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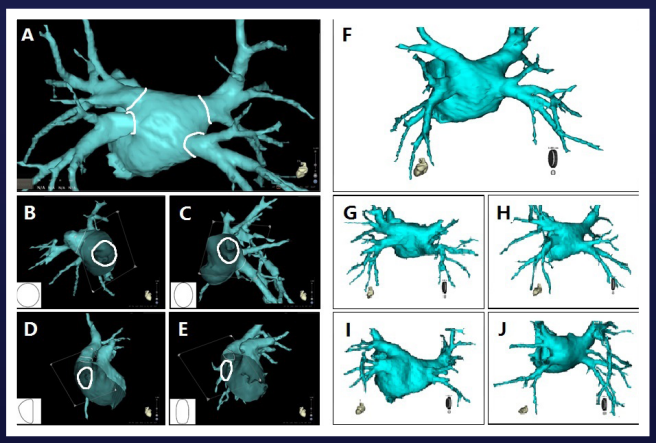

Figure 1 – *PV ostium shapes category and PV drainage patterns. A) PV ostia depicted semi-automatically using CartoMerge software. Four shapes of PV ostium; B) Type I (round); C) Type II (oval); D) Type III (triangular); and E) Type IV (narrow). Five patterns of PV drainage; F) Four PVs drains into LA in a typical pattern; G) Left superior and inferior PVs drains into LA both in a pattern of with common trunk; H) Left superior and inferior PVs drains into LA both in a pattern of with common antrum; I) Right inferior PV drains into LA in a pattern of with ostial branch; J) Right superior and inferior PVs drains in LA with supernumerary vein (middle vein). Page 442*

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Frequency of Subclinical Atherosclerosis in Brazilian HIV-Infected Patients

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Abstract

Background: AIDS as well as atherosclerosis are important public health problems. The longer survival among HIV-infected is associated with increased number of cardiovascular events in this population, and this association is not fully understood.

Objectives: To identify the frequency of subclinical atherosclerosis in HIV-infected patients compared to control subjects; to analyze associations between atherosclerosis and clinical and laboratory variables, cardiovascular risk factors, and the Framingham coronary heart disease risk score (FCRS).

Methods: Prospective cross-sectional case-control study assessing the presence of subclinical atherosclerosis in 264 HIV-infected patients and 279 controls. Clinical evaluation included ultrasound examination of the carotid arteries, arterial stiffness by pulse wave velocity (PWV) and augmentation index (AIx), laboratory analysis of peripheral blood, and cardiovascular risk according to FCRS criteria. The significance level adopted in the statistical analysis was $p < 0.05$.

Results: Plaques were found in 37% of the HIV group and 4% of controls ($p < 0.001$). Furthermore, carotid intima-media thickness was higher in the HIV group than in controls ($p < 0.001$). Patients with carotid plaque had higher fasting glucose, total cholesterol, low-density lipoprotein cholesterol, and triglycerides than those without plaques. The presence of HIV, adjusted for age, overweight/obesity, and smoking increased by almost fivefold the risk of atherosclerotic carotid plaque (OR: 4.9; 95%CI: 2.5-9.9; $p < 0.001$). Exposure to protease inhibitors did not influence carotid intima-media thickness, was not associated with carotid plaque frequency, and did not alter the mechanical characteristics of the arterial system (PWV and AIx).

Conclusions: HIV-infected patients are at increased risk of atherosclerosis in association with classical cardiovascular risk factors. Treatment with protease inhibitors does not promote functional changes in the arteries, and shows no association with increased frequency of atherosclerotic plaques in carotid arteries. The FCRS may be inappropriate for this population. (Arq Bras Cardiol. 2018; 110(5):402-410)

Keywords: Atherosclerosis / complications; HIV; Cardiovascular Diseases / mortality; Carotid Intima Media Carotideo; Vascular Stiffness; Risk Factors.

Introduction

By the end of 2012, about 35 million people were HIV positive worldwide. By June 2012 in Brazil, 656,701 cases had been identified since the first one detected in São Paulo in 1980; this includes 253,706 lethal cases between 1980 and 2011.[1,2] In the mid-1990s rates were increasing, but the current situation indicates a stable epidemic,[2] with signs of a reduction in mortality rate in the last decade.[1] The most important contributing factors were the introduction and easy access to highly active antiretroviral therapy (HAART). However, over the years, observations have shown that HAART may alter the patient's lipid profile, thereby accelerating atherosclerosis.[3-8] Despite this, cardiovascular disease (CVD) is the leading cause of death worldwide (World Health Organization, 2013) and represents the foremost cause of preventable death.

There is some indication of a possible direct effect from viral protein particles or infected cells liberating proteins in the receptors present in the vascular endothelium, thus favoring the presence of pro-coagulants, platelet activation, reduced nitric oxide production from the destruction of CD4 T lymphocytes ($CD4^+$ cell), and the production of inflammatory cytokines.[4,9,10] Recent publications have indicated that viral effect on the vascular endothelium can contribute to a reduction in the number of primary endothelial cells, which leads to endothelial dysfunction and atherosclerosis.[11]

Nevertheless, there is no consensus on the relationship between HAART and atherosclerosis; this may be due to the complexity of the factors involved.[4-6,8,10,11] In light of these facts, new strategies have been suggested to prevent cardiovascular events, including subclinical atherosclerosis research.[6,12-16]

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Carotid intima-media thickness rate (CIMT) and the presence of atherosclerotic plaque (PL) in the carotid have been associated with the Framingham coronary heart disease risk score (FCRS); individuals with this index elevated have a higher risk of developing CVD.[17-24] Another marker of CVD is high-sensitivity C-reactive protein (hs-CRP). In HIV-positive patients, hs-CRP, although low in sensitivity, is known to be a possible marker of disease progression and atherosclerosis.[25-28]

Arterial stiffness by pulse wave velocity (PWV), augmentation index (AIx), and ascending aortic pressure (AP) have been studied as promising indices of early endothelial dysfunction diagnosis.[29-32] Few publications have evaluated these indices in HIV-positive patients and the number of cases has been limited.[16,29-32]

The objectives of the present study were: 1- To identify the frequency of subclinical atherosclerosis in HIV-positive patients, comparing it with that of control subjects; 2- To associate the diagnosis of subclinical atherosclerosis with viral load, CD4 levels and antiretroviral treatment in HIV-positive patients; 3- To associate the presence of carotid atherosclerosis with cardiovascular risk factors and with the FCRS in HIV-positive patients.

Methods

Written informed consent was obtained from all participants, and the study protocol was approved by the Ethics Committee of the university.

This is a prospective cross-sectional case-control study with consecutively selected patients.

All HIV-infected patients from the Infectious Diseases outpatient clinic were included in the study. Exclusion criteria were evidence of atherosclerosis (interview, chart review and physical examination), age under 18 years, pregnancy, evidence of other causes of immunosuppression, and data acquisition failure due to technical difficulties.

Healthy controls were prospectively included.

Data source

Invitation to participate in the study was offered after exposure to the project in the waiting room during a routine visit.

Those who accepted were referred to a clinic where they received more information, had their doubts clarified, and underwent an interview guided by a structured questionnaire, a physical examination, and a carotid ultrasound assessment followed by a referral to collect a blood sample for laboratory tests.

HAART information, time since diagnosis and treatment, HIV-RNA viral load, and $CD4^+$ and $CD8^+$ cell counts were obtained from a review of medical records. Cardiovascular risk was calculated by FCRS.[12]

Carotid artery ultrasound

Carotid artery ultrasound was performed by the same appropriately trained expert using a Vivid I or Vivid S6 (General Electric Healthcare, USA) equipped with 7.0 MHz linear transducer and an image acquisition system. Images were obtained and analyzed according to the Consensus Statement from the American Society of Echocardiography and Mannheim Carotid Intima-Media Thickness Consensus recommendations.[21,22]

Carotid intima-media images were obtained by an automated method using GE developed software, to determine average thickness of the left and right carotid arteries.

A PL was defined as a focal structure that encroached into the arterial lumen at least 0.5 mm, or 50% of surrounding CIMT, or carotid thickness > 1.5 mm.[21]

Arterial stiffness

Arterial stiffness indices (PWV, AIx, and AP) were obtained by the same experienced operator using Sphygmocor CPV System equipment (AtCor Medical, Australia) and following current recommendations.[29]

Laboratory tests

A sample of 12-hour fasting peripheral blood was obtained from all patients to analyze hs-CRP, glucose, albumin, complete blood count, urea, creatinine, total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-c), and triglycerides (TGL). LDL-c was estimated using the Friedewald equation when TGL were lower than 400 mg/dL.[7]

Statistical analyses

All statistical analysis was performed using SAS/STAT (SAS Institute Inc., Cary, North Carolina, USA).

Continuous variables with normal distribution were presented as mean and standard deviation, and continuous variables with non-normal distribution were presented as medians and interquartile ranges. Categorical variables were presented as proportions. The Shapiro-Wilk test was performed as a normality test.

Multivariate logistic regression was used to estimate associations between carotid atherosclerosis and clinical variables.

Multiple linear regression was utilized to analyze associations between arterial stiffness and clinical variables or the presence of carotid atherosclerosis.

The Wilcoxon-Mann-Whitney test was used to compare two groups of non-parametric results. The unpaired Student *t* test was applied for parametric results.

One-way ANOVA was employed to compare the groups in FCRS classification.

All tests were two-tailed, and significance was set at $p < 0.05$.

Results

Study population

The study included 264 HIV-infected patients and 279 healthy volunteers (control group). In the HIV-infected group, median time since HIV diagnosis was 96 months (35-149 months) and treatment duration was 78 months (15-142 months). Viral load ranged from undetectable to 397,155 copies/mL (median: undetectable; 75th percentile: 253 copies/mL).

CD4+ counts ranged from 442 to 16,338 cells/μL (median: 1,739 cells; interquartile range: 1,350-2,212 cells). Of the HIV-infected patients, 35 were without HAART.

Table 1 shows the demographic and clinical variables of the HIV-infected patients and controls. Compared to controls, HIV-infected patients were six years older (43.2 ± 10.5 vs. 37.9 ± 11.5 years; p < 0.001), had lower BMI (25.5 ± 4.5 vs. 27.4 ± 5.4 kg/m²; p < 0.001), lower frequency of overweight/obesity (51.1 vs. 63.1%; p = 0.005), and higher active smoking incidence (43.6 vs. 16.1%; p < 0.001).

Table 2 shows clinical and laboratory variables of the patients, separated in treatment with protease inhibitors (PI). Those exposed to PI showed longer time since diagnosis [140 (74-175) vs. 72.5 (20-120) months; p < 0.001] and disease treatment duration [124 (56-155) vs. 44 (4-101) months; p < 0.001] and elevated TGL levels [190 (119-280) vs. 140 (100-188.5) mg/dL; p < 0.001]; but PI exposure had no effect on LDL-c, HDL-c, fasting glucose, creatinine, or hs-CRP levels.

Atherosclerotic plaques in carotid arteries and carotid intima-media thickness

Plaques were detected in 37% of the HIV group and 4% of the control group (p < 0.001), as shown in Figure 1.

Multivariate logistic regression analysis indicated that the presence of HIV, adjusted for age, overweight/obesity, and smoking, had an almost five-fold increase in the risk of carotid PL (OR 4.9, 95% CI 2.5 to 9.8; p < 0.001).

Patients with PL were 11 years older than those without PL (51.4 ± 9.21 vs. 40.2 ± 9.40 years, p < 0.001), and had higher levels of fasting blood glucose [90 (78-100) vs. 83 (76.5-90) mg/dL; p = 0.012], TC [200 (178-244) vs. 181 (156-208.5) mg/dL; p < 0.001], LDL-c [120.1 (96.2-148.4) vs. 96.8 (80-125) mg/dL; p < 0.001], TGL [188.5 (125.5-288.5) vs. 150.5 (108-226) mg/dL; p = 0.010] and creatinine [0.80 (0.70-1.10) vs. 0.80 (0.70-0.90) mg/dL; p = 0.027].

Patients with PL also had higher systolic (SBP: 132 ± 21 vs. 121 ± 16 mm Hg; p < 0.001) and diastolic blood pressure (DBP: 83 ± 12 vs. 77 ± 11 mm Hg, p < 0.001). In addition, PL was detected in approximately 34% of men versus 17.4% of women.

Regarding treatment with PI, exposure to this drug class was not associated with higher PL frequency. Nevertheless, results show significant interaction between PI and elevated TGL, even though no association with the presence of PL.

Figure 2 illustrates the significant association between age and CIMT in both groups, indicating that the oldest individuals have a higher CIMT, regardless of the presence of HIV infection. However, there was a significant interaction between age and the presence of HIV towards increasing CIMT (p < 0.001).

Arterial stiffness

Comparing patients exposed and not exposed to PI, this drug class had no effect on arterial mechanical characteristics, expressed by PWV [7.10 (6.20-8.20) vs. 7.20 (6.30-8.40) m/s; p = 0.727] and AIx [28 (17-37) vs. 26 (13-38)%; p=0.315]. In addition, no effect was observed on CIMT [0.645 (0.570-0.765) vs. 0.625 (0.565-0.740) mm; p=0.331].

Pulse wave velocity was associated with age (R = 0.573, p < 0.001), CIMT (R = 0.449, p < 0.001) and SBP (R = 0.557, p < 0.001), as shown in Figure 3.

The association between PWV and age persisted in the model corrected for smoking. However, smoking interacted with age to increase PWV (p = 0.05). The AIx was also associated with age (R = 0.411, p < 0.001), CIMT (R = 0.274, p < 0.001), and SBP (R = 0.348, p < 0.001).

Arterial stiffness index was elevated in patients with PL compared to no-plaque individuals with PWV [7.90 (7.0-9.5) vs. 6.80 (6.10-8.0) m/s; p < 0.001] and AIx [37 (25-42) vs. 24 (12-35) %; p < 0.001]. Furthermore, PL patients showed median CIMT about 0.170 mm greater than patients without injury [0.770 (0.680-0.910) vs. 0.597 (0.550-0.690) mm; p = 0.003].

Framingham coronary heart disease risk score

The FCRS was estimated in 252 HIV-infected patients. Of those, 207 were classified as low-risk (82.1%), 31 as intermediate-risk (12.3%), and 14 (5.56%) as high-risk for developing CVD within 10 years.

Table 1 – Demographic and clinical variables of HIV-infected patients and the control group.

Variables	HIV group (n = 264)	Control group (n = 279)	p
Age (years)	43.2 ± 10.5	37.9 ± 11.5	< 0.001
Sex (F/M)	125/139	144/135	0.321
O_ob (yes/no)	135 (51,1%)/129	176 (63.1%)/103	0.005
SAH (yes/no)	28/236	23/256	0.360
Smoking (yes/no)	115 (43.6%)/149	45(16.1%)/234	< 0.001
Diabetes (yes/no)	10/254	6/273	0.263
BMI (kg/m²)	25.5 ± 4.5	27.4 ± 5.4	< 0.001
SBP (mm Hg)	121 (111;133)	120 (110;130)	0.535
DBP (mm Hg)	77 (71;85)	80 (70;80)	0.616

F: female; M: male; O_ob: overweight/obesity; SAH: systemic arterial hypertension; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Table 2 – Clinical and laboratory variables of the patients treated or not with protease inhibitors

Variables	PI + (n=116)	PI - (n=148)	p
Time since diagnosis (months)	140 (74;175)	72.5 (20;120)	<0.001
Disease treatment duration (months)	124 (56;155)	44 (4;101)	<0.001
LDL-c (mg/dL)	103.2 (80.8;132.4)	102 (83.4;132.8)	0.796
HDL-c (mg/dL)	42 (35;56)	45 (37;53)	0.626
TGL (mg/dL)	190 (119;280)	140 (100;188.5)	<0.001
Fasting glucose (mg/dL)	83 (77;91)	83 (77;94)	0.764
Creatinine (mg/dL)	0.80 (0.70;1.0)	0.80 (0.70;0.90)	0.067
Hs-CRP (mg/dL)	0.50 (0.30;0.70)	0.50 (0.30;0.80)	0.344

PI +: in use of protease inhibitors; PI -: no use of protease inhibitors; LDL-c: low-density lipoprotein; HDL-c: high-density lipoprotein; TGL: triglycerides; hs-CRP: high-sensitivity C-reactive protein.

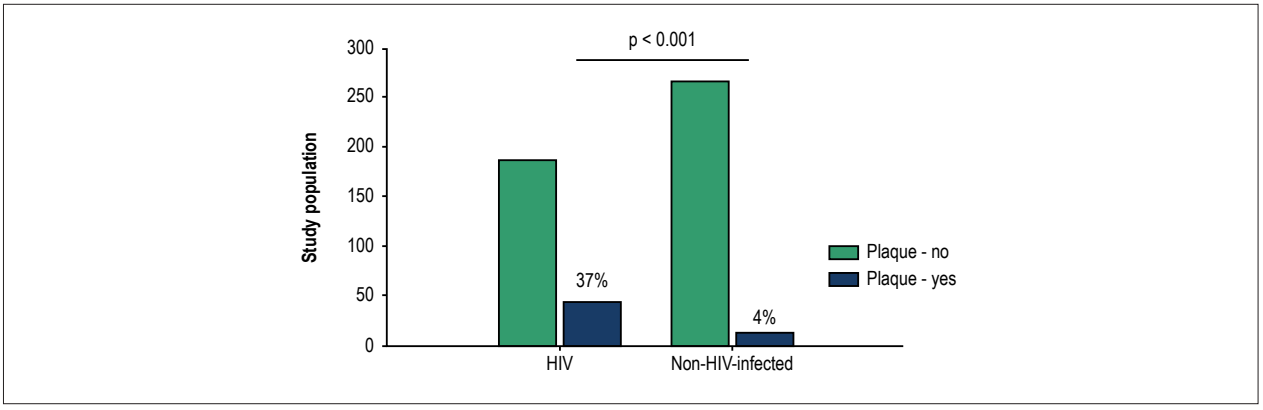

Figure 1 – *Frequency of carotid artery plaque in HIV-infected patients and non-HIV-infected controls.*

By grouping patients into two subgroups, low-risk (207 patients) and moderate/high-risk subgroups (45 patients), the PL frequency was 62.8% in the moderate/high-risk and 18.2% in the low-risk ($p < 0.001$) subgroup, as shown in Figure 4.

Low-risk individuals were 11 years younger than their moderate/high-risk counterparts (52.5 ± 10.3 years); $p < 0.001$.

Compared to the low-risk subgroup, the moderate/high-risk subgroup had higher CIMT [0.780 (0.710-0.935) vs. 0.605 (0.550-0.710) mm; $p < 0.001$], PWV [8.45 (7.15-10.05) vs. 6.90 (6.10-8.00) m/s; $p < 0.001$], TC [223 (188-253) vs. 182 (155-208) mg/dL; $p < 0.001$], LDL-c [130 (103-151) vs. 97.1 (79.6-126) mg/dL; $p < 0.001$], TGL [222 (160-309) vs. 143 (102-208) mg/dL; $p < 0.001$], fasting glucose [90 (80-102) vs. 83 (76-90) mg/dL; $p = 0.002$], and serum creatinine [0.90 (0.70-1.10) vs. 0.80 (0.70-0.90) mg/dL; $p < 0.001$], and lower HDL-c [38 (32-45) vs. 46 (37-56) mg/dL; $p = 0.002$].

From the 207 low-risk individuals, 83 had LDL-c lower than 130 mg/dL and were not using PI, and, of those, 14 (16.9%) were diagnosed with carotid artery PL ($p = 0.036$).

Discussion

According to the Brazilian Ministry of Health data, the prevalence of overweight individuals in the general population is around 50%, while that of obesity is 12% to 17%.[33] In the HIV-infected population, some studies have reported a prevalence of fat distribution changes of around 50%, with highly variable lipodystrophy data (20-80%) and obesity in 4-14%.[34,35] In this study, BMI was lower in the HIV-group than in the control group (25.5 ± 4.5 vs. 27.4 ± 5.4 kg/m²). The overweight and obesity frequency was 51.1%, similar to that in the literature and lower than that found in the control group (63.1%).

The literature shows a higher frequency of smoking among HIV-infected individuals, reaching approximately 50%, than in the general population.[36,37] We confirmed this in our series, finding active smoking in 43.6% of the patients and 16.1% of the control group ($p < 0.001$). Smoking had an effect on CIMT only in control subjects. This result could suggest that patients with HIV have other atherogenic factors that would neutralize the effects of smoking on intima-media thickness, with a tendency toward larger CIMT, independently of smoking.

LDL-c was associated with age ($R = 0.252$, $p < 0.001$) and time since HIV diagnosis ($R = 0.293$; $p = 0.041$), in direct association with increased serum levels.

These results suggest that atherosclerosis in the HIV population is influenced by other infection-related risk factors, in addition to presenting similar characteristics to the process classically described in other populations.[4-6,8,10,11]

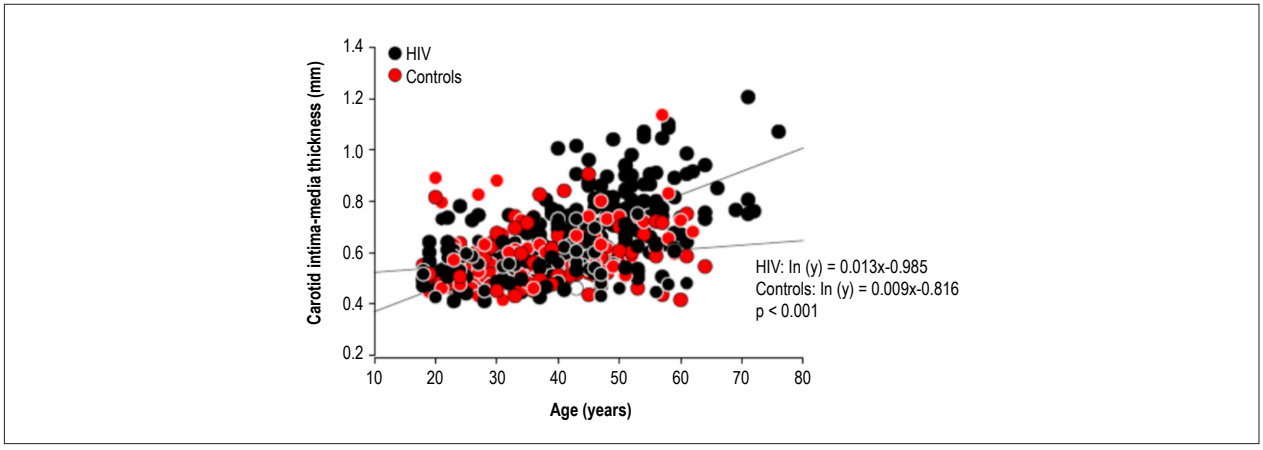

Figure 2 – *Association between carotid intima-media thickness and age in the control and HIV-infected group.*

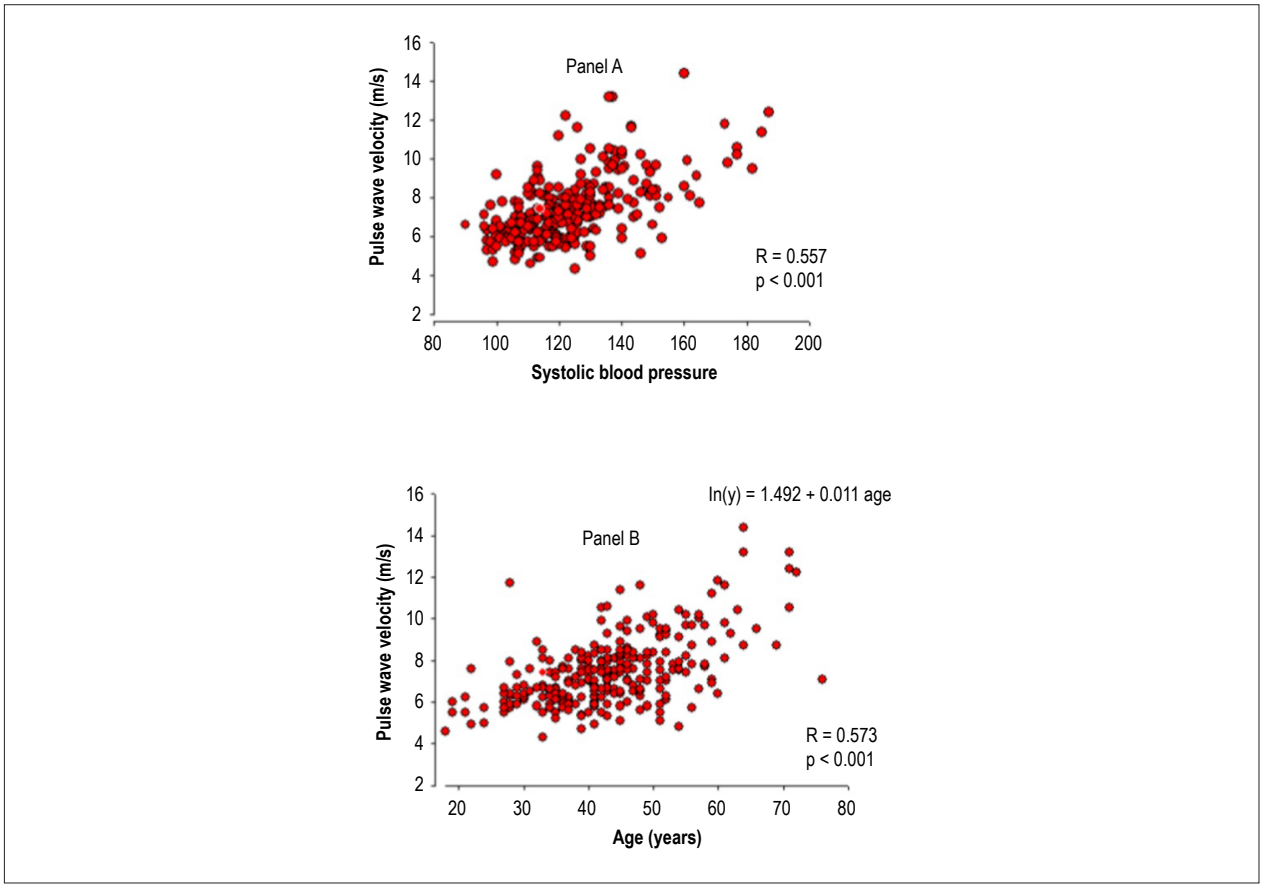

Figure 3 – *Association between pulse wave velocity and systolic blood pressure (panel A) and age (panel B).*

Plaques were found in 37% of the HIV-infected individuals, slightly lower than the 55% reported in some publications.[18,19,37]

This study found that the presence of HIV produced an almost fivefold increase in the risk of carotid PL in the model adjusted for age, overweight/obesity, and smoking. We may therefore suppose that the presence of HIV infection is a contributory factor to the development of atherosclerosis, in addition to the traditional risk factors, and in agreement with other studies.[10,11,15,18,38]

There was no association between the presence of carotid PL and time since diagnosis or treatment duration, abdominal circumference, BMI, HDL-c, and $CD4^+$ or $CD8^+$ cell count.

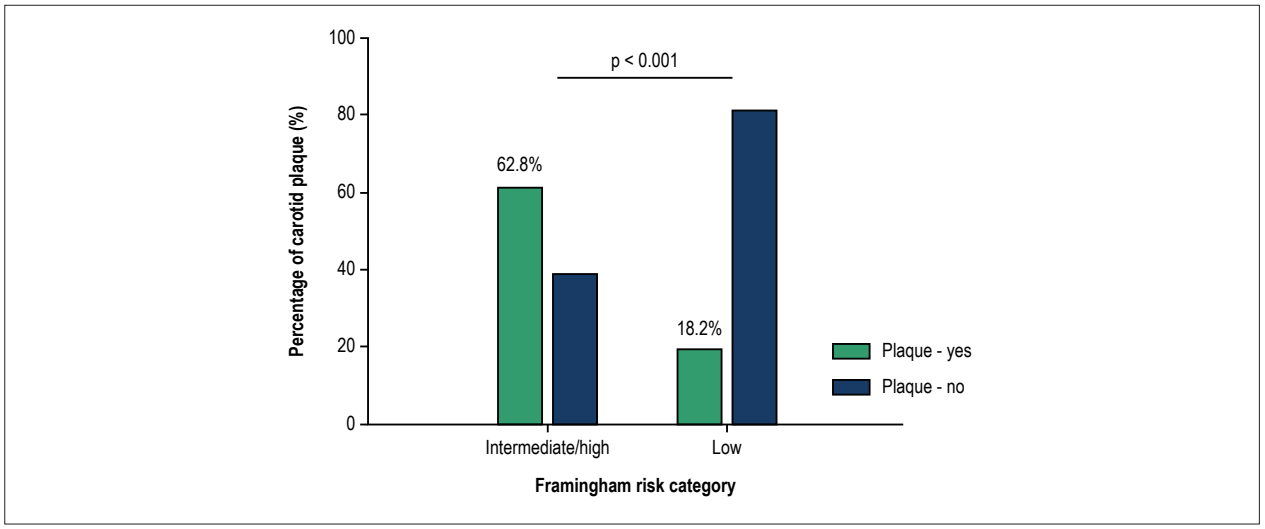

Figure 4 – *Frequency of plaques in HIV-positive patients according to risk stratification by Framingham risk score.*

Other studies have reported similar results, suggesting that the increased risk of atherosclerosis in the presence of HIV is not directly associated with time since diagnosis, but with conditions involved in HIV infection.[10,38,39]

Patients with PL were 11 years older than those without PL, and predominantly male. Fasting glucose, TC, LDL-c, and TGL were significantly higher in patients with the diagnosis of PL. In patients with PL compared to patients without PL, SBP and DBP were 10 and 6 mm Hg higher, respectively. These results agree with those of other studies and strengthen the concept that atherogenesis in HIV-infected patients follows the classical risk factors described in other populations.[4,20,37,38]

Our results indicate that older individuals had higher CIMT, regardless of the presence of HIV infection; however, there was an interaction between age and the presence of HIV to increase CIMT ($p < 0.001$). Although time since diagnosis did not affect PL frequency, HIV infection appears to enhance the effect of age on CIMT. In this case, younger individuals with HIV could have vascular changes compatible with those of older patients. Understanding this behavior is important in screening for atherosclerosis in HIV-infected patients, because the protective effect of lower age would have less relevance.

In the HIV group, CIMT was associated with age ($p < 0.001$), BMI ($p = 0.053$), LDL-c ($p = 0.005$), and serum creatinine ($p = 0.004$); this was also seen in other studies.[17-19,37,40] There were no associations with gender, smoking, diabetes, hypertension, statin therapy, HDL-c, or TGL. Interestingly, vessels may have PL with normal CIMT, which means that increased intima-media thickness and PL are not necessarily directly associated processes. However, both reflect the presence of endothelial dysfunction and are considered to favor cardiovascular events.[17-23]

Treatment with PI showed significant interaction with age and time since HIV diagnosis to increase TGL. Moreover, PI exposure was not associated with higher frequency of PL, in accordance with recent studies.[3,5,6,8,10,15,37-39]

In our study HAART showed correlation with unfavorable lipid profile, but without interfering in PL frequency or arterial stiffness.

The PWV was directly associated with age, CIMT, and SBP. These results are consistent with those from recent studies describing arterial stiffness indexes associated with age, hypertension, and vascular disease.[29-31] In addition, AIx showed a direct association with age, CIMT, and SBP, with no interaction between age and smoking to increase AIx.

The elevation of PWV and AIx in patients with PL suggests that atherosclerosis is associated with functional alterations in the vessels; stiffer vessels have a higher risk of developing PL. Furthermore, patients with PL showed higher CIMT than patients without lesions, supporting the hypothesis that CIMT and atherosclerosis are associated, even when excluding the evolutionary nature of an alteration in the other.

This study included 207 patients classified as low risk (82.1%), 31 as moderate (12.3%) and 14 as high risk (5.56%) according to FCRS. The literature shows that the greater the FCRS, the greater the CIMT.[23]

In relation to age, younger patients were seen to have lower scores. This is in accordance with the concept that the FCRS, when applied to young individuals, can result in a low risk score, without implying that these individuals are not at risk of future cardiovascular events. It is important to note that almost 20% of the low-risk patients had carotid PL.

Patients in the moderate/high-risk subgroup showed unfavorable lipid profile with low HDL-c and elevated TC and LDL-c, as described in the literature, but no difference in hs-CRP, when compared to those classified as low risk by the FCRS.[12,15,25,26] In addition, those classified as moderate/high-risk had higher intima-media thickness and PWV ($p < 0.001$), consistent with the hypothesis of a higher chance of vascular disease in the group.

Plaques were detected in 16% of the patients who were not treated with PI and had LDL-c lower than 130 mg/dL.

This result, associated with the presence of PL in almost 20% of the low-risk patients classified by the FCRS, would indicate that they are at risk of developing atherosclerosis. Thus, the group with such characteristics would be exposed to major cardiovascular events, such as myocardial infarction and stroke, even without symptoms.

The IV Brazilian Guidelines on Dyslipidemia and Atherosclerosis Prevention recommend that evaluation of cardiovascular risk in HIV-infected patients should be performed assessing lipid profile and FCRS.[12] Patients classified as low-risk have normal lipids and are not using HAART, and should undergo cardiovascular reevaluation in 2 years. In those with HAART, reevaluations are recommended one month after initiation of therapy and then every three months.

It is thus noted that the criteria established by the guidelines fail to consider the risks of this particular HIV-infected population, and that these patients have not been properly and specifically assessed for early CVD detection.

Limitations

There are some limitations in this study. The data are only observational. There is a gap between this study population and the population from Framingham in the original description of the risk score. The pathophysiological determinants of multifactorial conditions involved in the association between HIV-infection or HAART use and atherosclerosis were not analyzed in this study. Information on previous CVD and other causes of immunosuppression were obtained by medical record review only, without specific evaluation for each condition.

Conclusions

The data suggest that HIV-infected patients are at increased risk of atherosclerosis in association with the classical cardiovascular risk factors. In addition, HAART interacts with time since HIV infection diagnosis and patient age to modify lipid levels, but is not associated with higher PL frequency and does not promote functional changes in the arteries. Smoking, more prevalent in the HIV-infected population, influences the effect of age on the mechanical properties of arteries and may have an additional atherogenic effect in those patients. The FCRS may be inappropriate for this population.

Author contributions

Conception and design of the research: Salmazo PS; Acquisition of data: Salmazo PS, Shiraishi FG; Analysis and interpretation of the data: Salmazo PS, Bazan SGZ, Shiraishi FG, Bazan R, Okoshi K, Hueb JC; Statistical analysis: Bazan SGZ, Bazan R; Writing of the manuscript: Salmazo PS, Bazan SGZ, Shiraishi FG, Bazan R; Critical revision of the manuscript for intellectual content: Okoshi K, Hueb JC.

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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Experimental work involving human beings

This study was approved by the Ethics Committee of the Faculdade de Medicina de Botucatu under the protocol number CEP 3451-2010. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Frequency of Subclinical Atherosclerosis in HIV-infected Brazilians

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Short Editorial regarding the article Frequency of Subclinical Atherosclerosis in Brazilian HIV-Infected Patients

The advances in the treatment of the Human Immunodeficiency Virus (HIV) infection have resulted in a significant reduction in the mortality related to the acquired immunodeficiency syndrome (AIDS). Most patients get infected between the ages of 19 and 39 years, receive medicines from the time of diagnosis onward, with no perspective of interruption. In the follow-up of those patients, chronic non-infectious diseases related to several risk factors, such as age and cardiovascular disease, emerge. Some studies have shown the direct action of the HIV on the vascular endothelium (chronic inflammatory process), in addition to the action of the antiretroviral therapy (ART) on the lipid metabolism.[1]

The incidence of cardiovascular events among HIV-infected patients is low, being, thus, difficult to assess. Subclinical atherosclerosis is associated with an increased risk for events in the general population. It can be detected by use of non-invasive methods, such as carotid ultrasound, aimed at measuring the intimal medial thickness and at assessing the presence of atherosclerotic plaque, in addition to coronary computed tomography to calculate the calcium score. Coronary tomography angiography allows the assessment of the presence, composition and extension of coronary plaques, in addition to detecting stenosis.

Keywords

Cardiovascular Diseases; Acquired Immunodeficiency Syndrome; Atherosclerosis; Carotid Intima Media-Carotideo; Vascular Stiffness; Risk Factors.

