 0.001
Undetermined	20	5	15	70,5	5-44 (p < 0.05)	
Total Chagas	96	66	30	68,5	52-75 (p < 0.001)	
Without Chagas	40	1	39	2,5	1-4%	

**Fisher exact test*

vimentin production is devoid of association with the parasite, which has no reactivity with anti-vimentin antibodies in any form. Viral infection alters host cell architecture similarly, as parvovirus in mice[10] but other pathogens also affects vimentin distribution in infected cells, with similar perivacuolar distribution, as in Salmonella infections.[11] Proteomics studies in experimental models of *T.cruzi* infection had shown higher plasma levels of vimentin related to disease severity,[12] which can offer to the immune response intracellular filaments for antibody production. Those data were expected as vimentin autoantibodies could be related to antigen exposure during active infection, as proposed in experimental models of *T.cruzi* infection.[12] Several other immune diseases that interact with cardiac muscle cells also presented anti-vimentin antibodies. Murine models of viral myocarditis presented those antibodies[13] and as well as post-streptococcal rheumatic fever patients[14]. Noninfectious myocarditis, as in coronary artery disease patients[15] and kidney or heart transplants recipients[16] also showed those antibodies resulted from any exposure of antigen, unregard the origin of cardiac muscle cell damage. Our data were similar to those findings and anti-vimentin antibodies induced during *T.cruzi* infection could be a marker of active disease in the host and its levels could also justify drug therapy in American Trypanosomiasis chronic infection, as a large group of asymptomatic or indeterminate patients would be submitted to treatment with frequent adverse reactions of the available drugs. Anti-vimentin antibodies could be a marker of cardiac muscle cell damage, appearing in American Trypanosomiasis patients during active muscle cell damage.

Conclusions

Our data revealed that anti-vimentin antibodies induced during activity of *T. cruzi* infection could be a marker of active disease in the host, despite absence of evident clinical involvement. This assay could be also a non-invasive follow-up test during drug therapy in Chagas' disease or American Trypanosomiasis. This test could allow the selection of possible active patients for therapy and also to supply a marker of disease activity after therapy, avoiding that a large group of asymptomatic patients without active disease were submitted to treatment with frequent adverse reactions. Anti-vimentin antibodies could be a marker of cardiac muscle cell inflammatory involvement, showed by American Trypanosomiasis patients with active muscle cell damage and must be tested in other cardiac muscle inflammatory conditions as viral myocarditis.

Author contributions

Conception and design of the research: Nascimento MS, Stolf AMS, Umezawa ES; Acquisition of data: Nascimento MS, Stolf MAS; Analysis and interpretation of the data: Nascimento MS, Stolf AMS, Andrade Junior HF, Pandey RP, Umezawa ES; Statistical analysis: Nascimento MS, Andrade Junior HF; Obtaining financing: Nascimento MS, Umezawa ES; Writing of the manuscript: Nascimento MS, Stolf AMS, Pandey RP; Critical revision of the manuscript for intellectual content: Nascimento MS, Andrade Junior HF, Pandey RP.

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 das Clinicas da Universidade de São Paulo under the protocol number 0564/08. 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.

References

1. Calvet CM, Melo TG, Garzoni LR, Oliveira FO Jr, Neto DT, N S L M, et al. Current understanding of the *Trypanosoma cruzi*-cardiomyocyte interaction. Front Immunol. 2012 Oct 30;3:327. doi: 10.3389/fimmu.2012.00327.
2. Freire-de-Lima L, Fonseca LM, Oeltmann T, Mendonça-Previato L, Previato JO. The trans-sialidase, the major *Trypanosoma cruzi* virulence factor: three decades of studies. Glycobiology. 2015;25(11):1142-9. doi: 10.1093/glycob/cwv057.
3. Lowery J, Kuczmarski ER, Herrmann H, Goldman RD. 2015. Intermediate filaments play a pivotal role in regulating cell architecture and function. J Biol Chem. 2015;290(28):17145-53. doi: 10.1074/jbc.R115.640359.
4. Mahesh B. Leong HS, McCormack A, Sarathchandra P, Holder A, Rose ML. Autoantibodies to vimentin cause accelerated rejection of cardiac allografts. Am J Pathol. 2007;170(4):1415-27. doi: 10.2353/ajpath.2007.060728.
5. Azimzadeh AM, Pfeiffer S, Wu GS, Schröder C, Zhou H, Zorn GL 3rd, et al. Humoral immunity to vimentin is associated with cardiac allograft injury in nonhuman primates. Am J Transplant. 2005;5(10):2349-59. doi: 10.1111/j.1600-6143.2005.01022.x.
6. Delunardo F, Scalzi V, Capozzi A, Camerini S, Misasi R, Pierdominici M, et al. Streptococcal-vimentincross-reactive antibodies induce microvascular cardiac endotelial pro inflammatory phenotype in rheumatic heart disease. Clin Exp Immunol. 2013;173(3):419-29. doi: 10.1111/cei.12135.
7. Kaverina I, Rottner K, Small JV. Targeting, capture, and stabilization of microtubules at early focal adhesions. J Cell Biol. 1998;142(1):181-90. PMID: 9660872.
8. Umezawa ES, Nascimento MS, Stolf AM. Enzyme-linked immunosorbent assay with *Trypanosoma cruzi* excreted-secreted antigens (TESA-ELISA) for serodiagnosis of acute and chronic Chagas disease. Diagn Microbiol Infect Dis. 2001;39(3):169-76. PMID: 11337184.

9. Gladue DP, O'Donnell V, Baker-Branstetter R, Holinka LG, Pacheco JM, Fernández Sainz I, et al. Foot-and-mouth disease virus modulates cellular vimentin for virus survival. J Virol. 2013;87(12):6794-803. doi: 10.1128/JVI.00448-13

10. Nüesch JP, Lachmann S, Rommelaere J. Selective alterations of the host cell architecture upon infection with parvovirus minute virus of mice. Virology. 2005;331(1):159-74. doi: 10.1016/j.virol.2004.10.019.

11. Finlay BB, Ruschkowski S, Dedhar S. Cytoskeletal rearrangements accompanying salmonella entry into epithelial cells. J Cell Sci. 1991;99(Pt 2):283-96. PMID: 1909337.

12. Wen JJ, Garg NJ. Proteome expression and carbonylation changes during *Trypanosoma cruzi* infection and Chagas disease in rats. Mol Cell Proteomics. 2012;11(4):M111.010918. doi: 10.1074/mcp.M111.010918.

13. Sato Y, Matsumori A, Sasayama S. Autoantibodies against vimentin in a murine model of myocarditis. Autoimmunity. 1994; 18(2):145-8. PMID: 7742476.

14. Guilherme L, Kalil J. Rheumatic fever and rheumatic heart disease: cellular mechanisms leading autoimmune reactivity and disease. J Clin Immunol. 2010;30(1):17-23. doi: 10.1007/s10875-009-9332-6.

15. Nikkari ST, Solakivi T, Sisto T, Jaakkola O. Antibodies to cytoskeletal proteins in sera of patients with angiographically assessed coronary artery disease. Atherosclerosis. 1993;98(1):11-6. PMID: 8457245.

16. Banan B, Xu Z, Gunasekaran M, Mohanakumar T. Role of alloimmunity and autoimmunity in allograft rejection. ClinicalTransplant. 2013:325-32. PMID: 25095525.

Applicability of Longitudinal Strain of Left Ventricle in Unstable Angina

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Abstract

Background: Unstable angina (UA) is a common cause of hospital admission; risk stratification helps determine strategies for treatment.

Objective: To determine the applicability of two-dimensional longitudinal strain (SL2D) for the identification of myocardial ischemia in patients with UA.

Methods: Cross-sectional, descriptive, observational study lasting 60 days. The sample consisted of 78 patients, of which fifteen (19.2%) were eligible for longitudinal strain analysis. The value of $p < 0.05$ was considered significant.

Results: The group of ineligible patients presented: a lower proportion of women, a higher prevalence of diabetes mellitus (DM), use of ASA, statins and beta-blockers and larger cavity diameters. The main causes of non-applicability were: presence of previous infarction (56.4%), previous CTA (22.1%), previous MRI (11.5%) or both (16.7%) and the presence of specific electrocardiographic abnormalities (12.8%). SL2D assessment revealed a lower global strain value in those with stenosis greater than 70% in some epicardial coronary arteries (17.1 [3.1] versus 20.2 [6.7], with $p = 0.014$). Segmental strain assessment showed an association between severe CX and RD lesions with longitudinal strain reduction of lateral and inferior walls basal segments; (14 [5] versus 21 [10], with $p = 0.04$) and (12.5 [6] versus 19 [8], respectively).

Conclusion: There was very low SL2D applicability to assess ischemia in the studied population. However, the global strain showed a correlation with the presence of significant coronary lesion, which could be included in the UA diagnostic arsenal in the future. (Arq Bras Cardiol. 2018; 110(4):354-361)

Keywords: Angina, unstable / physiopathology; Ventricular Dysfunction, Left; Myocardial Ischemia / physiopathology; Strain; Echocardiography / methods.

Introduction

In United States, unstable angina (UA) is the most common cardiovascular cause of hospitalization and is responsible for most hospitalizations in coronary units.[1] The diagnosis of UA is performed by clinical criteria based on angina duration and intensity.[2] UA patient has a variable prognosis for unfavorable events such as acute myocardial infarction (AMI), recurrence of angina, necrosis biomarkers, ventricular function and need for myocardial revascularization.[3]

Speckle tracking (ST) is a technology introduced in the 1980s that allows the quantification of global and regional myocardial deformity by tracking the natural heart muscle "acoustic marks" by ultrasound, presenting reduced values in presence of myocardial ischemia.[4,5] ST allows myocardial strain calculation and has shown great utility in the identification of subendocardial ischemia as in unstable angina, with greater sensitivity and specificity than two-dimensional echocardiogram.[6]

However, for ST to track adequately speckles, there are some variables that may interfere in deformity analysis, so when present, they may give erroneous results or even impede myocardial strain analysis. In addition, for myocardial ischemia identification in UA patients, infarction previous myocardial presence or other myocardial injury (such as significant valvar heart disease) may alter myocardial deformity and cause an incorrect analysis of deformity decrease true cause. These are the variables that interfere in myocardial deformity correct analysis, and for that reason, they are considered exclusion criteria in the majority of published studies (aimed at analyzing acute ischemia): previous infarction, atrial fibrillation, left bundle branch block, ventricular arrhythmia aortic and/or mitral valvar disease, previous cardiac surgery, ventricular hypertrophy, cardiac pacemaker and inadequate acoustic window.[7]

The main objective is to study the applicability prevalence of two-dimensional longitudinal strain (SL2D) in all hospitalized patients diagnosed with UA during the 60-day observation period.

The secondary objective is to evaluate the diagnostic capacity of SL2D in the identification of culprit vessel due to ischemic event in UA patients.

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Methods

This is a cross-sectional, descriptive, performed at the Emergency Room (ER) and Coronary Unit (CU) of Dante Pazzanese Institute of Cardiology (IDPC).

Inclusion criteria were: hospitalized patients of both sexes, age greater than 18 years and clinical diagnosis of UA who were admitted to IDPC service during the study period and who accepted the participation in the study, having signed informed consent form. We emphasize that there was no calculation of sample size. A census was carried out of all patients who had inclusion criteria. Patient arrival to IDPC service was by convenience.

Exclusion criterion was the change in diagnosis during hospitalization. These cases occurred in patients who entered the service with initial chest pain and after propaedeutic and complementary exams, diagnosis of UA was ruled out. In case of differential diagnosis and closing as final diagnosis: acute myocardial infarction (AMI) with supra or no supra-ST segment, aortic dissection, pulmonary embolism and aortic stenosis.

We analyzed clinical-epidemiological and electrocardiographic characteristics, as well as tests collection for troponin I and creatinine.

Risk stratification was done using GRACE risk score.[8,9]

Electrocardiographic analysis was performed by two experienced cardiologists; in case of disagreement regarding the diagnosis, tracing would be analyzed by a specialized service in the electrocardiographic reports of the institution where the research was carried out. Transthoracic echocardiography was performed within 48 hours of patient precordial pain last episode in ER or CU. The equipment for conducting examination was GE® Vivid E9 (General Electric Medical System, Norway) with transducer "array in phase" with 3.5 megahertz emission frequency. Images obtained during the examination were acquired with harmonic, in a repetition of frames between 50 and 70 frames/second, in digital clips form (three consecutive cycles average) and recorded in CDs for later analysis in workstation EchoPAC PC version 6.0.1® (GE VingmedUltrasound).

According to American Society of Echocardiography and European Society of Echocardiography committee guidelines, which standardized the acquisition of tomographic sections obtained during echocardiographic examinations, with the patient in left lateral decubitus and electrocardiogram monitored, we acquired transthoracicly echocardiographic images by the Spectral Doppler (pulsatile and continuous) Doppler and flow mapping in color.[10]

Measures acquired:

- Two-dimensional: diastolic and systolic left ventricular (LV) diameter, left atrium anteroposterior diameter (LA), aortic root diameter, interventricular septum and posterior wall thickness. LV diastolic and systolic volume. Calculation of LV ejection fraction (EF) by the modified biplanar Simpson method.
- Doppler and Color Flow Mapping: Mitral flow with spectral Doppler (pulsatile and continuous) for diastolic function analysis and mitral valvopathy quantification, when present. Aortic flow with spectral Doppler (pulsatile and continuous), to determine aortic valve opening and closing (to mark the systolic event), and aortic valvopathy quantification, when present. Valve lesions diagnosis and quantification followed American Society of Echocardiography recommendations.[11]

The technique to obtain longitudinal tension was done as follows:

- Marking systolic event with aortic flow pulsating Doppler.
- Determination of three points of endocardial border in each of the following images: apical 3 chambers (at anterosseptal wall base, at inferolateral wall base and at apex), apical 4 chambers (at septum base, at lateral wall base and at apex) and apical 2 chambers (at inferior wall base, at anterior wall base and at apex).
- Through the Automatic Function Imaging® (AFI) tool, the deformation of each of the 17 myocardial segments was automatically calculated, providing posteriorly left ventricle global deformation (analyzed segments mean). The program provides SL2D curves and polar map with longitudinal strain values in each segment.

The maximum absolute value of the two-dimensional strain curve was defined as the systolic peak. Adjacent myocardial segments with altered strain value were defined as ischemic territory, correlating them with coronary irrigation, according to polar map shown in Figure 1.

According to the literature,[7,12,13] the situations mentioned below may lead to a change in myocardial deformity, or to a real deformity impairment, or by limitation of the software to identify acoustic marks during the cardiac cycle:

- Concentric ventricular hypertrophy (LVH);
- Aortic and/or mitral valvar diseases greater than moderate degree;
- Pacemaker pace;
- At least one of the following electrocardiographic changes: left bundle branch block (LBBB), atrial fibrillation (AF) rhythm and complex ventricular arrhythmia;
- Secondary unstable angina (acute anemia, tachyarrhythmia and infection);
- Prior AMI or prior myocardial (percutaneous or surgical) revascularization procedure and
- Inadequate acoustic window.

Based on the above, we hypothesized that the presence of one of these alterations may impair SL2D analysis in severe coronary disease identification in UA patients. These concepts has fundamental importance for the knowledge of SL2D real applicability in this population, when the examination purpose is to evaluate coronary disease responsible for the acute condition.

Patients eligible for bidimensional echocardiogram with longitudinal strain were submitted to the method by two skilled and experienced professionals, who did not have access to information on patient coronary anatomy evaluated until the conclusion of the study.

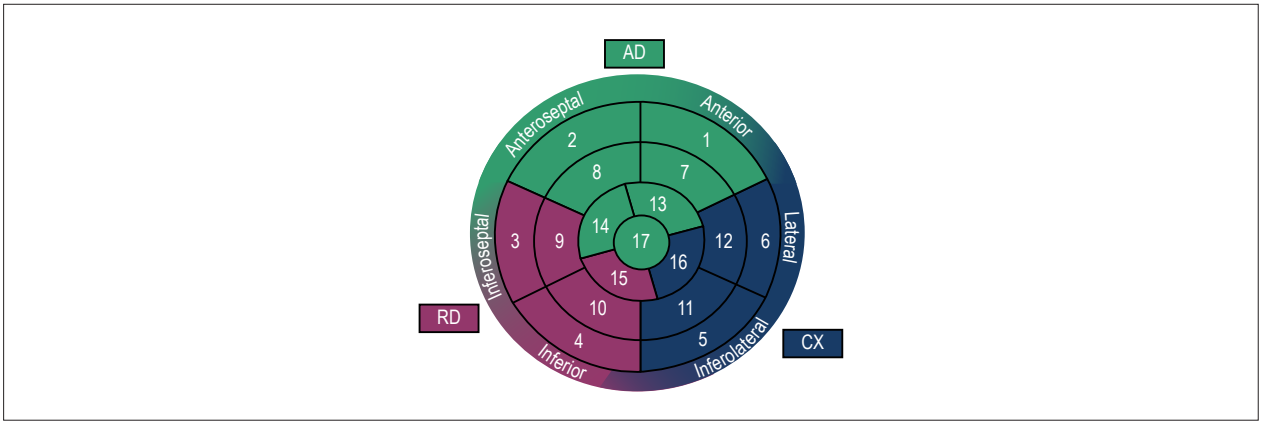

Figure 1 – *Polar map with coronary irrigation correlation. AD: anterior descending coronary artery; CX: circumflex coronary artery; RD: right coronary artery.*

Results of cardiac catheterization (CC) and Coronary Angiography by Computed Tomography (CACT) exams were also analyzed. Stenosis greater than or equal to 70% in epicardial coronary arteries or stenosis greater than or equal to 50% in left main coronary artery (LMCA) was considered.

The sample was divided into two groups: Group A - patients in whom it was possible to analyze by SL2D and Group B - patients in whom analysis by SL2D was not possible.

The research protocol was submitted and approved by the institution's Ethics and Research Committee.

There was no interference in individual medical conduct due to participation in the study. Such conduct was based on ER and CU routine that corresponds to US and national guidelines[3,14] for UA patients treatment patients.

Statistical analysis

Statistical analysis was performed with Statistical Package for Social Sciences (SPSS), version 19.0.

Kolmogorov-Smirnov and Shapiro-Wilk tests were performed to verify our sample normal distribution. As the normality hypothesis was rejected, we used nonparametric tests for analysis.

Groups were compared using Mann-Whitney test and Fisher exact test as appropriate.

Continuous variables were presented as median and interquartile range, and categorical variables were expressed as percentage (%).

ROC curve was used to evaluate SL2D discriminative power in severe coronary stenosis identification (≥ 70%) in UA patients.

Level of significance was 5%.

Results

We evaluated 93 patients diagnosed with UA at admission to ER; however, fifteen (16.2%) patients were excluded from the study due to diagnosis change during hospitalization, 13 (14%) cases with non-ST-segment AMI, one (1.1%) with UA post-MI and one (1.1%) with type A aortic dissection.

At the end, 78 UA patients were investigated, of which fifteen (19.2%) were eligible for longitudinal strain analysis.

Main population clinical characteristics are summarized in Table 1.

About 70% of sample had no change in QRS complex duration or morphology complex; more than half (60.3%) showed no change in ventricular repolarization. Five patients (6.4%) presented ST segment depression on admission. Main electrocardiographic changes are detailed in Table 2.

Of the 63 patients in whom the longitudinal strain was not applied, 40 (63.5%) performed two-dimensional echocardiography during ER stay. Main echocardiographic findings of this population, including the 15 patients submitted to SL2D, are shown in Table 3.

In total, 50 patients completed the investigation with CC and five with CACT. In the first exam, three patients presented LMCA severe lesions (3.9%), 22 (28.2%) anterior descending coronary artery lesions (AD), 21 (26.9%) in right coronary artery, 2%) in circumflex coronary artery (CX). In patients submitted to CACT, one presented AD severe damage (1.3%) and one in RD (1.3%).

During hospitalization, 23 patients (29.5%) were submitted to intervention. Coronary transluminal angioplasty (CTA) was the main revascularization therapy. In three cases (3.8%), revascularization was surgical.

Comparing patients eligible for longitudinal strain analysis (group A) to those not eligible (group B), we found that group B had a lower proportion of women, a higher prevalence of diabetes, left cavities larger dimensions, larger root aorta diameter and lower systolic function on two-dimensional echocardiography; in addition to a higher ASA use rate, statins and beta-blockers, according to the data in Table 4.

Main causes to strain non-applicability were presence of prior infarction (56.4%), previous CTA (22.1%), prior surgical (CTA) revascularization (MRI), MRI and previous CTA (16, 7%), and presence of the following electrocardiographic alterations: LBBB, AF, pathological Q wave and pacemaker pace (12.8%).

In group A, patient majority presented low or intermediate risk, as detailed in Table 5.

Table 1 – Clinical characteristics of studied population (n = 78)

	Median [p25– 75]
Age (years)	61,5 [53 – 69]
Gender (%)	
Male	60,3%
Female	39,4%
BMI (Kg/m^2)	28,16 [24,47 – 30,71]
SBP (mmHg)	137 [122,75 – 154,25]
HR (bpm)	74 [69 – 83,5]
Serum Creatinine (mg/dL)	0,9 [0,7 – 1,1]
GRACE (points)	95 [81 – 117]
Troponin (pg/mL)	0,02 [0,01 – 0,05]
High blood pressure (%)	88,5%
Diabetes (%)	38,5%
Smoking (%)	32,1%
Dyslipidemia (%)	65,4%
Family history for CAD (%)	19,2%
Known CAD (%)	66,7%
Medications in use (%)	
ACEI	32,1%
ARB	41%
Beta blocker	65,4%
Acetylsalicylic acid	82,1%
Other antiplatelet	29,5%
Calcium channel blocker	33,3%
Statin	76,9%
Nitrate	37,2%
Prior Intervention (%)	
Surgical revascularization	11,5%
Angioplasty	22,1%
Angioplasty + Surgical revascularization	16,7%
Previous MI (%)	56,4%

BMI: body mass index; SBP: systolic blood pressure; HR: heart rate; CAD: coronary artery disease; AMI: acute myocardial infarction; ACEI: angiotensinogen converting enzyme inhibitor; ARB: angiotensin receptor AT-2 blocker.

Table 2 – Electrocardiographic findings (n = 78)

Change	Frequency (%)
LBBCD	10,3%
RBBB	3,8%
LASDB	2,6%
RBBB + LASDB	2,6%
LBBB	3,8%
Q wave pathological	3,8%
Pacemaker pace	3,8%
High response AF	1,3%
CVR anterosseptal	5,1%
Previous CVR	5,1%
Lower CVR	9%
Side CVR	7,7%
Diffuse CVR	11,5%
Infra/ST > 0,5 mm	1,3%

LBBCD: left bundle branch conduction disorder; RBBB: right bundle branch block; LASDB: left anterior superior divisional block; CVR: change in ventricular repolarization; LBBB: left bundle branch block; AF: atrial fibrillation.

