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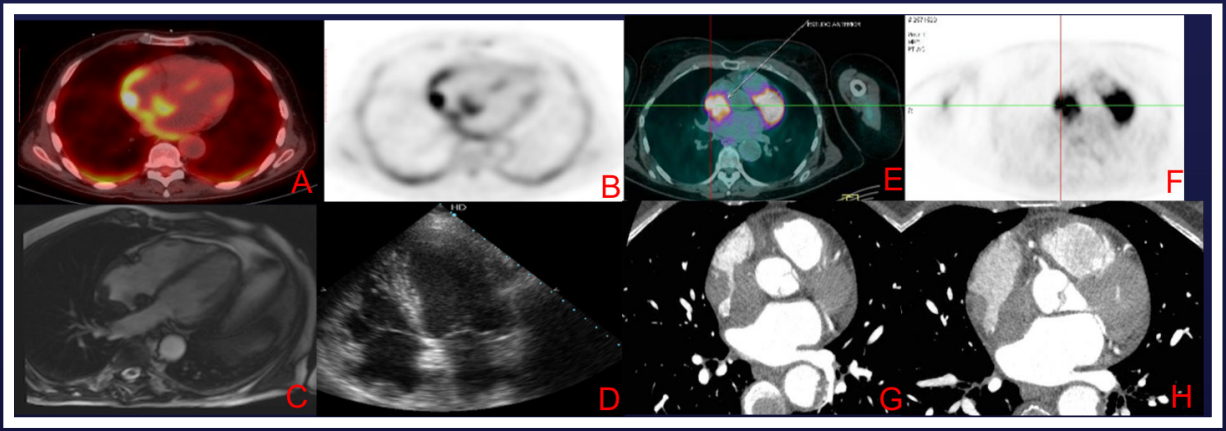

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Journal of Brazilian Society of Cardiology
REVISTA DA SOCIEDADE BRASILEIRA DE CARDIOLOGIA - Publicada desde 1948

Contents

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REVISTA DA SOCIEDADE BRASILEIRA DE CARDIOLOGIA - Publicada desde 1948

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From Evidence-Based Medicine to Precision Health: Using Data to Personalize Care

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The historical practice of medicine has evolved over centuries based on empirical knowledge derived from experience and observation rather than rigorous scientific data. Over the second half of the twentieth century, this form of medical knowledge progress was largely supplanted by rigorous scientific data collection, particularly in the realm of cardiovascular diseases, where virtually every new drug discovery has been thoroughly evaluated in randomized clinical trials (RCT). The impressive improvement in the quality of the information provided by such study design has led to the development of an entirely new field in the medical knowledge which became known as Evidence-Based Medicine (EBM).[1]

EBM soughs to move away from empirical information by providing a structured grading of the epistemological strength of evidence available. It further requires the highest levels of evidence to give strong recommendations for or against the use of any particular therapy. By this approach, RCTs are considered among the highest quality study designs which support those stronger recommendations. Still, despite their capability to avoid confounding and other biases, RCTs conclusions can only be interpreted as an overall averaged benefit for the collective population included in the study. Although such information may suffice to document the effect of any given therapy at the population level, this does not necessarily apply to any individual patient. While some individuals may benefit considerably more than the average population included in the study, other might benefit significantly less, whereas no benefit or even significant harm may occur in some individuals.

Moreover, the external validity in other subgroups of individuals is even more challenging. Although a significant proportion of drugs routinely used in medicine and cardiology are only approved to rather strict clinical indications, most clinicians extrapolate evidence beyond the validated population, including many subgroups of individuals in whom the benefit documented in the initial studies is unlikely to be replicated or in individuals whose risk for complications or side effects might be larger than in the initial cohort.

Though much of these limitations have long been known by individuals working with EBM, not too long ago little more than simple subgroup analysis could be performed in the quest to identify individuals more or less likely to benefit from the tested therapy. Since the identification of those individuals with unexpected response to therapy is rather complex, the simple subgroup analysis lacked the nuance needed to sort the wheat from the chaff in most cases.

Over the last decades, the development of two different fields has led medicine to change this paradigm. On one hand, the development of genetics and genomics provided extensive data on the differences between individuals that might, at least partially, explain the individual variability in risk for various diseases, its prognosis, response to therapy or risk for side effects. On the other hand, data science and computational power developed to an extent that allows data processing at orders of magnitude larger than previously known. This improvement in computational power allowed the capability to handle large amounts of data, such as those provided in genetic studies. Therefore, the insights provided by the combined use of those two fields can help tailor individualized treatment. Within this context, the concept of precision and individualized medicine have developed over the last couple of years.[2]

Precision medicine has been defined as a medical model using molecular profiling technologies to improve diagnostic accuracy, prognosis definition and tailor the right therapeutic strategy to the right person at the right time.[3] However, this definition has a limited scope on the potential of personalized care at the current state of healthcare delivery. First, individualized care now extends towards the broader spectrum of health care including primary and primordial prevention, as well as health promotion. Consequently, the broader term of precision health, not precision medicine may seem more appropriate. Within this concept, one can only naturally understand that to provide the full board of precision health to patients there is a compelling need to extend the data collection beyond genetic, molecular or genomic profiling to incorporate a more "holistic" definition of health. This health profiling should further embrace other social and environmental data but should also include the entirely new field of patient-generated data provided by

Keywords

Evidence Based Medicine/methods; Precision Medicine/trends; Comprehensive Health Care; Models,Educational; Teaching/methods; Research.

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newer devices such as smartphones, smartwatches and other wearables that can provide vast amounts of continuous monitoring data from each individual through exceedingly long periods of time. Finally, in order to provide truly personalized precision health, each healthcare provider will need to factor in individual patients' preferences.

This entire concept of personalized health is still at its early stages, and the exact blending of those parameters are not yet known. However, with the fast pace of experimentation allowed by studies derived for large datasets of real-life information, one can foresee this becoming routine standard of care in a not too distant future.

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Elevation of Oxidized Lipoprotein of Low Density in Users of Combined Oral Contraceptives

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Abstract

Background: The use of combined oral contraceptive (COC) has been related to changes in glycemic, lipid metabolism, increased oxidative stress, and systemic blood pressure, which could suggest a higher oxidation of low-density lipoprotein cholesterol (LDL-cholesterol) in women on use of COC.

Objective: To test the hypothesis that there is a difference in the plasma values of oxidized LDL among women who use and do not use COC, as well as to evaluate the correlation between it and the lipid profile and high-sensitivity C-reactive protein (hs-CRP).

Methods: Forty-two women with ages between 18 and 35 years old, who were eutrophic, irregularly active, with triglycerides < 150 mg/dL, blood glucose < 100 mg/dL, and who used or did not use COC were selected. These women were allocated in the COC group, formed by 21 women on COC use for at least 1 year; and a control group (CG), consisting of 21 women who had not used any type of hormonal contraceptive for at least 1 year. A significance level of 5% was adopted for statistical analyses.

Results: It was observed that GCOC showed higher values of oxidized LDL than the CG, respectively 384 mU/mL versus 283 mU/mL ($p < 0.01$). A positive correlation between oxidized LDL and LDL-cholesterol ($r = 0.3$, $p < 0.05$), with total cholesterol ($r = 0.47$, $p < 0.01$) and with triglycerides ($r = 0.32$, $p < 0.03$) was observed, and there was no correlation with the hs-CRP. In the categorized analysis of oxidized LDL, 71.4% of GCOC women, and 28.6% of the CG remained above the established cutoff point.

Conclusion: Women who use COC have higher plasma levels of oxidized LDL, and there is a positive correlation between oxidized LDL and other lipid variables. (Arq Bras Cardiol. 2018; 111(6):764-770)

Keywords: Cardiovascular Diseases/complications; Contraceptives, Oral, Combined; Lipid Metabolism Disorders; Oxidative Stress; Atherosclerosis; C-Reactive Protein.

Introduction

Studies have shown that women of reproductive age who use combined oral contraceptives (COCs) present changes in glycemic,[1] lipid metabolism,[2] oxidative stress,[3] and chronic subclinical inflammation.[4,5] Also, an increase in the atherogenic subfractions of low-density lipoprotein (LDL-cholesterol)[6] and elevated systemic blood pressure (SBP)[7] were identified. Together, these alterations are associated with LDL-cholesterol oxidation, which has been strongly related to a more atherogenic lipid profile.[8]

Once oxidized, LDL-cholesterol presents several actions in vascular physiology, among them, it inhibits the expression of the endothelial nitric oxide synthetase enzyme mRNA, resulting in a decrease in the production of nitric oxide and favoring the atherosclerotic process.[9] Furthermore, it also impairs cell proliferation, cell motility and endothelial stem cells action, which are key mechanisms in the endothelialization of damaged areas in the atherosclerotic process.[10,11] It has also been suggested that higher oxidized LDL values, even within the limits of normal, are associated with an increased risk of future cardiovascular events and metabolic syndrome.[1,12-14]

In addition, in Brazil, 33.8% of women aged 18-49 years used oral contraceptives, and of these, more than 13% (95% CI, 10.9-15.7%) had risk factors, such as smoking, systemic arterial hypertension, dyslipidemias and obesity.[15] These factors, associated with the use of COCs, can significantly increase the risk of atherothrombotic events, even in women of reproductive age.[16,17]

However, to our knowledge, there are still no studies that have investigated the oxidation of LDL-cholesterol in young women using COC, without other factors that justify their oxidation. Thus, the hypothesis that there is a difference in the plasma values of oxidized LDL among women who

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use and do not use COC was tested, and the correlation between oxidized LDL and the fasting lipid profile variables and C-reactive protein were evaluated.

Methods

Sample

The research is characterized as a cross-sectional analytical study, which has as a predictor variable the use of COC, and as an outcome variable, the oxidized LDL.

The study population consisted of 42 self-reported healthy, eutrophic, irregularly active women aged 19 to 30 years, nulliparous, with fasting values of triglycerides < 150 mg/dL, blood glucose < 100 mg/dL, and who used COC or not. All participants were students of a private college located in the city of Salvador, BA - Brazil.

The sample was divided into two groups: COC group (GCOC) consisting of 21 women using COC of low dose of ethinylestradiol (15 to 30 mcg) for at least 1 year; and control group (CG), consisting of 21 women who had not used any type of hormonal contraceptive for at least 1 year.

To determine if participants were irregularly active, the International Physical Activity Questionnaire (long version), developed by the World Health Organization and the US Centers for Disease Control and Prevention was used.[18]

Women who reported familial dyslipidemia, hypo- or hyperthyroidism, history of alcoholism or smoking, polycystic ovarian syndrome, hypo- or hyperlipidic diet, use of dietary or anabolic supplements, hypolipidemic agents, corticosteroids, diuretics or beta blockers were excluded. Those who presented, on the physical evaluation, values of SBP ≥ 140/90 mmHg, abdominal circumference ≥ 80 cm or, in the laboratory examination, alteration of pyruvic (TGP) or oxidative (TGO) glutamic transaminase, or creatinine were also excluded. TGP and TGO were evaluated to identify pancreatic and hepatic diseases, and creatinine, to identify the presence of renal dysfunction.

All the participants answered the semi-structured questionnaire, elaborated by the authors of the research and underwent physical examination. The latter consisted of resting blood pressure (BP), total body mass, height and waist circumference.

Body mass index (BMI) was calculated with mass and height measurements, according to the Quetelet equation: mass (kg)/height^2 (cm). The BMI cutoff points adopted were those recommended by the IV Brazilian Guidelines on Dyslipidemias and Prevention of Atherosclerosis of the Department of Atherosclerosis of the Brazilian Society of Cardiology (SBC),[19] that is, low weight (BMI < 18.5); eutrophy (BMI 18.5-24.9); overweight (BMI 25-29.9), and obesity (BMI ≥ 30).

The abdominal circumference was obtained with a Starrett® metric and inelastic tape, with a measurement definition of 0.1 cm. It was measured at the lowest curvature located between the last rib and the iliac crest without compressing the tissues.[20]

Laboratory Data Collection Protocol

To collect the laboratory data, the volunteers were referred to the Laboratory of Clinical Pathology in the city of Salvador, state of Bahia - Brazil, where blood samples were collected. Following antecubital vein puncture, 10 mL of blood were collected for triglycerides (TG), oxidized LDL, high-density lipoprotein (HDL-cholesterol), total cholesterol (TC), blood glucose, pyruvic glutamic and oxidative transaminase. LDL-cholesterol and the very low density cholesterol (VLDL-cholesterol) were calculated by the Friedewald equation:[21] TC = HDL-cholesterol + LDL-cholesterol + VLDL-cholesterol, with VLDL-cholesterol being equal to TG/5.

The collections were performed with the volunteers fasting for 12 hours. All were instructed not to change their diet during the week of the test, not to perform any physical exertion other than usual, and not to drink alcoholic beverages 24 hours before the laboratory examination. For the CG, the collections were performed between the 5th and 10th day of the menstrual cycle, considering the lower hormonal fluctuations, as recommended by Casazza et al.[22] Blood samples were collected by a trained professional and in a laboratory environment suitable for this type of procedure.

For determination of oxidized LDL in the serum samples, the ELISA kit was used. In this analysis, the oxidized LDL values considered normal were between 100 and 700 mU/mL. The triglycerides, HDL-cholesterol, total cholesterol and blood glucose values were obtained by the Trinder colorimetric enzyme method.[23] TGP and TGO were measured by the Reitman-Frankel colorimetric method.[24]

The sample adequacy calculation was performed in the GraphPad StatMate 2.0 for Windows software, which considered a difference between the means of 63 MU/mL and standard deviations of 119.5MU/mL (GCOC) and 43.6 MU/mL (CG), both extracted from a previous pilot study (n = 12). In order to eliminate the bias of the laboratory variation coefficient of oxidized LDL dosage, which was of 3%, a significant difference was considered between the groups, of 20% for alpha and beta of 0.05 (bidirectional) and 0.80, respectively. Thus, 20 women were needed in each group.

Statistical analysis

Initially, symmetry and kurtosis tests and the Shapiro-Wilk test were applied to check data distribution. The variables values with normal behavior were described in mean and standard deviation and the values of nonparametric variables in median and interquartile range. Categorical variables were presented as absolute and relative frequencies.

For the intergroup comparison of the parametric variables, we used the unpaired bidirectional Student t test, and for the non-parametric variables, the Mann-Whitney test. The correlation between the oxidized LDL values and all variables of the lipid profile - triglycerides, total cholesterol, HDL-cholesterol and LDL-cholesterol, and CRP was also verified. In the correlation analysis, the Spearman correlation coefficient was used.

In addition to the inter-group comparisons of oxidized LDL, the sample was categorized based on the median of oxidized LDL in women with LDL-oxidized values above and below the median. After the categorization, Fisher's exact test was used. All analyzes were performed in the BioStat 5.0 statistical package, adopting a significance level of 5%.

Ethical aspects

Throughout the study the guidelines on human research in the Declaration of Helsinki and Resolution 466/12 of the National Health Council were followed. This study was submitted and approved by the Research Ethics Committee of Faculdade de Tecnologia e Ciência de Salvador – BA with number 3.390/2011.

All participants received detailed information about the study objectives, risks and benefits involved in the procedures and signed the informed consent form. Two copies were filled, one being kept with the participants, and the other with the researchers.

Results

Table 1 presents the clinical and anthropometric characteristics of the sample. Homogeneity between the groups is observed, and the difference between the values of the SBP ($p < 0.02$) and the CRP ($p < 0.01$) are highlighted, which are higher in the GCOC.

When comparing the lipid fasting variables, and the TG/HDL-cholesterol ratio (Table 2), it is observed that the GCOC presents values of plasma triglycerides ($p < 0,01$), total cholesterol ($p < 0,01$), HDL-cholesterol ($p < 0,04$), VLDL-cholesterol ($p < 0,01$) and TG/HDL-cholesterol ratio ($p < 0,01$) higher than the GC.

As shown in Figure 1, GCOC women had higher oxidized LDL plasma levels (mU/mL) than the CG, 384 (198-410) versus 283 (208-250) ($p < 0.01$).

In Table 3, the analyses of correlation between oxidized LDL and the variables of the fasting lipid profile, as well as between oxidized LDL and the PCR are presented. Moderate and positive linear correlation was observed between oxidized LDL, and LDL-cholesterol, triglycerides and total cholesterol.

In Table 4, we can observe the intergroup analysis of oxidized LDL when categorized based on the value of the median. It can be seen that 71.4% of the women in the GCOC had higher plasma oxidized LDL values than the established cut-off when compared to the CG, which was 28.6% ($p < 0.01$).

Discussion

In response to the objectives of this study, we identified that women who use COC have higher oxidized LDL values, with a moderate and positive correlation of oxidized LDL with LDL-cholesterol, total cholesterol and triglycerides. In addition, 71.4% of the women who used COC presented oxidized LDL values above the cutoff point when compared to the control group (28.6%). Thus, although it is not possible to establish a perfect cause-effect relationship due to the method used, to the non-stratification of COC types, and to the effects of regionality, the results presented here are reinforced by the characteristics and homogeneity of the sample, which does not present the classic factors that could be known to induce the increase of oxidized LDL. In this context, although there is no clearly defined mechanism, some hypotheses may explain the elevation of oxidized LDL in women who use COC.

It should be noted that, in recent years, scientific evidence has increasingly made the role of oxidized LDL in the pathophysiology of atherosclerosis clearer.[25] However, there is still no clearly defined mechanism, but several hypotheses that help explain the oxidation of LDL-cholesterol in different populations.[8,25] One of these hypotheses demonstrates that the bioavailability of LDL-cholesterol in association with oxidative stress appears to be the main determinant for the formation of oxidized LDL.[8]

Thus, although we did not observe a difference in the fasting LDL-cholesterol levels among the groups studied, we suggest that the GCOC has a higher concentration of the more atherogenic LDL-cholesterol subfraction. This particle is small and dense, and has lower concentrations of antioxidants. Taken together, these factors make it more prone to oxidative damage.[26] In this study, the hypothesis in question is based on the TG/HDL-cholesterol ratio result, which we found to be significantly higher in GCOC. In addition, it has been suggested that the TG/HDL-cholesterol ratio may reflect the size of LDL-cholesterol particles, with values > 1 being indicative of small and dense particles.[26] Consistent with our study, Graaf et al.[6] showed that women who use COC have higher concentrations of atherogenic LDL-cholesterol subfraction, which may suggest a more atherogenic lipid profile in this population.

Table 1 – Clinical and anthropometric characteristics of women using and not using combined oral contraceptives (n = 42)

Variables	GCOC (n = 21)	CG (n = 21)	p value
Age (years)	23 ± 3.1	23 ± 3.4	0.98*
Body mass index (kg/m^2)	20 ± 2.1	19 ± 2.8	0.07*
Waist circumference (cm)	73 ± 7.8	70 ± 5.9	0.32*
Systolic blood pressure (mmHg)	118 ± 8.8	111 ± 9.7	0.02*
Diastolic blood pressure (mmHg)	77 (74 – 80)	70 (70 – 80)	0.18**
C-reactive protein (mg/L)	2.7 (1.8 – 6.4)	0.9 (0.5 – 1.1)	< 0.01 **
Blood glucose (mg/dL)	82 ± 6.9	83 ± 5.7	0.57*
Pyruvic glutamic Transaminase (U/L)	15 ± 4.2	14 ± 3.4	0.16*
Time of use of COC (years)	3.7 ± 2.3	–	–

*GCOC: combined oral contraceptive group; CG: control group; COC: combined oral contraceptive; *Bidirectional Student's t test for independent samples; **Bidirectional Mann-Whitney test.*

Table 2 – Comparison of fasting lipids (mg/dL) among the groups studied

Variables	GCOC (n = 21)	CG (n = 21)	p value
Triglycerides	95 (73 – 112)	49 (40 – 64)	< 0.01 **
Total cholesterol	210 ± 38.6	183 ± 29.7	0.01*
HDL-c	58 ± 19.3	48 ± 11.5	0.04*
LDL-c	134 ± 35.1	126 ± 27.7	0.42*
VLDL-c	19 (15 – 22)	10 (8 – 13)	< 0.01 **
TG/HDL-c ratio	1.7 ± 0.5	1.1 ± 0.5	< 0.01*

*GCOC: combined oral contraceptive group; CG: control group; HDL-cholesterol: high-density lipoprotein cholesterol; LDL-cholesterol: low-density lipoprotein cholesterol; VLDL-cholesterol: very low-density lipoprotein cholesterol; TG: triglycerides;*Two-way t-test for independent samples; ** Bidirectional Mann-Whitney test.*

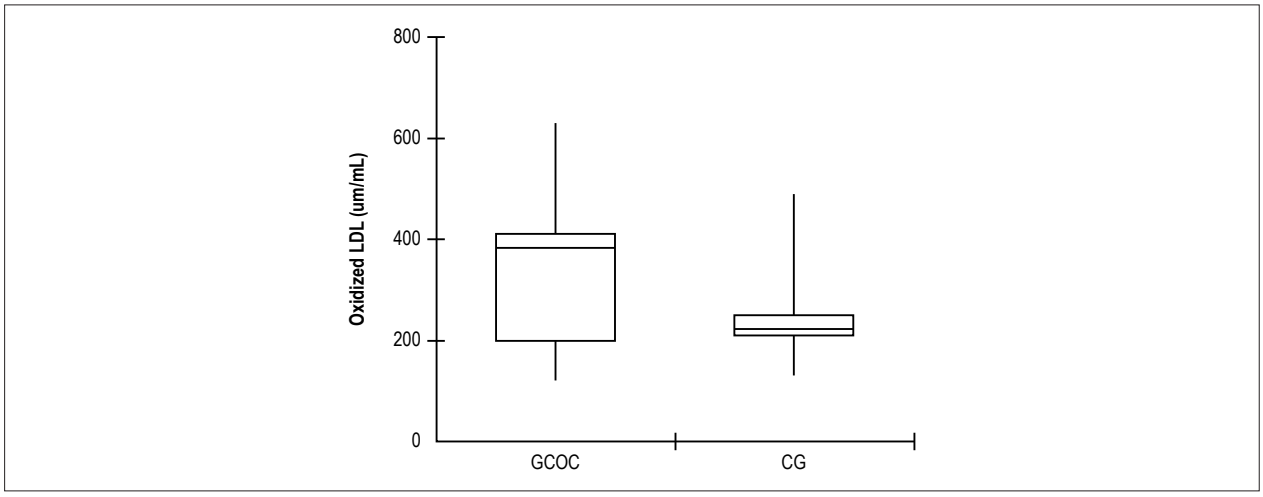

Figure 1 – *The boxplot shows a higher concentration of oxidized LDL in women using combined oral contraceptives compared to those who did not use this group of drugs (p < 0.01). In addition, it is noted that in the GCOC the concentration of this oxidized lipoprotein is in the first quartile, while the CG is in the third quartile. The comparison of the median between groups was compared by bidirectional Mann-Whitney test.*

In contrast to our findings, although in a population of 40-48 years of age, different oral contraceptive formulations, and factors such as smoking, intestinal disease and physical activity, the ELAN study[3] did not identify any significant changes in plasma oxidized LDL of women who use and do not use oral contraceptives. However, it was noted that in women using this group of drugs, the lipid oxidation, marked by the highest concentration of peroxides (-OOH), was 1.7 times higher. According to the authors, this result could be explained by the higher oxidative stress induced by ethinylistradiol present in the formulations of COC.[3]

In line with this observation, we can suggest, as well as other studies, that women on COC have higher oxidative stress.[3] This hypothesis can be supported by the significant increase in oxidized LDL in GCOC, because according to the literature this oxidized lipoprotein is a variable of oxidative stress.

According to literature data, the estrogenic and androgenic properties of COCs have an influence on oxidative stress, because these hormones have several actions on the vascular endothelium, increasing the bioavailability of nitric oxide, a fact that does not seem to protect, but rather attacks the endothelium, due to increased oxidative stress.[27]

Another fact that calls attention is that oxidized LDL has a correlation with other lipid variables. In fact, our results, as well as other studies, indicate that oxidized LDL has a moderate positive correlation with total cholesterol, triglycerides and LDL.[8,12] This relationship may be partially justified by findings indicating that an increase of 1mg/dL in serum levels of total cholesterol or LDL-cholesterol, as well as an increase of one unit in the total cholesterol/HDL-cholesterol ratio, can predict increases of 0.22, 12.21 and 15.78 U/L at oxidized LDL levels.[28] According to the literature, triglycerides can predict, regardless of variables such as LDL-cholesterol, elevated oxidized LDL values.[27]

Consistent with the literature, our study demonstrated a significant increase in serum TG, HDL-cholesterol, CRP, and systolic blood pressure values in GCOC, whereas no difference was detected in LDL-cholesterol values.[29-31] However, caution should be taken when analyzing the LDL-cholesterol and HDL-cholesterol results, because the TG/HDL-cholesterol ratio is significantly higher in this group of women, indicating a higher atherogenic potential related to LDL cholesterol. Regarding HDL cholesterol, although in our sample its values are significantly high, it is not yet known what the effects of COC on its subfractions are, since atherogenic particles of HDL-cholesterol are present.[32]

Table 3 – Correlation analysis between LDL-oxidized (mU/mL) and fasting lipid profile variables (mg/dL) and CRP (mg/dL)

Crossings	Correlation coefficient (rs)	p value*
Oxidized LDL and TG	0.32	0.03
Oxidized LDL and CT	0.47	< 0.01
Oxidized LDL and LDL-cholesterol	0.29	0.05
Oxidized LDL and HDL-cholesterol	0.26	0.08
Oxidized LDL and PCR	0.20	0.19

*Oxidized LDL: oxidized low-density lipoprotein; TG: triglycerides; TC: total cholesterol; HDL-cholesterol: high-density lipoprotein cholesterol; LDL-cholesterol: low-density lipoprotein cholesterol; CRP: C-reactive protein; * Spearman's correlation test.*

Table 4 – Categorical analysis based on the median of oxidized LDL

		COC		p value*
		No n (%)	Yes n (%)	
Oxidized LDL	< 247	15 (71.4%)	6 (28.6%)	< 0.01
	> 247	6 (28.6%)	15 (71.4%)	

*Oxidized LDL: oxidized low-density lipoprotein; COC: combined oral contraceptive. *Fisher's exact test.*

It is also interesting to note that the use of COC has been suggested as an independent factor for plasma CRP elevation in women of reproductive age. This increase appears to be associated with changes in estrogen β receptor function and levels, increased cortisol, increased TNF-α, hypomethylation in the DNA of macrophages, and alterations in hepatic PCR synthesis. It is also worth noting that the current use of COC can independently represent 20 to 32% of the variation of CRP in these women.[33] In addition, it was also shown that one in three women on COC shows CRP > 3 mg/L, which according to the literature can markedly increase the risk of cardiovascular events.[29]

In addition, as in our results, research has shown a significant elevation of blood pressure in women on use of COC.[7,34,35] In fact, according to some studies, COC use may be related to mild and moderate arterial hypertension, with increases ranging from 20 to 40 mmHg in SBP and 10 to 20 mmHg in the diastolic pressure. Also, according to the studies, this elevation can be reversed within 3 months after COC descontinuation.[34] Such elevation of blood pressure may occur due to changes in electrolyte concentrations, oxidative stress, insulin resistance, and increased production of renin and hepatic angiotensinogen in these women.[34,35]

Therefore, in addition to the fact that oxidized LDL emerges as a non-traditional risk factor for future cardiovascular events in postmenopausal women,[14] and that, in the pathophysiology of atherosclerosis, besides being present in all stages of the atherosclerotic process, it begins to be deposited in the arterial wall of young adults, even before the initial formation of the atheromatous plaque,[36] it is suggested that women taking COC present a greater future cardiovascular risk than women who do not use this group of drugs.

Oxidation of LDL-cholesterol is closely related to endothelial dysfunction in a positive feedback process. The endothelial dysfunction associated with the arterial vascular inflammatory process are mainly responsible for the oxidation of LDL cholesterol, which in turn causes endothelial cell toxicity and chemotactic attraction of monocytes/macrophages through feedback of endothelial dysfunction. This mechanism is known as the oxidative theory of atherogenesis.[37,38]

The results presented here point to mechanisms that may help elucidate the outcome of a multicenter study that showed that COC use is associated with a 5-fold increased risk of myocardial infarction in Europe and more than 4-fold in non-European countries. It is worth mentioning that this increase is closely linked to COC formulations with estrogen (≥ 50 μg), and the presence of classic risk factors such as smoking, hypertension, dyslipidemia, and obesity.[16,17] Another interesting study showed that women taking COC with ethinyl estradiol dosages between 30 and 40 μg had a risk of arterial thrombosis between 1.3 and 2.3. At lower dosages (20 μg), the risk was 0.9 and 1.7 times, when compared to women who did not use this group of drugs. These results suggest that even at low dosages, COCs may increase the risk of atherothrombosis, a fact that should be taken into consideration during its prescription, especially in women presenting cardiovascular and metabolic disease risk factors.[17,39]

Finally, the present study has limitations that need to be discussed. One of them is the non-stratification of COC types. Although being of 3rd generation, COC has different formulations in concentrations of estrogen and progestin, a fact that, in addition to being able to cause different effects on the metabolism, limits the generalization of the results as to the type of hormone present in the formulation of contraceptives. In addition, dietary control was not adequately performed, although we did not select volunteers in control or dietary limitation, and the influence of diet on our results cannot be completely excluded. It is also

important to point out that the limitations presented do not impair the results of this study. On the contrary, they add data that facilitate the understanding of alterations in the lipid profile of women of reproductive age who use COC.

Conclusion

In summary, the findings of this study indicate that women who use COC have a significant increase in plasma oxidized LDL values, as well as higher concentrations of small and dense LDL-cholesterol subfractures, identified by the TG/HDL-cholesterol ratio. We also identified a moderate and positive correlation of oxidized LDL with atherogenic variables of the lipid profile, which may suggest a greater vascular aggression and, consequently, a higher cardiovascular risk in this population. Finally, we can also suggest higher oxidative stress, represented indirectly by the higher concentration of oxidized LDL in these women.

Author contributions

Conception and design of the research: Santos ACN, Petto J, Ladeia AMT; Acquisition of data: Santos ACN, Diogo DP, Rocha CS, Souza LH, Araújo WS; Analysis and interpretation of the data: Santos ACN, Petto J, Diogo DP, Ladeia AMT, Araújo WS; Writing of the manuscript: Santos ACN, Petto J, Araújo WS, Diogo DP, Souza LH, Rocha CS, Ladeia AMT; Critical revision of the manuscript for intellectual content: Santos ACN, Petto J, Araújo WS, Diogo DP, Ladeia AMT.

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 Faculdade de Tecnologia e Ciência de Salvador under the protocol number 3.39012011. 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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Warning Against Low-Density Lipoprotein Oxidation in Users of Oral Combined Contraceptives

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Short Editorial regarding to the article: Elevation of Oxidized Lipoprotein of Low Density in Users of Combined Oral Contraceptives

Cardiovascular diseases are the main cause of morbidity and mortality in the Western World and in our country.[1] In the last years, this scenario has shown a decrease in the incidence of stroke, formerly the first cause of death.[2] Today, its place has been taken by coronary heart disease.[2] This change was due to better diagnosis and treatment of hypertension, the main cause of strokes, and the increase of the prevalence of risk factors for coronary heart disease such as obesity, diabetes, bad dietary habits, emotional stress and social deprivation, among others.[3] Recently, an increase in myocardial infarction mortality, attributed to several causes, has been observed specifically among Brazilian[4] and North-American[5] young women. The article by dos Santos ACN et al.[6] has focused on one of these possible causes. They studied low-density lipoprotein (LDL) oxidation in users of combined oral contraceptives, showing that this alteration of lipoproteins is increased in this group. LDL oxidation is considered one of the main participants in the atherosclerosis process development, as well as in its major clinical manifestations.[7] They properly discussed the many possible causes of their findings and tried to establish correlations between LDL oxidation with many other variables. They referred to other studies that showed elevated C-Reactive Protein[8] and blood pressure levels[9] in users of combined oral contraceptives, which along with the known thrombogenicity of these agents (mainly in combination with tobacco smoking),[10] can demonstrate the potential increase in cardiovascular risk in this group. The authors did not specify the types of oral contraceptives that were studied, which could be considered a study limitation. A practical consequence of the presented data is the fact that they are relevant for young women, who will need to find other kinds of contraception, such as IUDs, other oral contraceptives, and other possibilities to prevent the potentially deleterious effects of the combined oral contraceptives.

Keywords

Cardiovascular Diseases/mortality; Oxidation; Lipoproteins, LDL; Contraceptives, Oral; Stroke.

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Original Article

Comparison of Cardiac and Vascular Parameters in Powerlifters and Long-Distance Runners: Comparative Cross-Sectional Study

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Abstract

Background: **Cardiac remodeling is a specific response to exercise training and time exposure. We hypothesized that athletes engaging for long periods in high-intensity strength training show heart and/or vascular damage.**

Objective: **To compare cardiac characteristics (structure and function) and vascular function (flow-mediated dilation [FMD] and peripheral vascular resistance [PVR]) in powerlifters and long-distance runners.**

Methods: **We evaluated 40 high-performance athletes (powerlifters [PG], n = 16; runners [RG], n = 24) and assessed heart structure and function (echocardiography), systolic and diastolic blood pressure (SBP/DBP), FMD, PVR, maximum force (squat, bench press, and deadlift), and maximal oxygen uptake (spirometry). A Student's t Test for independent samples and Pearson's linear correlation were used ($p < 0.05$).**

Results: **PG showed higher SBP/DBP ($p < 0.001$); greater interventricular septum thickness ($p < 0.001$), posterior wall thickness ($p < 0.001$) and LV mass ($p < 0.001$). After adjusting LV mass by body surface area (BSA), no difference was observed. As for diastolic function, LV diastolic volume, wave E, wave e', and E/e' ratio were similar for both groups. However, LA volume ($p = 0.016$) and BSA-adjusted LA volume were lower in PG ($p < 0.001$). Systolic function (end-systolic volume and ejection fraction), and FMD were similar in both groups. However, higher PVR in PG was observed ($p = 0.014$). We found a correlation between the main cardiovascular changes and total weight lifted in PG.**

Conclusions: **Cardiovascular adaptations are dependent on training modality and the borderline structural cardiac changes are not accompanied by impaired function in powerlifters. However, a mild increase in blood pressure seems to be related to PVR rather than endothelial function. (Arq Bras Cardiol. 2018; 111(6):772-781)**

Keywords: **Hypertrohy,Ventricular; Exercise; Exercise MovementTechniques; Blood Pressure; Resistance Training; Running/physiology.**

Introduction

Exercise training induces cardiovascular adaptations secondary to changes in blood pressure as well as other hemodynamic and metabolic changes in response to physical exertion. These adaptive changes can induce left ventricular (LV) hypertrophy in the long run.[1] Some authors claim that borderline physiological and anatomical changes occur as part of an adaptive process of high-performance training and they have sparked off debate on their implications.[2] They postulate that volume overload generally increases LV pumping ability producing eccentric hypertrophy while, in contrast, pressure overload decreases ventricular cavity size producing concentric hypertrophy. Moreover, peripheral vascular resistance (PVR) is an important factor of cardiac overload by specifically modulating LV afterload. Furthermore, the endothelium is central to vasodilation by producing nitric oxide (NO), which is a vasodilator and has a direct effect on PVR. Therefore, it is important to highlight that after exercise there is a stimulation of NO production and eNOS phosphorylation, which contributes directly to a reduction in PVR.[3,4]

Aerobic exercise increases shear stress leading to increased release and synthesis of NO and higher active muscle vasodilation.[5] LV pressure overload is reduced over time.[6] However, high-intensity resistance training such as weightlifting and powerlifting involves a number of very slow-speed contractions that produce transient mechanical compression of resistance vessels, increasing PVR and LV pressure overload during exercise.[7] It has been postulated that chronic increase in afterload induces the parallel addition of new sarcomeres in the myocardium leading to concentric ventricular hypertrophy.[8] Yet, this form of ventricular hypertrophy has not been demonstrated in strength training athletes,[9] and it is thus an inconsistent finding.

Given the limited body of evidence in support of these cardiovascular adaptations as well as concerning endothelial function and PVR in strength athletes, this study aimed

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to compare structural and functional cardiac changes in powerlifters and long-distance runners. Secondarily, we compared endothelium-dependent vasodilation and PVR in these athletes. Our hypothesis is that athletes engaging in high-intensity strength training for long periods of time show changes in cardiac structure associated with reduced cardiac function when compared to long-distance runners. Furthermore, long-time exposure to high-intensity strength training could lead to a reduction of endothelial function caused by pressure overload.

Methods

Study participant selection and groups

The study convenience sample comprised 40 male individuals aged 18–40 years. We selected athletes of powerlifting (powerlifters group [PG], n = 16) and long-distance (over 10 km) running events (runners group [RG], n = 24). Eligible athletes were those competing for at least 3 years. Individuals with any medical condition in the preceding 6 months; those not competing in the preceding 6 months; those on use of illicit (doping) substances in the last 12 months; or those who refused to sign an informed consent were excluded.

The study sample was recruited using an open invitation at training sites (gyms, health clubs and sports centers) and selected after applying the inclusion criteria. Participants were assessed as follows: on the first visit they underwent blood pressure assessment, echocardiographic assessment, brachial artery flow-mediated dilation (FMD), PVR assessments. In addition, they were administered a comprehensive questionnaire with questions about training including time of training experience; performance timeline; any awards/prizes; current training routine (volume, intensity, and duration of weekly training sessions, frequency of competitive participation, rest times, etc.) among others. On the next day, they underwent a maximum load test; and on the last visit (48 hours later), they underwent a maximum oxygen uptake test. All assessments were carried out within the same period of time (8 a.m. to 11 a.m.).

Blood pressure assessment

Blood pressure measurements were taken using a semi-automatic blood pressure monitor (OMROM 705CP), with the participant in a seated position with both feet on the floor, after a 10-minute rest; the cuff was placed and adjusted to the arm circumference. In a completely quiet room, blood pressure measurements were taken in duplicate on both arms, and the higher value of these readings was used in the study.

Echocardiographic examination

Transthoracic echocardiographic examinations were performed by an echocardiography specialist (G.B.G.). An ultrasound device (EnVisor CHD, Philips, Bothell, WA, USA) equipped with a sector transducer probe (2–4 MHz) was used to obtain longitudinal, cross-sectional, two-dimensional 2- and 4-chamber, and M module images. Continuous-wave, pulsed-wave, and color Doppler techniques were used to examine ventricular tissues and walls. All images were stored and sent to a second echocardiography specialist (D.P.K.) for blind evaluation of images. Body surface area (BSA) was calculated using Du Bois method.[10]

Brachial artery flow-mediated dilation and peripheral vascular resistance

We used a high-resolution two-dimensional Doppler ultrasound device (EnVisor CHD, Philips, Bothell, WA, USA) equipped with a high-frequency (7-12 MHz) linear vascular transducer probe and electrocardiographic imaging and monitoring software. FMD measurements were taken with the participants in the supine position, and a properly fitting pressure cuff was placed on the arm 5 cm above the cubital fossa.[11] Baseline brachial artery longitudinal diameters were assessed. Following that, the occlusion cuff was inflated to 50 mmHg above the systolic blood pressure (SBP) for 5 minutes and then deflated. Brachial artery diameters were measured for 60 seconds after deflation of the cuff. All analyses were performed offline and brachial artery measurements were made at the end of diastole (at R-wave peak on the electrocardiogram). FMD responses were expressed as percentage change from the baseline brachial artery diameter.