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The study "*Frequency of Subclinical Atherosclerosis in HIV-Infected Brazilians*",[2] aimed at assessing those risk factors for cardiovascular disease, has reported results similar to those of other studies performed in several research centers around the world. It is worth noting the *Multicenter AIDS Cohort Study* (MACS) as a reference.[3]

The MACS is an ongoing prospective study that follows up HIV-infected and non-infected men who have sex with other men in four North American cities (Baltimore/Washington DC, Chicago, Los Angeles and Pittsburgh). The inclusion of cases began in 1987-1991, with new inclusions in 2001-2003, and from 2010 onward. Patients undergo two annual interviews, which include questions about behavior, physical exam and specific and non-specific laboratory tests. From January 2010 to August 2013, 1001 men underwent cardiac computed tomography, 618 of whom were HIV-infected, had ages ranging from 40 and 70 years, and no previous history of myocardial revascularization. That study concluded that coronary plaques, mainly non-calcified ones, were more prevalent and extensive in seropositive patients, regardless of the presence of other risk factors.

Some facts are worth noting: 1. The current increase in the number of HIV-infection cases among young men having sex with other men; 2. The World Health Organization's recommendation to begin specific therapy as soon as the etiological diagnosis is established; 3. The increased survival of the patients, with a decrease in the occurrence of opportunistic infections; 4. The relevance of the adverse effects presumably caused by ART, mainly osteonecrosis, metabolic syndrome and cardiovascular diseases.

The study in question contradicts the initial view relating atherosclerotic disease to ART and shows the importance of adopting preventive measures regarding the need for a healthy diet, physical exercise practice and the early introduction of medicines to correct the metabolic changes.

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Association between Microvolt T-Wave Alternans and Malignant Ventricular Arrhythmias in Chagas Disease

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Abstract

Background: Sudden cardiac death is the most frequent death mechanism in Chagas disease, responsible for 55% to 65% of the deaths of patients with chronic Chagas cardiomyopathy (CCC). The most often involved electrophysiological mechanisms are ventricular tachycardia and ventricular fibrillation. The implantable cardioverter defibrillator (ICD) has a beneficial role in preventing sudden death due to malignant ventricular arrhythmias, and, thus the correct identification of patients at risk is required. The association of microvolt T-wave alternans (MTWA) with the appearance of ventricular arrhythmias has been assessed in different heart diseases. The role of MTWA is mostly unknown in patients with CCC.

Objectives: To evaluate the association between MTWA and the occurrence of malignant ventricular arrhythmias in patients with CCC.

Method: This is a case-control study including patients with CCC and ICD, with history of malignant ventricular arrhythmias (case group), and patients with CCC and no history of those arrhythmias (control group). The MTWA test results were classified as negative and non-negative (positive and indeterminate). The significance level adopted was $\alpha = 0.05$.

Results: We recruited 96 patients, 45 cases (46.8%) and 51 controls (53.1%). The MTWA test was non-negative in 36/45 cases (80%) and 15/51 controls (29.4%) [OR = 9.60 (95%CI: 3.41 – 27.93)]. After adjustment for known confounding factors in a logistic regression model, the non-negative result continued to be associated with malignant ventricular arrhythmias [OR = 5.17 (95%CI: 1.05 – 25.51)].

Conclusion: Patients with CCC and history of malignant ventricular arrhythmias more often have a non–negative MTWA test as compared to patients with no history of arrhythmia. (Arq Bras Cardiol. 2018; 110(5):412-417)

Keywords: Chagas Disease; Chagas Cardiomyopathy; Arrhythmias, Cardiac/complications; Defibrillators,Implantable; Death, Sudden, Cardiac.

Introduction

Chagas disease remains a challenge of great importance in Brazil and Latin America, and is an emerging concern in North America and European countries.[1] It is considered to be endemic in 21 countries, infects 6 to 7 million people worldwide,[2] accounting for the death of around 12,000 patients per year.[3]

Chronic Chagas cardiomyopathy (CCC) is the most important presentation of Chagas disease, because of its high frequency, severity and great impact on morbidity and mortality. Chronic Chagas cardiomyopathy has a wide range of manifestations, such as heart failure, conduction blocks, thromboembolic events and sudden death.[4,5] Sudden death is the most common mechanism of death of those patients, occurs in the presence or absence of advanced heart disease, and can be the first manifestation of the disease. The electrophysiological mechanisms most frequently involved are the ventricular arrhythmias: sustained ventricular tachycardia and ventricular fibrillation.[4,6]

Implantable cardioverter-defibrillator (ICD) has a great impact on the prevention of sudden death due to malignant ventricular arrhythmias.[7,8] The use of the ICD in secondary prevention is well accepted in CCC, despite the lack of large studies, based on the results obtained from other populations.[7,9] However, its use in primary prevention is still controversial because of the high cost, intrinsic risks in implantation, and adverse effects.[10,11] Therefore, identifying patients with CCC at risk for sudden death due to malignant ventricular arrhythmias is necessary.

The microvolt T-wave alternans (MTWA) test is a non-invasive test associated with the appearance of ventricular tachyarrhythmias assessed in different clinical conditions with a high negative predictive value to identify patients at risk.[12-17] That test recognizes fluctuations of the T-wave morphology and amplitude beat to beat, measured in microvolts. Those fluctuations reflect space-temporal

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heterogeneity of ventricular repolarization, which is considered a predisposing condition to the beginning and perpetuation of ventricular arrhythmias.

It is worth noting the association of MTWA with malignant arrhythmias in several clinical conditions, but few studies have included patients with CCC. This study was aimed at assessing the possible association between MTWA and malignant ventricular arrhythmias in Chagas disease.

Method

Study

This is an observational, case-control study, approved by the Ethics Committee in Research of the Federal University of Minas Gerais (COEP 7918/12). The patients were recruited between 2011 and 2014.

Patients

The sample consists of patients diagnosed with CCC being followed up at the Hospital das Clínicas of the Federal University of Minas Gerais (HC-UFMG). The individuals agreed to participate and provided written informed consent. Patients should be older than 18 years, have a positive serology for Chagas disease and meet all the diagnostic criteria for CCC, which include asymptomatic structural heart disease with typical electrocardiographic changes,[18] or heart failure with preserved or reduced left ventricular ejection fraction (LVEF), with current or previous symptoms.

The case group consisted of patients with CCC and history of malignant ventricular arrhythmia, with indication for ICD implantation for secondary prophylaxis and authorization issued by the High-Complexity Commission of the Brazilian Unified Health System (SUS), according to the ordinance # 152, of March 8, 2007,[19] updated by the ordinance # 1, of January 2, 2014.[20] Patients with CCC and no previous history of malignant ventricular arrhythmia comprised the control group.

According to the ordinance # 152, of March 8, 2007, the major indications for ICD implantation in Brazil are as follows:[19]

- Individuals resuscitated from documented cardiac arrest due to tachycardia or ventricular fibrillation of non-reversible cause, with LVEF ≤ 35% or structural heart disease;
- Spontaneous, sustained ventricular tachycardia, of non-reversible cause, with LVEF ≤ 35%;
- On the electrophysiological study, syncope of undetermined etiology with induction of hemodynamically unstable sustained ventricular tachycardia, or clinically relevant ventricular fibrillation with LVEF ≤ 35% or structural heart disease.

Individuals with the following characteristics were excluded from the study: difficulty to walk on the treadmill; NYHA functional class IV heart failure; atrial fibrillation or flutter; pacemaker dependency. In addition, individuals with absolute contraindications to undergo exercise test, such as cardiac arrhythmias leading to hemodynamic instability, decompensated heart failure and acute non-cardiac conditions that could be aggravated by physical exercise, were excluded from the study.[21]

Microvolt T-wave alternans test

The individuals included in this study underwent a medical interview with a standard questionnaire, physical examination and transthoracic echocardiography. Left ventricular ejection fraction was calculated by use of the Simpson's method. Later, the patients underwent the MTWA test, at the ergometry sector of the Hospital das Clínicas of the UFMG.

For performing the MTWA test, the following items were used: Micro-V Alternans Sensors™ of Cambridge Heart high-resolution electrodes, which minimize noise and artifacts; the Cambridge Heart - HearTwave software for analysis and report; and a treadmill. Chronically used medications were maintained.

The MTWA test consists in proper preparation with skin cleansing and removal of the superficial layer of dead cells by use of abrasion, placement of electrodes in the 12 standard electrocardiographic leads and in the 3 orthogonal leads (X, Y and Z).

Data from the electrocardiographic tracing were collected at rest, during exertion on the treadmill, and during the recovery phase. During exertion, the patient should reach a heart rate between 100 and 110 beats per minute (bpm) and sustain it for 2 minutes and 30 seconds. Then, heart rate between 110 and 120 bpm should be reached and sustained for 1 minute and 30 seconds. For the test to be considered valid, target heart rate should be maintained for at least 60% of the determined time period.

The software provides an analysis with measurement of MTWA, characterizing the test as positive, negative or indeterminate. The positive test consists in T-wave alternans with amplitude ≥ 1.9 μV sustained for at least 1 minute, with an initial heart rate < 110 bpm or at rest, in an orthogonal lead or two adjacent precordial leads. The negative test does not detect any significant T-wave alternans for 1 minute with a heart rate ≥ 105 bpm, if there is no impairment to the tracing due to noise or more than 10% of ectopic beats.[22,23] The tests that do not meet any of those criteria are considered indeterminate. The indeterminate tests attributed to noise were repeated. Then the tests were grouped as negative or non-negative (positive and indeterminate), based on studies about the impact of the indeterminate test on the outcome of ventricular arrhythmias. An indeterminate test due to patient's factors, such as impossibility to keep heart rate between 105 and 110 bpm, frequent extrasystoles and MTWA not sustained for 1 minute, is associated with the occurrence of ventricular arrhythmias similarly to the way the positive test is.[24]

Sample calculation

The sample was calculated with the Power and Sample Size Calculations software.[25] Considering that Barbosa et al.[26] have found non-negative results in 81.8% of the Chagas disease patients wearing an ICD, estimating that those without malignant ventricular arrhythmia would have 30% less non-negative MWTA tests (57%), for a power of 80% and alpha error of 5%, we found 50 patients in each group.

Statistical analysis

Initially, the case and control groups were compared regarding their clinical characteristics by use of Fisher exact test. The variables tested were sex, age (older or younger than 60 years), reduced or preserved LVEF, and beta-blocker use. There was a significant disparity between the groups, and to assess the association between MTWA and the occurrence of malignant ventricular arrhythmias, multiple logistic regression models were adjusted, including the potential confounding covariables. The covariables age and LVEF were entered into the model continuously. The model calibration was assessed by use of Hosmer-Lemeshow test. The results were expressed as odds ratio (OR) with its respective confidence interval. The significance level adopted was $\alpha = 0.05$. All analyses were performed with the R statistical software, 3.3.2 version.[27]

Result

This study recruited 96 patients with CCC as follows: 45 patients (46.8%) with an ICD, constituting the case group; and 51 (53.1%) without an ICD and no known history of ventricular arrhythmia, constituting the control group. Table 1 describes the sample. Of the total sample, 48 patients (50%) were of the male sex, 42.2% of the case group and 53.1% of the control group, $p = 0.220$. Of the patients with an ICD, 57.8% were older than 60 years, while of those with no ICD, only 1.96% were older than 60 years, $p < 0.001$. Of the total sample, 37 patients had reduced LVEF (38.5%), 31 patients (68.9%) in the case group, and 6 patients (19.6%) in the control group, $p < 0.001$. In addition, the distribution of beta-blocker users was as follows: 37 patients in the case group (82.2%), and 10 patients in the control group (19.6%), $p < 0.001$.

The MTWA test had a non-negative result in 51 patients (53.1%) as follows: 36/45 patients (80%) in the case group and 15/51 patients (29.4%) in the control group, OR = 9.60 (95%CI: 3.41 – 27.93). Because of the difference in characteristics between the groups, a logistic regression model was created to correct the disparities between them, including age, sex, LVEF and beta-blocker use. Table 2 shows the results of data analysis.

The model showed that the difference is statistically significant between the case and control groups regarding the result of the MTWA test [OR = 5.17 (95%CI: 1.05 – 25.51)]. The Hosmer-Lemeshow test showed good calibration of the model ($p = 0.872$).

Discussion

In this case-control study with adjustments for other significant variables, we observed the association between the non-negative result of the MTWA test and the occurrence of ventricular tachyarrhythmias in patients with CCC, with OR = 5.17 (95%CI: 1.05 – 25.51), suggesting that MTWA may play a role in the assessment of the risk for sudden death of patients with Chagas heart disease.

The occurrence of ventricular tachyarrhythmias seems more common in Chagas disease than in heart diseases of other etiologies.[4] However, there is neither a method nor a score to properly identify patients at risk for sudden death due to those arrhythmias.

Table 1 – Characteristics of the sample.

	All (96)	Case group (45)	Control group (51)	p
Number of patients	96	45	51	-
Male sex *	48	19	29	0.220
Mean age (years)	55	62	49	-
Age > 60 years *	27	26	1	< 0.001
Mean ejection fraction (%)	48,8	39	58	-
Reduced ejection fraction (< 45%) *	37	31	6	< 0.001
Beta-blocker use *	47	37	10	< 0.001

**Number of patients*

Table 2 – Factors related to the presence of ventricular arrhythmias in the multivariate logistic regression model.

	p	OR	95%CI LL	95%CI UL
MWTA	0.044	5.17	1.05	25.51
Beta-blocker	0.139	3.73	0.65	21.40
Sex	0.118	0.27	0.05	1.39
LVEF	0.011	0.91	0.85	0.98
Age	0.005	1.13	1.04	1.22

LL: lower limit; UL: upper limit; MWTA: microvolt T-wave alternans; LVEF: left ventricular ejection fraction.

The MTWA test has been widely studied in heart diseases of several etiologies, and countless studies have evidenced the association between the non-negative result of the test and the occurrence of malignant ventricular arrhythmias.[13-17] The present study corroborates previous studies from our search group that have suggested a role for MTWA in the stratification of risk for sudden death in CCC.

Initially, Ribeiro et al. have observed that the T-wave amplitude variability measured in 11-minute high-resolution ECG tracings – a phenomenon analogous to MTWA – related to higher risk of death in patients with CCC after following 113 patients up at an outpatient clinic for 106 months [HR = 5.76 (95%CI: 1.31–25.23)].[28] In a subsequent study, Raadschilders et al. have demonstrated a higher occurrence of non-negative MTWA test among patients with CCC as compared to individuals with Chagas disease but no heart impairment and patients with negative serology for Chagas disease.[29] Barbosa et al., performing the test in patients with indication for ICD implantation and diagnosed with Chagas heart disease and heart diseases of other etiologies, have assessed the association between MTWA and the occurrence of the outcomes 'proper therapy' and 'death'. Those authors have concluded that there is a relationship between a non-negative (positive and indeterminate) MTWA test and higher occurrence of proper therapy during the follow up of patients with Chagas disease, which was not observed among patients with heart disease of other etiologies. For patients with CCC, the test had sensitivity and negative predictive value of 100%.[26]

The higher occurrence of an altered MTWA test in CCC can be explained by the inflammatory and fibrosing nature of the disease. Chagas heart disease is a chronic myocarditis, with damage to the tissue of the cardiac chambers and conduction system.[30] The destruction of cardiomyocytes and the resulting fibrosis cause architectural myocardial disarray, which can result in intercellular decoupling. This decoupling could cause a variability in cardiomyocyte membrane repolarization due to the difference in duration of their action potentials. Therefore, myocardial zones refractory to depolarization appear, tending to divide the depolarization current, the mechanism by which the variability would be linked to arrhythmogenesis, favoring conduction blocks and reentry induction.[31]

The spatial heterogeneity of ventricular repolarization is considered a predisposing condition to initiate and perpetuate ventricular arrhythmias. That heterogeneity can be measured by use of the MTWA test, which would justify finding more changes in the MTWA test of patients with CCC and previous history of malignant arrhythmias.

The MTWA test has difficulties related to the high cost of high-resolution electrodes and its own performance. Many individuals submitted to the test cannot reach and sustain the heart rate required or cannot undergo the exertion phase on the treadmill. The amount of indeterminate results due to noise or early interruption because of the patient's conditions are also a limiting factor. In addition, the result is classified qualitatively, which can be considered another limitation.

This study has limitations related partially to its observational, case-control design. The number of patients found for the case group was 45, not the 50 predicted in the sample calculation. The case group, defined by a previous history of malignant arrhythmias and indication for ICD, had a greater number of patients with reduced LVEF, of beta-blocker users and of patients with more advanced age. This is justified by the inclusion criterion in the group, because the patients with reduced LVEF would be more predisposed to develop ventricular arrhythmias. In addition, according to the 2007 ordinance,[19] patients with LVEF < 35% have an indication for priority to undergo ICD implantation. A logistic regression model was created to correct the disparity between the groups, maintaining the association between non-negative test and the occurrence of arrhythmias. The model may, however, not have corrected all differences between patients. Nevertheless, the large proportional difference of non-negativity between the case and control groups, corroborated by the magnitude of the association obtained on logistic regression, suggest that the phenomenon observed is real and significant.

Conclusion

This study assessed the presence of MTWA in patients with CCC and previous history of malignant ventricular arrhythmias and in patients with no previous history of those arrhythmias. The association between non-negativity of the MTWA test and the occurrence of malignant ventricular arrhythmias in CCC was evidenced. Further assessment in a prospective study is required to establish the causality and clinical application of the test in those patients.

Author contributions

Conception and design of the research: Almeida BCS, Carmo AAL, Ribeiro ALP; Acquisition of data: Almeida BCS, Carmo AAL, Barbosa MPT; Analysis and interpretation of the data: Almeida BCS, Carmo AAL, Barbosa MPT, Silva JLP, Ribeiro ALP; Statistical analysis: Almeida BCS, Silva JLP, Ribeiro ALP; Obtaining financing: Ribeiro ALP; Writing of the manuscript: Almeida BCS, Ribeiro ALP; Critical revision of the manuscript for intellectual content: Carmo AAL, Barbosa MPT, Silva JLP, Ribeiro ALP.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade Federal de Minas Gerais under the protocol number COEP 7918/12. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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The Use of Microvolt T-Wave Alternans in Chagas Disease

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Short Editorial regarding the article Association between Microvolt T-Wave Alternans and Malignant Ventricular Arrhythmias in Chagas Disease

Visible T-wave *alternans* (TWA) has been reported since 1909, being, thus, not a recent finding.[1] However, non-visible and far less rare microvolt TWA has gained importance because of its association with electrical disorders and the high risk for sudden cardiac death (SCD) or arrhythmic events,[2-6] being assessed in several clinical trials and population studies, such as TWA in HF,[7] ALPHA Study,[8] REFINE Study,[9] FINCAVAS,[10] the collaborative study by Ikeda et al.[11] and the MADIT-II-type research by Bloomfield et al.[12] All those studies have in common the fact that they evidence the high negative predictive value of TWA regarding SCD or arrhythmic events, with low to intermediate positive predictive value.

A specialized software is used to analyze the microvolt TWA, the beat-to-beat variability that occurs in ventricular repolarization (ST segment and T wave) and that cannot be seen by the naked eye.[13-16] The TWA allows indirect access to the increase in the dispersion to the action potentials of cardiac cells, a primordial factor in a sequence of events that will lead to reentry mechanisms and ventricular fibrillation, which will culminate with SCD. A fundamental property of its analysis is the high negative predictive power for the SCD risk that a normal TWA test has.[12]

Of the different methodologies to assess TWA, the two most used and relevant techniques in medical literature are: the spectral method (SM) and the modified moving average (MMA) method.[17]

The SM measures T-wave fluctuations by computing the point to point differences between 128 equally spaced sites in the ST-T complex, in a series of 128 consecutive aligned beats (having already ruled out ectopic beats and ECG noise).[18] There are 128 tachograms similar to those used in the analysis of heart rate variability. Then, 128 heart rate variability spectra, hence the name of the methodology, SM, are computed, and their mean is calculated. The value of TWA is then assessed at the frequency of 0.5 cycle per beat. In 1994, the adaptation of that technique to human patients was published for the first time.[19] Since then, SM is the most used method to analyze TWA, with the widest range of applications.

The MMA method repeatedly creates two patterns (models) of beats from any sequence of valid beats, one pattern associated only with the even beats, and the other associated with the odd beats. To clarify each pattern of the beats, the algorithm is as follows: the differences of amplitude between the current pattern (even or odd beats) and the next valid beat (even or odd) are measured along several equally spaced sites in the ST-T complex. Each of those differences is divided into X equal parts (where X can be 8, 16, 32 or 64), and the contribution of the current valid beat in the update of the standard beat is then limited to 1/X (named 'the update factor' or 'limiting fraction') of the differences between the model and the beat. Finally, the TWA values are made available every 15 seconds, as the difference between two representative patterns (and continuously updated) of the even beats and the odd beats.[20] That technique has been assessed in academic studies with good reproducibility.[21]

In a study of Chagas disease, published in this issue of the *Arquivos Brasileiros de Cardiologia*,[22] patients with chronic Chagasic cardiomyopathy and history of malignant ventricular arrhythmia most often had a non-negative result of microvolt TWA as compared to those with no previous arrhythmia, suggesting that TWA can play a role in the SCD risk stratification in Chagas disease. That study used the Cambridge Heart software with special electrodes (high resolution) and the SM. Its results are shown in terms of negative and non-negative (positive + indeterminate) TWA, the latter being compared to the former. That study emphasizes that Chagas cardiomyopathy has a true arrhythmogenic substrate confirmed by TWA.

Keywords

Chagas Disease; Electrocardiography; Cardiac Death, Sudden; Cardiac Risk Stratification; Cardiac Complexes, Premature.

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Atherosclerotic Plaque in Patients with Zero Calcium Score at Coronary Computed Tomography Angiography

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Abstract

Background: In view of the high mortality for cardiovascular diseases, it has become necessary to stratify the main risk factors and to choose the correct diagnostic modality. Studies have demonstrated that a zero calcium score (CS) is characteristic of a low risk for cardiovascular events. However, the prevalence of individuals with coronary atherosclerotic plaques and zero CS is conflicting in the specialized literature.

Objective: To evaluate the frequency of patients with coronary atherosclerotic plaques, their degree of obstruction and associated factors in patients with zero CS and indication for coronary computed tomography angiography (CCTA).

Methods: This is a cross-sectional, prospective study with 367 volunteers with zero CS at CCTA in four diagnostic imaging centers in the period from 2011 to 2016. A significance level of 5% and 95% confidence interval were adopted.

Results: The frequency of atherosclerotic plaque in the coronary arteries in 367 patients with zero CS was 9.3% (34 individuals). In this subgroup, mean age was 52 ± 10 years, 18 (52.9%) were women and 16 (47%) had significant coronary obstructions (> 50%), with involvement of two or more segments in 4 (25%) patients. The frequency of non-obese individuals (90.6% vs 73.9%, p = 0.037) and alcohol drinkers (55.9% vs 34.8%, p = 0.015) was significantly higher in patients with atherosclerotic plaques, with an odds ratio of 3.4 for each of this variable.

Conclusions: The frequency of atherosclerotic plaque with zero CS was relatively high, indicating that the absence of calcification does not exclude the presence of plaques, many of which obstructive, especially in non-obese subjects and alcohol drinkers. (Arq Bras Cardiol. 2018; 110(5):420-427)

Keywords: Cardiovascular Diseases/mortality; Plaque, Atherosclerotic; Coronary Artery Disease/diagnosis; Calcium Signaling; Coronary, Angiotomography; Risk Factors.

Introduction

Coronary artery disease (CAD) are the leading cause of death in the world, including in Brazil. Many methods for CAD diagnosis, risk stratification of patients and indication of revascularization are currently available.[1]

One of the greatest challenges of routine cardiology practice is to determine the best method to detect subclinical CAD. Coronary computed tomography angiography (CCTA) is a predominantly anatomical test with excellent diagnostic accuracy in detecting obstructive and nonobstructive lesions as compared with coronary angiography, which is considered the gold standard method for this purpose. Also, CCTA may provide relevant information regarding atheroma composition according to radiological density.[2,3]

The role of coronary calcification, identified by calcium score (CS), used for classification of patients into a higher risk for cardiovascular events, is well known. Although individuals with a zero CS may also have atherosclerotic plaques,[4,5] its presence has not been associated with increased risk for future cardiovascular events.[4]

Nevertheless, despite these results reported in international studies, we have not found Brazilian studies published on this specific subject. In fact, studies' results may not be replicated in different sociodemographic or anthropometric contexts, or even in different healthcare conditions. Reproducibility of a study is a *sine qua non* for an extensive validation of its results.

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Therefore, the main aim of this study is to evaluate the frequency of coronary atherosclerotic plaque, its degree of obstruction and associated factors in patients with zero CS and clinical indication for CCTA.

Methods

Subjects

This was a cross-sectional, analytical, prospective study carried out from April 2011 to November 2016. Subjects were consecutively and not randomly selected, and subjected to CCTA by referral from their assistant physicians in four diagnostic imaging centers, two public centers: Instituto Dante Pazzanese de Cardiologia de São Paulo-SP e Hospital Universitário do Campus da Saúde Dr. João Cardoso Nascimento da Universidade Federal de Sergipe and two private centers: Hospital Primavera e Clínica de Medicina Nuclear e Diabetes-CLIMEDI.

Data on cardiovascular risk factors were collected from each participant. Chest pain was classified according to the Diamond and Forrester method, and most patients were classified as at intermediate risk for CAD.

Patients with no calcium in the coronary arteries (zero CS) were included. Patients who had undergone percutaneous or surgical myocardial revascularization, patients with history of acute coronary syndrome or cardiomyopathy of ischemic cause, and those who declined to participate were excluded.

The tests performed at private institutions were free of charge for both patients and investigators.

The study was approved by the research ethics committee (CAAE identification number 0289.0.107.000-11).

CS and CCTA of coronary arteries

CCTA of coronary arteries were performed using a 64-slice (or greater) scanner of the following models and manufacturers: *Aquilion64*™ - Toshiba™ Medical Systems Corporation, Otawara, Japan and Discovery STE VCT - General Electric Company, Connecticut, USA.

Non-contrast computed tomography for CS analysis was carried out using a longitudinal scan coverage from the level of the tracheal bifurcation to the superior border of cardiac silhouette, including the whole diaphragm for evaluation of the whole cardiac area. For CS examination, a field of view (FOV) of 200 mm was used, slice thickness 2.5-3 mm and interval 1.25-1.5 mm, 2 x 32 x 0,6 mm collimaton, rotation time 350 msec, tube current up to 600 mAs.

The study was conducted in two phases: in the first phase, CS was determined by the Agatston score;[6] calcification was defined as the presence of a lesion with an area greater than 1 mm^2, and peak intensity equal to or greater than 130 Hounsfield Units (HU), which was automatically identified and marked with color by the software. The presence of coronary plaques and extension of stenosis was evaluated in patients with zero CS.

In the second phase, CCTA was performed using the CS parameters for FOV construction, voltage 120 kv, and 400 miliamperes. Up to 1.5mL/kg iopamidol was administered intravenously to patients still positioned on the table. Iopamidol is a nonionic, iodinated contrast, administered at concentrations of 350-370 mg/mL and rate of 4.5-5.5 mL/s (Ultravist® 370, Bayer HealthCare and Pharmaceuticals, Berlin, Germany; HenetiX® 350, Guerbet, Paris, France).

An oral betablocker was administered within 24 hours before the test, or intravenously on the day of the test in patients with sinus rhythm and heart rate (HR) > 70 bpm. The system uses HR values monitored during the exam to establish the parameters for imaging acquisition, such as the helical pitch (relationship between table distance traveled in one 360° X-ray tube rotation, slice thickness and the number of detector rows), speed of gantry rotation, and exposure time, to achieve the best possible temporal resolution.

Images were sent to the workstation for analysis of coronary arteries by three experienced observers. The presence of atherosclerotic plaque was examined in vessels with a luminal diameter larger than 2 mm, divided into 15 segments.[7] Extension of stenosis was estimated by calculating the area of the narrowest part of the lumen in relation to the area of the lumen immediately distal to the same segment. Plaques detected by the CCTA were classified into nonobstructive and obstructive lesions, with a reduction ≥ 50% of the lumen in the latter.

Data analysis

Quantitative variables were described as mean and standard deviation. Kolmogorov-Smirnov test was used to test normality of the sample. The Student's t-test was used for independent groups, according to data normality. Absolute and relative frequencies were used for categorical variables. For between-group comparisons of these variables, the chi-square test of the Fisher's exact test was used as appropriate.

Differences were considered statistically significant when probabilities were lower than 5% ($p \leq 0.05$) and power of 0.80.

For analysis of independent predictors for the presence of plaque, a manual backwards selection (Backward:Wald method) for logistic regression was used. A $p \leq 0.25$ was considered for an initial selection and the variable was maintained in the model when $p < 0.05$. The outcome variable presence of plaque was adjusted for age, sex, smoking, diabetes mellitus, systemic arterial hypertension, dyslipidemia, family history, obesity and alcohol consumption.

Statistical analyses of results were performed using the SPSS software for Windows version 20.0 (IBM® Corporation, Somers, USA).

Results

Clinical characteristics of the sample

In the study period, 1,639 patients were subjected to CCTA at the four participating centers; 619 of them had zero CS. However, 252 were excluded due to lack of clinical data or refusal to participate in the study. Patients were referred to CCTA for atypical chest pain (40.4%), typical chest pain (24.9%), risk factors for CAD, family history of early CAD (51.4%) and positive or inconclusive tests for ischemia (44.4%).

Of 367 patients, 211 (57.7%) patients were hypertensive, 180 (49.3%) dyslipidemic and 55 (15.0%) diabetic. Mean age was 53.7 (±10.5) years and 63.5% were women. Clinical data of patients with zero CS according to the presence or absence of atherosclerotic plaque at CCTA are described in Table 1.

Frequency of atherosclerotic plaque in coronary arteries was 9.3% (34/367); 95%CI 6.3 – 12.3. In this group, mean age was 52 ± 10 years and 18 (52.9%) were women (Table 2). A detailed analysis revealed the presence of obstructive lesions (larger than 50% of vessel lumen) in 47% (16/34) of cases, distributed as follows: a) in one segment – 12 patients; b) in two segments – 3 patients; and c) in more than two segments – 1 patient (Figure 1). In the subgroup of patients with nonobstructive lesions (18/34), 15 and 3 patients, respectively, had one and three coronary segments affected (Table 3).

The most affected artery was the anterior descending, 16 (35.56%) in its proximal segment, 10 (22.22%) in the middle segment, and 2 (4.44%) in the distal one.

It is worth mentioning that analysis of atheroma in the CCTA with contrast phase revealed that 3/34 (8.8%) patients had plaques with some degree of calcification that were not detected by the CS (Figure 2).

Clinical features of patients with zero CS, classified by the presence or absence of atherosclerotic plaques in coronary arteries

In patients with coronary artery plaque, most patients were obese (90.6% *vs.* 73.9%; BMI: 25.9 ± 3.3 k/m^2 *vs.* 27.5 ± 4.4 k/m^2; p = 0.046) and alcohol drinkers (55.9% *vs.* 34.8%) (Table 2). The other variables were not different between the groups.

Non-adjusted odds ratio of the factors associated with the presence of atherosclerotic plaque in patients with zero CS were 2.3 (95%CI = 1.1 – 4.8; p = 0.018) for alcohol consumption and 3.4 (95%CI = 1.0 – 11.5; p = 0.049) for absence of obesity (Table 4). Finally, analysis of contingency table for adjusted odds ratio confirmed higher OR values for alcohol drinkers (OR = 3.4; 95%CI = 1.1 – 5.19; p = 0.018) and non-obese patients (OR = 3.4; 95%CI = 1.0 – 11.7; p = 0.047) (Table 5).

Discussion

The main finding of the present study was the considerable presence (9.3%) of obstructive (≥ 50%) coronary atherosclerotic plaques in patients with zero CS.

Clinical features found to be associated with the presence of plaques were alcohol consumption and absence of obesity, in contrast to other risk factors usually associated with CAD, such as: diabetes mellitus, systemic arterial hypertension and dyslipidemia.[8]

Data on the literature have shown variable prevalence of atherosclerotic plaque in individuals with zero CS. In a study conducted in Isfahan (Iran), 385 patients with zero CS were studied, and 16 of them (4.1%) had atherosclerotic plaque at CCTA.[5] In another study involving symptomatic and asymptomatic patients showed that only symptomatic subjects with zero CS had atherosclerotic plaque (8.4%).[9] According to the CONFIRM study, in patients with zero CS, 13% had nonobstructive atherosclerotic lesions, and 3.5% had obstructive lesion greater than 50%.[4] A multicentric cohort study in which Brazil participates (a CORE64 sub-study) confirmed that a zero CS does not exclude the need for revascularization. With a sample of 291 patients (72 with zero CS), 19% had stenosis ≥50%, and 13% of them required revascularization.[10]

Table 1 – Clinical characteristics of patients with zero calcium score in diagnostic imaging centers in Sao Paulo and Aracaju, Brazil, from 2001 to 2016

Variable	n†	%
Mean age (years) *	367	53.7 ± 10.5
Female sex	233/367	63.5
Systemic arterial hypertension	211/367	57.5
Dyslipidemia	180/367	49.3
Diabetes mellitus	55/367	15.0
Body mass index (kg/m²)	316	27.3 ± 4.4
Obesity	77/316	24.4
Family history of CAD	187/364	51.4
Alcohol consumption	135/367	36.8
Smoking	51/366	13.9
Atypical chest pain †	138/342	40.4
Typical chest pain †	85/341	24.9

CAD: coronary artery disease; (*): Values in mean ± standard deviation; other values expressed as simple frequency (%); (†): "n" different from total population due to missing data in the records

Table 2 – Distribution of clinical characteristics of patients with zero calcium score with and without atherosclerotic plaque in four diagnostic imaging centers in Sao Paulo and Aracaju, Brazil, from 2001 to 2016

Variable	n†	With plaque n = 34	Without plaque n = 333	p
Age* (years)	367	52 ± 10.7	53.9 ± 10.5	0.31
Weight (Kg)	367	71.6 ± 12.9	73.7 ± 15.2	0.42
Body mass index (Kg/m^2)	316	25.9 ± 3.3	27.5 ± 4.4	0.046
Female	233/367	18 (52.9)	215 (64.6)	0.180
Smoking	51/366	8 (24.2)	43 (12.9)	0.073
Non-obese	55/316	29 (90.6)	210 (73.9)	0.037
Diabetes mellitus	55/367	6 (17.6)	49 (14.7)	0.648
Dyslipidemia	180/365	16 (47.1)	164 (49.5)	0.782
Systemic arterial hypertension	211/367	20 (58.8)	191 (57.4)	0.712
Alcohol consumption	135/367	19 (55.9)	116 (34.8)	0.015
Family history	187/364	18 (52.9)	169 (51.2)	0.848

(*): Values as mean ± standard deviation; other values expressed as simple frequency (%); p-value obtained by the chi-square test for associations; (†): "n" different from total population due to missing data in the records.

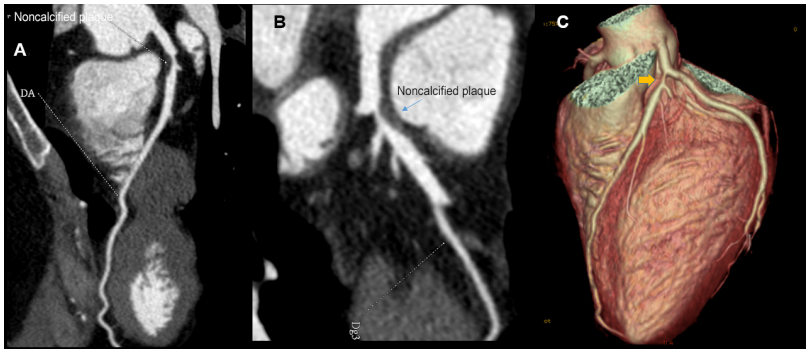

Figure 1 – *Noncalcified plaque with zero calcium score. Thirty-eight-year old woman; A and B) multiplanar reconstructions showing considerable lumen reduction in anterior descending artery (DA); C) Tridimensional reconstruction showing impairment in DA (yellow arrow).*

Also, studies involving patients with chest pain in the emergency department have shown frequencies of atherosclerotic plaques with zero CE of up to 39%,[11-13] although this is a different population from those attending outpatient services. It is of note, however, that our sample population was composed of patients referred to CCTA from their assistant physicians. As reported in international studies, we also found that the presence of atherosclerotic plaque cannot be ruled out in patients with zero CS.