Table 3 – Echocardiographic findings (n = 55)

Variable	Median [p25 – p75]
LVEF Simpson	0,59 [0,5 – 0,65]
LA (mm)	39 [36 – 42]
LVFDD (mm)	51 [48 – 56]
LVFSD (mm)	32 [30 – 37,75]
Septum (mm)	10 [9 – 11]
Posterior wall (mm)	9 [9 – 11]
Mass index (g/m^2)	124,5 [110 – 153,5]
PASP (mmHg)	32 [31 – 36]
Aorta root (mm)	34 [31 – 36]

LVEF: left ventricular ejection fraction; LA: measurement of the left atrium; LVFDD: left ventricle final diastolic diameter; LVFSD: left ventricular final systolic diameter; PASP: pulmonary artery systolic pressure.

Coronary anatomy evaluation revealed a severe lesion in LMCA in 1 case (6.7%). Number of patients with severe lesions in coronary arteries AD, CX and RD was 2 (13.3%), 4 (26.7%) and 4 (26.7%), respectively.

SL2D evaluation revealed a reduced global strain value in those who had severe lesion in any epicardial coronary artery (17.1 [3.1] versus 20.2 [6.7] with p = 0.014), area under the ROC curve 0.875, as shown in Figures 2 and 3.

Segmental strain assessment showed an association between severe CX lesion and longitudinal strain reduction of lateral wall basal segment (14 [5] versus 21 [10] with p = 0.04 and area under ROC curve = 0.864), and (12.5 [6] versus 19 [8] with p = 0.026 and area under ROC curve = 0.86).

Discussion

Acquisition of images by ST with longitudinal strain determination allows a more complete myocardial function assessment and can detect subtle alterations in segmental contractility in ischemic heart disease patients, with good inter and intraobserver reproducibility.[7,12] Thus, this method has been gaining more space in coronary artery disease evaluation, with a large number of studies produced in recent years.[15-17]

Table 4 – Clinical and echocardiographic characteristics of patients undergoing longitudinal strain analysis (group A, n = 15) compared to non-submitted patients (group B, n = 63)

	Group A		Group B		p
	Median	Interquartile Interval	Median	Interquartile Interval	
Age (years)	57	16	62	16	0,899
Gender (%)					
Male	33,3%		66,7%		0,037
Female	66,7%		33,3%		
BMI (Kg/m^2)	28,62	7,2	28,12	6,56	0,903
SBP (mmHg)	143	33	137	31	0,510
HR (bpm)	78	23	74	14	0,824
Creatinine (mg/dL)	0,7	0,5	0,9	0,3	0,127
GRACE (points)	94	27	97	36	0,287
Hypertension (%)	80%		90,5%		0,363
Diabetes (%)	13,3%		44,4%		0,037
Smoking (%)	33,3%		31,7%		1
Dyslipidemia (%)	60%		66,7%		0,764
Family history for CAD (%)	26,7%		17,5%		0,470
LVEF Simpson	0,65	0,08	0,55	0,18	0,006
LA (mm)	37	5	40	9	0,009
LVFDD (mm)	48	5	53,5	9	0,007
LVFSD (mm)	31	6	37	7	0,112
Septum (mm)	10	2	10	3	0,668
Posterior wall (mm)	9	1	10	2	0,118
Mass index (g/m^2)	109	49	133,5	26	0,095
PASP (mmHg)	34	13	29,5	10	0,895
Aorta root (mm)	31	4	35	4	0,006
Medications in use (%)					
ACEI	33,3%		31,7%		1
ARB	20%		46%		0,084
Beta blocker	20%		76,2%		< 0,001
Acetylsalicylic acid	60%		87,3%		0,023
Calcium channel blocker	26,7%		34,9%		0,762
Statin	53,3%		82,5%		0,035
Nitrate	40%		36,5%		1

BMI: body mass index; SBP: systolic blood pressure; HR: heart rate; LVEF: left ventricular ejection fraction; LA: measurement of the left atrium; LVFDD: left ventricular final diastolic diameter; LVFSD: left ventricular final systolic diameter; PASP: pulmonary artery systolic pressure. ACEI: angiotensinogen converting enzyme inhibitor; ARB: angiotensin receptor AT-2 blocker. Mann-Whitney was used for continuous variables (expressed in median and interquartile range) and Fisher's exact test for categorical variables (expressed as percentage).

Table 5 – Risk score of patients submitted to longitudinal strain analysis

Score	Frequency (%)
GRACE	
≤ 108 points	86,7%
109-139 points	13,3%
≥ 140 points	0%

GRACE - Low risk - ≤ 108, moderate risk - 109 to 139, ≥ 140 - high risk

The present study is one of the pioneers in longitudinal strain applicability evaluation in UA patients attended at the Emergency Room of a Tertiary-level Cardiology Hospital.

The studied population clinical, electrocardiographic and echocardiographic characteristics demonstrate the complexity of patients with coronary artery disease (CAD). This probably justifies the method low applicability, since there are many variables (existing in the majority of patients studied) that could impair detection of reduced deformity

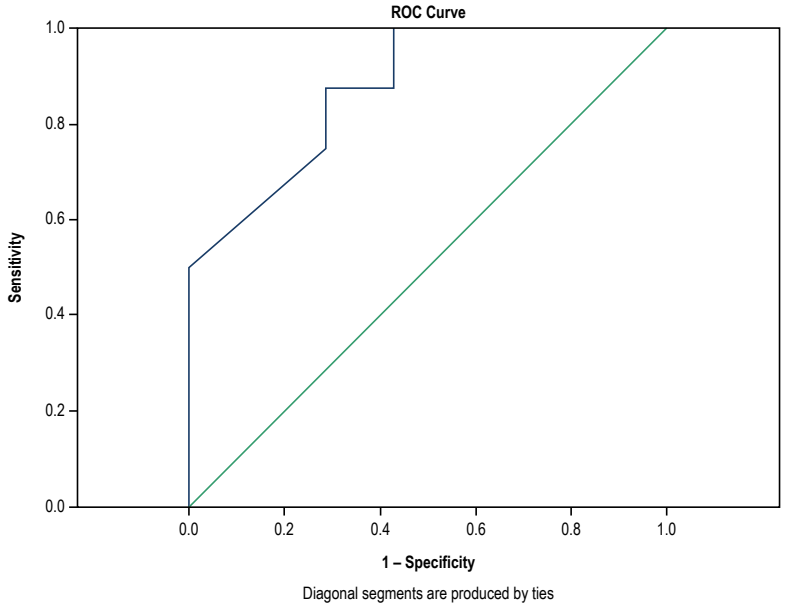

Figure 2 – *ROC curve to evaluate ability of global strain to identify severe lesion (> 70%) in any epicardial coronary artery. Area under the ROC curve 0.875, with p < 0.014.*

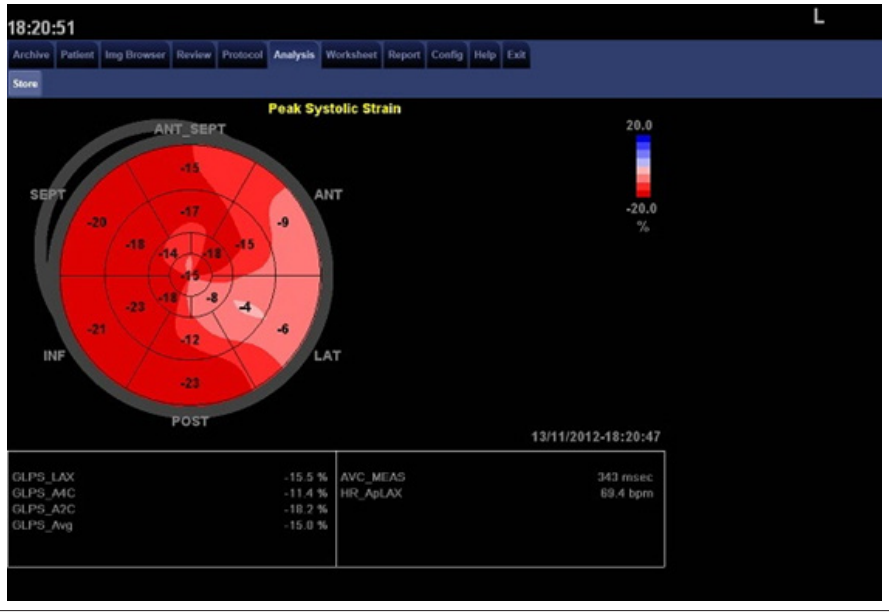

Figure 3 – *Case of patient with unstable angina, anterior descending coronary artery with 90% lesion in the proximal third and circumflex coronary artery with lesion of 70% in the middle third.*

due to ischemia. We emphasize that in the study population, 56.1% had previous infarction and 44.6% had previous cardiac procedure (CTA, MRI or both).

Shimoni et al.,[18] evaluated SL2D in 97 hospitalized patients with angina and normal ventricular function; of these, 69 patients had major coronary disease. Global strain analysis was -17.3 ± 2.4 with an area under the ROC curve (AUC) of 0.80 to identify significant CAD in patients with angina; in the subgroup of patients with unstable angina the global strain also demonstrated good accuracy in predicting angiographic obstructive CAD (AUC = 0.86).[18] Findings of this study are similar to those found in relation to strain diagnostic accuracy to identify significant CAD in angina , however, there was no reference as to method applicability to the sample.

We verified in the present study a statistically significant association between reduced global strain values and the presence of anatomically severe CAD, and similar accuracy to data available in the literature.[19] When we analyzed

segmental strain, we found a significant association only in basal segment deformity reduction of lateral and inferior walls, with stenosis ≥ 70% in CX and RD coronaries, respectively. We believe that segmental strain findings would be more robust if the sample was larger.

In a meta-analysis published in 2016 with 1385 patients included in 10 studies, global longitudinal strain demonstrated good accuracy in detecting moderate to severe CAD in symptomatic patients with AUC of 0.81, sensitivity of 74.4% and specificity of 72.1%.[19]

Despite the low SL2D applicability in ER and CU, most probably due to patients profile that our institution attends, current evidence and our findings indicate that this method may be a complementary exam in diagnostic algorithm of CAD and useful tool in early ischemia evaluation.

Conclusion

In 80.8% of the cases, it was not possible to apply longitudinal strain, mainly due to the following criteria: presence of previous infarction or prior revascularization (percutaneous or surgical). We believe that the method applicability in a profile of patients with less clinical complexity would be greater, due to the method technical limitations.

In spite of this limitation, we can observe that the global strain showed a correlation with the presence of anatomically severe coronary lesion. In this way, SL2D could be included in the diagnostic arsenal of UA, in emergency units, since it is a noninvasive examination with diagnostic information available in a short period.

Author contributions

Conception and design of the research: Santos NSS, Vilela AA, Barretto RBM, Rezende MO, Ferreira MC, Andrade AJA, Scorsioni NHG, Queiroga OX, Le Bihan D; Acquisition of data: Santos NSS, Vilela AA, Vale MP, Rezende MO, Ferreira MC, Andrade AJA, Scorsioni NHG, Queiroga OX; Analysis and interpretation of the data: Santos NSS, Vilela AA, Barretto RBM, Vale MP, Rezende MO, Ferreira MC, Andrade AJA, Scorsioni NHG, Queiroga OX, Le Bihan D; Statistical analysis and Critical revision of the manuscript for intellectual content: Santos NSS, Vilela AA, Rezende MO, Ferreira MC, Andrade AJA, Scorsioni NHG, Queiroga OX; Obtaining financing and Writing of the manuscript: Vilela AA.

Potential Conflict of Interest

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

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Ethics approval and consent to participate

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

References

1. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI IIIB Trial. Thrombolysis in Myocardial Ischemia. Circulation. 1994;89(4):1545-56. doi: https://doi.org/10.1161/01.CIR.89.4.1545.
2. Braunwald E. Unstable angina: a classification. Circulation. 1989;80(2):410-4. https://doi.org/10.1161/01.CIR.80.2.410.
3. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE, et al. 2012 ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;61(23):e179-347. doi: 10.1016/j.jacc.2013.01.014. Erratum in: J Am Coll Cardiol. 2013;62(11):1040-1.
4. Amundsen BH, Helle-Valle T, Edvardsen T, Torp H, Crosby J, Lyseggen E, et al. Noninvasive myocardial strain measurement by speckle tracking echocardiography; validation against sonomicrometry and tagged magnetic resonance imaging. J Am Coll Cardiol. 2006;47(4):789-93. doi: https://doi.org/10.1016/j.jacc.2005.10.040.
5. Choi JO, Cho SW, Song YB, Cho SJ, Song BG, Lee SC, et al. Longitudinal 2D strain at rest predicts the presence of left main and three vessel coronary artery disease in patients without regional wall motion abnormality. Eur J Echocardiogr. 2009;10(5):695-701. doi: 10.1093/ejechocard/jep041.
6. Perk G, Tunick PA, Kronzon I. Non-Doppler two-dimensional strain imaging by echocardiography–from technical considerations to clinical applications. J Am Soc Echocardiogr. 2007;20(3):234-43. doi: http://dx.doi.org/10.1016/j.echo.2006.08.023.
7. Geyer H, Caracciolo G, Abe H, Wilansky S, Carerj S, Gentile F, et al. Assessment of myocardial mechanics using speckle tracking echocardiography: fundamentals and clinical applications. J Am Soc Echocardiogr. 2010; 23(4):351-69. doi: 10.1016/j.echo.2010.02.015. Erratum in: J Am Soc Echocardiogr. 2010;23(7):734.
8. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, et al; Global Registry of Acute Coronary Events Investigators. Predictors of hospital mortality in the global registry of acute coronary events. Arch Intern Med. 2003;163 (19): 2345-53. doi: 10.1001/archinte.163.19.2345.
9. Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, Van de Werf F, et al; Grace Investigators. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. JAMA. 2004;291(22):2727-33. doi: 10.1001/jama.291.22.2727.
10. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al; Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification

Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005;18(12):1440-1463. doi: 10.1016/j.echo.2005.10.005.

11. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Fleisher LA, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease. A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017;70(2):252-89. doi: 10.1016/j.jacc.2017.03.011.

12. Del Castillo JM, Herszkowicz N, Ferreira C. Speckle tracking–a contratilidade miocárdica em sintonia fina. Rev bras ecocardiogr imagem cardiovasc. 2010;23(3):46-54.

13. Leitman M, Lysyansky P, Sidenko S, Shir V, Peleg E, Binenbaum M, et al. Two dimensional strain: a novel software for real-time quantitative echocardiographic assessment of myocardial function. J Am Soc Echocardiogr. 2004;17(10):1021-9. doi: 10.1016/j.echo.2004.06.019.

14. Nicolau JC, Timerman A, Marin-Neto JA, Piegas LS, Barbosa CJ, Franci A, et al; Sociedade Brasileira de Cardiologia. [Guidelines of Sociedade Brasileira de Cardiologia for unstable angina and non-ST-segment elevation myocardial infarction (II edition, 2007) 2013-2014 update]. Arq Bras Cardiol. 2014;102(3 Suppl 1):1-61. doi: http://dx.doi.org/10.5935/abc.2014S001.

15. Eek C, Grenne B, Brunvand H, Aakhus S, Endresen K, Smiseth AO, et al. Strain echocardiography predicts acute coronary occlusion in patients with non-ST-segment elevation acute coronary syndrome. Eur J Echocardiogr. 2010;11(6):501-8. doi: 10.1093/ejechocard/jeq008.

16. Grenne B, Eek C, Sjoli B, Dahlslett T, Uchto M, Hol PK, et al. Acute coronary occlusion in non-ST-elevation acute coronary syndrome: outcome and early identification by strain echocardiography. Heart. 2010;96(19):1550-6. doi: 10.1136/hrt.2009.188391.

17. Dahlslett T, Karlsen S, Grenne S, Eek C, Sjoli B, Skulstad H, et al. Early assessment of strain echocardiography can accurately exclude significant coronary artery stenosis in suspect non-ST-segment elevation acute coronary syndrome. J Am Soc Echocardiogr. 2014;27(5):512-9. doi: 10.1016/j.echo.2014.01.019.

18. Shimoni S, Gendelman G, Ayzenberg O, Smirin N, Lysyansky P, Edri O, et al. Differential effects of coronary artery stenosis on myocardial function: the value of myocardial strain analysis for the detection of coronary artery disease. J Am Soc Echocardiogr. 2011;24(7):748-57. doi: 10.1016/j.echo.2011.03.007.

19. Liou K, Negishi K, Ho S, Russell EA, Cranney G, Ooi SY. Detection of obstructive coronary artery disease using peak systolic global longitudinal strain derived by two-dimensional speckle-tracking: a systematic review and meta-analysis. J Am Soc Echocardiogr. 2016;29(8):724-35.e4. doi: 10.1016/j.echo.2016.03.002.

Speckle-Tracking Echocardiography - Ready for Use in Acute Coronary Syndrome?

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Population aging and the increase of risk factors such as arterial hypertension and diabetes, mainly associated with obesity, have greatly contributed to increased hospitalizations of patients with acute coronary syndrome (ACS).[1,2] Patients with ACS may have different prognosis and, for this reason, risk stratification of ACS, including unstable angina (UA), is mandatory.[3,4] In this context, anatomical definition of culprit artery using coronary cineangiography and percutaneous intervention has been the first choice for patients at moderate-to-high risk.[5] Doppler echocardiography has a key role at the emergency room to assess left ventricle function and to rule out other conditions that may influence the diagnosis.[6]

Recently, the use of two-dimensional speckle-tracking echocardiography (2D-STE) for measurement of myocardial strain has gained importance for its applicability in the clinical practice.[7] Its high sensitivity to measure systolic function and identify left ventricular subclinical dysfunction, as compared with left ventricular ejection fraction, extends its applicability and makes it a test of additional value in many areas of cardiology.[8]

Despite promising data, 2D-STE has not been sufficiently standardized as a routine method for the diagnosis of myocardial ischemia. Characteristics inherent to the technique affect its applicability in both acute and chronic phase of the ischemic event, as previous ventricular deformities may affect the interpretation of results.[9]

The study by dos Santos et al.[10] provides us with a pioneer study on the real applicability of left ventricular longitudinal strain in UA. The authors describe the frequency at which 2D-STE is indicated in cardiac emergencies and evaluate the values of the test in patients with severe coronary artery lesions. We highlighted some interesting findings of this study.

The authors assessed 78 patients with clinically suspected UA, and found that 2D-STE was indicated in less than 20% of the patients. History of infarction or percutaneous intervention were the main limitations for the use of the technique in more than half of the sample. These findings highlight the limitation of the method in the assessment of coronary disease in emergency situations.

The authors then compared eligible and non-eligible patients for 2D-STE and did not find a pattern of association between the applicability of the test and the clinical variables measured, except for the frequency of diabetes, which was significantly higher in the non-eligible group. Although the power of the test is limited in this study design, this finding could raise the hypothesis that the presence of diabetes, usually associated with a more severe prognosis, could represent a limitation for application of the method.

Another interesting finding in this series was the accuracy of 2D-STE. The presence of severe coronary lesions was confirmed by coronary cineangiography in most of the fifteen patients considered eligible for 2D-STE. Besides, the authors observed that global strain was significantly reduced in patients with severe lesions in any epicardial coronary artery and that the longitudinal strain was significantly reduced in the basal segments of left ventricular inferior and lateral walls of the right and circumflex coronary arteries. It is of note that there was no association between myocardial strain and severe lesion in anterior descending artery, probably due to the small sample size, as reported by the authors. These findings corroborate the current evidence showing that reduced (global and segmental) strain is correlated with the severity of myocardial ischemia in terms of the number of coronary vessels affected.[11]

In their conclusion, the authors suggested that 2D-STE can help in the decision-making process of patients in emergency care for investigation of coronary disease. However, based on current knowledge, further studies are still needed to recommend the 2D-STE in the routine clinical practice. Until that happens, caution is needed, and indication of this feasible but still not formally recommended method should be carefully considered in cardiology emergency centers of both private and public services.

Keywords

Acute Coronary Syndrome; Speckle Tracking; Strain; Echocardiography, Doppler; Risk Factors/prevalence; Echocardiography.

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References

1. Damman P, Clayton T, Wallentin L, Lagerqvist B, Fox KA, Hirsch A, et al. Effects of age on long-term outcomes after a routine invasive or selective invasive strategy in patients presenting with non-ST segment elevation acute coronary syndromes: a collaborative analysis of individual data from the FRISC II – ICTUS – RITA 3 (FIR) trials. Heart. 2012;98(3):207-13.
2. Alame AJ, Karatasakis A, Karacsonyi J, Danek B, Resendes E, Parachini JR, et al. Comparison of the American College Cardiology/American Heart Association and the European Society of Cardiology guidelines for the management of patients with non-ST-segment elevation acute coronary syndromes. Coron Artery Dis. 2017;28(4):294-300.
3. Fox KA, Fitzgerald G, Puymirat E, Huang W, Carruthers K, Simon T, et al. Should patients with acute coronary disease be stratified for management according to their risk? Derivation, external validation and outcomes using the updated GRACE risk score. BMJ Open. 2014;4(2):e004425.
4. Markman Filho B, Almeida MC, Markman M, Chaves A, Moretti MA, Ramires JA, et al. Stratifying the risk in unstable angina with dobutamine stress echocardiography. Arq Bras Cardiol. 2006;87(3):294-9
5. Bawamia B, Mehran R, Qiu W, Kunadian V. Risk scores in acute coronary syndromes and percutaneous coronary intervention: a review. Am Heart J. 2013;165(4):441-50.
6. Nicolau JC, Timerman A, Marin-Neto JA, Piegas LS, Barbosa CJ, Franci A, et al; Sociedade Brasileira de Cardiologia. [Guidelines of Sociedade Brasileira de Cardiologia for unstable angina and non-ST-segment elevation myocardial infarction (II edition, 2007) 2013-2014 update]. Arq Bras Cardiol. 2014;102(3 Suppl 1):1-61.
7. Mondillo S, Galderisi M, Mele D, Cameli M, Lomoriello VS, Zacá V, et al; Echocardiography Study Group Of The Italian Society Of Cardiology (Rome, Italy). Speckle-tracking echocardiography. a new technique for assessing myocardial function. J Ultrasound Med. 2011;30(1):71-83.
8. Almeida AL, Gjesdal O, Mewton N, Choi EY, Teixido-Tura G, Yoneyama K, Lima JA. Speckle-tracking pela ecocardiografia bidimensional – aplicações clínicas. Rev Bras Ecocardiogr Imagem Cardiovasc. 2013;26(1):38-49.
9. Smiseth AO, Torp H, Opdahl A, Haugaa KH, Urheim S. Myocardial strain imaging: how useful is it in clinical decision making? Eur Heart J. 2016;37(15):1196-207.
10. dos Santos NS, Vilela AA, Barretto RB, Vale MP, Rezende MO, Ferreira MC, et al. Aplicabilidade do Strain Longitudinal do Ventrículo Esquerdo na Angina Instável. Arq Bras Cardiol. 2018; 110(4):354-361.
11. Liou K, Negishi K, Ho S, Russel EA, Cranney G, Ooi, SY. Detection of obstructive coronary artery disease using peak systolic global longitudinal strain derived by two-dimensional speckle tracking: a systematic review and meta-analysis. J Am Soc Echocardiogr. 2016;29(8):724-35.

Infection in Patients with Decompensated Heart Failure: In-Hospital Mortality and Outcome

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Abstract

Background: Heart failure (HF) is a syndrome, whose advanced forms have a poor prognosis, which is aggravated by the presence of comorbidities.