PVR was calculated from mean blood pressure (MBP) and baseline blood flow obtained in the FMD test (PVR = MBP/baseline blood flow in mmHg/cm.s^{-1}).

Maximum load test

Maximum strength was assessed in the one-repetition maximum test (1-RM) for the squat, bench press and deadlift exercises, which are specifically performed at competitions, and through the total sum of these three exercises (total load). Distance runners attended a familiarization session within 48 hours of the test when the order of strength exercises and proper performance were introduced. For the 1-RM, the participants performed the maximum number of repetitions with the proposed load, up to a maximum of 10 repetitions. Exercise loads were increased according to Lombardi (1989) up to a point where participants were able to perform only one repetition with a maximum of 3 attempts to achieve the maximum load.

Maximum oxygen uptake

Maximum oxygen uptake (VO_2peak or VO_2max) was assessed through cardiopulmonary exercise test on a treadmill with respiratory gases collected (VO2000 model, Inbramed, Porto Alegre, Brazil). Powerlifters attended a familiarization session within 48 hours of the test where test procedures were introduced (Bruce protocol and mask placement for gas collection). The highest value, either VO_2 peak or VO_2 max was recorded at the end of the test as VO_2 max.

Statistical analyses

We performed the Shapiro-Wilk test to test normality of the data and homogeneity of variance was tested using Levene's test. All results are described as mean ± SD and confidence

interval. We conducted Student's t Test for independent samples to assess differences between groups and calculated Pearson's linear correlation coefficients ($\alpha = 0.05$ for all tests). All statistical analyses were performed using SPSS Statistics (version 21 for Windows).

Results

The participants had similar age and height (Table 1). However, all anthropometric measurements for PG were greater compared to distance RG. In turn, Table 2 shows loads for the squat, bench press, and deadlift exercises and total load (total sum of these three exercises). For all types of exercises, weight loads were higher in PG than RG as expected. The total load was greater by ~133% in PG than RG. The differences remained unchanged when loads were adjusted for body mass.

Table 3 shows hemodynamic and cardiopulmonary parameters. Powerlifters had higher resting SBP (~10%) and resting DBP (~12%); the absolute differences between the two groups were 13.6 mmHg and 10.1 mmHg, respectively. Resting heart rate was higher in PG compared to RG (~19%, Δ15.7 bpm). VO_2max was much higher in RG than PG (~65%): the highest VO_2 max value among powerlifters was lower than the lowest VO_2 max value among runners.

Table 4 shows the echocardiographic results. As for cardiovascular adaptations, aorta diameter, left atrium (LA) diameter, right ventricle diameter, LV systolic diameter, and LV diastolic diameter were similar in both groups. However, PG showed greater interventricular septum thickness (Δ2.4 mm) and posterior wall thickness (Δ1.2 mm). They also showed greater LV mass (Δ46.5 g), but this difference disappeared after adjusting for BSA. As for diastolic function, LV diastolic volume, transmitral E wave, e' wave, and E/e' ratio were similar in both groups. However, LA volume (~22%), and LA volume adjusted for BSA (~40%) were found in PG, when compared to RG, but they were all within normal ranges. Although PG showed some degree of anatomical remodeling and different diastolic function parameters compared to RG, systolic function reflected in LV systolic volume, ejection fraction, and ejection fraction calculated by Simpson's rule were similar in both groups. Of the 40 participants, 9 (22.5%) had physiological ventricular hypertrophy in response to exercise; 10 (all powerlifters) had interventricular septum thickness greater than 11 mm. Of the 27 participants with LV mass greater than 225 g and LV mass adjusted by BSA greater than 115g/m^2, 13 (82%) were PG and 14 (63%) RG.

Figure 1 shows FMD (%) and PVR measurements. Interestingly, FMD values were similar in both groups ([PG] 14.7 ± 2.3 vs. [RG] 15.9 ± 2.5%). However, PG had higher PVR values compared to RG ([PG] 12.6 ± 5.3 vs. [RG] 8.2 ± 3.8 mmHg/cm.s^{-1}, Δ35%).

The correlations between training parameters and echocardiographic and cardiopulmonary variables in PG are displayed in Table 5. There was a direct correlation between interventricular septum thickness and weight load in the deadlift, squat, and total load. Interestingly, no correlation was found with time of exposure, i.e., duration in years of strength training among powerlifters. SBP levels were directly correlated with training intensity; and DBP showed a stronger correlation with duration of strength training. For runners, interventricular septum thickness and resting heart rate were inversely correlated with VO_2max and duration of strength training (Table 6).

Finally, FMD measurements were directly proportional to training intensity (% 1-RM) in PG and weight load for the squat (Table 7). For RG, no correlation of FMD values was found with cardiopulmonary variables and resting heart rate. Furthermore, FMD values were correlated with duration of powerlifting training (years) and daily duration of training session. However, this same correlation was not seen among runners.[12]

Table 1 – General characteristics of the study participants

	PG (n = 16) Mean ± SD (95% CI)	RG (n = 24) Mean ± SD (95% CI)	p-value
Age (years)	29.9 ± 4.4 (27.5–32.2) Min 20 and Max 36	28.7 ± 5.7 (26.3–31.1) Min 18 and Max 40	0.490
Body mass (kg)	99.2 ± 21.5 (87.6–110.7) Min 75 and Max 135	71.7 ± 9.2 (67.7–75.6) Min 58 and Max 84	< 0.001
Height (cm)	176 ± 0.8 (172–181) Min 164 and Max 195	175 ± 0.8 (172–179) Min 161 and Max 193	0.736
Chest circumference (cm)	113.2 ± 13.4 (106–120.4) Min 94.5 and Max 144	86.9 ± 8.6 (83.2–90.5) Min 61 and Max 100	< 0.001
Waist circumference (cm)	95.1 ± 12.9 (88.2–102) Min 78 and Max 117	78.6 ± 5.7 (76.2–81.1) Min 69 and Max 92	< 0.001
Duration of training (years)	5.12 ± 2.0 (4.0–6.2) Min 3 and Max 10	7.8 ± 2.6 (6.7–8.9) Min 3 and Max 10	0.001
Weekly duration of training (days)	3.9 ± 1.0 (3.3–4.4) Min 3 and Max 5	5.4 ± 1.0 (4.9–5.8) Min 3 and Max 7	< 0.001
Daily duration of training (min/day)	69.3 ± 14.4 (61.7–77.0) Min 60 and Max 90	98.7 ± 28.6 (86.6–110.8) Min 60 and Max 120	0.001

PG: powerlifters group; RG: long-distance runners group. Weekly number of training sessions and session average time correspond to the average duration for the last 3 months. Differences between means were assessed using Student's t Test for independent samples.

Table 2 – Maximum load test results in absolute values and adjusted for body mass

	PG (n = 16) Mean ± SD (95% CI)	RG (n = 24) Mean ± SD (95% CI)	p-value
Squat (kg)	212.2 ± 46.4 (187.4–236.9) Min 140 and Max 302	98.9 ± 27.1 (87.4–110.6) Min 56 and Max 160	< 0.001
Squat/body mass	2.16 ± 0.27 (2.01–2.30) Min 1.6 and Max 2.6	1.37 ± 0.30 (1.24–1.50) Min 1.0 and Max 2.3	< 0.001
Bench press (kg)	145.5 ± 32.9 (127.9–163.1) Min 110 and Max 220	59.0 ± 16.5 (52.0–66.0) Min 40 and Max 94	< 0.001
Bench press/body mass	1.49 ± 0.26 (1.35–1.62) Min 1.1 and Max 2.1	0.81 ± 0.17 (0.74–0.89) Min 0.6 and Max 1.2	< 0.001
Deadlift (kg)	239.0 ± 66.5 (203.6–274.5) Min 150 and Max 370	102.4 ± 27.8 (90.6–114.2) Min 53 and Max 140	< 0.001
Deadlift/body mass	2.43 ± 0.49 (2.16–2.69) Min 1.5 and Max 3.1	1.45 ± 0.41 (1.28–1.63) Min 0.6 and Max 2.0	< 0.001
Total load (kg)	596.8 ± 137.4 (532.6–670.1) Min 413 and Max 890	260.4 ± 43.8 (241.9–278.9) Min 191 and Max 341	< 0.001
Total load/body mass	6.07 ± 0.89 (5.59–6.55) Min 4.4 and Max 7.4	3.64 ± 0.48 (3.44–3.85) Min 2.6 and Max 4.6	< 0.001

PG: powerlifters group; RG: long-distance runners group. Differences between means were assessed by Student's t Test for independent samples.

Table 3 – Hemodynamic and cardiopulmonary parameters

	PG (n = 16) Mean ± SD (95% CI)	RG (n = 24) Mean ± SD (95% CI)	p-value
Resting SBP (mmHg)	130.0 ± 8.2 (124.5–134.0) Min 120 and Max 140	116.4 ± 8.6 (112.8–120.1) Min 110 and Max 140	< 0.001
Resting DBP (mmHg)	82.1 ± 6.9 (78.1–68.1) Min 70 and Max 95	72.0 ± 6.5 (69.3–74.8) Min 60 and Max 80	< 0.001
Resting heart rate (bpm)	80.4 ± 7.5 (76.0–84.8) Min 69 and Max 94	64.7 ± 10.3 (60.3–69.1) Min 45 and Max 90	< 0.001
Maximum heart rate (bpm)	180.2 ± 13.7‡ (173.2–188.2) Min 158 and Max 209	184.3 ± 14.7‡ (178.1–190.5) Min 167 and Max 224	0.403
VO_2 max ($mL.kg^{-1}.min^{-1}$)	33.9 ± 7.5 (29.6–38.9) Min 24 and Max 43	56.0 ± 7.3 (52.7–62.1) Min 45 and Max 74	< 0.001
VCO_2 max ($mL.kg^{-1}.min^{-1}$)	36.6 ± 9.3 (31.2–42.0) Min 24 and Max 57	58.0 ± 7.5 (55.2–61.6) Min 45 and Max 87	0.028
Pulmonary ventilation ($L.min^{-1}$)	103.5 ± 17.6 (93.3–113.7) Min 76 and Max 136	112.4 ± 14.9 (106.1–118.7) Min 85 and Max 157	0.106

SBP: systolic blood pressure; DBP: diastolic blood pressure; PG: powerlifters group; RG: long-distance runners group. VO_2: oxygen uptake; VCO_2: carbon dioxide production. Differences between means were assessed by Student's t Test for independent samples. ‡ p < 0.05 vs. baseline value within the same group.

Discussion

Our study found that, compared with long-distance runners, powerlifters showed greater interventricular septum thickness, LV posterior wall thickness and LV mass. However, after adjusting for BSA, no difference was observed in LV mass.Cardiac function was similar in powerlifters and runners. Together, these parameters suggest that specific cardiac remodeling may occur as a result of training, but with no impairment of cardiac functions. A major finding of our study was similar FMD measurements in both powerlifters and runners despite PVR being higher in powerlifters.[12] Although our findings are comparative and derive from a cross-sectional design, they suggest that high-intensity strength training does not necessarily cause damaging cardiovascular changes as it has been generally believed.

Cardiac parameters

Regarding cardiac parameters (anatomical structure, and diastolic and systolic function), the echocardiographic assessments showed increased interventricular septum thickness with slight or no chamber diameter reduction and slight increase in posterior wall thickness in powerlifters compared to runners. These changes may be because powerlifting involves a great amount of slow-speed contractions using high loads close to the maximum[13] in daily training sessions leading to LV pressure overload.

Table 4 – Echocardiographic parameters

	PG (n = 16) Mean ± SD (95% CI)	RG (n = 24) Mean ± SD (95% CI)	p-value
Anatomical structures			
Aorta diameter (mm)	31.3 ± 3 (29.7–32.9) Min 25 and Max 36	32.0 ± 2.7 (30.8–33.2) Min 29 and Max 38	0.410
LA diameter (mm)	36.0 ± 2.5 (34.6–37.3) Min 30 and Max 39	35.6 ± 2 (34.7–36.5) Min 32 and Max 39	0.632
RV diameter (mm)	20.3 ± 1.2 (19.6–20.9) Min 18 and Max 22	20.5 ± 2 (19.6–21.4) Min 16 and Max 25	0.689
LV end-systolic diameter (mm)	30.7 ± 3.9 (28.6–32.8) Min 23 and Max 37	30.2 ± 2.9 (28.9–31.5) Min 25 and Max 36	0.671
LV end-diastolic diameter (mm)	53.4 ± 3.3 (51.5–55.3) Min 45 and Max 60	53.7 ± 3.3 (52.2–55.2) Min 45 and Max 57	0.770
Interventricular septum thickness (mm)	12.0 ± 1.0 (10.6–12.3) Min 10 and Max 14	9.6 ± 0.4 (9.4–9.9) Min 9 and Max 10	< 0.001
Ventricular posterior wall thickness (mm)	10.4 ± 0.9 (9.9–10.9) Min 9 and Max 12	9.1 ± 0.5 (8.9–9.4) Min 8 and Max 10	< 0.001
LV mass (g)	282.2 ± 73.4 (243–321.4) Min 150 and Max 406	235.7 ± 26.0 (224.2–247.3) Min 179 and Max 276	< 0.001
LV mass/BSA (g/m^2)	135.6 ± 24.9 (136.1–133.6) Min 90 and Max 173	127.8 ± 16.9 (120.3–135.4) Min 104 and Max 166	0.262
Diastolic function			
End-diastolic volume (mL)	145.0 ± 18.9 (134.9–155.1) Min 92 and Max 173	138.1 ± 17.2 (130.5–145.8) Min 92 and Max 160	0.251
Transmitral E-wave velocity	0.83 ± 0.15 (0.75–0.90) Min 0.6 and Max 1.1	0.91 ± 0.15 (0.84–0.97) Min 0.6 and Max 1.3	0.124
e' wave	0.15 ± 0.03 (0.13–0.17) Min 0.1 and Max 0.2	0.17 ± 0.34 (0.15–0.19) Min 0.1 and Max 0.2	0.062
E/e' ratio	5.69 ± 1.05 (5.12–6.24) Min 4.1 and Max 8.0	5.56 ± 1.76 (4.78–6.34) Min 3.0 and Max 11.8	0.808
Transmitral A-wave velocity	0.35 ± 0.03 (0.33–0.37) Min 0.3 and Max 0.4	0.38 ± 0.04 (0.36–0.40) Min 0.3 and Max 0.5	0.047
LA volume (mL)	35.7 ± 8.5 (31.2–40.2) Min 22 and Max 53	43.6 ± 10.2 (39.1–48.2) Min 32 and Max 76	0.016
LA volume/BSA (mL/m^2)	16.7 ± 4.1 (14.5–18.8) Min 11 and Max 27	23.4 ± 4.6 (21.4–25.5) Min 16 and Max 37	< 0.001
Systolic function			
End-systolic volume (mL)	38.0 ± 11.2 (31.9–44) Min 18 and Max 58	34.8 ± 9.3 (30.6–38.9) Min 22 and Max 54	0.348
Ejection fraction (%)	73.0 ± 4.5 (70.5–75.4) Min 67 and Max 80	74.3 ± 4.6 (72.3–76.3) Min 65 and Max 86	0.383
Ejection fraction by Simpson's rule (%)	71.6 ± 4.8 (69.1–74.2) Min 62 and Max 79	72.7 ± 5.9 (70.1–75.4) Min 61 and Max 81	0.568

PG: powerlifters group; RG: long-distance runners group; LA: left atrium; RV: right ventricle; LV: left ventricle; BSA: body surface area. Differences between means were assessed using Student's t Test for independent samples.

As for the cutoff values, several studies with high-performance athletes have used to determine pathological hypertrophy cutoff values of 12-13 mm for maximum interventricular septum thickness and 55-60 mm for end-diastolic dimension, as described below.Whyte (2004) examined 306British elite male athletes (judo, n = 22; skiing, n = 10; pole vault, n = 10; kayak, n = 11; rowing, n = 17; cycling, n = 11; power lifters, n = 29; triathlon, n = 51; modern pentathlon, n = 22; middle distance, n = 45; rugby, n=30; tennis, n = 33; swimming, n = 19) and found interventricular septum thickness > 13 mm in ~3.0% of them. Riding (2012) examined 836 athletes (soccer, n = 586; basketball, n = 75; volleyball, n = 41 and handball, n = 35) and found interventricular septum thickness > 12 mm and typical features of concentric left

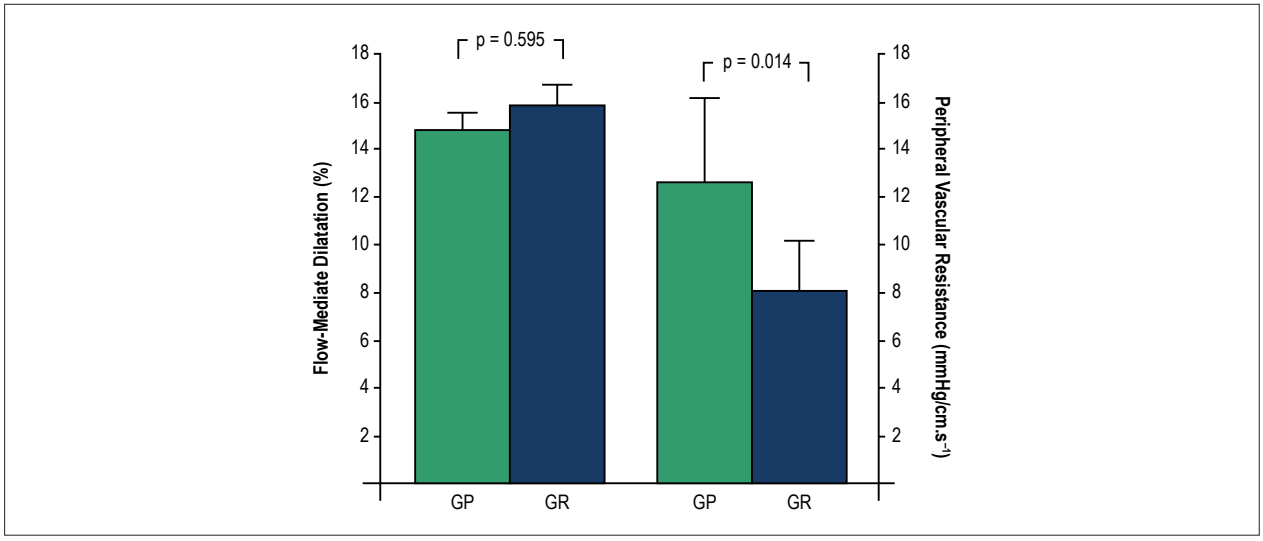

Figure 1 – *Flow-mediated dilation measurements and peripheral vascular resistance. PG: powerlifters group, RG: long-distance runners group. The differences were assessed by Student's t Test for independent samples.*

Table 5 – Pearson linear correlation coefficients between training parameters and echocardiographic /cardiopulmonary variables (PG = 16)

	Total load (kg)	Duration of strength training (years)	Weekly duration of training (days)	Daily duration of training (min/day)
Interventricular septum thickness (mm)	0.733†	0.411	0.286	0.212
Posterior ventricular wall thickness (mm)	0.680†	0.365	0.274	0.225
LV mass (g)	0.689†	0.407	0.213	0.248
Resting heart rate (bpm)	0.706†	0.505	–0.149	0.201
Baseline SBP (mmHg)	0.029	0.377	0.258	0.453
Baseline DBP (mmHg)	0.490	0.762†	0.581*	0.151
VO_2 max (mL.kg^{-1}.min^{-1})	–0.459	–0.093	0.048	0.135
VCO_2 max (mL.kg^{-1}.min^{-1})	–0.623*	–0.133	–0.051	–0.022

*PG: powerlifters group; 1-RM: one-repetition maximum test; LV: left ventricle, SBP: systolic blood pressure; DBP: diastolic blood pressure; VO_2: oxygen uptake; VCO_2: carbon dioxide production. Significance level † p < 0.001 and * p < 0.05.*

ventricular hypertrophy in ~2.0%. Pelliccia (1999) examined 1,309 Italian elite athletes engaged in different sporting disciplines (soccer, n = 119; gymnastics, n = 87; rowing, n = 80; tennis, n = 64;basketball, n = 62; track and field, n = 59; alpine skiing, n = 59; shooting, n = 57; handball, n = 56; cycling, n = 49; water polo, n=43; ice hockey, n = 42; cross-country skiing, n = 41; canoeing, n = 39; rugby, n = 39; skating, n = 36; fencing, n= 35; yachting, n = 33; swimming, n = 29; equestrian sports, n = 24; karate, n = 24; volleyball, n = 21; bobsledding, n = 17; boxing, n = 15; wrestling, n = 14; judo, n = 13; luge, n = 13; field hockey, n = 13; table tennis, n=11; pentathlon, n = 7; weight-lifting, n = 7; golfing, n = 6; baseball, n=5; triathlon, n = 3; motor-racing, n = 3; body-building, n=3; other modalities n = 72) and found interventricular septum thickness > 13 mm in 1.1% of them. Moreover, they also found that 45% and 14% of the athletes studied exhibited end-diastolic dimension > 55 mm and > 60 mm, respectively. Thus, if we use these cutoffs, despite some anatomical cardiac changes, none of the study participants showed cardiac dimensions consistent with pathological hypertrophy. However, it is important to note a strong correlation between weight loads lifted in the squat and total load and cardiac dimensions including septum thickness, posterior wall thickness, and LV mass. Yet again, a possible explanation is that powerlifting involves a great amount of slow-speed contractions using high loads close to the maximum leading to a pressure overload.[9-17]

With regard to LV mass, Gardin et al.,[18] reported values of 225 g and 115 g/m^2 adjusted by BSA in individuals chronically exposed to pressure overload. LV mass was also measured in our study and we found values of 282 g and 135 g/m^2, among powerlifters. Interestingly, runners also showed high LV mass (236 g and 128 g/m^2 adjusted by BSA). Regardless of the training modality, cardiac remodeling occurred in response to exercise training in both groups. Though still controversial, echocardiographic measurements indexed to BSA allow to

Table 6 – Pearson linear correlation coefficients between training parameters and echocardiographic variables (RG = 24)

	VO_2 max ($mL.kg^{-1}.min^{-1}$)	VCO_2 max ($mL.kg^{-1}.min^{-1}$)	Pulmonary ventilation ($L.min^{-1}$)	Duration of strength training (years)	Weekly duration of training (days)	Daily duration of training (min/day)
Interventricular septum thickness (mm)	–0.640*	0.362	0.303	–0.630*	0.150	0.136
Posterior ventricular wall thickness (mm)	0.001	–0.016	0.209	0.260	–0.139	0.032
LV mass (g)	–0.140	–0.137	–0.015	–0.110	–0.248	–0.100
Resting heart rate (bpm)	–0.650*	–0.550	–0.414	–0.659*	–0.163	–0.244
Baseline SBP (mmHg)	0.177	0.311	0.341	–0.074	–0.023	–0.212
Baseline DBP (mmHg)	0.183	0.279	0.258	0.701	0.254	–0.101

*RG: long-distance runners group; LV: left ventricle; SBP: systolic blood pressure; DBP: diastolic blood pressure; VO_2: oxygen uptake, VCO_2: carbon dioxide production. Significance level * p < 0.05.*

Table 7 – Pearson linear correlation coefficients between training parameters and brachial artery flow-mediated dilation measurements

	Squat (kg)		Bench press (kg)		Deadlift (kg)		VO_2 max ($mL.kg^{-1}.min^{-1}$)		Resting heart rate (bpm)		Duration of strength training (years)		Weekly duration of training (days)		Daily duration of training (min/day)	
	PG	RG	PG	RG	PG	RG	PG	RG	PG	RG	PG	RG	PG	RG	PG	RG
FMD (%)	0.710†	0.351	0.242	0.165	0.654†	–0.383	0.073	–0.349	0.489	–0.107	0.688*	0.165	0.491	–0.123	0.770†	–0.079

*PG: powerlifters group; RG: long-distance runners group; FMD: flow-mediated dilation. Significance level † p < 0.001, * p < 0.05.*

comparing individuals of different body sizes. BSA is affected by fat mass, and fat mass is neither correlated with nor predicts LV mass.[19] An alternative approach is to adjust echocardiographic parameters for lean mass. However, accurate measurements are not widely available and substitute methods such as skin-fold thickness measurements are relatively inaccurate.[20,21]

Diastolic function assessment in the study revealed consistently normal values in long-distance runners.[22] In contrast, lower LA volume and transmitral A-wave velocity measures were found in powerlifters although these values were within normal limits. The difference of LA volume measures between both groups was ~22%, and it was even more pronounced after adjustment for BSA (~40%). D'Andrea et al.,[23] and coworkers have assessed LA volume and BSA-indexed LA volume in 350 endurance athletes and 245 strength athletes.[23] For BSA-indexed measures, these authors defined values between 29 and 33 mL/m^2 as mild LA enlargement and values greater than 33 mL/m^2 as moderate LA enlargement. Thus, our results were all below the cutoff values set in D'Andrea et al.,[23] As for LV systolic function assessed through estimates of ejection fraction and ejection fraction calculated by Simpson's rule, the echocardiographic assessment showed values within the normal range in all cases.

Blood pressure

The association of aerobic training with lower resting blood pressure is well established.[24,25] But a growing body of evidence shows that strength training can have a similar effect on blood pressure,[26] though there is not yet a consensus in the literature.[27] However, high-intensity strength training has been reported to negatively affect blood pressure. A meta-analysis showed that training modalities that basically consist of strength training (powerlifting, bodybuilding, and Olympic weightlifting) are associated with a higher risk of high blood pressure with mean SBP of 131.3 ± 5.3 mmHg and mean DBP of 77.3 ± 1.4 mmHg.[28] These values are consistent with those found in our study (SBP 130.0 ± 8.2 and DBP 82.1 ± 6.9 mmHg).

Vascular function

FMD measurements were similar in both powerlifters and runners. This is an interesting finding given that these two training modalities have different biomechanical and metabolic characteristics. Exercise training has been shown as an effective means for the improvement of endothelium-dependent vasodilation capacity.[29] Among high-performance athletes, long-distance runners with above average normal cardiac function show lower arterial stiffness, lower oxidative stress, and increased endothelium-dependent dilation[30] capacity when compared to sedentary individuals of the same age.[31] These data suggest that outstanding cardiac performance in athletes may be associated with improved vascular function induced by aerobic exercise training.

It is well known that aerobic exercise improves endothelial function by producing increased shear stress on the vessel walls during exercise.[32] Yet, it has been suggested that strength training can increase hemodynamic stress due to the mechanical compression of blood vessels during active movements together with excessive vascular tension produced during strength exercises.[7] Thus, we can speculate that high-intensity strength training could acutely affect endothelium-dependent vasodilation and lead to permanent

damage in the long run. In this regard, impaired vascular function has been demonstrated in strength athletes, though it appears to be related to the use of anabolic agents rather than an effect of training.[33,34]

Heffernan et al. found increased forearm reactive hyperemia in healthy young individuals after 6-month strength training.[35] The most likely explanation for increased endothelium-dependent dilation in strength training is the assumption of the mechanical compression of resistance vessel walls during exercise, followed by blood flow release after cessation of exercise, producing a sharp increase in vessel wall shear stress.[36] Although training modalities involve different stimuli (running training: increased continuous blood flow; strength training: intermittent compression of the muscles and restoring blood flow) they ultimately produce the same effects on vessel wall shear stress.

It is important to note that, despite increased blood pressure levels and greater posterior wall thickness and LV mass found in our study among powerlifters, they showed no cardiac and endothelial function impairment when compared to runners and all the parameters were above average. Therefore, high blood pressure found in powerlifters seems to be related to increased PVR rather than endothelial function impairment.

Study strengths and limitations

The key strengths of our study are the use of a homogeneous sample (within each group) and that all echocardiographic images were assessed by two independent examiners, one of them blinded. However, our data should be interpreted with caution due to some limitations including the small sample size (due to recruitment challenges as anabolic steroid use is common among powerlifters and few met our inclusion criteria), and the challenge of recruiting a sample of untrained healthy subjects; however, all parameters evaluated were compared with those findings of other studies and/or current guidelines.

Conclusion

Our study showed that cardiac remodeling seems dependent on training modalities and not on structural difference, as in BSA-indexed LV mass in both powerlifters and long-distance runners. Systolic and diastolic functions were preserved in both modalities. Powerlifters showed higher resting blood pressure, which can be explained by increased PVR. However, FMD measurements were similar in both groups studied and were well above average. Although our findings are comparative in nature and derive from a cross-sectional design, it is possible to speculate that high-intensity strength training for a significant number of years (~5 years or more) may be associated to borderline structural cardiac changes, though they are not accompanied by reduced cardiac function.

Author contributions

Conception and design of the research: Silva DV, Lehnen AM; Acquisition of data, Analysis and interpretation of the data, Statistical analysis and Writing of the manuscript: Silva DV, Waclawovsky G, Kramer AB, Stein C, Eibel B, Grezzana GB, Schaun MI, Lehnen AM; Obtaining financing: Waclawovsky G, Lehnen AM; Critical revision of the manuscript for intellectual content: Waclawovsky G, Eibel B, Grezzana GB, Schaun MI, Lehnen AM.

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 Instituto de Cardiologia do RS / Fundação Universitária de Cardiologia under the protocol number #417492. 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 Nature of Cardiac Remodeling Due to Physical Exercise: More Evidence Towards to the Normal Adaptive Responses of the Heart

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Short Editorial related to the article: Comparison of Cardiac and Vascular Parameters in Powerlifters and Long-Distance Runners: Comparative Cross-Sectional Study

Cardiac remodeling due to exercise training overload (the so-called "athlete's heart") has been widely investigated since the 70's and is still acknowledged by the scientific community. To differentiate normal adaptive responses ("benign") from abnormal ones remains a challenge. Here we address some important issues related to the discussion on cardiac remodeling in exercise, recently revisited by Vidaletti-Silva and colleagues[1] in this issue.

In terms of morphological adaptations, the left atrial and ventricular hypertrophy call attention due to their potential association with the onset of supraventricular tachyarrhythmias[2] and also of ventricular arrhythmias,[3] which may result in undesirable events.[4]

However, mounting evidence has been suggesting that the remodeling response due to exercise training load (e.g., length of exposure, intensity, modality etc.) may not configure a state of disease – i.e., the "physiological but nor pathological" remodeling.[5]"

With a focus on the left chambers, it is known that the blood pressure and the volumetric overload may result in two classical morphological characteristics, accordingly to the Morganroth hypothesis[6] - an increase of the left cavities' volume for those overloaded by the cardiac output (i.e., endurance athletes); or the hypertrophy of the left ventricle (LV) septum for those overloaded by blood pressure levels (i.e., strength-trained athletes). As a minor comment, the Morganroth hypothesis has been recently revisited after the observation of cases of septal hypertrophy in endurance athletes.[7]

Although well-established in scientific literature, Vidaletti-Silva et al.[1] have addressed the question of differences in cardiac remodeling due to sports modalities through a cross-sectional, comparator-group design, comparing endurance athletes (i.e., runners) and strength-trained athletes (i.e., powerlifters) – two classes and levels of modalities that seem appropriate for this comparison. In their findings, no moment-differences between groups were observed for the LV mass, when adjusted for their surface area. As expected, septal and posterior LV thickness were different between endurance and strength athletes, but not the LV end-diastolic volume. The vascular function (i.e., flow-mediated dilation and peripheral vascular resistance) was also evaluated and no differences were found. The take-home message of this study, at least in light of our interpretation, is that athletes in a range of 5 to 7 years of training have adaptations no bigger than the established thresholds for normality for LV dimensions[8] and wall thickness.[9]

We should acknowledge that, even within borderline values, there were no impairment of the systolic and diastolic function of the myocardium in either groups, depicting the normal adaptive nature of the cardiac structure findings. Even though a simple experiment, this cross-sectional study corroborates the hypothesis of different cardiac adaptations due to different training modalities. Finally, to detect some abnormal morphological adaptations in athletes remains a challenge, especially for those within borderline values. We welcome studies such as this one - that sheds a light on this gray area.

Keywords

Ventricular Remodeling; Atrial Remodeling; Cardiac Remodeling; Exercise; Exercise Movement Techniques; Resistance Training; Running; Weight Lifting; Blood Pressure; Arrhythmias.

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The Prognostic Value and Clinical Use of Myocardial Perfusion Scintigraphy in Asymptomatic Patients after Percutaneous Coronary Intervention

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Abstract

Background: **The role of myocardial perfusion scintigraphy (MPS) in the follow-up of asymptomatic patients after percutaneous coronary intervention (PCI) is not established.**

Objectives: **To evaluate the prognostic value and clinical use of MPS in asymptomatic patients after PCI.**

Methods: **Patients who underwent MPS consecutively between 2008 and 2012 after PCI were selected. The MPS were classified as normal and abnormal, the perfusion scores, summed stress score (SSS), and summed difference score (SDS) were calculated and converted into percentage of total perfusion defect and ischemic defect. The follow-up was undertaken through telephone interviews and consultation with the Mortality Information System. Primary endpoints were death, cardiovascular death, and nonfatal acute myocardial infarction (AMI), and secondary endpoint was revascularization. Logistic regression and COX method were used to identify the predictors of events, and the value of $p < 0.05$ was considered statistically significant.**

Results: **A total of 647 patients were followed for 5.2 ± 1.6 years. 47% of MPS were normal, 30% were abnormal with ischemia, and 23% were abnormal without ischemia. There were 61 deaths, 27 being cardiovascular, 19 non-fatal AMI, and 139 revascularizations. The annual death rate was higher in those with abnormal perfusion without ischemia compared to the groups with ischemia and normal perfusion (3.3% × 2% × 1.2%, $p = 0.021$). The annual revascularization rate was 10.3% in the ischemia group, 3.7% in those with normal MPS, and 3% in those with abnormal MPS without ischemia. The independent predictors of mortality and revascularization were, respectively, total perfusion defect greater than 6%, and ischemic defect greater than 3%. Forty-two percent of the patients underwent MPS less than 2 years after PCI, and no significant differences were observed in relation to those who underwent it after that period.**

Conclusion: **Although this information is not contemplated in guidelines, in this study MPS was able to predict events in asymptomatic after PCI patients, regardless of when they were performed. (Arq Bras Cardiol. 2018; 111(6):784-793)**

Keywords: **Myocardial Infarction; Coronary Artery Disease; Myocardial Revascularization; Heart/diagnostic imaging; Percutaneous Coronary Intervention.**

Introduction

The coronary artery disease (CAD) is the leading cause of death in the world.[1] Percutaneous coronary intervention (PCI) is currently the most commonly used method of coronary artery revascularization in all clinical settings of CAD.[2] However, despite the technical and pharmacological changes in the last decades, patients undergoing percutaneous revascularization remain at risk of developing cardiovascular events, and the main mechanisms responsible for that are restenosis and progression of atherosclerotic disease.[3,4]

Functional tests, including myocardial perfusion scintigraphy (MPS), are recommended in the evaluation of patients who develop symptoms after PCI.[2,5] In the presence of significant ischemia, a new revascularization may be proposed. In contrast, in the follow-up of asymptomatic patients, although studies have demonstrated the ability of the MPS to predict future events,[6] the guidelines do not recommend ordering routine functional tests in a period of less than 2 years, with their performance being acceptable only within this interval in specific subgroups, such as those undergoing incomplete revascularization or with prior silent ischemia, in whom a new approach is feasible.[2,5]

The present study aims to evaluate the association between the clinical and scintigraphic data of asymptomatic patients submitted to MPS after PCI and the occurrence of outcomes; to estimate the prevalence of ischemia and its predictors; to evaluate the indications and MPS timing in these patients; and to compare the characteristics of the patients who underwent MPS befor and after two years of PCI.

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Methods

Population

Among the 6,698 MPS that were consecutively performed at the Clínica de diagnóstico por imagem in Rio de Janeiro from March 2008 to November 2012, 1,220 patient exams were identified as previously undergoing PCI. Of these, 322 were excluded because the patients had symptoms at the time of the exam, and 186 because they had already undergone a revascularization surgery. Forty-six patients underwent more than one exam in the period and, in those cases, only the first exam was considered. Thus, 647 patients were enrolled in the study, as shown in figure 1.

The study was approved by the Ethics and Research Committee of the Hospital Clementino Fraga Filho, and each patient signed a consent form to include their information in the database, including clinical characteristics and the data of the examination.

Image protocol

MPS were performed using the 2-day protocol. In the resting phase, a dose of 20mCi ^{99}mTc-sestamibi was injected with acquisition of the images after 30 to 40 minutes, and in the stress phase a dose of 20mCi of ^{99}mTc-sestamibi was injected during the exercise test or pharmacological stress test, and image acquisition was performed after 15 to 30 minutes. The physical and pharmacological stress protocols were performed as described in a previous study.[7] MPS images were acquired through the gated-SPECT technique in the Ventri gamma-camera, GE Healthcare.

The exams were classified as normal, or with reversible, fixed or mixed perfusion defects. The semi-quantitative visual analysis was independently performed by two cardiologists with extensive experience, through the standard 17-segment model, in which the quantification of radiotracer uptake was evaluated in each segment, graduated on a scale of 0 to 4, where 0 = normal uptake; 1 = slight reduction of uptake; 2 = moderate reduction of uptake, 3 = severe reduction of uptake; 4 = no uptake.[8]

The values attributed to each of the 17 segments were added in the stress phase, called summed stress score (SSS), and in the resting phase, called summed rest score (SRS). The difference between these two scores is called summed difference score (SDS), and represents the degree of transient reversibility. Abnormal MPS was defined by SSS > 3, and abnormal MPS with ischemia by SDS > 1. SSS and SDS were converted, respectively, into percent of total perfusion defect and ischemic defect by dividing the score by 68 (maximum value of the score) and then multiplying by 100. The ejection fraction (EF) and the left ventricular diastolic and systolic volumes were measured automatically using the software.