In our study, only the variables alcohol consumption and absence of obesity were associated with higher risk of atherosclerotic plaque, in contrast to classical risk factors for CAD (diabetes mellitus, systemic arterial hypertension and dyslipidemia). Interestingly, higher BMI was associated with absence of atherosclerotic lesion. Previous studies have suggested obesity as a protective factor for CAD, the so-called obesity paradox.[14] Nevertheless, such paradox is not concerned to abdominal obesity, which has been associated with CAD and considered more pathological than subcutaneous fat accumulation.[14-16] In our study, we did not measure abdominal circumference, which may have influenced the consistency of results. Besides, obese patients included in many studies that indicated obesity as a protective factor were younger, which may be a source of bias.[17]

Alcohol consumption has also yielded diverging results. While some studies have indicated alcohol consumption as a risk factor for CAD, others have pointed out its beneficial effects, such as studies performed with wine and its component resveratrol.[18-20] Resveratrol is known for its antioxidant and anti-inflammatory effects, in addition to promote the synthesis of HDL in the liver and inhibit LDL production, thereby preventing LDL oxidation and reducing the risk of cardiovascular diseases.[21] In this regard, further studies that specify the type of beverage consumed and not only whether the subjects consumed or not alcohol are needed.

Table 3 – Distribution of atherosclerotic lesions at coronary computed tomography angiography in patients with zero calcium score

Variable	One vessel affected	Two vessels affected	Two or more vessels affected	Total n = 34
Obstructive lesion > 50%	12 (75%)	3 (18.7%)	1 (6.3%)	16 (47.0%)
Nonobstructive lesion	15 (83.3%)	3 (16.6%)	0	18 (53%)

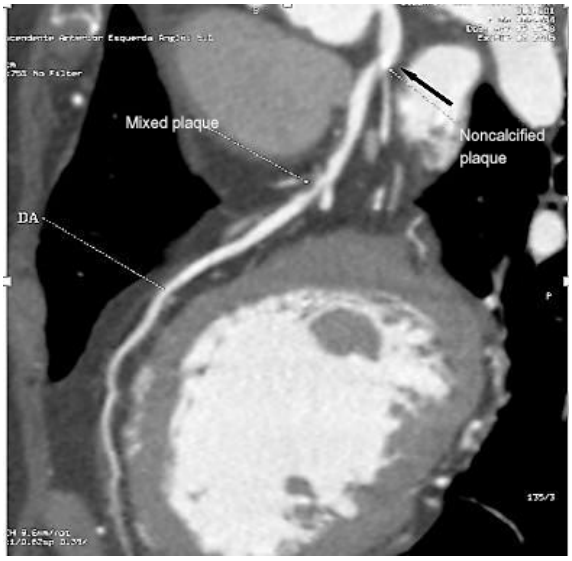

Figure 2 – *Presence of calcification in zero calcium score. Female patient, 67 years old; Black arrow - Partially calcified plate in anterior descending ostium (AD), not detected by calcium score, followed by noncalcified plaques in proximal and middle thirds (white arrows)*

Limitations

Some inherent limitations deserve to be mentioned – first, as previously described, patients were referred to CCTA with CS from their assistant physicians, and the possibility of a selection bias cannot be excluded; second, coronary risk stratification of patients was not performed before their inclusion and data on risk factors were obtained by questionnaires; third, sample was collected in four different centers and, although the tests were performed following similar protocols, some characteristics are particular of each service which may have cause a bias in the analysis; fourth, since we studied patients with clinical indication for CCTA, our sample differed from asymptomatic patients without positive ischemic test, who would be referred to CS alone, and in whom coronary calcification would predict cardiovascular events.

Conclusions

The frequency of atherosclerotic plaque in patients with zero CS was relatively high, indicating that in patients with clinical indication for CCTA, the absence of coronary calcification does not exclude atherosclerotic plaque or obstructive lesion, especially in obese and alcohol drinkers.

Author contributions

Conception and design of the research: Gabriel FS, Gonçalves LFG, Pinto IMF, Oliveira JLM; Acquisition of data: Gabriel FS, Gonçalves LFG, Santana SMM, Matos CJO, Conceição FMS, Souto MJS; Analysis and interpretation of the data: Gabriel FS, Gonçalves LFG, Melo EV, Sousa ACS, Oliveira JLM; Statistical analysis: Gabriel FS, Melo EV; Writing of the manuscript: Gabriel FS, Gonçalves LFG, Sousa ACS, Pinto IMF, Oliveira JLM; Critical revision of the manuscript for intellectual content: Gabriel FS, Gonçalves LFG, Melo EV, Sousa ACS, Pinto IMF, Santana SMM, Matos CJO, Conceição FMS, Oliveira JLM, Souto MJS.

Potential Conflict of Interest

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

Table 4 – Factors associated with the presence of plaque† (diagnostic imaging centers in Sao Paulo and Aracaju, Brazil, from 2001 to 2016)

Variable	Non-adjusted odds ratio	95%CI	p
Age	0.976	0.940 - 1.01	0.216
Sex			
Male	1.62	0.796- 3.29	0.183
Smoking			
Yes	2.15	0.919 - 5.09	0.079
Obesity			
No*	3.40	1.01 – 11.51	0.049
Diabetes mellitus			
Yes	1.24	0.489 – 3.15	0.649
Dyslipidemia			
Yes	1.10	0.545 – 2.24	0.782
Systemic arterial hypertension			
Yes	1.06	0.519 – 2.17	0.869
Alcohol consumption			
Yes	2.37	1.16 - 4.83	0.018
Family history			
Yes	1.07	0.528 -2.17	0.366

Outcome variable: presence of plaque; other variables described in the table are associated factors; (*): presence of obesity was used as reference for the variable obesity, CI: confidence interval; (†): adjusted for age, sex, smoking, diabetes mellitus, systemic arterial hypertension, dyslipidemia, family history, obesity and alcohol consumption.

Table 5 – Factors associated with the presence of plaque† after model adjustment in diagnostic imaging centers in Sao Paulo and Aracaju, Brazil, from 2001 to 2016

Variable	Adjusted odds ratio	95%CI	p
Alcohol consumption	3.46	1.16 - 5.19	0.018
Non-obese*	3.45	1.01 – 11.7	0.047

Outcome variable: presence of plaque; other variables described in the table are associated factors; (*): presence of obesity was used as reference for the variable non-obese, CI: confidence interval; (†): adjusted for age, sex, smoking, diabetes mellitus, systemic arterial hypertension, dyslipidemia, family history, obesity and alcohol consumption.

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade Federal de Sergipe under the protocol number CAAE 0289.0.107.000-11. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Not Everything that Shines is Calcium

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Short Editorial regarding the article Atherosclerotic Plaque in Patients with Zero Calcium Score at Coronary Computed Tomography Angiography

Coronary calcification is involved in the pathophysiological process of atherosclerosis, particularly at later stages of the disease, as part of its healing process.[1] In fact, calcification is not required for plaque development or progression, or luminal obstruction, or even for the development of cardiovascular events – these processes, in addition to plaque instability is commonly seen.[2] Our group showed, in a randomized clinical trial on symptomatic patients, that 20% of vessels with complete obstructions in invasive angiography had no calcification according to calcium scoree,[3] corroborating histopathological studies that demonstrated the absence of calcification in a considerable number of the coronary plaques evaluated.[4] Understanding or the pathophysiology of coronary disease is essential to contextualize calcium score in population studies.

These studies, however, have shown some controversial results on the rates of cardiovascular events and obstructive lesions. The reason for this apparent divergence of results is the study population. Asymptomatic patients with zero calcium score are different from symptomatic ones without calcification, who in turn, are different from patients with history of early coronary disease, diabetics or smokers with zero calcium score.

We may cite the contrasting example of two hypothetical populations – one of young adults (30-35 years old), with symptoms of precordial pain, and another one composed of elderly smokers (70-75 years old), with no cardiovascular symptom. It will be no surprise to find an overwhelmingly higher frequency of significant coronary obstruction in the group of asymptomatic elderly subjects with zero calcium score than in the first group with some coronary calcification. Also, it will be no wonder to find a higher rate of cardiovascular events in the group of 70-75-year-old subjects than in the group of 30-35-year old subjects. Such paradox is obviously grounded in the difference of the study populations – the prevalence of atherosclerosis is so much higher in the elderly than in the young group that even comparisons between subgroups with and without calcification and with and without symptoms will always reveal a higher prevalence of cardiovascular diseases and events in the group of elderly smokers than in the other one.

The attempt of using the zero calcium score as a gatekeeper for coronary computed tomography angiography (or other tests) in symptomatic patients should be considered with caution, be it in an emergency room or in an outpatient clinic. Subtle differences in population profiles, including ethnical differences, may result in considerable differences in the diagnostic and prognostic performance of a zero calcium score.[5,6] Since calcification is only an indirect marker of coronary obstruction, differing from a direct visualization of the obstructive plaque by coronary computed tomography angiography, characteristics of the population studied become critical. An analogy can be made between the low prevalence of obstructive coronary disease in patients with zero calcium score and young women; both are mere population filters. No one would today underestimate symptoms in young women only because of a low pre-test probability.

In the current issue of the ABC, Gabriel et al.[7] elegantly show a high prevalence of coronary disease, detected by computed tomography coronary angiography, in patients with zero calcium score. Interestingly, alcohol consumption and obesity, but not age showed an association with the presence of plaques in the absence of calcification. This has important implications on the development of prevention strategies for cardiovascular diseases.

Finally, the use of calcium score for detection of coronary calcification is an important tool for stratification of cardiovascular risk in asymptomatic individuals, especially because the score is an easy and low-cost instrument. However, in the context of atherosclerosis, disease status goes beyond calcification and, definitely, not everything that shines is calcium.

Keywords

Atherosclerosis / physiopathology; Vascular Calcification; Coronary Artery Disease; Heredity; Diabetes Mellitus.

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Prevalence of Metabolic Syndrome and Framingham Risk Score in Apparently Healthy Vegetarian and Omnivorous Men

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Abstract

Background: **Recent studies have shown a lower prevalence of metabolic syndrome (MSyn) in vegetarians (VEG) despite the inconclusive evidence from others.**

Objective: **To verify the association between diet and other lifestyle characteristics and the prevalence of MSyn, cardiovascular risk factors (CRF), and Framingham Risk Score (FRS) in apparently healthy VEG and omnivorous (OMN) men.**

Methods: **In this cross-sectional study, 88 apparently healthy men ≥ 35 years, 44 VEG and 44 OMN, were assessed for anthropometric data, blood pressure, blood lipids, glucose, C-reactive protein (CRP) and FRS. To test the association between lifestyle and MSyn, Student t test, chi-square test, and multiple logistic regression model were used. A significance level of 5% was considered in all statistical analyses.**

Results: **Several CRF were significantly lower in VEG than in OMN: body mass index, systolic blood pressure, diastolic blood pressure, fasting serum total cholesterol, LDL-cholesterol, apolipoprotein b, glucose, and glycated hemoglobin (all $p < 0.05$). The FRS mean was lower in VEG than in OMN (2.98 ± 3.7 vs 4.82 ± 4.8, $p = 0.029$). The percentage of individuals with MSyn was higher among OMN than among VEG (52.3 vs.15.9%) ($p < 0.001$). The OMN diet was associated with MSyn (OR: 6.28 95%CI 2.11-18.71) and alterations in most MSyn components in the multiple regression model independently of caloric intake, age and physical activity.**

Conclusion: **The VEG diet was associated with lower CRF, FRS and percentage of individuals with MSyn. (Arq Bras Cardiol. 2018; 110(5):430-437)**

Keywords: **Metabolic Syndrome; Coronary Artery Disease; Vegetarians; Men; Risk Factors; Diet, Vegetarian**

Introduction

The number of individuals consuming a vegetarian (VEG) or plant-based diet is increasing, and there is evidence that this habit is associated with a lower prevalence of risk factors for cardiovascular diseases (CVD).[1-5] A few studies in the literature have evaluated the association between the VEG diet and the lower risk of coronary heart disease (CHD),[5,6] according to the Framingham Risk Score (FRS), an algorithm for assessing risk for CHD in the short term (< 10 years).[7] Furthermore, recent studies have shown a lower prevalence of metabolic syndrome (MSyn) in VEG[8,9] despite the inconclusive evidence from others.[10-14] The only study found in the scientific literature that evaluated the relationship in a Latin American population has demonstrated no association.[5] The importance of MSyn rests in the fact that approximately one in four adults in the United States has MSyn, which is considered a risk factor for atherosclerotic cardiovascular disease.[15] In addition, 20-25% of adults worldwide have MSyn, which doubles the risk for having a heart attack and triples the risk for stroke,[16-18] in addition to increasing the risk of death in the general population.[19] The aim of this observational study was to investigate the association between the type of diet and the prevalence of MSyn assessed in apparently healthy VEG and omnivorous (OMN) men. Our hypothesis is that VEG men have better indicators of these conditions compared to OMN men.

Methods

In the recently published cross-sectional *Carotid Atherosclerosis and Arterial Stiffness in Vegetarians and Omnivorous Subjects* (CARVOS) study,[20] 745 adult volunteers initially were recruited in São Paulo through social activities and the Internet. The participants filled out questionnaires regarding past medical history, family history, dietary preferences, and personal data. Exclusion criteria

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were: 1) being female 2) history of diabetes; 3) history of dyslipidemia; 4) history of CVD or cerebrovascular diseases; 5) history of hypertension or intake of antihypertensive medication; and 6) smoking. All individuals who declared themselves to be "smokers" or "occasional smokers" at the interview or had quit smoking in the last month prior to the interview were considered smokers.

Although the exclusion criteria of the research project were related to factors that are MSyn components, they were the reference of the individual on previous diagnosis, and it was verified that several individuals presented MSyn, enabling the development of the present study, which aims to compare the percentage of individuals with MSyn in the two groups according to the type of diet.

Healthy participants ≥ 35 years were divided into two groups – VEG and OMN – according to their dietary patterns. Vegetarian men were defined as exclusively consuming a vegetarian diet void of meat, fish, and poultry for at least four years; these men could be lacto-ovo-vegetarians (consuming eggs, milk, and dairy products), lacto-vegetarians (consuming milk and dairy products) or vegans (consuming no eggs or milk or dairy products). Matched OMN men were defined as consuming any type of meat at least four or more servings per week.

From June 2013 to January 2014, after applying inclusion and exclusion criteria, 88 apparently healthy men were enrolled in the study (44 VEG and 44 OMN).

All 88 subjects were screened for health status with questionnaires regarding educational level, personal data, past medical history, smoking status and habitual alcohol consumption (yes or no).

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured twice in the right arm after a 10-minute rest in a supine position using a calibrated and averaged digital sphygmomanometer.

Subjects were interviewed, and the average of two 24-hour dietary recalls (one on weekdays and one on weekends) was used to estimate daily consumption of different nutrients. A database for Brazilian food composition was used to calculate the daily energy and nutrient intake.[21]

For measuring weight, we used a 150-kg platform scale (Filizola®) with 100-gram divisions. The patient was positioned in the center of the scale, standing barefoot, wearing as little clothing and as few accessories as possible. To measure height, a portable stadiometer was used, positioned in an appropriate place, with the barefoot volunteer with feet together, standing erect, with the back of the head, shoulders, buttocks, calves and heels touching the wall, and the head in the Frankfurt horizontal plane (imaginary line from the external auditory canal to the lower eye socket).[22]

Body mass index (BMI) was calculated by dividing body weight (kg) by the square of height (m).

To measure waist circumference (WC), the individual remained upright with arms relaxed along the body, with the region for measurement unclothed. For WC, the measurement was made with a tape measure at the midpoint between the last rib and the iliac crest, with the abdomen relaxed, at the end of expiration.[23]

All measures were performed in triplicate, and the mean value was used for analysis.

After fasting for 10–12 hours overnight, participants had blood samples drawn from the antecubital vein. Serum lipids, including triglycerides (TG), total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-c), were assayed by using enzymatic methods with an automatic multichannel chemical analyzer (Siemens Healthcare, Newark, USA) in the central laboratory of the InCor. Low-density lipoprotein cholesterol (LDL-c) was calculated using the Friedewald formula.[24]

Glycosylated hemoglobin (HbA1c) was determined using the immunoturbidimetric method certified by the NGSP-National Glycohemoglobin Standardization Program, using the Flex kit (Siemens Healthcare, Newark, USA). For apolipoprotein b (Apo b) and fasting glucose measurements, blood samples were centrifuged at 3000 rpm for 15 minutes within 60 minutes of collection and stored at −70°C until analysis. Fasting serum glucose (FSG) was determined by the glucose oxidase method using a Dimension RXL (Siemens Healthcare, Newark, NJ, USA) through standard laboratory techniques. Quality control assessment was performed daily for all determinations.

Subjects reported activity levels using the International Physical Activity Questionnaire-Short Form (IPAQ),[25] which measures leisure time, domestic, work-related, and transport-related physical activities. Four domains were measured: sitting, walking, moderate-intensity activity, and vigorous-intensity activity during the previous seven days.

For analysis, we considered the following categorization: physically active (≥ 20 minutes/vigorous activity sessions ≥ 3 days/week; and/or ≥ 30 minutes/moderate activity sessions or hiking ≥ 5 days/week; and/or ≥ 150 minutes/week of any added activities - vigorous or moderate or walking), and irregularly active (<150 minutes/week of any added activities - vigorous or moderate or walking).[26]

Metabolic syndrome (MSyn) was defined according to the criteria of the International Diabetes Federation (IDF), that considers that an individual with MSyn must have central obesity (defined as WC with ethnicity specific values) plus any two of the following four factors: TG ≥ 150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality, HDL-c < 40 mg/dL (1.03 mmol/L) in males or specific treatment for this lipid abnormality, SBP ≥ 130 mm Hg or DBP ≥ 85 mm Hg or treatment of previously diagnosed hypertension, FSG ≥ 100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes.[16,17]

For South and Central Americans, the IDF recommends the use of South Asian WC values until more specific data are available. Thus, this study considered the WC value to be ≥ 90 cm.[18] The BMI was categorized according to the values suggested by the World Health Organization.[27]

The Framingham Heart Study provides an algorithm for assessing risk for CHD in the short term (≤ 10 years). The FRS classifies the individual CHD risk based on assigned points for

age, TC, HDL-c, smoking status, SBP, and the use of medication to treat high blood pressure. The results of the FRS range are from 1% to 30% of CHD risk in 10 years.[7]

Statistical analysis

The continuous variables were tested by the Kolmogorov-Smirnov test and presented Gaussian distribution, being demonstrated in means ± standard deviation (SD). Unpaired Student's *t* test was used for testing differences for numerical variables. The chi-square test was used to compare categorical variables between groups. Level of significance was set $p < 0.05$.

To test the association between the type of diet (OMN or VEG) and MSyn and its components, multiple logistic regression was used. The magnitude of effect was measured by using the OR (odds ratio) and respective 95% confidence interval (95%CI). Univariate analysis and variables with $p < 0.20$ were included in the multiple regression, and adjusted for caloric intake, age, physical activity level, and alcohol consumption. All analyses were performed using Stata 10.0.

Results

No difference was found in age between the VEG and OMN groups. Vegetarians had significantly lower values for BMI, WC, SBP, DBP, TC, LDL-c, Apo b, TG, TC/HDL-c ratio, FSG, and HbA1c. Most of the individuals had less than 10 points on the FRS, only three VEG and eight OMN had FRS 10 to 20 points. No statistical difference was found when this distribution was compared by categories, but the CHD risk evaluated by FRS was higher in OMN based on a comparison of the mean score between the two groups (Table 1).

Although there was no significant difference in caloric intake between the two groups, VEG consumed significantly more carbohydrates (63.2 vs. 51.9% of energy, $p > 0.001$), dietary fiber (28.2 vs 17.9 g, $p < 0.001$), and polyunsaturated fat (4.0 vs. 2.7% of energy, $p = 0.004$) than OMN did. Moreover, OMN ingested significantly greater amounts of protein (19.5 vs. 17.1% of energy, $p = 0.04$), total fat (29.1 vs. 24.8% of energy, $p = 0.006$), saturated fat (6.9 vs. 4.4% of energy, $p < 0.001$), and monounsaturated fat (6.8 vs. 4.5% of energy, $p < 0.001$) (Table 2).

Most individuals had ≥ 8 years of schooling (83.2%), but a higher percentage of OMN (30.8%) had less than 8 years of schooling compared to VEG (4.6%) ($p = 0.001$). Considering physical activity assessed by IPAQ, a significantly greater number of VEG was classified as physically active ($n = 36$, 81.8%) compared to OMN ($n = 25$, 56.8%; $p = 0.011$). Regarding alcohol consumption, 43.2% of VEG ($n = 19$) and 59.1% ($n = 26$) of OMN reported drinking alcohol, but without a statistical difference ($p = 0.14$).

Considering the MSyn proposed by the IDF, there were more OMN (52.3%) than VEG (15.9%) with MSyn ($p < 0.001$). OMN had a significantly higher occurrence of abnormal values for most of the MSyn components, WC, TG, FSG, SBP, and DBP, as shown in Table 3.

Being OMN increased the chance of having MSyn (OR: 5.79, 95%CI 2.13-15.76) and having altered different MSyn components: WC (OR: 6.80, 95%CI 2.62-17.70), SBP (OR: 2.83, 95% CI 1.13-7.12), DBP (OR: 4.38, 95%CI 1.53-12.53), TG (OR: 2.5, 95%CI 1.01-6.18), and FSG (OR: 4.67, 95%CI 1.89-11.52). Despite the higher risk of OMN developing CHD according to FSG, this difference was not shown in the logistic regression model (OR: 3.04, 95%CI 0.75-12.32).

Table 1 – Anthropometric, clinical and biochemical characteristics of apparently healthy vegetarian and omnivorous men

	Vegetarian (n = 44)	Omnivorous (n = 44)	p
Age	45.5 ± 7.8	46.8 ± 9.6	0.23
BMI (kg/m²)	23.1 ± 2.9	27.2 ± 4.8	< 0.001
WC (cm)	84.9 ± 7.71	95.7 ± 13.8	< 0.001
SBP (mm Hg)	119.5 ± 10.4	129.2 ± 15.1	< 0.001
DBP (mm Hg)	75.2 ± 8.6	83.9 ± 10.4	< 0.001
TC (mg/dL)	180.1 ± 40.5	202.7 ± 35.3	0.003
LDL-c (mg/dL)	110 ± 33.2	128.5 ± 32.4	0.005
Apo b (mg/L)	0.88 ± 0.28	1.01 ± 0.26	0.009
TG (mg/dL)	112.2 ± 72.2	143.9 ± 64	0.016
HDL-c (mg/dL)	47.6 ± 9.3	45.5 ± 11.6	0.17
TC/HDL-c ratio	4.0 ± 1.3	4.7 ± 1.3	0.005
FSG (mg/dL)	94.8 ± 7.2	102.9 ± 13.1	< 0.001
HbA1c (%)	5.3 ± 0.3	5.5 ± 0.5	0.004
FRS	2.98 ± 3.70	4.82 ± 5.17	0.029

Data are means ± SD. Significant values for p < 0.05. Unpaired Student's t-test. BMI: body mass index; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; LDL-c: low-density lipoprotein cholesterol; Apo b: apolipoprotein b; TG: triglycerides; HDL-c: high-density lipoprotein cholesterol; FSG: fasting serum glucose; HbA1c: glycosylated hemoglobin; FRS: Framingham Risk Score.

Table 2 – Pattern of energy and nutrient ingestion of apparently healthy vegetarian and omnivorous men.

Energy and nutrient ingestion	Vegetarian (n = 44)	Omnivorous (n = 44)	p
Energy (kcal)	2,177 ± 559	2,348 ± 736	0.11
Protein (% of energy)	17.1 ± 7.8	19.5 ± 4.5	0.04
Carbohydrates (% of energy)	63.2 ± 11.6	51.9 ± 9.7	< 0.001
Total Fat (% of energy)	24.8 ± 8.3	29.1 ± 7.2	0.006
Saturated fat (% of energy)	4.4 ± 3.2	6.9 ± 2.9	< 0.001
Mono-unsaturated fat (% of energy)	4.5 ± 2.4	6.8 ± 2.8	< 0.001
Polyunsaturated fat (% of energy)	4.0 ± 2.7	2.7 ± 1.6	0.004
Cholesterol (mg)	69.3 ± 224	258.1 ± 169	< 0.001
Fiber (g)	28.2 ± 15.9	17.9 ± 13.6	< 0.001

Data are means ± SD. Significant values for p < 0.05. Unpaired Student's t-test.

Table 3 – Distribution of individuals with metabolic syndrome and inadequacy of its components in apparently healthy vegetarian and omnivorous men

	Vegetarian (n = 44) % (n)	Omnivorous (n = 44) % (n)	p
MSyn	15.9 (7)	52.3 (23)	< 0.001
WC (≥ 90 cm)	20.5 (9)	63.6 (28)	< 0.001
SBP (≥ 130 mm Hg)	22.7 (10)	45.5 (20)	0.025
DBP (≥ 85 mm Hg)	13.6 (6)	40.9 (18)	0.004
TG (≥ 150 mg/dL)	25.0 (11)	45.5 (20)	0.045
HDL-c (< 40 mg/dL)	22.7 (10)	36.4 (16)	0.16
FSG (≥ 100 mg/dL)	27.3 (12)	63.6 (28)	0.001

Data are means ± SD. Significant values for p < 0.05. Chi-square test. MSyn: metabolic syndrome; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; TG: triglycerides; HDL-c: high-density lipoprotein; FSG: fasting serum glucose.

The OMN diet was associated with a prevalence of MSyn (OR: 6.28, 95%CI 2.11-18.71) and alterations in most MSyn components [WC (OR: 7.54, 95%CI 2.55-22.29), SBP (OR: 3.06, 95%CI 1.06-8.82), DBP (OR: 4.08, 95%CI 1.27-13.07), and FSG (OR: 5.38, 95%CI 1.95-14.88)] in the multiple regression, independently of caloric intake, age, level of physical activity, and alcohol consumption (Table 4).

Discussion

This study brought the scientific evidence that in apparently healthy men a VEG diet was associated with a lower percentage of individuals with MSyn compared to an OMN diet. This difference remained after the adjustment of other lifestyle characteristics, such as smoking, alcohol intake, and physical activity. In addition, FRS and other cardiovascular risk factors (CRF) were also lower in VEG subjects.

Our study is considered a pioneer for being the first to prove the association between the VEG diet and the development of MSyn in a population of Brazilian men, although an association has been reported between red meat consumption and an increase in the risk of developing MSyn after adjusting for confounders, in a cohort of Japanese-Brazilians.[28]

In the present study, VEG had significantly lower values for BMI, WC, SBP, DBP, TC, LDL-c, Apo b, TG, TC/HDL-c ratio, FSG, and HbA1c, which is in accordance with other studies around the world.

The Lima Study, conducted in Peru, with 45 OMN, 105 VEG, and 34 semi-vegetarians, has reported lower TC and LDL-c values in VEG compared to OMN.[1] In a cross-sectional analysis of 773 subjects from the Adventist Health Study 2, in the United States, a VEG dietary pattern was associated with a more favorable profile for BMI, WC, SBP, DBP, TG, and FSG.[8,29] Studies in the Brazilian population have found similar results to these of the present study. A study with OMN, VEG, and semi-vegetarians from the Adventist Church of São Paulo has found lower values for SBP, DBP, TC, and LDL-c in the VEG group.[5]

In another study comparing 56 VEG and 40 OMN in São Paulo, the VEG group had lower BMI and WC, but the levels of TG, TC, and LDL-c were equal between the groups, and VEG had higher HDL-c,[30] in contrast to our study, in which HDL was similar between groups.

In addition, a few studies in the literature have evaluated the association of the VEG diet with FRS,[5,6] which is an algorithm for assessing risk for CHD in the short term.[7] In a study conducted with 67 VEG and 134 OMN, the MONICA Project, in the state of Espírito Santo, Brazil, blood pressure, FSG, TC, LDL-c, TG, and FRS were lower among VEG.[6]

Table 4 – Multivariate regression models of the association between type of diet and metabolic syndrome and its components

	OR	95%CI	p value	p value of the model
MSyn				
Vegetarian	1			
Omnivorous	6.28	2.11-18.71	0.001	0.006
Caloric intake	1.00	0.99-1.00	0.783	
Age	1.01	0.96-1.07	0.674	
Physically active	0.56	0.18-1.71	0.307	
Alcohol consumption	1.74	0.64-4.69	0.275	
WC (≥ 90 cm)				
Vegetarian	1			
Omnivorous	7.54	2.55-22.29	<0.001	<0.001
Caloric intake	0.99	0.99-1.00	0.700	
Age	1.01	0.96-1.08	0.636	
Physically active	0.66	0.21-2.04	0.470	
Alcohol consumption	3.04	1.11-8.25	0.029	
SBP (≥ 130 mm Hg)				
Vegetarian	1			
Omnivorous	3.06	1.06-8.82	0.039	0.006
Caloric intake	1.00	0.99-1.00	0.843	
Age	1.10	1.03-1.17	0.004	
Physically active	0.84	0.27-2.55	0.751	
Alcohol consumption	0.78	0.29-2.12	0.628	
DBP (≥ 85 mm Hg)				
Vegetarian	1			
Omnivorous	4.08	1.27-13.07	0.018	0.007
Caloric intake	1.00	1.27-13.07	0.018	
Age	1.09	1.02-1.16	0.012	
Physically active	0.99	0.31-3.17	0.986	
Alcohol consumption	1.32	0.45-3.86	0.617	
TG (≥ 150 mg/dL)				
Vegetarian	1			
Omnivorous	3.46	1.25-9.64	0.017	0.079
Caloric intake	0.99	0.99-1.00	0.293	
Age	0.99	0.93-1.04	0.611	
Physically active	0.35	0.11-1.07	0.066	
Alcohol consumption	1.68	0.66-4.30	0.280	
FSG (≥ 100 mg/dL)				
Vegetarian	1			
Omnivorous	5.38	1.95-14.88	0.001	0.005
Caloric intake	1.00	0.99-1.00	0.974	
Age	1.06	0.99-1.12	0.084	
Physically active	0.79	0.27-2.29	0.666	
Alcohol consumption	0.67	0.26-1.74	0.407	

OR: odds ratio; 95%CI: 95% confidence interval. Multiple logistic regression adjusted for caloric intake, age, physical activity, and alcohol consumption. MSyn: metabolic syndrome; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; TG: triglycerides; FSG: fasting serum glucose.

In a sample of 391 female VEG and 315 OMN from Taiwan, the VEG status was associated with lower BMI, smaller WC, lower TC, LDL-c, HDL-c, TC/HDL-c and LDL-c/HDL-c ratios.[9]

Regarding the differences in CRF between VEG and OMN, one seems more consistent in the literature, the difference in blood pressure. In an elderly Taiwanese population, SBP was independently associated with VEG status,[11] and a recent meta-analysis confirms that a VEG diet is associated with lower blood pressure.[4]

Despite scientific plausibility that can explain the impact of the higher fat content of the OMN diet on lipid metabolism, a large number of studies has found that glucose profile is improved by adopting a VEG diet. In a study conducted with a sample of 425 adults from the Isfahan Diabetes Prevention Study, a population-based prospective cohort in Iran, the VEG dietary pattern was inversely associated with the risk of abnormal FSG levels.[3] In Taiwan, OMN had a greater risk of developing high FSG (HR: 1.16, 95%CI 1.02-1.32).[12] In our study, similar differences were observed in indices evaluated in glucose metabolism.

We found no difference between the levels of HDL-c, but other studies have found statistical differences in this lipoprotein. Gadgil et al.[13] have observed a higher amount of HDL-c in VEG Asian Indians living in the San Francisco Bay area. In São Paulo, VEG individuals have higher HDL-c too.[28] In Taiwan, OMN individuals had a smaller risk of having lower HDL-c.[12]

A significantly greater number of VEG individuals was classified as physically active compared to OMN individuals. Data from the Elderly Nutrition and Health Survey in Taiwan (1999–2000) have shown that regular exercise was independently associated with VEG status.[11] Pimentel has observed a higher tendency to be physically active among VEG individuals living in São Paulo, compared to OMN individuals.[30] In this study, VEG individuals were more physically active; however, the observed differences in CRF were due to neither physical activity nor caloric intake.

In our study, the OMN diet was associated with the prevalence of MSyn and alterations in most of the MSyn components (WC, SBP, DBP, and FSG), independently of caloric intake, age, and level of physical activity. Some studies with different populations have shown this association, as discussed below.

A study aiming to verify the association of MSyn risk factors with selected markers of oxidative status (advanced glycation end products, advanced oxidation protein products) and microinflammation (C-reactive protein and leukocytes) in healthy OMN and VEG individuals has found that OMN individuals consumed significantly more protein, total fat, saturated as well as unsaturated fatty acids, and dietary cholesterol, and less dietary fiber; in addition, the VEG diet seems to exert beneficial effects on MSyn and risk factors associated with microinflammation.[10]

Rizzo et al.[8] have observed in subjects from the Adventist Health Study 2 that a VEG dietary pattern was associated with a lower risk of MSyn, and this relationship persists after adjusting for lifestyle and demographic factors. For the female VEG individuals from a Buddhist hospital in Taiwan, the risks for MSyn were lower for ovo-lacto-vegetarians of 1–11 years and > 11 years, respectively, 45% and 42%, compared to OMN individuals after adjusting for other covariates.[9]

It should be noted that although the sample from the CARVOS study includes only men who are self-assessed as "healthy", many individuals were found to have MSyn among those who consumed an OMN diet. MSyn is defined by a constellation of interconnected physiological, biochemical, clinical, and metabolic factors that directly increase the risk of atherosclerotic cardiovascular disease, type 2 diabetes mellitus, and all-cause mortality. Lifestyle is one of the major predisposing factors of MSyn.[31]

In our study, the multivariate regression models show that the VEG diet was independently the best indicator of MSyn, and was associated with its components WC, SBP, DBP, and FSG, suggesting that the prevalence of MSyn could be due to the influences on its components. We hypothesize that the mechanism responsible for these differences exists in the composition of one's diet. VEG subjects consume smaller amounts of total fat, saturated fat, and cholesterol, and larger amounts of unsaturated fat and fiber than OMN subjects do.[10,14] The absence of red and processed meat intake could have an additional role.[14]

In our study, VEG and OMN individuals did not have a significant difference in caloric intake. VEG consumed significantly more carbohydrates, dietary fiber, and polyunsaturated fat. Moreover, OMN significantly ingested larger amounts of protein, total fat, saturated fat, and monounsaturated fat.

In addition, dietary patterns like VEG and the Mediterranean diet have a beneficial synergistic combination of antioxidants, fiber, potassium, magnesium, and phytochemicals,[31] which may be responsible for the health benefits demonstrated in several scientific studies.

There are some limitations to this study. It had a relatively small number of subjects, and the cross-sectional design did not allow us to draw conclusions in terms of causal relationships. Future research must be conducted, especially prospective cohort studies in different populations to prove the impact of the vegetarian diet on the outcomes evaluated in this study.

The strength of our study is its highly homogenized sample, where all were nonsmokers, had no previous diagnosis of diabetes, dyslipidemia, cardiovascular or cerebrovascular diseases, hypertension or intake of antihypertensive medication, and had no difference in the frequency of alcohol beverage intake. The only difference between groups was our independent variable, diet, and physical activity, which was demonstrated but did not account for the differences found. In addition, we found in the same sampling a better profile of subclinical vascular disease evaluated by arterial stiffness, determined by carotid-femoral pulse wave velocity and carotid intima-media thickness, and distensibility in VEG compared to OMN subjects.[20]

Our study is important because its sample included only apparently healthy men, which is a large segment of society and, therefore, of great interest in terms of primary prevention of CVD. The study findings therefore will have a great positive impact in terms of public health economics and quality of life.

Conclusion

This study provides evidence that, in apparently healthy men, a VEG diet is associated with lower levels of some CRF, as well as lower FRS and percentage of individuals with MSyn, suggesting a VEG diet can be considered a protective factor against the development of CVD.

Author contributions

Conception and design of the research: Navarro JCA; Acquisition of data: Navarro JCA, Antoniazzi L, Oki AM, Bonfim MC, Hong V, Acosta-Cardenas P; Analysis and interpretation of the data: Navarro JCA, Antoniazzi L, Oki AM, Bonfim MC, Hong V, Bortolotto LA; Statistical analysis: Navarro JCA, Antoniazzi L, Hong V; Writing of the manuscript: Acosta-Cardenas P; Critical revision of the manuscript for intellectual content: Navarro JCA, Antoniazzi L, Oki AM, Hong V, Sandrim V, Miname MH, Santos Filho RD.

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 study was approved by the Ethics Committee of the Instituto do Coração (InCor) da Faculdade de Medicina da Universidade de São Paulo under the protocol number CAAE: 03540812.2.0000.0068. File: 35704. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Prevalence of Metabolic Syndrome and Framingham Risk Score in Vegetarian and Omnivorous Apparently Healthy Men

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Short Editorial regarding the article Prevalence of Metabolic Syndrome and Framingham Risk Score in Apparently Healthy Vegetarian and Omnivorous Men

The Life Style Heart Trial[1] was a milestone; published in 1990, the study showed that a healthy lifestyle associated with a vegetarian diet can promote the regression of coronary lesions, even in patients not using lipid-lowering drugs.