Objective: We assessed the impact of infection in patients with decompensated HF admitted to a tertiary university-affiliated hospital in the city of São Paulo.

Methods: This study assessed 260 patients consecutively admitted to our unit because of decompensated HF. The presence of infection and other morbidities was assessed, as were in-hospital mortality and outcome after discharge. The chance of death was estimated by univariate logistic regression analysis of the variables studied. The significance level adopted was $p < 0.05$.

Results: Of the patients studied, 54.2% were of the male sex, and the mean age ± SD was 66.1 ± 12.7 years. During hospitalization, 119 patients (45.8%) had infection: 88 (33.8%) being diagnosed with pulmonary infection and 39 patients (15.0%), with urinary infection. During hospitalization, 56 patients (21.5%) died, and, after discharge, 36 patients (17.6%). During hospitalization, 26.9% of the patients with infection died vs 17% of those without infection ($p = 0.05$). However, after discharge, mortality was lower in the group that had infection: 11.5% vs 22.2% ($p = 0.046$).

Conclusions: Infection is a frequent morbidity among patients with HF admitted for compensation of the condition, and those with infection show higher in-hospital mortality. However, those patients who initially had infection and survived had a better outcome after discharge. (Arq Bras Cardiol. 2018; 110(4):364-370)

Keywords: Heart Failure / complications; Mortality; Hospitalization; Comorbidity; Lung Diseases / complications; Urinary Tract / physiopathology.

Introduction

Of the cardiovascular diagnoses, heart failure (HF) is the most frequent cause of hospitalization of patients older than 65 years in Brazil and worldwide.[1,2] Usually HF is controlled at the doctor's office, but when advanced or associated with any disease or comorbidity, the patients can decompensate, requiring hospitalization.[3] Several factors can contribute to aggravate HF: acute coronary syndrome, arrhythmias and acute respiratory disease were identified as the most common precipitating factors of heart decompensation.[2] In the OPTIMIZE-HF Registry, acute coronary syndrome and acute respiratory disease were associated with higher in-hospital mortality.[4] In the emergency department of our hospital, the factors associated with decompensation were non-adherence to treatment, renal failure, arrhythmias and infections.[5] This study was aimed at analyzing the role of infection in the outcome of patients admitted to our unit, a supporting ward of the emergency department.

Methods

This is a cohort study assessing 260 patients consecutively admitted to our unit, a supporting ward of the emergency department of the Instituto do Coração (InCor) of the Hospital das Clínicas of the São Paulo University Medical School (HCFMUSP), in 2014 because of decompensated HF. Only the first admission of each patient was considered. All patients had New York Heart Association (NYHA) functional class III or IV HF. They were followed up for up to one year, and underwent clinical, echocardiographic and laboratory assessment.

The following data were assessed: identification, heart disease etiology, comorbidities, clinical findings, such as heart rate and blood pressure at the first assessment, hemodynamic clinical profile, and echocardiographic and laboratory findings. The diagnosis of HF was established by use of the Framingham criteria, and type B natriuretic peptide (BNP), in case of diagnostic doubt, in addition to assessment of ejection fraction by use of two-dimensional echocardiography with

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color doppler. The comorbidities were identified based on the description of the attending physicians. Renal failure was confirmed by the presence of high levels of urea and creatinine, while diabetes mellitus, by the prescription of hypoglycemic agents on admission. Hypothyroidism was identified in the presence of a prescription of levothyroxine or increased levels of TSH. Atrial fibrillation was diagnosed based on the electrocardiographic tracing, while pulmonary infection was diagnosed based on signs and symptoms, in addition to chest X-ray, blood cell count and C-reactive protein (CRP). Urinary infection was diagnosed based on signs and symptoms, in addition to blood cell count, urinalysis and urine culture. We assessed the characteristics of the patients with infection, and compared them with those of the patients without infection.

Statistical analysis

The Kolmogorov-Smirnov test was used to test data normality ($p > 0.05$ = normal distribution). Regarding the characteristics of the population, continuous variables with normal distribution were presented as mean ± standard deviation. Continuous variables without normal distribution were presented as median (interquartile range 25%-75%). Categorical variables were presented as absolute number and percentage.

When comparing the groups, the continuous variables were presented as mean ± standard deviation. Unpaired Student *t* test was used for variables with normal distribution, and Mann-Whitney *U* test for variables with non-normal distribution. Chi-square test of association or Fisher exact test was used to compare the categorical variables. All tests performed are two-tailed and a p value < 0.05 was considered statistically significant. All statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) software.

Results

This study included 260 patients, with a mean age of 66.1 ± 12.7 years, 54.2% of the male sex. The patients were followed up during hospitalization and after discharge. The length of follow-up was 240.05 days (standard error = 10.47, 95% confidence interval = 219.52 – 260.57 days). During hospitalization, 119 patients (45.8%) had infection, 88 (33.8%) being diagnosed with pulmonary infection and 39 patients (15.0%), with urinary infection. Eight patients had both pulmonary[7] and urinary infections concomitantly. Renal failure was present in 142 patients (54,6%), chronic obstructive pulmonary disease (COPD) in 34 patients (13.1%),[7] hypothyroidism in 47 patients (18.1%), diabetes mellitus in 95 patients (36.5%), and atrial fibrillation in 119 patients (45.8%). Table 1 shows the major characteristics of the population studied, of which, 170 patients (65.4%) had HF with left ventricular ejection fraction (LVEF) < 40%, 37 (14.2%) had LVEF of 40%-49%, and 53 (20.4%) had LVEF ≥ 50%.

The mean length of stay was 28.6 days (20.52). During hospitalization, 56 patients (21.5%) died. Within 30 days from discharge, 58 patients (28.43%) required a visit to the emergency department, and 28 (13.73%), a new admission.

When comparing the groups with and without infection, the following characteristics were similar: age, sex, hemoglobin, blood pressure, heart rate and LVEF (Table 2). Renal failure was present in 73 patients (61.3%) with infection vs 69 patients (48.9%) without infection ($p = 0.045$). The mean dose of furosemide was similar in both groups: 68.06 mg/day (37.58) for the infected patients vs 71.84 mg/day (39.23) for non-infected ones ($p = 0.568$). In the group with infection, 42 patients (35.3%) died during the total follow-up vs 50 patients (35.5%) of the group without infection ($p = 0.977$). During hospitalization, 32 patients with infection (26.9%) died vs 24 patients without infection (17%) ($p = 0.054$). When assessing only the discharged patients, 10 of the group with infection (11.5%) died during follow-up vs 26 (22.2%) of the group without infection ($p = 0.047$).

Table 3 shows the characteristics related to in-hospital mortality, and Table 4 shows mortality during total follow-up. Renal failure was observed in 54.6% of the patients, more frequently in those who died during hospitalization (Table 3) or during the total study period (Table 4).

Discussion

Infection was associated with decompensated HF in 45.8% of the patients, and in that group of infected patients, an increase in mortality was observed during hospitalization. However, after hospital discharge, the group with infection showed better outcome as compared to those without infection. The most frequent comorbidity in our study was renal failure, affecting 54.6% of the patients, and relating to in-hospital mortality during follow-up after discharge.

The causes of heart decompensation varied according to the population studied. Acute coronary syndrome, arrhythmias and acute respiratory disease are the most frequent precipitating factors of heart decompensation.[2] At the emergency department of our hospital, the most common cause of hospitalization was non-adherence to treatment, and infections were considered the cause of hospitalization in 8% of the cases.[5] In the BREATHE Registry, poor adherence was also the most frequent cause, and infection was the second one, contributing to decompensation in 22.9% of the cases.[6] The association between infection and decompensation and worse prognosis is well known. An investigation performed at the InCor, via the statistics department, showed that, in the last 10 years, 27,528 patients were hospitalized and diagnosed with HF (I50), most of the male sex (55%). The mean length of stay was 14.8 days, and the in-hospital mortality of that population with HF was 24.8%.[6]

In the present study, of the patients admitted to our ward in 2014, the in-hospital mortality of those with HF and infection was 26.9% versus 17.0% of those without infection ($p = 0.05$). The increase in mortality due to infection has been also reported in the OPTIMIZE-HF Registry.[4]

Comparing the characteristics of the patients with and without infection based on the variables analyzed, those with infection decompensated with a milder ventricular impairment than that of those without infection, suggesting that decompensation resulted from the overload and systemic changes that infection causes and not only from the severity of cardiac impairment. Patients with infection

Table 1 – Characteristics of the population

Characteristics	P (K-S)	N = 260 patients
Age (years)	0.062	66.1 ± 12.7
Male sex – n (%)	-	141 (54.2)
HF etiology – n (%)		
Chagasic	-	46 (17.7)
Ischemic	-	97 (37.3)
Non-ischemic, non-Chagasic	-	117 (45.0)
Comorbidities – n (%)		
Renal failure	-	142 (54.6)
COPD	-	34 (13.1)
Hypothyroidism	-	47 (18.1)
Diabetes mellitus	-	95 (36.5)
Atrial fibrillation	-	119 (45.8)
Urinary infection	-	39 (15.0)
Pneumonia	-	88 (33.8)
Infection (any site)	-	119 (45.8)
Vital signs		
SBP (mm Hg)	< 0.001	100.0 (82.8 - 120.0)
DBP (mm Hg)	< 0.001	60.0 (56.0 – 80.0)
HR (bpm)	0.005	80.0 (70.0 – 98.0)
Echocardiogram		
LVDD (mm)	0.523	62.0 ± 10.4
LA (mm)	0.071	48.4 ± 7.2
LVEF (%)	< 0.001	30.0 (25.0 – 45.0)
PAP (mm Hg)	0.392	51.3 ± 15.6
Hemodynamic profile – admission – n (%)		
Profile B	-	131 (50.4)
Profile C	-	111 (42.7)
Profile L	-	18 (6.9)
Laboratory tests		
Hemoglobin (g/dl)	0.851	13.1 ± 2.3
Urea (mg/dL)	0.019	79.0 (51.0 – 108.0)
Creatinine (mg/dL)	< 0.001	1.6 (1.2 – 2.0)
Sodium	0.014	138.0 (134.0 – 140.0)
Potassium	0.002	4.3 (4.0 – 4.9)
C-reactive protein	< 0.001	18.0 (7.5 – 53.6)
CKMB mass	< 0.001	2.0 (1.4 – 3.6)
Troponin I	< 0.001	0.05 (0.022 – 0.107)
BNP	< 0.001	1020.0 (457.5 – 2014.3)

P (K-S): teste de Kolmogorov-Smirnov (p > 0.05 = normal distribution). Data are presented as mean ± standard deviation for continuous variables with normal distribution, or median (interquartile range 25% - 75%) for continuous variables with non-normal distribution. Categorical variables are presented as absolute numbers (percentage). COPD: chronic obstructive pulmonary disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; LVDD: left ventricular diastolic diameter; LA: left atrium; LVEF: left ventricular ejection fraction; PAP: pulmonary artery pressure.

Table 2 – Comparison of the characteristics of the patients with and without infection

Characteristics	Infection		p*
	Yes (n = 119)	No (n = 141)	
Age (years)	67.33 ± 12.18	65.03 ± 13.04	0.147
Male sex - n (%)	58 (48.7)	83(58.9)	0.102
Hemoglobin (g/dl)	12.93 ± 1.93	13.25 ± 2.47	0.251
SBP (mm Hg)	100.0 (83.5 – 123.5)	96 (81.5 – 120.0)	0.109
DBP (mm Hg)	61.0 (53.0 – 80.0)	60.0 (56.0 – 76.0)	0.701
HR (bpm)	84.0 (70.0 – 100.0)	80.0 (67.8 – 94.5)	0.493
LVEF (%)	30.0 (25.0 – 46.0)	30 (25.0 – 45.0)	0.019
LVDD (mm)	60.60 ± 10.07	63.24 ± 10.46	0.044
LVSD (mm)	48.72 ± 12.52	52.45 ± 12.74	0.022
Urea (mg/dL)	78.0 (56.0 – 107.0)	79.0 (49.3 – 108.0)	0.391
Creatinine (mg/dL)	1.62 (1.23 – 2.17)	1.54 (1.22 – 2.00)	0.680
Renal failure - n (%)	73 (61.3)	69 (48.9)	0.045
Length of stay (days)	29.43 ± 19.43	21.3 ± 27.89	0.546
Mortality – n (%)			
Total	42 (35.3)	50 (35.5)	0.977
In-hospital	32 (26.9)	24 (17)	0.050
Post-discharge	10 (11.5%)	26 (22.2%)	0.046

Data are presented as mean ± standard deviation for continuous variables with normal distribution, or median (interquartile range 25% - 75%) for continuous variables with non-normal distribution. Categorical variables are presented as absolute numbers (percentage). P: To calculate P value, Student t test was used for the variables with normal distribution, Mann-Whitney U test for the variables with non-normal distribution. P value was estimated by use of the chi-square test or Fisher exact test for the categorical variables. SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; LVDD: left ventricular diastolic diameter; LVSD: left ventricular systolic diameter; LVEF: left ventricular ejection fraction.*

had smaller heart dilatation than those without infection, 60.6 mm (10.07) vs 63.4 mm (10.46), p = 0.04. After hospital discharge, patients of the group with infection had better outcome. Mortality during follow-up of those who were hospitalized with infection was 11.5% versus 22.2% of those without infection (p = 0.046). That lower mortality can be attributed to the milder cardiac impairment of those who had infection, a fact that can explain the best outcome after discharge with infection under control. This result shows that infection worsens the prognosis of patients who, even without significant cardiac impairment, decompensate and have a tendency towards worse outcome during hospitalization. Our data confirm that infection worsens the outcome of patients with HF.

In addition, in their study, M. Arrigo et al. have also reported similar findings for patients with infection, as well as lower re-hospitalization rates as compared to those of patients without in-hospital infection.[2] Those data show that infections, by overloading impaired hearts, worsen the clinical findings, leading to decompensation, and such patients with impaired hearts have a worse outcome than those without infection. Once infection is under control, the milder heart impairment of those patients determines their better outcome as compared to those who decompensated without infection, because of their more severe heart impairment.

Those findings emphasize the importance of pulmonary infection prevention, avoiding the worsening of patients and their consequent hospitalization. That benefit has been confirmed in octogenarian patients, and those who received vaccination were less frequently hospitalized.[8] Pneumococcal and influenza vaccinations as recommended in our guideline might be very useful to prevent pulmonary infection.

Limitations

This is an observation study, with its inherent limitations. The patients were selected from those admitted to a tertiary hospital, which might determine the bias of more severe cases.

Conclusions

Infection is a frequent morbidity among patients with HF admitted for compensation of the condition, and those with infection show higher in-hospital mortality. However, those patients who initially had infection and survived had a better outcome after discharge.

Author contributions

Conception and design of the research: Cardoso JN, Del Carlo CH, Ochiai ME, Barretto ACP; Acquisition of

Table 3 – Comparison of the characteristics of the patients regarding in-hospital mortality

Characteristics	In-Hospital Death		p*
	Yes (n =56)	No (n = 204)	
Age (years)	65.7 ± 12.6	66.2 ± 12.8	0.817
Male sex – n (%)	33 (58.9)	108 (52.9)	0.426
HF etiology – n (%)			
Chagasic	11 (19.6)	35 (17.2)	0.666
Ischemic	21 (37.5)	76 (37.3)	0.973
Comorbidities – n (%)			
Renal failure	43 (76.8)	99 (48.5)	< 0.001
COPD	7 (12.5)	27 (13.2)	0.885
Hypothyroidism	11 (19.6)	36 (17.6)	0.731
Diabetes mellitus	18 (32.1)	77 (37.7)	0.441
Atrial fibrillation	28 (50.0)	91 (44.6)	0.473
Urinary infection	10 (17.9)	29 (14.2)	0.499
Pneumonia	24 (42.9)	64 (31.4)	0.108
Infection (any site)	32 (57.1)	87 (42.6)	0.054
Vital signs			
SBP (mm Hg)	91 (80-110)	100 (84-120)	0.109
DBP (mm Hg)	60 (58.5-77)	61.5 (55.25-80)	0.701
HR (bpm)	79 (62-98)	80 (70-97.75)	0.493
Echocardiogram			
LVDD (mm)	64.6 ± 9.4	61.4 ± 10.6	0.043
LVSD (mm)	53.88 ±10.95	49.93 ± 13.12	0.050
LA (mm)	48.7 ± 8.0	48.4 ± 7.0	0.746
LVEF (%)	28 (24.25-35)	32 (25-47)	0.019
PAP (mm Hg)	55.7 ± 16.4	50.1 ± 15.2	0.035
Hemodynamic profile – admission – n (%)			
Profile B	23 (41.1)	108 (52.9)	0.116
Profile C	30 (53.6)	81 (39.7)	0.063
Profile L	3 (5.4)	15 (7.4)	0.771
Laboratory tests			
Hemoglobin	12.3 ± 2.1	13.3 ± 2.2	0.004
Urea (mg/dL)	83 (55-114)	74.5 (51-107)	0.391
Creatinine (mg/dL)	1.66 (1.09-2)	1.55 (1.23-2.06)	0.680
Sodium	137 (133-140)	138 (135-140)	0.598
Potassium	4.3 (4-5)	4.3 (4-4.8)	0.583
C-reactive protein	19.44 (8.82-50.2)	18 (7.39-54)	0.766
CKMB mass	1.94 (1.24-3.64)	2.03 (1.41-3.58)	0.950
Troponin I	0.05 (0.02-0.12)	0.05 (0.02-0.10)	0.951
BNP	1283 (853-2095)	969 (422.5-1951.5)	0.101
Total cholesterol	134.9 ± 44.7	145.8 ± 46.0	0.308
HDL	30.5 ± 14.9	38.3 ± 15.0	0.015
LDL	82.4 ± 36.1	86.6 ± 36.3	0.504
Vasoactive drugs on admission – n (%)			
Dobutamine	48 (85.7)	111 (54.4)	< 0.001
Levosimendan	2 (3.6)	16 (7.8)	0.378
Milrinone	5 (8.9)	4 (2.0)	0.024

Data are presented as mean ± standard deviation for continuous variables with normal distribution, or median (interquartile range 25% - 75%) for continuous variables with non-normal distribution. Categorical variables are presented as absolute numbers (percentage). P: To calculate P value, Student t test was used for the variables with normal distribution, Mann-Whitney U test for the variables with non-normal distribution. P value was estimated by use of the chi-square test or Fisher exact test for the categorical variables. COPD: chronic obstructive pulmonary disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; LVDD: left ventricular diastolic diameter; LVSD: left ventricular systolic diameter; LA: left atrium; LVEF: left ventricular ejection fraction; PAP: pulmonary artery pressure.*

Table 4 – Comparison of the characteristics of the patients regarding total mortality (in-hospital + post-discharge)

Characteristics	Total Death		p*
	Yes (n = 92)	No (n = 168)	
Age (years)	65.9 ± 12.4	66.2 ± 12.9	0.828
Male sex – n (%)	55 (59.8)	86 (51.2)	0.184
HF etiology – n (%)			
Chagasic	21 (22.8)	25 (14.9)	0.108
Ischemic	31 (33.7)	66 (39.3)	0.373
Comorbidities – n (%)			
Renal failure	64 (69.6)	78 (46.4)	<0.001
COPD	10 (10.9)	24 (14.3)	0.435
Hypothyroidism	17 (18.5)	30 (17.9)	0.901
Diabetes mellitus	28 (30.4)	67 (39.9)	0.130
Atrial fibrillation	47 (51.1)	72 (42.9)	0.203
Urinary infection	14 (15.2)	25 (14.9)	0.942
Pneumonia	31 (33.7)	57 (33.9)	0.970
Infection (urinary and/or pulmonary)	42 (45.7)	77 (45.8)	0.978
Vital signs:			
SBP (mm Hg)	91 (84-110)	100 (82-125)	0.023
DBP (mm Hg)	60 (57.5-70)	63.5 (55-80)	0.465
HR (bpm)	80 (69.5-100)	80 (70-94.5)	0.898
Echocardiogram:			
LVDD (mm)	64.0 ± 9.4	61.0 ± 10.8	0.029
LA (mm)	48.3 ± 7.3	48.5 ± 7.1	0.859
LVEF (%)	28.5 (24.25-35)	35 (25-49)	0.002
PAP (mm Hg)	54.2 ± 15.8	49.8 ± 15.3	0.058
Hemodynamic profile – admission – n (%)			
Profile B	37 (40.2)	94 (56.0)	0.015
Profile C	50 (54.3)	61 (36.3)	0.005
Profile L	5 (5.4)	13 (7.7)	0.484
Laboratory tests			
Hemoglobin	12.4 ± 2.1	13.5 ± 2.3	< 0.001
Urea (mg/dL)	82 (54-114)	74.5 (51-107)	0.453
Creatinine (mg/dL)	1.66 (1.23-2)	1.54 (1.22-2.03)	0.481
Sodium	137 (134-139)	138 (135-140)	0.325
Potassium	4.3 (4-4.9)	4.4 (4-4.8)	0.835
C-reactive protein	17.97 (8.94-48.8)	18.88 (7.31-60.42)	0.927
CKMB mass	1.98 (1.32-3.26)	2.1 (1.5-3.6)	0.759
Troponin I	0.05 (0.02-0.11)	0.05 (0.02-0.1)	0.941
BNP	1274 (774-2095)	969 (383.5-1951.5)	0.098
Total cholesterol	138.0 ± 44.9	147.0 ± 46.2	0.306
HDL	32.6 ± 15.0	39.1 ± 15.0	0.013
LDL	83.5 ± 35.8	87.1 ± 36.5	0.499
Vasoactive drugs on admission – n (%)			
Dobutamine	72 (78.3)	87 (51.8)	< 0.001
Levosimendan	6 (6.5)	12 (7.1)	0.850
Milrinone	5 (5.4)	4 (2.4)	0.286

Data are presented as mean ± standard deviation for continuous variables with normal distribution, or median (interquartile range 25% - 75%) for continuous variables with non-normal distribution. Categorical variables are presented as absolute numbers (percentage). P: To calculate P value, Student t test was used for the variables with normal distribution, Mann-Whitney U test for the variables with non-normal distribution. P value was estimated by use of the chi-square test or Fisher exact test for the categorical variables. COPD: chronic obstructive pulmonary disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; LVDD: left ventricular diastolic diameter; LA: left atrium; LVEF: left ventricular ejection fraction; PAP: pulmonary artery pressure.*

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References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129-200. doi: 10.1093/eurheartj/ehw128.
2. Brasil. Ministério da Saúde. Datasus: mortalidade - 1996 a 2015, pela CID-10 [Internet] [Citado em 2016, Dez 12] Disponível em: http://tabnet.datasus.gov.br/cgi/deftohtm.exe?sim/cnv/obt10uf.de
3. Arrigo M, Tolppanen H, Sadoune M, Feliot E, Teixeira A, Laribi S, et al. Effect of precipitating factors of acute heart failure on readmission and long-term mortality. ESC Heart Fail. 2016;3(2):115-21. doi: 10.1002/ehf2.12083.
4. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, et al; OPTIMIZE-HF Investigators and Hospitals. Factors identified as precipitating hospital admissions for heart failure and clinical outcomes: findings from OPTIMIZE-HF. Arch Intern Med. 2008;168(8):847-54. doi: 10.1001/archinte.168.8.847.
5. Mangini S, Silveira FS, Silva CP, Grativvol PS, Seguro LF, Ferreira SM, et al. Decompensated heart failure in the emergency department of a cardiology hospital. Arq Bras Cardiol. 2008;90(6):433-40. doi: http://dx.doi.org/10.1590/S0066-782X2008000600008.
6. Albuquerque DC, Souza Neto JD, Bacal F, Rohde LE, Pereira SB, Berwanger O, et al; Investigadores Estudo BREATHE. I Registro Brasileiro de Insuficiência Cardíaca: aspectos clínicos, qualidade assistencial e desfechos hospitalares. Arq Bras Cardiol. 2015;104(6):433-42. doi: http://dx.doi.org/10.5935/abc.20150031.
7. Pereira-Barretto AC, Cardoso JN, Del Carlo CH, Ramos Neto JA, Kalil Filho R. Pneumonia em pacientes com Insuficiência Cardíaca aumenta a mortalidade durante hospitalização. In: 14 Congresso Brasileiro de Insuficiência Cardíaca, Rio de Janeiro, 18 a 19 de junho; 2015.
8. Ahmed MB, Patel K, Fonarow GC, Morgan CJ, Butler J, Bittner V, et al. Higher risk for incident heart failure and cardiovascular mortality among community-dwelling octogenarians without pneumococcal vaccination. ESC Heart Fail. 2016;3(1):11-7. doi: 10.1002/ehf2.12056.