Follow-up

Patients' follow-up was carried out through biannual telephone interviews and application of a standardized

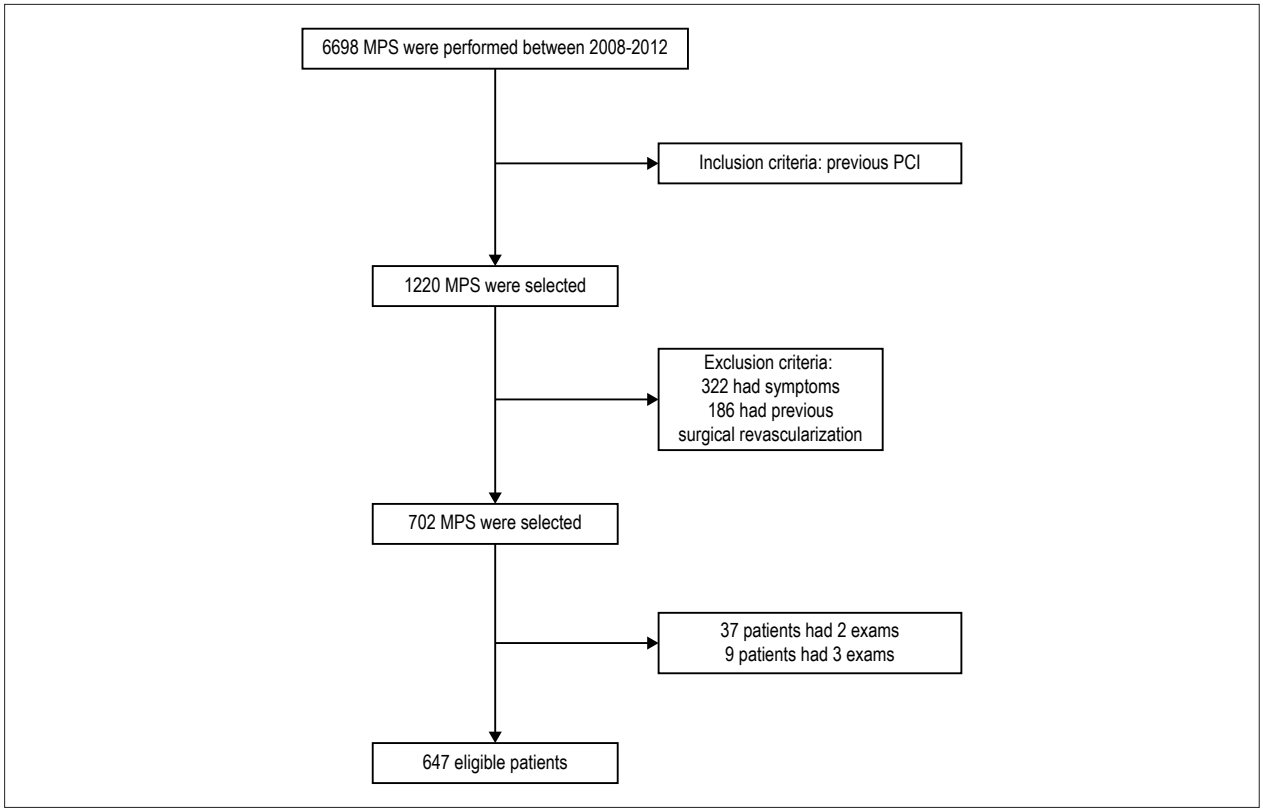

Figure 1 – *Flow chart of patient selection. PCI: percutaneous coronary intervention; MPS: myocardial perfusion scintigraphy.*

questionnaire. Deaths were confirmed consulting the Mortality Information System (SIM) database, and the basic cause of death was identified, and all those included in Chapter IX of the International Classification of Diseases (ICD-10), which comprises the diseases of the circulatory system, were considered cardiovascular. Patients not contacted through telephone calls were considered alive if they were not found in the SIM database, but were considered as loss of follow-up in relation to the other outcomes. Primary endpoints were mortality, cardiovascular mortality, and nonfatal AMI, and surgical or percutaneous revascularization was considered a secondary endpoint.

Statistical analysis

The analysis was performed in the SPSS statistical package version 23.0. Categorical variables are presented as frequencies and percentages and compared using the chi-square test. Numerical variables are presented as mean and standard deviation, or median and interquartile range, according to the normal distribution pattern assessed by the Kolmogorov-Sminorv test, and compared using Student's t-tests or Mann-Whitney test, as appropriate. Variables with statistical significance in the univariate analysis were included in the multivariate model, using logistic regression and the COX model. Variables with significant correlations among them were excluded from the model. Survival curves of different subgroups were evaluated by the Kaplan Meier estimator and compared by the log-rank test. Statistical significance was defined as a value of $p < 0.05$.

Table 1 – Characteristics of the study population.

Characteristics	N (%) or mean ± SD
Age (years), mean ± SD	66.1 ± 10
Male gender	464 (72%)
Arterial hypertension	411 (64%)
Dyslipidemia	378 (58%)
Diabetes Mellitus	189 (29%)
Previous AMI	342 (53%)
Current smoking	48 (7%)
Previous smoking	204 (32%)
Family history of CAD	193 (30%)

SD: standard deviation; CAD: coronary artery disease; AMI: acute myocardial infarction.

Results

A total of 647 patients was included and mean follow-up time was 5.2 ± 1.6 years for mortality analysis. In the analysis of the other outcomes, there was a loss of follow-up of 18 patients and the mean follow-up time was 3.9 ± 1.5 years. The analysis of the demographic characteristics of the population, as shown in Table 1, revealed a mean age of 66.1 ± 10 years and a predominance of males. Arterial hypertension (AH) was the most frequent risk factor, followed by dyslipidemia and diabetes mellitus (DM). Fifty-three percent had a previous history of acute myocardial infarction (AMI). The 18 patients lost at follow-up were compared to 629 contacts and no statistically significant clinical differences were observed between the two groups.

The median dates for prior PCI were March 2008, and 44% were performed in the context of acute coronary syndrome (ACS). The interval between PCI and MPS was a median of 3 years, and was less than 2 years in 42% of the cases.

Among the MPS indications, a control examination after PCI was the most frequent, reaching 75% of the cases. Incomplete revascularization was the second most common justification (12%), followed by preoperative evaluation (7%). The physical stress protocol was used in 59.5% of the exams. MPS were normal in 47% of patients, abnormal with no ischemia in 23%, and abnormal with ischemia in 30%. Previous AMI and incomplete revascularization as an indication of MPS were independently associated with the presence of ischemia, as shown in Table 2.

During follow-up, 61 deaths were recorded, of which 27 were due to cardiovascular causes. Mortality was higher among patients with abnormal MPS without ischemia, followed by the group with abnormal MPS with ischemia, and less found in the group with normal perfusion. The annual rate of death in each group was 3.3%, 2% and 1.2% respectively. Cardiovascular mortality followed the same pattern of incidence in the groups, with annual rates of 1.4%, 0.9% and 0.5%, respectively.

Table 2 – Predictors of ischemia

Characteristics	Univariate analysis OR (95% CI)	p value	Multivariate analysis OR (95% CI)	p value
Age > 70 years	0.36 (0.65 to 1.30)	0,489	0.82 (0.55 to 1.20)	0,309
Male gender	1.13 (0.78 to 1.63)	0,515	1.35 (0.89 to 2.05)	1,155
Diabetes Mellitus	1.22 (0.85 to 1.76)	0,288	1.30 (0.88 to 1.93)	0,179
Previous AMI	2.51 (1.77 to 3.59)	< 0,001	2.87 (1.60 to 5.13)	< 0,001
Previous PCI by ACS	1.90 (1.36 to 2.68)	< 0,001	0.71 (0.41 to 1.24)	0,229
Ejection fraction < 50%	1.52 (1.08 to 2.16)	0,018	1.61 (0.78 to 1.71)	0,454
Pharmacological stress	1.34 (0.95 to 1.89)	0,091	1.22 (0.84 to 1.78)	0,294
MPS indication, incomplete revascularization	3.43 (2,11 to 5.57)	< 0,001	2.99 (1.80 to 4.98)	< 0,001

AMI: acute myocardial infarction; PCI: percutaneous coronary intervention; ACS: acute coronary syndrome; MPS: myocardial perfusion scintigraphy.

There were 19 nonfatal AMI and this outcome was also more prevalent among those with abnormal MPS without ischemia compared to the other participants, but without statistical relevance.

A total of 139 revascularizations was documented, 10 patients underwent coronary artery graft bypass surgery, 126 underwent PCI, and 3 underwent both. Among the groups, revascularization was more frequent among patients with ischemia, with an annual rate of 10.3%, and less expressive among patients with normal and abnormal perfusion without ischemia, with an annual rate of 3.7% and 3%, respectively. Data on the occurrence of outcomes according to the perfusion groups are shown in Table 3.

In the univariate analysis, including clinical and scintigraphic characteristics, age above 70 years, AH, DM, use of pharmacological stress protocol, indication of preoperative MPS, and total perfusion defect higher than 6% were considered predictors. After multivariate adjustment, with the exception of AH, the other variables emerged as independent predictors of death (Table 4). The Kaplan-Meier survival curve stratified by ranges of total perfusion defect in Figure 2 shows the direct relationship between the extent of the defect and mortality, especially when it reaches values greater than 6%.

The independent predictors of revascularization were incomplete revascularization as an indication for MPS, the interval between PCI and MPS of less than 2 years, and the ischemic defect greater than 3%, as shown in Table 5. The Kaplan-Meier curve that was stratified by ischemic defect ranges demonstrates the strong association between the extent of ischemia and the occurrence of the endpoint (Figure 2). The only factor independently associated with cardiovascular mortality was the total perfusion defect greater than 6%, and with non-fatal AMI was the presence of DM.

When analyzing the group of patients with ischemia at MPS (n = 189), there was a greater presence of males (73% × 63%, p = 0.031), a higher frequency of incomplete revascularization as an indication of the MPS (39% × 14%, p = 0.02) and a higher prevalence of the interval prior PCI-CPM less than 2 years (54% × 30%, p = 0.001) among those submitted to revascularization (36%), compared to the group that did not undergo intervention (64%). The extent of ischemic defect was greater among revascularized patients (7% × 6%, p = 0.162), but different from expected, with no statistical significance. Similarly, mortality was lower among revascularized patients (9% × 12%, p = 0.453), however, with no statistical value.

When comparing the populations that underwent MPS in the interval of less than or more than 2 years after PCI, no significant clinical or scintigraphic differences were observed between them. Mortality in the follow-up period was also similar, as shown in Figure 3.

Discussion

The use of MPS in the follow-up of asymptomatic patients after PCI has been studied in the last decades. The first studies evaluated the use of MPS in the first 6 months after the procedure;[9-12] then, some authors tried to establish the use of this functional test later in this subgroup.[13,14] Most of the publications included patients who underwent MPS after fixed intervals following PCI, ranging from 4 months[12] to 60 months.[14] In the current study, this interval varied from days to years, allowing assessment of the prognostic value of MPS when performed at varying intervals after percutaneous revascularization.

Table 3 – Outcomes according to perfusion

Endpoints	Normal	Abnormal with ischemia	Abnormal without ischemia	p value
Patients, n	304	193	150	
Death (61)	19 (6,3%)	21 (10,9%)	21 (14%)	0,021
Cardiovascular death (27)	7 (2,3%)	9 (4,7%)	11 (7,3%)	0,064
Patients, n	295	289	245	
Non-fatal AMI (19)	10 (3,4%)	3 (1,5%)	6 (4,1%)	0,855
Revascularization (139)	52 (17,6%)	68 (36%)	19 (13,1%)	< 0,001

AMI: acute myocardial infarction.

Table 4 – Predictors of mortality

Characteristics	Univariate analysis HR (95% CI)	p value	Multivariate analysis OR (95% CI)	p value
Age > 70 years	4.27 (2.40 to 7.60)	< 0,001	3.40 (1.85 to 6.24)	< 0,001
Arterial Hypertension	2.26 (1.20 to 4.28)	0,010	1.48 (0.73 to 3.00)	0,276
Diabetes Mellitus	3.50 (2,04 to 5.99)	< 0,001	2.37 (1.30 to 4.31)	0,004
Preoperative MPS, indication	3.85 (1.88 to 7.90)	< 0,001	2.25 (1.02 to 4.98)	0,044
Pharmacological stress	4.67 (2.56 to 8.50)	< 0,001	2.51 (1.35 to 4.67)	0,003
TPD > 6%	2.40 (1.40 to 4.08)	0,001	2.33 (1.31 to 4.12)	0,004

MPS: myocardial perfusion scintigraphy; TPD: total perfusion defect.

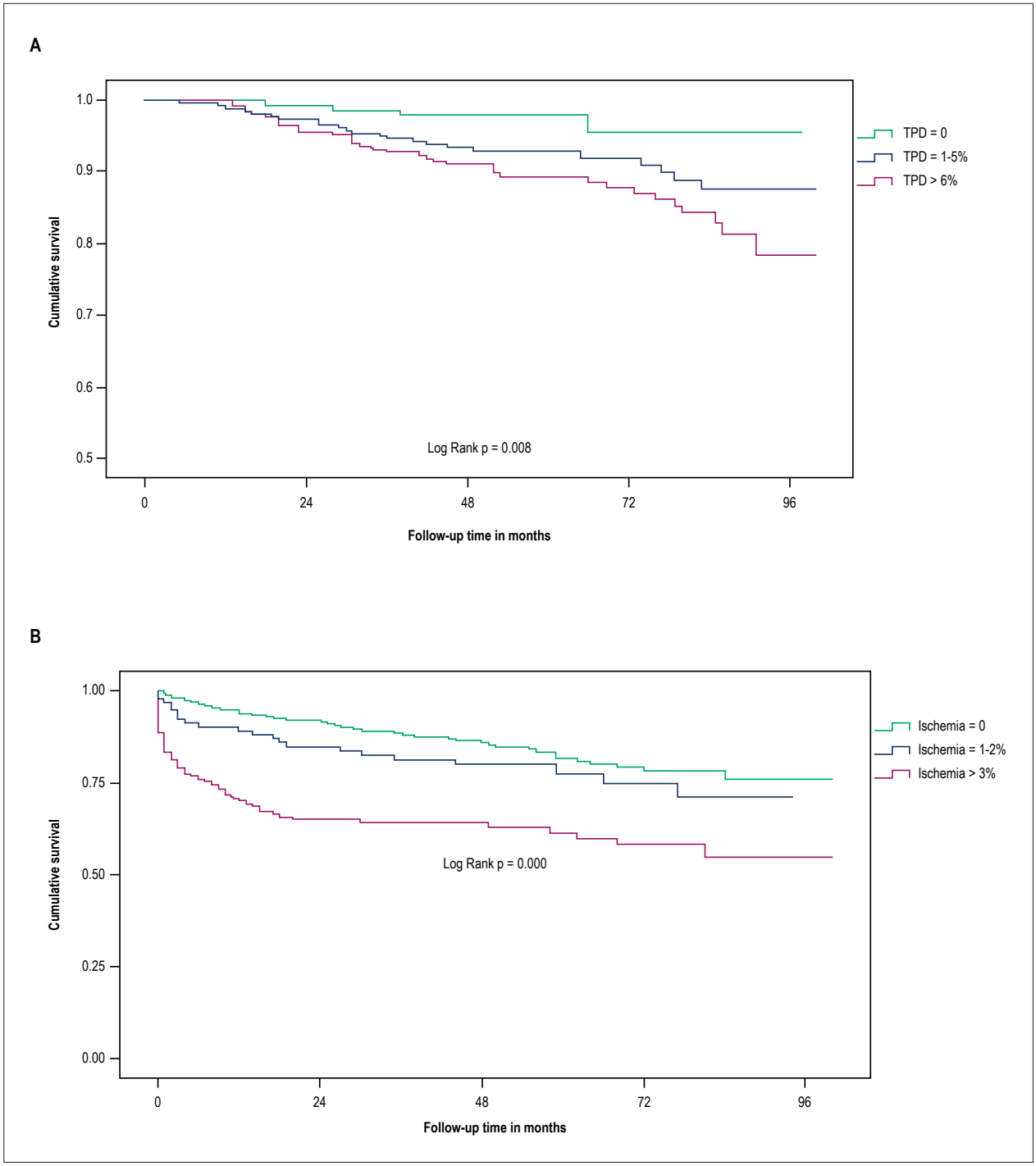

Figure 2 – *A. A kaplan-Meier survival curve of mortality according to ranges of total perfusion defect (TPD). B. Kaplan-Meier survival curve of revascularization according to ranges of ischemia defect.*

In the present study, 647 patients were included and the mean follow-up time was 5.2 years. Previous studies have selected a smaller number of participants, ranging from 196[13] to 370 patients,[11] and had less follow-up time, an average of 3 years. Regarding the population characteristics, the predominance of males and the mean age of 66 years were common to other publications, and consistent with data from the literature.[15] In contrast, the prevalence of comorbidities was quite variable. The current study presented a higher frequency of diabetics. In addition, more than half of the participants had previous AMI, and the prevalence of AH pressure was close to those described above.[11,14]

Table 5 – Predictors of revascularization

Characteristics	Univariate analysis OR (95%)	p value	Multivariate analysis OR (95% CI)	p value
Age > 70 years	0.78 (0.52 to 1.16)	0,223	0.84 (0.55 to 1.28)	0,419
Diabetes Mellitus	1.30 (0.87 to 1.95)	0,198	1.38 (0.89 to 2.15)	0,145
Previous AMI	1.04 (0.71 to 1.52)	0,823	0.69 (0.45 to 1.06)	0,092
MPS indication, control	0.41 (0.27 to 0.61)	0,000	0.86 (0.46 to 1.63)	0,655
MPS indication, incomplete revascularization	4.80 (2.93 to 7.87)	0,000	3.55 (1.65 to 7.60)	< 0,001
PCI-MPS Time < 2y	1.51 (1.35 to 1.75)	0,001	1.55 (1.36 to 1.83)	0,005
Ischemic defect > 3%	3.07 (2.09 to 4.64)	0,000	2.87 (1.83 to 451)	< 0,001

AMI: acute myocardial infarction; MPS: myocardial perfusion scintigraphy.

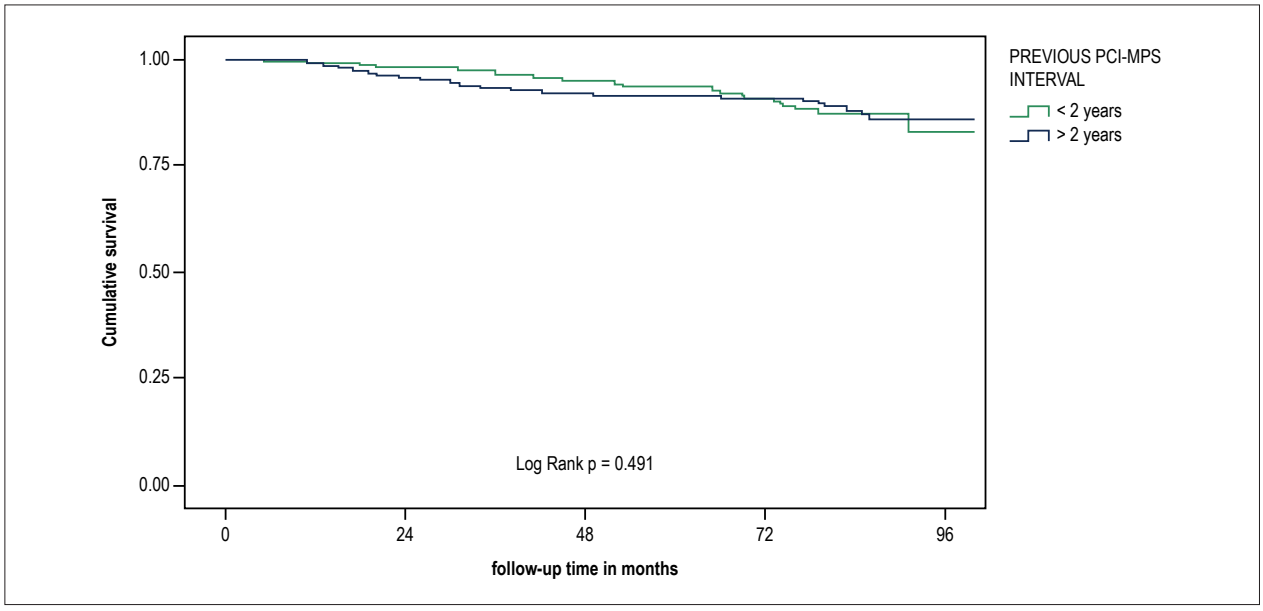

Figure 3 – *Kaplan-Meier survival curve of mortality according to previous PCI-MPS interval shorter or longer than 2 years.*

Such variations can be attributed to the use of different diagnostic definitions of pathologies. On the other hand, they may reflect the selection of populations with different severity profiles, thus with different prognostic aspects.

Despite the lack of information on prior PCI, considering that only 11% of the procedures were performed before 2003, time at which drug-eluting stents were introduced, and that MPS exams were performed in a private clinic in patients with wide access to care, including 30% of diabetics, it is believed that the stents used in previous angioplasties have been almost entirely drug-eluting stents. In previous studies, patients were treated with balloon angioplasty and conventional stent implantation,[9-13] with the exception of the study by Zellweger et al. in which 69% of the participants were treated with a drug-eluting stent.[14] Such findings should be taken into account in the interpretation of outcomes, because after the advent of drug-eluting stents, there was a decrease in the incidence of early and late complications of the procedure and, consequently, in the occurrence of events.

Although the current guidelines[2,5,16] do not indicate routine functional tests, especially in the period of less than 2 years in asymptomatic patients after PCI, in the present study, 42% of MPS were performed within less than 2 years after PCI, and the control examination was the most frequent indication, independent of the period. Similarly, Luca et al.,[17] in an observational study including 12,380 patients undergoing PCI in Canada from 2004 to 2012, and Shah et al.,[18] in a study including 21046 patients undergoing percutaneous revascularization between 2004 and 2007 in the USA, observed that 60% and 61%, respectively, underwent at least one functional test within a 2-year period.[17,18] One possible justification for functional evaluation to remain a frequent clinical practice among asymptomatic patients after PCI is the lack of robust information about the theme that defines the correct management of these patients, and the fact that the current recommendations are based on the opinion of specialists.[2,5,16]

The prevalence of 30% of ischemia among patients was higher than that found in previous studies. Zellweger et al.[14] detected ischemia in 19% of patients after 60 months of PCI, and Rajagopal et al.[11] in 23% of those evaluated after 3.9 months. The exception was the study by Galassi et al.,[12] which included only patients known to undergo incomplete revascularization and, as expected, detected more abnormal perfusions. Similar to previous studies,[9,11] incomplete revascularization as an indication of MPS and the presence of previous AMI were considered independent predictors of ischemia. In contrast, the presence of DM was not independently associated with ischemia, as described by other authors. One possible explanation, given that all patients are asymptomatic, is the valorization of the presence of comorbidity leading to a higher indication of exams. Seventy percent of the diabetics in this study had indication of control MPS.

Previous studies that analyzed the role of MPS in the follow-up after percutaneous revascularization used the composite endpoint model, which impaired the comparison of the results. It should be noted that the evaluation of events separately, as performed in this study, is important because the endpoints analyzed (death, cardiovascular death, non-fatal AMI and revascularization) have different clinical relevance and occurred at different frequencies in all the studies described.[9-14]

The mortality rate observed was 2% per year, comparable to the rate described by Leon et al.,[19] in the 5-year follow-up of patients treated with conventional and drug-eluting stents. However, comparing the different perfusion groups, patients with abnormal MPS without ischemia had a mortality rate of 3.3% per year, higher than that found in patients with abnormal perfusion with ischemia and normal perfusion, respectively, 2% and 1.2%. In addition, the extent of the total perfusion defect was independently associated with death when greater than 6%.

In the evaluation of other variables, age greater than 70 years was considered an independent predictor of mortality, which is expected in the natural evolution of coronary disease. Likewise, the presence of DM was associated with a higher risk of death, similar to data in the literature that showed a more diffuse atherosclerotic involvement among diabetics and a higher propensity to develop restenosis after percutaneous intervention, thus leading to greater mortality in the long term.[20]

Acampa et al.[21] had emphasized that patients undergoing pharmacological stress had a higher age group and a higher prevalence of clinical predictors of ischemia compared to those who underwent physical stress, and, therefore, had a poorer prognosis. Similarly, in the current study, the pharmacological stress protocol was used in 70% of the patients who died and was significantly associated with the endpoint risk. Aspects related to MPS indications also directly influenced the results, with a preoperative examination being associated with a greater chance of death. One possible justification for such finding is the risk inherent to the surgical procedure itself, and the potential severity of the underlying pathology. This variable was not addressed by the other studies already cited.[9-14]

Although they were not included in the multivariate analysis because of a strong correlation with perfusion scores, the presence of prior AMI and lower EF values were more frequently found among those who died, respectively, 69% × 51%, p = 0.009 and 47 ± 16 × 54 ± 12, p = 0.001. Other studies had already demonstrated the impact of ventricular function on survival of patients with coronary artery disease, among which the Coronary Artery Surgery Study (CASS) is highlighted, which observed an inverse relationship between EF and mortality. In this register, survival rates after 12 years of follow-up of coronary arteries disease with EF ≥ 50%, between 35 and 49% and < 35% were, respectively, 73%, 54% and 21% (p = 0,001).[22]

Similar to what was found in the mortality analysis, the outcomes of cardiovascular mortality and non-fatal AMI had a higher incidence in the group with abnormal perfusion without ischemia compared to the others. The absence of statistical significance may be justified by the small number of events, but certainly does not compromise the importance of the findings, especially cardiovascular mortality with p= 0.064, close to what is considered relevant. The only factor independently associated with cardiovascular mortality was the total perfusion defect greater than 6%, and to non-fatal AMI was the presence of DM. Georgoulias et al.,[10] after an 8-year follow-up of 246 asymptomatic patients undergoing CPM after PCI, also observed that the occurrence of the composite endpoint, cardiovascular death, and non-fatal AMI was greater the greater the extent of the total perfusion defect.

The annual rate of endpoint revascularization was 4.6%, more significant during the 1st year of follow-up compared to that found in subsequent years, 11.9% × 3.4%, respectively. Leon et al.[19] observed similar results, 20.4% of patients treated with conventional stents, and 11.2% of those treated with drug-eluting stents underwent a new approach in the 1st year of follow-up; then, the annual rate of revascularization was a constant of 3.5% between the 2nd and 5th years. In view of these findings, it should be pointed out that, as suggested by Leon et al.,[19] the events taking place in the first year seem to be related to the initial procedure, with markedly reduced rates of conventional therapy to pharmacological therapy, whereas later revascularizations reflect the progression of disease, with constant rate, regardless of the type of stent used.

Zellweger et al.,[9] in the follow-up of patients undergoing percutaneous intervention, demonstrated that the cumulative rate of composite outcome was statistically higher among patients with ischemia than those without ischemia at MPS, and revascularization corresponded to 65% of these events. Similarly, Galassi et al.,[12] in a cohort consisting of asymptomatic patients submitted to incomplete percutaneous revascularization, reported that 42% of the participants performed a new approach at the mean follow-up of 33 months, and that the extent of ischemia in the MPS performed 4 to 6 months after the procedure was a predictor of this outcome.

In the current study, in addition to the presence and extent of ischemia, incomplete revascularization as an indication of MPS and the interval between percutaneous intervention and MPS before 2 years were also significantly associated with revascularization. These results suggest that

the decision for the new approach was probably influenced by the initial procedure. This hypothesis was reinforced when it was observed that in the group of patients with ischemia, among the 36% who underwent the new revascularization, there was a predominance of males and, again, incomplete revascularization as an indication of MPS, and of the interval between PCI and MPS of less than 2 years.

The extent of ischemia was also higher among those referred to repeated revascularization, but, unlike expected, this finding was not statistically significant. It is possible that in some cases the presence and not the extent of ischemia has been a variable with greater impact in the decision making for revascularization. Regarding male gender, it shows a higher prevalence of coronary disease and greater precocity in the event occurrence; this may have contributed to the valorization of the findings and the indication of approach in the patients of this gender.

Aldweib et al.,[23] in the evaluation of 769 asymptomatic patients previously undergoing PCI with ischemia in MPS, subsequently referred for drug therapy or revascularization, found greater extent of ischemia and greater presence of DM among the revascularized patients. Different from the current study, the interval between PCI and MPS was similar between the groups and the presence of incomplete revascularization was not mentioned. After an average of 5.7 years, mortality rates were similar in the two treatment groups ($p = 0.84$).

In our study, the mortality among those who revascularized was lower than those who received clinical treatment (9% × 12%), but with no statistical significance. Although this study was not designed for this purpose, and the possible impairment of the statistical analysis due to the small number of events, it is worth questioning whether the patients referred to the new revascularization would not be at greater risk and after the procedure had this risk matched to the ones targeted for clinical treatment.

Although the current literature recommends the functional evaluation of asymptomatic patients after PCI only after 2 years,[2,5,16] in the present study, the clinical features and results of MPS, including perfusion findings, were similar among patients who underwent MPS in the smallest interval and in the one greater than 2 years. In this selected population, the delimitation currently recommended in 2 years did not separate distinct populations.

Although incomplete revascularization is a satisfactory solution when the culprit lesion is identified and has a favorable anatomy for percutaneous approach, especially in the context of ACS, patients with remaining lesions need to be monitored and stratified, regardless of the presence of symptoms. In the present study, in this scenario MPS was shown to be a tool used in clinical practice capable of providing incremental prognostic information about the occurrence of events, directly interfering with the decision to indicate new revascularization.

Previous studies[13,21] that performed MPS in the follow-up of patients previously undergoing percutaneous revascularization described an excellent prognosis associated with normal perfusion, with an annual event rate of less than 1%. Similarly, in the current study, at the mean follow-up of 5 years, among patients with normal perfusion, the annual mortality rate was 1%, and cardiovascular mortality was 0.5%, characterizing this group as low risk.

Limitations

This is a single center retrospective study in which the patients were referred to the clinic for MPS at the recommendation of their attending physician. Therefore, extrapolation of the results should be done with caution.

Another limitation is the lack of information on the type of stent used in the prior revascularization procedure in most patients. However, considering that only 11% of the procedures were performed before 2003, at which time drug-eluting stents were introduced, and that the population was selected in a private clinic that mainly serves complementary health users with a DM prevalence of 30 %, it is believed that the stents used have been mostly drug-eluting ones.

Conclusion

In this study, MPS performed in asymptomatic patients after various periods of PCI was able to provide future prognostic information, the extent of the total perfusion defect was associated with a higher mortality rate and cardiovascular death, the presence and extent of ischemia were associated with higher rate of revascularization, while normal perfusion lead to an excellent prognosis with a low rate of events at the mean follow-up of 5 years.

In spite of the recommendations of the guidelines, in this study, 42% of MPS were performed within less than 2 years after PCI and no relevant clinical differences were observed in relation to those who performed after this period.

Author contributions

Conception and design of the research and Acquisition of data: Andrade LF, Sousa AC, Peclat T, Bartholo C, Pavanelo T; Analysis and interpretation of the data and Statistical analysis: Andrade LF, Lima RSL; Writing of the manuscript: Andrade LF; Critical revision of the manuscript for intellectual content: Lima RSL.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital Universitário Clementino Fraga Filho under the protocol number 1643951. 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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Myocardial Perfusion Scintigraphy after Percutaneous Coronary Intervention in Asymptomatic Patients: Useful or Futile?

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Short Editorial regarding the article: The Prognostic Value and Clinical Use of Myocardial Perfusion Scintigraphy in Asymptomatic Patients after Percutaneous Coronary Intervention

Myocardial perfusion scintigraphy (MPS) is a well-established non-invasive method for the evaluation of patients with suspected ischemic heart disease or with coronary artery disease (CAD).[1] Its major diagnostic indication is in the assessment of patients with intermediate likelihood of CAD,[2] with the diagnostic value being difficult to be dissociated from the prognostic information obtained with the method. Through several criteria validated in the literature, such as the extent of ischemia, the patient's risk of presenting cardiovascular events in the future[3] can be assessed. In patients with established CAD, MPS has an important role in the evaluation of symptoms suggestive of myocardial ischemia, and can also assess the risk of non-fatal myocardial infarction and cardiac death. Although the value of quantification of ischemia has been the subject of debate in recent years, it is undeniable that in clinical practice it can assist in therapeutic decision-making.[4,5]

MPS may be useful in the evaluation of patients undergoing surgical or percutaneous revascularization procedures, especially if the patient has symptoms. Although MPS can be indicated in asymptomatic patients after 2 years of percutaneous coronary intervention (PCI) or 5 years of surgical procedure,[6] few studies in the literature have analyzed the adequate time to perform the functional study in asymptomatic patients, and the clinical impact of this information. Cardiologic practice often contradicts what is recommended, and it is not uncommon to evaluate asymptomatic patients in a shorter period than that suggested in the literature.

In this edition of the Arquivos Brasileiros de Cardiologia, de Andrade et al.[7] evaluated the prognostic value and clinical use of MPS in asymptomatic patients after PCI.[7] The authors conducted a retrospective study evaluating 647 patients that were submitted to MPS after PCI. Fifty three percent of the patients presented abnormal MPS (30% abnormal with ischemia and 23% abnormal without ischemia). The annual rate of death was higher in those with abnormal perfusion without ischemia compared to the groups with ischemia and with normal MPS (3.3% x 2% x 1.2%, p = 0,021). The annual revascularization rate was 10.3% in the group with ischemia, 3.7% in those with normal MPS, and 3% in the group with abnormal MPS without ischemia. The independent predictors of mortality and revascularization were, respectively, a total perfusion defect greater than 6%, and an ischemic defect greater than 3%. Forty-two percent of the patients underwent MPS less than 2 years after PCI, and no significant differences were observed in relation to those who underwent it after this period.

The presence of silent ischemia in patients undergoing PCI is not uncommon, and is usually related to persistent or progressive CAD in remote vessels, rather than in the treated vessels.[8,9] The study by de Andrade et al.[7] demonstrated that 30% of the patients had silent ischemia, and that the 2-year period did not influence the power of MPS to predict events. However, there are no data in the literature demonstrating consistently that the diagnosis of ischemia after PCI modifies clinical outcomes.ISCHEMIA trial was designed to determine the value of the quantification of ischemia through non-invasive methods, and whether an invasive management strategy improves clinical outcomes when added to optimal medical therapy in patients with CAD and moderate or severe ischemia, but the results are not yet known.[10] In the light of current knowledge, the presence of ischemia detected by MPS is an excellent cardiovascular risk marker, and can be a gatekeeper for invasive management strategy. In patients undergoing PCI, particularly if CAD was not fully revascularized, or if the patient did not present angina as a manifestation of CAD, MPS before the time suggested in the literature may be useful and not futile. It is up to the attending physician to consider whether the time suggested in the literature should be waited to reassess the asymptomatic patient after PCI, since the data to support this practice is not robust.

Keywords

Coronary Artery Disease/radionuclide imaging; Myocardial Revascularization; Percutaneous Coronary Intervention; Myocardial Ischemia.

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Original Article

Association Between Increased Levels of Cystatin C and the Development of Cardiovascular Events or Mortality: A Systematic Review and Meta-Analysis

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Abstract

Background: **Cystatin C seems promising for evaluating the risk of cardiovascular events and mortality.**

Objective: **To evaluate the association between high levels of cystatin C and the development of cardiovascular events or mortality.**

Methods: **The articles were selected in the Medline/PubMed, Web of Science, and Scielo databases. The eligibility criteria were prospective cohort observational trials that assessed the association of high serum levels of cystatin C with the development of cardiovascular events or mortality in individuals with normal renal function. Only studies that evaluated the mortality outcome compared the fourth with the first quartile of cystatin C and performed multivariate Cox's proportional hazard regression analysis were included in the meta-analysis. A p value < 0,05 was considered significant.**

Results: **Among the 647 articles found, 12 were included in the systematic review and two in the meta-analysis. The risk of development of adverse outcomes was assessed by eight studies using the hazard ratio. Among them, six studies found an increased risk of cardiovascular events or mortality. The multivariate regression analysis was performed by six studies, and the risk of developing adverse outcomes remained significant after the analysis in four of these studies. The result of the meta-analysis [HR = 2.28 (1.70-3.05), p < 0.001] indicated that there is a significant association between high levels of cystatin C and the risk of mortality in individuals with normal renal function.**

Conclusion: **There is a significant association between high levels of cystatin C and the development of cardiovascular events or mortality in individuals with normal renal function. (Arq Bras Cardiol. 2018; 111(6):796-807)**

Keywords: **Cardiovascular Diseases/mortality; Cystatin C; Coronary Artery Disease; Myocardial Infarction; Renal Insufficiency, Chronic; Meta-Analysis as Topic.**

Introduction

Cardiovascular diseases are the leading cause of death in the world, accounting for 31% of all deaths. In 2015, an estimated 17.7 million people died from cardiovascular diseases, mainly coronary heart disease, cerebrovascular disease, and peripheral arterial disease.[1] In addition to high mortality, cardiovascular diseases are also associated with high morbidity, contributing to a significant share of public expenditure on health.[2]

Chronic kidney disease is an important risk factor for the development of cardiovascular events, and is also responsible for increased morbidity and mortality in patients with cardiovascular disease[3]. Cystatin C consists of a marker of renal dysfunction that has been shown to be more sensitive than serum creatinine to assess the early stages of renal failure[4]. It consists of a relatively stable cysteine protease inhibitor, produced in all nucleated cells at a constant rate.[5]

Because of the greater sensitivity of cystatin C for detecting the early and milder stages of renal dysfunction, the evaluation of serum levels has been shown to be promising for assessing the risk of cardiovascular events and mortality in individuals with apparently normal renal function. In recent years, some studies have demonstrated an association between serum cystatin C levels and the development of AMI.[6] In addition, cystatin C has been shown to be useful for prognostic stratification in patients with ACS.[7]

However, there is a divergence between the results of studies performed to date on the clinical utility of cystatin C to assess the risk of cardiovascular events and mortality in individuals with normal renal function.[3,7,8] Although some meta-analyses.[9-12] have been published on the subject, the population of the studies selected did not consist only of patients with normal renal function. Therefore, the objective of this systematic review and meta-analysis was to evaluate the association between high levels of cystatin C and the development of cardiovascular events or mortality in subjects with normal renal function.

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Methods

This systematic review followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[13]

Articles Selection

The articles selection was performed through the data bases *Medline (PubMed)* and *Web of Science*, using the descriptors "cystatin C", "post-gamma-globulin", "post-gamma globulin", "neuroendocrine basic polypeptide", "basic polypeptide, neuroendocrine", "cystatin 3", "gamma-trace", "gamma trace", combined with the descriptors "acute coronary syndrome", "acute coronary syndromes", "coronary syndrome, acute", "coronary syndromes, acute", "syndrome, acute coronary", "syndromes, acute coronary", "myocardial infarction", "infarction, myocardial", "infarctions, myocardial", "myocardial infarctions", "cardiovascular stroke", "cardiovascular strokes", "stroke, cardiovascular", "strokes, cardiovascular", "heart attack", "heart attacks", "myocardial infarct", "infarct, myocardial", "infarcts, myocardial", "myocardial infarcts", "myocardial ischemia", "ischemia, myocardial", "ischemias, myocardial", "myocardial ischemias", "ischemic heart disease", "heart disease, ischemic", "disease, ischemic heart", "diseases, ischemic heart", "heart diseases, ischemic", "ischemic heart diseases", using the connector "AND" between the terms. The Medical Subject Headings (MeSH) was used to define these descriptors.

The selection of the articles was also performed in *Scielo* database, using the descriptors "cystatin C" with the Boolean operators "acute coronary syndrome", "coronary disease", "coronary heart disease", "myocardial infarction", "heart attack", "cardiac attack", "myocardial ischemia", "heart disease, ischemic", "ischemia, myocardial" and "ischemic heart disease" using AND connector between the terms. The Descriptors in Health Sciences (DeCS) was used to define these descriptors.