There is a large epidemic of cardiovascular disease today. Sedentary lifestyle, obesity, diabetes and dyslipidemia are triggers of mechanisms related to cardiovascular diseases, such as changes in the gut microbiota, increase in inflammatory markers and prothrombotic factors, and impaired immune response.

Traditional guidelines provide information on the identification of patients at high risk, and establishment of therapy targets of cardiovascular disease in advanced stage when only lifestyle changes seem insufficient for an effective, early reduction in cardiovascular events.

In 1988, Gerald Reaven delivered a historical Banting Lecture,[2] presenting a link between insulin resistance and obesity, hyperglycemia, hypertension and dyslipidemia (notably hypertriglyceridemia and low HDL-c levels). Reaven was the pioneer in describing the Metabolic Syndrome, initially named X Syndrome, which constituted a high-risk situation for coronary disease. The author showed that high cholesterol levels are not the only mechanism for this condition, but rather, other components of the syndrome could be deeply modified by lifestyle changes.[3-5]

Keywords

Metabolic Syndrome; Diet, Vegetarian; Healthy Lifestyle; Prevention and Control.

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In the present issue of *Arquivos Brasileiros de Cardiologia*,[6] the authors show that vegetarian diet is strongly associated with a lower prevalence of Metabolic Syndrome and a lower cardiovascular risk predicted by the Framingham score as compared with an omnivorous diet, defined by individuals who consumed at least four portions of meat a week.

The study included a relatively small, but homogeneous sample of apparently healthy adults. In addition, the total number of male subjects was higher than that in the classical study by Ornish (The Lifestyle Heart Trial). Its cross-sectional design limits the ability to make any inferences, which should be confirmed by prospective studies. However, the strict inclusion criteria (minimum of four years following a vegetarian or omnivorous diet) and the quality of the results obtained from the subjects demonstrate the importance of nutrition and how different metabolic, clinical and laboratory aspects are between these groups.[6]

Recently, during the annual American College of Cardiology's meeting (ACC.18), professor Valentin Fuster suggested different strategies for primoradial (first 25 years of age), primary (25-50 years) and secondary (after 50 years of age) prevention, aiming at reducing the incidence and complications of cardiovascular diseases.

Results of this study on vegetarian diet highlight not only its effects on individual markers of cardiovascular risk, but also substantial changes in the global risk score and Metabolic Syndrome components.[6]

We have witnessed a phase of epidemiological transition, where the greatest challenges are not to achieve cholesterol, glycemic and blood pressure control, but to primarily reduce obesity and metabolic disorders associated with hyperglycemia. Much attention has been paid to patients with coronary, cerebrovascular or renal events or to advanced peripheral vascular disease. However, a greater impact on the health of a larger number of people would be achieved if we focused on simpler, lifestyle changing measures, towards primordial and primary prevention.

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Pulmonary Vein Anatomy is Associated with Cryo Kinetics during Cryoballoon Ablation for Atrial Fibrillation

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Abstract

Background: **The influence of pulmonary vein (PV) anatomy on cryo kinetics during cryoballoon (CB) ablation is unclear.**

Objective: **To investigate the relationship between PV anatomy and cryo kinetics during CB ablation for atrial fibrillation (AF).**

Methods: **Sixty consecutive patients were enrolled. PV anatomy, including ostial diameters (long, short and corrected), ratio between short and long diameters, ostium shape (round, oval, triangular, and narrow), and drainage pattern (typical, with common trunk, common antrum, ostial branch and supernumerary PV) were evaluated on multi-detector computed tomography (MDCT) images pre-procedure. Cryo kinetics parameters [balloon freeze time from 0 to -30°C (BFT), balloon nadir temperature (BNT) and balloon warming time from -30 to +15°C (BWT)] were recorded during procedure. All p values are two-sided, with values of $p < 0.05$ considered to be statistically significant.**

Results: **606 times of freezing cycle were accomplished. Moderate negative correlation was documented between BNT and corrected PV diameter ($r = -0.51$, $p < 0.001$) when using 23-mm CBs, and mild negative correlation ($r = -0.32$, $p = 0.001$) was found when using 28-mm CBs. Multivariate logistic regression analysis revealed that PV corrected ostial diameter (OR, 1.4; $p = 0.004$) predicted a BNT < -51°C when using 23-mm CBs, while PV ostium oval shape (OR, 0.3; $p = 0.033$) and PV locations (left inferior PV: OR, 0.04; $p = 0.005$; right superior PV: OR, 4.3; $p = 0.025$) predicted BNT < -51°C when using 28-mm CBs.**

Conclusions: **MDCT can provide PV anatomy accurate evaluation prior CB ablation. PV anatomy is associated with cryo kinetics during ablation. (Arq Bras Cardiol. 2018; 110(5):440-448)**

Keywords: **Pulmonary Veins / anatomy & histology; Atrial Fibrillation; Catheter Ablation; Multidetector Computed Tomography; Cost-Benefit Analysis.**

Introduction

CB ablation has an increasing clinical application worldwide, it has been proved a comparable technique to radiofrequency (RF) ablation in safety and efficacy for the AF treatment,[1] and maybe more cost-effective.[2] By achieving appropriate occlusion in targeted PVs with the balloon and getting good balloon – PV ostium contact, it can simplify the procedure with a "single-shot" approach to get circumferential PV isolation.[3] It is reported that some parameters of cryo kinetics, such as balloon temperature,[4] balloon warming time,[5] can predict acute PV isolation or late PVs reconnection. Some parameters of PV anatomy have been used to predict occlusion,[6] or acute, mid- and long-term success of CB ablation.[7-9] It is reasonable to imaging that PV anatomy plays a role in cryo kinetics, thus exerting an influence on ablation efficacy. However, limited data exist regarding the association between PV anatomy and cryo kinetics during CB ablation. We aimed to investigate the relationship between PV anatomy parameters and cryo kinetic parameters in patients undergoing CB ablation using either 23- or 28-mm CB for AF.

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Methods

Patients

Between January and October 2014, a prospective study was carried out at our institution. Sixty consecutive patients with symptomatic and drug-refractory AF underwent CB ablation. In these patients, pre-procedural MDCT images and complete recordings of cryoballoon temperature during each CB ablation were available. All patients provided written informed consent. The study followed the ethical standards of the Declaration of Helsinki of 1975, revised in 2008 and was approved by the local institutional ethics committee.

PV Anatomy Assessment

Image acquisition

Prior to the procedure, MDCT studies were performed on a MDCT scanner (SOMATOM Definition Flash, Siemens). Scanning parameters were the following: tube voltage 100 - 120 kV, 3D automatic tube current modulation, thickness / increment of reconstruction 0.625 / 0.625 mm. ECG-gating was not used, and patient breath holding was required during image acquisition. A bolus tracking protocol with 50 ~ 70 mL i.v. contrast agent (Ultravist 370, Bayer Schering) and 3 ~ 5 mL/s flow rate was applied.

Image analysis

MDCT images were reconstructed and analyzed using CartoMerge software (Biosense Webster, Diamond Bar, CA, USA) right before the procedure. PV ostia were defined anatomically at the parietal pericardium point of reflection[10] and were depicted semi-automatically (Figure 1A), together with ostia perimeters calculated automatically by computerized image analysis. Long (D_{long}) and short (D_{short}) ostia diameters were then measured. Corrected ostial diameters ($D_{corrected}$) were calculated using the formula $D_{corrected}$ = perimeter / π. The ratio between D_{short} and D_{long} (D_{short} / D_{long}) was also calculated for analysis. Taking consideration of D_{short} / D_{long} values, PV ostium shapes were divided into 4 types: type I (round), ostia with value between 0.90 ~ 1.00; type II (oval), value between 0.60 ~ 0.90 and a smoothly curved edge; type III (triangular), value between 0.60 ~ 0.90 and an obviously straight part at the edge; and type IV (narrow), value less than 0.60. (Figure 1B-E).

Five PV drainage patterns were defined for the targeted superior/inferior PVs based on the definition by Marom et al.[11] When the superior and inferior PVs on the same side joined together to form a common trunk vein and drained into LA through a common ostium, the superior and inferior PV were defined as "with common trunk". If the superior and inferior PVs on the same side drained into LA through two independently trunk but drained into LA through ostia hardly separated by LA wall (the minimum distance between the two ostia was less than 2 mm on MDCT images), the two PVs were then defined as "with common antrum". PV "with ostial branch" was defined as a PV branch joining within 10 mm from the ostium. PV "with supernumerary vein" was defined as the superior or inferior PV with neighboring additional vein(s), when a middle PV existed, both the superior and inferior PV on the same side were defined as "with supernumerary vein". PV "with typical drainage" was defined as a superior or inferior PV drained into LA independently, through neither a common trunk nor antrum, and that did not have an ostial branch or supernumerary vein. (Figure 1F-J)

Anatomical assessment reproducibility

In order to assess evaluating methods reproducibility of diameters described above, 40 PVs ostial diameter of first 10 patients were measured on CT images by two blind experienced observers at the beginning of the study. One observer measured two times in different moments to study the inter-observer reproducibility. The other observer measured one time, and the intra-observer reproducibility between the two observers was studied. The ostium shapes and drainage patterns were also assessed by two experienced observers in consensus during the study.

Ablation procedure

The ablation procedures were carried out as previously reported.[12] Briefly, an octapolar electrode catheter was placed into the coronary sinus and a phrenic nerve (PN) pacing electrode catheter into the superior vein cava (SVC). After a single transseptal puncture, selective PV angiography was carried out and a CB catheter (Arctic Front, Medtronic, Quebec, Canada) was inserted into LA together with a spiral catheter (SC) (Achieve, Medtronic, CA, USA). There are currently two sizes of balloon catheters (23 or 28 mm) and two sizes of SCs (15 or 20 mm) available. PV ostia diameters were determined from MDCT images; CB and SC size were selected accordingly: If long diameters of three or four PVs were < 22 mm, 23-mm CB a 15-mm SC were selected; If that ≥ 22 mm, a 28-mm CB and a 20-mm SC were preferred; otherwise the choice would be made by the operator temporaly. As soon as good contact of balloon to PV ostium indicated by the contrast retention in PV was obtained, freezing cycle was started with two to three applications per vein. Generally each freeze lasted 240s, and ideal freezing temperature was between -45°C and -55°C. If exists a common PV, freezing was analyzed separately as in superior or inferior PV based on location of balloon distal end during freezing. Supernumerary PVs were not taken as targeted PV as there are usually too small in dimension.

PN was constantly paced (10 mA, 2 ms, 50/min) with PN pacing catheter in SVC when freezing at right PVs. After each freeze, PV conduction was re-evaluated by adjusting SC position within the PV. In all patients, PVI of all targeted PVs with primary use of CB only was the procedural endpoint. If PVI was not achieved for a particular vein following a minimum of two freezing, either further cryoablation would be performed or conventional RF ablation would be undertaken, depending on the initial contrast-guided occlusion and the minimum temperature achieved.

Cryo kinetics

Three parameters of cryo kinetics[5] were introduced: balloon freezing time from 0 to -30°C (BFT), balloon nadir temperature (BNT) and balloon warming time from -30 to +15°C (BWT). Freezing cycles with a BNT lower than -30°Cwere taken into analysis.

Statistical analysis

After being tested for normality distribution and variances equality using One-Sample Kolmogorov-Smirnov test and Levene's test, continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range), and were compared using the unpaired Student's t-test or nonparametric variables Mann-Whitney U test as appropriate. Categorical variables were expressed as number (percentage) and were compared by means of χ^2 analysis or Fisher exact test. Measuring reproducibility of PV ostial diameters was assessed using intra-class correlation coefficient (ICC). Pearson or Spearman correlation was used to evaluate the

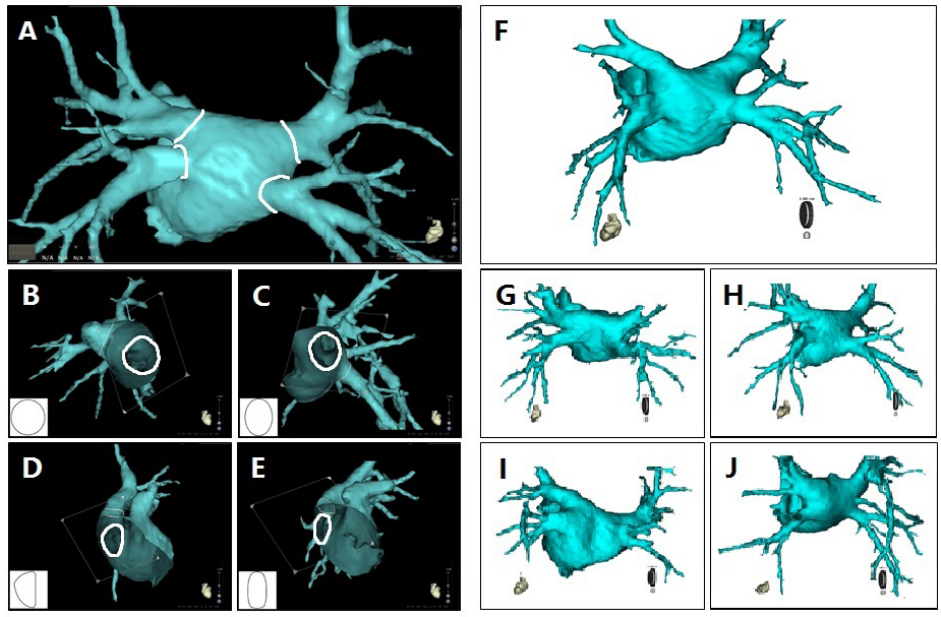

Figure 1 – *PV ostium shapes category and PV drainage patterns. A) PV ostia depicted semi-automatically using CartoMerge software. Four shapes of PV ostium; B) Type I (round); C) Type II (oval); D) Type III (triangular); and E) Type IV (narrow). Five patterns of PV drainage; F) Four PVs drains into LA in a typical pattern; G) Left superior and inferior PVs drains into LA both in a pattern of with common trunk; H) Left superior and inferior PVs drains into LA both in a pattern of with common antrum; I) Right inferior PV drains into LA in a pattern of with ostial branch; J) Right superior and inferior PVs drains in LA with supernumerary vein (middle vein).*

association between two variables based on its distributions. Logistic regression was performed to investigate the predictive values of PV anatomic parameters for cryo kinetic effect. Variables with a p value < 0.10 in univariate analysis were included into the multivariate analysis, which was performed using an enter approach with criteria of $p < 0.05$ for inclusion in and $p > 0.05$ for exclusion from the model. A two-sided $p < 0.05$ was considered statistically significant. All statistical analysis were performed using IBM SPSS statistical software (Version 20.0, SPSS).

Results

Study population and procedural data

The study population baseline characteristics and ablation procedure parameters are presented in Table 1.Compared with 28-mm CB only, the acute PVI rates were not significantly different when ablation was using 23-mm CB only either on PV level (92.5% vs. 96.9%, $p = 0.16$) or on patient level (79.4% vs. 91.7%, $p = 0.28$). No significant difference was found in total complication rate between 28- or 23-mm CBs (8.8% vs. 4.2%, $p = 0.64$). One case of PN palsy, taken as major, was detected during freezing in a right inferior PV using a 28-mm CB and did not recover until discharge. One case of pericardial and pleural effusion, two cases of left groin hematomas were all resolved within one month post-procedure.

Anatomy data

The pre-analysis on reproducibility revealed that inter-observer ICC of D_{long}, D_{short} and $D_{corrected}$ was 0.93, 0.95 and 0.96 (all $p < 0.001$), and intra-observer ICC of three measured diameters was 0.90, 0.96 and 0.93 respectively (all $p < 0.001$).

Diameters of 240 PVs measured on CT images were listed in Table 2. Compared with ablation using 23-mm CBs, ratio of $D_{corrected}$ and CB diameter was much smaller when frozen using 28-mm CBs (0.76 ± 0.14 vs. 0.68 ± 0.13, $p < 0.001$). Linear correlation analysis showed that $D_{corrected}$ was strongly correlated with D_{long} (correlation coefficient: 0.93, $p < 0.001$) and D_{short} (correlation coefficient: 0.90, $p < 0.001$), while the latter two were moderately correlated with each other (correlation coefficient: 0.74, $p < 0.001$). Values of D_{short} / D_{long} were between 0.38 and 1.00. Proportions of different ostium shapes and drainage patterns of four targeted PVs are presented in Figure 2 and Table 3.

Cryo kinetics

238 targeted PVs were frozen 606 times. Of which, 102 PVs were frozen 254 times using 23-mm CB, and 141 PVs 352 times using 28-mm CB. Compared with 28 mm CBs, BFT was shorter and BNT was lower when using 23-mm CBs in all PV locations (all $p < 0.001$), while BWT was shorter only in superior PVs (see Table 4).

Table 1 – Baseline Characteristics of study population and CB PVI Procedure Parameters

Baseline Characteristics	
Age (years)	56.8 ± 12.5
Gender, male	32(53.3)
BMI (kg/m2)	24.6 ± 3.1
AF type, paroxysmal AF	58 (96.7)
AF duration (months)	25.5 (12, 69)
CHA_2DS_2-VASc score	1(0, 2)
LAD (mm)	35.2 ± 4.8
LVEF (%)	65.6 ± 5.4
Procedure Parameters	
Balloon type, 28-mm /23-mm/double	34 (56.7) / 24(40) / 2(3.3)
N°. of freeze	10.8 ± 3.2
Acute PVI	
Patient level *	60(100)
With CB only, PV level#	225 (94.5)
With CB only, patient level	51(85)
Complications	4 (6.7)
Phrenic nerve palsy	1 (1.7)
Pericardial & pleural effusion	1 (1.7)
Left groin hematomas	2 (3.3)

*Values are n (%), mean ± SD, or median (interquartile range). CB: cryoballoon; PVI: pulmonary vein isolation; PV: pulmonary vein; AF: atrial fibrillation; BMI: body mass index; LAD: left atrial diameter; LVEF: left ventricular ejection fraction (measured from transthoracic echocardiography); CHA_2DS_2-VASc score = stroke risk score [cardiac failure, hypertension, age ≥ 75 years (doubled), diabetes, stroke (doubled)-vascular disease, age of 65–74 years and sex category (female)]. *: PVI with CB ablation only or plus conventional RF ablation. #: 1 right superior and 1 right inferior PV has no potential.*

Correlation between BNT and BFT (correlation coefficient: 0.77, $p < 0.001$), and between BNT and BWT (correlation coefficient: - 0.85, $p < 0.001$) was stronger than that between BFT and BWT (correlation coefficient: - 0.60, $p < 0.001$) when using 23-mm CB. The same result was found when using 28-mm CB (correlation coefficient: 0.79, - 0.86, and - 0.62, respectively; all $p < 0.001$).

PV anatomy and BNT

As mentioned above, $D_{corrected}$ has much stronger correlations with both D_{long} and D_{short}, and BNT has much stronger correlations with the two other kinetic parameters as well, $D_{corrected}$ and BNT were chosen as parameters to investigate the relationship between PV diameter and cryo kinetic parameter. To reflect the maximal biological effect and avoid the confounding effect caused by manipulation between different cycles (e.g., occlusion degree, time of freezing circle), the lowest BNT achieved by using the same size of balloon was chosen to analyze each PV.

Correlation analysis revealed that the correlation coefficient between $D_{corrected}$ and BNT was -0.51 when ablation was with 23-mm CB, and it was -0.32 with 28-mm CB (both $p < 0.001$). Correlation between the two parameters was stronger when using 23-mm CB (see Figure 3). However, there was no significant correlation between value of D_{short} / D_{long} and BNT either using 23- (correlation coefficient: -0.11, $p = 0.23$) or 28-mm CB (correlation coefficient: -0.09, $p = 0.30$).

In order to investigate the predict value of PV anatomic parameters for cryo kinetic effect, BNT was transformed into a binary variable with a cut-point of -51°C (< -51°C and ≥ -51°C)[4] and taken as dependent variable. PV anatomic parameters including $D_{corrected}$, value of D_{short} / D_{long}, ostium shape, drainage pattern and location were included in logistic regression model as independent variables. Univariate and multivariate analyses revealed that, among the above-mentioned variables, $D_{corrected}$ [OR, 1.4(95% CI: 1.1 – 1.8), $p = 0.004$] predicted a BNT of < -51°C when using 23-mm CBs, while an oval shape of PV ostium [OR, 0.3(95% CI: 0.1 – 0.9), $p = 0.033$] and PV locations [left inferior PV: OR, 0.04(95% CI: 0.004 – 0.4), $p = 0.005$; right superior PV: OR, 4.3(95% CI: 1.2 – 15), $p = 0.025$] predicted a BNT of < -51°C when using 28-mm CB. However, PV drainage patterns did not predict it when using either 23- or 28-mm CBs. (see Figure 4).

Discussion

Main findings

This study aimed to investigate the relationship between PV anatomy and cryo kinetics during CB ablation. The present study main findings can be summarized as follows: Firstly, MDCT was accurate and useful in pre-procedural evaluation of PV anatomy for CB ablation of AF; $D_{corrected}$ was a better parameter for ostial measurement than D_{long} and D_{short}. Secondly, BNT, BFT and BWT were associated to each other, BNT was a better parameter for evaluating cryo kinetics effect than the latter two. Thirdly, there is an association between $D_{corrected}$ and BNT both when using 23- and 28-mm CBs; $D_{corrected}$ predicted cryo kinetic effect with a BNT of < -51°C when using 23-mm CB, while PV ostial shape and location predicted the effect when using the 28-mm CB.

PV anatomy evaluated with MDCT

MDCT images can provide accurate and detailed PVs anatomic information.[10] Our study found that variations existed in dimensions, ostial shapes and drainage patterns of PVs among different patients and PV locations, which was consistent with prior studies.[11,13,14] Values of PV ostia D_{short} / D_{long} that we studied were between 0.38~1.00, and only 20.8% PVs (50/240) had a round-shape ostia. Therefore, it is a partial evaluation using only D_{long} or D_{short} as PV ostial dimension. Considering PVs compliance and deformation to adapt the CB during procedure, $D_{corrected}$, diameter calculated from the perimeter was more reliable. Correlation analysis on PV ostial dimension measurement also demonstrated $D_{corrected}$ was more representative than the two others.

Table 2 – PV ostia diameters measured on CT images

PV location	D_{long} (mm)			D_{short} (mm)			$D_{corrected}$ (mm)		
	23-mm CB	28-mm CB	p	23-mm CB	28-mm CB	p	23-mm CB	28-mm CB	p
LSPV	20.3 ± 3.0	21.7 ± 2.8	0.06	13.5 ± 2.7	15.2 ± 3.3	.04	17.7 ± 2.7	19.3 ± 2.5	0.02
LIPV	17.4 ± 3.4	17.6 ± 2.1	0.80	11.7 ± 3.3	12.9 ± 2.1	.13	15.3 ± 3.2	15.9 ± 1.9	0.41
RIPV	18.3 ± 3.0	19.6 ± 3.0	0.09	15.6 ± 2.9	17.1 ± 3.0	.054	17.3 ± 2.6	18.8 ± 2.7	0.046
RSPV	21.2 ± 3.0	24.3 ± 3.4	0.001	18.0 ± 3.7	20.4 ± 3.8	.02	20.0 ± 3.0	22.7 ± 3.4	0.01
Total	19.2 ± 3.4	20.8 ± 3.8	0.001	14.6 ± 3.9	16.4 ± 4.1	.001	17.6 ± 3.3	19.1 ± 3.6	0.001

Values are mean ± SD. p: p-value (unpaired Student's t-test). D_{long}: PV ostium long diameter; D_{short}: PV ostium short diameter; $D_{corrected}$: Corrected diameter calculated from PV ostium perimeter PV ostium; CB: cryoballoon; LSPV: left superior pulmonary vein; LIPV: left inferior pulmonary vein; RIPV: right inferior pulmonary vein; RSPV: right superior pulmonary vein.

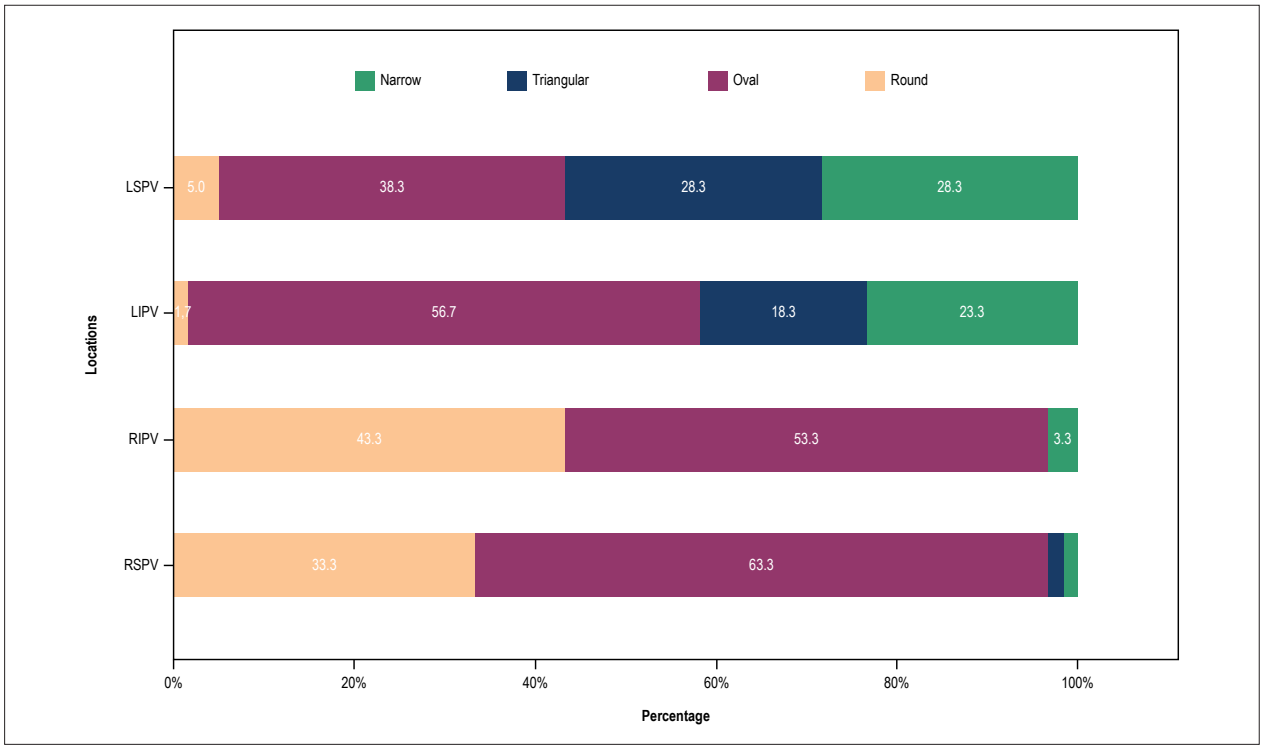

Figure 2 – *Proportions of different ostium shapes of the four targeted PVs. D_{long}: PV ostium long diameter; D_{short}: PV ostium short diameter; $D_{corrected}$: Corrected diameter calculated from PV ostium perimeter PV ostium; CB: cryoballoon; LSPV: left superior pulmonary vein; LIPV: left inferior pulmonary vein; RIPV: right inferior pulmonary vein; RSPV: right superior pulmonary vein.*

CB ablation and cryo kinetics

Cryo kinetics can be evaluated from two aspects: freezing temperature and time course. Furnkranz et al.[4] found that BNT could predict acute PVI when using 28-mm CB. Ghosh et al.[5] reported that -30~+15°C BWT was a strong predictor for pulmonary vein reconnection. The current study revealed that BFT, BNT and BWT had significant correlations to each other, which was higher between BNT and the two others. For this reason, we chose BNT as the representative cryo kinetic parameter for analyzing the relationship between PV anatomy and cryo kinetics. A cut-point of < -51°C was selected for logistic regression because BNT < -51°C was invariably associated with PVI, as Ghosh et al.[5] concluded.

Relationship between PV Anatomy and Cryo Kinetics

The CB ablation basic technique is to achieve cryoenergy-induced PVI on a condition of appropriate occlusion of PV blood flow and circumferential contact between PV ostia and CB surface, ideally the equatorial region of CB.[15] Sorgente et al.[6] found that PV ostium shape was useful in predicting the degree of occlusion. PV ovality[16] and drainage patterns[9] were reported to have an impact on AF recurrence in some studies. In this study, though a mild to moderate association was found between BNT and $D_{corrected}$, no association existed either between BNT and PV ostium shape or between BNT and PV drainage pattern. The main reasons for this may be as follows: (1) PV ostia had certain compliance

Table 3 – Proportion of PV drainage patterns

Location	typical	with common trunk	with common antrum	with ostial branch	with supernumerary vein (MPV)
LSPV	23(38.3)	11(18.3)	25(41.7)	2(3.3)	0
LIPV	23(38.3)	11(18.3)	25(41.7)	3(5.0)	0
RIPV	24(40)	0	6(10)	27(45)	4(6.7)
RSPV	37(61.7)	0	6(10)	14(23.3)	4(6.7)
Total	107(44.6)	22(9.2)	62(25.8)	46(19.2)	8(3.3)

Values are n (%). MPV: middle pulmonary vein; LSPV: left superior pulmonary vein; LSPV: left superior pulmonary vein; LIPV: left inferior pulmonary vein; RIPV: right inferior pulmonary vein; RSPV: right superior pulmonary vein.

Table 4 – Parameters of cryo kinetics

PV location	BFT (s)			BNT (°C)			BWT (s)		
	23-mm CB	28-mm CB	p	23-mm CB	28-mm CB	p	23-mm CB	28-mm CB	p
LSPV	13.7 ± 4.2	23.8 ± 9.1	< 0.001	-52.8 ± 6.5	-46.8 ± 7.1	< 0.001	19.8 ± 7.7	25.3 ± 11.0	0.001
LIPV	14.5 ± 3.4	27.3 ± 7.8	< 0.001	-50.2 ± 4.9	-42.0 ± 4.8	< 0.001	17.5 ± 5.7	17.9 ± 5.9	0.656
RIPV	13.9 ± 4.0	28.1 ± 8.9	< 0.001	-52.6 ± 5.9	-42.3 ± 6.9	< 0.001	20.0 ± 7.6	18.4 ± 8.4	0.237
RSPV	12.1 ± 3.0	21.3 ± 7.6	< 0.001	-56.8 ± 5.1	-49.7 ± 6.7	< 0.001	26.0 ± 6.8	30.4 ± 11.5	0.008
Total	13.6 ± 3.8	25.2 ± 8.8	< 0.001	-53.1 ± 6.1	-45.1 ± 7.1	< 0.001	20.8 ± 7.6	22.7 ± 10.6	0.014

Values are mean ± SD. p: p-value (unpaired Student's t-test). CB: cryoballoon; BFT: balloon freezing time from 0 to -30°C; BNT: balloon nadir temperature; BWT: balloon warming time from -30 to +15°C; LSPV: left superior pulmonary vein; LIPV: left inferior pulmonary vein; RIPV: right inferior pulmonary vein; RSPV: right superior pulmonary vein.

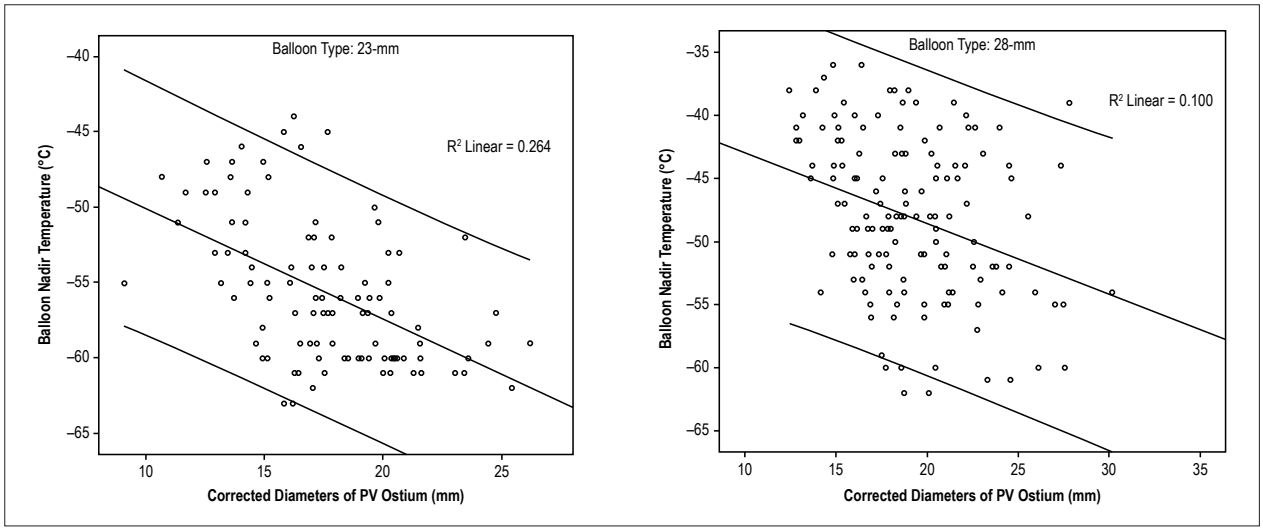

Figure 3 – *Scatterplot of PV ostium corrected diameters and balloon nadir temperature using two sizes of cryoballoon.*

and could deform to adapt to the CB during procedure; (2) Different definitions of PV ostium shape and drainage pattern between studies; (3) cryo kinetic effect is associated with but not equal to occlusion degree or ablation effect.

Compared with 23-mm CB, the association between BNT and $D_{corrected}$ was weaker when using the 28-mm CB. This may be because: (1) 28-mm CB had a higher requirement for PV compliance and "free space" to handle (e.g., PV location, puncturing site of interatrial septum); (2) PV ablated using the 28-mm CB had a smaller ratio of $D_{corrected}$ and diameter of CB in this study, which limited the comparability.

Efficacy and safety of two CB sizes

Some studies reported that 23-mm CBs was associated with higher success rates but came at the cost of safety, referring mainly to the complication of PN palsy.[15,17,18]

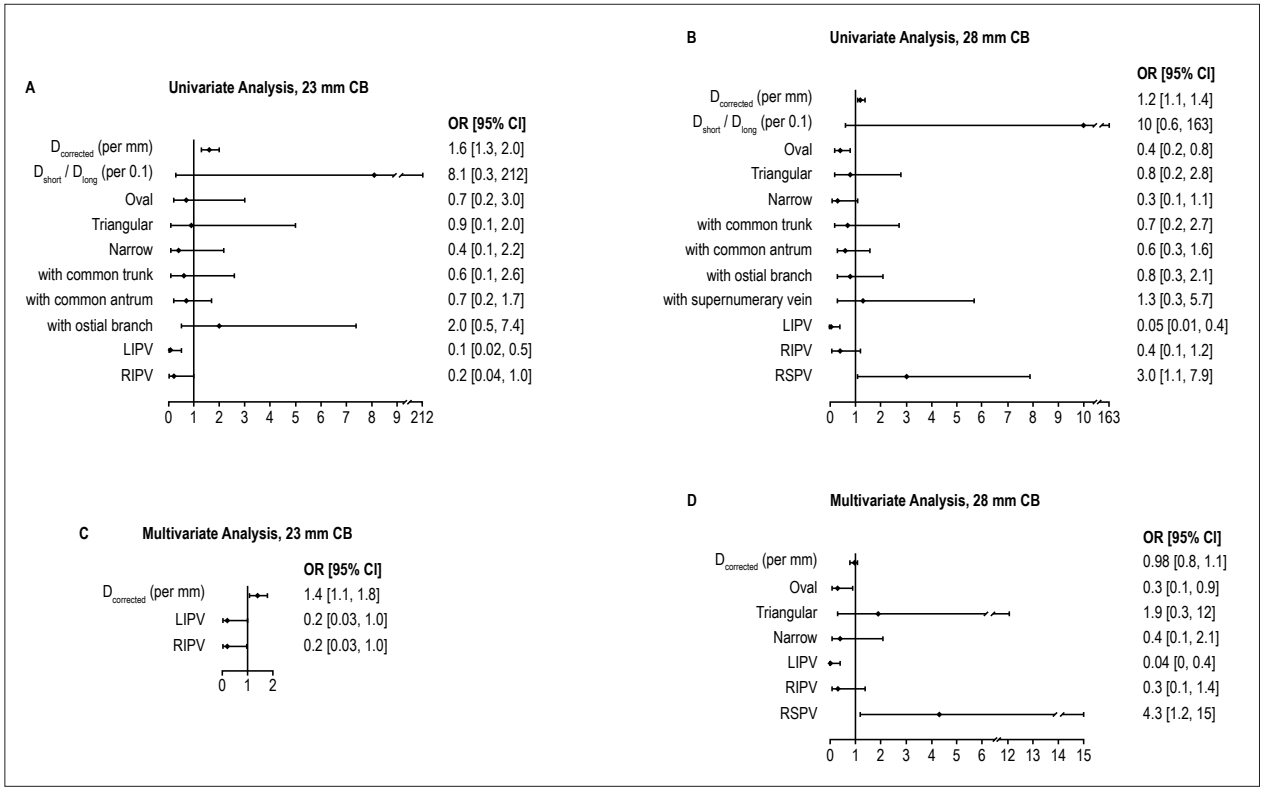

Figure 4 – *Univariate and multivariate logistic regression analysis for BNT (< -51°C and ≥ -51°C). A and C. Univariate and multivariate analysis of 23mm CB. B and D. Univariate and multivariate analysis of 28 mm CB. D_{long}: PV ostium long diameter; D_{short}: PV ostium short diameter; $D_{corrected}$: Corrected diameter calculated from PV ostium perimeter PV ostium; CB: cryoballoon; LSPV: left superior pulmonary vein; LIPV: left inferior pulmonary vein; RIPV: right inferior pulmonary vein; RSPV: right superior pulmonary vein.*

PN palsy occurs more frequently in right PVs with an incidence of 2.0% ~ 24.4%.[12,19,20] Our study demonstrated that the overall complication rate were not significantly different between using the two CBs, while ablation using 23-mm CB only had a similar rate of acute PVI on PV level and nonsignificant higher rate on patient level comparing with using 28-mm CB only. It is worth mention that the only one case of PN palsy (1.7%) occurred when using 28-mm balloon, this indicates that, with the improvement of operators' skills and monitoring methods, smaller CB can be just as safe as the bigger CB while achieving comparable or even higher efficacy when using for the selected patients.