Infections in Heart Failure – Impact on Mortality

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Infections represent an important emerging clinical problem that cause decompensation of heart failure (HF), and in many cases, life-threatening acute systemic disorder (sepsis) and septic shock. Cardiovascular system plays an important role in the development of multiorgan dysfunction in sepsis and refractory septic shock. Although intra-hospital death for sepsis decreased from 35% in 2000 to 18% in 2002, one third of patients die within one year after a septic event. Cardiovascular dysfunction significantly increases mortality rates in sepsis as compared with sepsis without cardiac dysfunction.[1] Infection, *per se*, precipitates the occurrence of cardiac decompensation and is a direct marker of mortality in HF patients.[2]

The study by Cardoso et al.[3] report a high hospital infection rate (45.8%) and relevant mortality (21,5%) among patients with decompensated HF. Interestingly, during the first year after hospital discharge, mortality rate was lower in patients with infection as compared with those without infection (11.5% *vs.* 22.2%; p = 0.04).

A recent study conducted with Murinae rodents showed myocardial injury, abnormal electrical conduction, cardiac dysfunction and increased cardiac apoptosis that may explain the cardiac instability observed in patients with severe infections. Studies have reported an interaction between the infectious agent, immune system and chemical mediators, with direct and indirect effects on myocardium.[1,4]

Clinical cardiologists have incorporated new criteria for early detection and treatment of sepsis and septic shock in HF, based on clinical protocols and imaging and microbiological tests, in addition to specific biomarkers. Elevated C protein (> 25 mg/mL) and procalcitonin levels are helpful in identifying infections as cause of HF decompensation.[5,6]

HF-related infections may be acquired in the community or during hospitalization, consisting primarily of pulmonary followed by urinary infections. From my clinical experience, infections on skin and intracardiac devices, and vascular access infections are relevant infection sites that should be examined in every patient with suspected infection.

In the present study, the authors show a group of inpatients with severe decompensated HF, who require high doses of inotropes, which makes the analysis of the real impact of sepsis/septic shock difficult. In the real world, many patients with severe HF (stage D) are at the end-of-life stage, where infections are common. For these patients, palliative care, instead of intensive care, is the most appropriate therapy. This reality is faced in our hospitals today and will certainly become more and more common in hospitals for chronic diseases in the future.

Some factors may explain the lower mortality seen in the post-hospital follow-up, including greater attention paid to these patients with infection (e.g. vaccination and healthcare services), and selection bias in which patients with more severe HF may have died during hospitalization due to infection. Arrigo et al.[7] showing similar findings of lower mortality after hospital discharge involves a group of patients with decompensated HF associated with respiratory diseases (chronic obstructive pulmonary disease, asthma and pulmonary infection) rather than patients with respiratory infections only (without cardiac disease).

In summary, infections are an important cause of decompensation of HF that should be early detected and treated using specific protocols and in the presence of sepsis and/or septic shock. Volemic resuscitation, early antibiotic treatment, and referral to cardiac intensive care units are considered good clinical practices that can reduce the occurrence of hard outcomes such as death. On the other hand, it has become more and more recognized that sepsis promotes cardiovascular changes with multisystemic involvement that increase the frequency of cardiac and non-cardiac events after recovery from sepsis.

Keywords

Heart Failure/mortality; Infections; Hospitalization; Sepsis; Shock,Septic; Infection Control.

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References

1. Kakihana Y, Ito T, Nakahara M, Yamaguchi K, Yasuda T. Sepsis-induced myocardial dysfunction: pathopysiology and management. J Intensive Care. 2016 Mar 23;4:22.
2. Alon D, Stein GY, Korenfeld R, Fuchs S. Predictors and outcomes of infection – related hospital admissions of heart failure patients. PLoS One. 2013 Aug 23;8(8):e72476.
3. Cardoso JN, Del Carlo CH, Oliveira Jr MT, Ochiai ME, Kalil Filho R, Pereira Barretto AC. Infecção em pacientes com insuficiência cardiac descompensada: mortalidade hospitalat e evolução. Arq Bras Cardiol. 2018; 110(4):364-370.
4. Sergi C, Shen F, Lim DW, Liu W, Zhang M, Chiu B, et al. Cardiovascular dysfunction in sepsis at the dawn of emerging mediators. Biomed Pharmacother. 2017 Nov;95:153-60
5. Aïssou L, Sorbets E, Lallmahomed E, Goudot FX, Pop N, Es-Sebbani S, et al. Prognostic and diagnostic value of elevated serum concentration of procalcitonin in patients with suspected heart failure. A review and meta-analysis. Biomarkers. 2018 Mar 12:1-7.
6. Demissei BG, Cleland JG, O'Connor CM, Metra M, Ponikowski P, Teerlink JR, et al. Procalcitonin-based indication of bacterial infection identifies high risk acute heart failure patients. Int J Cardiol. Feb;204:164-71.
7. Arrigo M, Tolppane H , Sadoune M , Feliot E, Teixeira A, Laribi S, et al. Effect of precipitating factors of acute heart failure on readmission and long-term mortality. ESC Heart Failure 2016; 3(2)115-21.

Impact of a High-Intensity Training on Ventricular Function in Rats After Acute Myocardial Infarction

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Abstract

Background: **Physical exercise should be part of the treatment of post-acute myocardial infarction (AMI) patients.**

Objective: **To evaluate the effects of two training prescription models (continuous x interval) and its impact on ventricular function in rats after AMI with normal ventricular function.**

Methods: **Forty Wistar rats were evaluated by echocardiography 21 days after the AMI. Those with LVEF = 50% (n = 29) were included in the study and randomized to control group (CG n = 10), continuous training group (CTG n = 9) or interval training group (ITG, n = 10). Then, a swimming test with control of lactate production was performed. Based on its result, the lactate threshold (LT) was established to define the training intensities. After six weeks, the animals were reassessed by echocardiography and lactate production. Outcome measures were end-diastolic diameter (EDD), end-systolic diameter (ESD), left ventricular ejection fraction (LVEF, %) lactate at rest, lactate without overload, and lactate with 12g and 13.5g of additional load. Group comparisons of quantitative variables of the study were performed by one-factor analysis of variance (ANOVA). The Newman-Keuls test was used for multiple comparisons of the groups. Within-group comparisons of dependent variables between the two training protocols were performed by Student's t-test. Normality of the variables was tested by the Shapiro-Wilks test. Values of $p < 0.05$ indicated statistical significance.**

Results: **EDD, ESD, and LVEF before and after the training period were similar in within-group comparisons. However, EDD was significantly different (p=0.008) in the CG. Significant differences were found for L12g (p=0.002) and L13.5g (p = 0.032) in the ITG, and for L12g (p = 0.014) in the CG. No differences were found in the echocardiographic parameters between the groups. Significant differences were found in lactate without overload (p = 0.016) and L12 (p = 0.031) in the second assessment compared with the first, and between the groups – ITG vs. CG (p = 0.019) and CTG vs. CG (p = 0.035).**

Conclusion: **Both methods produced a training effect without altering ventricular function. (Arq Bras Cardiol. 2018; 110(4):373-380)**

Keywords: **Myocardial Infarction; Exercise; Ventricular Function, Left; Rats; Anaerobic Threshold.**

Introduction

Cardiovascular diseases (CVDs) are considered the main cause of death in Brazil and in the world in individuals older than 30 years, and acute myocardial infarction (AMI) is responsible for approximately 10% of these deaths.[1]

Treatment after AMI should be pharmacological combined with life habit changes and exercise. Therefore, physical training plays an essential role in AMI treatment.[2] Current guidelines recommend prescription of physical exercises according to individual's risk stratification, and the most accepted is the combination of moderate-intensity aerobic and resistance exercises.[3] However, with the progression of prescribed physical training, some authors have decided to prescribe high-intensity training for post-AMI patients.[4] Experimental studies involving high-intensity training have shown controversial results in terms of benefits to this population.[5,6]

Zhang et al.[5] investigated the effects of high-intensity sprint training on post-AMI cellular adaptations. Myocytes isolated from hearts with chronic myocardial infarction had a 10% increase in length but not in width, which is consistent with hypertrophy. This may minimize ventricular remodeling and prevent the occurrence of dilated cardiomyopathy.

Benito et al.[6] used an animal model to evaluate whether sustained intensive exercise training would induce structural changes in the heart. The authors reported cardiac fibrosis after long-term intensive exercise training, together with changes in ventricular function and increased arrhythmia inducibility.

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Therefore, the aim of this study was to compare the effects of high-intensity training on post-AMI ventricular function with those of moderate-intensity training.

Methods

We conducted an experimental study according to the norms and ethical principles of the Brazilian College of Animal Experimentation (COBEA), and approval by the ethics committee for animal research of Pontifical Catholic University of Parana.

First, 40 adult, male Wistar rats weighing 250–300 grams were selected by convenience. The animals had water and food *ad libitum*.

The rats were anesthetized with intramuscular ketamine (Ketamin® / Cristalia - 70 mg/kg) and xylazin (Calmiun®/ Agener União- 20 mg/kg). Then, the animals were intubated and mechanically ventilated with oxygen at 2.5 mL/min (small-animal volume). The animals were placed in the supine position (with the body slightly inclined to the right to facilitate the access to the area that would be operated), and all four limbs were fixed using adhesive tape. The chest was shaved and disinfected with povidone-iodine. A left posterolateral thoracotomy was performed at the third intercostal space; as the left pleura was open, the pericardium was removed to expose the operation site. The left auricle was isolated, and the left coronary artery, identified between the pulmonary artery and the left atrium, was ligated with a blue, non-absorbable 7.0 monofilament polypropylene suture thread. The infarcted area was identified by its different color. The heart was then repositioned within the chest, the lungs hyperinflated and the thoracic wall sutured using a non-absorbable, 4.0 nylon monofilament.[7]

Two M-mode echocardiographic examinations (MyLab 40, Esaote®) were performed with a 7.5-10.0 MHz sector transducer. The parameters analyzed were left ventricular ejection fraction (LVEF[%]), end-diastolic diameter (EDD[mL]) and end-systolic diameter (ESD[mL]).

Rats with a LVEF > 50% in the first echocardiographic exam were included in the study. The sample was composed of 29 animals, which were randomized using piece of folded papers inside a white envelope. The envelopes were drawn by the main author, and the animals allocated to one of the three groups – control group (CG, n = 10), continuous training group (CTG, n = 9), and interval training group (ITG, n = 10).

The ideal training intensity was determined by a swimming test, with incremental load and control of lactate production. The animals were put in a tank filled to a depth of 40 cm of water (deep enough to prevent the animals to sustain their bodies with their tails on the bottom).[7] Then, the rats underwent swimming exercise with progressive, additional load (proportional to body weight) - 4.0; 4.5; 5.0; 5.5 e 6.0% of body weight for five minutes each.[8] The main purpose of this test was to determine the lactate threshold (LT), which was used as the cutoff point for the continuous and interval training loads. Then 25 μL of blood samples were collected from the tail of the animal at rest and at each load progression.[9,10] Lactic acid production was analyzed using a portable lactate analyzer (Accutrend®).

Lactate concentration values were organized in an excel spreadsheet, and a line graph obtained for each animal. LT was visually identified and defined as the point where linearity was lost. This process was performed for both training groups in the swimming tests, one day after each echocardiographic examination.

According to the lactate test results, training intensities prescribed to the CTG and the ITG were at the LT and above the LT, respectively. The CG did not undergo physical training.

Training program of CTG and ITG consisted of a 42-day macrocycle, divided into six 7-day microcycles of 30 exercise sessions (five a week, once a day). The overload method defined for both groups was of volume, i.e., a weekly increase in the time of swimming (min). In the first two weeks of training, CTG underwent swimming training for 10 minutes continuously. In the third and fourth week, the rats swam for 15 minutes, and for 20 minutes in the last two weeks. The ITG underwent five 2-minute sessions with 2-minute intervals between them and 1:1 training density in the first two weeks. In the third and fourth weeks, the rats swam seven 2-minute sessions, with the same interval between them. Finally, in the two last weeks, the animals swam ten 2-minute series, with the same interval between them.

Our outcome measures were LVEF, ESD, ESD and the effect of training (lactate curve). Within-group and between group comparisons of these parameters were performed by a blinded investigator.[9]

At the end of the experiment, the animals were euthanized by sodium pentobarbital (i.v. 200-250 mg/Kg).

Statistical analysis

Continuous variables were expressed as mean ± standard deviation. Comparisons of quantitative variables were performed by one-factor analysis of variance (ANOVA), and the Newman-Keuls test was used for multiple comparisons. Comparisons between the two evaluations within each group were performed by Student's t-test for dependent variables. Normality of the variables was tested by the Shapiro-Wilks test. Statistical significance was set at $p < 0.05$. Analyses were performed using the Statistica software, version 8.0.

Results

Pre- and post-training echocardiographic results and results of lactate tests were compared within and between groups.

Tables 1 and 2 describes the results of within and between group comparisons, respectively, of LFEV, and left ventricular EDD and ESD, and Tables 3 and 4 describes the results of within and between group comparisons, respectively, of pre- and post-training results of lactate testing with incremental load.

Graphs 1 and 2 show comparative results of pre-training *versus* post-training lactate in ITG and CTG, respectively.

Discussion

The main findings of the present study were: 1) No differences were found in within-group and between-group comparisons of echocardiographic parameters in CTG and ITG;

Table 1 – Within-group echocardiographic comparison of mean left ventricular ejection fraction, end-diastolic diameter and end-systolic diameter

GROUP	EDD1	EDD2	p	ESD1	ESD2	p	LVEF1	LVEF2	p
CG	0.26	0.13	0.008*	0.17	0.74	0.120	76.10	71.20	0.112
CTG	0.50	0.58	0.741	0.83	0.19	0.422	73.67	71.89	0.579
ITG	0.19	0.88	0.153	0.78	0.01	0.510	70.70	71.50	0.792

*CG: control group, CTG: continuous training group; ITG: interval training group; EDD1: end-diastolic diameter at first evaluation; EDD2: end-diastolic diameter at the second evaluation; ESD1: end-systolic diameter at first evaluation; ESD2: end-systolic diameter at second evaluation; LVEF1: left ventricular ejection fraction at first evaluation; LVEF2: left ventricular ejection fraction at second evaluation; p = p-value of LVEF between the two study days. Student's t-test, * p < 0.05.*

Table 2 – Between-group echocardiographic comparisons of left ventricular ejection fraction, end-diastolic diameter and end-systolic diameter

Variable	Group	Mean ± SD	p
	CG	76.10 ± 6.89	
LVEF1 (%)	CTG	73.67 ± 10.01	0.368
	ITG	70.70 ± 8.15	
	CG	71.20 ± 6.44	
LVEF 2 (%)	CTG	71.89 ± 8.68	0.981
	ITG	71.50 ± 7.53	
	CG	5.26 ± 0.80	
EDD 1 (mm)	CTG	6.50 ± 1.63	0.103
	ITG	6.19 ± 1.30	
	CG	6.20 ± 0.58	
EDD2 (mm)	CTG	6.00 ± 1.15	0.404
	ITG	6.00 ± 1.69	
	CG	3.17 ± 0.70	
ESD1 (mm)	CTG	3.83 ± 0.93	0.308
	ITG	3.78 ± 1.40	
	CG	3.74 ± 0.75	
ESD 2 (mm)	CTG	4.19 ± 1.23	0.709
	ITG	4.01 ± 1.46	

LVEF1: left ventricular ejection fraction at first evaluation; LVEF2: left ventricular ejection fraction at second evaluation; p: p-value of LVEF between the two study days EDD1: end-diastolic diameter at first evaluation; EDD2: end-diastolic diameter at the second evaluation; ESD1: end-systolic diameter at first evaluation; ESD2: end-systolic diameter at second evaluation; CG: control group, CTG: continuous training group; ITG: interval training group; One-factor ANOVA

2) A worsening of EDD was observed in the CG; 3) Both groups subjected to exercise showed significant differences in lactate production in the pre- *versus* post-training periods: ITG for the loads L12g and L13.5g, and CTG for L12g; 4) No difference was found between initial and final tests in the CG.

The lack of difference in the pre- and post-training period between ITC and CTG indicates that high-intensity training, above LT, may be recommended for this sample. Current national and international guidelines[1,3] recommend a moderate-intensity, predominantly aerobic training (between the ventilatory thresholds, when evaluated by ergospirometry), i.e., below LT, to post-AMI patients. If these findings were extended to humans, these patients would benefit from this type of training, since it enables higher energy expenditure, better cardiovascular fitness and hence better control of cardiovascular risk factors.[11] Nevertheless, the same cannot be affirmed for animals with reduced LVEF, and further studies with the same study design are needed to assess the impact of a high-intensity training on ventricular remodeling.

It is worth mentioning that an inadequate volume/intensity load of cardiac training or exercise may be assessed by changes in ventricular wall kinetics,[12] as evaluated by Neilan et al.,[13] in a study with nonelite participants in the Boston marathon who were less trained. These findings were not observed in our trained groups, which implies that training density (relationship between volume and intensity) was well distributed. In addition, the training protocol proposed in this study may be applied to post-AMI patients with LVEF ≥ 50%, as long as a training/interval ratio of 1:1 for aerobic training and 1:2 for high-intensity interval training were respected.

Table 3 – Within-group comparisons of pre- and post-training lactate test parameters

Variables	Group	N	Mean T1 (SD)	Mean T2 (SD)	p
	CG	10	3.90 ± 1.07	4.32 ± 0.47	0.240
LR	CTG	9	3.83 ± 0.96	3.96 ± 0.22	0.720
	ITG	10	4.18 ± 0.81	4.24 ± 0.32	0.830
	CG	10	5.92 ± 1.11	5.99 ± 0.74	0.850
LO	CTG	9	5.90 ± 2.26	5.07 ± 0.88	0.392
	ITG	10	5.96 ± 1.04	5.18 ± 0.47	0.084
	CG	10	6.58 ± 1.16	6.76 ± 1.04	0.735
L12g	CTG	9	7.32 ± 1.83	5.66 ± 1.06	0.062
	ITG	10	8.08 ± 1.56	5.82 ± 0.65	0.002*
	CG	10	6.80 ± 1.32	6.52 ± 1.80	0.733
L13.5g	CTG	9	8.11 ± 2.14	5.67 ± 0.92	0.014*
	ITG	10	8.40 ± 2.28	5.97 ± 0.80	0.032*

*CG: control group, CTG: continuous training group; ITG: interval training group; SD: standard deviation; LR: lactate at rest; LO: lactate without overload; L12g: lactate with 12 grams of additional load; L13.5g: lactate with 13.5 grams of additional load. Student's t test. * p < 0.05.*

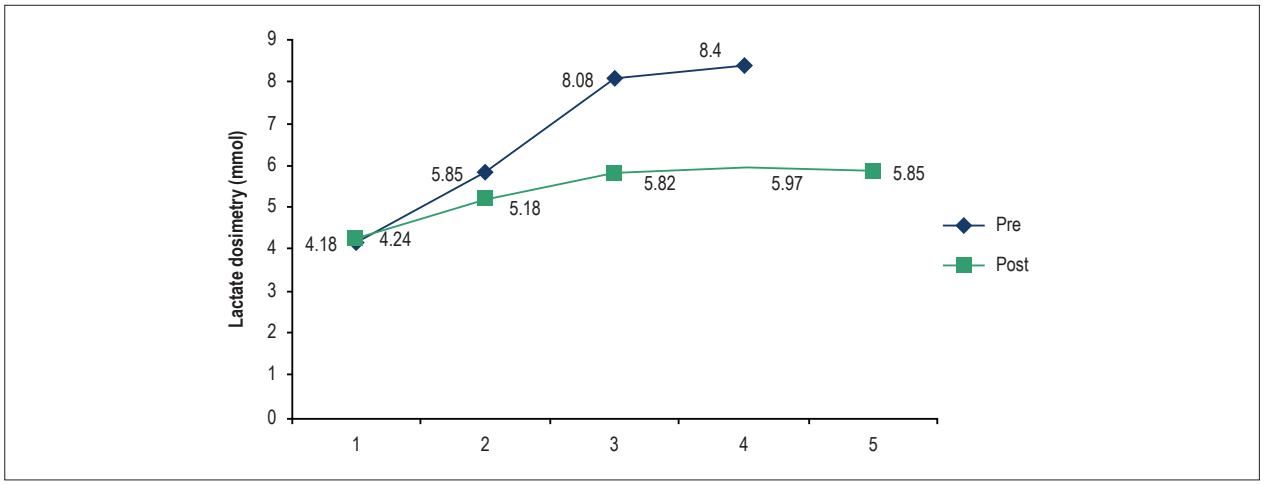
Table 4 – Between-group comparison of lactate test parameters

Variable	Group	n	Mean ± SD	p-value
	CG	10	5.92 ± 1.11	
LWO 1	CTG	9	5.90 ± 2.26	0.996
	ITG	10	5.96 ± 1.04	
	CG	10	5.99 ± 0.74	
LWO 2	CTG	9	5.07 ± 0.88	0.016*
	ITG	10	5.18 ± 0.47	
	CG	10	6.58 ± 1.16	
L 12 g 1	CTG	9	7.32 ± 1.83	0.110
	ITG	10	8.08 ± 1.56	
	CG	10	6.76 ± 1.04	
L 12g 2	CTG	9	5.66 ± 1.06	0.031*
	ITG	10	5.82 ± 0.65	
	CG	10	6.80 ± 1.32	
L 13.5g 1	CTG	9	8.11 ± 2.14	0.176
	ITG	10	8.40 ± 2.28	
	CG	10	6.52 ± 1.80	
L 13.5 g 2	CTG	9	5.67 ± 0.92	0.341
	ITG	10	5.97 ± 0.80	

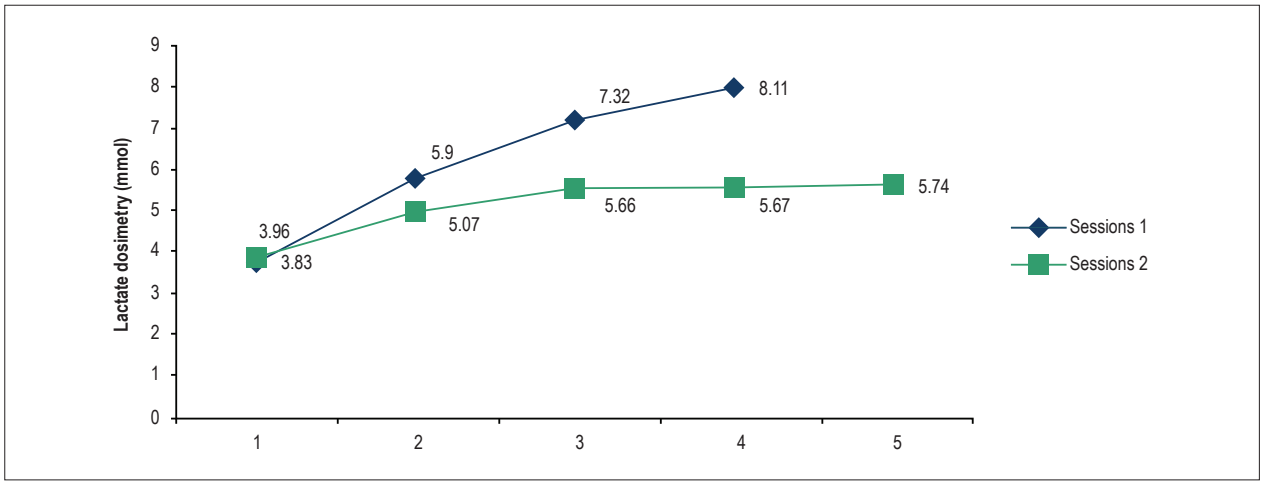
*CG: control group; CTG: continuous training group; ITG:interval training group; SD: standard deviation; LR: lactate at rest; LWO: lactate without overload; L12g: lactate with 12 grams of additional load; L13.5g: lactate with 13.5 grams of additional load. 1: first evaluation; 2: final evaluation. One-factor ANOVA * p < 0.05.*

The only significant change detected in the echocardiographic analysis after the study was the increase in EDD (p = 0.008) in the CG, which suggests that, after a six-week period of rest, these animals had an unfavorable ventricular remodeling when compared to the other groups.