Eligibility criteria

The eligibility criteria were established according to the PRISMA recommendation,[13] and consist of prospective cohort observational studies written in English, Portuguese or Spanish evaluating the association between high levels of cystatin C, and the development of cardiovascular events or mortality in individuals with normal renal function. There was no restriction of the period of publication of articles in the research. PECOS strategy was used to elaborate the research question:

1. Population of interest: Individuals with normal renal function.
2. Exposure: High levels of cystatin C.
3. Outcome: Cardiovascular events or mortality.
4. Study Design: Prospective cohort.

Extracting data from selected articles

The following data were obtained from the studies that met the eligibility criteria: method used for measuring serum levels of cystatin C, patient group size, patient follow-up time, patient age range, criterion used to define normal renal function, outcome obtained in the study, outcome assessed, study population, patient classification, and parameters included in Cox proportional hazards multivariate regression analysis.

Quality of the selected articles

The methodological quality evaluation process of the studies included in the review was carried out by two reviewers using the Newcastle-Ottawa Scale (NOS)[14] questionnaire for cohort studies, which contains the following categories of evaluation: cohort selection; comparability of the cohort and outcome. The quality of the study is indicated with a maximum of nine stars, with only one star being allowed to be assigned in the selection and outcome categories, and two stars in the comparability category. The articles reaching a score of five to six stars were considered as articles of good methodological quality, and those with seven or more stars were considered articles of excellent methodological quality.

Meta-Analysis

The meta-analysis included only those studies that assessed the outcome all-cause mortality comparing the fourth quartile of cystatin C with the first quartile and that conducted multivariate regression analysis of Cox proportional hazards. The *hazard ratio* value and the 95% confidence interval adjusted by the multivariate regression analysis were used in the meta-analysis and the I^2 test was used to assess the heterogeneity among the studies. The studies were considered heterogeneous when $I^2 > 50\%$ and $p < 0.10$. When there was homogeneity, the *hazard ratio* was calculated using the fixed effect model. The distribution of the studies included in the meta-analysis was analyzed by a funnel plot. The statistical software *Review Manager* version 5.3 was used to perform the statistical analysis. The p value < 0.05 was considered significant.

Results

Literature search

The initial search through the descriptors in the electronic databases resulted in a total of 647 articles. After completing the selection steps, 12 articles were included in the systematic review, and two were included in the meta-analysis. The flow chart for the selection of articles according to the eligibility criteria is presented in Figure 1.

Characteristics and results of selected articles

The studies that met the eligibility criteria were published between 2007 and 2016 and their characteristics are found in Table 1.

Population

The population of the studies analyzed consisted of patients at risk for cardiovascular events,[15] with ST-elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI),[7,16] and stable coronary artery disease (CAD),[17,18] ACS,[17] patients undergoing percutaneous coronary intervention,[19] with congestive heart failure (CHF),[20,21] with

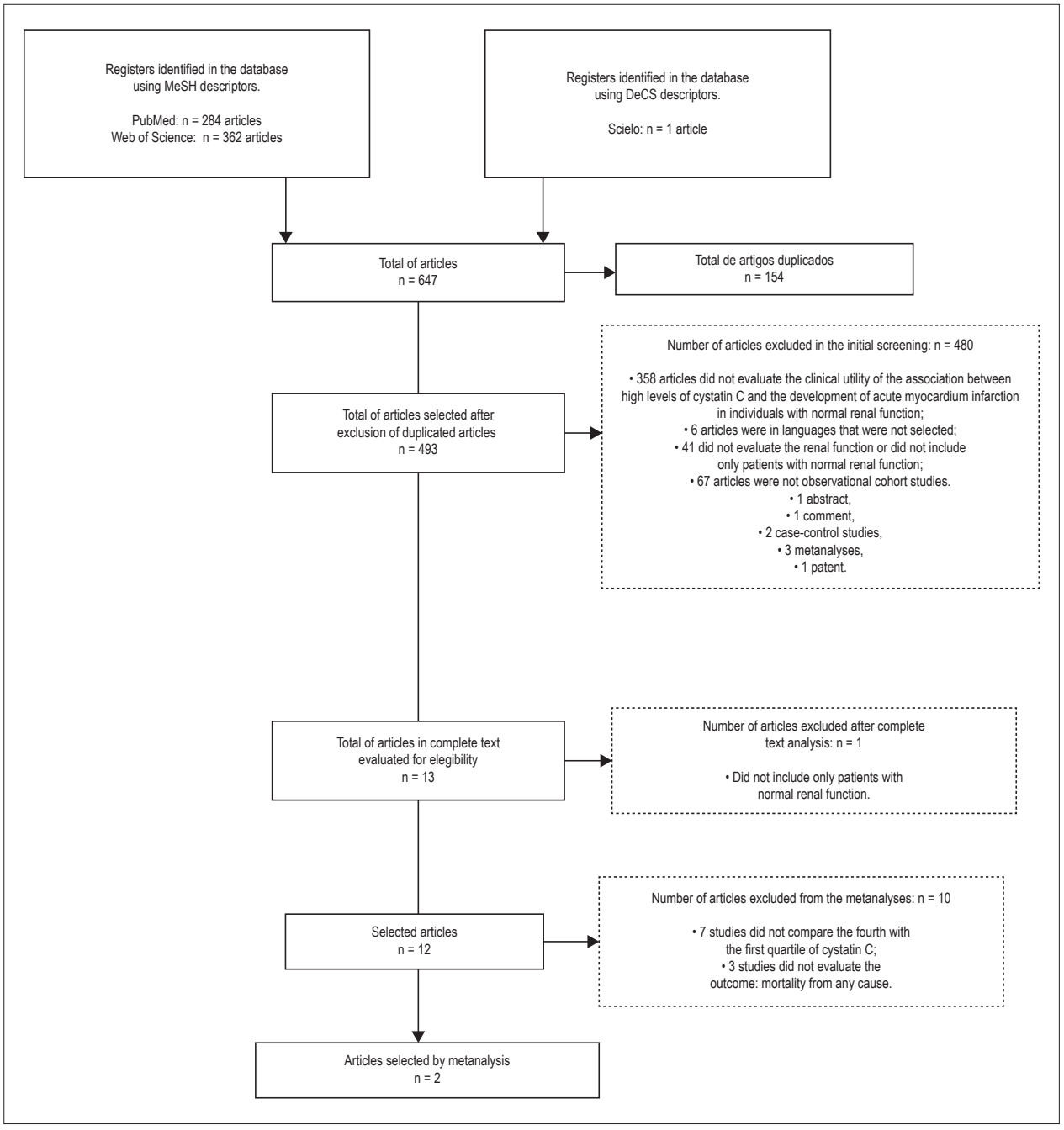

Figure 1 – *Flow chart of the articles selected for review, according to the elegibility criteria used in the study.*

CHF who underwent coronary angiography,[9] with stable angina and AMI,[22] with a history of AMI that had angiographic evidence of stenosis greater than 50%,[23] or healthy elderly individuals (older than 65 years).[24]

Sample size, age group and follow-up time

The sample size varied from 127 to 4,663 individuals, and the sample number of 25% (n = 3)[8,20,23] of the studies ranged from 400 to 1000 individuals, 41.67% (n = 5)[7,16,19,21,22] of the studies had a sample number of less than 300 patients, and 33.33% (n = 4)[15,17,18,24] had a sample size greater than 1000. The mean age ranged from 37 to 87 years, with 41.66% (n =5)[7,8,16,18,21] of the studies evaluating both adult and elderly population (over 60 years), 50% (n = 6)[17,19,20,22-24] evaluating only the elderly population, and one study [8,33% (n = 1)][15] analyzing only the adult population (below 60 years). The study follow-up time ranged from 6 months to 10 years, with 25% (n = 3)[7,16,22] accompanying patients for less than 15 months, 41.67% (n = 5)[8,17,19,21,23] following for 3 to 6 years, and 33.33% (n = 4)[15,18,20,24] following for a period of more than 9 years.

Table 1 – Characteristics of selected studies

Author/Year	Number of patients/ Age group	Study population	Patient follow-up time	Evaluated outcome
Sai et al., 2016[19]	277/64	Patients undergoing PCI	5 years and 3 months	Cardiovascular death, cerebrovascular death, ACS including non-fatal AMI and unstable angina, non-fatal stroke and hospitalization due to worsening CHF
Bansal et al., 2016[15]	2410/40,2 ± 3,6	Patients at risk for cardiovascular events who underwent echocardiography	10 years	Left ventricular hypertrophy
Abid et al., 2016[7]	127/58 ± 11,65	Patients with STEMI and NSTEMI	1 year	Cardiovascular death, myocardial reinfarction, NSTEMI, HF
Woitas et al., 2013[18]	2356/64 ± 10	Patients with CAD and healthy individuals	10 years	Cardiovascular death and death from any cause
Dupont et al., 2012[8]	615/65 ± 11	Patients with CHF who underwent coronary angiography	3 years	Death from any cause, non-fatal AMI and non-fatal stroke
Gao et al., 2011[21]	13 8/65,4 ± 11,0	Patients with chronic or new onset systolic CHF	3 years	Cardiovascular death, development or progression of HF requiring hospitalization, intravenous treatment of HF within the first 3 days after admission, cardiac transplantation
Keller et al., 2009[17]	1827/62	Patients with stable CAD or ACS	4 years	Cardiovascular death
Gao et al., 2009[22]	160/60	Patients with stable, unstable angina and AMI and healthy individuals	6 months	AMI, cardiovascular death, refractory angina, PCI and angiography
Alehagen et al., 2009[20]	464/65 to 87	Patients with CHF	10 years	Cardiovascular death
Acuna et al., 2009[16]	203/66,6 ± 13,16	Patients with STEMI and NSTEMI	1 years and 3 months	Cardiovascular death and HF
Koenig et al., 2007[24]	466 3/≥ 65	Elderly subjects (≥ 65 years)	9,3 years	Death from any cause, cardiovascular death, incident HF, stroke and AMI
Ix et al., 2007[23]	990/67	Patients with a history of AMI, angiographic evidence of stenosis greater than 50% in 1 or more coronary vessels, evidence of treadmill-induced ischemia or nuclear testing, or history of coronary artery bypass grafting	3 years and 1 month	Cardiovascular death, non-fatal AMI, stroke, death from all causes and HF

AMI: Acute Myocardial Infarction; HF: Heart failure; CHF: congestive heart failure; NSTEMI: Non-ST-segment elevation myocardial infarction; PCI: Percutaneous coronary intervention; ACS: acute coronary syndrome; STEMI: ST-segment elevation myocardial infarction; CAD: Coronary artery disease.

Outcome

The main outcomes evaluated by the studies were cardiovascular death (n = 10; 83.33%),[7,16-24] heart failure (n = 6; 50%),[7,16,19,21,23,24] and acute myocardial infarction (n = 6; 50%),[7,8,19,22-24] followed by stroke (n = 4; 33,33%),[8,19,23,24] death from any cause (n = 3; 35%,)[8,23,24] and unstable angina (n = 2; 16,67%).[19,22] Only one study (8.33%) evaluated each of the following outcomes: cerebrovascular death,[19] left ventricular hypertrophy,[15] myocardial reinfarction,[7] need for percutaneous coronary intervention,[22] and angiography.[22]

Method for dosing cystatin C and criteria for the definition of normal renal function

The cystatin C dosing method and the criteria used to define normal renal function in the selected studies are shown in Table 2. The methods used for cystatin C dosing were immunonephelometry [41.67% (n = 5)],[15-18,23] immunoturbimetry [33.33% (n = 4)],[7,8,19,20] and immunoenzymatic assay [8.33% (n = 1)].[22] Two studies (16.66%)[21,24] did not report the method used for cystatin C dosing. The criteria used to define normal renal function were the GFR, estimated by the MDRD equation, above 60 mL/min/1.73 m^2 [66.67% (n = 8)],[7,8,16-19,23,24] the GFR, estimated by the CKD-EPI equation based on cystatin C, above 60 mL/min/1.73 m^2, and normal albuminuria [8,33% (n = 1)][15] and serum creatinine levels below 115 μmol/L [8,33% (n = 1)].[20] Two studies (16.67%)[21,22] did not mention the method of evaluation of renal function.

Classification of patients and variables included in the multivariate regression analysis

The way patients were classified in each of the selected studies, and the variables included in the multivariate Cox proportional hazards regression analysis are presented in Table 3, while the results of the studies are presented in Table 4. Among the studies included in this systematic review, five (41.66%)[8,17,18,20,23] classified patients according to cystatin C quartiles; three (25%)[8,21] classified patients according to whether or not there were fatal or non-fatal cardiovascular events; two (16.66%)[19,21] divided the patients according to the median of cystatin C; one study (8.33%)[17] classified patients according to whether or not they developed cardiovascular death; another study (8.33%)[18] compared patients with coronary disease in relation to the healthy control group;

Table 2 – Method of dosing cystatin C and criteria for the definition of normal renal function in the selected studies

Author/Year	Method of dosing cystatin C	Criteria used to define normal renal function
Sai et al., 2016[19]	Immunoturbimetry	GFR calculated using the MDRD equation > 60 mL/min/1.73m^2
Bansal et al., 2016[15]	Immunonephelometry	GFR based on cystatin C using the equation CKD-EPI > 60 mL/min/1.73 m^2 and normal albuminuria
Abid et al., 2016[7]	Immunoturbimetry	GFR calculated using the MDRD equation > 60 mL/min/1.73 m^2
Woitas et al., 2013[18]	Immunonephelometry	GFR calculated using the MDRD equation > 60 mL/min/1.73 m^2
Dupont et al., 2012[8]	Immunoturbimetry	GFR calculated using the MDRD equation > 60 mL/min/1.73 m^2
Gao et al., 2011[21]	NI	NI
Keller et al., 2009[17]	Immunonephelometry	GFR calculated using the MDRD equation > 60 mL/min/1.73 m^2
Gao et al., 2009[22]	Enzyme immunoassay	NI
Alehagen et al., 2009[20]	Immunoturbimetry	Creatinine < 115 µmol/L
Acuna et al., 2009[16]	Immunonephelometry	GFR calculated using the MDRD equation > 60 mL/min/1.73 m^2
Koenig et al., 2007[24]	NI	GFR calculated using the MDRD equation > 60 mL/min/1.73 m^2
Ix et al., 2007[23]	Immunonephelometry	GFR calculated using the MDRD equation > 60 mL/min/1.73 m^2

MDRD: Modification of diet in renal disease; NI: Not informed; GFR: Glomerular filtration rate.

a study (8.33%)[22] classified the patients into four groups: stable angina, unstable angina, AMI and healthy control group; another study (8.33%)[15] classified patients according to the GFR estimated by the CKD-EPI equation based on cystatin C: between 60 and 75 mL/min/1.73 m^2; between 76 and 90 mL/min/1.73 m^2; and above 90 mL/min/1.73 m^2; two other studies (16.66%)[7,16] further divided patients into two groups according to cystatin C levels above or below 0.95 mg/L and above and below 1.2 mg/L; and one study[24] divided them according to high or low levels of cystatin C without mentioning the cutoff point.

Studies results

Among the included studies, two (16.66%)[16,19] analyzed the difference between the proportion of patients with high levels of cystatin C who developed fatal or non-fatal cardiovascular events,[19] cardiovascular death,[16] and CHF[16] compared with the proportion of patients with reduced levels of Cystatin C that developed these events, and all of them found a significant difference. A study (8.33%)[24] further observed that patients with high levels of cystatin C had more adverse cardiovascular events than those with reduced levels of cystatin C. The difference between cystatin C levels in patients who developed fatal or non-fatal cardiovascular events, and those who did not develop these events was evaluated by four studies (33.33%),[7,17,19,21] and all found significantly higher levels of cystatin C in the group of patients who developed the events. A study (8.33%)[18] also found that cystatin C levels in patients with CAD were higher than in the control group and another study (8.33%)[22] observed that cystatin C levels in patients with AMI were higher than in patients with unstable angina, stable angina, and control group, and that cystatin C levels in patients with unstable angina were higher than in those with stable angina and control group. Another study (8.33%)[7] found a higher survival rate in patients with lower levels of cystatin C.

The risk of developing adverse outcomes was assessed by eight studies (66.66%)[15,17-21,23,24] calculating the hazard ratio. Among these, two studies (22,22%)[19,21] found an increased risk of fatal or non-fatal cardiovascular events in patients with higher levels of cystatin C; one study (11.11%)[18] observed a higher risk of death from any cause and non-fatal cardiovascular events; another study found an increased risk of cardiovascular death and death from any cause; two studies (22.22%)[17,20] found an increased risk of cardiovascular death; one study (11.11%)[23] found an increased risk of death from any cause, cardiovascular events and CHF; and one study (11.11%)[15] still observed a higher risk of left ventricular hypertrophy. Finally, one study[24] found that each increase of 0.18 mg/L of cystatin C was associated with an increased risk of cardiovascular death, death from any cause, HF, stroke and AMI. The multivariate regression analysis was performed by six (50%)[15,17-19,21,23] of these studies, with the risk of developing evaluated adverse outcomes remaining significant after the performance of this analysis in four of these studies.[18,19,21,23]

Methodological quality

The results of the evaluation of the methodological quality of the studies included in this review are shown in Table 5, and the detailed description of the criteria used for the distribution of the stars is presented in the legend. After the quality analysis, a study (8.33%)[22] was found to have good methodological quality and 11 studies (91.66%) had excellent methodological quality.

Meta-analysis

Only two studies evaluated the outcome of all-cause mortality, compared the fourth quartile of cystatin C with the first quartile, and performed a multivariate regression analysis of Cox proportional hazards and were therefore included in the meta-analysis, the result of which is shown in Figure 2. Homogeneity was observed among the studies (I^2 = 53,423 and p = 0,14); therefore, the fixed-effect model was used to calculate the hazard ratio. The result of the meta-analysis [HR = 2.28 (1.70 - 3.05), p < 0.001] indicates that there is a significant association between high levels of cystatin C and the risk of all-cause mortality in individuals with normal renal function. A symmetric distribution of the articles included in the meta-analysis was observed in the *funnel plot*, indicating that there is no publication bias.

Table 3 – Classification of patients and variables included in multivariate regression analysis of Cox proportional hazards in selected studies

Author/Year	Classification of patients	Variables included in the multivariate regression analysis
Sai et al., 2016[19]	Patients with cystatin C levels above (n = 138) and below (n = 139) median. (Median = 0.637)	BMI, hypertension, HbA1c, HDL, BNP, cystatin C.
Bansal et al., 2016[15]	GFR between 60 and 75 mL/min/1.73 m^2 (n = 29). GFR between 76 and 90 mL/min/1.73m^2 (n = 153). GFR > 90 mL/min/1.73 m^2 (n = 2228).	Age, gender, race, smoking, DM, LDL, HDL, albuminuria, BMI, systolic blood pressure.
Abid et al., 2016[7]	Patients who developed fatal (n = 6) or non-fatal (n = 26) cardiovascular events and patients who did not develop these events. Patients with cystatin C levels> 1.2 mg/L and <1.2 mg/L	NA
Woitas et al., 2013[18]	Patients with coronary disease (n = 2,346) and control group (n = 652). First quartile < 0.8 mg/L (n = 731). Second quartile 0.81 to 0.91 mg/L (n=769). Third quartile 0.91 to 1.06 mg/L (n=752). Fourth quartile > 1.07 mg/L (n=746)	Hypertension, HDL, LDL, triglycerides, statin use, smoking, DM, usPCR, GFR CKD-EPI based on creatinine, age, gender, BMI
Dupont et al., 2012[8]	Cystatin C quartiles.	NA
Gao et al., 2011[21]	Patients who developed fatal or non-fatal (n = 21) cardiovascular events and patients who did not develop these events (n = 117). Patients with cystatin C levels above the median and below the median (0.9 mg/L).	Male gender, history of hypertension, high creatinine, reduced triglycerides, high homocysteine, high usPCR, high cystatin C.
Keller et al., 2009[17]	Patients with cardiovascular death (n = 66) and patients without cardiovascular death (n = 1761). Cystatin C quartiles.	Age, gender, BMI, smoking, DM, hypertension, LDL/HDL ratio, PCR, GNP.
Gao et al., 2009[22]	Patients with stable angina (n = 34), patients with unstable angina (n = 56), patients with AMI (n = 36) and control group (n = 34). Patients who developed fatal or non-fatal (n = 26) cardiovascular events and patients who did not develop these events (n = 22).	NA
Alehagen et al., 2009[20]	First quartile: < 1.22 mg/L (n = 109). Second quartile: 1.22 to 1.42 mg/L (n = 120). Third quartile: 1.43 to 1.66 mg/L (n = 117). Fourth quartile: > < 1.66 mg/L (n = 118).	NA
Acuna et al., 2009[16]	Patients with cystatin C levels> 0.95 mg/L (n = 63) and ≤ 0.95 mg/L (n = 76)	NA
Koenig et al., 2007[24]	Patients with high (n = 1261) and reduced levels of cystatin C (n = 1347)	NA
Ix et al., 2007[23]	First quartile: ≤ <0.91 mg/L (n = 239). Second quartile: 0.92 to 1.05 mg/L (n = 248). Third quartile: 1.06 to 1.29 mg/L (n = 262). Fourth quartile:> ≥ <1.30 mg/L (n = 241).	Age, gender, race, smoking, DM, hypertension, previous AMI, smoking, HDL, BMI, CRP.

DM: Diabetes mellitus; HDL-high density lipoprotein; AMI: Acute Myocardial Infarction; BMI: Body mass index; LDL: low density lipoprotein; NA: Not applicable; CRP: C-reactive protein; GFR: Glomerular filtration rate; usPCR: Ultra-sensitive C-reactive protein.

Discussion

The present study aimed to evaluate the association between high levels of cystatin C and the risk of cardiovascular events or mortality in subjects with normal renal function through a systematic review of the scientific literature and meta-analysis.

The difference between the proportion of patients with high levels of cystatin C who developed cardiovascular events or mortality, compared with the proportion of patients with reduced levels of Cystatin C that developed these events was evaluated by two studies and both of them found a significant difference. The difference between cystatin C levels in patients who developed fatal or non-fatal cardiovascular events and those who did not develop these events was assessed by four studies (33.3%) and all found significantly higher levels of cystatin C in the group of patients who had the events. The risk of developing adverse outcomes was assessed by eight studies (66.66%) calculating the hazard ratio. Among these, six studies found an increased risk of cardiovascular events or mortality. The multivariate regression analysis was performed by six (50%) of these studies, with the risk of developing the adverse outcomes remaining significant after the performance of this analysis in four of these studies.

The meta-analysis also demonstrated that there is a significant association between high levels of cystatin C and the risk of all-cause mortality. Thus, the results presented by the studies included in this systematic review and meta-analysis

Table 4 – Results of selected studies

Author/Year	Result
Sai et al., 2016[19]	Proportion of patients with cystatin C levels> 0.637 mg/L who developed fatal or non-fatal cardiovascular events was higher than in patients with cystatin C < 0.637 mg/L [22 (15.9%) x 7 (5, 0%), p = 0.0025]. Risk of fatal or non - fatal cardiovascular events in patients with cystatin C levels > 0.637 mg/L was greater than in patients with cystatin levels < 0.637 mg/L [(univariate) HR = 1.37 (1.10 - 1.66), p = 0.004; HR (multivariate) = 1.30 (1.01 - 1.63), p = 0.0038].
Bansal et al., 2016[15]	Risk of left ventricle hypertrophy was higher in patients with GFR between 60 and 75 ml/min/1.73 m^2 than in those with GFR > 90 ml/min/1.73 m^2 [(univariate) HR = 10.12 (5.22 – 15.02), p < 0.001; HR (multivariate analysis) = 5.63 (0.90 - 10.36), p = 0.02] Risk of left ventricular hypertrophy was higher in patients with GFR between 76 and 90 mL/min/1.73m^2 than in those with GFR> 90 mL/min/1.73 m^2 [HR (univariate analysis) = 3.48 (1, 29 - 5.68), p = 0.002].
Abid et al., 2016[7]	Patients who developed non-fatal cardiovascular events showed higher levels of cystatin C compared to patients who did not develop these events (1.19 ± 0.4 mg/L x 1.01 ± 0.35 mg/L, p = 0.01) Patients who developed fatal cardiovascular events showed higher levels of cystatin C compared to patients who did not develop these events (1.21 ± 0.36 mg/L x 0.96 ± 0.27 mg/L, p = 0.03) Survival of patients with cystatin C levels < 1.2 mg/L was higher than in patients with cystatin levels > 1.2 mg/L (p < 0.01).
Woitas et al., 2013[18]	Patients with CAD showed higher levels of cystatin C than the control group (1.02 ± 0.44 mg/L x 0.92 ± 0.26 mg/L, p = 0.065 Risk of cardiovascular death and death from any cause of fourth quartile patients was higher than that of first quartile patients [HR (univariate) = 4.82 (3.69 - 6.29), p < 0.001; HR (multivariate) = 2.05 (1.48 - 2.84), p < 0.001]. Risk of cardiovascular death and death from any cause of third quartile patients was higher than that of first quartile patients [HR (univariate) = 2.11 (1.58 - 2.81), p < 0.001; HR (multivariate) = 1.20 (0.88 - 1.65), p < 0.243].
Dupont et al., 2012[8]	Risk of death from any cause and non-fatal cardiovascular event of patients in the fourth quartile was higher than in patients in the first quartile (p = 0.002).
Gao et al., 2011[21]	Patients who developed fatal or non-fatal cardiovascular events showed higher levels of cystatin C compared to patients who did not develop these events (1.63 ± 0.81 mg/L x 0.91 ± 0.27 mg/L, p = 0.001) Risk of fatal or non-fatal cardiovascular events in patients with cystatin C levels> 0,9 mg/L was higher than in patients with cystatin levels < 0.9 mg/L [(univariate) HR = 3.58 (2.61 - 4.82), p = 0.033; HR (multivariate) = 7.10 (3.36 – 23.75), p = 0,006].
Keller et al., 2009[17]	Patients with cardiovascular death had higher levels of cystatin C than patients without cardiovascular death [0.94 (0.79 - 1.08 x 0.79 (0.70 - 0.90), p < 0.001]. Risk of cardiovascular death of patients in the fourth quartile was higher than in patients in the other quartiles [OD (univariate) = 3.87 (2.33-6.42), p < 0.001; OD (multivariate) = 1.86 (0.90-3.81), p = 0.09].
Gao et al., 2009[22]	Patients with AMI and unstable angina had higher levels of cystatin C than the control group (2873.55 ± 1148.48 ng/mL x 1509.99 ± 408.65 ng/mL, p < 0.01 and 2013.83 ± 633.85 ng/mL x 1509.99 ± 408.65 ng/mL, p < 0.05, respectively). Patients with AMI and unstable angina had higher levels of cystatin C than the patients with stable angina (2873.55 ± 1148.48 ng/mL x 1348.41 ± 369.62 ng/mL, p < 0.01 and 2013.83 ± 633.85 ng/mL x 1348.41 ± 369.62 ng/mL, p < 0.01, respectively). Patients with AMI had higher levels of cystatin C than the patients with stable angina (2873.55 ± 1148.48 ng/mL x 2013.83 ± 633.85 ng/mL, p < 0.05). Patients who developed fatal or non-fatal cardiovascular events showed higher levels of cystatin C compared to patients who did not develop these events (2356,73 ± 897,64 ng/L x 1469.51 ± 574.83 ng/L, p = 0.006)
Alehagen et al., 2009[20]	Risk of cardiovascular death of fourth quartile patients was higher than that of first quartile patients [HR (univariate analysis) = 3.61 (1.81 – 7.14)].
Acuna et al., 2009[16]	The proportion of patients with cystatin C levels > 0.95 mg/L who had cardiovascular death was higher than that of patients with cystatin C levels ≤ 0.95 mg/L [16 (27.1%) x 6 (7.8%), p = 0.01]. The proportion of patients with cystatin C levels> 0.95 mg/L who develop HF was higher than that of patients with cystatin C levels ≤ 0.95 mg/L [22 (40.7%) x 6 (7.5%), p = 0.01].
Koenig et al., 2007[24]	Each increase of 0.18 mg/L cystatin C was associated with an increased risk of cardiovascular death [OD = 1.42 (1.30 -1.54)], death from any cause [OD = 1.33 1.25-1.40)], HF [OD = 1.28 (1.17-1.40)], stroke [OD = 1.22 (1.08-1.38)] and AMI [OD = 1.20 (1.06-1.36)]. Patients with high levels of cystatin C had more adverse events than those with reduced levels of cystatin C (p < 0.001).
Ix et al., 2007[23]	Risk of death from any cause of fourth quartile patients was higher than that of first quartile patients [HR (univariate) = 5,7 (3,1 - 10,5), p < 0.001; HR (multivariate) = 3,6 (1,8 - 7,0), p < 0.001]. Risk of cardiovascular events of fourth quartile patients was higher than that of first quartile patients [HR (univariate) = 3.8 (2.1 – 6.9), p < 0.001; HR (multivariate) = 2.0 (1.0 – 3.8), p < 0.04]. Risk of CHF in patients in the fourth quartile was higher than in patients in the first quartile [HR (univariate) = 6.1 (2.5 - 14.5), p = 0.001; HR (multivariate) = 2.6 (1.0 - 6.9), p = 0.05].

CAD: Coronary artery disease; AMI: Acute Myocardial Infarction; GFR: Glomerular filtration rate; HR: Hazard Ratio.

Table 5 – Evaluation of study quality according to Newcastle-Ottawa Scale

Author/Year	Selection 1 2 3 4				Comparability 5	Outcomes 6 7 8			Total score
Sai *et al*., 2016[19]	*	*	*	-	**	*	*	*	8
Bansal et al., 2016[15]	*	*	*	-	**	*	*	*	8
Abid et al., 2016[7]	*	*	*	-	*	*	*	*	7
Woitas *et al*., 2013[18]	*	*	*	-	**	*	*	*	8
Dupont et al., 2012[8]	*	*	*	-	*	*	*	*	7
Gao et al., 2011[21]	*	*	-	-	**	*	*	*	7
Keller *et al*., 2009[17]	*	*	*	-	**	*	*	*	8
Gao et al., 2009[22]	*	*	-	-	*	*	-	*	5
Alehagen et al., 2009[20]	*	*	*	-	*	*	*	*	7
Acuna et al., 2009[16]	*	*	*	-	*	*	*	*	7
Koenig *et al*., 2007[24]	*	*	-	*	*	*	*	*	7
Ix et al., 2007[23]	*	*	*	-	**	*	*	*	9

1 - Representativeness of the exposed cohort: all the studies received one star, because the exposed cohort was a little representative of the average in the community; 2 - Selection of the unexposed cohort: all studies received one star, because the unexposed cohort was obtained in the same community of the exposed cohort; 3- Determination of exposure: only studies that dosed cystatin C using the immunonephelometry or immunoturbidimetry methods received a star; 4 - Demonstration that the outcome of interest was not present at the beginning of the study: studies in which patients did not present any cardiovascular disease at the beginning of the study received one star; 5 - Cohort comparability based on design and analysis: studies that performed multivariate regression analysis of Cox proportional hazards and defined normal renal function as GFR > 60 mL/min/1.73 m^2 received 2 stars. Studies that only defined normal renal function as GFR > 60 mL/min/1.73 m^2 but did not perform multivariate regression analysis of Cox proportional hazards received 1 star. 6 - Determination of outcome: all studies received one star, because the evaluation of the outcome was performed by the physicians independently; 7 - Adequate follow-up period for the occurrence of outcome (s): studies in which patients were followed for at least six months received one star, and studies in which patients were followed for less than six months did not receive a star; 8 - Adequacy of the follow-up period of the cohort: studies in which at least 90% of the patients were followed to the end or who did not comment if there were significant loss of patients during follow-up received one star.

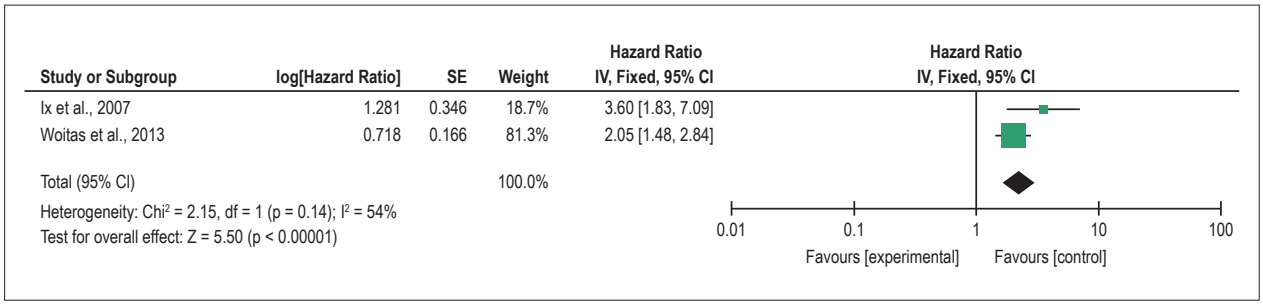

Figure 2 – *Metanalysis of studies evaluating the association between high levels of cystatin C and the risk of mortality from any cause through the comparison between the fourth and first quartiles of cystatin C.*

indicate that there is a significant association between high levels of cystatin C and the development of cardiovascular events or mortality in subjects with normal renal function assessed by serum creatinine-based GFR.

A possible mechanism for the association between high levels of cystatin C and the development of cardiovascular events is related to the atherogenic process. The development of lesions in the arteries endothelium results in the accumulation of cholesterol in the artery wall, and in the development of the atherosclerotic plaque.[25] It has been suggested that lysosomal cathepsins, whose production is stimulated by inflammatory cytokines, may contribute to the degradation of the atherosclerotic plaque. As cystatin C is able to inhibit lysosomal cathepsins, it is possible to suggest that elevated levels of cystatin C may contribute to non-degradation of atherosclerotic plaque, resulting in increased risk of cardiovascular events.[26,27]

Another possible mechanism is related to the fact that cystatin C presents a greater sensitivity for the detection of the initial stages of renal dysfunction than serum creatinine or creatinine-based GFR.[28,29] Several authors have already demonstrated that renal dysfunction is associated with an increased risk of cardiovascular events.[30,31] Thus, it is possible to suggest that patients who have normal renal function assessed by GFR based on creatinine or serum creatinine but who have high levels of cystatin C may present with renal dysfunction at an earlier stage, which could be associated with an increased risk of cardiovascular events.

Although cystatin C is a more sensitive marker for detecting the early stages of CKD than creatinine, especially in groups at risk for CKD, such as patients with diabetes mellitus and renal transplant recipients, it has some limitations.[32,33] High doses of glucocorticoids and hyperthyroidism may result in increased serum levels of cystatin C, whereas hypothyroidism may result in a decrease.[34] Some factors, such as age, male gender, body weight, smoking, C-reactive protein, cancer, inflammatory processes and steroid therapy may also influence serum levels of cystatin C, limiting its assessment in clinical practice.[35]

Renal weight and volume decrease gradually between the ages of 30 and 90 years, resulting in a natural decline of renal function with increasing age.[36] Thus, elderly patients have a lower GFR, which may be associated with higher levels of cystatin C and an increased risk of cardiovascular events.[28] As most of the studies that performed the multivariate regression analysis [66.66% (n = 4)][15,17,18,23] included age in this analysis, and nonetheless found a significant association between high levels of cystatin C and the development of adverse outcomes, it is possible to conclude that this association is age-independent. It should be noted that the two studies[20,25] that were included in the meta-analysis are among these studies that included age in the multivariate regression analysis, indicating that the association between high levels of cystatin C and any cause-related mortality observed in meta-analysis is age-independent.

All selected studies have described the renal function of patients as being normal. The estimated GFR calculated by the MDRD formula, greater than 60 mL/min/1.73 m^2, was used as a criterion for normal renal function in 66.67% of the studies, and 8.33% used serum creatinine levels below 115 μmol/L. The estimated GFR is a better marker for renal function evaluation than serum creatinine, because it undergoes interference of muscle mass, gender, age, physical activity and diet. Moreover, unlike GFR, serum creatinine is not able to detect the presence of chronic renal disease early because its levels increase only when renal disease is already at an advanced stage.[31] The inclusion of individuals with estimated GFR greater than 60 mL/min/1.73 m^2 by most studies, including studies of the meta-analysis, supports the information that the association between high levels of cystatin C and the risk of cardiovascular events or mortality is not dependent on the renal function of the patient evaluated by creatinine-based estimated GFR, which is a marker that has good sensitivity for the detection of renal dysfunction in the early stages.

Immunonephelometry and immunoturbidimetry were the most commonly used methods [75% (n = 9)] for the laboratory dosage of cystatin C and were even used by the studies included in the meta-analysis. These methods have good precision, specificity, adequate time to result, and minimum amount of sample required, being the methods of choice for cystatin C[37,38] dosage. Therefore, the use of these methods by most of the studies included in the systematic review brings greater reliability to the results.

The sample size of the studies ranged from 127 to 4,663 individuals, with most of them having more than 400 individuals [58.33% (n = 7)].[8,15,17,18,20,23,24] The study[7] that obtained the smallest sample size still included more than 100 individuals, which can be considered a significant number if the follow-up is performed for an adequate time.[39] It should be noted that this study found a significant difference between patients who developed fatal or non-fatal cardiovascular events and those who did not develop these events.

This systematic review had some limitations, such as the population studied, which varied widely among the studies. Only one study[24] included healthy elderly subjects, while the population of the other studies consisted of patients at risk for cardiovascular events,[15] with STEMI and NSTEMI,[7,16] with stable CAD,[17,18] SCA,[17] patients undergoing percutaneous coronary intervention,[19] with CHF,[20,21] with CHF who underwent coronary angiography,[8] with stable angina and AMI,[22] and with a history of AMI that had angiographic evidence of stenosis greater than 50%.[23] This variation may lead to bias in the results, because cardiovascular impairment varied among the populations at the beginning of the studies, which may influence cystatin C levels, since patients with CHF or AMI could present higher levels of cystatin C at the beginning of the study if compared to patients who only present risk of cardiovascular events.[23] Since most studies evaluated a population at risk of cardiovascular events or who already have some degree of cardiovascular impairment, it is possible to suggest that cystatin C is an interesting marker for assessing the risk of cardiovascular events or mortality in these population groups and may complement the currently available markers.

In addition to the variation of the study population, follow-up time, patient classification, and outcomes also varied widely across studies. The follow-up time ranged from six months to ten years, and three studies (25%)[7,16,22] followed the patients for less than 15 months and four studies (33.33%)[15,18,20,24] have followed for more than nine years. The prevalent time of follow-up of the studies was three to six years [41.67% (n = 5)].[8,17,19,21,23] The follow-up time should be adequate for the outcome to be observed, and should be greater for the detection of mortality than for cardiovascular events. The study[22] with shorter follow-up (6 months) found higher levels of cystatin C among patients who developed fatal and non-fatal cardiovascular events compared to patients who did not develop these outcomes, indicating that even shorter follow-up time was sufficient for the detection of both outcomes and for the observation of a significant association with Cystatin C levels. Both studies included in the meta-analysis assessed the outcome for all-cause mortality. One of them followed the patients for three years and the other for ten years, with these times being adequate for the evaluation of the outcome.