Study limitation

In this single-center study with a small sample, PV anatomy variations might only partially represent the universal situation among population; BNT cut-point < -51°C was just used to facilitate the analysis and it is not a cut-point between effective and non-effective ablation, so was the cryo kinetic effect not equal to ablation effect. As SCs were used not only to record PV potentials, but also to support the CBs, real-time PV isolation recording, a more direct and better parameter to evaluate acute ablation effect, could only be achieved in some of the patients. However, this situation is expected to change with the progress of technology and manipulation skills,[21] and investigation of relationship between PV anatomy and real time isolation will be the future research direction. Current results only apply to the use of first-generation CB. With the spreading use of CB second generation, cryo kinetics needs further discussion. In addition, the evaluation of PV anatomy was carried out with Carto system in electrophysiological lab for convenience and efficiency. Other post processing platforms and reconstructing software could also be used for analysis.

Conclusions

MDCT images can provide accurate evaluation of PV ostial anatomy and preprocedural guidance for CB ablation. PV anatomy is associated with cryo kinetics, and PV diameter plays a more prominent role when using 23-mm CBs, while PV location is more prominent when using 28-mm CBs.

Author contributions

Conception and design of the research: Xiongbiao C, Pihua F, Tang M; Acquisition of data and Critical revision of the manuscript for intellectual content: Xiongbiao C, Pihua F, Zheng L, Jia H, Tang M, Jun L, Bin L, Shu Z; Analysis and interpretation of the data: Xiongbiao C, Pihua F, Zheng L, Jia H, Tang M, Jun L, Bin L; Statistical analysis: Xiongbiao C, Pihua F, Zheng L, Jun L; Writing of the manuscript: Xiongbiao C.

Potential Conflict of Interest

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

Sources of Funding

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Fuwai Hospital under the protocol number 2013078. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Paroxysmal Atrial Fibrillation in Females: Understanding Gender Differences

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Abstract

Background: The catheter ablation of atrial fibrillation (AF) is performed less frequently in women. In addition, there is divergent information in the literature regarding the effectiveness and safety for the ablative procedure to females.

Objectives: The objective of this study was to compare the clinical characteristics and outcomes in men and women undergoing paroxysmal atrial fibrillation (PAF) ablation.

Methods: Cohort study of patients undergoing first-ever PAF catheter ablation procedure refractory to antiarrhythmic drugs. The information was taken from patients' records by means of a digital collection instrument and indexed to an online database (Syscardio®). Clinical characteristics and procedures were compared between each gender (M x F), adopting a level of statistical significance of 5%. The primary endpoint associated with efficacy was freedom from atrial arrhythmia over the follow-up time.

Results: 225 patients were included in the study, 64 (29%) women and 161 (71%) men. Women presented more symptoms due to AF according to the CCS-SAF score (1.8 ± 0.8M x 2.3 ± 0.8F p = 0.02) and higher CHADS2 score compared to men (0.9 ± 0.8M x 1.2 ± 1F). Post-ablation recurrence occurred in 20% of the patients, with no difference based on gender (21% M x 20% F p = 0.52). The rate of complications was less than 3% for both groups (p = 0.98).

Conclusion: Women undergoing the first-ever PAF catheter ablation procedure present similar complication rate and clinical outcome compared to men. These findings suggest that the current underutilization of AF catheter ablation in women may represent a discrepancy in care. (Arq Bras Cardiol. 2018; 110(5):449-454)

Keywords: Arrhythmias,Cardiac; Atrial Fibrillation; Catheter Ablation; Cardiac Electrophysiology; Gender.

Introduction

Although age-adjusted prevalence of atrial fibrillation (AF) is relatively higher in men than in women, the absolute number of arrhythmia patients between genders is similar, with most cases occurring in patients between 65 and 85 years of age, a period in which, proportionately, more women are alive.[1]

Population studies show lower indication and execution rates of ablative treatment for AF in women with atrial fibrillation compared to men.[2-5] However, it is not clear whether this represents a discrepancy in assistance or a real difference. Based on the assumption that higher rates of complications and recurrence occur in women compared to men, the underutilization of AF ablation in women in this case, could be understood as an appropriate difference and not a direct lack of assistance.

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Previous studies evaluating differences between genders regarding safety and efficacy AF catheter ablation have conflicting results, and Brazilian literature on the topic is scarce.[6-13] In this study, we evaluated clinical characteristics and outcomes of a current Brazilian women cohort undergoing ablation of AF per catheter compared to results obtained in men.

Methods

Study design and participants

Cohort study of patients undergoing the first catheter ablation procedure for paroxysmal atrial fibrillation (FAP) refractory to antiarrhythmic drugs with minimum follow-up time per patient of 12 months. The study was conducted between 2013 and 2015 in a single center. Information was collected from patients' records by means of a digital collect instrument and indexed to an online database (Syscardio®). Clinical characteristics and procedures were compared between genders (M x W). Primary endpoint associated with efficacy was atrial arrhythmia absence lasting > 30 seconds during the follow-up period after first and only ablation procedure.

Procedures

All patients underwent circumferential isolation of pulmonary veins (PVs) through irrigated catheter ablation with a 3.5 mm tip without contact force measurement, using radiofrequency energy applications up to 35 Watts and 43°C per 10-45 seconds and demonstration of entrance and exit electrical blockade of PVs in relation to left atrium at the insulation end. All procedures were performed under general anesthesia, orotracheal intubation and invasive blood pressure monitoring by radial or left femoral puncture by the anesthesiologist. Transseptal punctures were performed with the help of intracardiac Eco, which was maintained throughout the procedure. Applications to left atrium posterior wall were monitored by an oesophageal thermometer with multiple covered sensors (Circa) and stopped whenever there was a change in esophageal temperature above 38°C. During all procedures, performed with an electro-anatomical mapping system based on thoracic impedance (EnSite Navx - Abbott), IV heparin bolus of 100mg / kg was performed followed by continuous infusion to maintain coagulation time activated between 350 and 450 sec.

After the procedure, patients remained on antiarrhythmic drugs (propafenone, sotalol or amiodarone depending on preference of attending physician) for 1 month and anticoagulant for a 3 months minimum period regardless CHA2DS2-VASc. It was done clinical follow-up 1, 3, 6 and 12 months after the procedure, performing ECG and at least two Holters throughout all the clinical follow-up. At the 10th week after ablation, patients were encouraged to perform continuous electrocardiographic monitoring (Holter) for 5 days. Any atrial arrhythmia greater than 30 seconds documented duration after 1 month of blanking period indicated arrhythmia recurrence.[14] Symptoms severity before ablation and during eventual recurrences was characterized by the Canadian Cardiovascular Society Severity of Atrial Fibrillation score (CCS-SAF).[15]

Statistical analysis

Clinical characteristics and procedures were compared between genders (M x W). Recurrence rates after a single procedure, as well as complications were also compared between groups. A convenience sample (non-probabilistic) was adopted during the study time, respecting the inclusion/exclusion criteria and follow-up time.

Continuous variables were described as mean and standard deviation and compared using unpaired Student's t-test (two-tailed), respecting the criteria of normality by the Shapiro-Wilk test. Categorical variables were described by absolute number and percentages in relation to total sample, and were compared using the χ^2 test or Fisher's exact test. Level of statistical significance adopted was 5%. Kaplan-Meier curve was used to evidence recurrence rates on the follow-up time and the Log-Rank test to evaluate difference between groups (M x W). Statistical analysis was performed using IBM SPSS Statistics Editor software, version 22.0.

Results

Patients

225 patients undergoing AF ablation were included in the study: 161 (71%) men and 64 (29%) women. Regarding follow-up time, there was no difference between men and women. Table 1 summarizes clinical characteristics

Table 1 – Clinical characteristics of patients undergoing AF ablation, categorization by gender

Variables	Men (n = 161)	Women (n = 64)	p-value
Age (years)	57 ± 11	62 ± 9	0.001*
BMI	27 ± 3.7	27 ± 5	0.64
Ejection Fraction (%)	63 ± 10	66 ± 6	0.02*
LA Diameter (mm)	38 ± 5	38 ± 5	0.93
CHADS2	0.9 ± 0.8	1.2 ± 1	0.04*
CHF	12 (7%)	4 (6%)	0.73
SAH	85 (52%)	43 (67%)	0.06
Diabetes Mellitus	17 (10%)	11 (17%)	0.18
Coronary Artery Disease	25 (15%)	12 (19%)	0.44
Prior Stroke/TIA	6 (4%)	5 (8%)	0.06
CCS SAF score	1.8 ± 0.8	2.3 ± 0.8	0.02*
Statin Use	44 (27%)	26 (40%)	0.03
ACE/ARA-2 Inhib	66 (41%)	30 (46%)	0.25
Previous / current use of AA	134 (83%)	58 (90%)	0.21
Diagnostic time (months)	11 ± 12	14 ± 10	0.87
Follow-up time (months)	34 ± 17 (12 – 66)	33 ± 14 (13 – 64)	0.87

*Values with ± indicate mean and standard deviation; CCS SAF: Canadian Cardiovascular Society Severity of Atrial Fibrillation scale; ACE: angiotensin converting enzyme; ARA-2: Angiotensin 2 receptor antagonist; Student t test and χ^2 for independent samples. * p-value indicates a statistically significant difference at the level of 5%.*

of men and women who underwent paroxysmal AF ablation during the study period. Regarding the mean age, women undergoing catheter ablation were older than men (57 ± 11 M x 62 ± 9 W p < 0.01) but there was no difference between groups in relation to body mass index (BMI) and left atrium anteroposterior diameter, although a smaller LV ejection fraction, possibly without clinical relevance, was observed among males (63 ± 10% M x 66 ± 6% W p < 0.05).

There was also no difference between genders regarding comorbidities such as hypertension, diabetes mellitus, heart failure, coronary disease and previous history of stroke/TIA. However, women presented a higher CHADS2 score (0.9 ± 0.8 M x 1.2 ± 1 W, p = 0.04) and were more symptomatic than men according to the CCS-SAF score (1.8 ± 0.8 M x 2.3 ± 0.8 W p = 0.02). Between genders, there was no difference in the proportion of the use of ACE/ARA-2 inhibitors and antiarrhythmic drugs; however, women showed greater use of statins compared to men (27% M x 40% W p = 0.03 - Table 1).

Efficacy and safety of procedures

Recurrence rates after single ablation procedure were similar between groups (21% M x 20% W p = 0.52). Table 2 summarizes procedures results as well as complications by gender. There were 3 inguinal pseudoaneurysms, 1 inguinal hematoma and 1 urethral trauma during bladder catheterization in men; among women, 1 inguinal hematoma and 1 retroperitoneal hematoma (5 (3%) M x 2 (3%) W p = 0.98) were observed. Despite prolonging hospitalization time, none of the complications required surgical intervention to be controlled. Throughout the study, atrium-esophageal fistulas, pericardial effusions, TIA/stroke after ablation or death were not reported.

The Kaplan-Meier curve (Figure 1) shows, throughout the study, gender equity in relation to recurrence rates, which occurred more frequently in first 12 months of follow-up, regardless of patient's gender. There was no difference in patients hospitalization time (days) categorized by gender (2.5 ± 0.7 M x 2.1 ± 0.8 W p = 0.76).

Discussion

Gender-specific differences may influence clinical and therapeutic behaviors in women with AF assistance. In a Canadian study, Singh et al.[16] characterized safety and efficacy equivalence and homogeneity of ablative procedure between men and women with persistent AF (post-hoc MAGIC-AF Trial),[16] guaranteeing its safety. In present study, in a current patients cohort with paroxysmal AF undergoing the first catheter ablation procedure, it is suggested that recurrence rates and complications are independent of patient's gender. These findings indicate that possible clinical considerations about safety and efficacy of ablative procedures in women with AF may be the main cause of ablation underutilization in female patients.

Gender-related differences in cardiac rhythm pharmacological control are well described in literature. Women are more symptomatic by the CCS-SAF score and report a lower improvement in quality of life when submitted to drug treatment, compared to men.[17] In addition, female patients have a higher toxicity and intolerability rate to antiarrhythmic drugs than men, being more prone to *Torsade de Pointes* and need for pacemaker implants due to drug induced bradycardia.[17,18] Therefore, catheter ablation can be considered as an early alternative for treatment of women with AF; it is a therapeutic method superior to drug therapy in maintenance of sinus rhythm[19] with low complications rates in same proportion than men.

It is speculated that there are biological differences in the mechanism of AF between men and women, that, in theory, could justify different results when they undergo ablation, but such hypothesis seems unlikely. In previous studies, Walters et al.[20] demonstrated left atrium and pulmonary veins electrophysiological characteristics similarity in men and women.[20] Similarly; Pfannmuller et al.[21] verified that there were no specific differences between genders due to atrial remodeling in AF through the expression of amyloid, collagen or bound junctions.[21]

In our study, the hypothesis that women in advanced age with AF present greater atrium electrical and structural remodeling and, consequently, worse post-ablation outcome, was not validated. The group of women was older than men and yet the time of diagnosis of arrhythmia is similar in both genders. In addition, left atrial diameter, a marker for post-ablation clinical recurrence, stroke, and death,[22,23] was similar in both groups. The fact that same clinical outcomes were observed in the long term between the groups also suggests that, in our study, there were no significant biological differences between men and women undergoing AF ablation.[24]

Limitations

In addition of being retrospective, the sample size may not have been sufficient to show differences between groups (M x W). The existence of selection bias in our cohort should also be considered, since only female candidates

Table 2 – Results of the procedures: Efficacy and safety

Variables	Men (n = 161)	Women (n = 64)	p-value
N°. of procedures	195	77	-
Complications *	5 (3%)	2 (3%)	0.98
Length of stay	2.5 ± 0.7 days	2.1 ± 0.8 days	0.76
Recurrence	34/161 (21%)	13/64 (20%)	0.89

*Values with ± indicate mean and standard deviation; * Men: 3 inguinal pseudo-aneurysms, 1 inguinal hematoma and 1 urethral trauma (bladder catheter). Women: 1 inguinal hematoma and 1 retroperitoneal hematoma; there were no deaths. Student's t-test and χ^2. P-value indicates a statistically significant difference at the level of 5%*

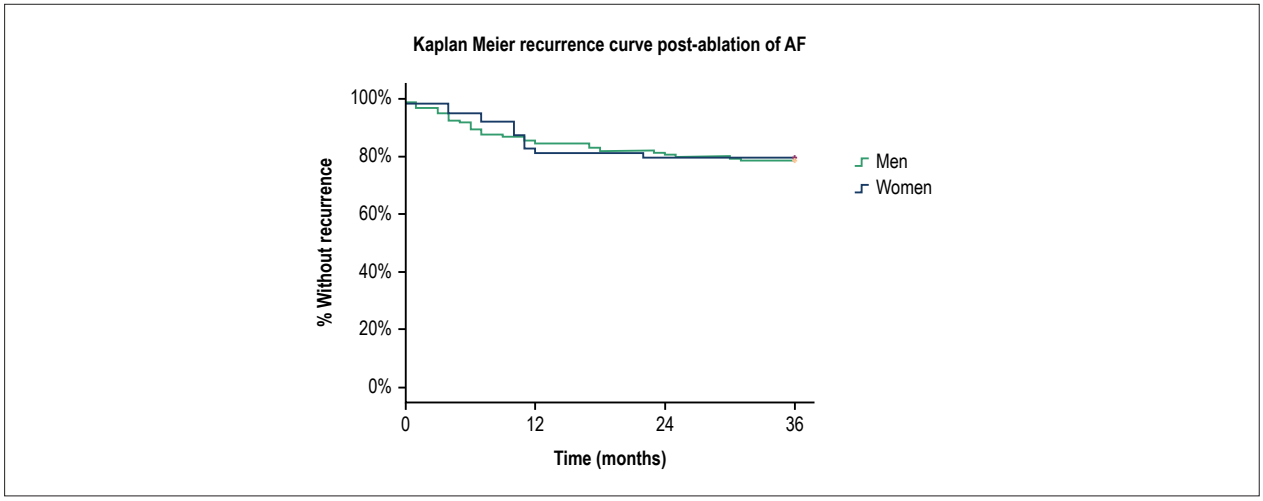

Figure 1 – *Kaplan Meier curves for clinical recurrence post ablation by catheter categorized by gender; Log Rank test for trend comparison between groups (MxW) p-value = 0.89*

submitted to ablation procedure were included in the analysis. Finally, a detailed analysis was not performed in the evaluation of symptoms resulting from AF; instead, the CCS-SAF score was used comprehensively.

Conclusion

In conclusion, in this population, women undergoing first AF catheter ablation procedure present clinical results regarding procedure safety and efficacy similar to men.

Author contributions

Conception and design of the research and Acquisition of data: Odozynski G, Dal Forno ARJ, Lewandowski A, d'Avila A; Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Odozynski G, Dal Forno ARJ, Lewandowski A, Nascimento HG, d'Avila A; Statistical analysis and Obtaining financing: Odozynski G, d'Avila A; Writing of the manuscript: Odozynski G, Lewandowski A, Nascimento HG, d'Avila A.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade Federal de Santa Catarina under the protocol number 45509015600000121. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Prevalence and Factors Associated with Metabolic Syndrome among Brazilian Adult Population: National Health Survey – 2013

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Abstract

Background: In Brazil, population-based researches analyzing prevalence and factors associated with metabolic syndrome (MS), a recognized predictor of cardiovascular diseases (CVD), and an important cause of disability and death in the country are scarce.

Objective: To evaluate prevalence of MS and its associated factors in Brazilian population.

Methods: Secondary analysis of the 2013 National Health Survey, a cross-sectional survey with national representativeness of Brazilian adult population (n = 59,402). MS was the outcome variable, defined from harmonization of cardiology international consensus as load ≥ 3 of the following components: self-reported diabetes and hypercholesterolemia, high blood pressure and high waist circumference. Analysis were stratified by sex and prevalence ratios, with their respective 99% confidence intervals (PR [CI 99%]) calculated by simple and multiple Poisson regression models.

Results: MS prevalence was 8.9%, being significantly higher among women compared to men; in general, this pattern was maintained in relation to exposure variables studied. Additionally, less than 25% of population did not present any MS component. In final multiple models, sociodemographic, behavioral and comorbidity variables were associated with MS, however, while low schooling (1.46 [1.23-1.74], cerebrovascular accident (1.36 [1], 00] (1.28 [1.03-1.62]) were associated among women, chronic renal failure (1.85 [2.23-2.76]) was associated exclusively among men.

Conclusion: We identified MS high prevalence in Brazilian population; on the other hand, factors associated with this condition were different depending on sex. (Arq Bras Cardiol. 2018; 110(5):455-466)

Keywords: Cardiovascular Diseases / mortality; Metabolic Syndrome / epidemiology; Epidemiology; Adult; Public Health Surveillance; Health Surveys.

Introduction

Changes that occurred in population socioeconomic and cultural patterns, as rapid urbanization and economic development consequence, resulted in significant changes in different population group life habits.[1] This new society organization form, associated with alimentary transition and population aging, promoted transformations in the way that people get sick, increasing morbidity and mortality by Noncommunicable Diseases (NCD).[2]

Concerning specific cardiovascular diseases (CVD), risk factors concomitant presence such as hypertension, hypercholesterolemia, diabetes, insulin resistance and central fat deposition is associated with an approximately 2.5-fold increase in cardiovascular morbidity and mortality risk.[3] This complex aggregate of CVD predisposing factors constitutes the condition defined as metabolic syndrome (MS).[4]

Worldwide MS recent estimate points to prevalence between 20-25% in adult population.[3] In U.S. MS prevalence was 34.7% in 2011-2012. It was defined by harmonized criterion, which synthesizes other classification criteria developed by different organizations to define this condition.[5] In Latin America cities, MS prevalence found between 2003 and 2005 was 21%, defined by National Cholesterol Education Program Expert Panel (NCEP-ATPIII) American criterion, presenting variation of 14% to 27%, according to studied territories.[6] In Brazil, prevalence was even higher, varying around 30% among individuals aged 19 to 64 years in different country regions.[7]

In this situation, Brazilian government launched the Strategic Action Plan to Tackle Noncommunicable Diseases (NCD) in Brazil 2011-2022, which includes, among other actions, generating information and knowledge about health-disease process and its social determinants for health policies formulation in Brazil.[8] In this sense, it was conceived the first National Health Survey (NHS) focused on risk factors surveillance and chronic diseases protection in Brazilian population.[9]

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In this perspective, based on 2013 NHS data, this study objective was to estimate MS prevalence and its components on Brazilian population aged ≥ 18 years and its association with sociodemographic, behavioral and biological variables.

Methods

Design and sample of the study

NHS is a household-based cross-sectional survey with representativeness of Brazilian adult population conducted between August and December 2013. NHS was a population survey on health and its determinants, carried out in Brazil by the Brazilian Institute of Geography and Statistics (IBGE) allied to the Ministry of Health.[9]

The sampling process was organized by clusters in three stages, where the primary sampling unit (PSU) was composed by census sectors, secondary unit was households and tertiary unit, inhabitants 18 years old or older. Within each stage, participants were selected through simple random sampling. It was considered the corresponding households weight, the dweller selection probability, non-response adjustments by sex and calibration by population totals, by sex and estimated age classes, with all the dwellers weight. A detailed methodology applied description for NHS-2013 was previously published.[9]

To describe Brazilian population health conditions, NHS was constituted by thematic modules that addressed health and lifestyle individual perception, chronic diseases presence, as well as sociodemographic information. For the study purposes, individuals with data on the factors that make up MS were selected, that is, diabetes mellitus and hypercholesterolemia self-referred medical diagnosis, in addition to blood pressure (BP) values and waist circumference measurements (WC).

Among the 69.954 domiciles occupied with resident selected for NHS-2013 interview, 60,202 individuals 18 years old or older were interviewed, representing response rate of selected residents of 86%.[9] We excluded 800 pregnant women from the total, generating a final sample composed of 59.402 individuals.

The National Commission of Ethics in Research (CONEP) approved the NHS project in June 2013, under Opinion N°. 328,159. All the interviewees who agreed to participate in the investigation signed the term of free and informed consent.[9]

Outcome variable

In this study, MS outcome variable was defined according to the international cardiology consensus harmonization proposal (IDF / NHLBI / AHA / WHF / IAS / IASO), characterized by the presence of three out of five metabolic risk factors.[4]

In our work, once NHS did not provide biochemical data, MS classification was made considering at least the presence of three of four situations available in database: 1) self-reported diabetes diagnosis; 2) BP values considered borderline for Systemic Hypertension diagnosis (HAS) (systolic ≥130 mmHg and/or diastolic ≥ 85 mmHg); 3) WC values above the cut-off point established as abdominal obesity threshold for South America population (men ≥ 90 cm and women ≥ 80 cm); and, 4) self-reported hypercholesterolemia diagnosis.

A trained team using a calibrated digital device evaluated BP. Individuals needed to be at rest and were oriented to empty their bladders, not smoke or drink during the 30-minute period prior to measurement and not perform any physical activity during the period of one hour before the measurement. BP measurements were made with individuals in sitting position, after having rested for at least five minutes. The individuals were instructed to stay relaxed and leaning against the back of the chair, not crossing their legs and leaving their left arm free of clothes and leaning on a table at the same level as their chest or heart. Three BP measurements were evaluated, with two minutes intervals between them. For the present study, the mean between the second and the third measures was used. In this technique, systolic and diastolic pressures were calculated by algorithms from the maximum oscillation point corresponding to average BP.[9]

As for anthropometric measurements, weight (kg), height (m) and WC (cm) were measured - having as reference for the perimeter the midpoint between last rib and iliac crest, being used, respectively, portable electronic scale, portable stadiometer, flexible and inelastic measuring tape with 0.1 cm precision. The procedures for anthropometry realization followed the same protocol used in the Brazilian Institute of Geography and Statistics (IBGE) 2008-2009 Family Budget Survey (FBS).[9]

Independent variables

Independent variables selection was performed based on distal and proximal determinants conceptual model, developed to show sociodemographic, behavioral and comorbid multiple factors impact for MS on population health status.[10]

Sociodemographic factors used included: sex, age (18-59 years and ≥ 60 years), schooling (≤ 8 years and > 8 years), skin color (white / non-white), marital status (living with partner or not), macro-region (South / Southeast /Center-West and North/Northeast). Macro regions were dichotomized in order to contrast Brazilian development poles, with the South, Southeast and Central West regions being the most developed. Behavioral variables were self-perceived health, considering the combination of "very good" and "good" responses, defining as reference "regular", "poor" and "very poor" responses.

For variable physical activity construction (PA), the following information were considered regarding free time and volume, effort duration and intensity for physical activity, using three months preceding the day of the interview as reference period for PA questions in the questionnaire. Effort intensity was obtained by conversion of physical exercise type or sport reported in vigorous or moderate PA as determined by the Physical Activity Compendium (PAC).[11] Effort duration in each session was expressed in minutes and divided into three groups: < 19; 20 to 29; > 30 minutes. Weekly frequency was determined by PA practice day number per week and, for analysis purpose, was divided into 0 to 2 days, 3 to 4 days and > 5 days per week.

Thus, PA variable was initially grouped into three categories, according to World Health Organization recommendation: active (individual that reaches or exceeds moderate physical activity for 150 minutes or vigorous physical activity for 75 minutes per week in at least 10 minutes sessions); inactive (which refuses to practice PA at leisure) and insufficient assets (when performing PA below recommendation).[11] Finally, it was decided to combine inactive and insufficient assets categories, transforming them into dichotomous variable (active/inactive).

Variables corresponding to comorbidities analyzed here were previous self-reported cerebral vascular accident medical diagnoses (CVA), chronic renal failure (CRF), depression and other cardiovascular diseases (CVD). For the latter, previous CVD diagnoses reports were considered, such as: infarction, angina, heart failure, among others. Overweight was identified according to body mass index cut-off points (BMI). In individuals aged between 18 and 59 years, values ≥ 25 kg/m² were considered overweight.[11] For those aged 60 years or older, values > 27 kg/m² were considered as overweight.[12]

Statistical analysis

Statistical analysis were processed with Stata software version 13.0 (Stata Corp., College Station, USA), using survey commands, whose analysis procedures take into account sampling design and weight.[13]

The comparison between MS prevalence, for each comorbidity and for disease burden was based on their respective confidence intervals of 99% (CI 99%). Prevalence ratios (PR) with their respective CI 99%, were calculated by simple and multiple Poisson regression models.[14]

Statistical modeling process was conducted using determinants conceptual model to MS,[10] applying hierarchical approach in analysis and using stepwise forward method for variables introduction, considering as eligible those with $p < 0.20$ (univariate analysis); variables in which the CI 99% did not include "1" or contributed to model adjustment remained in the model.

Associations between MS and potential associated factors were introduced according to sociodemographic, behavioral and comorbidity factors, analyzed by three multiple models. At distal level of analysis (Model 1), the sociodemographic variables age, schooling, skin color, conjugal situation and housing region were considered; for Model 2 composition we used, behavioral variables physical activity and health self-perception adjusted by Model 1; In model 3, variables referring to proximal determinants (comorbidities) were introduced and their effects being adjusted by model 2. It is emphasized that once variables set was defined in a hierarchically superior model, it did not suffer any alteration in others levels of analysis.

Justification for preserving variables in each model was based on result importance for MS occurrence understanding and effect magnitude, as well as its variability, represented here by CI 99%.[14] In addition, analysis were stratified by sex, considering that in descriptive analysis, MS showed to affect in different way male and female population, which may reflect different association factors between the groups.

Results

Sociodemographic, behavioral and comorbidities characteristics of 59.402 individuals over 18 years are described in Table 1 according to MS absence or presence. Physically inactive individual high frequency was identified (98.1%) and 53.8% who were overweight. Self-perception predominant report of very good or good health was observed (65.9%) and low schooling significant frequency (39.1%) among individuals.

Table 2 shows MS prevalence, comorbidities and MS components burden in Brazilian population. Abdominal obesity was the factor with highest prevalence in this study (65.2%, CI 99% 64.4-65.9), followed by high BP (40.7%, CI 99% 39.6-41.7). It was observed that in all comorbidities, women presented the most expressive results, with high BP (46.9%, CI 99% 45.5-48.3) the only condition in which men showed a higher prevalence. In components sum, it is observed that only 1/4 of population did not present any of studied changes (23.8% [CI 99% 22.9-24.7]), while 38.1% (CI 99% 37.2-39.0) of participants already presented at least one MS component and 29.2% (CI 99% 28.3-30.1) coexisted with two considered factors. MS condition was estimated at 8.9% (CI 99% 8.4-9.5) of Brazilian population, with women proportion in this condition (10.3% [CI 99% 9.6-11.2]) statistically surpassing what was observed in the male population (7.5% [CI 99%, 6.7-8.3]).

Table 3 presents MS prevalence according to studied exposure variables. There are greater aggravation prevalence among older individuals (≥ 60 years), lower schooling time (≤ 8 years) and living with a partner. MS was greater among individuals residing in SE/S/CW regions, physically inactive, with overweight and who considered their health precarious. Regarding comorbidities, in general, MS higher prevalence were found among individuals who reported prior CKD diagnosis, stroke and other cardiovascular diseases, in relation to those who said they did not have the disease. In addition, we identified that, regardless of characteristic or condition considered as risk, MS prevalence was always higher among women.

Results referring to factors associated with MS in hierarchical modeling process (hypothetical-causal model), different for men and women, are available in tables 4 and 5. In female population final model, we identified that MS probability was higher among individuals in the following situations: age ≥ 60 years (PR 3.20 [CI 99% 2.76-3.72]), education ≤ 8 (PR 1.46 [CI 99% 1, 23-1,74]), living with partner (PR 1.27 [CI 99% 1,11-1,45]), residing in SE/S/CW regions (PR 1.18 [CI 99% 1, 02-1.38]), regular to very bad health self-perception (PR 2.35 [CI 99% 1.99-2.78]), stroke (PR 1, (CI 99% 1.00-1.86), other CSD (PR 1.29 [CI 99% 1.03-1.62]), overweight (PR 2.09 [CI 99% 1, 79-2.42]) and depression (PR 1, 31 [CI 99% 1.07-1.59]) (Table 4).

Regarding male population, final model did not include variables as schooling, skin color, other CVD and CVA, age remaining in ≥60 years (PR 2.60 [CI 99% 2.04-3.31]), living with partner (PR 1.48 [CI 99% 1.17-1.88]), residing in SE/S/CW regions (PR 1.57 [CI 99% 1.28-1.94]), have worse ("regular to very bad") self-referred health (RP 2.59 [IC99% 2.01-3.33])

Table 1 – Sociodemographic, behavioral and comorbidity characteristics of adults and elderly - National Health Survey (NHS), Brazil, 2013

Variables	MS*					
	Total*		Male		Female	
	N = 59.402†		N = 25.920†		N = 33.482†	
	%*	CI 99%	%*	CI 99%	%*	CI 99%
Age						
18-59 years	81,8	80,9 - 82,5	83,3	82,4 - 84,1	80,4	79,6 - 81,1
≥ 60 years	18,2	17,4 - 19,0	16,7	15,9 - 17,5	19,6	18,8 - 20,9
Education						
> 8 years	60,9	59,7 - 62,0	60,2	58,9 - 61,4	61,5	60,5 - 62,5
≤ 8 years	39,1	37,9 - 40,2	39,8	38,6 - 41,0	38,5	37,4 - 39,5
Skin color						
White	47,4	46,4 - 48,5	46,8	45,7 - 47,9	48,1	47,0 - 49,1
Non-white §	52,5	51,5 - 53,6	53,2	52,1 - 54,3	51,9	50,9 - 53,0
Conjugal situation						
Do not live with a partner	55,7	54,6 - 56,7	53,4	52,2 - 54,6	57,8	56,8 - 58,8
Live with a partner	44,3	43,2 - 45,3	46,6	45,4 - 47,8	42,2	41,2 - 43,2
Housing region						
NE/N	34,0	33,3 - 34,7	34,2	33,4 - 35,1	33,8	32,9 - 34,6
SE/S/CW	66,0	65,3 - 66,7	65,8	64,9 - 66,6	66,2	65,4 - 67,0
Physical activity						
Active	1,9	1,6 - 2,2	2,2	1,9 - 2,5	1,6	1,3 - 1,9
Inactive	98,1	97,8 - 98,4	97,8	97,5 - 98,1	98,4	98,0 - 98,6
Health self-perception						
Very good/good	65,9	65,0 - 66,9	70,3	69,3 - 71,2	62,1	61,1 - 63,1
Regular – Very bad	34,1	33,0 - 34,9	29,7	28,8 - 30,7	37,9	36,9 - 38,9
Overweight						
No	46,2	45,1 - 47,3	47,5	46,4 - 48,7	45,0	43,9 - 45,9
Yes	53,8	52,7 - 54,9	52,5	51,3 - 53,6	55,0	54,0 - 56,0
Another CVD ‡						
No	95,8	95,3 - 96,2	96,1	95,6 - 96,5	95,5	95,1 - 95,9
Yes	4,2	3,8 - 4,7	3,9	3,5 - 4,4	4,5	4,1 - 4,9
Chronic renal failure						
No	98,6	98,3 - 98,8	98,6	98,4 - 98,9	98,5	98,2 - 98,7
Yes	1,4	1,2 - 1,7	1,4	1,1 - 1,6	1,5	1,3 - 1,7
Stroke						
No	98,5	98,2 - 98,7	98,4	98,1 - 98,6	98,5	98,3 - 98,7
Yes	1,5	1,3 - 1,8	1,6	1,4 - 1,9	1,5	1,3 - 1,7
Depression						
No	92,3	91,7 - 92,9	96,1	95,6 - 96,5	88,9	88,3 - 89,6
Yes	7,7	7,1 - 8,2	3,9	3,5 - 4,4	11,1	10,4 - 11,7

MS: metabolic syndrome; CI 99%: confidence interval 99%; N: norte; NE: northeast; SE: southeast; S: south; CW: central-west; CVD: cardiovascular disease; (*) Generated considering the sample weight; (†)Number of individuals in the database; (§)Yellow, indigenous, brown, black; (‡) infarction, angina, heart failure or other.

Table 2 – Prevalence (%) of comorbidities and burden of diseases (risk factors for MS), by sex, of adults and elderly. National Health Survey (NHS), Brazil, 2013

Disease, burden and MS	Total N = 59.402		Male N = 25.920		Female N = 33.482	
	%*	CI 99%	% *	CI 99%	% *	CI 99%
Diabetes	7,1	6,6 - 7,6	6,3	5,6 - 7,2	7,8	7,1 - 8,5
High BP	40,7	39,6 - 41,7	46,9	45,5 - 48,3	34,9	33,7 - 36,3
Hypercholesterolemia	14,7	14,0 - 15,5	11,9	10,9 - 13,1	16,9	16,0 - 17,9
High WC	65,2	64,4 - 65,9	55,6	54,0 - 57,1	73,9	72,7 - 75,0
Disease burden						
0	23,8	22,9 - 24,7	28,0	26,7 - 29,4	19,9	18,8 - 21,1
1	38,1	37,2 - 39,0	34,8	33,5 - 36,2	41,0	39,8 - 42,3
2	29,2	28,3 - 30,1	29,7	28,4 - 31,0	28,7	27,6 - 29,9
3	7,5	7,1 - 8,1	6,5	5,8 - 7,3	8,5	7,8 - 9,3
4	1,4	0,9 - 1,2	1,0	0,7 - 1,3	1,8	1,5 - 2,2
MS Condition †	8,9	8,4 - 9,5	7,5	6,7 - 8,3	10,3	9,6 - 11,2

MS: metabolic syndrome; N: number of individuals in the database; CI 99%: confidence interval 99%; BP: blood pressure; WC: waist circumference; (*) Generated considering the sample weight; (†) MS Condition, sum of disease burden ≥ 3 factors.

and present IRC (RP 1.85 [IC99% 2.23-2, 76]), overweight (RR 3.58 [IC99% 2.73-4.70]) and depression (RP 1.41 [IC99% 0.98-2.02]) (Table 5).