In an experimental study by Gaudron et al.,[14] 156 rats were randomized after coronary occlusion into three groups – sedentary, those who started training 4 days after AMI and those who started training 21 days after AMI. The aim of the study was to assess the influence of continuous training (8 weeks'



Graph 1 – *Comparison between the pre and post-training CTG lactate tests.*



Graph 2 – *Comparison between pre-versus post-training CTG.*

duration), initiated early or delayed, on ventricular function and mortality. The authors demonstrated that 1) neither infarction nor exercise had any effect on the animals' survival; 2) in rats with small infarcts, left ventricular volume and shape, and long-term survival were not altered by chronic exercise initiated early or late after coronary artery ligation; 3) Mortality rose in animals with large infarction as a result of exercise ($p < 0.0001$) and was 47.6% with early exercise and 26.7% with late exercise ($p < 0.05$, early *versus* late).

It is of note that findings of left ventricular volume reported by Gaudron et al.[14] are similar to those described in our study, since no differences between pre- and post-training in cavity diameter were found in the training groups (ITG and CTG). On the other hand, mortality rates were different, since no deaths occurred in the present study. This may be explained by different training volumes between their study by Gaudron et al.,[14] and ours; in their study, the animals underwent continuous training for 90 minutes, with no progression or periodization program, whereas in our study, the maximum training period was 20 minutes, completed after a periodization program with progressive loads.

The development of a training program in a subjective manner, without load (intensity and/or volume) individualization or progression, and without temporal organization (periodization) should be considered inadequate, since the effects of training may be underestimated by an arbitrary exercise prescription. Therefore, studies in which exercises are prescribed in such arbitrary manner may yield inconsistent results, as exercises may be less effective than expected.

Therefore, aiming to provide the most effective exercise prescription, we elaborated an individualized method of exercise assessment and prescription. First, the animals underwent a LT test with incremental load before training. Based on this LT results and training group allocation (CTG or ITG), the optimal training load of each animal was defined. The model of load progression adopted was the volume progression (every two weeks) according to the pre-established periodization.

At the end of the training program, the LT test was repeated aiming to evaluate the effect of the training. When pre- and post-training results were compared in the ITG and CTG (intragroup comparison), the LT graph moved to the right (Graphs 1 and 2), indicating a positive effect of the training, i.e., the animals can tolerate a higher training load with similar energy consumption. Anaerobic threshold has been used as a measurement of physical fitness to assess the effects of training in patients with CVD and in healthy subjects, acting as a sensitive indicator of aerobic conditioning.[15] In addition, measurement of LT establishes an effective training intensity in terms of aerobic metabolic dynamics of active muscles. This training effect behavior has a high practical applicability, as improvements in physical fitness may be detected during the training sessions.[16]

However, between-group comparisons did not show any significant differences between ITG and CTG (Table 4), which indicates that both models had a similar effect in this sample. Besides, as expected, no differences were found between the results before and after the training period in the CG, as favorable effects of training cannot be produced during resting condition. Also, Table 1 shows significant differences between the training groups (CTG and ITG) and the CG in two-by-two comparisons.

The fact that the ITG and the CTG showed similar results after the training period may be justified by studies[17,18] that support that there is no evidence of the superiority of one exercise prescription model over another one in improving aerobic conditioning. However, the study by Vona et al.[11] concluded that both methods or their combination are efficient and safe to correct endothelial dysfunction in recent AMI. Schjerve et al.[12] demonstrated that high-intensity interval exercise was more effective in improving endothelial function and in reducing cardiovascular risk than moderate-intensity continuous exercise.

It is worth pointing out that high-intensity training tends to have a better effect on maxVO_2 and lactate tolerance than on anaerobic threshold (or LT); in contrast, continuous training improves LT, but not necessarily peak VO_2. Since the aim of the incremental test in this study was to determine the LT and thereby establish the optimal training load, changes in maximum physical capacity were not evaluated, which could be favored by the interval training.

Since interval training has been recently investigated in cardiac rehabilitation programs and periodization of this type of exercise has not been well defined, it is possible that changes in the number of training repetitions and resting periods may produce more positive and favorable results than continuous training.[19] We believe that the same training prescription used for the animals in the present study may be performed for post-AMI patients in rehabilitation programs.

Conclusion

This study demonstrated that high-intensity training, above the LT, did not worsen endothelial function, and was safe for post-AMI rats. Both training methods proposed improved cardiorespiratory fitness in the animals.

Study limiation

One possible limitation of this study was the use of a portable lactate analyzer instead of a micropipette.

Author contributions

Conception and design of the research: Winter SCN, Macedo RM, Meira LF, Guarita-Souza LC; Acquisition of data: Winter SCN, Francisco JC, Santos PC, Lopes APS, Meira LF; Analysis and interpretation of the data: Winter SCN, Macedo RM, Santos PC, Lopes APS, Guarita-Souza LC; Statistical analysis: Winter SCN, Macedo RM, Guarita-Souza LC; Writing of the manuscript: Winter SCN, Macedo RM, Carvalho KAT, Faria Neto JR, Guarita-Souza LC; Critical revision of the manuscript for intellectual content: Winter SCN, Macedo RM, Francisco JC, Carvalho KAT, Faria Neto JR, Macedo ACB, Guarita-Souza LC.

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 on Animal Experiments of the Colégio Brasileiro de Experimentação Animal (COBEA) under the protocol number 723/2012.

References

1. Balady GJ, Williams MA, Ades PA, Bittner V, Comoss P, Foody JM, et al; American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee, the Council on Clinical Cardiology; American Heart Association Council on Cardiovascular Nursing; American Heart Association Council on Epidemiology and Prevention; American Heart Association Council on Nutrition, Physical Activity, and Metabolism; American Association of Cardiovascular and Pulmonary Rehabilitation. (2007) Core components of cardiacr rehabilitation / secondary prevention programs: 2007 uptade: a scientific statement from the American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee, the Council on Clinical Cardiology; the Councils on Cardiovascular Nursing, Epidemiology and Prevention, and Nutrition, Physical Activity, and Metabolism; and the American Association of Cardiovascular and Pulmonary Rehabilitation. Circulation. 2007;115(20):2675-82. doi: 10.1161/CIRCULATIONAHA.106.180945.

2. Piegas LS, Avezum A, Pereira JC, Rossi Neto JM, Hoepfner C, Farran JA, et al; AFIRMAR Study Investigators. Risk factors for myocardial infarction in Brazil. Am Heart J. 2003;146(2):331-8. doi: 10.1016/S0002-8703(03)00181-9.

3. Cortez AA, Ferraz A, Nóbrega AC, Brunetto AF, Herdy AH, Hossri CA, et al. Diretriz de reabilitação cardiopulmonar e metabólica: aspectos práticos e responsabilidades. Arq Bras Cardiol. 2006;86(1):74-82. doi: 10.1590/S0066-782X2006000100011.

4. Wisloff U, Stoylen A, Loennechen JP, Bruvold M, Rognmo O, Haram PM, et al. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. Circulation. 2007;115(24):3086-94. doi: 10.1161/CIRCULATIONAHA.106.675041.

5. Zhang LQ, Zhang XQ, Musch TI, Moore RL, Cheung JY. Sprint training restores normal contractility in postinfarction rat myocytes. J Appl Physiol. 2000;89(3):1099-105. PMID: 10956356.

6. Benito B, Gay-Jordi G, Serrano-Mollar A, Guasch E, Shi Y, Tardif JC, et al. Cardiac arrhythmogenic remodeling in a rat model of long-term intensive exercise. Circulation. 2011; 123(1):13-22. doi: 10.1161/CIRCULATIONAHA.110.938282.

7. Cosmo S, Francisco JC, Cunha RC, Macedo RM, Faria-Neto JR, Simeoni R, et al. Effect of exercise associated with stem cell transplantation on ventricular function in rats after acute myocardial infarction. Rev Bras Cir Cardiovasc. 2012;27(4):542-51. doi: http://dx.doi.org/10.5935/1678-9741.20120096.

8. Xu X, Wan W, Ji L, Lao S, Powers AS, Zhao W, et al. (2008) Exercise training combined with angitensin II receptor blockade limits post-infarct ventricular remodelling in rats. Cardiovasc Res. 2008;78(3):523-32. doi: 10.1093/cvr/cvn028.

9. Voltarelli FA, Mello MA, Gobatto CA. Limiar anaeróbio determinado pelo teste do lactato mínimo em ratos: efeito dos estoques de glicogênio muscular e do treinamento físico. Revista Portuguesa de Ciências do Desporto 2004;4(3):16-25.

10. Manchado FB, Gobatto CA, Contarteze RV, Papoti M, Mello MA. The maximal lactate steady state is ergometer-dependent in experimental model using rats. Rev Bras Med Esporte. 2006;12(5):259-62. doi: http://dx.doi.org/10.1590/S1517-86922006000500007.

11. Vona M, Codeluppi GM, Iannino T, Ferrari E, Bogousslavsky J, von Segesser LK. Effects of different types of exercise training followed by detraining on endothelium-dependent dilation in patients with recent myocardial infarction. Circulation. 2009;119(12):1601-8. doi: 10.1161/CIRCULATIONAHA.108.821736.

12. Schjerve IE, Tyldum GA, Tjonna AM, Stolen T, Loennechen JP, Hansen HE, et al. Both aerobic endurance and strength training programmes improve cardiovascular health in obese adults. Clin Sci (Lond). 2008;115(9):283-93. doi: 10.1042/CS20070332.

13. Neilan TG, Januzzi JL, Lee-Lewandrowski E, Ton-Nu TT, Yoerger DM, Jassal DS, et al. Myocardial injury and ventricular dysfunction related to training levels among nonelite participants in the Boston marathon. Circulation. 2006;114(22):2325-33. doi: 10.1161/CIRCULATIONAHA.106.647461.

14. Gaudron P, Hu K, Schamberger R, Budin M, Walter B, Ertl G. Effect of endurance training early or late after coronary artery occlusion on left ventricular remodeling, hemodynamics, and survival in rats with chronic transmural myocardial infarction. Circulation. 1994;89(1):402-12. doi: https://doi.org/10.1161/01.CIR.89.1.402.

15. Wasserman K, Mcilroy MB. Detecting the threshold of anaerobic metabolism in cardiac patients during exercise. Am J Cardiol. 1964;14(6):844-52. doi: https://doi.org/10.1016/0002-9149(64)90012-8.

16. Olbrecht J, Cunha RR, Cunha VN, Segundo PR, Moreira SR, Kokubun E, et al. Determination of the lactate threshold and maximal blood lactate steady state intensity in aged rats. Cell Biochem Funct. 2009;27(6):351-7. doi: 10.1002/cbf.1580.

17. Olbrecht J, Madsen O, Mader A, Liesen H, Hollman W. Relationship between swimming velocity and lactic acid concentration during continuous and intermittent training exercise. Int J Sports Med. 1985;6(2):74-7. doi: 10.1055/s-2008-1025816.

18. Cornish AK, Broadbent S, Cheema BS. Interval training for patients with coronary artery disease: systematic review. Eur J Appl Physiol. 2011;111(4):579-89. doi: 10.1007/s00421-010-1682-5.

19. de Macedo RM. Fisioterapia cardiorrespiratória: um novo conceito para o tratamento em fase hospitalar. Curitiba (PR): Juruá Editora; 2012.

High-Intensity Interval Training for Early Post-Acute Myocardial Infarction – A Promising Approach for Rats, but what about Human Beings?

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Acute coronary syndromes (ACSs), in particularly, acute myocardial infarction (AMI), kill or debilitate a large number of patients in the world. Despite the fact that not all patients develop ventricular dysfunction after the event, there is still a high prevalence of post-AMI heart failure,[1,2] which is considered a public health problem. Although the management of post-ACS is based on a wide range of drugs, usually associated with the revascularization procedure, different non-pharmacological strategies have been shown useful. In this regard, physical exercise is indicated,[3] including cardiac rehabilitation programs that usually combine aerobic and resistance training with stretching exercises.

Nevertheless, there is no single recipe for prescribing exercise after an acute coronary event. In my opinion, cardiologists should formally prescribe physical exercise in addition to cardiovascular drugs, considering aspects such as dosage, intervals, intensity and potential side effects. With respect to physical training, a vast of different exercise modalities have emerged and applied in health. Pilates, Tai Chi Chuan, functional training, crossfit, high-intensity interval training (HIIT) among others have spread across gyms and physical centers over the country and have been practiced primarily by apparently healthy individuals. As time passed, animal experiments and clinical studies on cardiovascular disease patients have been conducted.[4-7] HIIT was first proposed to Japanese Olympic skaters by Izumi Tabata. Today, HIIT consists in sessions of one to four-minute of high-intensity submaximal load alternating with low-to-moderate intensity exercises. Randomized clinical trials involving small samples have suggested a superiority of the method in increasing peak oxygen uptake (VO_2 peak) as compared with conventional continuous training. Due to its peculiarities and results, HIIT has boomed all over the world; however, international literature showing the impact of the method in ischemic heart disease patients, particularly in post-AMI patients is still lacking.[4,8,9]

Keywords

Acute Coronary Syndrome; Cardiac Rehabilitation; Exercise.

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In this journal issue, Winter et al.[10] report information on the effects of HIIT on functional capacity and ventricular function in 29 Wistar rats after AMI. On day 21 after the event, the animals were randomized to control group (n = 10), or to undergo continuous training (n = 9) or HIIT (n = 10). All animals had ejection fraction equal to or greater than 50%, i.e., without ventricular dysfunction. An important finding was that the authors did not find within- or between group differences in echocardiographic findings before and after training in the animals allocated to continuous training or to HIIT. The authors suggest that both methods can increase functional capacity without altering ventricular function (remodeling). Based on this, one may ask the following question: can patients at early stage after AMI, without ventricular dysfunction, undergo this type of physical training?

In a classical study by Wisloff et al.,[5] the authors evaluated three groups of elderly patients with heart failure and reduced ejection fraction (HFrEF), who were clinically stable and had had a myocardial infarction more than one year before the study. Patients were randomized to control, moderate continuous training (MCT) or HIIT group.[5] Individuals assigned to HIIT showed improved peak VO_2, left ventricular remodeling and reduced natriuretic peptide (BNP) levels as compared with MCT. Also, a meta-analysis involving 160 patients showed that interval training (regardless of its intensity) increased peak VO_2 in HFrEF patients.[11] Similarly, in a meta-analysis including 230 patients, Elliott et al.[12] reported that interval training seems to increase peak VO_2 in patients with stable coronary artery disease.[12]

In the last years, different strategies that can be included in early post-acute rehabilitation programs have emerged, such as Tai Chi Chuan.[13] In any case, all interventions that may improve patients' recovery and functional capacity, and whenever possible, increase patients' survival should be used. With respect to the applicability of HIIT in the management of early post-AMI patients, it may be speculated that the method is efficient in improving peak VO_2, an important prognostic marker. In fact, in the world of coronary stents and since post-AMI myocardial function is preserved in many patients, HIIT may be an attractive training strategy for some patients. On the other hand, the body of scientific knowledge is not sufficiently consistent to definitely recommend HIIT as a training modality for early post-AMI patients. Anyway Winter et al.,[10] in their investigation on laboratory animals, take an important step towards an effective alternative for cardiac rehabilitation programs in this group of patients.

References

1. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. Circulation. 2017;135(10):e146-e603.
2. Piegas LS, Avezum A, Pereira JC, Rossi Neto JM, Hoepfner C, Farran JA, et al; AFIRMAR Study Investigators. Risk factors for myocardial infarction in Brazil. Am Heart J. 2003;146(2):331-8.
3. Herdy AH, López-Jiménez F, Terzic CP, Milani M, Stein R, Carvalho T, et al. South American guidelines for cardiovascular disease prevention and rehabilitation. Arq Bras Cardiol. 2014;103(2 Suppl 1):1-31.
4. Zhang LQ, Zhang XQ, Musch TI, Moore RL, Cheung JY. Sprint training restores normal contractility in postinfarction rat myocites. J Appl Physiol (1985). 2000,89(3):1099-105.
5. Wisløff U, Støylen A, Loennechen JP, Bruvold M, Rognmo Ø, Haram PM, et al. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. Circulation. 2007;115(24):3086-94.
6. Ellingsen Ø, Halle M, Conraads V, Støylen A, Dalen H, Delagardelle C, et al; SMARTEX Heart Failure Study (Study of Myocardial Recovery After Exercise Training in Heart Failure) Group. High-intensity interval training in patients with heart failure with reduced ejection fraction. Circulation. 2017;135(9):839-49.
7. Da Silveira AD, De Lima JB, Piardi, D, Horn T, Macedo DS, Santos F, et al. Treinamento intervalado de alta intensidade versus treinamento contínuo moderado em pacientes com insuficiência cardíaca com fração de ejeção preservada. In: 72º Congresso da Sociedade Brasileira de Cardiologia, 3-5 nov 2017. Arq Bras Cardiol. 2017;109(5 supl.1):98.
8. Cardozo GG, Oliveira RB, Farinatti PT. Effects of high intensity interval versus moderate continuous training on markers of ventilatory and cardiac efficiency in coronary heart disease patients. Scientific World Journal. 2015; 2015:192479.
9. Hannan AL, Hing W, Simas V, Climstein M, Coombes JS, Jayasinghe R, et al. High-intensity interval training versus moderate-intensity continuous training within cardiac rehabilitation: a systematic review and meta-analysis. Open Access J Sports Med. 2018;9:1-17.
10. Winter SCN, Macedo RM, Francisco JC, Santos PC, Lopes APS, Meira LF, et al. Impact of a High-intensity training on ventricular function in rats after acute myocardial infarction. Arq Bras Cardiol. 2018 Mar 12:0. doi: 10.5935/abc.20180036. Arq Bras Cardiol. 2018; 110(4):373-380.
11. Haykowsky MJ, Timmons MP, Kruger C, McNeely M, Taylor DA, Clark AM. Meta-analysis of aerobic interval training on exercise capacity and systolic function in patients with heart failure and reduced ejection fractions. Am J Cardiol. 2013;111(10):1466-9.
12. Elliot AD, Rajopadhyaya K, Bentley DJ, Beltrame JF, Aromataris EC. Interval training versus continuous exercise in patients with coronary artery disease: a meta-analysis. Hear Lung Circ. 2015;24(2):149-57.
13. Nery RM, Zanini M, de Lima JB, Bühler RP, da Silveira AD, Stein R. Tai Chi Chuan improves functional capacity after myocardial infarction: a randomized clinical trial. Am Heart J. 2015;169(6):854-60.

Influence of Aerobic Training on The Mechanics of Ventricular Contraction After Acute Myocardial Infarction: A Pilot Study

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Abstract

The study of myocardial contractility, based on the new anatomical concepts that govern cardiac mechanics, represents a promising strategy of analysis of myocardial adaptations related to physical training in the context of post-infarction.

We investigated the influence of aerobic training on physical capacity and on the evaluation parameters of left ventricular contraction mechanics in patients with myocardial infarction.

Thirty-one patients (55.1 ± 8.9 years) who had myocardial infarction in the anterior wall were prospectively investigated in three groups: interval training group (ITG) (n = 10), moderate training group (MTG) n = 10) and control group (CG) (n = 10). Before and after 12 weeks of clinical follow-up, patients underwent cardiopulmonary exercise testing and cardiac magnetic resonance imaging. The trained groups performed supervised aerobic training on treadmill, in two different intensities.

A statistically significant increase in peak oxygen uptake (VO_2) was observed in the ITG (19.2 ± 5.1 at 21.9 ± 5.6 ml/kg/min, $p < 0.01$) and in the MTG 18.8 ± 3.7 to 21.6 ± 4.5 ml/kg/min, $p < 0.01$). The GC did not present a statistically significant change in peak VO_2. A statistically significant increase in radial strain (STRAD) was observed in the CG: basal STRAD (57.4 ± 16.6 to 84.1 ± 30.9%, $p < 0.05$), medial STRAD (57.8 ± 27, 9 to 74.3 ± 36.1%, $p < 0.05$) and apical STRAD (38.2 ± 26.0 to 52.4 ± 29.8%, $p < 0.01$). The trained groups did not present a statistically significant change of the radial strain.

The present study points to a potential clinical application of the parameters of ventricular contraction mechanics analysis, especially radial strain, to discriminate post-infarction myocardial adaptations between patients submitted or not to aerobic training programs.

Keywords

Exercise; Rehabilitation; Myocardial Infarction; Myocardial Contraction; Stroke Volume; Magnetic Resonance Imaging.