Patients classification to carry out the statistical analysis also varied considerably among the studies. Only five studies (41.66%),[8,17,18,20,23] including the studies of the meta-analysis, classified patients according to quartiles of cystatin C, which is the best classification to establish a cutoff point above which the risk of developing cardiovascular events or mortality would be higher.

Despite these study limitations, of the articles selected in this systematic review, 11 have excellent methodological quality and only one has good quality.

Conclusion

The systematic review has shown that there is a significant association between high levels of cystatin C and the risk of cardiovascular events or mortality in subjects with normal renal function. The meta-analysis also demonstrated that there is a significant association between high levels of cystatin C and the risk of all-cause mortality. As individuals included in the studies had normal renal function, it is possible to conclude that the association between high levels of cystatin C and the risk of cardiovascular events or mortality does not depend on the presence of renal dysfunction assessed by serum creatinine-based GFR. Therefore, cystatin C is a very interesting marker to assess the risk of cardiovascular events or mortality, especially in populations at risk of cardiovascular events or that already have some degree of cardiovascular impairment, and can complement the currently available markers.

Author contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Statistical analysis e Writing of the manuscript: Einwoegerer CF, Domingueti CP; Critical revision of the manuscript for intellectual content: Domingueti CP.

Potential Conflict of Interest

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

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Cystatin C as a Candidate Biomarker of Cardiovascular Outcomes: Too Near, but too Far from Reality

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Short Editorial regarding the article: Association Between Increased Levels of Cystatin C and the Development of Cardiovascular Events or Mortality: A Systematic Review and Meta-Analysis

While the development of novel risk factors for cardiovascular risk assessment is necessary to improve risk stratification, proving its clinical value on top of traditional risk factors is routinely challenging.[1-3] Besides all the innovative and straightforward biomarker research published in the last decades, only very few markers of cardiovascular risk have shown clinical significance.[4,5] Among many of them, cystatin C has emerged some years ago as a candidate for improving cardiovascular risk stratification.

In the *Cardiovascular Health Study* (CHS),[6] a community-based and longitudinal study with over 4,600 elderly individuals, cystatin C has shown to predict cardiovascular outcomes. As compared with the lowest quintile, the highest quintile of cystatin C was associated with a significantly increased risk of death from cardiovascular causes (hazard ratio [HR] 2.27 [1.73 to 2.97]), myocardial infarction (HR 1.48 [1.08 to 2.02]), and stroke (HR 1.47 [1.09 to 1.96]) after multivariate adjustment. However, cystatin C is typically known as a marker of renal function, being roughly correlated with glomerular filtration rate in early stages of kidney diseases.[7,8] Reasonably, since glomerular function is a strong surrogate marker of cardiovascular disease, it suggests an obvious association between cystatin C and cardiovascular outcomes. A mechanism to avoid the impact of this inexorable bias was to study only individuals with normal kidney function. Yet, additional studies have shown inconsistent magnitudes of effect between cystatin C and cardiovascular outcomes.

In that context, Einwoegerer and Domingueti[9] in this issue of the *Brazilian Archives of Cardiology* investigated the role of plasma cystatin C levels on the risk of all-cause mortality and other softer endpoints by pooling studies of individuals with normal renal function. Unfortunately, only two studies compared quartiles of cystatin C with multivariate regression analysis, hence providing a sample size that is not too far from the original *Ludwigshafen Risk and Cardiovascular Health* (LURIC) study.[10] The meta-analysis suggested a robust association between high levels of cystatin C and the risk of all-cause mortality in individuals with normal renal function (HR 2.28 [1.70 - 3.05], $p < 0.001$). Heterogeneity among studies was substantial ($I^2 > 50\%$) and no sensitivity analysis was provided. Besides the critical limitations in meta-analysis data, authors also provided substantial elements in a systematic review of studies on the same topic.

Although a first step for a candidate biomarker is to show strong association with a clinical outcome, this is not sufficient to prove its complementary clinically usefulness beyond traditional cardiovascular risk factors, such as age, gender, smoking, hypertension, diabetes, hyperlipidemia, obesity and aortic stenosis. A next fundamental step is to show whether cystatin C could improve risk prediction of cardiovascular outcomes in Receiver operating characteristic (ROC) curves models, net reclassification index (NRI) and integrated discrimination index (IDI) compared-to or added-to the Framinghan Heart Risk, ASCVD risk score, or any validated cardiovascular risk scores/engines.[11,12]

Besides the potential mechanistic link between cystatin C and atherosclerotic disease, this association is unlikely to be causal. By using a Mendelian randomization approach, which takes into account both the genetic association with cystatin C and CVD to triangulate the causal effect, and combining a set of cohorts of over 250,000 individuals with 63,000 cases of cardiovascular events from the *Cystatin C Mendelian Randomization Consortium* no association could be found.[13] This finding in no way suggests that we should abandon the use of cystatin C for risk stratification purposes in kidney diseases, but there are two key messages in it: (i) it alerts against the chase of therapeutic strategies that target at lowering plasma cystatin C levels; (ii) it also indicates a low likelihood of association between cystatin C as a surrogate cardiovascular marker on top of classical risk factors. However, the last word in favor or against the use of cystatin C in clinical practice for cardiovascular risk stratification of individuals with normal renal function should be based on studies evaluating detrimental effects of this marker on established risk scores/engines.

Keywords

Cardiovascular Diseases; Cystatin C; Biomarkers; Atherosclerosis; Glomerular Filtration Rate.

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Statin Treatments And Dosages In Children With Familial Hypercholesterolemia: Meta-Analysis

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Abstract

Background: Children with familial hypercholesterolemia may develop early endothelial damage leading to a high risk for the development of cardiovascular disease (CVD). Statins have been shown to be effective in lowering LDL cholesterol levels and cardiovascular events in adults. The effect of statin treatment in the pediatric population is not clearly demonstrated.

Objective: To systematically review the literature to evaluate the effects of different statins and dosages in total cholesterol levels in children and adolescents with familial hypercholesterolemia. We also aimed to evaluate statin safety in this group.

Methods: PubMed, EMBASE, Bireme, Web of Science, Cochrane Library, SciELO and LILACS databases, were searched for articles published from inception until February 2016. Two independent reviewers performed the quality assessment of the included studies. We performed a meta-analysis with random effects and inverse variance, and subgroup analyses were performed.

Results: Ten trials involving a total of 1543 patients met the inclusion criteria. Our study showed reductions in cholesterol levels according to the intensity of statin doses (high, intermediate and low): (-104.61 mg/dl, -67.60 mg/dl, -56.96 mg/dl) and in the low-density lipoprotein cholesterol level: [-105.03 mg/dl (95% CI -115.76, -94.30), I2 19.2%], [-67.85 mg/dl (95% CI -83.36, -52.35), I2 99.8%], [-58.97 mg/dl (95% CI -67.83, -50.11), I2 93.8%. The duration of statin therapy in the studies ranged from 8 to 104 weeks, precluding conclusions about long-term effects.

Conclusion: Statin treatment is efficient in lowering lipids in children with FH. There is need of large, long-term and randomized controlled trials to establish the long-term safety of statins. (Arq Bras Cardiol. 2018; 111(6):810-821)

Keywords: Statins; Hydroxymethylglutaryl-CoA Reductase Inhibitors; Hypercholesterolemia Type II/genetic; Children; Meta-Analysis.

Introduction

Familial hypercholesterolemia (FH) is a dominant autosomal genetic disease. The worldwide prevalence is of 1 in 250 people affected with the heterozygous form (HeFH) of HF.[1] FH is characterized by high levels of low-density lipoprotein (LDL) cholesterol due the reduced hepatic capacity to remove LDL-cholesterol from blood circulation,[2] which can result in early atherosclerosis development.[3] Further, children with FH have damage in the endothelial function and increased intima-media thickness (IMT)[4] indicating early atherogenesis.

The hydroxy-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors or statins decrease the coronary morbidity and mortality in high-risk adults. They have proven to be effective in decreasing LDL-cholesterol levels and cardiovascular events in adults.[5] Statins are one of the most prescribed drugs in the world[6] for adults and, in usual doses, are notably safe.

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The expert consensus recommends drug treatment for children older than 10 years old with LDL-cholesterol level ≥ 5 mmol/L (190 mg/dl), whose cholesterol levels remain elevated despite diet measures during the period from 8 weeks to 2 years for children ages 8–18 years. It is also considered the treatment for those with LDL-cholesterol ≥ 4 mmol/L (160 mg/dl) with the presence of two or more cardiovascular risk factors or family history of CVD.[2,7]

The US Food and Drug Administration (FDA)[8] has approved the use of some statins like simvastatin, atorvastatin, fluvastatin, pravastatin, rosuvastatin and lovastatin for pediatric and adolescent patients. Pravastatin is approved for use at 8 years of age, other statins are approved for use from 10 years on. FDA[8] recommends statins for children with FH, primary or genetic dyslipidemia. The treatment to reduce cholesterol levels in pediatric patients is based on evidence involving only adults.[9] The effect of statins in pediatric population has been limited to short-term randomized clinical trials (RCTs).[10,11]

Thus, the aim of this study was to systematically review the literature to evaluate the effects of different statins and the dosages in elevated plasma levels of total cholesterol (TC), LDL- cholesterol and apolipoprotein B (APOB) and in decreased high-density lipoprotein (HDL) cholesterol levels in children and adolescents with FH. We also aimed to evaluate statin safety in this group.

Methods

A systematic review was conducted according to Cochrane Collaboration and Preferred Reporting Items for Systematic Review and Meta-analyses: the PRISMA Statement.[12]

Eligibility criteria

Studies included RCTs performed in children and adolescents from 8 to 18 years old, submitted to statin therapy for treatment of familial hypercholesterolemia. The intervention was considered as the use of statins at any dose, for at least eight weeks. Our protocol has assessed increased plasma levels of TC, LDL-cholesterol and APOB, and decreased HDL-cholesterol, in addition to seeking evidence on the effectiveness, safety and effects of statins. The RCTs were included if fulfilled the inclusion criteria and had at least one primary or secondary outcome. Studies that did not provide information on the magnitude of the intervention's effect in the control or experimental groups were excluded. When a study had several publications (or sub-studies), only the most recent was included. The other publications were used to supplement information.

Information sources

The review protocol was registered in the International Register of Prospective Systematic Reviews (PROSPERO), under registration number: CRD42015029350. The search comprised seven online databases - PubMed, EMBASE, Bireme, Web of Science, Cochrane Library, SciELO and LILACS. It lasted from the beginning to February 2016 and was composed by entries related to the following terms: "*child*", "*adolescents*", "*cholesterol*", "*hypercholesterolemia*", "*statins*", "*dyslipidemia*", "*inhibitor hidroximethylglutaril-CoA reductase*". There was no language restriction and we adopted a high-sensitivity strategy for the search of randomized controlled trials.[13] To identify other primary studies, the authors searched and checked for reference lists of previously published systematic reviews and meta-analyses. The detailed strategies for PubMed are in Appendix I. The strategies for other databases are available upon request.

Study selection and data extraction

Two investigators (G.R. and G.S.), in duplicate and independently, evaluated the titles and abstracts of all articles identified by the search strategy. The abstracts that provide enough information regarding the inclusion and exclusion criteria were selected for full-text evaluation. In the second phase, the same reviewers independently evaluated the full text of these articles and made their selection in accordance with the eligibility criteria. Disagreements between reviewers were solved by consensus, and when disagreement persisted it was solved by a third reviewer (L.C.P.). These two reviewers (G.R. and G.S.) independently conducted data extraction regarding the methodological characteristics of the studies, interventions and outcomes using standardized forms. The CONSORT analysis instrument was used to evaluate methodological quality (internal and external validation) of the included clinical trials. The outcomes extracted in this meta-analysis were: TC (mg/dl), LDL-C (mg/dl), HDL-C (mg/dl), APOB (mg/dl).

Assessment of risk of bias

Quality assessment of studies included adequate sequence generation, adequate allocation concealment, blinding of investigator, participants, and outcomes assessors, intention-to-treat analysis and description of losses and exclusions. Studies had to have a clear description of an adequate sequence generation to fulfill these criteria. The description of how the allocation list was concealed could include terms like "central", "web-base" or "telephone randomization" or computer-generation.

Intention-to-treat analysis was considered as confirmation on study assessment that the number of participants randomized and the number analyzed were identical, except for patient lost to follow-up or those who withdrew consent for study participation. Two reviewers independently performed quality assessment, and, for each criterion, studies were classified as adequate, not adequate or unclear/not reported.

Data Synthesis and Statistical Analysis

All analyses were conducted using Software RStudio.[14] For continuous outcomes, if the unit of measurement was consistent throughout trials, results were presented as weighted mean difference with 95% of confidence intervals (CIs). Calculations were performed using random effects method and the statistical method used was inverse variance. Statistical significance defined for the analyzes as $p < 0.05$. Statistical heterogeneity of the treatment effects among studies was assessed using Cochran's Q test and the inconsistency I^2 test. In addition, sensitivity analysis of RCTs was performed to assess differences in the intervention approach (intervention group versus placebo). In studies where statins therapy compared three different arms of treatment (intervention group) versus placebo (control group), we will conduct weighted average and divide the total number of patients to the distribution of the control group.[15]

Results

Description of studies

We initially identified 16793 potentially relevant citations from electronic databases. A total of 15 RCTs were included in the synthesis of qualitative studies and10 RCTs[10,11,16-23] were selected to the quantitative analysis. Studies that were not eligible for the quantitative analysis did not provided data on cholesterol levels[24-27] in a way that we could extract them from the article, and one study[28] was not performed with a control group. Figure 1 shows the summary of evidence search and study selection in this review. The included studies comprised a total of 1543 subjects, and they were all full peer-reviewed publications.

Participants

Table1 summarizes the characteristics of participants and included studies. The number of participants in the studies ranged from 54 to 248. A total of 934 subjects received statin therapy and 609 received placebo. The age also varied from 8 to 18 years old. The studies have evaluated different types of statins for a period of 8 to 104 weeks.

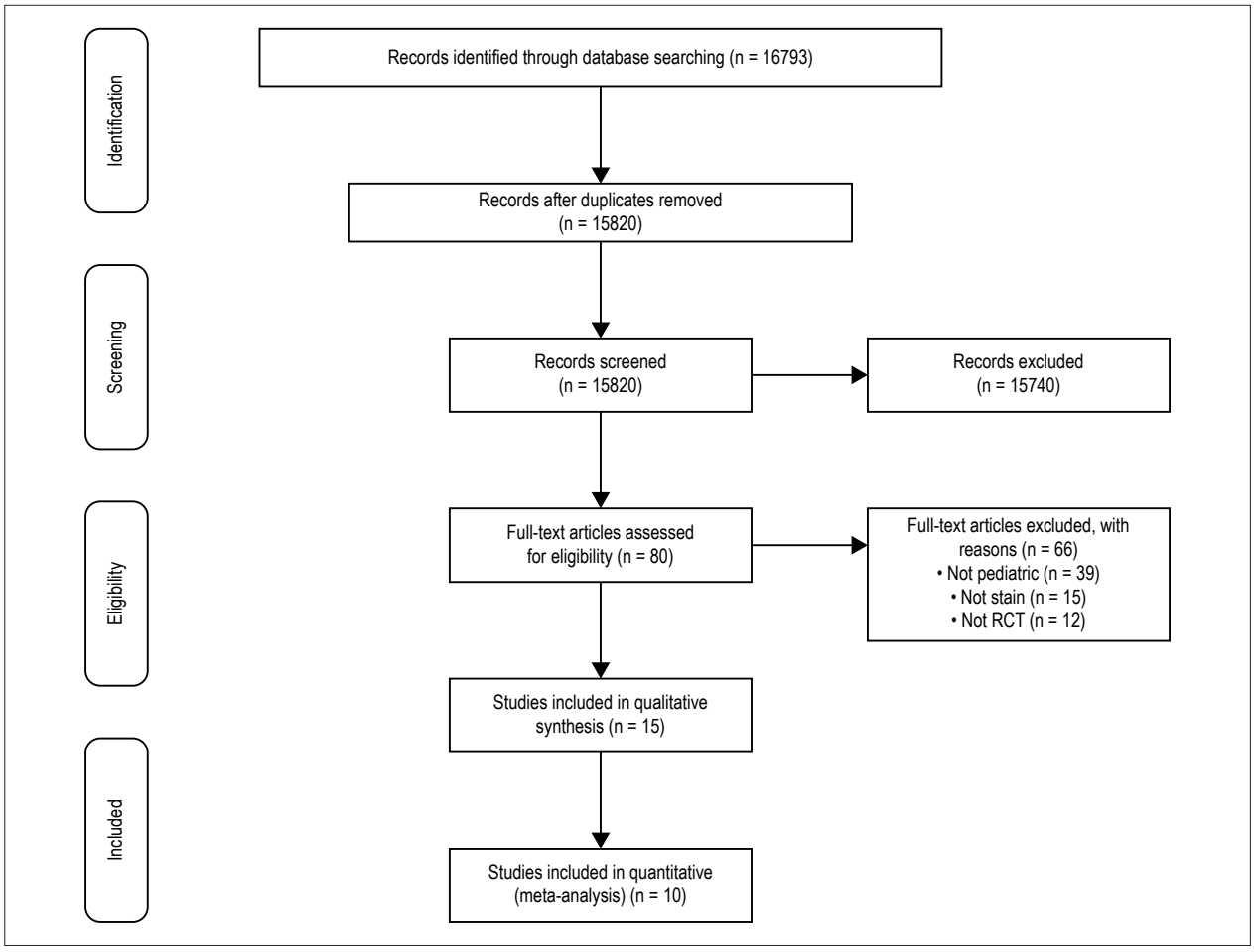

Figure 1 – *Summary of evidence search and study selection.*

Risk of bias in included studies

Allocation

Generation of sequence

The generation of the allocation sequence was adequate in two studies since the sequence was computer-generated.[10,18] The remaining ten studies were described as randomized, but no further details of the process were given (Table 2).

Concealment of allocation

None of the included studies described how the allocation sequence was concealed from the investigators, the outcome assessors or the participants in the study (Table 2).

Blinding

All studies were described as double blind, indicating that participants and those participating in treatment procedures were blinded to treatment (Table 2).

Incomplete outcome data

From the studies included, 90% reported intention-to-treat analyses and 80% described losses due to follow-up and exclusions.

Effects of interventions

Statins versus placebo

All included studies describe the use of therapy with statins: atorvastatin,[16] lovastatin,[10,21] pravastatin,[17,18,19] rosuvastatin,[20] simvastatin[11,22] and pitavastatin.[23] The dosage and duration of treatment with statins varied between them (Table 1). The detailed analyzes are in Appendix II, III, IV, and V.

Change in Total cholesterol

Ten of the included studies evaluated the effect of statin therapy on the TC level.[10,11,16-23] A subgroup analysis was performed in line with the intensity of statin doses, classified according to expected LDL-cholesterol reduction effect[29]: ≤ 30% as low; 30–40%, intermediate, and ≥ 40%, high.

Table 1 – Characteristics of included studies

Study, year	Randomized patients (n) intervention/placebo	Participants Age range	Intervention group	Control group	Duration of intervention	Statistical significance	Evaluated outcomes
Knipscheer et al., 1996	54/18	8 to 16 years	Pravastatin: (1) 5 mg/day, (2) 10 mg/day, and (3) 20 mg/day	Placebo	12 weeks	p < 0.05	TC, LDL-C, TGs, HDL-C, apo A-I, apo B, Lp(a), VLDL-C, ALT, AST, hormones
Stein et al., 1999	67/65	10 to 17 years	Lovastatin 10 mg/day for 8 weeks; 20 mg/d for 8 weeks, 40 mg/day	Placebo	48 weeks	p < 0.05	LDL-C, TGs, TC, HDL-C, apo A-I, apo A-II, apo B, Lp(a), testicular volume, ALT, AST, hormones, growth and development
de Jongh et al., 2002	106/69	10 to 17 years	Sinvastatin 10 mg/day for 8 weeks; 20 mg/day for 8 weeks; 40 mg/day	Placebo	48 weeks	p < 0.05	LDL-C, CT, TGs, HDL-C, apo A-I, apo B, VLDL-C, hsCRP, ALT, AST, hormones
McCrindle et al., 2003	140/47	10 to 17 years	Atorvastatin 10 mg/day; 20 mg/day if LDL ≥ 3.4 at weeks 4	Placebo	26 weeks	p < 0.05	LDL-C, CT, TGs, HDL-C, apo A-I, apo B, ALT, AST, hormones
Wiegman et al., 2004	106/108	8 to 18 years	Pravastatin 20 mg/day if <14 years of age; 40 mg/day if ≥ 14 years of age	Placebo	104 weeks	p < 0.05	LDL-C, TGs, TC, HDL-C, Lp(a), carotid IMT, growth, maturation, hormone level, liver and muscle enzymes
Clauss et al., 2005	35/19	10 to 17 years	Lovastatin 20 mg/day for 4 weeks; 40 mg/day	Placebo	24 weeks	p ≤ 0.05	LDL-C, TGs, HDL-C, apo A-I, apo B, Lp(a), VLDL-C, ALT, AST, hormones
Rodenburg et al., 2006	90/88	8 to 8 years	Pravastatin 20 mg/day if <14 years of age; 40 mg/day if ≥ 14 years of age	Placebo	104 weeks	p < 0.05	LDL-C, TC, TGs, HDL-C, apo B, Lp(a), VLDL-C, carotid IMT, C-reactive protein, OxLDL markers, Immune complexes
	intervention/placebo	Age range			intervention		outcomes
Van der Graaf et al. 2008	126/122	10 to 17 years	Simvastatin: (1) 10 mg/day, 20 mg/day, or 40 mg/day plus ezetimibe 10 mg/day or placebo for 6 weeks; Sinvastatin: (2) 40 mg/day plus ezetimibe 10 mg/day or placebo for 27 weeks; All subjects received open-label: (3) simvastatin 10 mg/day or 20 mg/day plus ezetimibe 10 mg/day for 20 weeks;	Placebo	53 weeks	p < 0.05	LDL-C, TC, TGs, HDL-C, apo B
Avis et al., 2010	131/46	10 to 17 years	Rosuvastatin: 5 mg/day, 10 mg/day, 20mg/day	Placebo	12 weeks	p < 0.05	ALT, AST, CK, GFR, urine, TC, LDL-C, TGs, HDL-C, apo A-I, apoB
Braamskamp et al., 2015	79/27	6 to 17 years	Pitavastatin: 1 mg/day, 2 mg/day, 4 mg/day	Placebo	12 weeks	p < 0.05	TC, LDL-C, HDL-C, TGs, apo A-I, apoB

Abbreviations: hsCRP: high-sensitivity c-reactive protein, ALT: alanine aminotransferase, AST: aspartate aminotransferase, CK: creatine phosphokinase, apo B: apolipoprotein B, apo A-I: apolipoprotein A-I, apo A-II: apolipoprotein A-II, DHEAS: cortisol and dehydroepiandrosterone sulfate, FSH: follicle-stimulating hormone, LH: lutropin, IMT: carotid intima-media thickness, CK: creatine kinase, GFR: glomerular filtration rate; sPLA2: secretory phospholipase A2, TGs: triglyceride, VLDL-C: very low dfensity lipoprotein – cholesterol, LDL-C: low-density lipoprotein – cholesterol, TC: total cholesterol, HDL-C: high density lipoproteins – cholesterol, Lp(a): lipoprotein, Lp-PLA2: lipoprotein-associated phospholipase A2, OxLDL markers: oxidized low-density lipoprotein.

Table 2 – Risk of bias of included studies

Study, year	Adequate sequence generation	Allocation concealment[a]	Blinding of investigator	Blinding of participant	Blinding of outcome assessors	Intention - to-treat analysis[b]	Description of losses and exclusions
Knipscheer et al., 1996	Not reported	Unclear	Not reported	Not reported	Not reported	Yes	No
Stein et al., 1999	Not reported	Unclear	Not reported	Not reported	Not reported	Yes	Yes
de Jongh et al., 2002	Not reported	Unclear	Not reported	Not reported	Not reported	Yes	Yes
McCrindle et al., 2003	Not reported	Unclear	Not reported	Not reported	Not reported	Yes	Yes
Wiegman et al., 2004	Yes	Unclear	Not reported	Not reported	Not reported	No	Yes
Clauss et al., 2005	Yes	Adequate	Not reported	Not reported	Not reported	Yes	Yes
Rodenburg et al., 2006	Not reported	Unclear	Not reported	Not reported	Not reported	Yes	No
Van der Graaf et al. 2008	Not reported	Unclear	Not reported	Not reported	Not reported	Yes	Yes
Avis et al., 2010	Not reported	Unclear	Not reported	Not reported	Not reported	Yes	Yes
Braamskamp et al., 2015	Not reported	Unclear	Not reported	Not reported	Not reported	Yes	Yes

[a] Allocation concealment: Adequate (randomization method described that prevents caregivers or investigators from interfering or identifying before randomization; Unclear (randomization stated but no further information provided).
[b] Intention-to-treat analysis: Intention-to-treat and completeness of follow-up are assessed by results available at the end of trial. Yes (specified by authors and confirmed by our analysis). No (specified or not specified by authors but no evidence of intention-to-treat confirmed by our analysis).

In this analysis, all subgroups maintained significant reductions in cholesterol levels (-104.61 mg/dl, -67.60 mg/dl, -56.96 mg/dl), and intragroup heterogeneity was lower (18%, 99.7%, 95.4%). This analysis explained 99.4% of the original heterogeneity found in the main analysis (Figure 2).

Change in LDL-cholesterol level

Ten included studies evaluated the effect of statin therapy on the LDL-cholesterol level.[10,11,16-23] All subgroup analysis demonstrated significant reduction in this level: [-105.03 mg/dl (95% CI -115.76, -94.30), I^2 19.2%], [-67.85 mg/dl (95% CI -83.36, -52.35), I^2 99.8%], [-58.97 mg/dl (95% CI -67.83, -50.11), I^2 93.8%], (Figure 3). The detailed analyzes are in Appendices II, III, IV, and V.

Discussion

We quantitatively analyzed ten randomized placebo-controlled trials in children with FH. Studies showed a clinically significant reduction in LDL-cholesterol levels in children treated with statin, compared to those treated with placebo. In addition, therapy with statins slightly increased HDL-cholesterol. The reduction in LDL-cholesterol levels varied between studies, probably due to different statins and dosages, and, possibly due to different settings of HeFH.

In our meta-analysis, the results of all studies using statins were combined. All statins included present a common mechanism of action, i.e., inhibition of hydroxy-methyl-glutary-Coa. All statins have shown beneficial effects in lowering lipid levels and have been approved for use in adult patients with dyslipidemia.

When comparing some results: the study using lovastatin to evaluate efficacy and safety in children, focusing on female population, concluded that the lovastatin group showed a reduction in LDL-cholesterol levels of 23% to 27% against an increase of 5% in the placebo group ($p < 0.001$), TC of 17% to 22%, and APOB of 20% to 23%.[10] Whereas another study with young male patients,[21] lasting 24 weeks, lovastatin significantly reduced LDL-cholesterol levels at all dosages compared with placebo (17%, 24%, 27% with dosage of 10, 20, and 40 mg/day, respectively; $p < 0.001$). Further treatment with the dose of lovastatin at 40 mg/day (from 24 to 48 weeks) reduced LDL-cholesterol by 25% compared to placebo ($p < 0.001$).

In a study with pravastatin, the assessed primary efficacy outcome was the IMT, showing a significant difference between pravastatin versus placebo ($p = 0.02$).[18] Also, pravastatin reduced LDL-cholesterol levels (-24.1%) versus placebo (+0.3%) and $p < 0.001$. The authors suggest that IMT findings and efficacy of treatment with pravastatin in this study should be limited to children with FH.

The efficacy results of this study were similar to others. At the end of 48 weeks, patients treated with simvastatin showed statistically significant reductions in LDL- cholesterol levels (-41%), TC (31%), APOB (-34%), very low-density lipoprotein (VLDL) cholesterol (-21%) and triglycerides (TG) (-9%).[11] In the study of atorvastatin versus placebo, there was an average reduction in LDL-cholesterol (40%), TC (32%), TG (12%) and APOB (34%) in the atorvastatin group compared to the placebo group ($p < 0.001$). The increase

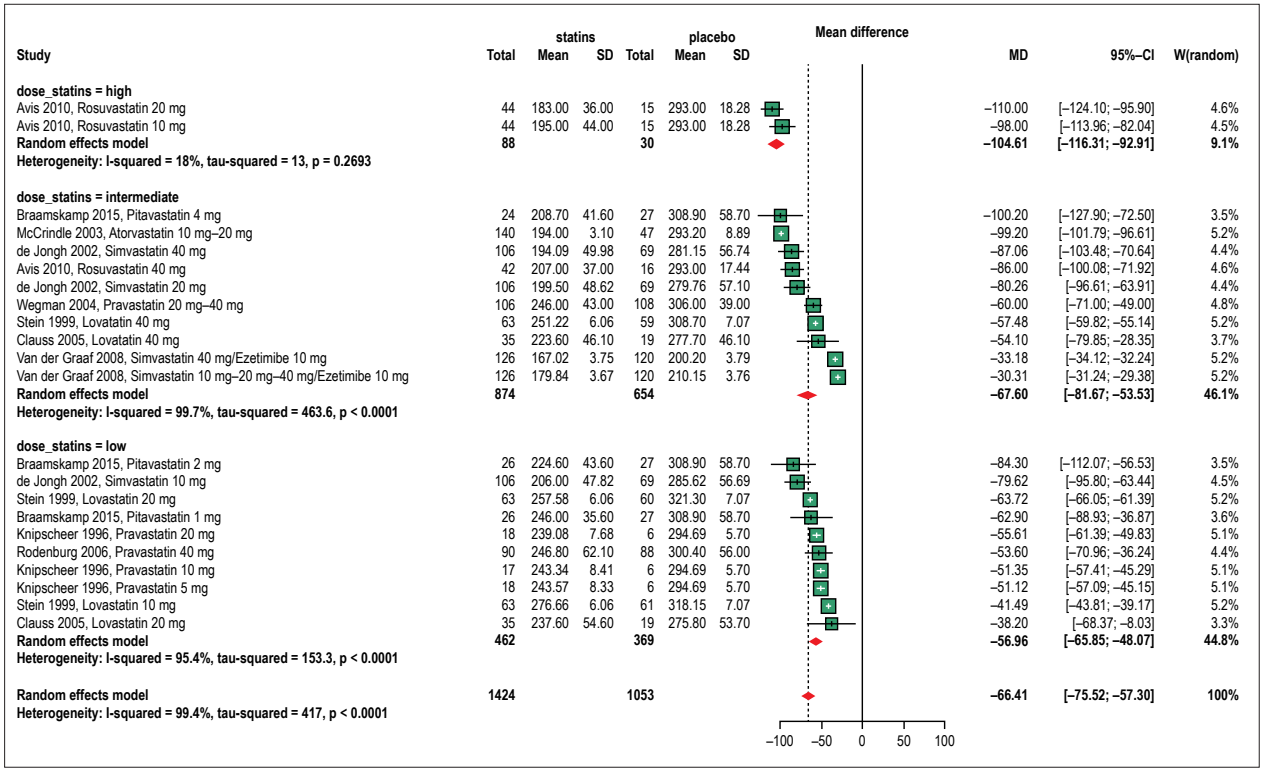

Figure 2 – *Forest plots showing the effect of statin therapy (high, intermediate and low dose) on total cholesterol (TC) levels.*

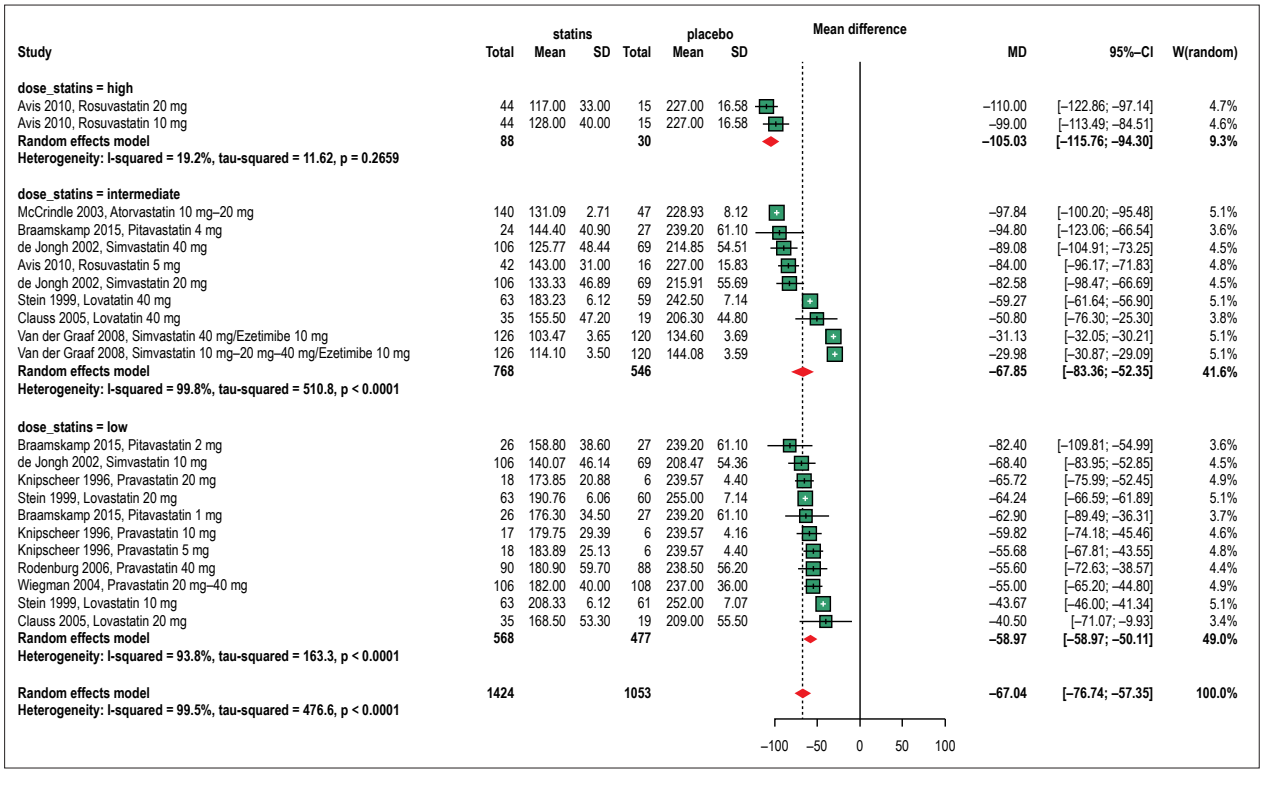

Figure 3 – *Forest plots showing the effect of statin therapy (high, intermediate and low dose) on low-density lipoprotein (LDL) cholesterol levels.*

in HDL-cholesterol levels (2.8%) was also statistically significant.[16] In the study comparing rosuvastatin versus placebo, changes in LDL-cholesterol, TC, and APOB levels were statistically significant compared to placebo for all three doses (5 mg, 10 mg, 20 mg) ($p < 0.001$).[19]

Most of the studies included in this meta-analysis focused on the effect of statins on LDL. As seen in these results in children with FH, statins are effective in lowering LDL-cholesterol and TC levels. The effectiveness of reducing the LDL-cholesterol and TC levels with statin treatment is consistent in all RCTs analyzed. The effects of statins on other levels of lipids, such as HDL-cholesterol and TG are not so consistent; that is why the results are not extrapolated to the entire pediatric population. Patients without FH must focus on changes in lifestyle first, before relying on a drug to improve their cholesterol levels.

The included studies had essential elements that determine the quality of studies, which are important for the generation of evidence. Conducting a randomized controlled trial in the pediatric population is not as common as in adults. However, there is a lack of a recognized methodology to assess the quality of pediatric studies. That is the reason why we used the clinical testing format, as used in the adult population.

The adverse event profile of a pharmacological agent is a particular concern in pediatric population. Thus, in general, data suggest that the risk of adverse events in children treated with statins are similar to those observed in adults treated with statin, at least in the short term. Studies evaluated the effect of statin therapy on clinical outcomes, hormonal status, biochemical measures of growth, nutrition and liver or kidney toxicity. For most of these parameters, there was no statistically significant difference between treatment and placebo groups. There were no reports of serious adverse events. Hepatic transaminase elevation and Creatine-phosphokinase, which are of particular concern in adults, did not differ in the studied groups.

Current guidelines for FH indicate pharmacological treatment in affected subjects between 8 to 10 years and in younger children only with extreme elevation of LDL-cholesterol and associated risk factors, having risk for premature CAD.[30-33] Statins can be considered as first line treatment in children with HeFH and having an increase of LDL, after changes in diet and lifestyle. Response to treatment with statins should be assessed in 1 to 3 months after the start of therapy and periodically thereafter according to guidelines.[34] Children treated with statins should also be frequently monitored for adverse events (for example, hepatic transaminases, creatine kinase, liver enzymes) and statins are contraindicated during pregnancy.[34] There is also a need for further studies to evaluate the safety of these pediatric patients throughout their lives. The results for the growth and sexual development should be considered in children under 10 years of age. Future studies should seek to include pediatric patients with secondary forms of dyslipidemia and start examining the combination of therapy in children.

However, we found some limitations in these studies. One of them is the duration of statin therapy in the included studies, which ranged from 8 to 104 weeks, whereas in the clinical practice, patients with FH are subjected to continue with statin treatment for the rest of their lives, once the therapy was initiated.[35] Another limitation of these studies is the conduction only in children with FH and children with secondary dyslipidemia were not included.[35] They also do not include information on the use of high doses of statins, such as those used in adults. Besides, the long-term efficacy data also are not available and remain unknown.

Braamskamp et al.[36] published the first study evaluating hormonal concentrations of FH subjects before and 10 years after the start of treatment with statins, compared with their unaffected siblings, which minimizes genetic and environmental variation between groups. Their results demonstrated that the hormone concentrations in patients with FH are among the reference range compared to their unaffected siblings.

Conclusion

Based on the evidence available in this meta-analysis, statins significantly reduced LDL-cholesterol in children with HeFH. However, there is no data regarding long-term outcomes of both effectiveness and safety.

Author contributions

Conception and design of the research: Radaelli G, Pellanda LC; Acquisition of data: Radaelli G, Sausen G; Analysis and interpretation of the data: Radaelli G, Cesa CC, Pellanda LC; Statistical analysis: Radaelli G, Cesa CC; Writing of the manuscript: Radaelli G, Sausen G, Cesa CC, Santos FS; Critical revision of the manuscript for intellectual content: Portal VL, Neyeloff JL, Pellanda LC.

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 article is part of the thesis of Doctoral submitted by Graciane Radaelli, from Programa de Pós Graduação - Fundação Universitária de Cardiologia (IC-FUC).