Regarding the physical activity variable, in order not to compromise analysis, we chose not to include it in the model, given the low prevalence of physically active individuals (1.8%), which would result in inaccurate estimates, due to large standard error (Table 4 and 5). In addition, considering the referential adopted, such comparisons become unnecessary, since almost entire Brazilian population is characterized as physically inactive (98.1%) (Table 1).

Discussion

MS is a multidimensional phenomenon determined by an interaction factor set that affects people quality of life.[3] Despite the existence of studies on chronic diseases and their risk factors in Brazilian population,[15] as the Adult Health Longitudinal Study, we do not yet have MS prevalence national representativeness in the country. Thus, the present study evaluated for the first time the factors associated with MS in a Brazilian population representative sample aged over 18 years, representing a milestone in the MS investigation in Brazil, collaborating in construction of evidence capable of directing resolute strategies for prevention and control of this problem.

We identified that approximately 9% Brazilian population presented MS status, according to consensuses harmonization definition.[4] Nevertheless, our study reveals worrying data, accounting that only 23.8% of population does not present any MS component, and that 67.3% have between one and two components to characterize this outcome, which demonstrates high number of individuals under developing MS risk.

Considering sex, highest MS occurrence was found among female population (10.3%, CI 99% 9.6-11.2), fact that has been widely recorded in scientific literature, [16,17] especially among those with age > 59 years, which can be explained by hormonal changes that occurred after menopause.[17] At this moment of life, there is tendency to accumulate abdominal fat and also to increase density of LDL particles circulating in bloodstream that become more atherogenic, known condition associated to increased risk of CVD.[18] It is also possible to highlight the high number of morbidity found among women in this study, who presented higher prevalence of diabetes, hypercholesterolemia and abdominal obesity in relation to masculine sex.

Considerable differentiation in MS abnormalities prevalence and combinations between the sexes suggests different physiopathology between men and women[19] possibly explained by sex hormones different levels that influence metabolism regulatory mechanisms.[20] The greater androgenic activity found among men as well as postmenopausal estrogen levels reduction among women are conditions that favor an increase in visceral abdominal fat and in bloodstream lipids concentration, which is correlated with insulin resistance, hypertension, and increased cardiovascular risk.[20]

Among MS components, high WC results (65.2%, CI 99% 64.4-65.9) are highlighted in the study population. Abdominal obesity plays an important role in MS,[21,22] because it is associated with a metabolic disorder capable of damaging the artery wall, leading to vasoconstriction deregulation, inflammatory cascades activation, and adipokines effects elevation, considered to be factors that induce CVD.[22] Cohort study conducted by Lee et al.[22] showed that the additional 500 cm^3 volume increase of subcutaneous and visceral fat is associated with MS incidence and risk factors aggravation for CVD.[22] A obese individuals cohort study conducted in Italy showed that abdominal obesity contributed to MS prevalence in obese women, but not in men.[19]

Table 3 – MS Prevalence according to exposure variables studied - National Health Survey (NHS), Brazil, 2013

Variables	MS*					
	Total		Male		Female	
	N = 59.402		N = 25.920		N = 33.482	
	p (%)*	CI 99%	p (%)*	CI 99%	p (%)*	CI 99%
Age						
18-59 years	5,8	5,3 - 6,3	5,4	4,7 - 6,3	6,1	5,5 - 6,8
≥ 60 years	23,2	21,4 - 25,1	17,5	14,7 - 20,8	27,6	25,0 - 30,3
Education						
> 8 years	6,3	5,7 - 6,9	6,8	5,8 - 7,8	5,8	5,1 - 6,6
≤ 8 years	13,1	12,1 - 14,2	8,4	7,1 - 9,9	17,6	15,9 - 19,3
Skin color						
White	9,7	8,9 - 10,6	8,9	7,7 - 10,5	10,4	9,3 - 11,6
Non-white†	8,3	7,5 - 9,0	6,1	5,2 - 7,1	10,3	9,2 - 11,4
Conjugal situation						
Do not live with a partner	6,9	6,4 - 7,6	4,6	3,8 - 5,6	8,9	8,1 - 9,8
Live with a partner	11,5	10,5 - 12,5	10,7	9,3 - 12,2	12,3	10,9 - 13,7
Housing region						
NE/N	7,3	6,6 - 8,0	5,3	4,4 - 6,2	9,1	8,0 - 10,3
SE/S/CW	9,8	9,1 - 10,6	8,6	7,5 - 9,8	10,9	9,9 - 12,1
Physical activity						
Active	1,8	0,7 - 4,9	2,5	0,7 - 8,6	1,0	0,3 - 3,4
Inactive	9,1	8,6 - 9,7	7,6	6,8 - 8,4	10,5	9,7 - 11,3
Health self-perception						
Very good/good	4,8	4,3 - 5,3	4,5	3,8 - 5,4	5,0	4,4, 5,7
Regular – Very bad	17,1	15,9 - 18,3	14,4	12,5 - 16,5	19,0	17,4 - 20,7
Overweight						
No	4,8	4,3 - 5,5	3,4	2,6 - 4,4	6,2	5,4 - 7,2
Yes	12,5	11,7 - 13,4	11,1	9,9 - 12,5	13,7	12,5 - 14,9
Another CVD ‡						
No	8,3	7,7 - 8,8	6,9	6,1 - 7,7	9,5	8,8 - 10,3
Yes	24,9	20,9 - 29,4	21,8	15,9 - 29,2	27,3	22,2 - 33,2
Chronic renal failure						
No	8,8	8,2 - 9,3	7,2	6,4 - 8,1	10,2	9,4 - 11,0
Yes	21,9	16,6 - 28,3	25,7	17,3 - 36,3	18,8	12,8 - 26,8
Stroke						
No	8,7	8,1 - 9,2	7,2	6,4 - 8,1	10,0	9,3 - 10,8
Yes	27,0	20,6 - 34,5	22,7	14,2 - 34,2	31,4	22,6 - 41,7
Depression						
No	8,3	7,7 - 8,8	7,1	6,3 - 7,8	9,4	8,6 - 10,3
Yes	17,1	14,6 - 19,9	15,6	10,7 - 22,3	17,6	14,7 - 20,9

MS: metabolic syndrome; CI 99%: confidence interval 99%; N: norte; NE: northeast; SE: southeast; S: south; CW: central-west; CVD: cardiovascular disease; (*) Generated considering the sample weight; (†)Number of individuals in the database; (§)Yellow, indigenous, brown, black; (‡) infarction, angina, heart failure or other.

Table 4 – Bivariate analysis and multivariable models for factors associated with metabolic syndrome among Brazilian women according to hierarchical levels of exposure variables studied - National Health Survey (NHS), Brazil, 2013

Variables	Bivariate analysis		Model 1		Model 2		Model 3	
	PR	CI 99%	PR	CI 99%	PR	CI 99%	PR	CI 99%
Age								
18-59 years	1		1		1		1	
≥60 years	4,49	3,90- 5,18	3,44	2,95- 4,01	2,99	2,56- 3,48	3,20	2,76- 3,72
Education								
>8 years	1		1		1		1	
≤ 8 years	3,01	2,55- 3,55	1,98	1,67- 2,34	1,54	1,29- 1,83	1,46	1,23- 1,74
Conjugal situation								
Do not live with a partner	1				1		1	
Live with a partner	1,37	1,18- 1,58	1,38	1,21- 1,58	1,33	1,17- 1,52	1,27	1,11- 1,45
Housing region								
NE/N	1		1		1		1	
SE/S/CW	1,20	1,02- 1,41	1,18	1,01- 1,36	1,30	1,12- 1,52	1,18	1,02- 1,38
Skin color								
White	1							
Non-white*	0,98	0,84- 1,15						
Physical activity								
Active	1							
Inactive	10,06	3,08- 32,84						
Health self-perception								
Very good/good	1				1		1	
Regular – Very bad	3,76	3,23- 4,38			2,65	2,24- 3,14	2,35	1,99- 2,78
Stroke								
No	1						1	
Yes	3,13	2,29- 4,27					1,36	1,00- 1,86
Another CVD†								
No	1						1	
Yes	2,86	2,32- 3,51					1,29	1,03- 1,62
Overweight								
No	1						1	
Yes	2,19	1,85- 5,59					2,09	1,79- 2,42
Depression								
No	1						1	
Yes	1,86	1,54- 2,26					1,31	1,07- 1,59
Chronic renal failure								
No	1							
Yes	1,84	1,26- 2,69						

PR: prevalence ratio; CI 99%: confidence interval 99%; N: norte; NE: northeast; SE: southeast; S: south; CW: central-west; CVD: cardiovascular disease; (*) Yellow, indigenous, brown, black; (‡) infarction, angina, heart failure or other.

Table 5 – Bivariate analysis and multivariable models for factors associated with metabolic syndrome among Brazilian men according to hierarchical levels of exposure variables studied - National Health Survey (NHS), Brazil,2013

Variables	Bivariate analysis		Model 1		Model 2		Model 3	
	PR	CI 99%	PR	CI 99%	PR	CI 99%	PR	CI 99%
Age								
18-59 years	1		1		1		1	
≥ 60 years	3,23	2,55- 4,08	2,74	2,17- 3,46	2,07	1,61- 2,67	2,60	2,04- 3,31
Education								
> 8 years	1							
≤ 8 years	1,24	0,99- 1,54						
Conjugal situation								
Do not live with a partner	1		1		1		1	
Live with a partner	2,30	1,82- 2,92	1,81	1,43- 2,30	1,74	1,37- 2,20	1,48	1,17- 1,88
Housing region								
NE/N	1		1		1		1	
SE/S/CW	1,63	1,31- 2,02	1,49	1,20- 1,85	1,74	1,40- 2,14	1,57	1,28- 1,94
Skin color								
White	1							
Non-white†	0,67	0,54- 0,84						
Physical activity								
Active	1							
Inactive	3,02	0,84- 10,90						
Health self-perception								
Very good/good	1				1		1	
Regular – Very bad	3,17	2,51- 4-01			2,72	2,12- 3,50	2,59	2,01- 3,33
Stroke								
No	1							
Yes	3,15	1,99- 4,98						
Another CVD‡								
No	1							
Yes	3,17	2,29- 4,39						
Overweight								
No	1						1	
Yes	3,27	2,45- 4,37					3,58	2,73- 4,70
Depression								
No	1						1	
Yes	2,19	1,49- 3,23					1,41	0,98- 2,02
Chronic renal failure								
No	1						1	
Yes	3,57	2,41- 5,28					1,85	1,23- 2,76

PR: prevalence ratio; CI 99%: confidence interval 99%; N: norte; NE: northeast; SE: southeast; S: south; CW: central-west; CVD: cardiovascular disease; (*) Yellow, indigenous, brown, black; (‡) infarction, angina, heart failure or other.

In our study, a possible explanation for elevated WC high prevalence can be derived from the lower cut-off points established by ethnicity standardization for abdominal obesity (≥ 90 cm for men and ≥ 80 cm for women),[4] when compared with limit values NCEP-ATPIII (102 cm for men and 88 cm for women).[23] Therefore, this high and worrisome abdominal obesity prevalence in Brazilian population reflects in the increased risk of developing some cardiovascular disease[22] and consequent risk for increased morbidity and mortality and impact on the health system.[2]

Positive relationship between MS prevalence and increase in age, found here, has been widely disseminated, especially due to differences attributed to sex,[17] not only due to cumulative effect, reflecting the exposure time to risk factors related to inappropriate eating behaviors and unhealthy lifestyles, as well as the biological factors contribution in both sexes, due to direct relationship with testosterone/estrogen levels balance, specifically among women.[20] MS has been slightly more diagnosed among men with less than fifty years of age, fact that is reversed after fifty years, affecting female population with greater magnitude.[17]

From sociodemographic point of view, this study showed that living in SE/S/CW regions was presented as factor associated with MS, which can be explained, in part, by these regions concentrating the country main urban centers, contributing to lifestyles promotion characterized by unhealthy eating habits and physical exercises low frequency, which have as consequence, increased risk of obesity, type 2 DM, arterial hypertension, CVD and MS.[5]

In a systematic review carried out among South American countries, this hypothesis was confirmed by showing that western eating habits and lifestyle pattern were found in greater proportion in large urban areas where chronic no communicable diseases were related to these behaviors.[24] In addition, through an investigation conducted in Brazil, it was evident that there was a high calories consumption in the capitals located in the South, Southeast and Center-West regions, while in the capitals in the North and the Northeast a consumption below average was observed among the population.[25]

It is important to point out that in these large urban centers regions, society is increasingly induced by food offers messages, diets and western behaviors.[26] In recent years, in Brazil, metropolitan regions have shown reduction in household consumption of polished rice, beans, cereals and legumes (down 60%, 49% and 25%, respectively), with a concomitant continuous consumption increase of foods such as: beverages and infusions (22% and 24%), prepared foods and industrial mixtures (67%), highlighting 490% increase in the amount of non-alcoholic beverage purchased between 1974 and 2009, evidencing a change in food behavior that is not always favoring healthy choices in developed regions.[27]

Our results showed that education lowest level was associated with MS prevalence in women, but this association was not evident among male population. This finding is consistent with the international literature, as observed in a study conducted in China, where educational level was also inversely related to MS prevalence strictly among women.[28] In Korea, distinctly, it was identified that men with less schooling had lower odds ratios (OR) for both SM (OR 0.76, 95% CI 0.60-0.96), as well as for two of its isolated components: high WC (OR 0.73, 95% CI 0, 60-0.91) and low HDL cholesterol (OR 0.73, 95% CI 0.59-0.91), compared to men with higher education.[29] In this study, a higher MS prevalence was observed among the socially disadvantaged women who had lower education level, unemployed, lower income level and who performed manual labor, as highlighted in our results in educational level terms.[29]

However, an antagonistic result was observed in high educational level male population, where cardiovascular risk factors distribution was more observed in this population stratum. This may be a reflection of the socioeconomic environment, which increases MS risk in one of the genders more specifically.[30]

In relation to conjugal situation variable, it is not clear how civil status contributes to MS. In the present study, the situation of living with a partner was associated to MS and to a greater extent in male population. This finding was also evident among Australians, where women who married gained more weight compared to unmarried women, after adjusting for potential confounding factors.[31] Similarly, in the study by Averett et al.,[32] marriage was associated with an increased risk of overweight/obesity, both for men and women.[32]

Ortega et al.,[33] identified that sex affects the relationship between obesity, cardiometabolic risk factors and marital status due to changes in behavioral factors.[33] Although most studies have reported that married people became more sedentary,[34] with direct reflection in overweight and impact on MS comorbidities, collaborating with the results found in this work, other studies show different results, attributing to marital relationship type the MS outcome.[26,35] In this case, it is considered that positive conjugal relationships can protect from stressful situations, providing both material and support benefits, while negative relationships or lack of relationship can increase exposure to conflicts, with consequent stress level elevation,[35] factor recognized as associated to MS.[10]

Regarding behavioral aspects, we identified that "regular to very bad" health negative self-perception was important factor associated to MS. Health self-perception is global indicator in which the person considers, in addition to possible diseases, the impact they generate on physical, social and mental well-being.[32] In Spain, by contrasting our results, in a multicenter study performed with DM and/or MS carriers recently diagnosed, 42.2% of the individuals believed to have good or excellent health, representing little awareness of the cardiovascular risk they presented.[36] In this work, the association of negative self-perception "regular to very bad "with MS draws attention, because it may reflect that the studied population was aware of their health condition, but remains within the risk range for metabolic complications development, assuming that there may be other factors that prevent them from leaving this condition and deserve to be better investigated.

Regarding MS prevalence and association with comorbidities (CVD, stroke and depression), all were more frequent among females compared to males, with

CRF exception. Association between MS and CRF found exclusively among men can be partly justified by hypertension high prevalence installed in this group.[19] In recent decades, it has become increasingly evident that hypertensive patients prognosis is strongly affected by renal impairment especially in terms of mortality and cardiovascular events.[37] In relation to the greater number of comorbidities associated to MS among women in the study, it can be explained in part by the low demand of men for health services, which generates an underdiagnosis.[2]

CVDs are the leading cause of death in Brazil,[2] and should be a public health priority, through policies for their prevention and control. Association between DCV and MS was demonstrated in a Danish cohort, in which older women with MS presented risk of 1.7 (95% CI 1.44-2.05) for CVD development.[38] Correlation can also be explained by Salas et al.,[16] who showed that obese adults, mainly women, are particularly at risk of developing MS, with significant implications for their health, especially CVD and diabetes. These results highlight the weight loss importance to reduce morbidities associated to MS.[16]

Another disease condition associated with MS was depression, with higher prevalence found among women. Similarly, study conducted in Korea with middle-aged individuals aged 40-64 years found high prevalence among women with 11.7%, compared to 4.1% in men.[39] These findings may be similar to what was found in disease prospective cohort among the Dutch population, where depression was significantly associated with higher WC and triglyceride levels during a 6-year follow-up.[40] In this context these results may imply that older age may be associated with an increased response to stress and cortisol levels, more frequently among women than men.[39]

Methodological pattern reinforced presented results robustness; however, some limitations must be addressed. Up to the time of submission of this study, IBGE had not published HDL laboratory data, which led us to characterize MS in the occurrence of three of the four - and not five - components available in the database.

Another point refers to the use of self-reported medical diagnoses. The investigated population answered if "*some doctor already gave him the diagnosis of diabetes*?" Or "(...) *hypercholesterolemia*?", which reduces classification bias, because they were considered present when there was a positive response to the previous medical diagnosis of these diseases; On the other hand, given the issues of underdiagnoses, there is a real possibility of the presence of individuals who did not know their health condition at the time of the interview. In any case, even in these situations, we observed that MS high prevalence in our study is consistent with the literature,[7,10,16] which warns of the possibility that this prevalence may be underestimated, implying a negative prognosis for Brazilian population aged ≥18 years.

Another limitation of this study is its cross-sectional design, which is why socioeconomic, behavioral and comorbidities factors analyzed here can not be unequivocally considered causal for MS. Especially in reference to comorbidities, it is important to highlight reverse causality role in identified associations, since clinical course start for CVD, stroke, depression and CRI would be in MS, despite the fact that delineation does not allow to affirm that this fact occurred in the studied population. However, use of data with national representativeness and conceptual model to base not only variables selection, but also analytical strategy, allows relevant information production for Brazilian population health conditions diagnosis, in which refers to MS, aligned with national public health priorities.

Conclusion

We identified high prevalence of MS in adult and elderly population in Brazil, being associated with sociodemographic variables (age, schooling, conjugal status and housing region), behavioral (self-perception of health) and comorbidities (stroke, CVD, weight, depression and CRF) differently between the sexes.

Finally, the relevance of the burden of each MS component, reiterates MS as a clinical and epidemiological tool in the identification of individuals and population groups with greater vulnerability to CVD occurrence and as a guideline to cost-effective interventions on factors presented. Thus, our results suggest the need to strengthen public policies for health promotion in order to encourage the adoption of healthy behaviors; otherwise, it will be unlikely to fulfill the goals set forth in the Strategic Action Plan to Tackle Noncommunicable Diseases (NCD) in Brazil 2011-2022.

Author contributions

Conception and design of the research and Analysis and interpretation of the data: Ramires EKNM, Menezes RCE, Silveira JAC, Longo-Silva G, Santos TG; Acquisition of data: Marinho PM; Statistical analysis: Ramires EKNM, Menezes RCE, Silveira JAC, Marinho PM; Writing of the manuscript: Ramires EKNM, Menezes RCE, Silveira JAC; Critical revision of the manuscript for intellectual content: Menezes RCE, Silveira JAC, Santos TG.

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 study was approved by the Ethics Committee of the Brazil Platform, directed to the Comissão Nacional de Ética em Pesquisa (CONEP) the protocol number 10853812.7.0000.0008. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Safety and Efficacy of Aerobic Exercise Training Associated to Non-Invasive Ventilation in Patients with Acute Heart Failure

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Abstract

Background: Exercise training (ET) improves functional capacity in chronic heart failure (HF). However, ET effects in acute HF are unknown.

Objective: To investigate the effects of ET alone or combined with noninvasive ventilation (NIV) compared with standard medical treatment during hospitalization in acute HF patients.

Methods: Twenty-nine patients (systolic HF) were randomized into three groups: control (Control - only standard medical treatment); ET with placebo NIV (ET+Sham) and ET+NIV (NIV with 14 and 8 cmH_2O of inspiratory and expiratory pressure, respectively). The 6MWT was performed on day 1 and day 10 of hospitalization and the ET was performed on an unloaded cycle ergometer until patients' tolerance limit (20 min or less) for eight consecutive days. For all analyses, statistical significance was set at 5% ($p < 0.05$).

Results: None of the patients in either exercise groups had adverse events or required exercise interruption. The 6MWT distance was greater in ET+NIV (Δ120 ± 72 m) than in ET+Sham (Δ73 ± 26 m) and Control (Δ45 ± 32 m; $p < 0.05$). Total exercise time was greater (128 ± 10 vs. 92 ± 8 min; $p < 0.05$) and dyspnea was lower (3 ± 1 vs. 4 ± 1; $p < 0.05$) in ET+NIV than ET+Sham. The ET+NIV group had a shorter hospital stay (17 ± 10 days) than ET+Sham (23 ± 8 days) and Control (39 ± 15 days) groups ($p < 0.05$). Total exercise time in ET+Sham and ET+NIV had significant correlation with length of hospital stay ($r = –0.75$; $p = 0.01$).

Conclusion: Exercise training in acute HF was safe, had no adverse events and, when combined with NIV, improved 6MWT and reduce dyspnea and length of stay. (Arq Bras Cardiol. 2018; 110(5):467-475)

Keywords: Exercise; Acute Heart Failure; Non-Invasive Ventilation; Physiotherapy; Rehabilitation.

Introduction

Heart failure (HF) is a complex syndrome characterized by reduced left ventricular function, skeletal myopathy and exercise intolerance.[1,2] Previous studies have shown evidences that exercise training (ET) can be an effective non-pharmacological intervention for patients with chronic HF.[3-6] However, periods of acute/decompensated HF may occur, which represent the most frequent cause of hospitalization,[7] leading to long periods of bed rest and sarcopenia[8,9] and, consequently, complications during hospitalization.

Acute HF patients show worsening pulmonary congestion, dyspnea, increased respiratory effort, exercise intolerance[10] and frequently, decreased alveolar ventilation, which results in blood shunting and hypoxemia.[11] In this context, noninvasive ventilation (NIV) has been widely used in acute HF cases to reduce dyspnea and improve oxygenation.[12,13]

In addition, patients with chronic HF have displayed a progressive reduction in functional capacity and decreased exercise tolerance compared to healthy individuals, due to both cardiac disease and peripheral factors (endothelial dysfunction, inflammation, and increased neurohormonal activation).[14,15] Moreover, it has been already demonstrated that exercise with NIV in chronic HF increases exercise tolerance and reduces dyspnea and leg effort.[16,17]

Several studies have shown that early exercise after admission can benefit critical patients in the intensive care unit[18,19] and patients with chronic obstructive pulmonary disease exacerbations.[20,21] These studies showed a reduction in length of stay and rehospitalization, as well as improved quality of life. However, ET in acute HF patients has been contraindicated and there have been no studies to evaluate the effects of cardiac rehabilitation on acute/decompensated HF. Thus, despite extensively documented evidence regarding the benefits of exercise[5,22] and NIV combined with exercise[16] in chronic HF patients, the safety and effectiveness of aerobic ET in acute HF patients remains unknown.

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Therefore, in the present study, we aimed to investigate in acute/decompensated HF patients, (i) the safety of in-hospital aerobic ET; and (ii) the effectiveness of aerobic ET combined with NIV during hospitalization in patients with acute HF.

Methods

This was a controlled, prospective and randomized study. A convenience sample of 29 patients was recruited from the acute HF ward of a cardiology hospital. These patients had an established diagnosis of acute HF and a previous Doppler echocardiography with left ventricle ejection fraction (LVEF) < 30%. All of them were in NYHA class IV.

Patients were excluded from the study if they had unstable angina, complex cardiac arrhythmias, pacemaker, cardiac resynchronization therapy or left ventricular assist device, myocardial infarction within the previous 12 months, oxyhemoglobin saturation by pulse oximetry (SpO_2) at rest <88% without oxygen supplementation, or acute pulmonary edema with clinical indications for mechanical ventilation. In addition, patients with clinical indication of NIV besides the proposed by this protocol were excluded.

Study protocol

All of the subjects underwent an individualized clinical evaluation after hospital admission on day 1 (D1) by the cardiologist and physiotherapist involved in the study. Pulmonary function tests (spirometry), blood sample (brain natriuretic peptide [NT-proBNP] and high sensitivity C-reactive protein [hs-CRP]), six-minute walk test (6MWT), and maximal inspiratory pressure (MIP) test were performed.

All patients received standard medical treatment[7] and after clinical and laboratorial tests they were randomized into three groups: ET+NIV, ET+Sham and Control. We decided to include a placebo NIV group to test the hypothesis that exercise alone (ET+Sham) or exercise associated to NIV (ET+NIV) were better than conventional treatment (Control group) in acute heart failure patients.

The ET+NIV group performed aerobic ET associated with NIV once a day, for 8 consecutive days; and the ET+Sham group performed aerobic exercise with placebo NIV once a day, also for 8 consecutive days. The control group (Control) received only medical treatment and did not perform aerobic exercise training.

At D10 all patients underwent the same clinical evaluation as D1. After the protocol, all patients continued receiving only medical treatment, and were followed-up until hospital discharge or transfer to the intensive care unit.

Exercise protocol

The ET+NIV and ET+Sham groups performed aerobic exercise on an unloaded in-bed cycle ergometer (Cajumoro, Brazil) for 20 minutes or less, until limit of tolerance. The exercise groups were blinded to pressure applied to NIV or Sham. SpO_2 (Nonin® Medical, USA) and heart rate (HR) were continuously measured with a heart rate monitor (Polar® RS800, Finland). Systolic and diastolic arterial pressures (SAP and DAP) were obtained by the auscultatory method (Unilec™ sphygmomanometer and Littmann Quality stethoscope; USA). Blood lactate (Accutrend Plus®, Germany) was collected during the exercise protocol, at rest, every two minutes, and at the end of exercise. The patients were asked to rate their "shortness of breath" at exercise cessation by the 0–10 Borg's category ratio scale.[23]

Noninvasive positive pressure ventilation

Noninvasive ventilation was delivered using the bi-level ventilator (BiPAP Vision®; Respironics, USA), applied via oronasal mask in two conditions: bi-level positive airway pressure ventilation – inspiratory positive airway pressure: 14 cmH_2O, and expiratory positive airway pressure: 8 cmH_2O, without supplementary oxygen (FiO_2 0.21) and sham ventilation – inspiratory positive airway pressure: 4 cmH_2O, and expiratory positive airway pressure: 4 cmH_2O, without supplementary oxygen (FiO_2 0.21).

The pressure values were selected based on previous evidence that an inspiratory positive pressure range of 8–20 cmH_2O and a positive end-expiratory pressure range of 4–10 cmH_2O were associated with positive clinical effects in a population with similar levels of acute HF.[24,25] The inspiratory positive pressure and positive end-expiratory pressure values in the sham NIV were set to minimum value (4 cmH_2O), since the BiPAP Vision cannot be reduced below 4 cmH_2O. Those values in sham NIV were able to overcome the resistance imposed by the ventilator circuit (as directed by the manufacturer) and to ensure that patients remained blinded to the intervention being applied.

Pulmonary function test and maximal inspiratory pressure

Spirometric tests were performed, and forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC ratio were measured (EasyOne® Plus Diagnostic spirometer, Switzerland).

MIP was measured with a digital manometer (MVD-300® V.1.1 Microhard System; Globalmed, Brazil). Patients were instructed to perform a maximum inspiration from residual volume; each patient performed five maximum inspirations with differences smaller than 10% between them, and the highest result was used for the analysis. Therefore, all results were compared to predicted values.[26]

Six-minute walk test

The 6MWT was performed on a 30-m flat corridor, according to the American Thoracic Society.[27] Blood pressure, HR, and SpO_2 were measured, and the modified dyspnea Borg scale was applied. All measurements were performed before and immediately after completion of the tests, and after a two-minute recovery period. HR and SpO_2 were monitored throughout the test (Nonin™ portable oximeter – USA).

Statistical analysis

Statistical analysis was carried out with the SPSS software (version 20.0, SPSS Inc., USA). Data were expressed as mean ± standard deviation or as median and interquartile range, as appropriate, and categorical data are expressed as frequency (n and %). The normality of data distribution was determined by Shapiro-Wilk test. The chi-square test was used to assess differences between categorical data, and repeated-measures ANOVA followed by Bonferroni corrections were used for multiple comparisons. Pearson's correlation was used for parametric correlations. For all analyses, statistical significance was set at 5% ($p < 0.05$).

Results

Baseline measures

Twenty-nine patients who fulfilled all the inclusion criteria were enrolled in the study and randomized into three groups: Control (n = 9, 58 ± 7 years of age), ET+Sham (n = 9, 57 ± 5 years) and ET+NIV (n = 11, 56 ± 8 years). All patients had diagnosis of acute HF. There were no differences in anthropometric and demographic variables, cause of HF, LVEF, main comorbidities, medications, and NT-proBNP or hs-CRP plasma levels among groups (Table 1). The functional class, exercise tolerance and pulmonary function were not different among groups (Table 2).

Effects of exercise training associated with NIV and sham ventilation

None of the patients of group ET+NIV or ET+Sham had any criteria for exercise interruption. Total exercise time was shorter in the ET+Sham group (~30% lower compared to ET+NIV) (Table 2).

On D10, the ET+NIV and ET+Sham groups had a greater walking distance compared to the control group (Table 2). In addition, Δ6MWT distance on D10 was greater in the ET+NIV group (Figure 1, Panel C) than in the ET+Sham group (Figure 1, Panel B) and the control group (Figure 1, Panel A). There were no differences in blood pressure, HR and SpO_2 during 6MWT between the groups (data not shown).

Dyspnea score at rest was higher at baseline (D1) and decreased over time in all three groups. Moreover, ET+NIV group had the lowest dyspnea value on D10 (Figure 2). The number of patients receiving dobutamine infusion at D1 was similar among groups; however, on D10 the exercise

Table 1 – Baseline characteristics of hospitalized acute heart failure patients allocated into one of the three groups – exercise training + non-invasive ventilation (ET+NIV), ET + Sham or Control group

	Control (n = 9)	ET+Sham (n = 9)	ET+NIV (n = 11)
Anthropometrics/Demographics			
Male, n (%)	7 (78%)	8 (89%)	7 (64%)
Age, years	58 ± 7	57 ± 5	56 ± 8
Weight, kg	65.3 ± 14.8	74.0 ± 13.5	66.4 ± 10.8
Height, m	1.60 ± 0.71	1.68 ± 0.10	1.64 ± 0.40
BMI, kg/m^2	24.2 ± 5.0	26.9 ± 4.6	24.8 ± 4.0
LVEF, %	23.8 ± 4.9	25.4 ± 6.7	26.0 ± 4.8
NTpro-BNP, pg/mL	2467 ± 547	2331 ± 429	2594 ± 633
hs-CRP, mg/L	8 ± 3	9 ± 4	9 ± 5
Length of stay, days	39 ± 15	23 ± 8*	17 ± 10*†
Main comorbidities			
Hypertension, n (%)	5 (56%)	3 (33%)	5 (54%)
Dyslipidemia, n (%)	4 (44%)	1 (11%)	1 (9%)
Diabetes mellitus, n (%)	2 (22%)	2 (22%)	1 (9%)
Etiology			
Ischemic, n (%)	6 (67%)	7 (80%)	7 (44%)
Main medications			
β-blocker, n (%)	7 (78%)	6 (67%)	8 (73%)
ACE inhibitors or ARBs, n (%)	4 (43%)	6 (63%)	7 (64%)
Diuretics, n (%)	9 (100%)	9 (100%)	11 (100%)

*Definition of abbreviations: BMI: body mass index; LVEF: left ventricular ejection fraction; NTpro-BNP: brain natriuretic peptide; hs-CPR: high sensitive C-reactive protein; ACE: angiotensin conversor enzyme; ARBs: angiotensin II receptor blockers. Values expressed as mean ± standard deviation or frequency (n and %). Repeated-measures ANOVA with appropriate Bonferroni corrections was applied to variables described as mean ± standard deviation and the chi-square test was used to assess differences in categorical data. * p < 0.05 vs. Control; † p < 0.05 vs. ET+Sham*

Table 2 – Characteristics of the "exercise training + non-invasive ventilation (ET + NIV)", "ET + Sham" and Control groups at hospital admission and after study protocol

	Day 1			Day 10		
	Control	ET+Sham	ET+NIV	Control	ET+Sham	ET+NIV
NYHA						
II, n (%)	-	-	-	3 (33%)	5 (55%)*	8 (72%)*
III, n (%)	-	-	-	4 (44%)	3 (33%)*	2 (18%)*
IV, n (%)	9 (100%)	9 (100%)	11 (100%)	2 (22%)	1 (11%)*	1 (10%)*
Dobutamine, n (%)	5 (55%)	4 (44%)	6 (54%)	3 (33%)	2 (22%)*‡	2 (18%)*‡
Exercise tolerance						
Total exercise time, min	-	-	-	-	92 (60 – 120)	128 (90 – 160)†
6MWT, m	221 ± 58	238 ± 51	224 ± 30	266 ± 83	311 ± 67*‡	345 ± 61*†‡
Δ6MWT, m	-	-	-	45 ± 32	73 ± 26*	120 ± 72*†
Pulmonary function						
MIP, cmH_2O	-65 ± 20	-53 ± 20	-60 ± 11	-64 ± 31	-61 ± 36	-63 ± 15
MIP, % predicted	73 ± 25	77 ± 33	72 ± 24	72 ± 32	75 ± 42	77 ± 22
FEV_1, % predicted	57 ± 21	59 ± 20	61 ± 22	68 ± 29	60 ± 20	65 ± 21
FEV_1/FVC	0.72 ± 0.18	0.79 ± 0.10	0.75 ± 0.12	0.74 ± 0.17	0.78 ± 0.18	0.76 ± 0.10

*Definition of abbreviations: NYHA: New York Heart Association; 6MWT: six minute walk test; MIP: maximal inspiratory pressure; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity. Values are expressed in mean ± standard deviation; median (interquartile range) and frequency (n and %). Repeated-measures ANOVA with the appropriate Bonferroni corrections was applied to variables described as mean ± standard deviation and the chi-square test was used to assess categorical data differences in frequency variables; * p < 0.05 vs. Control; † p < 0.05 vs. ET+Sham; ‡ p < 0.05 vs. Day 1*

groups (ET+Sham and ET+NIV) had a lower number of patients receiving dobutamine infusion compared to the control group (Table 2).

From D1 to D10, there was a significant reduction in NT-proBNP (ΔNT-proBNP: -892 ± 112 ρg/mL [Control]; -1184 ± 299 ρg/mL [ET+Sham]; -1002 ± 356 ρg/mL [ET+NIV]) and hs-CRP levels (Δhs-CRP: -4 ± 2 mg/L [Control]; -4 ± 3 mg/L [ET+Sham]; -5±3 mg/L [ET+NIV]), but without differences among groups. In addition, there was a similar reduction in body weight from D1 to D10 between the three groups studied (Δweight: -3.3 ± 2.2 kg [Control]; -5.3 ± 3.9 kg [ET+Sham]; -5.0 ± 2.0 kg [ET+NIV]). No differences in small airway obstruction, MIP and blood lactate were found between the groups at D1 and at D10 (Table 2).

Follow-up

None of the patients of the exercise groups needed to be transferred to the intensive care unit. In addition, more patients in the ET+NIV and ET+Sham groups had an early hospital discharge compared to the control group. Of note, the control group had a significantly greater length of stay compared to the exercise groups. In addition, the ET+NIV group had a shorter length of stay compared to the ET+Sham group (Table 1). Interestingly, total exercise time performed in both groups (ET+Sham and ET+NIV) was inversely related to length of stay (Figure 3).