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Introduction

The helical conformation of the myocardial fibers, anchored in the pulmonary and aortic rings, determines a heart rotation movement around its longitudinal axis and confers a maximum mechanical efficiency to the cardiac muscle. The magnitude and characteristics of the present phenomenon are sensitive to left ventricle segmental and global contractile alterations.[1,2]

The parameters of myocardial deformation analysis and ventricular rotation represent a promising strategy for the study of cardiac contractility, allowing a reliable analysis of the left ventricular contraction dynamics, based on the new anatomical concepts that govern cardiac mechanics.[1,2]

Aerobic physical training (AFT) after myocardial infarction (MI) improves cardiac output, peak oxygen uptake (VO_2), autonomic function and peripheral metabolism. Exercise programs, based on variables obtained through stress tests, are considered beneficial and safe for patients in the context of post-IM.[3]

However, scientific papers that investigated the effects of TFA on post-MI ventricular remodeling process, particularly through cavitary volumes measurement, as well as by estimating cardiac function by left ventricle ejection fraction, in resting conditions, showed heterogeneous and inconsistent results.[4-7]

Cardiac magnetic resonance allows an integrated analysis of myocardial function with the underlying pathology. Myocardial deformation curves, obtained by cardiac magnetic resonance imaging, represent tools capable of identifying initial or subclinical alterations, both in the segmental function and in the global function of the left ventricle.[8]

The use of these new methodologies incorporated into cardiac magnetic resonance can have a potential application in the identification of incipient contractile alterations in the post-infarction myocardium related to physical training. In this sense, we do not find in the scientific literature, articles that have tried to document, by myocardial deformation parameters analysis and ventricular rotation, the effects of AFT in patients in the context of post-MI.

It was investigated the influence of TFA, prescribed in two different intensities, on physical capacity and the analysis parameters of myocardial deformation and ventricular rotation in patients with a diagnosis of MI.

Methods

Patients

Thirty patients, 55.1 ± 8.9 years, with the diagnosis of MI, were prospectively investigated after signing a informed

consent form; randomized into three groups: moderate training (MTG), interval training (ITG) and control (CG).

The inclusion criteria established were: anterior wall MI with exclusive involvement of anterior descending artery proximal third and asymptomatic ventricular dysfunction with left ventricular ejection fraction < 50%. Patients who progressed with heart failure, sustained ventricular tachycardia, chronic obstructive pulmonary disease, chronic renal failure and orthopedic or neurological limitations for physical exercise were excluded.

The study was conducted in accordance with the Helsinki declaration. The research ethics committee of our Institution (n° 11612/2008) approved the consent form and study protocol.

Cardiopulmonary exercise test

An exercise test was performed with uptake of gases expired by the CPX/D analyzer MedGraphics (Saint Paul, USA). BreezeEX software was used for the acquisition, processing and storage of cardiorespiratory variables. A modified Balke protocol was applied on treadmill, with speed 1.5 mph in the first minute, 2.5mph in the 2nd minute and fixed in 3.0 mph from the third minute, followed by increasing increments of the slope of 2% every minute until the effort is interrupted, due to physical exhaustion. Continuous cardiac monitoring was performed by the 13-lead modified Mason-Likar shunt system, and blood pressure was measured manually every minute during the exercise and recovery period.

Cardiac magnetic resonance

Tests were performed on the Magneton Vision, Siemens, 1.5T (Erhlangen, Germany), with 25 mT circular polarization gradient coils. The sequence used was the fast gradient echo with steady state acquisition (TRUE_FISP) with parameters adjusted to optimize the signal-to-noise ratio. Flip angle = 10°, cut thickness = 8mm; interval between cuts = 0 mm; 13 phases of the cardiac cycle in a single cut, each expiratory apnea, always synchronized to ECG, becoming a cardiac cycle film with optimal temporal and spatial resolution. The images were obtained along the vertical axis (4 chambers) and the short axis to cover the entire extension of the left ventricle.

Evaluation of myocardial deformation and ventricular rotation

The evaluation of myocardial deformation and ventricular rotation was performed by the Multimodality Tissue Tracking computer program (MTT, version 6.6.0, Toshiba, Japan) through the analysis of cardiac magnetic resonance images generated with pulse sequences Steady State Free Precession (SSFP)).

Prescription of physical training

Patients randomized to the training groups were subjected to three supervised weekly sessions of aerobic exercise on a treadmill, for a period of 12 weeks.

Training sessions were constituted by the following phases: warm-up, with 5 minutes duration; conditioning, with load adjustments (speed and incline) to maintain the heart rate (HR) within the training zone for 30 minutes; and the descent with a duration of 5 minutes.

The intensity of the TFA, defined by training HR interval, was established from a percentage of peak HR reached in the cardiopulmonary exercise test.

The HR of training for the randomized patients for the MTG was calculated in the following way: the minimum HR was established as representative of 60% of the peak HR, while the maximum HR of training was the representative of 70% of the Peak HR reached in the cardiopulmonary exercise test.

Patients randomized to ITG performed TFA applying a model called 4x4, consisting of 4 periods of 4 minutes duration with training HR between 85 to 95% of the peak HR reached in the cardiopulmonary exercise test, interspersed with periods of active recovery time of 3 minutes duration with training HR between 60 to 70% of the peak HR reached in the cardiopulmonary exercise test.

Statistic analysis

Data are expressed as mean ± standard deviation. A value of $p < 0.05$ was considered statistically significant. The analysis of the distribution of the data was verified with the Kolmogorov-Smirnov test. The reason for the use of nonparametric tests was that the distributions of the analyzed variables did not present Gaussian distribution. The Kruskal-Wallis test with the Dunn post-test was used for intergroup comparison. The *Wilcoxon* rank-*sum test* was used for intragroup comparison. The statistical analysis was carried out with the SPSS 10.0 program (SPSS Inc., Chicago Illinois, USA).

Results

The comparative analysis between the groups did not present statistically significant differences for variables initial evaluation of exercise cardiopulmonary test.

In contrast to the CG, the trained groups presented, after the 12-week period of TFA, increase with statistical significance of peak VO_2, peak ventilation-minute (VM) and peak pulse oxygen (PO_2) ($p < 0.05$) (Table 1).

The comparative analysis between the groups did not present statistically significant differences for variables initial evaluation of cardiac magnetic resonance, myocardial deformation and ventricular rotation.

In contrast to the trained groups, the CG presented, after the 12-week period of clinical follow-up, a statistically significant increase in radial strain (STRAD) ($p < 0.05$) (Table 2).

Discussion

We conducted a pilot study in order to evaluate the influence of TFA, prescribed in two different intensities, on the physical capacity and mechanical contraction of the left ventricle in the context of post-MI.

The main finding of this study was the documentation of a different behavior from the STRAD in the CG in comparison with the trained groups. This result is important insofar as it

Brief Communication

Table 1 – Exercise Cardiopulmonary Test Variables

	CG (n = 10)		ITG (n = 10)		MTG (n = 10)	
	Before	After	Before	After	Before	After
VO_2 peak (ml/kg/min)	18,2 ± 4,4	17,1 ± 4,6	19,2 ± 5,1	21,9 ± 5,6*	18,8 ± 3,7	21,6 ± 4,5*
VM peak (L/min)	55,9 ± 17,5	48,4 ± 15,9†	61,4 ± 20,6	72,2 ± 21,9*	62,1 ± 14,5	68,6 ± 15,5†
Basal PO_2 (ml/systole)	4,3 ± 1,1	4,1 ± 0,8	3,75 ± 0,7	4,3 ± 0,9	4,5 ± 1,5	4,1 ± 1,0
PO_2 peak (ml/systole)	11,7 ± 3,1	11,3 ± 3,1	11,6 ± 3,0	12,8 ± 2,5†	11,1 ± 1,1	12,3 ± 1,7†
RER	1,08 ± 0,08	1,08 ± 0,08	1,12 ± 0,11	1,19 ± 0,10	1,15 ± 0,07	1,19 ± 0,08
HR rest (bpm)	64,1 ± 12,8	65,6 ± 6,6	63,1 ± 9,9	62,1 ± 6,0	63,6 ± 11,6	64,8 ± 8,2
HR peak (bpm)	122,9 ± 28,3	123,1 ± 28,2	131,8 ± 20,6	133,2 ± 21,7	131,6 ± 12,3	129,0 ± 18,3
SBP (mmHg)	158,5 ± 22,4	159,5 ± 15,5	149,5 ± 25,2	146,5 ± 16,8	153,0 ± 20,1	145,2 ± 17,9
DBP peak (mmHg)	8,2 ± 0,6	8,4 ± 0,7	8,1 ± 0,6	8,0 ± 0,5	8,3 ± 0,7	8,1 ± 0,6
DP (bpm.mmHg)	19628 ± 5523	19422 ± 3870	19989 ± 5770	19596 ± 4468	20229 ± 3864	19566 ± 3990

*VO_2: oxygen uptake; VM: ventilation-minute; PO_2: oxygen pulse; RER: respiratory exchange rate; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; DP: double product. * p < 0.01: different, in the comparative analysis before and after, after the period of clinical follow-up. † p < 0.05: different, before and after comparative analysis, after the clinical follow-up period.*

Table 2 – Cardiac Magnetic Resonance Variable

	CG (n = 10)		ITG (n = 10)		MTG (n = 10)	
	Before	After	Before	After	Before	After
FDV (ml)	156,6 ± 39,3	148,2 ± 34,1	174,8 ± 55,8	178,8 ± 44,9	143,8 ± 52,9	141,0 ± 45,5
FSV (ml)	91,6 ± 37,0	83,9 ± 38,3	96,3 ± 52,3	96,3 ± 36,3	82,6 ± 38,9	76,2 ± 36,5
FE (%)	43,9 ± 11,5	45,7 ± 14,4	47,0 ± 10,8	47,2 ± 6,8	44,6 ± 9,5	47,6 ± 10,4
STLONG (%)	-9,0 ± 5,4	-9,1 ± 6,2	-9,2 ± 4,7	-8,6 ± 4,6	-10,1 ± 4,5	-10,5 ± 4,5
STCIRC_B (%)	-15,5 ± 4,3	-17,8 ± 3,3	-17,0 ± 3,3	-17,2 ± 3,0	-14,2 ± 4,6	-14,9 ± 3,4
STCIRC_M (%)	-13,5 ± 4,5	-14,4 ± 3,6	-13,5 ± 3,6	-14,5 ± 3,5	-12,0 ± 2,1	-12,5 ± 2,4
STCIRC_A (%)	-10,5 ± 4,6	-12,2 ± 6,9	-10,3 ± 5,6	-11,5 ± 4,5	-11,2 ± 4,4	-12,5 ± 8,4
STRAD_B (%)	57,4 ± 16,6	84,1 ± 30,9†	63,3 ± 19,5	58,6 ± 18,8	67,9 ± 24,5	60,4 ± 25,5
STRAD_M (%)	57,8 ± 27,9	74,3 ± 36,1†	59,1 ± 21,3	58,5 ± 25,8	57,5 ± 21,0	55,6 ± 19,8
STRAD_A (%)	38,2 ± 26,0	52,4 ± 29,8*	41,8 ± 25,0	41,4 ± 19,4	38,3 ± 25,8	38,9 ± 17,9
ROT_B (°)	-2,2 ± 1,4	-2,3 ± 0,9	-1,6 ± 1,3	-1,5 ± 1,1	-1,9 ± 0,9	-2,3 ± 1,2
ROT_A (°)	3,2 ± 1,7	4,0 ± 3,4	4,3 ± 2,4	4,0 ± 2,0	3,9 ± 1,7	3,5 ± 2,1
TWIST (°)	5,4 ± 2,1	6,3 ± 3,3	5,9 ± 2,8	5,5 ± 2,0	5,9 ± 1,5	5,9 ± 2,5

*FDV: final diastolic volume; FSV: final systolic volume; EF: ejection fraction; STLONG: overall longitudinal strain; STCIRC_B: basal circumferential strain; STCIRC_M: medial circumferential strain; STCIRC_A: apical circumferential strain; STRAD_B: basal radial strain; STRAD_M: medial radial strain; STRAD_A: radial apical strain; ROT_B: basal rotation; ROT_A: apical rotation; Twist: angular difference between apical rotation and basal rotation. * p < 0.01: different, in the comparative analysis before and after, after the period of clinical follow-up. † p < 0.05: different, before and after comparative analysis, after the clinical follow-up period.*

suggests that the myocardial deformation parameters may be more sensitive, in comparison with the classical parameters of evaluation of ventricular remodeling, in the identification of post-infarction myocardial adaptations between patients submitted or not to TFA programs.

We postulate that in order to improve the mechanical efficiency of the cardiac muscle, there was an adaptation of the post-infarction myocardium in the GC that required an increase in systolic thickening as a probable mechanism for maintaining adequate systolic volume and cardiac output in the resting state.

On the other hand, TFA may have contributed to compensatory adaptive mechanisms sensitive to radial strain analysis not to be triggered in trained groups as part of post-infarction myocardial adaptations, necessary to meet the metabolic and tissue demands in resting state.

From the perspective of parameters analysis of myocardial deformation and ventricular rotation, the interval aerobic training did not show significant changes in left ventricle contraction mechanics in comparison with continuous moderate aerobic training.

Throughout last decades, since the publication of Jugdutt et al,[9] several scientific works emerged that attempted to evaluate TFA influence on ventricular remodeling process in post-MI context. Giannuzzi et al.,[4] showed an increase

in cardiac function and maintenance of cavitary volumes. Kubo et al.,[5] observed an increase in cavitary volumes and maintenance of cardiac function. Giallauria et al.,[6] documented maintenance of both cavitary volumes and cardiac function.

In the present study, the cavitary volumes and the cardiac function estimated by left ventricle ejection fraction did not present statistically significant changes. Moreover, in this way, they were not able to identify different patterns of ventricular remodeling in the training groups compared to the CG.

From the point of view of functional capacity, we observed a comparable increase of 14% in ITG and MTG VO_2 peak. We used the 4x4 aerobic interval training model recommended in several studies for promoting expressive increases in VO_2 peak, compared to continuous moderate aerobic training.[10,11] However, we did not show a statistically significant difference between the ITG and the MTG VO_2 peak, after the period of physical training.

We highlight that the present study data are corroborated by SAINTEX-CAD Study findings that showed a similar increase in physical fitness, comparing interval aerobic training versus continuous moderate aerobic training, in a large casuistry of patients with coronary artery disease.[12]

Study limitations

It is known that HR increases linearly with VO_2 within defined limits in the bands of 50 to 90% maximum VO_2. However, in the present study, we could not establish a relationship between training intensity and ventilatory thresholds.

Finally, the area of fibrosis was not analyzed. The extension of fibrosis in the infarction area infarction can be an important determinant of the results of AFT in myocardial deformation parameters and ventricular rotation.

Conclusions

The findings of this study point to a potential clinical application of ventricular contraction mechanics parameters analysis, notably radial strain, in discriminating post-infarction myocardial adaptations between patients submitted or not to aerobic training programs.

Author contributions

Conception and design of the research: De Santi GL, Schmidt A, Gallo-Júnior L; Acquisition of data: De Santi GL, Moreira HT, Carvalho EEV, Crescêncio JC; Analysis and interpretation of the data: De Santi GL, Moreira HT, Carvalho EEV, Schmidt A, Marin Neto JA, Gallo-Júnior L; Statistical analysis: De Santi GL, Crescêncio JC; Writing of the manuscript: De Santi GL, Gallo-Júnior L; Critical revision of the manuscript for intellectual content: Marin Neto JA, Gallo-Júnior L.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo under the protocol number 11612/2008. 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.

References

1. Shaw SM, Fox DJ, Williams SG. The development of left ventricular torsion and its clinical relevance. Int J Cardiol. 2008;130(3):319-25. doi: 10.1016/j.ijcard.2008.05.061.
2. Mor-Avi V, Lang RM, Badano LP, Belohlavek M, Cardim NM, Derumeaux G, et al. Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE Consensus Statement on Methodology and Indications. Endorsed by the Japanese Society of Echocardiography. J Am Soc Echocardiogr. 2011;24(3):277-313. doi: 10.1016/j.echo.2011.01.015.
3. Ghorayeb N, Costa RV, Daher DJ, Oliveira Filho JA, Oliveira MA, et al. [Guidelines on exercise and sports cardiology from the Brazilian Society of Cardiology and the Brazilian Society of Sports Medicine]. Arq Bras Cardiol. 2013;100(1 Suppl 2):1-41. doi: http://dx.doi.org/10.5935/abc.2013S002. Erratum in: Arq Bras Cardiol. 2013;100(5):488.
4. Giannuzzi P, Temporelli PL, Corra U, Gattone M, Giordano A, Tavazzi L. Attenuation of unfavorable remodeling by exercise training in postinfarction patients with left ventricular dysfunction: results of the Exercise in Left Ventricular Dysfunction (ELVD) trial. Circulation. 1997;96:1790-1797. PMID: 9323063.

5. Kubo N, Ohmura N, Nakada I, Yasu T, Katsuki T, Fujii M, et al. Exercise at ventilatory threshold aggravates left ventricular remodeling in patients with extensive anterior acute myocardial infarction. Am Heart J. 2004;147(1):113-20. PMID: 14691428.

6. Giallauria F, De Lorenzo A, Pilerci F, Manakos A, Lucci R, Psaroudaki M, et al. Reduction of N terminal-pro-brain (B-type) natriuretic peptide levels with exercise-based cardiac rehabilitation in patients with left ventricular dysfunction after myocardial infarction. Eur J Cardiovasc Prev Rehabil. 2006;13(4):625-32. doi: 10.1097/01.hjr.0000209810.59831.f4.

7. Izeli NL, Santos AJ, Crescêncio JC, Gonçalves AC, Papa V, Marques F, et al. Aerobic training after myocardial infarction: remodeling evaluated by cardiac magnetic resonance. Arq Bras Cardiol. 2016;106(4):311-8. doi: http://dx.doi.org/10.5935/abc.20160031.

8. Mangion K, McComb C, Auger DA, Epstein FH, Berry C. Magnetic resonance imaging of myocardial strain after acute ST-segment-elevation myocardial infarction: a systematic review. Circ Cardiovasc Imaging. 2017 Aug;10(8). pii: e006498. doi: 10.1161/CIRCIMAGING.117.006498.

9. Jugdutt BI, Michorowski BL, Kappagoda CT. Exercise training after anterior Q wave myocardial infarction: Importance of regional left ventricular function and tomography. J Am Coll Cardiol. 1988;12(2):362-72. PMID: 3392328.

10. Helgerud J, Høydal K, Wang E, Karlsen T, Berg P, Bjerkaas M, et al. Aerobic high-intensity intervals improve VO2max more than moderate training. Med Sci Sports Exerc. 2007;39(4):665-71. doi: 10.1249/mss.0b013e3180304570.

11. Rognmo Ø, Hetland E, Helgerud J, Hoff J, Slørdahl SA. High intensity aerobic interval exercise is superior to moderate intensity exercise for increasing aerobic capacity in patients with coronary artery disease. Eur J Cardiovasc Prev Rehabil. 2004;11(3):216-22. PMID: 15179103.

12. Conraads VM, Pattyn N, De Maeyer C, Beckers PJ, Coeckelberghs E, Cornelissen VA, et al. Aerobic interval training and continuous training equally improve aerobic exercise capacity in patients with coronary artery disease: The SAINTEX-CAD study. Int J Cardiol. 2015 Jan 20;179:203-10. doi: 10.1016/j.ijcard.2014.10.155.

Case 2/2018 - 73-Year-Old Male with Ischemic Cardiomyopathy, Cachexia and Shock

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The patient is a 73-year-old male, born in the municipality of Jacupiranga, SP, and coming from São Paulo city, SP, complaining of 30-kg weight loss in the previous 4 months and worsening of his general state of health in the previous 24 hours.

He reported having coronary artery disease, with two episodes of infarction and one coronary angioplasty with stent implantation 8 years before. He had been diagnosed with ischemic cardiomyopathy and ejection fraction of 22%.

He was using spironolactone, losartan, carvedilol, furosemide and propatylnitrate.

His physical examination (April 29, 2004) showed emaciation, dehydration, heart rate of 80 bpm, inaudible blood pressure, increased jugular venous pressure, lungs with inspiratory wheezes, regular heart rhythm and no heart murmur on cardiac auscultation, liver palpable 3 cm from the right costal margin, and mild edema of the lower limbs. The patient received 1500 mL of 0.9% saline solution, which increased his blood pressure to 90/70 mm Hg.

The results of his laboratory tests (April 30, 2004) were as follows: hemoglobin, 17.2 g/dL; platelets, 99000/mm^3; leukocytes, 7850/mm^3; urea, 122 mg/dL; creatinine, 2.2 mg/dL; potassium, 6.5 mEq/L; sodium, 143 mE/L. His arterial blood gas analysis was as follows: pH, 7.3; bicarbonate, 16 mEq/L; and base excess, (-)7 mEq/L.

His electrocardiogram (April 29, 2004) (Figure 1) showed sinus rhythm, heart rate of 68 bpm, PR of 200 ms, dQRS of 120 ms, QT of 440 ms, left atrial overload and indirect signs of right overload (Peñaloza-Tranchesi), in addition to left anterior hemiblock. No pathological Q wave was seen.

He was admitted to the Hospital Auxiliar de Cotoxó to compensate his heart failure and acute renal failure.

Keywords

Atherosclerosis; Heart Failure/physiopathology; Cardiomyopathy, Dilated/complications; Weight Loss; Cachexia

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The patient progressed with oliguria, dyspnea, and, on the third day of admission, he had sudden lowering of consciousness, fever and respiratory failure, requiring endotracheal intubation.

His previous laboratory tests on that same day were as follows: hemoglobin, 14.5 g/dL; leukocytes, 8500/mm^3; sodium, 139 mEq/L; potassium, 3.7 mEq/L; urea, 170 mg/dL; creatinine, 2.2 mg/dL; leukocyturia, 10000/mL; and hematuria, 280000/mL.

During that episode, the findings were as follows: heart rate, 75 bpm; blood pressure, 100/60 mm Hg; temperature, 37.8°C; arterial saturation, 97%; and crepitant rales at pulmonary bases. His heart rhythm was regular, with neither murmur nor accessory heart sound. His capillary glycemia was 166 mg/dL.

The patient was referred to the emergency unit of Incor. Pulmonary aspiration and stroke were his clinical suspicions.

His physical examination on admission (April 3, 2004) revealed an agitated and intubated patient, with heart rate of 90 bpm, blood pressure of 68/49 mm Hg, respiratory rate of 36 bpm, lungs with diffuse rhonchi, no abnormality on cardiac auscultation. His liver was palpated 3 cm from the right costal margin. There was edema (+++) of the lower limbs, with no signs of calf swelling.

Sedation was prescribed, as were dobutamine, noradrenaline, enoxaparin, vancomycin and imipenem/cilastatin.

His cranial tomography (May 4, 2004) showed a right occipital low attenuation area, widening of the cortical sulci, and no other significant change, findings compatible with right occipital ischemic stroke.

The patient remained shocked despite the administration of vasoactive amines, had bradycardia and asystole, and died (May 5, 2004; 16 h).

Clinical aspects

The patient here reported is a male elderly with ischemic cardiomyopathy, and significant weight loss in the previous 4 months, in addition to worsening of his general state of health and clinical instability in the 24 hours prior to admission. Some diagnostic possibilities could explain his significant weight loss.