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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Appendix I

PuBMed Search Strategy

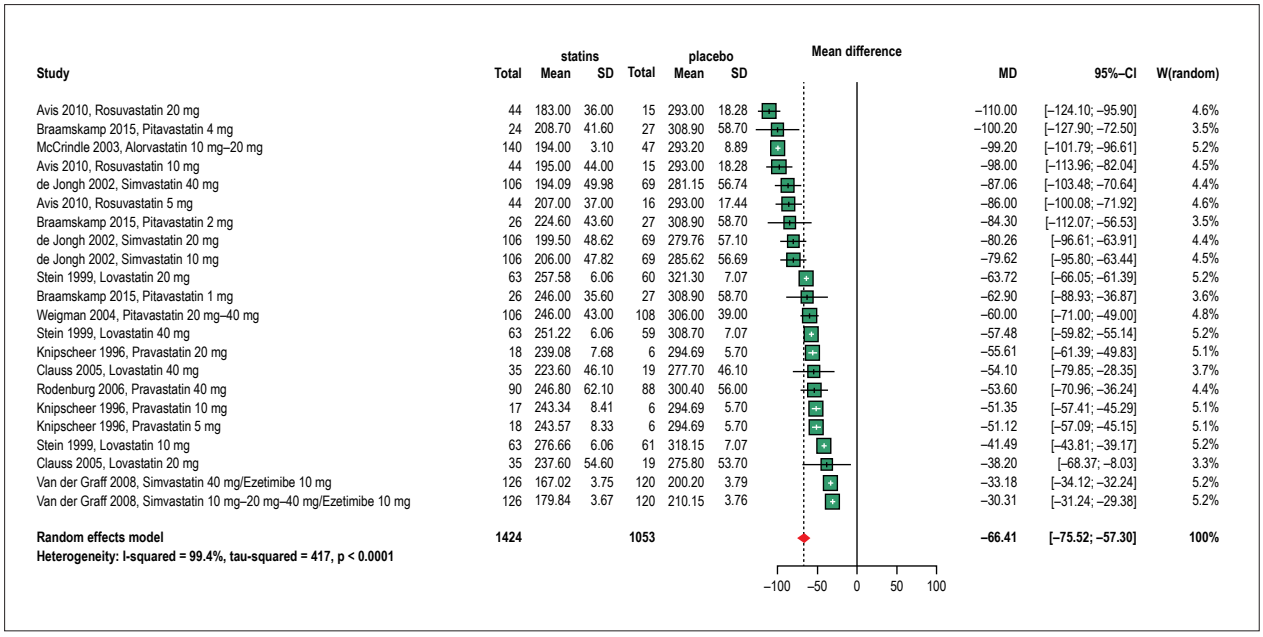
#1. Search (Child OR Adolescent)

#2. Search (Hypercholesterolemia OR Statin OR Dyslipidemias OR Cholesterol OR Hydroxymethylglutaryl-CoA Reductase inhibitors)

#3. Search (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation [mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR ("latin quare"[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR comparative studies[mh] OR evaluation studies[mh] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control* [tw] OR prospectiv*[tw] OR olunteer*[tw]) NOT (animal[mh] NOT human[mh])

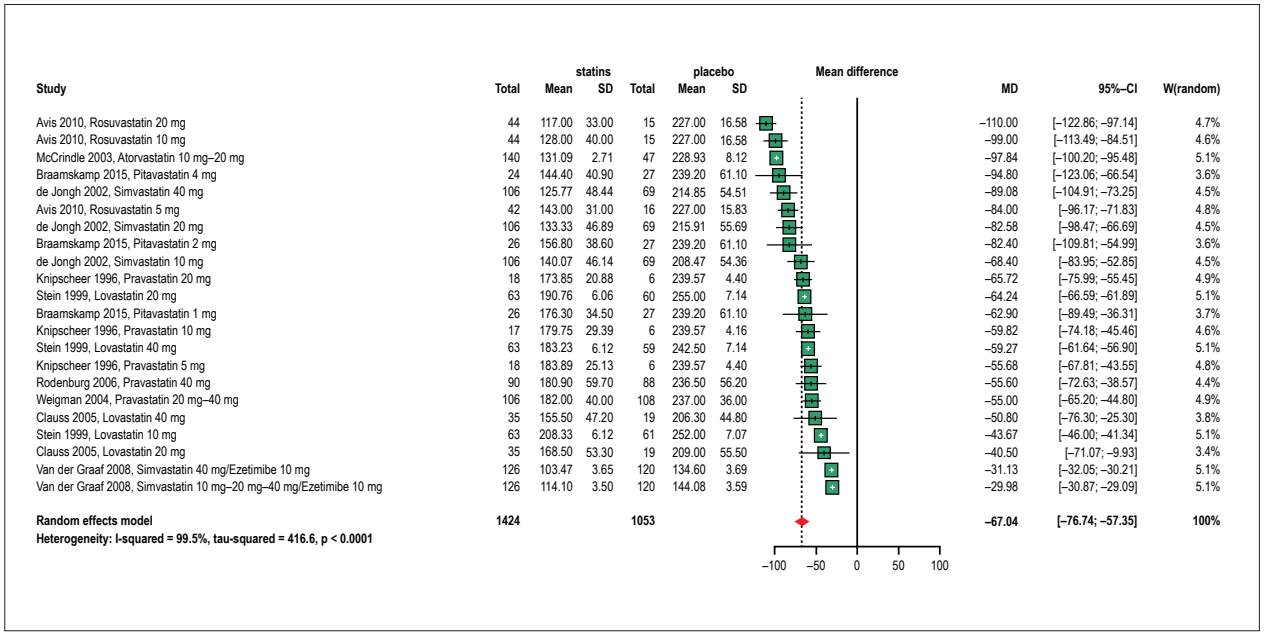
#4. Search (#1 AND #2 AND #3)

Appendix II



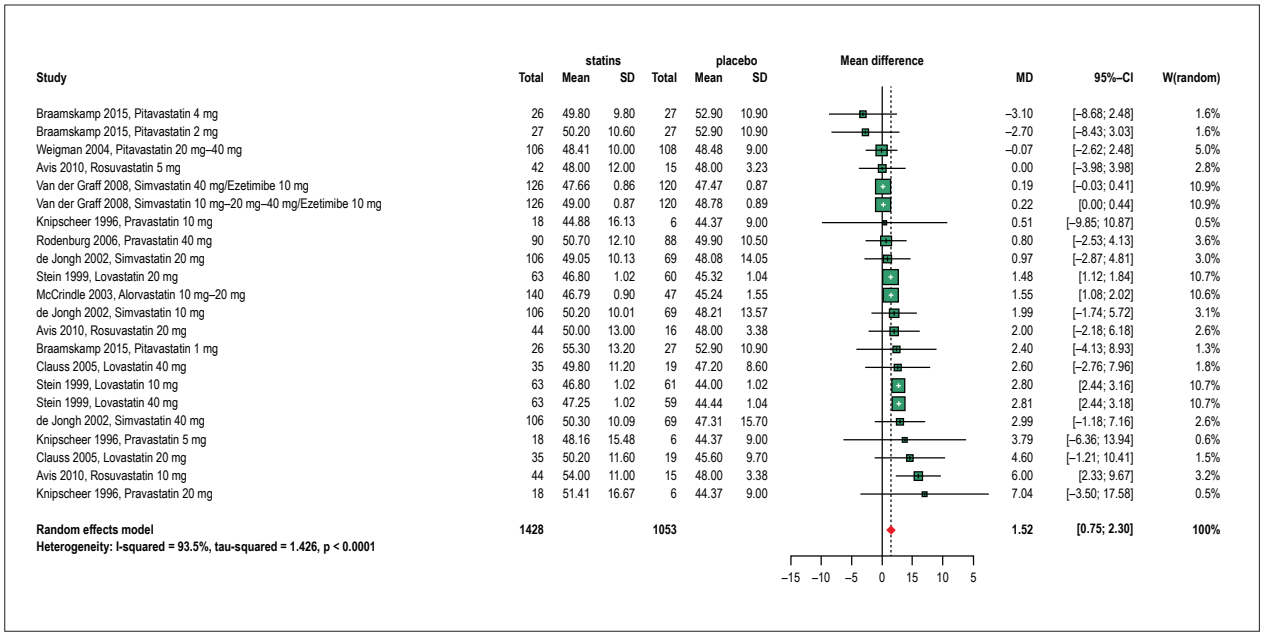
Appendix 2 – *Forest plots showing the effect of statin therapy on total cholesterol (TC) levels.*

Appendix III



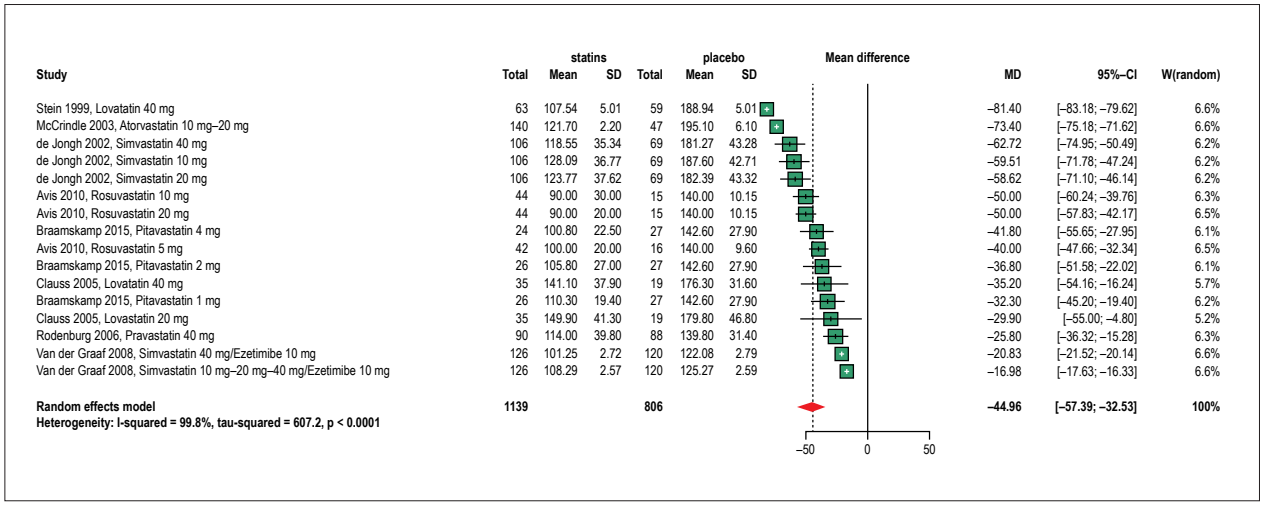
Appendix 3 – *Forest plots showing the effect of statin therapy on low-density lipoprotein (LDL) cholesterol levels*

Appendix IV



Appendix 4 – *Forest plots showing the effect of statin therapy on high-density lipoprotein (HDL) cholesterol levels.*

Appendix V



Appendix 5 – *Forest plots showing the effect of statin therapy on apolipoprotein B levels.*

Can Non-Pharmacological Treatment Promote Additional Benefit for Children with Familial Hypercholesterolemia Treated with Statins?

Luiza Antoniazzi

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Short Editorial related to the article: Statin Treatments And Dosages In Children With Familial Hypercholesterolemia: Meta-Analysis

Familial hypercholesterolemia (FH) is described as an autosomal dominant hereditary disease characterized by elevation of total cholesterol and low density lipoprotein (LDL-c).[1]

FH is considered a major modifiable risk factor for the development of atherosclerosis and cardiovascular disease (CVD).[2] The early institution of lipid-lowering therapy and its lifelong maintenance are important aspects in the prevention of premature CVD and the risk of death in this population, increasing life expectancy in these patients.[3]

The current guidelines[4-7] recommend, pharmacological treatment for individuals aged 8 to 10 years. It should only be used for younger children with extreme elevation of LDL-c and associated risk factors. Radaelli et al.[8] performed a meta-analysis with ten randomized clinical trials conducted with children and adolescents from 8 to 18 years of age who underwent therapy with statins for FH. They showed the statins significantly reduced LDL-c in children with FH.

This study contributed to the evaluation of the effectiveness of lipid-lowering therapy in children with FH. However, there are no data on efficacy and safety in the long term. The included studies ranged from 12 to 104 weeks and considering that individuals with FH will need lifelong treatment, it is extremely important that safety studies of different types of treatment be carried out with longer study times.

The importance of drug treatment to avoid unfavorable outcomes in individuals with FH should be considered, but care should be broader and include good detection strategies as well as the implementation of non-pharmacological treatment.

The most cost-effective strategy for FH diagnosis is the screening of mutations in first degree relatives of individuals identified with FH.[9] In screening rounds, first degree relatives identified with FH become the index cases and their relatives are traced. This is referred to as cascading genetic screening. The molecular diagnosis of FH can, in addition to identifying affected relatives, allows them to receive the adequate treatment. Children are the biggest beneficiaries of the screening program as they have the possibility of initiating treatment before high cholesterol levels have caused a high degree of atherosclerosis.[3]

The consensus of the European Atherosclerosis Society[4] and the I[st] Brazilian Guideline for Familial Hypercholesterolemia[1] is that dietary treatment is required in addition to pharmacological treatment of patients with FH.[10,11]

The nutritional treatment is of great importance, as it helps to control classical and additional factors. Adequate eating habits, which may help reduce LDL-c levels in people with FH, are also important in treating and preventing additional risk factors such as systemic arterial hypertension, diabetes, obesity, oxidative stress, inflammatory process, and endothelial dysfunction, involved in the complex multifactorial mechanism of atherosclerosis.[4,12,13]

Among the dietary recommendations for FH, one of the few tested with a sample of individuals with this genetic disease is the possibility of reducing total cholesterol and LDL-c with phytosterol consumption, with most of the evidence coming from samples of children.[14,15]

The study by Radaelli et al.[8] has great relevance and reinforces the need for constant searches for advances in treatment of FH individuals from childhood. Future studies should be conducted drug treatment and lifestyle changes jointly, considering dietary patterns and levels of physical activity, also little studied in children with FH. Adopting the best lifelong treatment may have benefits beyond lipid control, for example controlling comorbidities such as inflammation, obesity, and changes in blood pressure.

Keywords

Child; Dietary Fats; Diet; Hyperlipoproteinemia Type II; Hypercholesterolemia/blood; Statins/therapy; Hydroxymethylglutaryl-CoA Reductase Inhibitors.

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Paroxysmal Atrial Fibrillation Catheter Ablation Outcome Depends on Pulmonary Veins Anatomy

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Abstract

Background: Pulmonary veins (PV) are often the trigger to atrial fibrillation (AF). Occasionally, left PVs converge on a common trunk (LCT) providing a simpler structure for catheter ablation.

Objective: To compare the clinical characteristics and outcomes of ablation in paroxysmal atrial fibrillation (PAF) of patients with or without LCT.

Methods: Case-control study of patients undergoing first-ever catheter ablation procedure for drug refractory PAF. 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 patients with or without LCT (LCT x n-LCT), adopting a level of statistical significance of 5%. The primary endpoint associated with efficacy was lack of atrial arrhythmia over the follow-up time.

Results: One hundred and seventy two patients with PAF were included in the study, 30 (17%) LCT and 142 (83%) n-LCT. The clinical characteristics, comorbidities, symptoms scale and risk scores did not differ between the groups. There was AF recurrence in 27% of PAF patients in the n-LCT group and only 10% of patients in the LCT group (OR: 3.4 p: 0.04) after a follow-up of 34 ± 17 months and 26 ± 15 months respectively.

Conclusion: Patients with a LCT have a significantly lower recurrence rate when compared to patients without this structure. It is mandatory to report the results of AF catheter ablation as a PV anatomical variation function. (Arq Bras Cardiol. 2018; 111(6):824-830)

Keywords: Atrial Fibrillation/physiopathology; Arrhythmias, Cardiac; Catheter Ablation; Pulmonary Veins/physiopathology; Electrophysiologic Techniques, Cardiac.

Introduction

The electrical activity trigger responsible for triggering paroxysmal atrial fibrillation (PAF) is often located in the pulmonary veins (PV), so that the electrical isolation of the PVs is the therapeutic mainstem in the invasive treatment of this arrhythmia.[1-3]

In most patients, four PV reach the left atrium. However, previous studies suggest that PV anatomical variations are related to a higher incidence of AF.[4,5] The left common trunk (fusion of the 2 left PVs in a common trunk [LCT]) is the most common of the PV anatomical variations, occurring in 4 to 18% of patients undergoing catheter ablation.[6] However, it is not clear whether the presence of these anatomical variations changes the outcome and the recurrence rates in the invasive treatment of PAF. As LCT can be easily identified by computed tomography (CT), knowing the clinical outcome of ablation in this population may be relevant in clinical decision-making when an ablative procedure is indicated. Therefore, the objective of this study was to compare the clinical characteristics and outcomes of patients undergoing PAF ablation with and without PV common left trunk.

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DOI: 10.5935/abc.20180181

Methods

Study design and participants

This is a single-center, case-control study conducted between January 2011 and December 2015, with the inclusion of patients (≥ 18 years old) undergoing the first catheter ablation procedure to treat PAF that does not respond to antiarrhythmic drugs with a minimum follow-up of 12 months. The information was collected and indexed in a digital database aimed at AF ablation (SysCardio® software). Along with CT, the presence of the LCT was confirmed through

a 3D atrial model constructed during the procedure with an electroanatomic mapping system by (NavX®). Patients with persistent or long-term persistent AF, patients with previous ablations and AF of reversible etiology, hypertrophic cardiomyopathy, rheumatic heart disease, congenital heart disease and prior catheter ablation were excluded from the sample (Figure 1).

Procedures and ablation protocol

All procedures were performed under general anesthesia, orotracheal intubation, and invasive monitoring of blood pressure by radial or left femoral puncture, under the care of an anesthesiologist. Transseptal punctures were performed with echocardiography assistance, which was maintained throughout the procedure.

All patients underwent circumferential isolation of the PVs through a 3.5-mm tip irrigated catheter ablation without contact force measurement, using radiofrequency energy with applications of up to 35 watts and 43°C for 30-45 seconds, and demonstration of electrical VPs entrance and exit block in relation to the left atrium at the end of the isolation. After the demonstration of entrance and exit block, patients received 18 mg of IV adenosine bolus. In cases of electrical reconnection, new mapping-guided radiofrequency applications were performed until adenosine-mediated reconnection no longer occurred. The applications in the left atrium posterior wall were performed with 20 watts for up to 15 seconds, and were interrupted in case of increased esophageal temperature > 38°C. Applications to the left atrium posterior wall were monitored through an esophageal thermometer with multiple coated sensors (Circa®), and were stopped whenever there was a change in esophageal temperature above 38°C. During all procedures performed with an electroanatomical mapping system based on thoracic impedance (EnSite Navx - Abbott®), IV heparin *bolus* of 100mg/kg was performed, followed by continuous infusion to keep activated coagulation time between 350 and 450s.

Definitions of anatomical variants of the pulmonary veins

The vein anatomy was defined as normal when two right PV and two distinct left PV were viewed, and the presence of the left common trunk was defined when the two left PV coalesced on a path > 10 mm from before insertion into the left atrium in a common ostium (Figure 2).

Clinical follow-up

After the procedure, patients remained on antiarrhythmic drugs (propafenone, sotalol or amiodarone depending on the preference of the attending physician) for 1 month, and anticoagulant for at least 3 months regardless of CHA_2DS_2-VASc. There was a clinical follow-up of 1, 3, 6 and 12 months after the procedure with ECG and at least two continuous 5-day electrocardiographic *(Holter)* monitoring throughout the whole clinical follow-up. At the 10th week after ablation, patients were encouraged to undergo a 5-day Holter. Any atrial arrhythmia greater than 30 seconds duration documented after 1 month of *blanking period* indicated arrhythmia recurrence.[2] Symptoms severity before ablation and during any recurrences was characterized by the *Canadian Cardiovascular Society Severity of Atrial Fibrillation* (CCS-SAF) score, and the score of atrial fibrillation related symptoms of the *European Heart Rhythm Association* (EHRA).[7]

Statistical analysis

Patient characteristics and procedures, recurrence rates after a single procedure, and complication rates were compared according to the groups: LCT (case) or non-LCT (control). The sample size was determined by a 1: 4 ratio for cases and controls with study power of 80%.

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 Shapiro-Wilk test. Categorical variables were described by absolute number and percentages in relation to the total sample, and were compared using the χ^2 test or Fisher's exact test. The level of statistical significance adopted was 5%. Kaplan-Meier curve was used to evidence the relapse-free rates over the follow-up time, and Log-Rank test was used to evaluate the difference between the groups (LCT x non-LCT). Statistical analysis was performed using IBM SPSS Statistics Editor software, version 22.0.

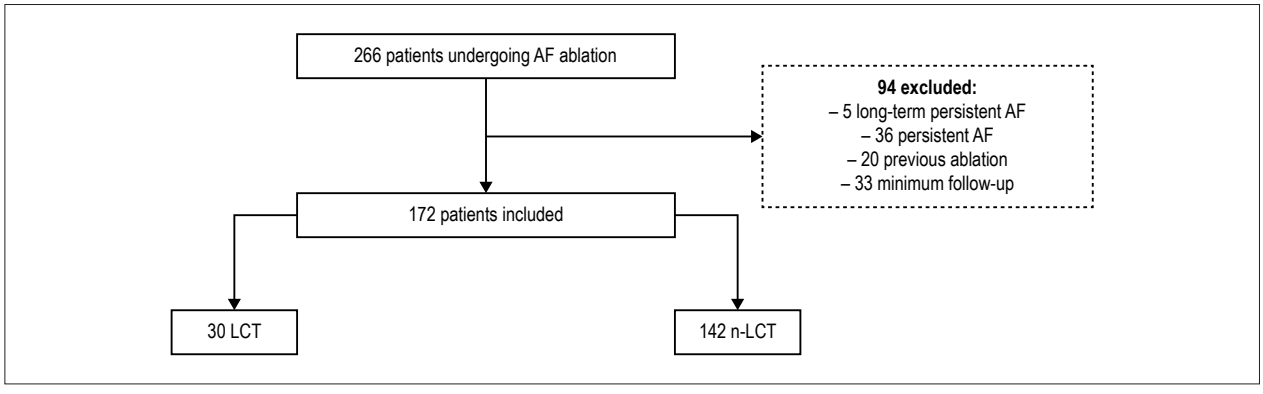

Figure 1 – *Flowchart study: patients undergoing ablation of AF categorized by presence of left trunk of the pulmonary veins.*

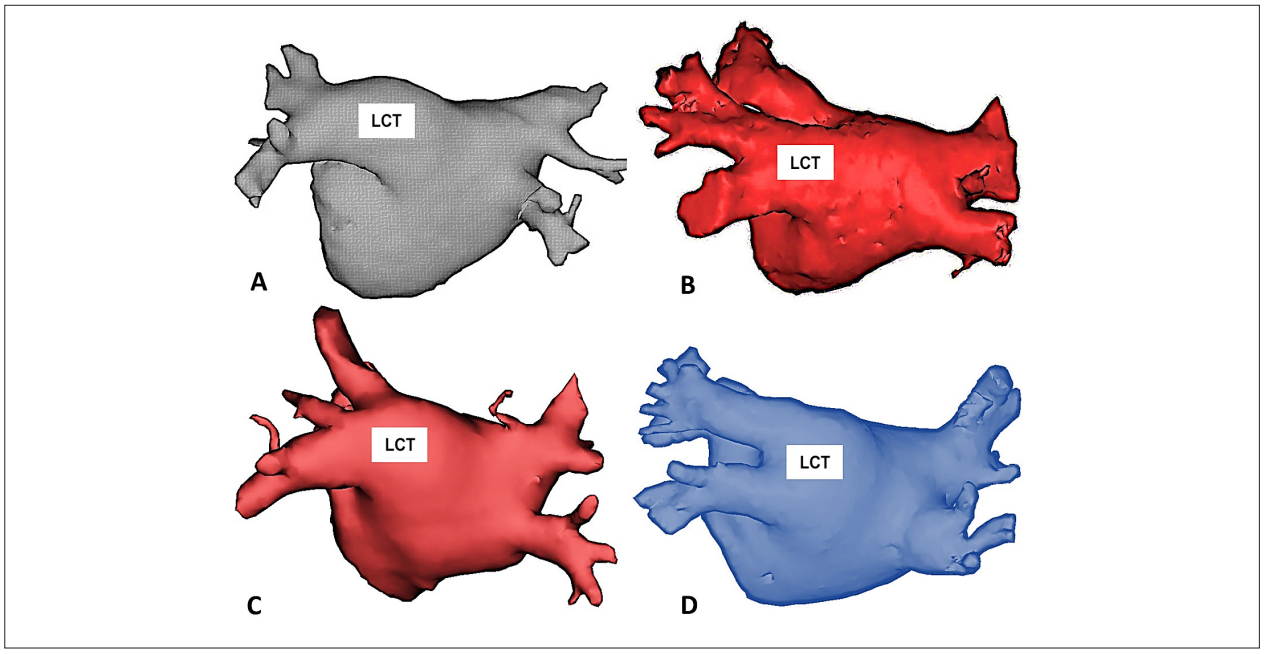

Figure 2 – *Examples of patients with Common Trunk of the Left Pulmonary Veins (LCT) obtained from Computed Tomography performed before the catheter ablation procedure. In all cases, the left pulmonary veins coalesce before insertion into the left atrium and the minimum distance between the common ostium and the beginning of the bifurcation between the lower and upper branches of the common trunk is 10 mm. All the examples are in the posterior-anterior projection highlighting the posterior wall of the left atrium.*

Results

One hundred and seventy-two patients were enrolled between 2011 and 2015 in a single center in Brazil. Thirty (17%) had LCT. There was no difference in follow-up time between cases and controls, with all patients completing a minimum follow-up of 12 months.

Table 1 summarizes the clinical characteristics of patients with LCT and non-LCT undergoing PAF ablation during the study. Variables such as age (58 ± 10 vs 62 ± 11 years), gender (71% vs 69% men), BMI (28 ± 4 vs 27 ± 3.5 kg/m^2), LVEF (65 ± 8% vs 66 ± 9%), diameter of the left atrium (38 ± 5 mm vs. 39 ± 6 mm) presented no differences between the non-LCT and LCT groups, respectively. The prevalence of other comorbidities including hypertension, diabetes mellitus, coronary artery disease and risk score (CHA_2D_2-VASc) for stroke were similar among the samples. There was no significant difference in the severity of symptoms associated with AF (CCS-SAF and EHRA scores) between cases and controls. Four percent of the patients had a previous history of stroke.

Procedure efficacy and safety

Table 2 shows a relapse rate for AF of 27% and 10% in the non-LCT and LCT groups (OR: 3.4; p: 0.04), after a follow-up time of 34 ± 17 and 26 ± 15 months respectively for cases and controls. Kaplan-Meier curve (Figure 3) highlights the lower proportion of relapse in the LCT group during the study.

There were no major complications (TIA / stroke / Peripheral embolism, atrial-esophageal fistula or cardiac perforation / tamponade requiring surgery) related to procedures and / or hospitalization. Among the minor complications (inguinal hematoma, retroperitoneal bleeding, pseudoaneurysms or AV fistulas, PV stenosis, pericardial effusions or phrenic nerve palsy) there were 4 pseudoaneurysms and 1 inguinal hematoma, all in the non-LCT group, treated clinically without surgical intervention (Table 2). There were no deaths or reports of esophageal fistula during the study follow-up time.

Discussion

The durability of PVs electrical isolation is directly related to the efficacy of the percutaneous treatment of AF, so that PVs electrical reconnection seems to be the main mechanism for post-ablation AF relapse.[2,7-10] Our study suggests that pulmonary vein common left trunk patients have a more favorable clinical outcome after catheter ablation, with a clinical relapse around 10%. These results can be obtained without comprising procedure safety.

LCT, when present, has been indicated as the predominant origin of the triggers of AF.[11] In the past, when the need for ablation of the 4 PV in the same procedure was still discussed, and maneuvers were used to trigger AF, some authors suggested that when AF originated in LCT, it was not necessary to perform right PV ablation.[12,13] Over the years, this concept proved to be inadequate because some recurrences occurred from foci in the right PVs.[2,8] For this reason, currently the information on the presence of the left common trunk helps more in the indication of the procedure rather than in the definition of the ablation strategy, which, unless otherwise indicated, will include the ablation of the LCT and the right PVs.

Table 1 – Clinical characteristics of patients undergoing AF ablation, categorization by presence of common trunk of the pulmonary veins

Variables	n-LCT (n = 142)	LCT (n = 30)	p-value
Age (years)	58.1 ± 10	62.5 ± 11	0.11
Gender (Male)	101 (71)	20 (69.2)	0.64
BMI	27.6 ± 4.5	26.6 ± 3.5	0.37
LV ejection fraction - %	64.4 ± 8.7 (33 – 86)	66.2 ± 8.5 (46 – 77)	0.33
Diameter of the LA - mm	38 ± 5.2 (27 – 53)	38.7 ± 6.3 (31 – 50)	0.76
Comorbidities			
SAH	82 (58.3)	18 (61.9)	0.75
DM2	16 (11)	4 (13.3)	0.54
CAD	30 (21)	4 (13.3)	0.63
Prior Stroke/TIA	6 (4.2)	1 (3.3)	0.86
CCF	10 (7)	3 (10)	0.41
CHA2DS2-VASc	1.49 ± 1.2	1.0 ± 1.9	0.49
AF - Symptoms			
CCS SAF score	2.07 ± 0.8	1.9 ± 0.8	0.46
EHRA score	2.04 ± 0.3	2.1 ± 0.5	0.33
Medications			
Statins	41 (28)	12 (40)	0.12
ACE or ARA Inhibitor	45 (31)	13 (42)	0.21
Antiarrhythmic medication	121 (85)	22 (73)	0.44

*Values with ± indicate mean and standard deviation; BMI: body mass index; LV: left ventricle; LA: left atrium; SAH: systemic arterial hypertension; CAD: coronary artery disease; Stroke / TIA: stroke / transient ischemic attack; CCS SAF: Canadian Cardiovascular Society Severity of Atrial Fibrillation scale; EHRA: European Heart Rhythm Association; ACE: angiotensin converting enzyme; AF: atrial fibrillation; ARA: Angiotensin receptor antagonist 2. Student's t test and χ^2 for independent samples. * p-value indicates a statistically significant difference at the level of 5%.*

Table 2 – Efficacy of procedures and complications categorized by presence of left common trunk of the pulmonary veins

Procedures	n-LCT (n = 142)	LCT (n = 30)	OR	p-value
AF relapse	39 (27)	3 (10)	3.4	0.04*
Follow-up time	34 ± 17	26 ± 15	-	0.37
Complications				
Pseudoaneurysm	4 (3)	0 (0)	-	0.55
Inguinal hematoma	1 (0.7)	0 (0)	-	0.86

*AF: atrial fibrillation; OR: Odds ratio; NA: not applicable; Student t test and χ^2 for independent samples. * p-value indicates a statistically significant difference at the level of 5%.*

In the present case-control/single-centered study of patients undergoing the first ablation procedure for PAF, it is suggested that - in comparison to the standard anatomy - the presence of the LCT favors the results in the percutaneous treatment of AF, with lower recurrence rate and low complication rates in a long-term analysis. These findings highlight the importance of knowing PVs anatomy for the efficacy and safety of AF ablation.

The definition of LCT (approximately 20% of the sample) deserves discussion. In general, the diagnosis is quite simple, through detomography or cardiac resonance. In our study, we chose an unequivocal definition of common trunk, that is, when there was a minimum distance of 10 mm between the common ostium of the left PVs and the bifurcation of their left lower and upper branches. Thus, the diagnosis of LCT was intentionally simplified. This aspect has important clinical relevance. When identifying LCT, the clinical decision for catheter ablation can be simplified because the patient with this type of anatomical change has an excellent clinical result after ablation. In fact, there was no comparison between ablation and the use of antiarrhythmic drugs in this subgroup, but it is worth remembering that all patients ablated in our study were unresponsive to antiarrhythmic drugs.

This observation has an important practical effect. In clinical practice, it is not uncommon that patients with AF and anatomically normal heart by transthoracic echocardiography undergo numerous diagnostic tests. As a rule, these patients undergo multiple stress tests,

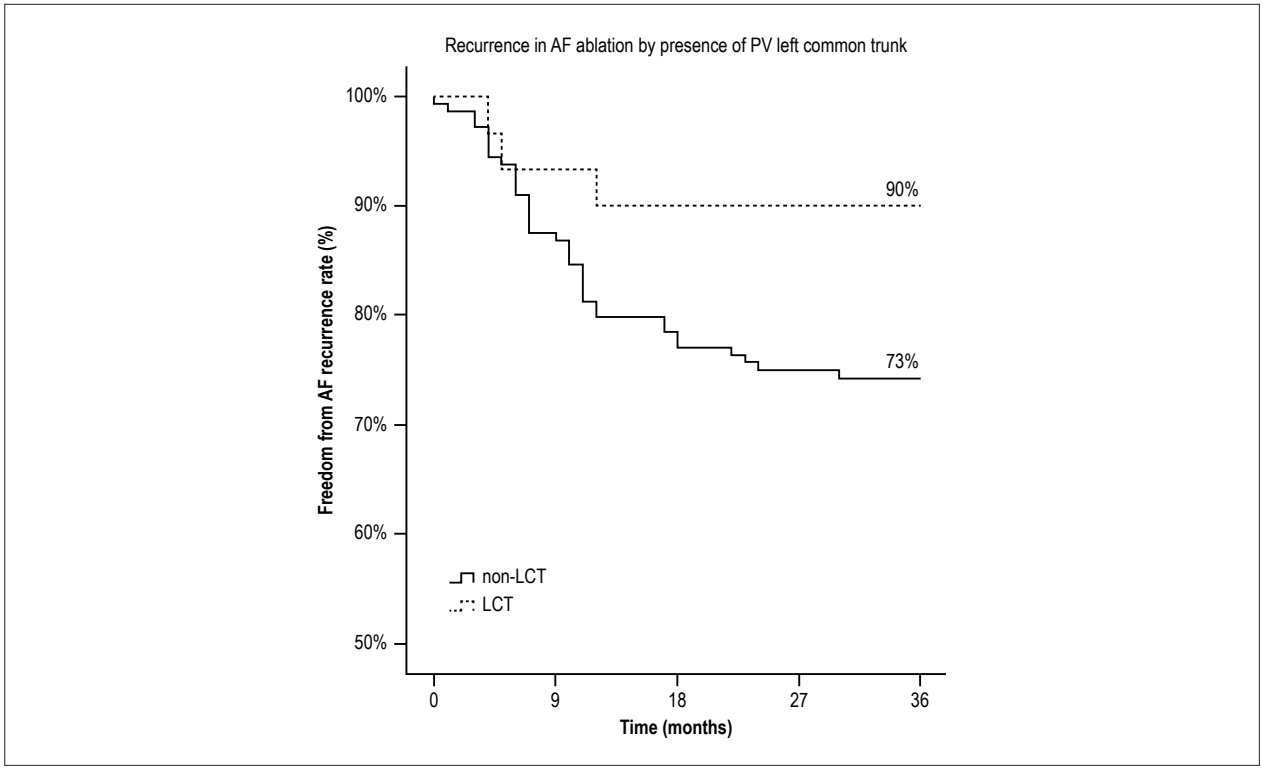

Figure 3 – *Kaplan-Meier curves for AF relapse after catheter ablation categorized by the presence of the left common trunk of the pulmonary veins; Log-rank test for comparison of recurrence curves between groups (LCT x n-LCT). p-value = 0.04. AF: atrial fibrillation; PV: pulmonary veins.*

24-hour *Holters,* and even coronary angiography with the intention of diagnosing a possible trigger for AF. Infrequently, however, these patients undergo heart CT/MRI that, if properly performed, could define the pulmonary venous anatomy and assist in the clinical decision facilitating the indication of catheter ablation.

Our study is not aligned with evidence that the presence of PVs anatomical variations (number and disposition) would be associated with a higher and more advanced degree of atrial remodeling from the electrical and structural point of view and, consequently, worse post-ablation outcome.[4,14,15] In our results, the relapse rate in the LCT group was 3 times lower than in the non-LCT group, with patients' clinical characteristics being similar and homogeneous in all analyzes.

From the technical point of view, the presence of LCT facilitates the manipulation and the contact of the ablation catheter in the left atrium. The simpler the manipulation, the better the contact with the region to be ablated. Recent studies have shown that the tissue-to-contact relationship during ablation is crucial for lesion formation and is linked to better outcomes.[16] Therefore, efficient tissue contact presumes a greater energy delivery through radiofrequency and formation of a more stable and homogeneous scar,[17] which would ultimately result in a longer lasting isolation of PVs. That way, other studies using cryoablation also presented a more favorable result in patients with LCT. In cryoablation studies, however, the presence of LCT was not related to a more satisfactory outcome when compared to patients without the structure.[18]

Limitations

The objective of this study was to describe the clinical characteristics and efficacy and safety outcomes in patients undergoing catheter ablation in the treatment of AF. This is a case-control study and, certainly, there are limitations. First, the sample size is small and may not be sufficient to detect differences between the two groups, particularly because of the low prevalence of LCT. Second, the presence of observation bias is recognized, since PVs anatomy is revealed during the procedure. Third, no detailed tool was used to assess symptoms in the presence of AF, but rather CCS-SAF and the EHRA score, which are generic scales for symptomatic evaluation. Despite this, the study provides an interesting perspective on the invasive treatment of AF in patients with LCT.

Conclusion

In our sample, patients with LCT who underwent the first catheter ablation procedure to treat PAF presented a lower rate of relapse compared to patients without this anatomical alteration. The research on LCT should be incorporated to the investigation of PAF patients because ablation is more effective in this group of patients.

Author contributions

Conception and design of the research, Acquisition of data, Critical revision of the manuscript for intellectual contente and Analysis and interpretation of the data: Odozynski G, Dal Forno ARJ, Lewandowski A, d'Avila A;

Statistical analysis, Obtaining financing e Writing of the manuscript: Odozynski G, 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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Paroxysmal Atrial Fibrillation Catheter Ablation of Pulmonary Veins: does Anatomy Influence the Outcome?

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Short Editorial related to the article: Paroxysmal Atrial Fibrillation Catheter Ablation Outcome Depends on Pulmonary Veins Anatomy

Atrial fibrillation (AF) is the most common cardiac arrhythmia found in clinical practice and a frequent cause of hospital admission. AF is associated with a 5-fold increased risk of stroke and an approximately 2-fold increased risk of death, in addition to also being associated with heart failure development.[1]

Approximately 20 years ago, the percutaneous radiofrequency ablation of the pulmonary veins (PVs) was described by Haissaguerre et al.[2] as an effective technique and curative treatment of paroxysmal AF (PAF). The initial technique of AF ablation was developed based on the observation that the electrical activity triggers (ectopic foci), responsible for causing PAF, are frequently located in the PVs. As a consequence, the initiation of PAF could be prevented through the ablation of these triggers.[2]

Subsequently, aiming to prevent potential procedure complications, such as PV stenosis, and also to improve its success rates, the PV ablation procedure was progressively modified, from the PV focal ablation technique to the segmental electrical isolation of the PV ostia, resulting in the predominant present-day technique of extended circumferential antral ablation of PVs (1 to 2 cm extended area from the PV ostia).[1,3]

Most of the available data[1,3] indicate that the circumferential antral ablation of the PVs is more effective than the ostial ablation of the PVs. The beneficial mechanisms of PV circumferential antral ablation are not fully established but are probably related to the isolation of the triggers in the PV antrum, the modification of the ganglionated plexi, or the interruption of AF initiation and/or maintenance mechanisms located within the PV antrum.[1,3]

The most frequent PV circumferential antral ablation technique uses radiofrequency energy, delivered point-by-point through an external irrigated-tip catheter, with the help of a three-dimensional, electroanatomical mapping system as a navigation guide and also for the creation of a visual record of the ablated sites.