Discussion

To the best of our knowledge, this is the first study to assess the role of aerobic exercise training in acute/decompensated HF (NYHA class IV). The main and new findings of this study are that exercise in acute/decompensated HF (i) is safe, since neither ET+Sham nor ET+NIV groups showed worse symptoms during exercise or signs of requiring exercise interruption and (ii) reduces the length of hospital stay. In addition, the exercise increases the 6MWT distance.

Studies have demonstrated that early mobilization therapy in intensive care unit patients can significantly reduce the length of stay.[19] It has also been demonstrated that rehabilitation immediately following an acute exacerbation of chronic obstructive pulmonary disease is associated with a reduced frequency of re-exacerbation and with an increase in quadriceps muscle strength.[20,21] In the same line, a recently study demonstrated that functional electrical stimulation improved exercise tolerance and muscle strength in acute HF patients.[28] Our study extends the knowledge about approaches to be used during hospitalization to treat decompensated HF patients. It suggests that aerobic exercise training *per se* is a safe and effective tool to reduce length of hospital stay in acute HF patients. It should be emphasized that none of the patients who performed exercise had worsening of symptoms during exercise or exhibited any signs of exercise intolerance.

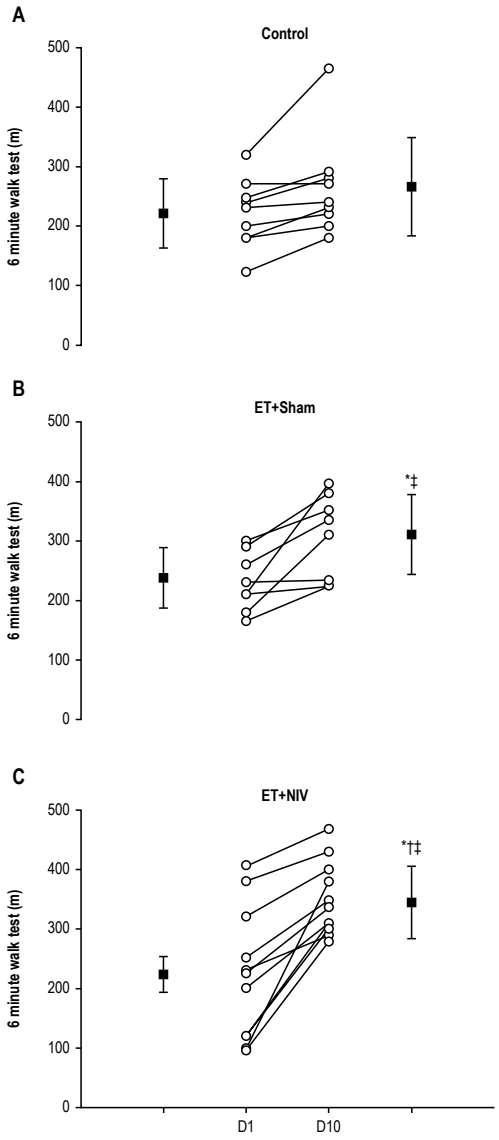

Figure 1 – *Six minute walk test distance achieved at D1 and D10 in Control, ET+Sham and ET+NIV groups. Notes: Open circles: individual distance achieved at D1 and D10. Dark square: mean and standard deviation of distance at D1 and D10. * p < 0.05 vs. Control; † p < 0.05 vs. ET+Sham; ‡ p < 0.05 vs. D1.*

Another important finding in our study was the increase in exercise tolerance in patients who underwent aerobic exercise. Actually, this finding has clinical implications. The 6MWT distance is associated with clinical outcome and quality of life in patients with HF.[29] Furthermore, it is possible that the aerobic exercise training improves exercise tolerance even in hospitalized HF patients.

In order to investigate if the use of NIV could have additional effects on aerobic exercise training, we found that ET+NIV group had improved exercise performance and decreased dyspnea during the exercise. In fact, NIV might reduce venous return and cardiac preload,[30] which could explain our findings. Another finding of great interest and clinical relevance was that the ET+NIV had a shorter hospital stay, enhanced 6MWT distance and exercise time compared to ET+Sham group, suggesting that the NIV can enhance the effectiveness of aerobic exercise in acute HF patients. The rationale for this theory is that NIV combined to exercise has some influence on redistribution of muscle blood flow.[16] Dempsey et al.[31] suggested that respiratory muscles influence vascular diameter and peripheral vasoconstriction. Respiratory muscles might compete for the reduced blood flow during exercise with the peripheral muscles, thereby promoting an inadequate oxygen transport and exercise fatigue. In addition, fatiguing contractions could stimulate IV phrenic afferents by muscle metabolic production, increasing sympathetic vasoconstriction with consequent reduction in oxygen delivery.[31,32]

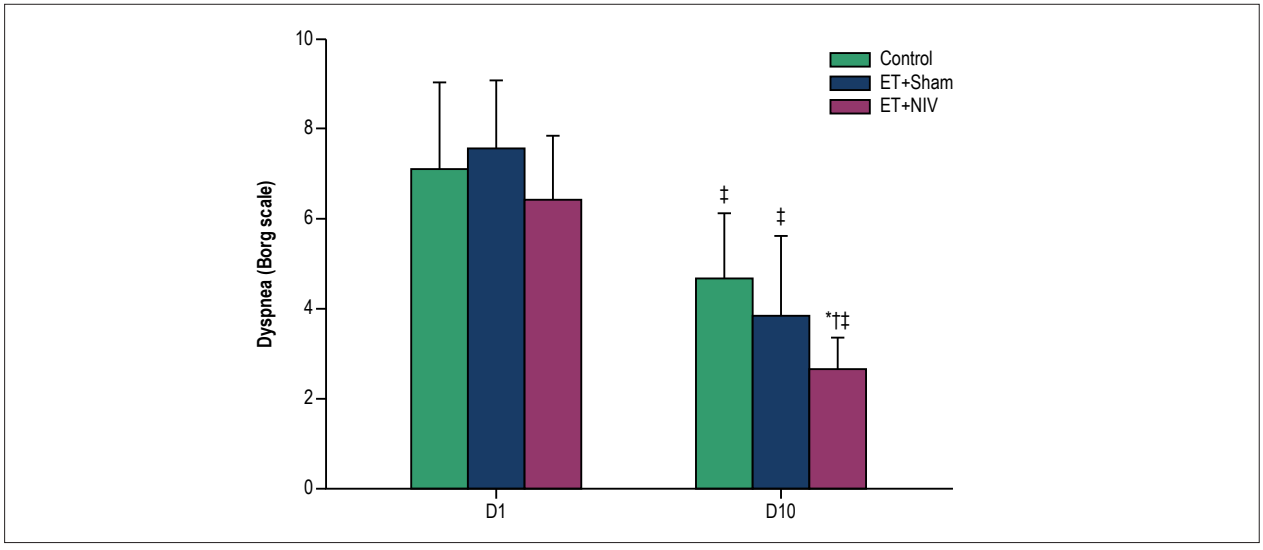

Figure 2 – *Dyspnea Borg scale at first day of hospitalization (D1) and at last day of protocol (D10) in Control, Exercise Training (ET) + Sham and ET+non-invasive ventilation (NIV) groups. Notes: * p < 0.05 vs. Control; † p < 0.05 vs. ET+Sham; ‡ p < 0.05 vs. D1.*

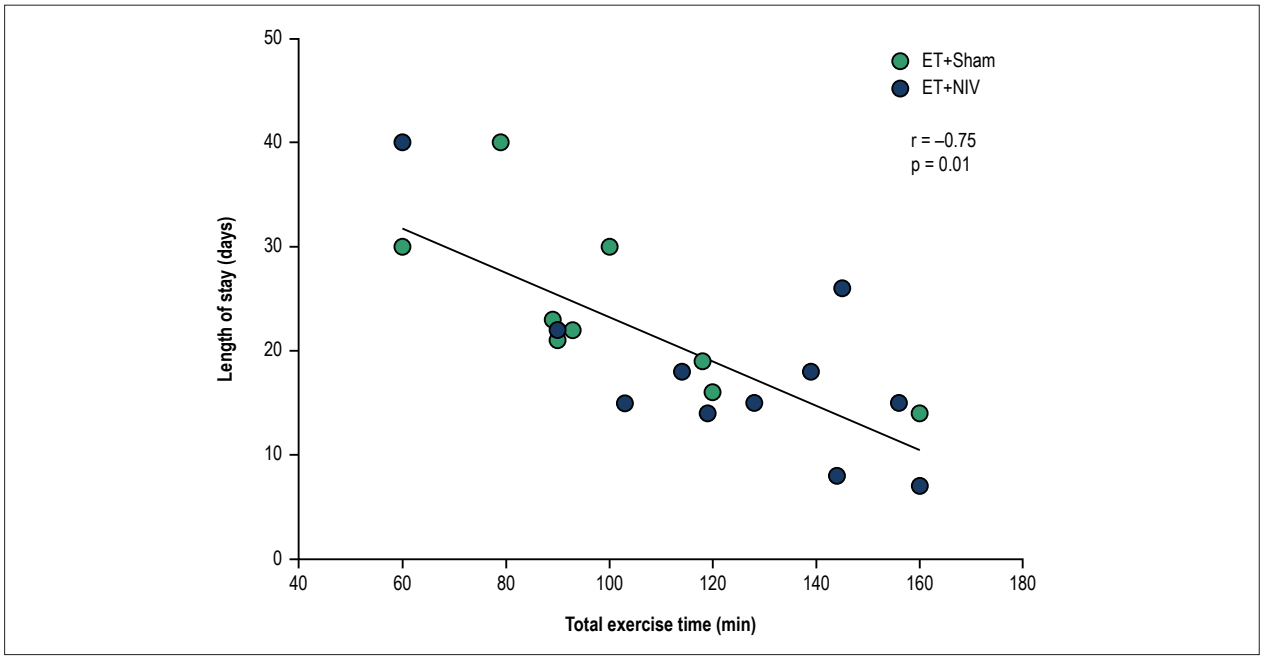

Figure 3 – *Correlation between total exercise time and length of hospital stay (days) in exercise groups.*

It was recently demonstrated that patients with chronic HF has slower oxygen kinetics with increased deoxyhemoglobin kinetics during exercise.[14] On the other hand, Borghi-Silva et al.[16] demonstrated that NIV was able to improve exercise tolerance and reduce the deoxyhemoglobin kinetics in peripheral muscle during exercise in patients with chronic HF. In our study, the ET+NIV group showed better response to aerobic exercise. The mechanism for this response is beyond the scope of our study, however it is likely that NIV influenced muscle blood flow redistribution, from the respiratory muscles to the peripheral muscles, improving oxygen delivery and utilization.

Study limitations

The present study has some limitations that should be addressed. First, we had a small number of patients. In addition, our patients performed an aerobic exercise

without workload (unloaded exercise). We chose this type of exercise because this is the first protocol of this type in acute HF patients, and the repercussions of the exercise were unknown.

Also, we acknowledge that exercise groups performed the protocol during 8 days only, but such period was established based on the mean length of stay in our institution. Further studies on exercise and its main outcomes should be performed including the whole hospitalization period. In fact, this was the first study to perform aerobic exercise training in acute HF, so a reduced exercise protocol duration was necessary to check the viability and safety of aerobic exercise in this patient population.

Our study raises new questions regarding exercise in acute HF. Further study protocols must be performed to confirm our data, including clinical outcomes as death and worsening HF, other exercise modalities (inspiratory muscle training, resistive, etc.) and how to perform the aerobic exercise prescription in acute HF, as recently demonstrated in chronic HF.[33]

Clinical implications

Our study provides evidences of the importance of aerobic exercise during hospitalization in acute HF patients. The findings of safety, reduced length of stay and increased exercise tolerance suggest aerobic exercise training as a new tool for the management of acute HF in combination with standard clinical therapy. Moreover, the enhance of the positive effects of aerobic exercise when combined to NIV, reinforce the relevance of our study, and opens new challenges to investigate the mechanisms of this strategy that contributes to better clinical outcomes in patients with decompensated HF.

Conclusion

Aerobic exercise is safe, improves the exercise tolerance and reduces hospital stay for decompensated HF patients. Moreover, NIV can enhance the effectiveness of aerobic exercise in these patients. These findings suggest that this simple tool associated with standard clinical therapy may be useful during hospitalization for the management of acute HF.

Author contributions

Conception and design of the research: Oliveira MF, Ferreira VM, Umeda IIK, Sperandio PA; Acquisition of data: Oliveira MF, Santos RC, Artz SA, Correia EB, Ferraz AS; Analysis and interpretation of the data: Oliveira MF, Santos RC, Artz SA, Ferreira VM, Lobo DML, Correia EB, Ferraz AS, Umeda IIK, Sperandio PA; Statistical analysis: Oliveira MF, Lobo DML; Writing of the manuscript: Oliveira MF, Santos RC, Artz SA, Ferreira VM; Critical revision of the manuscript for intellectual content: Lobo DML, Correia EB, Ferraz AS, Umeda IIK, Sperandio PA.

Potential Conflict of Interest

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

Sources of Funding

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Instituto Dante Pazzanese de Cardiologia under the protocol number #3911. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Percutaneous Coronary Intervention in Chronic Total Occlusion

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Abstract

Percutaneous coronary intervention in chronic total occlusion is a rapidly evolving area, being considered the last frontier of interventional cardiology. In recent years, the development of new techniques and equipment, as well as the training of specialized personnel, increased their success rates, making it the most predictable procedure available. Although the number of randomized and controlled studies is still limited, results from large multicentered registries allow us to safely offer this intervention to patients, as another treatment option along with the optimized drug treatment and myocardial revascularization surgery. This review summarizes the last and most relevant publications in the subject in order to provide an overall view of the field's current status.

Introduction

Percutaneous coronary intervention (PCI) in chronic total occlusion (CTO) has expressed great expansion and evolution with the development of new techniques and equipment, as well as with the training of specialized personnel. These factors have significantly raised success rates, making these procedures more effective and predictable. The aim of this manuscript is to present an update regarding indications, the aspects of the procedure, their results and clinical applicability of PCIs in CTO.

Definition and epidemiology

CTO are defined as coronary obstructions which produce total occlusion of vessel lumen with TIMI 0 flow and duration longer than 3 months. Occlusions with minimal passage of contrast without opacification of the distal vessel are considered "functional CTO".

CTOs are present in 18-52% of patients submitted to coronary angiography and who have coronary heart disease.[1-3] More recent registries showed a prevalence between 16 and 20%.[4,5] In these studies, the percentage of patients with CTO submitted to PCI was low. In two Canadian studies, only 9-10% of patients underwent PCI, while 57 to 64% of them remained in clinical treatment and 26 to 34% were referred for surgery.[2,4]

Keywords

Coronary Artery Disease / complications; Coronary Occlusion; Percutaneous Coronary Intervention.

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Histopathological aspects

Understanding the histopathology of CTOs is an essential step to define the best percutaneous therapeutic strategy. The CTOs are consisted of a proximal and a distal cap, with an occluded segment between them. Histological analysis of these lesions showed that, in the proximal cap, more fibrous and calcified components are more predominant than in the distal one and which, despite complete angiographic occlusion, may have intravascular microchannels which cross the occluded segment.[6-8] Blunt caps present histopathological differences when compared to tapered ones, with less frequent intravascular microchannels.[7]

The viability of the myocardium irrigated by the occluded artery is maintained by collateral circulation, which may be developed by angiogenesis or by the action of circulating endothelial progenitor cells.[9] It is difficult to assess the ability of collateral vessels to maintain coronary perfusion, and the angiography is not the most accurate method to predict the functionality of collaterals. The traditional knowledge that the occluded vessel has 'adequate and sufficient collaterals' for CTO ischemia prevention is challenged by physiological evidence with fractional flow reserve (FFR) analysis.[10]

Selection of patients

European guidelines for myocardial revascularization recommend that CTO PCI should be considered for ischemia reduction in the corresponding myocardial territory and/or for reduction of angina (class IIa, level of evidence B).[11] According to the guidelines for the management of stable coronary disease, indications for CTO revascularization should be the same as one for a subtotal stenosis, provided that viability, ischemia of a sufficiently large territory and/or angina symptoms are present.[12] With the current techniques, equipment, success and complication rate, patient selection should not depend on the type of lesion (total, subtotal or severely obstructive), but rather on symptoms and on the findings in complementary tests.[13] Although it is essential to ensure the viability of the myocardial territory supplied by a chronically occluded vessel, the presence of collateral circulation does not prevent the occurrence of ischemia in this area.[10] Thus, the size of the collateral circulation should not be used as a criterion to contraindicate revascularization.

Ischemia and myocardial viability

In addition to symptoms, evaluating the presence of ischemia and myocardial viability are fundamental steps. In asymptomatic patients, the evaluation of ischemia before CTO PCI is considered. The analysis of the receiver operating characteristic (ROC) curve of a cohort involving 301 patients showed 12.5% as the optimal amount of ischemia pre-procedure in order to identify patients who have benefited from the intervention in terms of ischemia reduction.[14]

The presence of myocardial viability is important to identify patients who would benefit from CTO recanalization. A combination of viability parameters may predict better and more accurate myocardial function than the use of a single parameter, such as transmural extension of the infarction, evaluation of the contractile reserve with dobutamine and thickening of the normal myocardial wall in cardiac magnetic resonance, especially in segments with intermediate extension of infarction.[15]

The procedure

Planning the procedure

The use of angiographic scores to estimate the probability of success and the type of approach is essential in the planning of the procedure. The J-CTO score is the oldest and most widespread one (Figure 1).[16] Patients with higher J-CTO scores have significantly lower success rates, longer procedures, greater use of contrast, and more frequent use of the retrograde approach.[17,18] Other relevant scores are the PROGRESS-CTO score and the Clinical and Lesion (CL) score.[19,20] These three scoring systems present similar predictive abilities for technical success, being more accurate in anterograde cases.[21]

Overall technical aspects

The performance of *ad hoc* CTO PCI to the diagnostic procedure is widely discouraged, in order to allow a careful and appropriate review of angiography, obtaining informed consent and limiting the use of contrast and procedure.

Contrast injection in the occlusion vessel simultaneously with injection into the donor vessel of the collateral circulation (simultaneous contralateral injection) is indispensable for the determination of CTO characteristics, including lesion length, proximal and distal cap morphology, lateral branches and the extension and morphology of the collateral branches. Anterograde injection should be avoided from the moment that subintimal dissection occurs in the anterograde space, since the hydraulic pressure of the contrast injection may increase the dissection plane, increasing the subintimal bruise. The use of combinations of bi-femoral, femoral-radial or bi-radial accesses will depend on the staff's preference, the availability of the necessary materials, the patient's characteristics, the procedure and the anatomy.[22]

In order to have better planning of treatments of CTOs, the so-called hybrid algorithm has been developed, which has allowed to maximize success and reduce the time of the procedure, radiation and the use of contrast, enabling the teaching and dissemination of techniques and reducing inter-and intra-operator approach variability and success rates. The core of this algorithm is the rapid identification of the failure of each strategy followed by immediate exchange for another type of technique.

The algorithm or hybrid approach consists of two paths (anterograde and retrograde) and two ways of crossing CTO: through true lumen or through the subintimal space (with dissection and then re-entry to the true lumen). The definition of which path to use and how to cross the occlusion is determined by 4 main anatomical factors: proximal cap anatomy, occlusion length, presence of a disease-free zone for reentry in the distal vessel and presence of usable septal or epicardial collaterals (Figure 2).

Even by using modern techniques in centers of excellence, failure can still occur, which does not make a new attempt unfeasible.[23] Unsuccessful cases in which the lesion is "modified" – especially the proximal cap, whether with multiple dissections made by wire-specific guides or micro catheters, whether through balloon angioplasty or even subintimal approach – are called "investment procedures", which aim to facilitate a future attempt at recanalization.[23]

Anterograde technique with wire scaling

Staggering of anterograde wires is the most commonly used approach. A micro catheter is advanced to the proximal cap, followed by attempts to cross CTO using specific guidewires according to the morphology of the cap. Generally, it starts with a soft and fine-tipped guidewire (1.0 g), coated with polymer. If the crossing is unsuccessful, a slightly heavier wire (4.0 g), also polymer coated, or a sharp, tapered 12-gauge wire is used. The recent introduction of rigid composite core guidewires seems to further enhance the success of anterograde crossover by allowing better torque control and transmission.

Understanding the guidewire path is critical both to increase the likelihood of success and to minimize the risk of complications. If the guidewire enters the true distal lumen (confirmed in two orthogonal projections), the micro catheter is advanced through the occlusion and the guidewire is replaced by a traditional one, followed by balloon angioplasty and stent implantation. If the guidewire comes out of the vessel architecture, it must be retracted and redirected. If the guidewire crosses the occlusion but enters the subintimal space, reentry into the true lumen can be achieved by the "parallel wires" technique (less commonly used today) or the use of a dedicated re-entry system.

Anterograde dissection and reentry technique

Dissection and reentry are related to the intentional use of the subintimal space to cross the occlusion, a strategy that should be considered when the CTO extension is greater than 20 mm. Strategies to induce limited and controlled dissections seem to have better short- and long-term results when compared to those that cause extensive dissections.[24-26]

Controlled dissection can be achieved with dedicated micro catheters that create a limited dissection plane. The reentry is obtained with the help of a specific balloon for this purpose. A recent study demonstrated that the use of

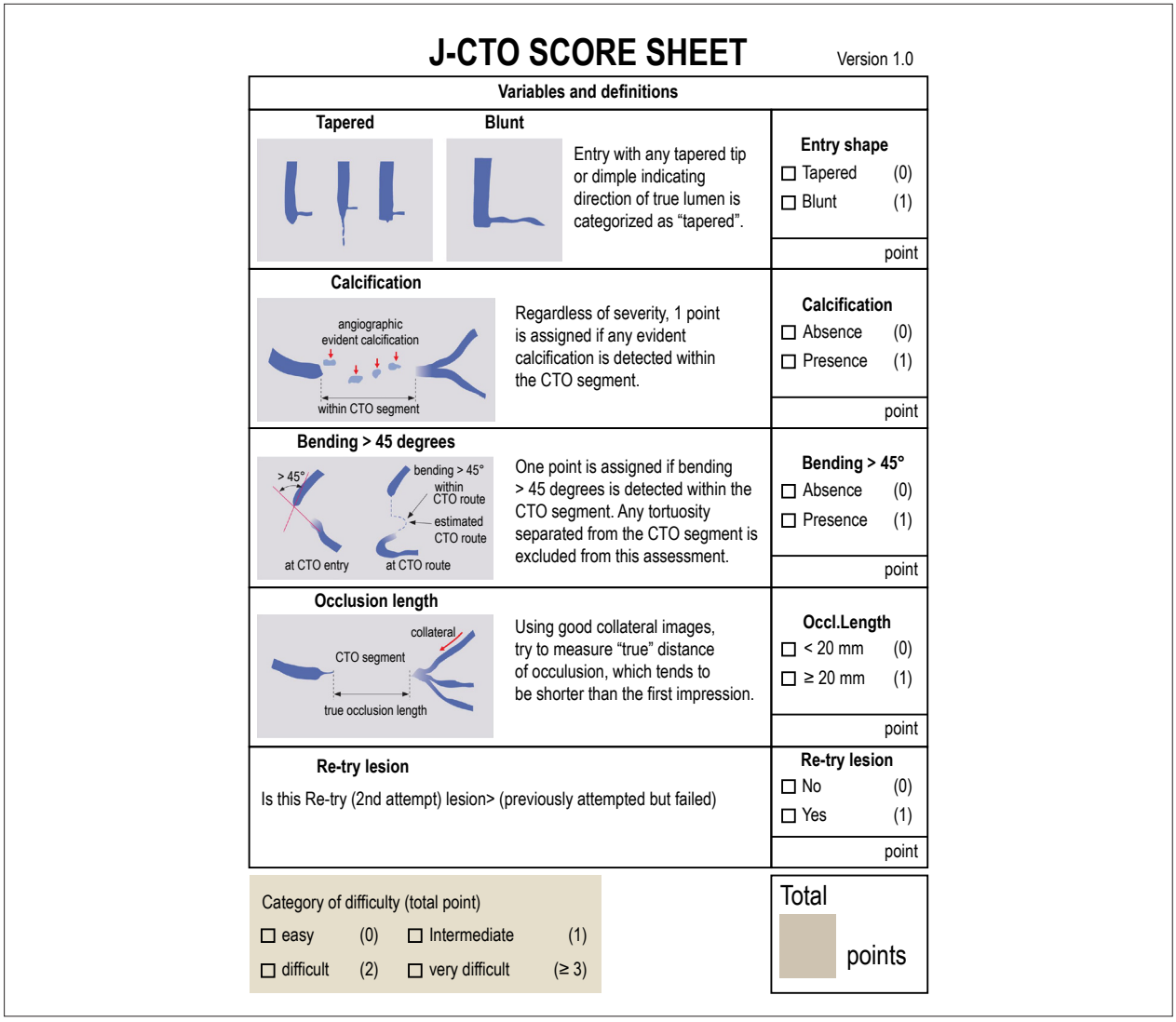

Figure 1 – *J-CTO score: angiographic score used to estimate the probability of success of the procedure. Five variables were analyzed: proximal cap (tapered or blunt), presence of calcification in chronic total coronary occlusions (CTO), presence of angulation greater than 45 degrees within the CTO segment, length of occlusion (greater or equal to 20 mm) and unsuccessful previous approach attempt. The degree of difficulty of the procedure increases the greater the J-CTO score.*[16]

dedicated equipment was associated with lower rates of major cardiovascular events (MACE) (4.3 *vs*. 15.4%, p = 0.02) and target vessel revascularization (3.1 *vs*. 15.5%, p = 0.02) when compared to older techniques.[27]

Retrograde technique

The retrograde approach to CTO crossing can significantly increase success rates, particularly in more complex lesions. It is considered the first line strategy when the proximal cap is ambiguous, the antegrade reentry zone is not adequate or the distal cap ends at a bifurcation. Retrograde crossing by grafts (especially venous grafts) and by septal collaterals are preferred to epicardial collaterals because they are easier to traverse and present lower risk of tamponade in case of perforation or rupture.[28,29] Through a collateral, the guidewire proceeds to the distal region of the occlusion and, from this point, the CTO is crossed in the opposite direction to the blood flow.[30] Retrograde crossing by the true lumen is generally easier, once that the distal lumen tends to have more favorable (softer, pencil-like, less ambiguous) characteristics than the proximal one.[8] If true lumen crossing is not possible, dissection and re-entry techniques, other than anterograde techniques, may also be applied.

Choice of *stents*

Intra-stent restenosis after CTO PCI with conventional stents was of approximately 50%, which practically prevented its use in this scenario. With the drug-eluting stent implantation, clinical outcomes improved significantly, leading to lower restenosis rates (relative risk: 0.25, 95% CI: 0.16-0.41, p < 0.001), reocclusion (relative risk: 0.30, 95% CI: 0.18-0.49, p < 0.001) and new target vessel revascularization (relative risk: 0.40, 95% CI: 0.28-0.58, p < 0.001).[31-34] Thus, the use of drug-eluting stents became mandatory.

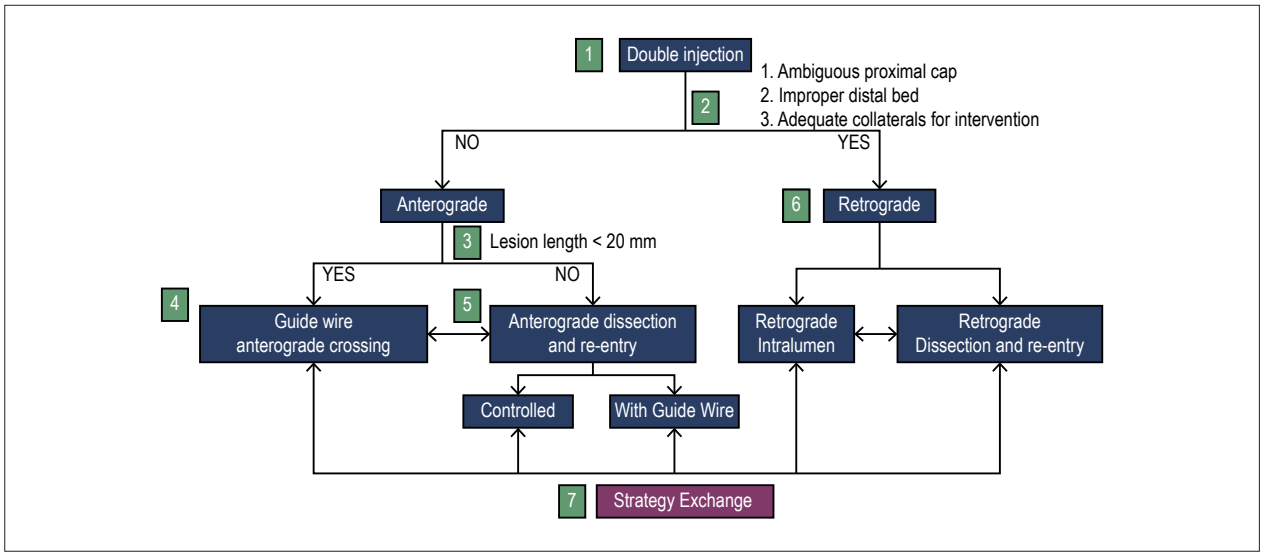

Figure 2 – *Hybrid Algorithm for Crossing Chronic Coronary Occlusions: The hybrid algorithm begins with double coronary injection (Item 1), which allows the evaluation of several angiographic parameters (Item 2) and selection of the type of primary approach: anterograde (Items 3 to 5) or retrograde (Item 6). Changes in strategy are performed (Item 7) depending on the evolution and progress of the procedure.*

The use of absorbable vascular platforms for the treatment of CTO has been evaluated in a number of studies, with promising results.[35-38] However, following the long-term results of the ABSORB III study indicating an increase in the rates of very late thrombosis, its use will probably be restricted.[39]

Use of intravascular imaging methods

Two intravascular imaging methods are currently available for clinical use: intravascular ultrasound (IVUS) and optical coherence tomography. Optical coherence tomography requires a fluid injection (usually contrast) to be performed, which may lead to an increase of an existing dissection plane, and therefore is not usually used in CTO ICPs.

The IVUS, on the other hand, can be used in a variety of procedure situations (defining the ambiguity of the proximal cap, facilitating the re-entry into the true lumen, limiting the dissection plane and confirming the distal positioning of the guidewire in the true lumen), in addition to those in which it is used in traditional PCIs.[40-43]

Results and complications

The hybrid approach has allowed success rates of 85-90% in the most recent studies.[23,44-47] The occurrence of in-hospital MACE ranges from 0.5 to 2.6%.[24-27] However, these procedures are still at larger risk of complications when compared to PCIs of non-CTO lesions.[48]

The incidence of peri-procedural myocardial infarction (MI) is associated with factors such as retrograde technique, moderate/severe calcification, and unsuccessful procedures.[49,50] The impact of MI peri-procedure on mid- and long-term follow-up is still not well defined.[51,52]

The prevalence of bifurcation lesions in CTO interventions is 33%. The lateral branches should be considered and treated as in conventional intervention procedures.[53] The occlusion of lateral branches may affect the long and short-term outcomes of CTO PCI, being more frequent when the stent is implanted on the branch and when the technique of dissection and reentry is used.[54]

CTO ICPs are at higher risk of perforations than those in non-occlusive lesions. In centers of excellence, using contemporary treatment, the incidence of perforations is approximately 1-2%.[55] The management of this complication varies with the type of perforation, and the operator should be familiar with the techniques and devices necessary for the treatment.[56]

The high doses of radiation required to perform increasingly complex procedures are of concern to physicians and patients. Protocols dedicated to CTO interventions, more modern equipment and the adoption by operators of attitudes that reduce exposure to ionizing radiation have allowed these procedures to be carried out with increasingly smaller radiation doses.[57,58]

The decision to interrupt the procedure should be individualized, and there is no scientific evidence to support the use of specific criteria. Five parameters are usually used (radiation, contrast, complications, futility and risk/benefit ratio), but the final decision depends heavily on the judgment of the operator.

Intra- and post-hospital care should be the same as any other complex PCI, taking into account the complications that occurred during the procedure and the amounts of contrast and radiation used.

Clinical benefits

Successful CTO recanalization is associated with a number of clinical benefits, such as improved angina, quality of life

and physical limitation, improved ventricular function, and decreased mortality when compared to patients whose recanalization was not successful.

Sapontis et al. evaluated the quality of life of 1,000 patients submitted to OCT PCI. One month follow-up showed a significant improvement in all domains of the Seattle Angina Questionnaire (SAQ), Rose Dyspnea Scale and PHQ-8 scores.[47] In another study with 184 patients in a one-year follow-up, a significant improvement in the quality of life of patients submitted to successful CTO PCI was also observed. The improvement was similar in all patients, regardless of their clinical, anatomical or procedural complexity.[59] In Mashayekhie et al., evaluated the impact of CTO recanalization on the physical capacity of 50 patients undergoing cardiopulmonary testing before and after 7 months. The successful intervention improved exercise capacity (maximal oxygen consumption and anaerobic threshold increased by 12 and 28%, respectively; $p = 0.001$ for both).[60]

Several observational studies show a relationship of CTO recanalization in the reduction of clinical events. Jang et al. compared CTO revascularization (by PCI or by surgery) with drug therapy in 738 patients with well-developed collaterals. The combined prognostic analysis at 42 months showed a 73% reduction in the incidence of cardiac death.[61] The Italian CTO Registry assessed the clinical outcomes of 1,777 patients, showing lower cardiac mortality (1.4, 4.7 and 6.3%, $p < 0.001$) and MACE at one year (2.6, 8.2 and 6.9%, $p < 0.001$) in patients treated with PCI when compared to clinical treatment or surgery. In this study, the group receiving optimized medical treatment presented higher rates of MACE, death and re-hospitalization.[62]

To date, three randomized controlled trials have evaluated the potential benefits of CTO PCI. The EXPLORE study included 304 patients with acute myocardial infarction (AMI) who underwent primary PCI and presented CTO in a non-infarct-related artery. They were randomized to CTO PCI in a second moment *versus* optimized medical treatment (OMT). At the 4-month follow-up, similar left ventricular function was observed in both groups, although a significant improvement in the ejection fraction was observed in the subgroup of patients with anterior wall AMI. The inclusion of patients without viability research may have limited a possible PCI positive result.[63]

The DECISION-CTO study randomized 834 patients with CTO for OMT *vs*. OMT + CTO PCI.[64] In the 3-year clinical follow-up, CTO PCI as the initial treatment strategy did not provide a decrease in MACE, the primary outcome of the study. However, this study had important limitations: it was terminated early before reaching the pre-specified number of patients required, with low inclusion rate of patients per center; patients with low severity and low symptomatic status were included; and there was high cross-over rate for the intervention group (20%).

The Euro CTO Trial randomized 407 patients with stable coronary disease for OMT *vs*. OMT + CTO PCI. The primary outcome was an improvement in the quality of life, as assessed by SAQ.[55] Although there were also limitations related to selection bias (termination of the study with only one third of the planned sample due to slow inclusion), randomized patients to PCI CTO showed a significant improvement in angina frequency, physical limitation, and quality of life in the 12-month follow-up.

In a recent meta-analysis including 9 studies with more than 6,400 patients, the long-term clinical outcomes of successful CTO recanalization were compared to those in whom the recanalization was unsuccessful. In this study, the risk of death, AMI and MACE was approximately 50% lower in patients with CTO recanalization, with a 90% lower incidence of myocardial revascularization.[65]

Brazilian reality

The percutaneous treatment of CTO in Brazil with the contemporary techniques described here can still be considered incipient due to the limited availability of dedicated materials in our country, affecting the adequate training of the operators. Recently, following the worldwide trend of treatment of these lesions based not only on the anatomy, but also on the symptoms and the clinical indication, several institutions and interventionists started to dedicate themselves to this area. The Brazilian Society of Hemodynamics and Interventional Cardiology (SBHCI) has stimulated this development, having already organized two dedicated courses (CTO Summit Brazil 2016 and 2017) and supporting specific regional events.

The role of specific training to perform this type of procedure is imperative, both for the knowledge of the techniques and the equipment used. Most operators develop their skills by participating in courses and procedures with proctors. There are also dedicated training programs, however limited to few centers in the world.[48, 66]

Conclusion

The CTO PCI is a rapidly advancing field. With the use of the right equipment and current techniques, high volume and expertise centers achieve high success rates. Although current evidence is favorable to PCI, prospective randomized controlled good quality trials are still needed to define the best indications and the most appropriate techniques for intervention in this challenging population.