Cardiac cachexia is a frequent complication in the advanced stages of congestive heart failure (CHF) and associates with shorter survival.[1] The physiopathology of that disorder has been first described by Pitman and Cohen[2] Later, new evidence showed that the cause is multifactorial, related mainly to anorexia, a change in the routine of food uptake, in absorption and in the metabolism of patients with heart

Anatomopathological Correlation

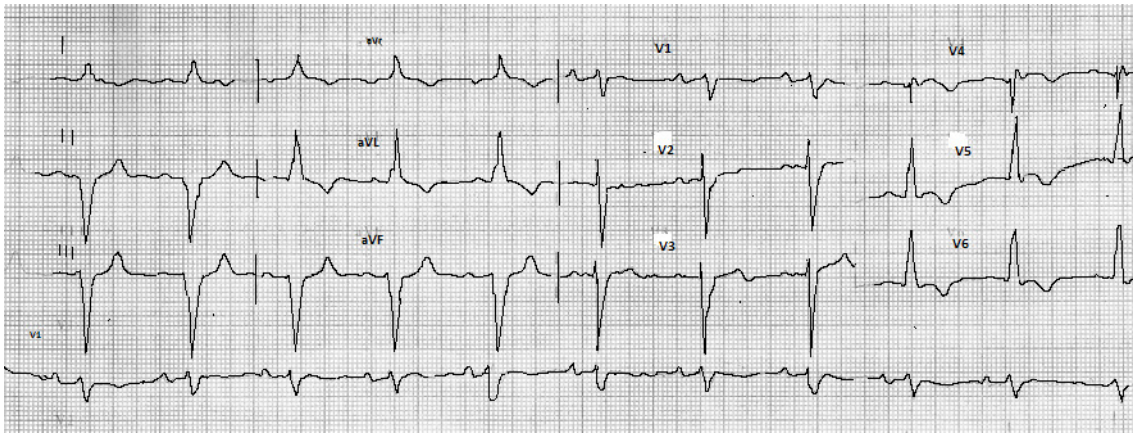

Figure 1 – *ECG: left atrial overload and indirect signs of right atrial overload (Peñaloza-Tranchesi), in addition to left bundle-branch block and left anterior hemiblock.*

failure.[3] Up to 34% of the patients with CHF being followed up on an outpatient basis are estimated to develop cardiac cachexia in the medium to long run.[4] The deleterious effects of that condition impair the cardiac and respiratory functions and decrease immunity, which leads to higher mortality. Our patient's systemic complications that hindered the reversion of his final findings might have been aggravated by cardiac cachexia. Regarding treatment, the literature reports many simultaneous actions that fight the most critical points in cachexia, such as nutritional therapy and the use of appetite stimulants, correction of anemia and edema, use of anabolic steroids and immunomodulation. Parallel to drug therapy, physical activity is indicated to maintain skeletal musculature,[5] respecting the limits imposed by the disease and requiring strict follow-up.

Another possible explanation for cachexia would be the development of malignant neoplasia in a patient previously debilitated by heart disease. New studies have recently shown a higher interaction between oncologic and cardiac diseases, no longer attributed to diagnostic coincidence, but to an interaction between their morbidities. A recent publication[6] has shown that the overlap between those two diseases results from the addition of shared risk factors, such as obesity, smoking, sedentary lifestyle and diabetes mellitus. In that context, the term cancer-related 'cardiac cachexia' appears. That complication is part of the natural history of neoplasms, leading to a progressive muscle mass loss (cachexia). However, many patients experience myocardial changes related to atrophy, remodeling and dysfunction, a set of findings known as cardiac cachexia.[7]

Insidious infectious diseases, such as tuberculosis and infectious endocarditis, can also be accompanied by consumptive findings. Usually, the manifestation most commonly associated with those conditions is fever (70% to 90% of the cases), which, in our patient, was only reported during hospitalization, but not in the last months of his disease. In addition, other symptoms and signs, such as cough, productive expectoration, nocturnal sweating or skin lesions (petechiae and subungual hemorrhages), lack.

On admission to the emergency service, the patient had signs of dehydration, arterial hypotension and systemic congestion, such as high jugular venous pressure, hepatomegaly and edema of the lower limbs. Such findings suggest a state of low cardiac output, which can correspond to an advanced stage of the underlying heart disease or decompensation associated with other contributing factors. On the admission electrocardiogram, signs of overload of the right chambers stand out, which might suggest a sudden increase in the pressures of the right atrium and ventricle, as observed in cases of acute pulmonary thromboembolism. Other factors that might contribute to acute decompensations in patients with chronic diseases and potentially immunosuppressed are bacterial infections, such as pneumonia and urinary tract infections.

Despite the treatment instituted, the patient's clinical status worsened with renal failure and metabolic acidosis. On the third day of hospitalization, he had lowering of consciousness, fever, oliguria and respiratory failure, being submitted to endotracheal intubation. These findings initially suggest infectious decompensation and a possible toxic-metabolic process, but cranial tomography revealed a right occipital low attenuation lesion compatible with acute ischemic stroke. In patients with structural heart disease, ischemic encephalic injuries are commonly secondary to cerebrovascular atherosclerotic disease or episodes of cardioembolism in the presence of atrial fibrillation or other intracardiac thrombi. Less frequently, the cardioembolic phenomenon can be related to infectious endocarditis or cardiac tumors. (Rafael Amorim Belo Nunes, MD, Jussara de Almeida Bruno, MD, and Hilda Sara Monteiro Ramirez, MD)

Diagnostic hypotheses: ischemic cardiomyopathy, cardiac cachexia, acutely decompensated chronic heart failure (progression of the underlying disease? pulmonary thromboembolism? subjacent infection?), ischemic stroke (atherothrombosis? cardioembolic?). (Rafael Amorim Belo Nunes, MD, Jussara de Almeida Bruno, MD, and Hilda Sara Monteiro Ramirez, MD)

Postmortem examination

The external examination revealed significant weight loss and moderate edema in the subcutaneous tissue, more marked in the lower limbs. On opening of the abdomen, 280 mL of yellow translucent ascitic fluid escaped. The heart weighed 644g (normal: 300-350g), and both ventricles were enlarged. Cross sections of the ventricles evidenced healed transmural myocardial infarction in the left ventricular anterior and anterolateral walls, involving at least 45% of the left ventricular myocardial mass and the anterior two-thirds of the ventricular septum, from the heart base to its tip (Figure 2). Significant left ventricular aneurysmatic dilatation was observed, with important fibrosis and thinning of the anterior wall, whose thickness ranged from 0.2 cm to 1.4 cm. In the middle and apical thirds of the left ventricle, an organizing laminated thrombus was identified, adhered to the endocardial surface of the anterior wall and ventricular septum (Figure 2). The myocardium not affected by the infarction in the left ventricle was hypertrophied. The right ventricle showed moderate mural hypertrophy and dilatation, with an organizing thrombus in the apical region. The microscopic study of the epicardial coronary arteries showed atherosclerotic impairment with fibrosis and calcification in atheromatous plaques and important obstruction of the vascular lumen of the major branches (Figure 3). The branches of the left coronary artery showed: maximal luminal obstruction of 75% in the first centimeter of the circumflex artery (CX), and 90% in the fourth centimeter of the anterior interventricular artery (AD). In addition, to aggravate the obstruction of the latter, in the fourth centimeter, there was an old recanalized thrombus in a calcified atherosclerotic plaque. The right coronary artery (RC) showed a maximal obstruction of 60% in its first centimeter, and 70% in the first centimeter of its posterior interventricular branch (PD). Neither recent myocardial infarction nor coronary thrombosis nor intracoronary stents were seen. The lungs, liver and spleen showed morphological changes of chronic passive congestion secondary to CHF (Figure 4). The aorta and cerebral arteries of the Willis polygon evidenced moderate atherosclerosis with calcification. The brain showed neither recent nor old ischemic infarction. There were benign nephrosclerosis, represented by hyalinization of the wall of the glomerular afferent arterioles, and myocardial sclerosis, with multifocal perivascular fibrosis in the left ventricular myocardium, due to systemic arterial hypertension. The lungs showed bilateral suppurative aspiration pneumonia, with particulate food matter and Gram-positive filamentous bacterial aggregates, morphologically compatible with *Actinomyces sp*, which are saprophyte microorganisms of the mouth (Figure 5). There was benign nodular prostatic hyperplasia, accompanied by a distended and thickened urinary bladder, with no morphological evidence of infection. There were acute tubular necrosis in the kidneys, hepatic centrilobular necrosis in the liver, and recent multifocal subendocardial infarctions in both ventricles, resulting from low cardiac output. Although the patient had reported coronary angioplasty with stent implantation 8 years before, no stent was identified in the coronary arteries. Neither malignant neoplasms nor morphological evidence of infection in other organs were found. (Léa Maria Macruz Ferreira Demarchi, MD)

Anatomopathological diagnoses: 1) systemic atherosclerosis; 2) coronary atherosclerosis; 3) ischemic heart disease, with healed infarction in the left ventricular anterior and anterolateral walls and in the anterior two-thirds of the ventricular septum; 4) left ventricular aneurysmatic dilatation

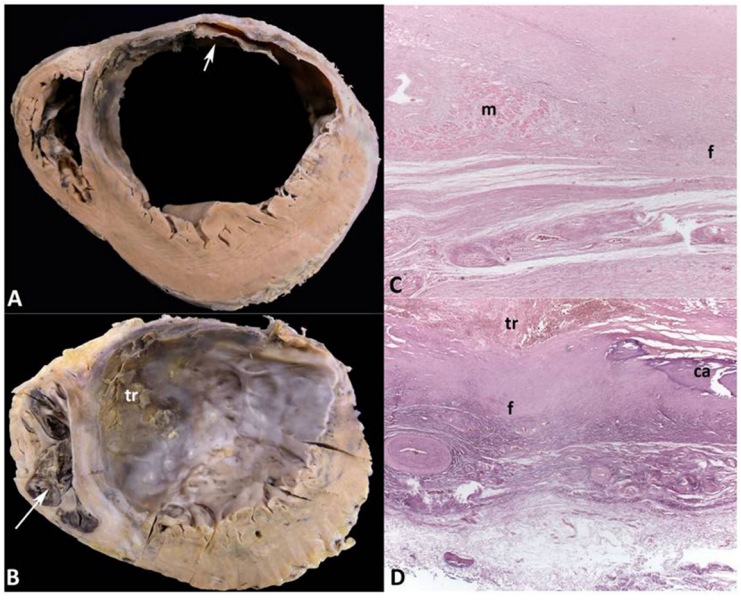

Figure 2 – *A and B: Cross sections of the ventricles in the middle-basal and apical regions, respectively. Healed transmural infarction in the left ventricular anterior and lateral walls and in the anterior two-thirds of the ventricular septum, with aneurysmal formation. Myocardial hypertrophy of the left ventricular walls not affected by the infarction is evident. Organizing thrombus in the endocardium of the left ventricular anterior and septal walls (arrow) in the middle-basal region, extending to the apical region (tr). Organizing thrombus in the right ventricular endocardium of the apex (arrow). C and D: Histological sections of the left ventricular aneurysm showing an isolated group of cardiomyocytes (m) and focal calcification (ca) amid mural fibrosis (f). Hematoxylin-eosin, 25x.*

Anatomopathological Correlation

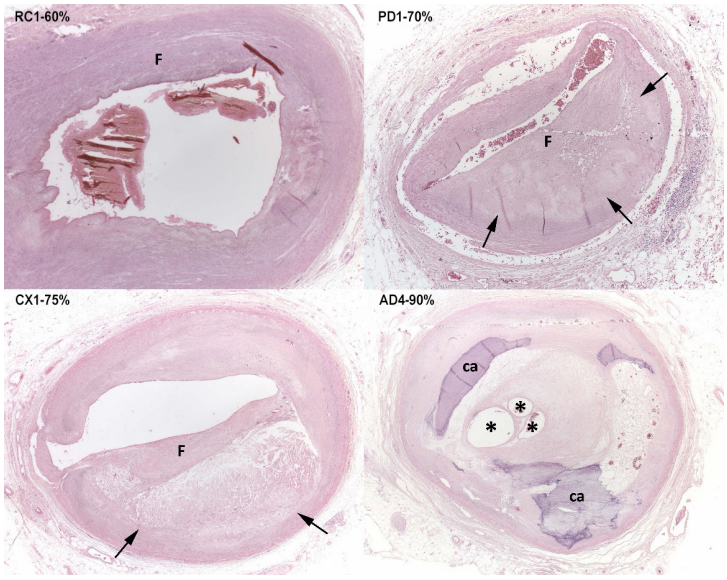

Figure 3 – *Histological sections of epicardial coronary arteries. Calcified atherosclerosis with luminal obstruction greater than 50% in the major branches. In the first centimeter of the right coronary artery (RC1), there is diffuse intimal fibrosis, with no lipid. In the first centimeter of the posterior interventricular branch of the right coronary artery (PD1) and of the circumflex branch (CX1), there are atherosclerotic plaques with fatty center and cholesterol crystals (arrows), surrounded by fibrosis (F). In the fourth centimeter of the anterior interventricular branch (AD4), there is luminal occlusion by an old recanalized thrombus, with multiple lumina and small vessels formed in the repairing process (*). Hematoxylin-eosin, 25x (RC1, CX1 and AD4) and 50x (PD1).*

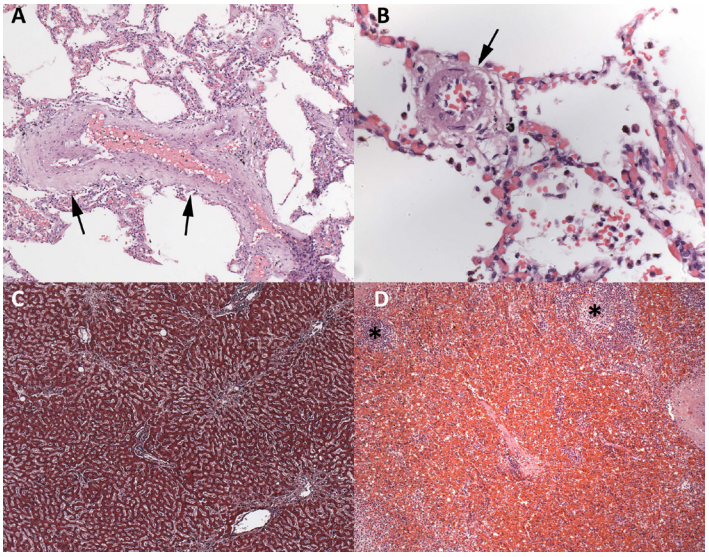

Figure 4 – *Chronic passive congestion. Lungs: thickening and tortuosity of the veins (A) and muscularization and hypertrophy of the media layer of an intra-acinar arteriole (B). Liver: sinusoidal dilatation in centrilobular areas (C). Spleen: intense congestion and widening of the red pulp; small, non-reactive lymphoid follicles (*). Hematoxylin-eosin, 100x (A and D) and 400x (B). Masson trichrome, 50x (C).*

in the left ventricular anterior wall with an organizing thrombus in the endocardium subjacent to the healed infarction area; 5) congestive heart failure; 6) aspiration pneumonia; 7) mixed hemodynamic shock (cardiogenic/infectious). (Léa Maria Macruz Ferreira Demarchi, MD)

Comments

Ischemic heart disease (IHD) is the major cause of death in Brazil and worldwide, with higher incidence in men aged 40 years and older.[8,9] Coronary atherosclerosis is the major contributor to the occurrence of IHD, despite the global

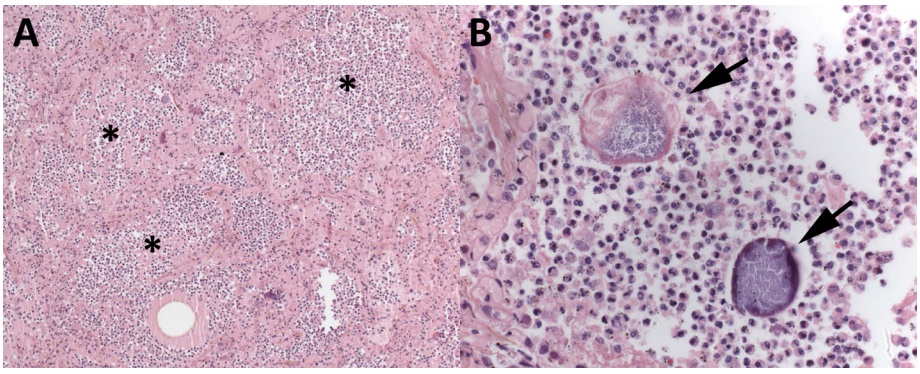

Figure 5 – *Lungs (A and B). Aspiration pneumonia: alveolar spaces filled with dense suppurative neutrophilic inflammatory infiltrate (*), amid which, particulate food material and filamentous bacterial aggregates, morphologically compatible with Actinomyces (arrows), can be seen. Hematoxylin-eosin, 100x (A).*

preventive measures and the advance in the hemodynamic and pharmacological techniques to treat atherosclerotic disease. Thus, the risk factors for the development of IHD are those for coronary atherosclerosis. This case shows the progression of coronary atherosclerosis and its complications in a male patient with risk factors, such as age (72 years) and systemic arterial hypertension. The atherosclerotic involvement of the coronary arteries, more marked in the AD and CX branches, and the old recanalized thrombus in DA explain the healed transmural infarction in the left ventricular anterior and anterolateral walls and in the ventricular septum, from the heart base to its tip. The complications of myocardial infarction depend on the location and extension of the myocardial necrotic area, which, in our patient, are represented by left ventricular aneurysmal dilation, extensive transmural myocardial fibrosis in the left ventricular anterior wall and organizing thrombus in the endocardium of the infarcted area. An aneurysm can occur early or later after myocardial infarction,[10] and its presence increases the risk for ventricular arrhythmias and CHF. On postmortem exams, aneurysms are found in cases of extensive myocardial infarction and the hearts are enlarged, with hypertrophy of the remaining left ventricular myocardium, left ventricular dilatation and significant luminal obstruction of the major branches of the epicardial coronary arteries. Congestive heart failure is frequent, being the major cause of death.[11] The mortality rate of patients of both sexes, aged at least 70 years, who develop CHF after myocardial infarction and have an abnormal left ventricular ejection fraction, varies from 41% to 92%, respectively, from the first to the fifth post-infarction year.[12] In the case here discussed, the complication cited contributed to CHF, morphologically identified as anasarca, chronic passive congestion of the lungs, liver and spleen, low cardiac output and cardiac cachexia, determining the patient's unfavorable outcome. The cause of death was hemodynamic shock, to which CHF and aspiration pneumonia contributed. (Léa Maria Macruz Ferreira Demarchi, MD)

References

1. Okoshi MP, Romeiro FG, Paiva SA, Okoshi K. Heart failure-induced cachexia. Arq Bras Cardiol. 2013;100(5):476-82.
2. Pittman JG, Cohen P. The pathogenesis of cardiac cachexia. N Eng J Med. 1964 Aug 27;271:453-60.
3. Rahman A, Jafry S, Jeejeebhoy K, Nagpal AD, Pisani B, Agarwala R. Malnutrition and cachexia in heart failure. JPEN J Parenter Enteral Nutr. 2016;40(4):475-86.
4. Anker SD, Negassa A, Coats AJ, Afzal R, Poole-Wilson PA, Cohn JN, et al. Prognostic importance of weight loss in chronic heart failure and the effect of treatment with angiotensin-converting-enzyme inhibitors: an observational study. Lancet. 2003; 361(9363):1077-83.
5. Bueno CR Jr, Ferreira JC, Pereira MG, Bacurau AV, Brum PC. Aerobic exercise training improves skeletal muscle function and Ca2+ handling-related protein expression in sympathetic hyperactivity-induced heart failure. J Appl Physiology (1985). 2010;109(3):702-9.
6. Koene RJ, Prizment AE, Blaes A, Konety SH. Shared risk factors in cardiovascular disease and cancer. Circulation. 2016;133(11):1104-14.
7. Murphy KT. The pathogenesis and treatment of cardiac atrophy in cancer cachexia. Am J Physiol Heart Circ Physiol. 2016;310(4):H466-77.
8. World Health Organization. (WHO). Global health estimates 2015: deaths by cause, age and sex, by country and by region, 2000-2015. Geneva; 2016. [Access in 2018 Feb 8]. Available from: http://www.who.int/healthinfo/global_burden_disease/estimates/en
9. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;385(9963):117-71.
10. Silver MD, Gotlieb AI, Schoen FJ. (eds.). Cardiovascular pathology. 3rd ed. New York: Churchill Livingstone; 2001.
11. Cabin HS, Roberts WC. True left ventricular aneurysm and healed myocardial infarction. Clinical and necropsy observations including quantification of degrees of coronary arterial narrowing. Am J Cardiol. 1980;46(5):754-63.
12. Aronow WS, Ahn C, Kronzon I. Prognosis of congestive heart failure after prior myocardial infarction in older men and women with abnormal versus normal left ventricular ejection fraction. Am J Cardiol. 2000;85(11):1382-4.

Primary Ventricular Fibrillation in a Patient with Mild Hypercalcemia

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Introduction

An abnormally short QT interval can be caused by several situations such as hypercalcemia, hyperkalemia, acidosis, hyperthermia, effects of drugs like digitalis or congenital short QT syndrome (SQTS).[1] Primary hyperparathyroidism (PHPT) can ultimately cause short QT interval since overproduction of parathyroid hormone (PTH) causes hypercalcemia. However, cardiac arrhythmias are uncommon and electrical storm has been rarely described in patients with hypercalcemia.[2]

Secondary causes of short QT must be ruled out before considering the diagnosis of SQTS.[3] First described in 2000, SQTS is a congenital primary electric disorder characterized by abnormally short corrected QT interval (QTc) on the surface electrocardiogram (ECG) that is associated with sudden cardiac death (SCD) in individuals with structurally normal heart. According to 2015 ESC Guidelines for the management of patients with ventricular arrhythmias,[4] SQTS is diagnosed in the presence of a QTc ≤ 330 msec or it can be diagnosed in the presence of a QTc < 360 ms and one or more of the following factors: pathogenic mutation, family history of SQTS, family history of sudden death before 40 years old and/or survival of a ventricular tacchycardia (VT)/ ventricular fibrillation (VF) episode in the absence of heart disease.

The authors present a case of an electrical storm due to polymorphic VT suspected to be caused by SQTS. However, PHPT was diagnosed one year later and mild hypercalcemia was thought to have been the cause or a contributor for the electrical storm.