More recently, irrigated catheters have become available, with contact force-sensing technology, which is able to measure the contact force intensity between the tip of the catheter and the myocardium, increasing the effectiveness of the radiofrequency ablation lesion in the myocardium, and reducing procedure complication rates.[1] Cryoablation, which uses a balloon-catheter to attain PV isolation, is an equally validated alternative technique.[1]

Currently, the shortcoming of the PV circumferential ablation is the AF recurrence during the first year after the ablation, an event typically related to the electrical reconnection of PVs to the left atrium.[1] Therefore, several lines of research are focused on identifying techniques and procedures that can provide a permanent electrical isolation of the PVs during the initial AF ablation procedure.

In this context, in the current issue of the Arquivos Brasileiros de Cardiologia, Odozynski et al.,[4] report the results of circumferential antral ablation of the PVs in PAF treatment, specifically comparing patients who had a common trunk of the left PVs (CTrL) versus those without CTrL.

An electroanatomical mapping system based on chest impedance was used in all procedures and patients underwent circumferential isolation of the VP antrum by delivering radiofrequency with an irrigated-tip catheter but without monitoring the contact force, aiming at obtaining entrance and exit block into the PVs.

In the present study, in agreement with the world's literature, approximately 17% of the patients had a CTrL. It should be emphasized that during the medium-term clinical follow-up, a lower recurrence rate of AF was observed in patients with CTrL when compared to patients without CTrL.[4]

The current study has the merit of providing a timely overview of the complexity found in the present-day percutaneous ablation of PVs, discussing the implications that PV anatomy can have on PAF ablation outcome. As reported in the study, four pulmonary veins reach the left atrium in most patients. The CTrL, defined as the fusion of the 2 left PVs into a common trunk, is the most common anatomical variation of the PVs, occurring in 4% to 18% of patients undergoing AF ablation.[5]

As pointed out by the authors, the possible reason for patients with CTrL to show a lower recurrence rate of PAF could be related to the fact that it is easier to handle and attain better contact between the ablation catheter and the left atrium in patients presenting with CTrL.[4] As previously reported,[1,3] the intensity of the contact force between the ablation catheter and the myocardium is crucial for the radiofrequency lesion formation and has been associated with longer-lasting PV isolation and better clinical outcomes.

Furthermore, as already has been discussed, circumferential antral ablation of the PVs is more effective than the ostial ablation of the PVs, probably related to the isolation of the triggers in the antrum of the PVs, modification of the ganglionated plexi, or the interruption of AF initiation and/or maintenance mechanisms located within the PV antrum.

Keywords

Heart Failure; Arrhythmias, Cardiac; Catheter Ablation; Pulmonary Veins.

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Serum Uric Acid Levels are Associated with Cardiometabolic Risk Factors in Healthy Young and Middle-Aged Adults

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Abstract

Background: Observational studies have highlighted an association between serum uric acid (SUA) levels and cardiovascular risk factors. Despite the growing body of evidences, several studies were conducted in older individuals or in carriers of diseases susceptible to affect SUA levels and cardiometabolic risk markers.

Objective: To evaluate the relationship of SUA with body adiposity, metabolic profile, oxidative stress, inflammatory biomarkers, blood pressure and endothelial function in healthy young and middle-aged adults.

Methods: 149 Brazilian adults aged 20-55 years, both sexes, underwent evaluation of body adiposity, SUA, fasting glucose and insulin, lipid profile, malondialdehyde (MDA), high sensitivity C-reactive protein (hs-CRP), adiponectin, blood pressure and endothelial function. Endothelial function was assessed by the reactive hyperemia index (RHI) derived from peripheral arterial tonometry method. Participants were allocated in two groups according to SUA levels: control group (CG; n = 130; men ≤ 7 mg/dL, women ≤ 6 mg/dL) and hyperuricemia group (HG; n = 19; men > 7 mg/dL, women > 6 mg/dL). A P-value < 0.05 was considered statistically significant.

Results: After adjustment for confounders, participants in HG compared with those in CG displayed higher body mass index (BMI): 34.15(33.36-37.19) vs.31.80 (26.26-34.42) kg/m^2,p = 0.008, higher MDA: 4.67(4.03-5.30) vs. 3.53(3.10-4.07) ng/mL, p < 0.0001 and lower RHI: 1.68 ± 0.30 vs. 2.05 ± 0.46, p = 0.03). In correlation analysis adjusted for confounders, SUA was positively associated (p < 0.05) with BMI, waist circumference, LDL-cholesterol, triglycerides and MDA, and negatively associated (p < 0.05) with HDL-cholesterol, adiponectin and RHI.

Conclusions: This study suggests that in healthy young and middle-aged adults higher SUA levels are associated with higher body adiposity, unfavorable lipid and inflammatory phenotype, higher oxidative stress and impaired endothelial function. (Arq Bras Cardiol. 2018; 111(6):833-840)

Keywords: Uric Acid/metabolism; Oxidative Stress; Inflammation; Endothelium/ dysfunction; Adults.

Introduction

Cardiovascular diseases (CVD) are the leading causes of death in the world. According to World Health Organization, ischemic heart disease and stroke together accounted for 15 million deaths in 2015.[1] Therefore, it is important to identify early and cost-effective markers of CVD risk.

Uric acid is the final product of endogenous and dietary purine metabolism.[2] In several cross-sectional and longitudinal observational studies, elevated serum uric acid (SUA) levels have been associated with increased risk for cardiovascular events and mortality, as well as with cardiovascular risk factors such as hypertension, obesity, metabolic syndrome, insulin resistance and dyslipidemia.[3] Increased SUA concentration has also been positively correlated with surrogate markers of CVD: impaired endothelial function, increased carotid intima-media thickness and aortic stiffness.[4-11]

It is noteworthy that the majority of the studies aimed at evaluating the relationship of SUA with vascular function and/or cardiometabolic markers were conducted in postmenopausal women, older individuals and/or in individuals with renal impairment or CVD risk factors (ex. hypertension and diabetes).[3,5-11] Therefore, the participants included in many previous studies were more likely affected by a compromised cardiocirculatory and/or metabolic status which would represent a confounding factor in the association between SUA and cardiometabolic risk factors.

The purpose of this study was to evaluate the relationship of SUA with body adiposity, metabolic profile, inflammatory biomarkers, oxidative stress, blood pressure and endothelial function in a sample of healthy young and middle-aged adults.

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Methods

The present cross-sectional study was conducted at the Discipline of Clinical and Experimental Pathophysiology (CLINEX), located at Pedro Ernesto University Hospital, Rio de Janeiro State University.

Potential participants were recruited in the waiting room of the Departments of orthopedics, plastic surgery and gynecology. Inclusion criterion was age between 18-55 years.

Exclusion criteria were smoking; use of dietary supplements; use of medications susceptible to interfere in body weight, metabolic profile and blood pressure; use of α-adrenergic blocking agents; recent changes (within previous 6 months) in body weight (> 3 kg), in dietary intake and in intensity or frequency of physical exercise; diagnosis of diabetes mellitus, hypertension, dyslipidemia (with drug treatment) and kidney disease; clinical history of thyroid dysfunction, angina pectoris, peripheral vascular disease, peripheral neuropathy, heart failure, liver failure, chronic pulmonary disease, myocardial infarction and stroke; and finger deformity that would prevent the proper use of the sensors necessary to evaluate endothelial function. Pregnant or lactating women were not allowed into the study.

Subjects who met eligibility criteria and agreed to take part in the study were scheduled to arrive at the CLINEX Laboratory between 08:00 and 10:00h a.m. after a 12h fasting period and abstinence from alcohol for 3 days. While fasting, they were submitted to clinical, nutritional, laboratory and endothelial function evaluations.

Nutritional assessment

A semi-quantitative food frequency questionnaire (FFQ) was used to assess the usual dietary intake of energy, proteins, carbohydrates, lipids, cholesterol, fiber and calcium over the previous 6 months. This FFQ containing 80 items and usual portions was developed for the Brazilian population based on commonly consumed foods.[12] Alcohol consumption was considered when reported frequency equaled one or more time per week.

Height was measured by a stadiometer accurate to ± 0.5 cm and weight was obtained with a calibrated scale accurate to ± 0.1 kg (Filizola S.A., São Paulo, SP, Brazil) after participants without shoes and wearing light clothing, attempted to empty their bladder. Body mass index (BMI) was calculated using the standard equation (kg/m^2). Waist circumference (WC) was measured in the standing position midway between the lower margin of the last rib and the iliac crest at mid-exhalation. Hip circumference was measured at the widest point of the hip/buttocks area with the measuring tape parallel to the floor. Waist-to-hip ratio was determined by dividing WC (cm) by hip circumference (cm). Waist-to-height ratio was obtained by dividing WC (cm) by height (cm). The anthropometric measurements were taken twice and mean values were used in all analysis.

Laboratory parameters

Aliquots of plasma and serum were stored at -80°C as appropriate for laboratory determinations. Laboratory parameters included fasting circulating levels of uric acid, glucose, insulin, urea, creatinine, lipid profile, high-sensitivity C reactive protein (hs-CRP), adiponectin and malondialdehyde (MDA).

Serum concentration of uric acid was determined by enzymatic colorimetric method and urea and creatinine by kinetic method. Fasting plasma glucose was measured by hexokinase method. Fasting plasma insulin levels were determined by the enzyme-linked immunosorbent *assay* (ELISA) method using the commercially available specific kit (EMD Millipore Corporation Billerica, MA, USA). Insulin resistance status was assessed by homeostasis model assessment of insulin resistance (HOMA-IR) index, calculated as fasting insulin (μU/mL) × fasting plasma glucose (mmol/L)/22.5.[13]

Total cholesterol and triglycerides (TG) were assessed by enzymatic method (cholesterol oxidase-peroxidase and glycerol phosphate oxidase-peroxidase, respectively). High density lipoprotein (HDL)-cholesterol was determined by a direct method. Low density lipoprotein (LDL)-cholesterol was estimated by Friedewald's formula.[14]

Circulating levels of hs-CRP and adiponectin were chosen as markers of inflammatory state and their serum concentration determined respectively by turbidimetry (BioSystems, Barcelona, Spain) and ELISA (EMD Millipore Corporation Billerica, MA, USA). Serum levels of MDA, regarded as a *measure* of oxidative stress, were determined by ELISA method using a commercial kit (USCN Life Science Inc., Missouri, USA).

Blood pressure and heart rate

Blood pressure and heart rate were recorded after a resting period of 10 minutes by a calibrated automatic sphygmomanometer: OMRON® Model HEM-742INT (Omron Healthcare, Lake Forest, IL, USA).The first reading was discarded and the mean of 3 consecutive measurements, taken with a 3 – minute interval in the non-dominant arm, was used in the study. An appropriate arm cuff was used and the patient was instructed to stay seated, legs uncrossed, feet on the floor, leaning back in his chair with the arm at heart level, free from tight clothing, supported with the palm facing up and elbow slightly flexed.

Endothelial function

Endothelial function was evaluated by peripheral artery tonometry (PAT) method, using Endo-PAT 2000®, a finger plethysmographic device (Itamar Medical, Caesarea, Israel). This is a non-invasive method that offers the possibility of an easy and rapid assessment of vascular function in which data are analyzed independently of the examiner. Alterations in pulsatile arterial volume detected by PAT have shown good correlation with flow-mediated dilatation measurement.[15]

The measurements were performed through fingertip probes placed on both index fingers. A 5 min measurement was taken at baseline. Sequentially, arterial flow was occluded by a cuff applied to the non-dominant arm, and inflated to 60 mmHg above systolic blood pressure, but never below 200 mmHg. The cuff was rapidly deflated after a 5-min occlusion period, to allow reactive hyperemia. The following 5 min were also recorded. The other arm served as a control and the difference between the two arms was used by Endo-PAT 2000® software to automatically calculate the reactive hyperemia index (RHI).

Statistical methods

Participants were stratified into two groups according to their SUA levels: control group and hyperuricemia group. The control group was formed by men and women presenting SUA ≤ 7 and ≤ 6 mg/dL, respectively, whilst the hyperuricemia group consisted of men and women with SUA > 7 and > 6 mg/dL, respectively.

Mean values and standard deviations were used to summarize continuous variables with normal distribution, while median and interquartile interval were used to summarize variables with non-normal distribution. Normality was tested by the Shapiro-Wilk test. The differences between groups were analyzed using unpaired Student's t-test or Mann-Whitney test, as appropriate. Multiple regression was used to adjust for confounding factors, including age, gender and BMI. Categorical variables were expressed as percentage and compared by X^2 test.[2]

Pearson's or Spearman's correlation coefficient was performed to analyze the degree of association of SUA and anthropometric indices, laboratory variables, blood pressure and endothelial function among all participants. Partial correlations controlled for different confounders, including parameters of body adiposity, were also used.

Statistical analyses were carried out through STATA version 12.0 (STATA Corp., College Station, TX, USA) and a P-value < 0.05 was considered statistically significant. Sample size was determined by convenience.

Results

A total of 149 volunteers were included in the statistical analysis. Their average age was 35.02 ± 9.57 years, mean BMI of 31.17 ± 5.87 kg/m^2 and mean SUA levels were 4.67 ± 1.41 mg/dL. Participants in control group (n = 130) and in hyperuricemia group (n = 19) were comparable in age, gender, alcohol intake, physical activity, ethnicity and serum levels of urea and creatinine (Table1).

Dietary intake of energy and carbohydrates were significantly higher in hyperuricemia group than in control group, while the intake of monounsaturated fatty acids was significantly lower. However, after adjustments for age, sex and BMI these differences were no longer significant (Table 2).

Individuals in hyperuricemia group compared with those in control group exhibited significantly higher BMI even after controlling for age and sex, regarded as variables able to interfere with theses parameters (Table 3). WC was higher in hyperuricemia group after controlling for age but not after further adjustment for sex.

Comparative analysis of biochemical variables between hyperuricemia group and control group showed similar serum levels of glucose, insulin, HOMA-IR, total cholesterol, LDL-cholesterol, TG and hs-CRP. HDL-cholesterol was higher in control group only before adjustments for age, sex and BMI (Table 4). As compared to subjects in control group, those in hyperuricemia group still exhibited significantly lower levels of MDA, after adjustments for potential confounders (age, sex and BMI) (Table 4).

The evaluation of endothelial function revealed significantly lower values of RHI in the hyperuricemia group than in control group even after adjustments for confounders. Mean values of systolic and diastolic blood pressure were similar in both study groups (Table 4).

Considering data from all participants (n = 149), correlation analyses of SUA with laboratory variables, blood pressure and endothelial function revealed some significant associations (Table 5). SUA was directly associated with BMI, WC, glucose, total cholesterol, LDL-cholesterol, TG, MDA, systolic blood pressure and diastolic blood pressure. It was inversely correlated with HDL-cholesterol, adiponectin and RHI. After adjustment for age and sex the association of uric acid with BMI and WC remained significant. The positive associations of SUA with triglycerides and MDA, and negative associations with HDL-cholesterol, adiponectin, and RHI also remained significant after adjustment for age, sex and BMI (Table 5).

Discussion

In the present study carried out in healthy young and middle-aged adults, subjects with hyperuricemia, as

Table 1 – Comparison of participants' characteristics according to diagnosis of hyperuricemia

	Control group (n = 130)	Hyperuricemia group (n = 19)	p
Male sex, n (%)	19 (14%)	6 (32%)	0.06
Alcohol intake, n (%)	44 (34%)	9 (47%)	0.30
Physical activity, n (%)	19 (14%)	2 (13%)	0.93
Non-white ethinicity, n (%)	83 (64%)	14 (74%)	0.40
Age (years)	34.00 (27.00 - 42.50)	31.00 (27.00 – 43.00)	0.93
Serum uric acid (mg/dL)	4.32 ± 1.09	7.18 ± 0.67	< 0.001
Serum urea (mg/dL)	29.31 ± 17.02	29.73 ± 8.28	0.84
Serum creatinine (mg/dL)	0.80 ± 0.17	0.83 ± 0.16	0.56

Values as mean ± standard deviation for normal distribution or as median (interquartile interval) for not normal distribution or absolute values (%). p: Control group vs.Hyperuricemia group.

Table 2 – Comparison of participants' usual dietary intake according to diagnosis of hyperuricemia

	Control group (n = 130)	Hyperuricemia group (n = 19)	p	p*
Energy (kcal/day)	1647.5 (1250.3 – 2099.0)	2212.2 (1543.4 – 2934.4)	0.02	0.77
Protein (g/day)	75.7 (63.5 – 93 9)	77.6 (67.1 – 112.8)	0.73	0.80
Carbohydrates (g/day)	196.0 (143.2 – 266.9)	296.2 (202.5 – 412.0)	0.01	0.49
Lipids (g/day)	60.3 (44.0 – 78.9)	75.9 (47.9 – 106.1)	0.23	0.71
Saturated fatty acids (g/day)	24.4 (18.4 – 31.0)	25.6 (14.9 – 29.5)	0.84	0.12
Poliunsaturated fatty acids (g/day)	7.1 (5.4 – 9.6)	8.8 (6.4 – 12.2)	0.15	0.75
Monounsaturated fatty acids (g/day)	11.1 (7.5 – 15.7)	7.0 (4.2 – 9.9)	0.01	0.12
Cholesterol (mg/day)	286.7 (207.1 – 425.0)	231.6 (152.8 – 417.7)	0.18	0.12
Fiber (g/day)	19.3 (14.9 – 25.4)	18.3 (12.7 – 19.6)	0.54	0.78
Calcium (mg/day)	706.6 (541.0 – 959.5)	773.1 (642.8 – 952.5)	0.46	0.55

Values as median (interquartile interval). p: Control group vs.Hyperuricemia group. p: Control group vs.Hyperuricemia group, after adjustment for age, sex, and body mass index.*

Table 3 – Comparison of participants' anthropometric parameters according to diagnosis of hyperuricemia

	Control group (n = 130)	Hyperuricemia group (n = 19)	p	p*	p**
Body mass index (kg/m^2)	31.80 (26.26 – 34.42)	34.15 (33.36 – 37.19)	0.006	0.003	0.008
Men	32.30 (30.60 – 34.61)	36.53 (33.50 – 37.19)	0.03	0.04	-
Women	31.68 (24.17 – 34.10)	33.90 (33.36 – 36.13)	0.04	0.05	-
Waist circumference (cm)	98.75 (85.60 – 106.00)	105.60 (99.00 – 112.00)	0.05	0.03	0.12
Men	106.00 (102.50 – 114.50)	112.25 (106.00 – 113.00)	0.19	0.18	-
Women	97.00 (82.50 – 103.50)	99.50 (96.50 – 106.00)	0.26	0.38	-
Waist-to-hip ratio	0.89 (0.81 – 0.94)	0.89 (0.82 – 0.93)	0.76	0.70	0.69
Men	0.95 (0.93 – 0.96)	0.92 (0.89 – 0.95)	0.10	0.27	-
Women	0.86 (0.79 – 0.92)	0.87 (0.82 – 0.93)	0.96	0.68	-
Waist-to-height ratio	0.61 (0.55 – 0.65)	0.63 (0.59 – 0.66)	0.12	0.08	0.13
Men	0.62 (0.59 – 0.65)	0.64 (0.61 – 0.66)	0.46	0.36	-
Women	0.60 (0.52 – 0.63)	0.63 (0.59 – 0.66)	0.22	0.32	-

Values as median (interquartile interval). p: Control group vs.Hyperuricemia group. p: Control group vs.Hyperuricemia group, after adjustment for age. p**: Control group vs.Hyperuricemia group, after adjustment for age and sex.*

compared to those without this condition, presented higher BMI, higher oxidative stress status, and worse endothelial function even after adjustments for potential confounders. In correlation analysis, after controlling for confounders, SUA levels were positively associated with BMI, WC, MDA, TG and LDL-cholesterol; and negatively correlated with HDL-cholesterol, adiponectin and RHI.

Previous cross-sectional studies have also observed a direct association between SUA and parameters of total and/or central body adiposity in individuals presenting different characteristics, such as obese postmenopausal women,[16] patients with type 2 diabetes[17,18] and individuals aged 18-70 years without type 1 or 2 diabetes.[3] Accordingly, epidemiological longitudinal studies carried out in the general population, reported an association of higher levels of SUA and an increased risk of overweight/obesity.[19]

The mechanisms responsible for the relationship between elevated SUA and higher body adiposity are not completely understood. One possible explanation rests on the intake of fructose. The excessive consumption of fructose (via added sucrose or high-fructose corn syrup) stands as one of the dietary causes of hyperuricemia.[20] There is evidence that fructose causes intracellular ATP depletion, nucleotide turnover, and generation of uric acid. The fructose-induced uric acid generation causes mitochondrial oxidative stress which can in turn, favor fat accumulation.[21,22] Experimental studies also suggest that fructose intake may facilitate the development of overweight/obesity through other mechanisms, such as alteration in satiety and increase in food intake.[20,22] Conversely, there are studies indicating that adipose tissue possesses abundant xanthine oxidoreductase activity (similar to liver) and is capable of generating and secreting uric acid: a property which is enhanced in obesity.[23]

Table 4 – Comparison of participants' laboratory variables, reactive hyperemia index and blood pressure levels according to the diagnosis of hyperuricemia

	Control group (n = 130)	Hyperuricemia group (n = 19)	p	p*
Metabolic Variables				
Glucose (mg/dL)	86.00 (79.50 – 93.00)	87.00 (81.00 – 101.00)	0.51	0.78
Insulin (μU/mL)	12.28 (8.84 – 16.95)	12.70 (9.80 – 18.96)	0.41	0.59
HOMA-IR	2.61 (1.85 – 3.64)	2.68 (2.15 – 3.70)	0.41	0.39
Total cholesterol (mg/dL)	191.35 ± 40.55	194.47 ± 30.97	0.75	0.63
HDL-cholesterol (mg/dL)	52.00 (43.00 - 59.00)	43.00 (39.00 – 51.00)	0.01	0.17
LDL-cholesterol (mg/dL)	112.00 (89.00 – 140.00)	122.00 (96.00 – 145.00)	0.41	0.47
Triglycerides (mg/dL)	98.50 (68.00 – 142.00)	132.00 (108.00 – 142.00)	0.15	0.45
Inflammatory Profile				
Hs-CRP (mg/L)	0.37 (0.19 – 0.65)	0.45 (0.33 – 0.63)	0.24	0.70
Adiponectin (mg/mL)	5.65 (4.27 – 8.37)	4.02 (3.26 – 5.53)	0.04	0.11
Oxidative Stress				
Malondialdehyde (ng/mL)	3.53 (3.10 – 4.07)	4.67 (4.03 – 5.30)	0.0004	< 0.0001
Endothelial Function				
Reactive hyperemia index	2.05 ± 0.46	1.68 ± 0.30	0.005	0.03
Blood Pressure				
Systolic BP (mmHg)	119.67 (104.00 – 127.00)	121.30 (109.30 – 132.30)	0.23	0.46
Diastolic BP (mmHg)	76.76 ± 11.57	78.81 ± 8.63	0.46	0.28
Heart Rate (bpm)	74.00 (69.00 – 80.17)	69.00 (64.33 – 76.33)	0.10	0.16

Values as mean ± standard deviation for normal distribution or as median (interquartile interval) for not normal distribution. HOMA-IR, homeostasis model assessment of insulin resistance; HDL: high density lipoprotein; LDL: low density lipoprotein; Hs-CRP: high-sensitivity C-reactive protein; BP: blood pressure. p: Control group vs.Hyperuricemia group. p: Control group vs.Hyperuricemia group, after adjustment for age, sex and body mass index*

A direct association between SUA and oxidative stress as reflected by serum levels of MDA was observed in the present study. This finding is in agreement with the hypothesis suggested by some authors that the relationship of SUA with vascular and metabolic derangements is, at least, partially mediated by alterations in oxidative stress.[21,24] It is worth mentioning that the association of uric acid with oxidative stress is complex and may be paradoxical.[25] Uric acid has the ability to induce intracellular and mitochondrial oxidative stress but is a major antioxidant in human plasma[25] where it can account for roughly two-thirds of its total antioxidant capacity, through chelation of metals and oxygen radical scavenging.[20] However, there is evidence that under ischemic conditions and when SUA is above normal levels it becomes a prooxidant.[24-26] Xanthine oxidase, which is one of the two xanthine-oxireductase interconvertible isoforms, uses molecular oxygen as an electron acceptor, generating superoxide anion and other reactive oxygen species as byproducts, thereby raising oxidative stress which may ultimately contribute to CVD.[24,27]

Some studies, similarly to the present investigation, observed that SUA levels were related positively with TG[3,16,28] and negatively with HDL-cholesterol.[3,18,28] The mechanisms that underlie the relationship between SUA and TG are not yet known,[29] but there are some possible explanations. According to one of them, uric acid can induce lipogenesis in the liver and can block fatty acid oxidation.[30,31] Other investigators suggest that hepatic synthesis of fatty acids is associated with "de novo" synthesis of purine, with subsequent acceleration in uric acid production.[32]

In the present study hyperuricemia was associated with lower levels of serum adiponectin. Among the few studies that evaluated this association, one conducted by Park et al.[33] enrolled 841 postmenopausal women aged 50 years or older and found an inverse relationship, which was not reproduced in a cross-sectional analysis of Tromsø Study.[34] Although serum levels of CRP-hs were not significantly associated with SUA, they were higher in individuals presenting hyperuricemia. A positive association between SUA and CRP was observed in some studies carried out in octagenarians,[35] in postmenopausal women,[10] in type 2 diabetics,[36] in older persons[37] and in obese prepubertal children.[38] The impaired endothelial function observed in subjects with higher SUA levels in the present study was also found in previous studies.[4-6,9,11] However, as previously mentioned, most of them enrolled older and sick individuals, in contrast to the present study, where healthy young and middle aged subjects were recruited.

According to Johnson et al.[39] uric acid may be taken up by adipocytes, where it induces oxidative stress, generates inflammatory mediators and inhibits the synthesis of adiponectin.[39] The potential increase in oxidative stress induced by SUA may also favor an inflammatory response and

Table 5 – Correlations between serum levels of uric acid and biochemical variables, reactive hyperemia index and blood pressure (n = 149)

	Correlation		Partial correlation*	
	r	p	r	p
Anthropometric Parameters				
Body mass index (kg/m^2)	0.39	< 0.0001	0.30	0.0003
Waist circumference (cm)	0.43	< 0.0001	0.26	0.001
Metabolic Variables				
Glucose (mg/dL)	0.21	0.01	0.25	0.08
Insulin (μU/mL)	0.01	0.94	0.03	0.82
HOMA-IR	0.07	0.62	0.07	0.64
Total cholesterol (mg/dL)	0.22	0.01	0.14	0.10
HDL-cholesterol (mg/dL)	-0.42	< 0.0001	-0.28	0.0007
LDL-cholesterol (mg/dL)	0.29	0.0003	0.19	0.02
Triglycerides (mg/dL)	0.35	< 0.0001	0.21	0.01
Inflammatory Profile				
Hs-CRP (mg/L)	0.11	0.23	0.16	0.10
Adiponectin (mg/mL)	-0.40	0.0005	-0.25	0.03
Oxidative Stress				
Malondialdehyde(ng/mL)	0.28	0.04	0.31	0.03
Endothelial Function				
Reactive hyperemia index	-0.27	0.01	-0.25	0.02
Blood Pressure				
Systolic BP (mmHg)	0.32	0.0001	0.16	0.06
Diastolic BP (mmHg)	0.24	0.003	0.16	0.11

*HOMA-IR, homeostasis model assessment of insulin resistance; HDL: high density lipoprotein; LDL: low density lipoprotein; Hs-CRP: high-sensitivity C-reactive protein; BP: blood pressure. *After adjustment for age and sex (for the partial correlations with body mass index and waist circumference) or after adjustment for age, sex and body mass index (for the other variables).*

endothelial dysfunction through the reduction of nitric oxide bioavailability.[29] There is evidence that SUA can also decrease nitric oxide production via others mechanisms.[38]

The strength of this study relies on the careful selection of participants, excluding individuals with characteristics that might influence SUA levels, as well as the metabolic and vascular markers evaluated here. For example, exclusions encompassed postmenopausal women and elderly, patients taking any type of medications (including diuretics), and those with hypertension, diabetes or chronic renal disease.[40] It is not clear whether increased SUA is a causative agent or is simply a marker of CVD. The present study provides the information that even in healthy young and middle aged adults SUA is directly associated with oxidative stress and with metabolic and vascular alterations that may increase the risk of CVD. The limitation of this study is the cross-sectional design, implying that causality is not likely to be determined.

Conclusions

The results obtained in this study suggest that in healthy young and middle-aged adults, higher serum levels of uric acid are associated with excessive body adiposity, worse lipid profile, oxidative stress, inflammation and impaired endothelial function.

Author contributions

Conception and design of the research: Ferreira TS, Fernandes JFR, Araújo LS, Nogueira LP, Leal PM, Antunes VP, Kaiser SE, Klein MRST; Acquisition of data: Ferreira TS, Fernandes JFR, Araújo LS, Nogueira LP, Leal PM, Antunes VP, Rodrigues MLG, Valença DCT; Analysis and interpretation of the data and Writing of the manuscript: Ferreira TS, Fernandes JFR, Araújo LS, Nogueira LP, Leal PM, Antunes VP, Rodrigues MLG, Valença DCT, Kaiser SE, Klein MRST; Statistical analysis: Kaiser SE, Klein MRST; Obtaining financing: Klein MRST; Critical revision of the manuscript for intellectual content: Ferreira TS, Fernandes JFR, Araújo LS, Kaiser SE, Klein MRST.

Potential Conflict of Interest

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

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Pedro Ernesto University Hospital - Rio de Janeiro State University under the protocol number 2798-CEP/HUPE-CAAE: 0243.0.228.000-10 e 1152-CEP/HUPE - CAAE: 0039.0.228.000-08. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Validation of the Brazilian-Portuguese Version of a Short Questionnaire to Assess Knowledge in Cardiovascular Disease Patients (CADE-Q SV)

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Abstract

Background: **Patient education is an essential part of cardiovascular patients' care targeting self-management behavior to reduce risk factors and subsequent events. Herein, a short and reliable tool to assess patients' knowledge in Brazil is warranted.**

Objectives: **To translate, culturally-adapt and psychometrically validate the Portuguese version of the Coronary Artery Disease Education Questionnaire Short Version (CADE-Q SV).**

Methods: **The Portuguese CADE-Q SV – translated and culturally-adapted - was reviewed by five bilingual experts in cardiovascular disease. This version was then pre-tested in 21 patients, and clarity of items was checked using a Likert-type scale ranging from 1 = not clear to 10 = very clear. It was then psychometrically tested in 200 cardiovascular patients (41%women; mean age = 58.4 ± 11.6 years old). The internal consistency was assessed using Kuder-Richardson-20 (KR-20) and Cronbach's alpha, test-retest reliability through intraclass correlation coefficient (ICC), factor structure using confirmatory factor analysis, and construct validity regarding educational level, family income, and time of diagnosis.**

Results: **All questions were considered clear by patients (clarity range:7.8-9.6). KR-20 was 0.70. All ICC values were > 0.70. Factor analysis revealed 6 factors, all internally consistent. Construct validity was supported by significant differences in total scores by educational level and family income ($p < 0.001$). The overall mean was 13.08 ± 2.61. The area with the highest knowledge was risk factors and the lowest was psychosocial risk.**

Conclusions: **The Portuguese CADE-SV was demonstrated to have good validity and reliability. This tool can be applicable in clinical and research settings, assessing cardiovascular patients' knowledge as part of an education programming. (Arq Bras Cardiol. 2018; 111(6):841-849)**

Keywords: **Cardiovascular Diseases; Coronary Artery Disease; Surveys and Questionnaires; Patient Education as Topic; Knowledge; Educational Status.**

Introduction

Cardiovascular diseases (CVDs) are among the leading burdens of disease and disability worldwide,[1] particularly in low and middle-income countries (LMICs) such as Brazil.[2] Cardiac rehabilitation (CR) is an outpatient secondary prevention care model designed to mitigate this burden.[3] Indeed, participation in CR has been shown to reduce morbidity and mortality by 20%, in a cost-effective manner.[4-7] Improved risk factor control, psychosocial well-being, and health behaviors are also shown in LMICs with CR participation.[8] However, there are incredibly few studies in this setting showing the long-term success of CR, which rests in part on the patient's ability to maintain health behaviors, including participation in regular physical activity after the end of the program.[9,10]

Patient education is an essential part of the rehabilitation of CAD patients targeting self-management behavior to reduce risk factors and subsequent cardiac events.[11] The American and Canadian Cardiovascular Societies include patient education as a quality indicator of CR,[12,13] and this component is also recommended in the delivery of CR in LMICs.[14] Indeed, meta-analyses of education for cardiovascular patients suggest it is associated with improvements in self-management behaviors,[9-11,15] health-related quality of life,[16] decreases in healthcare costs,[16] and recurrence of acute events.[15]

In this context, the Coronary Artery Disease Education Questionnaire (CADE-Q) was previously developed and psychometrically validated as a valid and reliable tool to inform Brazilian healthcare providers oft what their cardiovascular patients know about their condition.[17] It was later validated to English.[18] It has also been used in several studies, including randomized controlled trials.[19] Although both versions demonstrated good reliability and validity, CADE-Q presented lack of detailed assessment of all core components of cardiac rehabilitation, such as nutrition and psychosocial risk. Therefore, a second version (CADE-Q II) was developed and validated in English.[20] However, both tools take around 20 minutes to be completed, and there was a need for a short and quick instrument to more easily assess CR patients' knowledge in clinical practice. This tool was validated in English and it is called CADE-Q SV.[21] The aim of this study was to translate, culturally-adapt and psychometrically validate a Brazilian-Portuguese version of CADE-Q SV.

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Methods

Design and Procedures

The design of this study consisted of a series of cross-sectional, observational studies. Data was collected between September 2017 and February 2018.

First, the translation and cultural adaptation was performed. This process followed strict norms approved by the author and co-authors and was based on the protocol proposed by Guillemin et al:[22] (1) initial translation, (2) back-translation, (3) committee review of those translations and back-translations, and (4) pre-testing for equivalence using bilingual individuals. The initial translation was performed by an independent translator, aware of the objectives and concepts underlying the study and sought to detect ambiguities and unexpected meanings in the original items. The back-translation was performed by a second translator, blinded to the initial objectives of the study and the original version. All versions were reviewed by a committee of three bilingual experts. This version was then pre-tested in 20 patients and clarity of items was checked. To assess clarity, patients were asked to rate each item on a Likert-type scale ranging from 1 (not clear) to 10 (very clear). Results were used to refine the Brazilian-Portuguese version of CADE-Q SV.

Second, a psychometric validation was performed. The refined tool was administered to a larger sample of current cardiovascular ambulatory patients from a public hospital in Belo Horizonte, Minas Gerais. The instrument was applied through monitored self-administration (i.e. researchers maintained a neutral stance during the administration, answering questions about the research and encouraging participants to answer all questions). The questionnaire was re-administered one month after the first application in 21 randomly selected participants to assess test-retest reliability. Data were collected between June and November 2017.

Participants

For the psychometric validation, a convenience sample of 200 ambulatory cardiovascular patients was recruited. The sample size calculation for this analysis was based on Hair &Anderson's[23] recommendation of 10 subjects per item. Since CADE-Q SV has 20 items, a sample size of 200 is considered valid. The inclusion criteria were the following: confirmed cardiac diagnosis or multiple cardiovascular risk factors. The exclusion criteria were the following: younger than 18 years old, illiterate, any significant visual, cognitive or mental impairment which precludes the participant's ability to answer the questionnaire.

CR participants were characterized according to gender, age, educational level, family income, comorbidities, clinical risk factors, and history and duration of participation in CR. The participant's clinical characteristics were obtained from the medical chart, and socio-demographic characteristics were self-reported.

Measure: The CADE-Q SV scale

CADE-Q SV assesses cardiovascular patients' knowledge about their condition. It was designed to be a true/false/I don't know questionnaire, with 20 items, four in each domain as follows: medical condition, risk factors, exercise, nutrition, and psychosocial risk. Each correct answer equals to one point; therefore, the maximum score possible is 20 overall, four by domain, and one per item. The tool has been developed in English and psychometrically tested in Canadian CR participants.[21] This tool can be used to tailor any type of educational intervention addressed to cardiovascular patients, not only in CR programs.

Statistical analysis

SPSS Version 24.0 was used.[24] The level of significance for all tests was set at 0.05. Psychometric properties were tested as per the Consensus-based Standards for the selection of health Measurement Instruments (COSMIN) taxonomy.[25] First, internal consistency was assessed by the Kuder-Richardson-20 (KR-20) overall, and by Cronbach's alpha of each factor (based on factor structure, described below). For this analysis, values equal to, or higher than 0.70 were considered acceptable,[23] reflecting the internal correlation between items of the same area.

Second, factor structure was assessed using confirmatory factor analysis. The main component method for factor extraction was used with consideration being given only to those with eigen values > 1.0. After the selection of the factors, a correlation matrix was generated, whereby the associations between items and factors were observed through factor loadings greater than 0.40 on only one factor.[23] The varimax method with Kaiser normalization was used to interpret the matrix.[26]

Third, test-retest reliability was assessed using intraclass correlation coefficient (ICC). ICC values lower than 0.70[27] were considered bad items. Finally, criterion validity was also assessed by comparing CADE-Q SV total scores with the participant's level of education, family monthly income and time of diagnosis, using independent sample t-tests and Pearson's correlation. Item completion rates were also described.

A descriptive analysis of the Portuguese CADE-Q SV was performed. A mean total score was computed to reflect total knowledge. Independent sample t-tests, one-way analysis of variance, and chi-square tests were used as appropriate to assess differences in total knowledge based on patient's socio-demographic and clinical characteristics. Continuous variables were all normally distributed (confirmed by Kolmogorov-Smirnov test) and were reported with mean and standard deviations. Categorical variables were reported by absolute numbers, percentages and, when applicable, confidence intervals.

Results

Participants' characteristics

The characteristics of participants from the psychometric validation are described in Table 1. Overall, 200 cardiovascular ambulatory patients completed the Portuguese version of CADE-Q SV, of which 118 (59.0%) were male, and the mean age was 58.4 ± 11.6 years old.