Author contributions

Conception and design of the research, Analysis and interpretation of the data and Writing of the manuscript: Ybarra LF, Quadros AS; Acquisition of data: Ybarra LF; Obtaining financing and Critical revision of the manuscript for intellectual content: Ybarra LF, Cantarelli MJC, Lemke VMG, Quadros AS.

Potential Conflict of Interest

Dr. Luiz Fernando Ybarra consultant and speaker: Boston Scientific (Canadá/Portugal) Dr. Alexandre S. Quadros educational support: Medtronic, Boston, Abbott Vascular, Terumo, Acrosstak; Research Funds: Sanofi, Amgen, Daiichi-Sanchio, Medtronic;

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Study Association

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

Ethics approval and consent to participate

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

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Paradoxical Aortic Stenosis: Simplifying the Diagnostic Process

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Severe aortic stenosis (AS) is defined as a significant reduction of the aortic valve area (aortic valve area [AVA] ≤ 1.0 cm²) associated with evidence of left ventricular hypertrophic response (aortic jet velocity > 4 m/s or mean gradient between the left ventricle and the aorta > 40 mmHg).[1-3] However, as Minners et al.[4] have demonstrated, inconsistencies in echocardiographic measurements are extremely frequent in daily clinical practice. In about 30% of the cases evaluated by AS, we found AVA ≤ 1.0 cm², indicative of severe AS, with a mean gradient < 40 mmHg, suggestive of moderate AS.[4] This dissociation makes it difficult to establish an adequate and definitive diagnosis to the patient with AS, fundamental point in the therapeutic decision making. If, on the one hand, patients with moderate AS do not benefit from valve intervention, those with severe AS require surgical aortic valve replacement or a transcatheter aortic bioprosthesis implant, especially if they are symptomatic.[1-3]

In 2007, Hachicha et al.,[5] in a pioneering work, defined such patients as having "paradoxical AS" (or low-flow, low-gradient AS with preserved ejection fraction). These patients present a pathophysiology similar to that of diastolic heart failure, with hypertrophy and left ventricular compliance reduction, leading to a "low-flow" state, defined by an ejected volume (stroke volume) of < 35 ml/m² (stroke volume = Diastolic Volume - Systolic Volume / Body Surface).[5-7]

Another important contribution of Hachicha et al[5], corroborated by some subsequent studies,[8-11] was the demonstration of a better survival of symptomatic patients with paradoxical AS after valve intervention when compared to clinical treatment. However, patients with paradoxical AS, despite being benefited by valve intervention, present higher surgical mortality when compared with patients with classic AS (mean gradient > 40mmHg).[1-3,8,9,11]

In this paper, we propose an algorithm to facilitate the diagnostic confirmation of paradoxical AS. In three steps, we perform the Recognition of Paradoxical AS, Measurement Error Evaluation and Pathophysiological Confirmation (Figure 1):

1. Recognition of Paradoxical AS: this step is the first and most important. The delay in the diagnosis of paradoxical AS causes delayed intervention, leading to an increase in mortality. The classification of "moderate to severe" or even "moderately-severe" valvulopathy is not described in any of the current guidelines and impairs clinical reasoning.[1-3] For this reason, patients with AVA ≤ 1.0 cm², jet velocity < 4 m/s or mean gradient < 40 mmHg and ejection fraction > 50% should be classified as having paradoxical AS or low-flow, low-gradient AS with preserved ejection fraction.
2. Evaluation of Measurement Errors: In this stage, we must identify eventual measurement errors that justify an underestimated gradient or AVA. The echocardiographer should be aware of the correct alignment of the Doppler continuous wave for velocity and gradient measurement, avoiding underestimating these measurements. Another orientation is to avoid AVA measurement by continuity equation and using whenever possible measurement by planimetry. AVA measurement by continuity equation may underestimate AVA, since such measurement takes into account left ventricular outflow tract area calculation (VSVE) (AVA = area of VSVE x VTI of VSVE/VTI

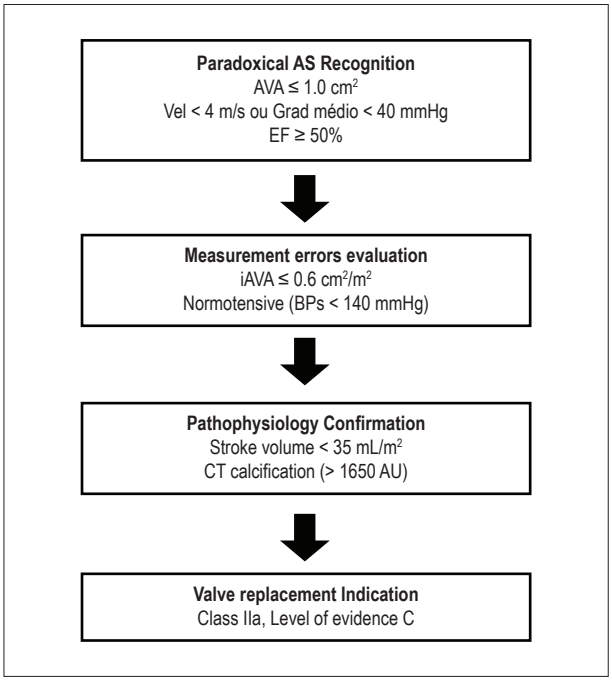

Figure 1 – *Algorithm proposed for the diagnosis of paradoxical aortic stenosis. * In patients with BMI above 30 kg/m², we must use 0.5 cm²/m² value as reference for iAVA. AS: aortic stenosis; AVA: aortic valve area; Vel: jet velocity; Grad: gradient; EF: ejection fraction; iAVA: indexed aortic valve area; sBP: systolic blood pressure; CT: computed tomography.*

Keywords

Aortic Valve Stenosis; Echocardiography; Aortic Valve.

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of aortic valve; where VTI is time-velocity integral). The VSVE dimension is usually measured with a 2D echocardiogram, assuming that the VSVE is circular. However, such a structure can often be elliptical, causing measurement errors.[7] 3D echocardiogram is a promising test for more accurate evaluation of VSVE and AVA by planimetry, however, specific studies for the population with paradoxical AS are necessary for its routine indication. Two points are extremely important for the clinical cardiologist. First, in patients with small corporeal surface, a reduced AVA may correspond to moderate AS. In this way we must always index AVA by the corporeal surface (iAVA), being that an iAVA ≤ 0.6 cm^2/m^2 suggests important AS. In obese patients (BMI ≥ 30 kg/m^2) we must assume a lower cut-off value (< 0.5 cm^2/m^2) so as not to overestimate the anatomical severity.[12] The second data that should be evaluated is systolic blood pressure in gradient measurement moment, which should be less than 140 mmHg.[1] Higher pressures contribute to underestimating the mean gradient and generate an increase in the valvulo-arterial impedance, a measure that estimates the ventricular afterload added to arterial and valvular overload ventricle, and it is also associated with mortality.[13] In summary, the clinical cardiologist should remember to index the AVA and make sure that the systolic blood pressure was < 140 mmHg at the time of gradient measurement, while the echocardiographer should be attentive to errors in gradient measurement and measure the AVA by the planimetry.

3. Pathophysiology Confirmation: Finally, we must confirm the pathophysiology of AS and low-flow, low-gradient. In developed countries, the main etiology of AS is degenerative, also known as calcific. Valvular calcification correlates with anatomic severity and values greater than 1650 AU, verified by computed tomography, suggest anatomically severe AS.[14] However, females may present the same anatomic severity as men, but with lower values of calcification, being advised to apply differentiated cutoff values for female patients (> 1200 AU).[15] Pathophysiology of low flow should be confirmed by stroke volume calculation, as previously described. In order to justify low gradient in a patient with severe AS, he must necessarily present a small cavity with stroke volume < 35 ml/m^2.[1-3,5-7]

Thus, through this 3 steps algorithm, we help in the recognition of paradoxical AS anatomical severity, facilitating the clinician to identify the ideal moment for intervention in this difficult diagnosis entity.

Author contributions

Conception and design of the research, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Rosa VEE, Fernandes JRC, Lopes ASSA, Sampaio RO, Tarasoutchi F

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Case 3 / 2018 – Corrected Transposition of the Great Arteries with Natural Progression to Severe Biventricular Dysfunction and No Associated Defects in a 51-Year Old Man

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Clinical data

Dyspnea on exertion for two years, progressing to low cardiac output and syncope lately, treated with dobutamine and usual drugs for congestive heart disease (currently using furosemide 40 mg, spironolactone 25 mg and losartan 12.5 mg).

Physical examination: Good general condition, eupneic, acyanotic, normal pulse rate in the four limbs. Weight: 70 Kg, Height: 160 cm, blood pressure (right arm): 90/60 mmHg, HR: 94 bpm.

Precordium: Apex beat was not palpable, without systolic impulses. Low heart sounds, and low intensity heart murmur heard in the left lower sternal border. Liver was not palpable and lungs were clear.

Complementary tests

Electrocardiography: Sinus rhythm, conduction abnormality seen in the left branch with long QRS duration (169 ms; AQRS = 0º), negative T-wave in I, aVL and V6 (AT = +155º), biatrial overload, and enlarged, peaked p-wave (AP+77º). (Figure 1).

Chest radiography: Enlarged heart due to round-shaped left ventricular arch and double-density left atrium with elevation of left bronchus. Congestion of pulmonary vessels, enlarged descending aorta, dilation of mid-aortic arch. Cardiothoracic index 0.61 (Figure 1).

Echocardiography: Atrioventricular and ventriculoarterial discordance, intact atrioventricular conduction. Ventricular septum is bulging to the right. Marked tricuspid insufficiency to the left (tricuspid annulus = 36 mm) and dilated atriums. Systolic dysfunction and diffuse hypokinesis of hypokinesis of right ventricle, TAPSE = 0.7 CM. Significant left ventricular dysfunction (Figure 1).

Computed tomography coronary angiography: Left-dominant coronary circulation. The right ventricle was perfused by an arterial branch originating at the posterior sinus of Valsalva and bifurcating into posterior circumflex artery, ventricular artery and marginal artery. It was also perfused by the anterior ventricular artery, a coronary artery branch that arises from the anterior Valsalva sinus. Left ventricle was perfused at right by the artery that arises from anterior Valsalva sinus as a thin branch and travels towards the anterior surface (Figure 2).

Holter: Sinus rhythm, with no arrhythmias.

Myocardial magnetic resonance imaging: Significant right and left ventricular dysfunction (EF = 29%; right ventricular end-systolic volume, RVESV = 154 mL/m^2 and EF = 36%; RVESV = 73 mL/m^2, respectively). Preserved right atrial function and enlarged left atrium. Delayed-enhancement in anterior and lower junction and in both ventricular outflow tracts. Significant tricuspid regurgitation.

Ergospirometry: Peak oxygen consumption of 16.4 ml/kg/min, 76% of peak VO2 (56% of peak VO2 predicted for age); respiratory compensation point was not reached. Slope VE/VCO2 of 31.

Clinical diagnosis: Corrected transposition of the great arteries with severe biventricular dysfunction and no associated defects.

Clinical reasoning: There were clinical evidence of corrected transposition of the great arteries, particularly a late ventricular dysfunction detected few years ago due to tiredness. This is corroborated by electrocardiographic signs, especially the orientation of ventricular repolarization characterized by orientation of the T-wave to the right. The diagnosis was well established by echocardiography and magnetic resonance imaging. The late ventricular dysfunction was probably caused by relative coronary insufficiency caused by systemic right ventricular hypertrophy, despite good irrigation seen in computed tomography coronary angiography.

Differential diagnosis: In adult patients, all other causes of ventricular dysfunction may be considered, including ischemic cardiomyopathy and dilated cardiomyopathy of other causes.

Management: Heart transplantation was indicated due to significant biventricular dysfunction.

Comments: Corrected transposition of the great arteries with no associated defects has an incidence of 10-15%. Both patients with natural progression of the disease and those who undergo surgical techniques for functional correction progress to different degrees of systemic right ventricular dysfunction in adult age.[1,2] It becomes even worse with advanced age and occurs in 50-80% of these cases. From eight more advanced age cases reported in the literature, five of them had congestive heart failure.[3] The congestive syndrome may be explained by relative coronary insufficiency related to the hypertrophied systemic right ventricle. In this regard, the decreased coronary flow has been well documented in the

Keywords

Congenitally Corrected Transposition of Great Arteries; Ventricular Dysfunction / surgery; Heart Failure, Cardiac Output, Low; Syncope.

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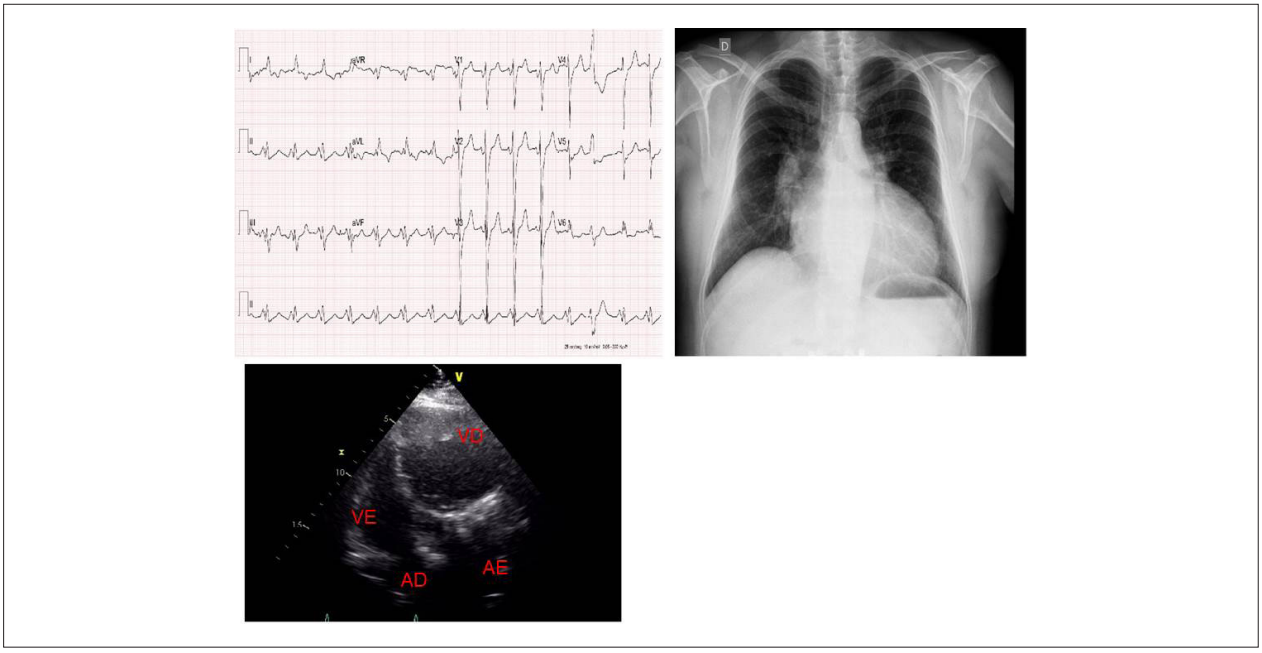

Figure 1 – *Electrocardiogram showing conduction abnormality in the left branch the, biatrial overload and T-wave orientation towards the left ventricle at right. Chest X-ray showing cardiomegaly with enlarged ventricle and left atrium. Four-chamber echocardiographic view showing enlarged right ventricle at left and deviation of the interventricular septum at right and enlarged left atrium.*

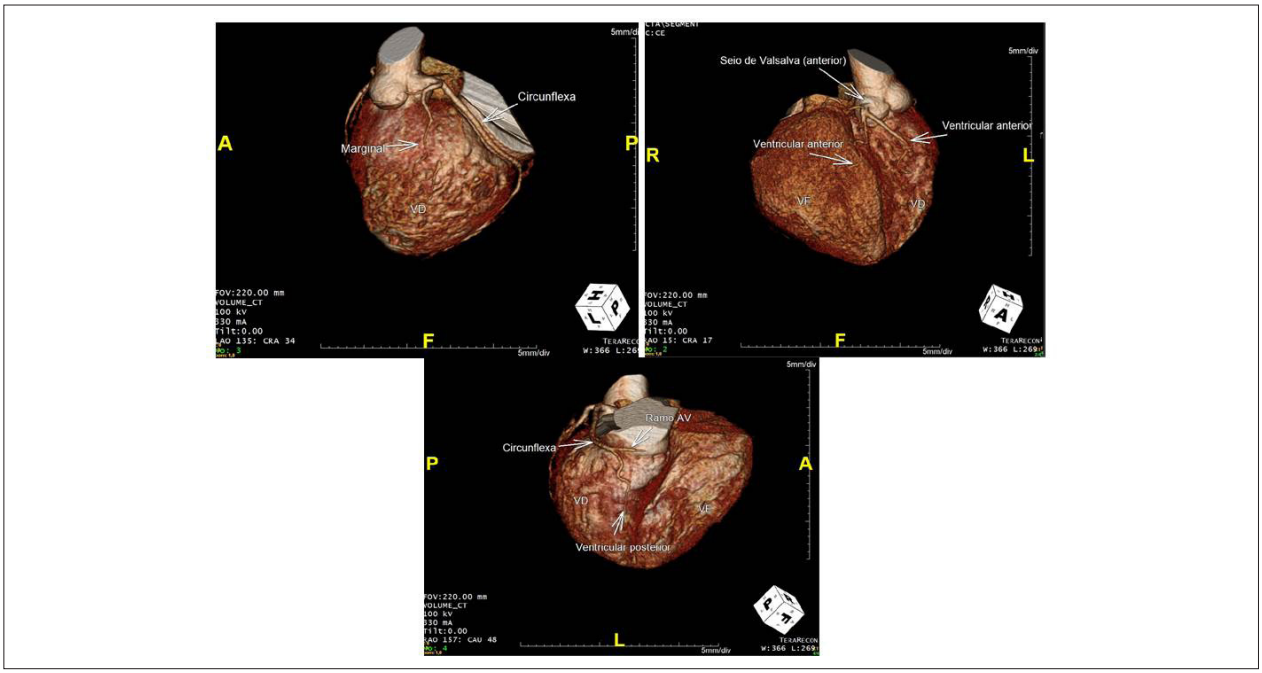

Figure 2 – *Computed tomography angiography of coronary arteries showing the right and left anterior ventricular branch originating from the anterior sinus of Valsalva (B). Larger arteries, composed by the circumflex, posterior ventricular and marginal arteries, arise from the posterior sinus of Valsalva that perfuses the entire right ventricle at left (A and C).*

literature and recognized as a consequence of right ventricular dysfunction, and the main long-term sequela of this condition. Decreased coronary flow after vasodilation with adenosine, resulting in altered vasoreactivity and possible microcirculation was previously reported,[4] which may explain the ventricular dysfunction. Therefore, the best option for these patients may be atrial and arterial anatomic repair by double switch operation in some stage of the disease.[1,2]

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Surgical Epicardial CRT-D Implantation in a Patient with Complete Obstruction of the Superior Vena Cava

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Introduction

Current guidelines clearly define the subset of heart failure patients who benefit from device implantation.[1] Although first-time trans-venous device implantation has a high success rate, some patients present complex and challenging technical problems.[2]

Case Report

We present a case of a 73-year-old male patient admitted to our cardiology department for acute heart failure and two episodes of monomorphic ventricular tachycardia with hemodynamic collapse. Eight years previously the patient was diagnosed with class NYHA II heart failure, non-ischemic dilated cardiomyopathy with 32% left ventricle (LV) ejection fraction and complete left bundle branch block. After optimized medical therapy, he underwent conventional CRT-D implantation through the left subclavian (SC) vein in another institution. Two years later defibrillator lead fracture was diagnosed. The lead was abandoned and another defibrillator lead was implanted through the right SC vein and further tunneled subcutaneously to reach the left-sided prepectoral pocket. The procedure was complicated with superior vena cava thrombosis and device infection and the patient underwent right defibrillator lead and generator extraction. The previously implanted right atrial lead, fractured defibrillator lead and LV pacing lead were abandoned. One year later the patient was diagnosed with complete heart block and was submitted to epicardial mono-chamber pacemaker (VVI-R) implantation with supra-peritoneal epigastrium pouch (Figure 1C).

On admission at our department, 12 lead electrocardiogram (Figure 1A) showed sinus P waves with dissociated right ventricular epicardial pacing (Vp). Device interrogation revealed 99% Vp. Echocardiographic evaluation showed a dilated LV with severely depressed ejection fraction (20%) due to diffuse hipokinesia. Coronary angiogram confirmed the absence of coronary disease. Venous angio computed tomography demonstrated complete obstruction of the superior vena cava drainage system and severe fibrosis around the abandoned leads.

A surgical off-pump complete epicardial CRT-D implantation was decided. A median sternotomy was performed and complete epicardial CRT-D implantation was accomplished with a Starfish® 2 heart positioner aid. The previously implanted epicardial mono-chamber pacemaker was extracted. A sutured bipolar lead [Capsure® Epi 4968 (Medtronic Inc., Minneapolis, Minnesota, USA)] was placed in the lateral wall of the right atrium (RA) and two sutureless screw-in bipolar leads (MyoDex® 1084T [St. Jude Medical Inc., Little Canada, Minnesota, USA]) were placed in the right ventricular outflow tract (RVOT) and lateral LV wall. Two defibrillator epicardial sutured patches were implanted in the anterior and posterior surface of the heart (Figure 1D). All these leads were then tunnelled to a left sided pre pectoral pocket and connected to the generator [Brava® CRT-D (Medtronic Inc., Minneapolis, Minnesota, USA)] – Figure 1E. Acute pacing parameters were excellent (RA – 1 mv/0,4 ms; RVOT – 2,5 mV/0,5 ms; LV - 2,5 mV/1,5 ms). Defibrillation testing was performed was performed at the time of implantation. Induced ventricular fibrillation was appropriately detected with successful defibrillation at 25J (Figure 1B, 1F). The patient remained for 24 hours in the intensive care unit and was thereafter transferred to the cardiology ward where he remained for 7 days before discharge under optimized medical therapy.

Discussion

There were three alternative percutaneous approaches to complete CRT-D implantation in the presented patient: 1) lead extraction and left sided implantation; 2) implantation through the inferior vena cava system;[3] 3) sub-xiphoid epicardial implantation.[4,5] The Heart Team considered lead extraction unfeasible due to complete obstruction of the superior venous system and severe fibrosis around the abandoned leads. Implantation through the ileo-femoral vein and inferior vena cava system was considered high risk as it was the only venous draining site to the heart. Also, defibrillating vectors would be inadequate and the risk of lead dislodgement and infection high. Percutaneous sub-xiphoid epicardial access was considered unfeasible due to the presence of the previous epicardial pacemaker. In addition, supra-peritoneal generator placement would also produce inadequate defibrillating vectors.

Epicardial pacing and defibrillator systems have long existed and defibrillator coils are though to offer better long-term outcomes than defibrillator patches due to the high rate of patch crinkling (36-54%).[6] This is associated with lead malfunction and chronic chest pain. However, access to epicardial defibrillator material is particularly difficult and in some countries only defibrillator patches are approved for epicardial usage.

Keywords

Heart Failure; Tachycardia, Ventricular; Vena Cava, Superior / physiopathology; Cardiac Resynchronization Therapy Devices; Cardiovascular Surgical Procedures.

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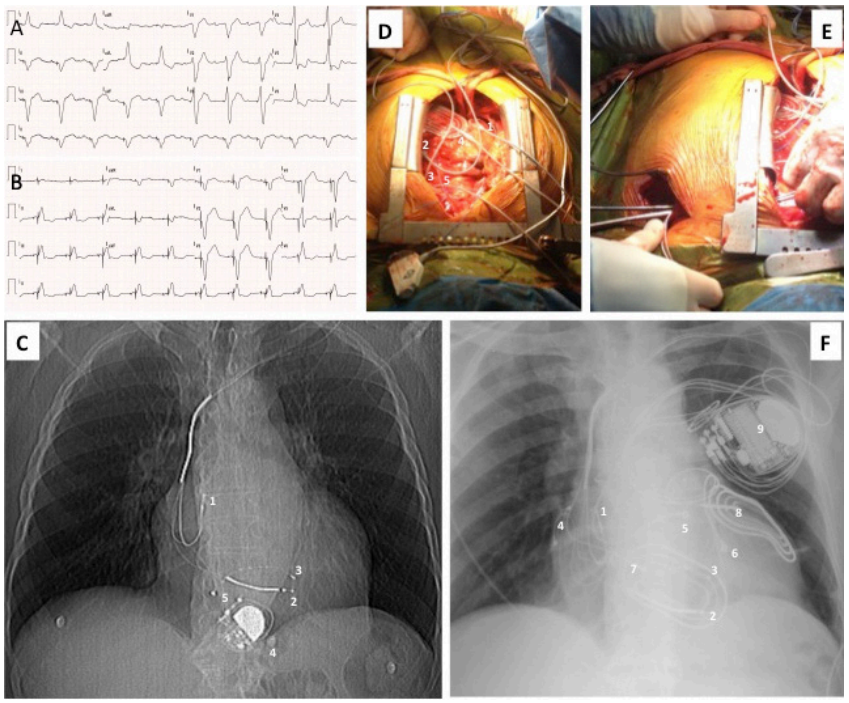

Figure 1 – *A) 12-lead ECG before epicardial CRT-D implantation: sinus P waves with dissociated right ventricular epicardial pacing; B) 12-lead ECG after epicardial CRT-D implantation: sequential atrial pacing and biventricular pacing. C) Chest x ray before epicardial CRT-D implantation: 1 Abandoned endocavitary right atrial lead; 2- Abandoned endocavitary right ventricular pacing/defibrillator lead; 3- Abandoned endocavitary left ventricular lead; 4 – Epicardial mono-chamber pacemaker generator; 5 - Epicardial mono-chamber pacemaker lead. D) Intra operatory situs after lead implantation: 1 - Epicardial right atrial lead; 2 – Epicardial right ventricular outflow tract lead; 3- Left ventricular lateral lead; 4- Epicardial anterior defibrillator patch; 5- Epicardial posterior defibrillator patch. E) Intra operatory situs showing lead tunneling to left sided pre pectoral pocket. F) Chest x ray after epicardial CRT-D implantation: 1 Abandoned endocavitary right atrial lead; 2 - Abandoned endocavitary right ventricular pacing/defibrillator lead; 3 - Abandoned endocavitary left ventricular lead; 4 - Epicardial right atrial lead; 5 – Epicardial right ventricular outflow tract lead; 6- Left ventricular lateral lead; 7 - Epicardial anterior defibrillator patch; 8 - Epicardial posterior defibrillator patch; 9 – Epicardial CRT-D generator. CRT-D: cardiac resynchronization and defibrillation; ECG: eletrocardiogram.*

Complete epicardial CRT-D implantation has been described in patients undergoing on-pump cardiac surgery for other reasons.[7] Minimally invasive surgery using a small thoracotomy or using video-assisted thoracoscopy with or without robotic assistance is well described for LV lead implantation when a percutaneous procedure fails.[8] A complete CRT-D has also been implanted using robotic assistance.[9] Since there is no surgical access to the RV and RA, the RV lead was placed on the anterior wall of the LV and the RA lead in the left atrial appendage. Also, it is not possible to implant a defibrillator patch using this technique, and its availability is scarce. Although there is no cost-effective data regarding minimally invasive LV lead surgical implantation, it is well known that robotic assisted mitral valve repair is associated with greater costs.[10]

Conclusion

To our knowledge, this is the first report of a complete off-pump epicardial sequential atrial-biventricular resynchronization and patch defibrillation device implantation requiring a median sternotomy. To clarify the effectiveness and safety of this procedure, more cases and longer-term observation are mandatory.

Author contributions

Conception and design of the research: Silva GL, Cortez-Dias N, Sousa J, Nobre A, Pinto FJ; Acquisition of data: Silva GL; Writing of the manuscript: Silva GL, Pinto FJ; Critical revision of the manuscript for intellectual content: Cortez-Dias N, Sousa J, Nobre A.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

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Computed Tomography-Guided Core Needle Biopsy of Cardiac Angiosarcoma

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A 34-year-old man was referred to our institution after an echocardiography performed at another center because of tachycardia (atrial flutter), which showed heterogeneous pericardial mass infiltrating the right chambers. Thoracic computed tomography (CT) and cardiac magnetic resonance (MR) imaging were performed for more accurate assessment of the exact tumor location, size, and potential infiltration of other cardiac and mediastinal structures. CT (Figure 1A) and MR imaging (Figure 1B) confirmed an 8-cm ill-defined heterogeneous enhancing pericardial mass infiltrating the anterior and superior walls of the right atrium and extending to lateral and inferior walls of the right ventricle, consistent with cardiac angiosarcoma. The patient was deemed inoperable, as the mass also invaded the superior vena cava, aortic root, and epicardial fat. CT-guided core needle biopsy of the cardiac mass was the method of choice for histological verification of tentative diagnosis. Once the patient signed the informed consent and was put in supine position, an 18-gauge biopsy needle was driven between the left thoracic internal arteries and the left border of the sternal body (Figure 1C) and a tissue specimen was safely obtained from the beating heart without adverse events. The procedure was performed by an experienced interventional thoracic radiologist under local anesthesia and in the presence of a thoracic surgeon. CT images obtained immediately after biopsy showed no post-procedural complications. Preliminary histological analysis performed on-site by a pathologist determined the adequacy of the tissue specimen. Final histopathologic diagnosis was high-grade cardiac angiosarcoma. To the best of our knowledge, only one case of a CT-guided core needle biopsy of a cardiac angiosarcoma involving the right chambers has been previously reported in English-language scientific literature.

Keywords

Hemangiosarcoma/diagnosis; Hemangiosarcoma/pathology; Biopsy, Large-Core Needle; Tomography, X-Ray Computed; Neoplasm Staging

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Author contributions

Acquisition of data: Cabañero-Sánchez A, Muñoz-Molina GM, Fernández-Méndez MA; Analysis and interpretation of the data: Gorospe L, Ayala-Carbonero AM; Writing of the manuscript: Cabañero-Sánchez A, Muñoz-Molina GM, Ayala-Carbonero AM, Fernández-Méndez MA; Critical revision of the manuscript for intellectual content: Gorospe L, Ayala-Carbonero AM, Fernández-Méndez MA.

Potential Conflict of Interest

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Sources of Funding

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Study Association

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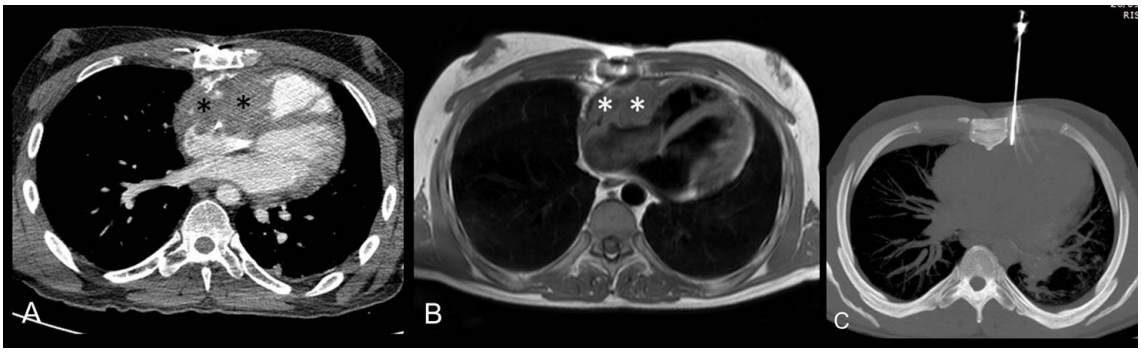

Figure 1 – *A) Axial contrast-enhanced CT image showing heterogeneous mass (asterisks) infiltrating the right atrium, the right atrioventricular groove, and the right ventricle; B) Axial T1-weighted MR cardiac image showing mass (asterisks) infiltrating the right cardiac chambers; C) Axial unenhanced CT MIP (maximum intensity projection) image showing core-needle biopsy, with the tip entering the cardiac mass.*

Prognostic Significance of Non-Sustained Ventricular Tachycardia Depends on Its Rate and Duration

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Dear Editor,

We read the article "Non-Sustained Ventricular Tachycardia (NSVT) Episodes Predict Future Hospitalization in ICD Recipients with Heart Failure" written by Uçar et al.[1] with great interest. NSVT identified on routine ICD interrogation should be considered an important clinical event as the authors state in this article. However, we would like to bring attention to some issues related to the article.

Keywords

Heart Failure / physiopathology; Tachycardia, Ventricular; Hospitalization; Defibrillators Implantables.

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NSVT was defined as 4 or more consecutive beats with a rate > 167 beats/min and shorter than 16 beats in this study. Both detection rate and number of intervals to detect (NID) ventricular tachycardia were slightly below the conventional interval (NID = 18/24) detection of VT/VF ≥ 188 bpm that have been proven effective.[2,3] If we also include the new long-detection programming strategies (NID = 30/40) into this subject, we can say that the authors documented the increase in hospitalization, just only with slower and shorter episodes of NSVT.

Previously published reports showed that faster and longer runs of NSVT were more predictive than slower and shorter ones for adverse events.[4] But, since there was no data about duration and rate of the NSVT episodes in the article, we could not establish an opinion about the importance of rate and duration of NSVT for predicting future hospitalizations.

More recently, the use of long-detection interval programming has received widespread acceptance based on several large randomized trials.[3,5] With these new programming strategy, we believe that the prognostic value of NSVT will increase even more.

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Reply

Dear Editor,

We thank the journal readers for their great interest in our original article titled "Non-Sustained Ventricular Tachycardia Episodes Predict Future Hospitalization in ICD Recipients with Heart Failure" recently published in *Arquivos Brasileiros de Cardiologia*.[1]

In our study, we programmed ICD's zones as ventricular tachycardia VT (167-200 bpm) with discriminators and VF (> 200 bpm). *Non-sustained ventricular tachycardia* NSVT was defined in the monitored zone of ICD as 4 or more consecutive beats arising below the atrioventricular node with a rate > 167 beats/min and shorter than 16 beats. We used the number of intervals to detect (NID) ventricular tachycardia in VF zone or fast VT(FVT) zone. In our device program FVT zone was off NID was 18/24 in VF zone. If we programmed NID as 30/40, maybe we could detect more NSVTs, but in our analyses, we did not have any NSVT patients in VF (> 200 bpm) zone. All our patients were in VT (167-200 bpm) zone.

Finally, it is difficult to make a final decision according to our findings with a relatively limited study population. Hence, the new long-detection programming strategies need to be confirmed in further and larger prospective multicenter trials about the prognostic value of NSVT.

Sincerely,

Fatih Mehmet Uçar

Reference

1. Uçar FM, Yilmaztepe MA, Taylan G, Aktoz M. Non-sustained ventricular tachycardia episodes predict future hospitalization in ICD recipients with heart failure. Arq Bras Cardiol. 2017;109(4):284-9.

Erratum

Edition of December 2017, vol. 109 (6), Supl. 2, p. 1-34

In the "Atualização das Diretrizes Brasileiras de Valvopatias: Abordagem das Lesões Anatomicamente Importantes", published as a supplement to the Arquivos Brasileiros de Cardiologia [Arq Bras Cardiol 2017; 109(6Supl.2):1-34], the following corrections should be considered:

- In table 18, column 5, line 6: replacement of "IIb" with "IIb C".
- In Table 24, line 4: the items "IB, IB, IC" should be aligned with the phrase" Fração de ejeção < 50%". In line 5, items "IIa, IIa B, I C" should be aligned with the phrase " Ausência de reserva inotrópica no teste ergométrico e/ou baixa capacidade funcional". On line 6, remove item "B".
- In table 24, section "Tratamento cirúrgico convencional", change from "Sem reserva contrátil" to "Sem reserva contrátil + escore de cálcio valvar elevado".
- In table 43, section " TAVI ritmo sinusal ", change of recommendations as follows:

  Varfarina – Correct: ESC - IIb B*.

  AAS + clopidogrel (6 meses, seguido por AAS por período indefinido) – Correct: SBC - IIa C; AHA - IIb C; ESC - IIa C.

  NOACs – Correct: SBC – III.
- Inclusion of the name of Dr. Samira Kaissar Nasr Ghorayeb in the document.

Edition of April 2016, vol. 106 (4), Supl. 1, p. 1-23

In the "III Diretrizes da Sociedade Brasileira de Cardiologia sobre Análise e Emissão de Laudos Eletrocardiográficos", published as a supplement to the Arquivos Brasileiros de Cardiologia [Arq Bras Cardiol 2016; 106(4Supl.1):1-23], the following corrections should be considered:

On page 1, section 2.1., text correction "O eixo de P pode variar entre -30° e +90°" to "O eixo de P pode variar entre 0° e +90°".

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