Case Report

A previous healthy 44-year-old woman was brought to the emergency room after an unwitnessed fall followed by extreme anxiety. She had no respiratory distress or others symptoms; she denied cardiovascular risk factors or alcohol and drugs consumption. Her family history was irrelevant. On physical examination, she was calm, apyretic, hemodynamically stable and her neurological exam and cardiac and pulmonary auscultations were normal. Her blood pressure was 90/61 mmHg and heart rate (HR) was 114 beats per minute (bpm). While she was under observation, she *lost consciousness*. Cardiac monitoring confirmed a VF episode and the patient was shocked and recovered. Her laboratory values were normal, including hemogram, electrolytes, renal function, thyroid hormones, cardiac enzymes and serum D-dimer. Her total calcium was 9.3 mg/dL and albumin was 3.0 g/dl (normal range 3.5 – 5.0 g/dL). The corrected calcium for hypoalbuminemia was 10.3 mg/dL (normal range 8.4 - 10.2 mg/dL). She had an ECG taken by emergency team before hospital admission (Figure 1) that showed a sinus rhythm at a HR of 75 bpm, normal PR interval (160ms) and QRS duration (90 bpm), no ST changes and a QTc of 349ms (according to Bazett´s formula). T_{peak} - T_{end} interval (0.50 msec) and T_{peak} - T_{end} / QT ratio (0.18) were not prolonged. Short QT interval was not detected in the subsequent ECGs, including in the one performed after the first shock. In the next hours, cardiac monitoring demonstrated premature ventricular contractions (PVC) with distinct morphologies and R-on-T phenomenon, which was responsible for polymorphic VT that degenerated to VF (Figure 2). Ten external shocks were applied and treatment with amiodarone and beta-blockers was ineffective. Sedation and orotracheal intubation were decided due to the requirement of successive shocks. Emergency coronary angiography excluded coronary artery disease (CAD). Since paroxysmal VT were presumably caused by PVC with short coupling intervals ("R-on-T" extrasystoles falling on the peak of the T wave), isoproterenol infusion was started (0.08 mg/h). HR increased and arrhythmic episodes disappeared. Twenty-four hours later this treatment was stopped and no more arrhythmias were detected.

A comprehensive approach was performed. During hospitalization, successive ECGs did not show short QTc interval or other alterations. PVCs were noted in some instances on ECGs but they had different morphologies and only a few of them had a short coupling interval. Laboratory values remain normal. Transthoracic echocardiogram was normal and cardiac magnetic resonance imaging (MRI) did not visualize late enhancement or other changes. Flecainide test was negative and electrophysiologic study (EPS) was normal with no arrhythmia induction. The treadmill test (Bruce protocol) was performed. In rest, her QT interval was 320 ms and HR 90 bpm (QTc = 392 ms); in peak effort (HR = 134 bpm), QT was 280ms (QTc = 418 ms). She requested to terminate the test in stage 1 (1.7 mph at 10% grade) since she was very tired.

Further investigation for SQTS as the cause of VF was not performed and a single chamber implantable cardioverter-defibrillator (ICD) (ProtectaVR D364VRM, Medtronic®) was implanted for secondary prevention. The patient was discharged with no medical therapy. Fifteen days later, the patient complained of palpitations and the ICD interrogation demonstrated non-sustained VT initiated by PVC with short coupling intervals. Quinidine was initiated and symptoms as well as non-sustained VT episodes disappeared.

Keywords

Ventricular Fibrillation; Shock, Cardiogenic; Hypercalcemia; Syncope; Unconsciousness.

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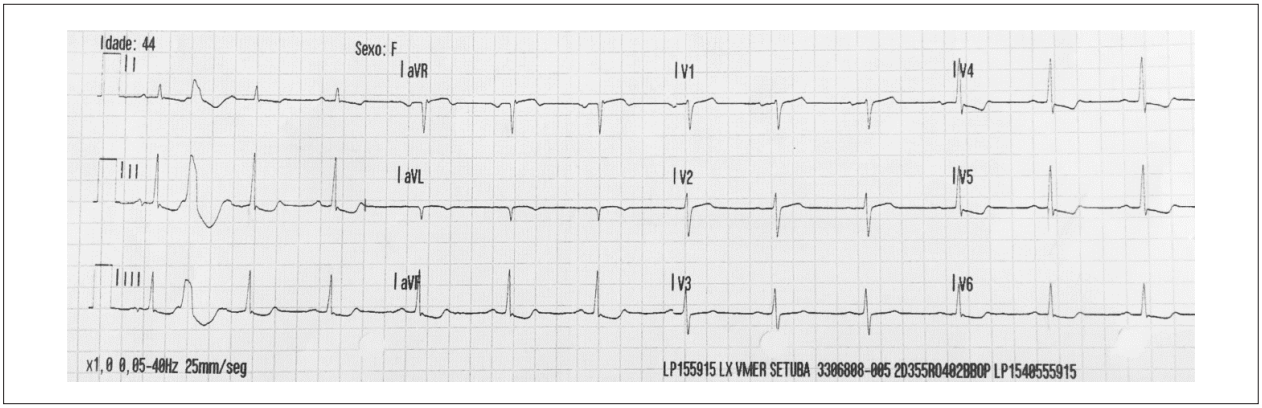

Figure 1 – *Twelve-lead electrocardiogram (ECG) taken by emergency team before hospital admission demonstrating a corrected QT interval (according to Bazett´s formula) of 349 milliseconds (msec).*

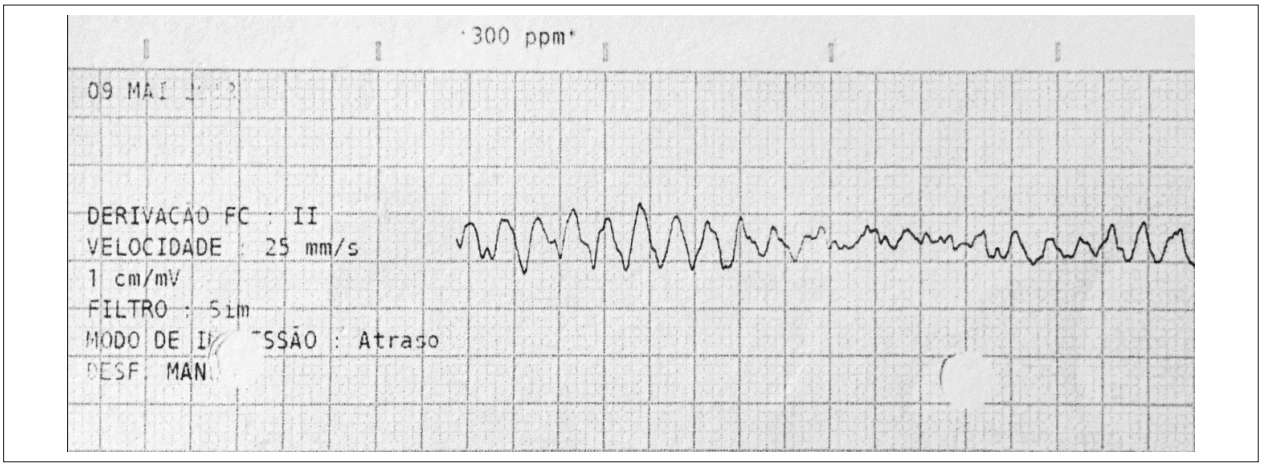

Figure 2 – *Electrocardiogram (ECG) during ventricular fibrillation (VF) episode.*

After one year, a laboratory study was done once again due to complains of asthenia and anorexia. Serum calcium was 10.2 mg/dL and albumin 3.2 g/dL, corrected calcium was 10,8 mg/dL. Serum phosphorus was 1.8 mg/dL (normal range 2,7 – 4,5 mg/dL). Potassium and magnesium were normal. Based on these results, PTH measurement was performed and it was elevated: 344.8 pg/mL (normal range 15 - 68.3 pg/mL) and PHPT was diagnosed. Bone densitometry (DEXA), renal function and urine calcium were normal. The patient was referred to endocrinology surgery but according to the NIH *criteria* for *parathyroidectomy, the surgery was not recommended.* She remains asymptomatic with no further VT episodes or frequent PVCs.

Discussion

VF causes vary according to the age group. In young, it is mostly due to channelopathies, cardiomyopathies, myocarditis and substance abuse, while in patients older than 40 years, CAD is the leading cause.[4] Taking into account the patient´s age, it seemed reasonable to perform coronary angiography. Brugada´s pattern was not evident but regarding intermittent alterations in this syndrome and the good response to isoproterenol, a flecainide test was performed to exclude this diagnosis. Cardiac MRI was also crucial to exclude cardiomyopathy. Although the EPS is not indicated to stratify risk in SQTS since its sensitivity and negative predictive value are low,[5] the SQTS diagnosis was not absolutely certain and so the EPS was performed and it was normal. Since SQTS patients show a reduced adaptation of the QT interval to HR,[6] the patient underwent the treadmill test but she did not reach maximum predicted HR. However, the variation from rest to peak effort of 40 ms is probably attenuated. After excluding all other causes of electric storm, SQTS was considered a reasonable diagnosis based on absence of structural heart disease, normal laboratory values and the presence of a short QT interval in one ECG. Serum calcium was only slightly increased (10,3 mg/dL) so secondary causes of SQTS were considered to be absent. According to the ESC guidelines, a SQTS diagnosis can be made based on a QTc < 360 ms and an episode of VF without structural heart disease.[4] The absence of short QT in the subsequent ECGs as well as the absence of other common electrocardiographic features present in

SQTS (short ST segment and prolonged T_{peak} - T_{end} interval and T_{peak} - T_{end} / QT ratio),[7] make SQTS diagnosis less probable. It is unclear if short QT interval can be intermittent or whether fluctuating QT intervals are of clinical significance in patients with SQTS.[8] Of note, a case of sudden cardiac death associated with intermittent short QT interval has been described.[9] Mazzanti et al.[10] proposed that SQTS and Brugada Syndrome (BrS) may have some features in common and intermittent pattern of short QT interval (same as ST elevation in right precordial leads) seems reasonable. The presence of short action potential duration, as well as abbreviated repolarization, suggests that the R-on-T phenomenon may precipitate arrhythmogenesis in SQTS. Obviously, performing genetic testing could be considered. Five genes have been linked to SQTS (KCNH2, KCNQ1, KCNJ2, CACNA1C and CACNB2b), but the yield of genetic screening remains low (20% overall).[10] In other words, the chances of a gene mutation be identified and confirm the diagnosis is low and a negative test does not rule out SQTS since there are mutations unidentified. Besides, our patient had no offspring or siblings so it was considered that genetic test would not add relevant information or change therapeutic management. The good response to quinidine in the follow-up supports the diagnosis of SQTS since quinidine can reduce arrhythmic events in this entity.[5]

The authors admit that alternative diagnosis can be considered. The occurrence of malignant ventricular arrhythmias in patients with PVCs with short coupling interval has been extensively reported. In these cases, PVCs have the same morphology suggesting one focal origin. Left bundle branch morphology and left axis were identified as most commonly related to VF,[11] which is usually not induced by an EP study. Verapamil is reported to be effective in suppressing these arrhythmias, while quinidine, β-blockers and amiodarone are ineffective. In our patient, quinidine is effective, PVCs had distinct morphologies and initially PVCs were suppressed by isoproterenol, which is not a consistent finding in these cases. Of note, transient metabolic or electrolytic disorders can influence PVC susceptibility to degenerate in VF[12] so hypercalcemia could have contributed to this phenomenon.

The initial diagnosis was rethought several months later when PHPT was confirmed although it is not clear if the arrhythmic events can be caused by mild hypercalcemia. Other reported cases described more severe hypercalcemia associated with arrhythmias. Alternatively, mild hypercalcemia could have been a trigger to ventricular arrhythmias in the case of SQTS or PVCs with short coupling. In fact, the patient had higher levels of calcium while on therapy with quinidine and no arrhythmias occurred. To establish a cause-effect relationship it is necessary to demonstrate that calcium perfusion would cause VF in EPS as described by Chang et al.[11] However it would imply repeating EPS with calcium perfusion and facing a potential electrical storm which could be difficult to control as it had been in the first episode. For these reasons, the authors considered it inappropriate.

Conclusion

The authors report a case of electrical storm possibly related to SQTS taking into account the presence of short QT interval and isoproterenol and quinidine efficacy.[13] However, it is not clear why short QT interval was present only in the first ECG and secondary causes could not be completely ruled out since mild hypercalcemia was present.

Up until now there are no reports regarding mild hypercalcemia as a cause of arrhythmic storm. The final diagnosis is still not certain but EPS with calcium perfusion could be dangerous and genetic testing yield in SQTS is too low to justify its use. Although without a definitive diagnosis, the authors emphasize the importance of excluding all reversible causes, especially in case of subtle hydroelectrolytic disorders like the one presented above.

Author contributions

Conception and design of the research: Marinheiro R, Sardinha F, Gonçalves S, Serra S; Acquisition of data: Marinheiro R, Sardinha F; Analysis and interpretation of the data: Marinheiro R, Parreira L, Sardinha F; Writing of the manuscript: Marinheiro R, Parreira L; Critical revision of the manuscript for intellectual content: Parreira L, Amador P.

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References

1. Mirvis DM, Goldberger AL. Electrophysiologic testing: therapy for cardiac arrhythmias. In: Braunwald E, Zipes DP, Libby P. (eds). Braunwald's heart disease: a textbook of cardiovascular medicine. 10th ed. Philadelphia: WB Saunders; 2001. p. 152-4.
2. Occhetta E, Bortnik M, Magnani A, Francalacci G, Vassanelli C. Primary hyperparathyroidism and arrhythmic storm in a patient with an implantable cardioverter defibrillator for primary prevention of sudden death. Europace. 2004;6(3):184-8. doi: 10.1016/j.eupc.2004.01.005.
3. Patel C, Yan GX, Antzelevitch C. Short QT syndrome: from bench to bedside. Circ Arrhythm Electrophysiol. 2010;3(4):401-8. doi: 10.1161/CIRCEP.109.921056.
4. Priori S, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J. 2015;36(41):2793-867. doi: 10.1093/eurheartj/ehv316.
5. Giustetto C, Schimpf R, Mazzanti A, Scrocco C, Maury P, Anttonen O, et al. Long-term follow-up of patients with short QT syndrome. J Am Coll Cardiol. 2011;58(6):587-95. doi: 10.1016/j.jacc.2011.03.038
6. Giustetto C, Scrocco C, Schimpf R, Maury P, Mazzanti A, Levetto M, et al. Usefulness of exercise test in the diagnosis of short QT syndrome. Europace. 2015;17(4):628-34. doi: 10.1093/europace/euu351.
7. Yan GX, Kowey PR. Management of cardiac arrhythmias. 2nd ed. New York: Springer / Humana Press; 2011.
8. Schimpf R, Wolpert C, Gaita F, Giustetto C, Borggrefe M. Short QT syndrome. Cardiovasc Res. 2005;67(3):357-66. doi: 10.1016/j.cardiores.2005.03.026.
9. Dorantes-Sánchez M, López-Delgado A, Castro-Hevia J, Méndez-Rosabal A. [Intermittent short QT interval in a patient with sudden cardiac death]. Arch Cardiol Mex. 2011;81(4):322-6. PMID: 22188888.
10. Mazzanti A, Kanthan A, Monteforte N, Memmi M, Bloise R, Novelli V, et al. Novel insight into the natural history of short QT syndrome. J Am Coll Cardiol. 2014;63(13):1300-8. doi: 10.1016/j.jacc.2013.09.078.
11. Chang C, Chen S, Tai C, Yu W, Chen YJ, Tsai CF, et al. Ventricular tachycardia in a patient with primary hyperparathyroidism. Pacing Clin Electrophysiol. 2000;23(4 Pt 1):534-7. PMID: 10793449.
12. Chokr M, Darrieux F, Hardy C, Hachul D, Britto AV, Melo SL, et al. Short-coupled variant of "Torsades de Pointes" and polymorphic ventricular tachycardia. Arq Bras Cardiol. 2014;102(6):e60-4. PMID: 25004426.
13. Sánchez Muñoz JJ, García-Alberola A, Martínez-Sánchez J, Peñafiel-Verdú P, Caro-Martínez C, Manzano-Fernández S, et al Premature ventricular complexes as a trigger for ventricular fibrillation. Rev Esp Cardiol. 2010;63(7):798-801. PMID: 20609313.

Simultaneous Dual Coronary Fistulas

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A 61-year-old man with type II diabetes mellitus was referred with breathlessness on exertion. On auscultation, there was a continuous ejection systolic murmur on the left upper sternal border. Transthoracic echocardiography showed a dilated vessel in aortic wall in the parasternal long axis view (Figure 1A) and a spherical lesion in the apical 4-chamber view (Figure 1B). A coronary computed tomographic angiographic (CTCA) study revealed a dilated and ectatic right coronary artery (RCA). It arose from the ascending aorta at the 12 o'clock position and followed a tortuous course around the right sided atrioventricular groove before passing into the basal inferoseptum draining into the base of the right ventricle. An additional fistulous connection could be detected between the posterior descending artery of the RCA and the left anterior descending artery (LAD-RCA fistula) (Figure 1G,H,I). After a normal dobutamine stress echocardiogram, a decision for continued medical therapy was taken.

Keywords

Systolic Murmurs; Echocardiography; Computed Tomography Angiography.

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Primary coronary artery fistulas (CAF) are rare congenital communications between one or more coronary arteries and a cardiac chamber or a great vessel. The RCA represents the most frequent site of origin of CAF in 60% of cases followed by the left coronary artery in 35% while two CAF are uncommon (< 5%).

The current case demonstrates the utility of CTCA in elucidating otherwise unusual transthoracic echocardiographic appearances.

Author contributions

Conception and design of the research and analysis and interpretation of the data: Ntalas I, Chambers JB, Karády J, Rajani R; Acquisition of data: Ntalas I, Karády J, Rajani R; Writing of the manuscript: Ntalas I, Rajani R; Critical revision of the manuscript for intellectual content: Ntalas I, Chambers JB, Karády J, Rajani R.

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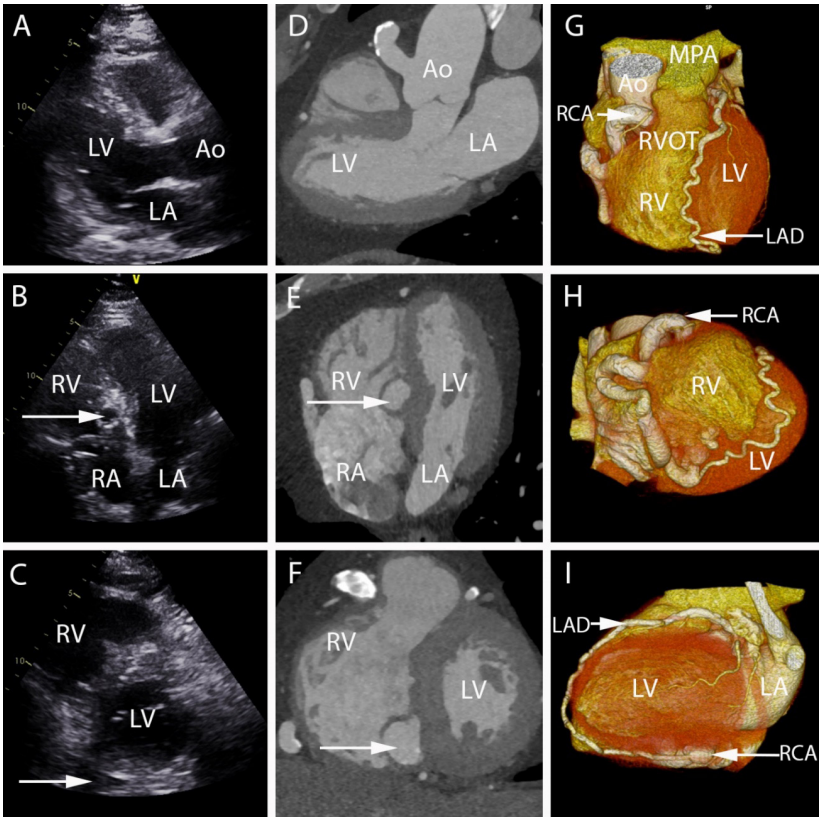

Figure 1 – *A-C) show the parasternal long axis (1A), apical 4-chamber (1B) and short axis (1C) TTE views of the left ventricle. The white arrow shows the presence of a spherical structure in the 4-chamber view and a dilated blood vessel in the short axis view. D-F) show the corresponding CTCA appearances of these findings in the same "echocardiographic views". G) shows the 3D volume rendered image of the heart with dilated and tortuous RCA and LAD. H) shows the anatomical connection of the RCA fistula to the base of the inferior RV and a continuation of the PDA to the LAD and I) shows the LAD to PDA continuation. LV: left ventricle; RV: right ventricle; LA: left atrium; RA: right atrium; Ao: aorta; MPA: main pulmonary artery; RVOT: right ventricular outflow tract; TTE: transthoracic echocardiogram; CTCA: cardiac computed tomography angiography; RCA: right coronary artery; LAD: left anterior descending artery; PDA: posterior descending artery.*

Incidence of Atrial High-Rate Episodes in Chagas Disease Patients

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Atrial high-rate episodes (AHRE) have been described as subclinical atrial fibrillation (AF), characterized by the occurrence of atrial arrhythmias (including AF and atrial flutter) with atrial rate greater than 190 bpm[1] or 250 bpm,[2] duration of 5-6 minutes or longer, asymptomatic, and detected by continuous monitoring, particularly with the use of implantable cardiac electronic devices (ICEDs). There is evidence that AHRE are associated with 2-2.5 times increased risk for stroke.[3] Although the incidence of AHRE may reach 70%,[4] this number decreases to 30%[1] when AF patients using oral anticoagulants are excluded. However, there are no data in the literature on AHRE incidence in some specific populations, vulnerable to thromboembolic complications, such as patients with Chagas Disease (CD). The incidence of AHRE was investigated in a cohort study with 67 Chagasic patients with ICEDs, conducted in the arrhythmia outpatient service of the University Hospital in Salvador, Brazil, between May 2016 and June 2017. Patients with AF or atrial flutter, and patients using anticoagulants were excluded. The ICEDs were set to detect AHRE episodes of atrial rate ≥ 190 bpm and duration ≥ 6 minutes, and patients were monitored for a mean period of 98 days (± 28.8 days). Mean age was 63.6 years (± 9.2 years), 67.2% were women and 50.7% were black. Cardiac pacemaker was the most common ICED (92.5%); 89.4% had the cardiac form of CD and mean ejection fraction was 58.5% (± 14.1%). The incidence of AHRE was 11.9% (8 patients) in this population. Duration of the episodes were variable among patients – 6-29min (1 patient), 30min-5h59min (5 patients), 6h-23h59min (1 patient). In one patient, the longest episode was greater than 24 hours. The mean time period for the first AHRE was 27.6 days (± 26.9). Evidence of the incidence of AHRE in Chagasic population aligns with the evidence of AHRE in other populations and gives support to the development of specific approaches involving antithrombotic therapy, until results of studies with anticoagulants become available.

Keywords

Atrial Fibrillation/complications; Cardiac Pacing, Artificial/methods; Defibrillators, Implantable; Chagas Disease/complications; Risk; Stroke/etiology.

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References

1. Healey JS, Connolly SJ, Gold MR, Israel CW, Gelder IC, Capucci A, et al; ASSERT Investigators. Subclinical atrial fibrillation and the risk of stroke. N Engl J Med. 2012;366(2):120-9.
2. Glotzer TV, Daoud EG, Wyse DG, Singer DE, Ezekowitz MD, Hilker C, et al. The relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke risk: the TRENDS study. Circ Arrhythm Electrophysiol. 2009;2(5):474-80.
3. Camm AJ, Simantirakis E, Goette A, Lip GY, Vardas P, Melanie C, et al. Atrial high-rate episodes and stroke prevention. Europace. 2017;19 (2):169-79.
4. Freedman B, Boriani G, Glotzer TV, Healey JS, Kirchhof P, Potpara TS. Management of atrial high-rate episodes detected by cardiac implanted electronic devices. Nat Rev Cardiol. 2017;14(12):701-14.