Translation, cultural adaptation and pre-testing

During the process of translation and cultural adaptation, it was observed that one item needed to be adapted to be

Table 1 – Sociodemographic/Clinical Characteristics of the Participants and total scores and differences among subgroups (n = 200)

Characteristic			CADE-Q SV Total Score	
Sociodemographic			(mean ± SD)	p
Age, years (mean ± SD)		58.4 ± 11.6	-	-
Age dichotomous n (%)	Less than 65 years old	132 (66.0)	13.6 ± 2.4	0.001†
	65 years old or older	68 (34.0)	12.2 ± 2.8	
Sex n (%)	Male	118 (59.0)	13.3 ± 2.5	0.23
	Female	82 (41.0)	12.8 ± 2.8	
Educational level n (%)	Never went to school	8 (4.0)	12.0 ± 3.2	< 0.001‡
	Less than High School	128 (64.0)	12.5 ± 2.5	
	High School	54 (27.0)	14.1 ± 2.4	
	University	8 (4.0)	15.5 ± 1.2	
	Post-graduation	2 (1.0)	17.0 ± 0.0	
Monthly family income n (%)	No income	15 (7.5)	12.6 ± 1.8	0.04*
	Less than 1 minimum salary	98 (49.0)	12.8 ± 2.7	
	Between 1 and 3 minimum salaries	69 (34.5)	13.2 ± 2.6	
	Between 4 and 5 minimum salaries	12 (6.0)	14.2 ± 2.0	
	6 or more minimum salaries	4 (2.0)	16.0 ± 2.0	
Clinical				
Acute Cardiac Event n (%)	Acute Myocardial Infarction	113 (56.5)	13.5 ± 2.5	0.03*
Comorbidities n (%)	Hypertension	179 (89.5)	13.1 ± 2.6	0.91
	Dyslipidemia	138 (69.0)	13.1 ± 2.5	0.81
	Stress	71 (35.5)	13.1 ± 2.5	0.81
	Peripheral Obstructive Arterial Disease	54 (27.0)	12.5 ± 3.0	0.06
	Diabetes Type II	53 (26.5)	13.4 ± 2.2	0.36
	Arrhythmia	51 (25.5)	12.4 ± 2.4	0.04*
	Stable Apnea	42 (21.0)	12.9 ± 2.9	0.58
	Depression	41 (20.5)	12.8 ± 2.4	0.37
	Obesity	40 (20.0)	13.3 ± 2.6	0.65
	Unstable Angina	37 (18.5)	12.7 ± 2.2	0.55
	Smoking	19 (9.5)	14.4 ± 2.2	0.08
	Alcoholic behaviour	6 (3.0	14.5 ± 1.9	0.18
Time from diagnosis				
Time from diagnosis, years (mean±SD)		8.6 ± 9.1	-	-
Time from diagnosis, n (%)	Less than 1 year	50 (25.0)	13.6 ± 2.4	0.23
	Between 1 and 5 years	44 (22.0)	12.6 ± 2.8	
	Between 6 and 10 years	23 (11.5)	12.9 ± 2.6	
	Between 11 and 15 years	25 (12.5)	13.9 ± 2.2	
	More than 15 years	38 (19.0)	12.6 ± 2.6	

SD-standard deviation; Significant differences between groups: (*) p < 0.05, (†) p < 0.01, (‡) p < 0.001. Note: Income shown in Brazilian minimum salaries. One minimum salary corresponds to BRL$ 954,00 or USD$ 292.95.

used in the Brazilian context *(item 11). Previously, this item had names of statin medications popular in North America, and since the tool was used in different countries it was adapted to read " '*Statin' medications (such as atorvastatin and simvastatin) limit how much cholesterol your body absorbs from food". Based on the feedback received from the experts we have included two examples of popular medications used in Brazil. No other adaptations were made. Table 2 displays all items of the Portuguese version of CADE-Q SV.

Table 2 also presents the clarity of items graded by 21 cardiovascular patients as part of the pre-testing using a Likert-type scale ranging from 1 (not clear) to 10 (very clear).

Table 2 – Clarity (n = 21), means and Standard Deviations of CADE-Q SV scores per item, item completion rates (n = 200), ICC (n = 20), and Mean Scores per area

Area	Item	Clarity* Mean ± SD	Score Mean ± SD	Item completion rates (%)	ICC	Mean Score Per area
1 – Medical	1. Heart disease only happens in older people who smoke or have high cholesterol.	8.5 ± 1.9	0.73 ± 0.45	98.5	0.75	2.38 ± 0.76
	3. "Angina" is chest pain or discomfort in your arm, back or neck.	8.1 ± 3.0	0.75 ± 0.44	98.5	0.71	
	6. Medications such as aspirin (ASA) help prevent blood clots from forming.	8.5 ± 2.6	0.86 ± 0.35	98.5	0.70	
	11. "Statin" medications (such as atorvastatin and simvastatin) limit how much cholesterol your body absorbs from food.†	8.8 ± 1.8	0.05 ± 0.21	98.5	0.72	
2 – Risk Factors	2. Lifestyle changes such as healthy eating can lower your chances of developing heart disease.	9.1 ± 1.9	0.89 ± 0.32	98.0	0.80	2.95 ± 0.88
	12. To help control your blood pressure, eat less salt and exercise regularly.	9.5 ± 0.8	0.97 ± 0.16	98.5	0.83	
	16. To control cholesterol, become a vegetarian and avoid eating eggs.	8.7 ± 1.5	0.51 ± 0.50	98.5	0.77	
	18. You cannot prevent diabetes with exercise and healthy eating.	8.7 ± 2.1	0.58 ± 0.49	98.5	0.85	
3 – Exercise	4. Resistance training (lifting weights or using elastic bands) can strengthen your muscles and help lower your blood sugar.	8.0 ± 2.5	0.63 ± 0.48	98.5	0.72	2.69 ± 1.01
	8. A warm-up before exercising raises your heart rate and lowers your chance of getting angina.	8.8 ± 1.6	0.63 ± 0.48	98.5	0.70	
	13. If you get chest discomfort while walking, speed up to see if it goes away.	9.0 ± 1.6	0.86 ± 0.35	98.5	0.79	
	17. You are exercising at the right level when your heart rate is in the target zone and you can still talk comfortably.	8.4 ± 2.4	0.57 ± 0.50	98.5	0.80	
4 – Diet	5. Eating more meat and dairy products is a good way to add more fiber to your diet.	8.1 ± 2.2	0.47 ± 0.50	98.0	0.72	2.09 ± 0.84
	9. Prepared or processed foods, such as canned soup and bacon, usually have a lot of salt (sodium).	8.8 ± 2.1	0.90 ± 0.30	98.5	0.98	
	14. Trans fat is an unhealthy type of fat that is often found in baked or fried foods.	7.8 ± 2.9	0.78 ± 0.41	98.5	0.74	
	20. To help lower your blood pressure, eat healthy foods more often, such as vegetables, fruits, and whole grains.	9.6 ± 0.9	0.94 ± 0.24	98.5	0.94	
5 – Psychosocial Risk	7. The only effective way to manage stress is to avoid people who cause unpleasant feelings.	8.2 ± 3.0	0.35 ± 0.48	98.5	0.77	1.97 ± 0.70
	10. Depression is common after a heart attack and increases the chance of having another heart attack.	8.5 ± 2.2	0.63 ± 0.48	98.0	0.78	
	15. Sleep apnea (pauses in breathing during sleep) can increase your chance of having another heart attack.	8.1 ± 2.7	0.05 ± 0.21	98.5	0.77	
	19. Stress increases your chance of having a heart attack as much as high blood pressure and diabetes.	9.1 ± 1.4	0.94 ± 0.23	98.5	0.72	
Total		8.6 ± 3.2	13.08 ± 2.61	-	-	-

SD-standard deviation; ICC-intraclass correlation coefficient; (*) Clarity was assessed using a Likert-type scale ranging from 1 = not clear to 10 = very clear; (†) item culturally adapted. Note: maximum score for item is 1 and for areas is 5.

Clarity of items ranged from 7.8 to 9.6, and overall clarity of the tool was 8.6 ± 3.2, which shows the Portuguese version of CADE-Q SV was clear to patients.

Psychometric validation

The internal consistency of the entire sample was assessed by KR-20(0.70). Regarding factor analysis, results from the Kaiser-Meyer-Olkin index (KMO = 0.78) and Bartlett's Sphericity tests (X^2 = 490.481, p < 0.001) indicated that the data were suitable for factor analysis. Six factors were extracted, representing 59.0% of the total variance. All factors were reliable (Cronbach's alpha ranged from 0.70-0.81). These factors were called: medical, risk factors, exercise, diet, psychosocial risk, and specific cases. Table 3 shows the factor loadings for each item based on loadings greater than 0.30 on only one factor.

The test-retest reliability was evaluated through the ICC for each item, and the ICCs for all items meet the minimum recommended standard. In regard to construct validity, CADE-Q SV total scores were compared by participant's level of education, family monthly income and time of diagnosis. As shown in Table 1, patients with lower educational level had significantly higher needs than those with higher education (p < 0.001), and participants with no income or less than 1 minimum salary had lower knowledge than participants that earn 4 minimum salaries per month or higher (p < 0.05). No differences were found regarding time of diagnosis.

Cardiovascular patients' knowledge about their condition

Table 2 displays the means and standard deviations of each CADE-Q SV item, as well as total scores per area. Items with the highest scores (i.e., with the highest number of correct answers) were the following: "to help control your blood pressure, eat less salt and exercise regularly", "stress increases your chance of having a heart attack as much as high blood pressure and diabetes", and "to help lower your blood pressure, eat healthy foods more often, such as vegetables, fruits, and whole grains". Items with the lowest knowledge (i.e., items with the lowest scores) were the following: " 'statin' medications (such as atorvastatin and simvastatin) limit how much cholesterol your body absorbs from food", "sleep apnea (pauses in breathing during sleep) can increase your chance of having another heart attack", and "the only effective way to manage stress is to avoid people who cause unpleasant feelings". The area with the highest knowledge was risk factors and the one with the lowest was psychosocial risk. Patients spend around 10 minutes to complete the tool.

Table 1 presents the total score per participant's characteristics. As displayed, patients that had a myocardial infarction or have arrhythmia had significantly higher knowledge than their counterparts (p < 0.05). In addition, younger participants (i.e. less than 65 years old) had significantly higher knowledge than participants who were 65 years old or older.

Discussion

Education is a core component of CR and cardiac care, and is necessary to promote patient's understanding of secondary prevention strategies and adherence to these strategies. Herein, a short and reliable tool to assess cardiovascular patients' knowledge – called CADE-Q SV - has been translated, culturally adapted, and psychometrically validated through a rigorous process. Internal consistency, test-retest reliability, criterion validity, and factor structure were all established, and demonstrate the utility of this tool.

Results of this study were consistent with those presented in the original validation,[21] particularly in relation to criterion validity (correlation to educational level) and all areas being considered internally consistent (α > 0.70). In this validation, there are 6 factors, even thoughthe tool has 5 areas. The new factor was called "specific cases" and included questions related to comorbidities and specific diagnosis that may not be relevant to all cardiovascular patients (e.g., diabetes and sleep apnea). Adult patients learn based on their personal needs and when the information is not relevant to them they may not have interest to learn about it.[28,29] Therefore, these items were combined in one factor and in future studies with the tool, researchers should flag these items and see if cardiovascular patients with or without these comorbidities will have the same knowledge.

The overall mean, as well as the means of the areas, were low, reinforcing the need for educational strategies to teach cardiovascular patients, which have been reinforced in publications about strategies to treat these patients in low-and middle-income countries.[14] Thus, the areas with higher knowledge in this study (risk factors) were different from the areas identified in the original validation (exercise and diet).[21] This result was expected since in this study we have administered the survey in ambulatory cardiovascular patients, while the original study was with CR patients.

Future research is needed to further establish the psychometric properties of the Portuguese version of CADE-Q SV. First, in relation to the potential strategies to educate cardiovascular patients, it should be determined whether the scale is sensitive to change (i.e., responsiveness), such as after CR or educational programs. Second, there are other measurement properties of the scale that require assessment, such as criterion validity. Moreover, test-retest reliability was performed in 20 patients, and the literature points that the minimum number should be 50.[27] Third, the type of sample and the fact that participants were recruited from only one site also limits this study. Therefore, the Portuguese CADE-Q SV should be administered in other health programs and Brazilian states, to ensure it is appropriate and performs well in more general settings. Finally, future research is needed to assess whether the scale is sensitive to change, such as following participation in CR, or to test implementation of new education materials. Second, whether CADE-Q SV is a valuable and valid tool to identify knowledge differences in CR patients should be explored.[30] For this study patients did not receive any feedback regarding their knowledge; however, we encourage clinicians and researchers to provide this to patients.

Conclusions

In conclusion, the Portuguese version of CADE-Q SV proved to have strong psychometric properties, providing

Table 3 – Factor loadings from confirmatory factor analysis

Items	Factor 1: Specific cases	Factor 2: Exercise	Factor 3: Diet	Factor 4: Medical	Factor 5: Risk factors	Factor 6: Psychosocial risk
10. Depression is common after a heart attack and increases the chance of having another heart attack.	0.47					
11. "Statin" medications (such as atorvastatin and simvastatin) limit how much cholesterol your body absorbs from food.	0.39					
15. Sleep apnea (pauses in breathing during sleep) can increase your chance of having another heart attack.	0.39					
18. You cannot prevent diabetes with exercise and healthy eating.	0.31					
4. Resistance training (lifting weights or using elastic bands) can strengthen your muscles and help lower your blood sugar.		0.33				
8. A warm-up before exercising raises your heart rate and lowers your chance of getting angina.		0.46				
13. If you get chest discomfort while walking, speed up to see if it goes away.		0.48				
17. You are exercising at the right level when your heart rate is in the target zone and you can still talk comfortably.		0.47				
5. Eating more meat and dairy products is a good way to add more fiber to your diet.			0.45			
9. Prepared or processed foods, such as canned soup and bacon, usually have a lot of salt (sodium).			0.46			
14. Trans fat is an unhealthy type of fat that is often found in baked or fried foods.			0.56			
20. To help lower your blood pressure, eat healthy foods more often, such as vegetables, fruits, and whole grains.			0.38			
1. Heart disease only happens in older people who smoke or have high cholesterol.				0.52		
3. "Angina" is chest pain or discomfort in your arm, back or neck.				0.39		
6. Medications such as aspirin (ASA) help prevent blood clots from forming.				0.44		
2. Lifestyle changes such as healthy eating can lower your chances of developing heart disease.					0.30	
12. To help control your blood pressure, eat less salt and exercise regularly.					0.56	
16. To control cholesterol, become a vegetarian and avoid eating eggs.					0.34	
7. The only effective way to manage stress is to avoid people who cause unpleasant feelings.						0.52
19. Stress increases your chance of having a heart attack as much as high blood pressure and diabetes.						0.32
Variance	17.3	11.1	9.4	8.2	6.9	6.6
Eigenvalues	3.3	1.6	1.5	1.2	1.2	1.1
Cronbach's Alpha	0.73	0.81	0.79	0.70	0.71	0.70

(*) item culturally adapted.

preliminary evidence of its validity and reliability to assess cardiovascular patients' knowledge in Brazil. It is hoped that this tool can support healthcare providers and CR programs to evaluate their patients' knowledge in clinical practice and promote greater provision of educational strategies.

The use of the Portuguese version of CADE-Q SV for clinical and research purposes will be free of charge, and all information – including the tool - is available online at https://cadeq.wordpress.com/.

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Author contributions

Conception and design of the research: Ghisi GLM, Chaves GSS, Britto R; Acquisition of data: Loures JB, Bonfim GM; Analysis and interpretation of the data: Ghisi GLM, Chaves GSS, Loures JB, Bonfim GM, Britto R; Statistical analysis and Writing of the manuscript: Ghisi GLM, Chaves GSS; Obtaining financing: Britto R; Critical revision of the manuscript for intellectual content: Ghisi G, Chaves GSS, Loures JB, Bonfim GM.

Potential Conflict of Interest

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

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade Federal de Minas Gerais under the protocol number 1.350.973. 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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CADE-Q SV: Practical and Relevant in the Assessment of Patients with Cardiovascular Diseases regarding their Health Condition

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Short Editorial related to the article: Validation of the Brazilian-Portuguese Version of a Short Questionnaire to Assess Knowledge in Cardiovascular Disease Patients (CADE-Q SV)

Cardiovascular diseases (CVD) remain the leading cause of death worldwide. According to estimates by the World Health Organization (WHO), approximately 17.9 million individuals die per year due to this clinical condition.[1] In Brazil, a registry of the Brazilian Society of Cardiology shows an increase in mortality over the years, affecting 383,961 individuals in 2017.[2]

Considering the strong association of CVD with morbidity and mortality, as well as the impairment of functional capacity and quality of life shown by these patients, strategies aimed at minimizing these impairments and that can be shown to be cost-effective should be implemented. In this scenario, cardiovascular rehabilitation (CVR) is crucial and should be part of the overall treatment of CVD.[3]

The WHO defines CVR as "the sum of activities required to ensure people with CVD have the best possible physical, mental and social conditions, so that the patients may, by their own efforts, preserve or resume when lost as normal a place as possible in the society."[4] According to the South-American Guideline for Cardiovascular Prevention and Rehabilitation,[3] for this process to be feasible and for the objectives to be attained, the integrated performance of a multidisciplinary team is required. Physical training, associated with drug treatment, is the central component of CVR. However, the professionals' performance is not restricted to creating the plan and applying the exercises. Special attention should also be given to the patients' full education regarding their health condition and appropriate management of risk factors, aiming at having a healthy lifestyle.[3] Specific characteristics of each patient, such as socioeconomic and educational levels, may influence the prior knowledge and understanding of information provided by professionals. In this sense, tools that evaluate the patients' knowledge regarding their health condition are useful and can help the professionals to create and apply effective strategies.

Recently, the validation of the Portuguese version of the Coronary Artery Disease Education Questionnaire - Short Version (CADE-Q SV) was published in this journal.[5] This questionnaire assesses the knowledge of CVD patients regarding their health condition, including the clinical aspects, risk factors, exercise, diet and psychosocial risk. Concerning the previously validated questionnaires (CADE-Q and CADE-Q II),[6,7] the new proposal maintains the assessment of central components of CVR, with differences being related to the fact that it is a more concise tool that can be applied in ten minutes, as reported by the researchers. The short time required, and the objective profile of the response options may favor the applicability of this tool in research and clinical practice, providing relevant information for better targeting of interventions in secondary prevention in Brazil.

It has been previously shown that the context in which the subject is placed can influence their knowledge about health. In a previous study, using the pioneer CADE-Q version, the researchers found that CVR participants in Brazil had lower levels of knowledge about their condition when compared to Canadian patients.[8]

In the most recent CADE-Q SV validation study, outpatients who did not necessarily participate in a formal CVR program were included. The area identified with greater knowledge was that related to risk factors and the one with the lowest score was that related to psychosocial risk. Overall, the patients showed a low level of knowledge, and those with lower educational level, as well as those with family income, showed significantly higher needs. On the other hand, characteristics such as age younger than 65 years and previous infarction or arrhythmia were associated with significantly higher level of knowledge.[6]

CADE-Q SV is a short, valid and reliable tool to evaluate the knowledge of CVD patients in Brazil. It can be useful in the characterization of groups of patients and especially in the identification of each individual's specific needs, allowing the implementation of targeted educational strategies. Therefore, it is a potential tool to be used in secondary prevention and should be tested and administered in different health programs and regions of our country. After applying the questionnaire, it is recommended that the professionals clarify doubts about the answers to the patients, in order to help in the process of learning and health care.

Keywords

Cardiovascular Diseases/mortality; Health Education; Survey and Questionnaires; Physical Fitness; Cardiac Rehabilitation; Exercise; Prevention and Control.

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Cardiovascular Manifestations of Erdheim-Chester's Disease: A Case Series

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Abstract

Erdheim-Chester Disease is a rare entity, classified as an inflammatory myeloid neoplasm, with an unknown incidence, occurring preferentially in men after 50 years of age. Classically, it has a multisystemic presentation, with the skeletal system being the most frequently affected (90% of the patients), followed by genitourinary involvement in 60% of cases and central nervous system in the pituitary and diabetes insipidus in 25% of the cases. Cardiovascular manifestations are present in more than half of the patients, with aortic infiltration and atrial pseudotumor being the most common forms.

Introduction

Erdheim-Chester disease (ECD), described by William Chester in 1930, is a histiocytic disorder classified as a member of the L Group, together with Langerhans cell histiocytosis. It is commonly characterized by multifocal osteosclerotic lesions in long bones that shows layers of foamy histiocytes at the histological analysis, accompanied or not by histiocytic infiltration of extra-skeletal tissues.[1]

Its pathophysiology involves the accumulation of xanthoma-like clonal histiocytes (CD68+) in the affected organs. Immune system hyperstimulation by histiocytes causes extensive local and systemic inflammatory reaction[2] resulting from senescence induction during the oncogenesis process, via hyperactivation of the Ras-Raf-MEK-ERK intracellular signaling pathway. The presence of the BRAF V600E gene mutation is present in up to 2/3 of the patients.[3]

Most patients with ECD are diagnosed between the ages of 40 and 70 years, with a slight predominance of males.[4] In addition to the long bones, the central nervous system (CNS), cardiovascular system, lung, pancreas, breast, and testicles can also be affected.[1] The cardiovascular involvement occurs in different ways, with periaortic fibrosis being the most common manifestation, with a tomographic finding typically described as a "coated aorta", which is asymptomatic in most patients.[5] The presence of cardiovascular system impairment is associated with a worse prognosis,[6] and its identification is of the utmost importance for the adequate management of these patients.

Since the disease has a systemic involvement, it is recommended that all patients be investigated with: 18-Fluorodeoxyglucose positron emission tomography – computed tomography (18-FDG PET-CT), brain magnetic resonance imaging with contrast and detailed examination of the sella turcica and cardiac magnetic resonance (CMR) imaging.[6] When the CMR is unavailable or contraindicated, a transthoracic echocardiogram (TTE) is performed. Vascular involvement can be assessed through a complementary test to 18-FDG PET-CT with total aorta angiotomography.

Case reports

Eleven patients with a diagnosis of ECD are followed at our Service. Of these, 4 (36.4%) have cardiovascular disease attributed to the underlying disease; 2 (18.2%) are males, with a mean age of 57 years (38-64 years); 2 (18.2%) patients have cardiovascular manifestation in the form of atrial involvement and aortic involvement; 1 (9.1%) has heart failure with a left ventricular ejection fraction (LVEF) of 40% and 1 (9.1%) has isolated thoracic and abdominal aortic involvement.

Case 1

A 63-year-old male, diabetic and former smoker patient was referred to the cardiology service one year after the TTE showed an echogenic image suggestive of a mass in the right atrium (RA) measuring 2.5 x 1.3 cm in its largest axis, and increased thickness and density of the atrial septum, suggestive of lipomatous infiltration. Additionally, he had a slight aortic root dilatation, ascending aorta (3.9 cm in diameter) and signs of atherosclerotic plaque in the aortic arch. The complementary CMR showed a solid image in the septal region of the RA, projecting into the mediastinum in the retroaortic position and another image in the region of the RA roof measuring 1.5 x 1.3 cm, adhered to the interatrial septum, with the presence of perfusion and heterogeneous enhancement suggestive of lymphoma.

The lesion biopsy was carried out; however, the diagnosis was inconclusive. He was referred to the hematology service, where he underwent 18-FDG PET-CT, which identified bone, CNS and skin involvement compatible with ECD. The 18-FDG PET-CT showed a moderate / marked uptake in the RA walls, in topography coincident with CMR alterations, were located on the RA roof (maximum standardized uptake value – SUV_{max}: 6.28) and in the interatrial septal region (SUV_{max}: 5.65) (Figure 1).

Keywords

Erdheim-Chester Disease/diagnosis; Erdheim-Chester Disease/drug therapy; Erdheim-Chester Disease/pathology; Biopsy; Prognosis.

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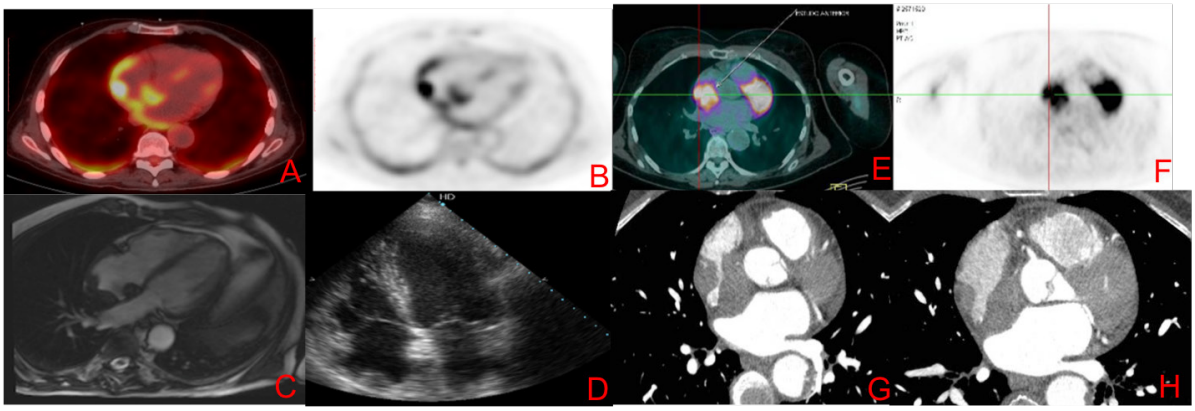

Figure 1 – *Images A to D refer to case 1 and the images from E to H refer to case 2. Images A and B represent images of 18-FDG PET-CT showing lesion in the right atrium roof. The C image represent CMR image, SSFP cine 4 chambers with hypointense lesion in the right atrium roof. The D image represents a transthoracic echocardiogram image with the same topography. The images E and F represent 18-FDG PET-CT with capturing lesion in the right atrium and G and H images represent contrast computed tomography showing evidence of expansive right atrial.*

Skin biopsy was indicated, of which anatomopathological analysis showed accumulation of xanthomized histiocytes in the dermis, suggestive of xanthelasma, with negative S-100, positive CD68, negative CD1a and positive BRAF V600E staining. The patient underwent initial treatment with interferon, but due to bone disease progression, he is currently undergoing treatment with vemurafenib. In the follow-up 18-FDG PET-CT, RA roof uptake (SUV_{max} = 5.7) was maintained.

Case 2

This was a 64-year-old female patient, with no prior comorbidities, who was followed by the Hematology team with a diagnosis of ECD, with bone, lymph node and cardiovascular involvement, demonstrated by 18-FDG PET-CT examination. She showed radiotracer hyper-uptake with a heterogeneous pattern in the RA walls (SUV_{max}: 5.8) and right ventricle (SUV_{max}: 5.8) and discreet pericardial thickening/effusion. The TTE performed in the Cardiology department showed atrial pseudotumor in an echogenic image in the interatrial septum, measuring 2.2 cm x 1.2 cm, suggestive of lipomatous infiltration. The coronary artery angiotomography showed a calcium score (Agatston) of 4, at the 58th percentile of the MESA (Multi-Ethnic Study of Atherosclerosis) study, with no significant coronary luminal reduction. As an additional finding, it showed a soft tissue density expansive lesion in the RA roof related to the interatrial septum and opening into the inferior vena cava. The sinus node artery, the right coronary artery branch, had a partial trajectory through the mass, in addition to atheromatosis in the descending thoracic aorta (Figure 1).

Case 3

A 38-year-old male patient, with no prior comorbidities, diagnosed with ECD since 2005, identified through lung biopsy with CD68+ histiocyte, negative S-100, started treatment with interferon and prednisone. In 2017, he developed dyspnea at small efforts with NYHA III.

The TTE identified left ventricle (LV) with moderate systolic dysfunction (LVEF of 40%) with diffuse hypokinesia, dilated left chambers, and preserved valvular system. The CMR showed discrete LV dilatation, with an end-diastolic diameter of 6.7 cm and an end-systolic diameter of 5.1 cm, mild diffuse hypokinesia, mild systolic dysfunction (LVEF of 46%) and late enhancement of the junction between the ventricles.

Additional investigations were performed to rule out other etiologies of ventricular dysfunction: serology for Chagas' disease was negative, angiotomography of the coronary arteries with zero calcium score and absence of luminal reduction. Treatment for ventricular dysfunction was started, and the patient showed low tolerance for hypotension and cardiopulmonary rehabilitation was indicated, with an important improvement in dyspnea.

Case 4

A 63-years-old female patient, a former smoker, with hypothyroidism, arterial hypertension and dyslipidemia, had generalized xanthomatous skin lesions in 2001. In 2004, due to abdominal pain, she underwent a computed tomography (CT) scan of the upper abdomen with contrast, which demonstrated hypoattenuating tissue involving the abdominal aorta and its branches. This promoted a discrete segmental narrowing of some of the vessels characterized by narrowing of the aorta in the emergence region of the renal arteries and the left subclavian artery (Figure 2). Tissue biopsy showed the presence of a pseudotumor, confirming the diagnosis of ECD. The 18-FDG PET-CT showed signs of retroperitoneal fibrosis involving the abdominal aorta immediately above and at the emergence region of the renal arteries. Concomitantly, there was infiltrative tissue surrounding the aortic arch, descending aorta and left common iliac artery. Initially, cardiac involvement had been ruled out by CMR, which had shown normal-sized chambers and preserved systolic function.

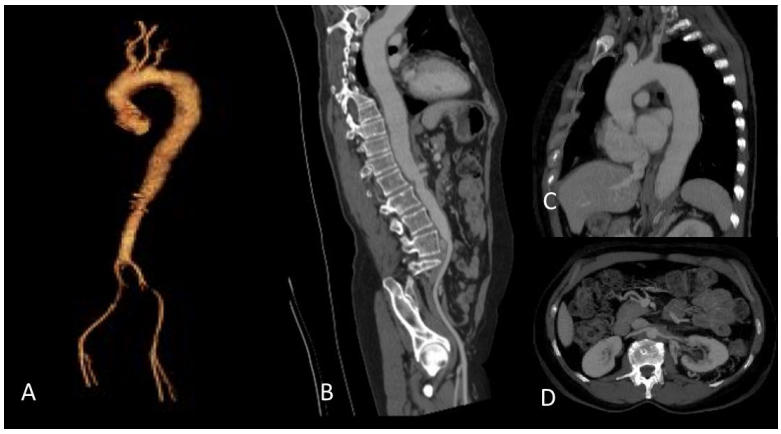

Figure 2 – *A) Thoracic and abdominal aorta in 3D reconstruction. B) Aorta seen in the sagittal view, showing diffuse thickening of the entire wall with a narrowing area in the infra-renal aorta. C) Thoracic aorta with parietal thickening and luminal reduction in the origin of left subclavian artery. D) Thickening at the origin of the renal arteries, without significant obstruction characterization.*

Discussion

DEC is a rare disease, which is difficult to diagnose. The symptoms are varied and not present in all patients. The main complaint is bone pain and there may be fever, night sweats, adynamia, and weight loss, among other symptoms.[7] These symptoms are not pathognomonic but are useful for assessing treatment response. The interaction of the Cardiology and Hematology services in this scenario allows the adequate diagnosis and management of the cardiovascular system involvement.

The definitive diagnosis is attained through the histological analysis of biopsy samples of affected tissues showing granulomatous infiltration, with CD68 expression, but with negative CD1a staining. Treatment is based on the administration of interferon-α and Vemurafenib, Cladribine and AnA-kinase may be used as the second treatment line, aiming to achieve disease control.[6]

Cardiac involvement in ECD has a worse prognosis and most of the time, it is asymptomatic. Approximately 75% of patients with ECD have some cardiovascular impairment and 60% will be diagnosed with ECD[7] based on cardiovascular findings, such as in cases 1 and 4 reported above. The cardiologist's knowledge about this disease allows an early diagnosis in these situations.

The most characteristic cardiovascular finding of ECD is aortic involvement,[5] as seen in case 4, and the most common cardiac lesion is found in the pericardium as pericardial effusion, rarely being associated with cardiac tamponade. The myocardium, endocardium and valvular apparatus may also be involved.

Left ventricular dysfunction, as seen in patient 3, is less frequently observed, but it has also been previously described.[7,8]

Aortic infiltration by ECD is visualized on CT scans as a "coated aorta." This phenomenon results from periaortic infiltration by histiocytes, predominantly in the adventitial layer.[5] The periaortic fibrosis degree varies from patient to patient, as well as the affected segment. It can occur symmetrically, circumferentially and limited to a specific segment of the aorta or throughout the vessel.

Perivascular infiltration in vessels adjacent to the aorta can also occur in the brachiocephalic trunk, left carotid artery, left subclavian artery, coronary arteries, pulmonary trunk, celiac trunk, superior mesenteric artery, and renal arteries.[7] The clinical presentation depends on which artery is involved and its degree of stenosis. Cerebral ischemia may occur due to carotid involvement, as identified in case 4, and myocardial infarction due to coronary involvement. Renal artery involvement occurs in approximately 20% of cases[7,8] and may result in stenosis of these vessels and renovascular hypertension. Treatment is performed through angioplasty and stenting.

Pericardial infiltration can manifest as pericardial thickening with or without fibrosis, and symptoms vary according to the degree of disease severity. Myocardial involvement occurs sequentially to the pericardial involvement and manifests as myocardial hypertrophy, easily diagnosed by the echocardiogram. Thickening can be found in the ventricles, atria, coronary sulci [7] and interatrial septum.[9]

Most patients have atrial involvement, often as a pseudotumor, affecting mainly the atrial posterior wall, often projecting into the atrium. Another observed lesion is the infiltration of the right atrioventricular sulcus, where the tissue usually surrounds or infiltrates the right coronary artery.[10]

Haroche et al.,[11] retrospectively analyzed 37 patients with ECD using CT and CMR: 70% had abnormal cardiac imaging, of which 49% had abnormal infiltration of the right cavities, including 30% with pseudotumor infiltration in the RA, as demonstrated in cases 1 and 2, and 19% with infiltration of the atrioventricular sulcus.

Lipomatous hypertrophy of the interatrial septum (LHIS) is a differential diagnosis that should be considered in some cases, since the TTE often describes the alterations as lipomatous infiltrations. All patients with LHIS show uptake at the 18-FDG PET-CT; however, with smaller mean SUVs

(mean of 1.84).[12] The CMR is an important diagnostic tool in the differentiation of findings, since it can better characterize the tissues. The brown adipose tissue is characterized by hypersignal in T1-weighted images and intermediate signal intensity in T2-weighted images. Specific sequences used to suppress the fat signal, such as the triple inversion-recovery pulse sequence, allow for distinguishing between fatty lesions and other types of tissue.

In another review of 53 patients,[4] 17% had symptomatic valvular disease, mainly aortic and mitral regurgitation and 3 patients required valve replacement. Technically, surgical valve repair is difficult because of the infiltration of adjacent heart tissue.

ECD is a disease with poor prognosis, with a mean 5-year survival of 68%[5] and of difficult diagnosis. The scarcity of patients contributes to the lack of knowledge about the disease and the difficulty to develop randomized studies. With this series of cases, we report the largest Brazilian case series to date, focusing on cardiovascular involvement, aiming to contribute to the knowledge of this rare and complex disease.

Author contributions

Conception and design of the research, acquisition of data and writing of the manuscript: Costa IBSS, Abdo ANR, Bittar CS, Fonseca SMR, Moraes ASHT, Kalil Filho R, Pereira J, Hajjar LA; analysis and interpretation of the data: Costa IBSS, Fonseca SMR, Moraes ASHT, Kalil Filho R, Pereira J, Hajjar LA; critical revision of the manuscript for intellectual contente: Pereira J, Hajjar LA.

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Sudden Death in Young Brazilian Athletes: Isn't It Time We Created a Genuinely National Register?

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Abstract

Young competitive athletes (≤ 35 years old) with or without a previous diagnosis of cardiovascular disease may suddenly die in competitive activities, potentially leading to an impact in society through the media. Although the relative risk for sudden death (SD) in athletes is twice as high as for their counterparts, the absolute incidence is low. While there is consensus among medical societies worldwide that early detection of causal factors is highly desirable, there is debate among different screening schemes to that end. In Brazil, the recommendations of the Brazilian Society of Cardiology mirror the guidelines of the European Society of Cardiology (ESC), which indicate a clinical examination combined with a 12-lead resting electrocardiogram, regardless of the presence of risk factors. The possibility of genetic screening is also plausible, since most clinical entities that cause SD in young competitive athletes are related to genotype. Finally, considering the diversity of practiced sports, and the population miscegenation, we emphasize the need to a national registry of cases.

Introduction

Sudden death (SD) in young athletes (under 35 years old) is a peculiar event. Despite being rare, cases have been reported by far-reaching media, which may cause a major impact on both health agencies and the society. The counterintuitive feeling that young, presumably asymptomatic individuals with above-average physical fitness may die suddenly during sports practice seems particularly striking to many people, especially when it affects elite athletes.

People involved in intense competitive activities have a relative SD risk that is nearly twice as high as that of their non-athlete counterparts, though incidence in absolute numbers is very low – 0.5 to 2 events per 100,000 athletes per year.[1] Usually, clinical entities of cardiac or vascular nature, whether previously diagnosed or not, are the most prevalent causes of SD, and participation in sports events one of is the triggering factor for its occurrence. The most frequent are of genetic origin and hereditary, whether they structural (e.g., myocardiopathies) or not (e.g., channelopathies). On the other hand, the aortic (e.g., Marfan Syndrome) and coronary artery diseases are less prevalent but have also been described in this age group.[2] Based on evidence unrelated to exercise, external causal factors can also be considered. For example, the use of central nervous system stimulant drugs and anabolic steroids seems to increase the risk of SD in adults,[3,4] so it is plausible to hypothesize that athletes exposed to these risk factors may add to that statistic.

In relation to its prevention, some success rate can be achieved if the disease is detected in time. There is treatment available for some illnesses and, on certain occasions, there may be a medical decision to suspend the athlete's participation in competitive sport (disqualification), thereby protecting them. Therefore, whenever possible, early detection of triggering diseases should be made. However, medical societies in various countries recommend different screening schemes.[5,6] Since the etiology of causative factors can differ regarding geography, ethnicity, sporting modality, genetic inheritance, and age, this point-of-view article aims to discuss the need for a national register of cases so the best prevention and early detection strategy may be laid out in Brazil – an idea already mentioned in this journal seven years ago.[7]

Screening Schemes Suggested and the Absence of a Brazilian Register

In 2011, Peidro, Froelicher and Stein published a point of view discussing particularities of Pre-Participation Physical Examination (PPE) for SD prevention in young athletes in Argentina and Brazil.[7] At the time, given the experiences that the American and Italian communities had about the effectiveness of the different decision algorithms, the need for national registers (in Argentina and Brazil) for SD cases was suggested. Since then, little has been done, and the national recommendation is not based on local data or robust evidence, such as: a) the prevalence of SD and its causes; b) ideally, subsequent evaluation of the effectiveness of potential screening strategies by means of randomized clinical trials; c) health technology assessment the algorithm to be proposed.

The Brazilian Society of Cardiology (SBC) and the Brazilian Society of Exercise and Sports Medicine (SBMEE) jointly recommend the same screening scheme as the European Society of Cardiology (ESC)[6,8] – i.e., anamnesis, physical examination

Keywords

Cardiovascular Diseases; Athletes; Adolescent; Youth Sports; Death, Sudden, Cardiac; Genotype.

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and 12-lead resting electrocardiogram (ECG), regardless of the presence or absence of risk factors. The scheme proposed by the ESC is heavily influenced by observational evidence collected in Italy. Initially, it was found that young athletes from the Veneto region were at high risk of SD during competitive sports practice, compared to other regions of the world.[9] In 2006, Corrado et al.[10] highlighted a high prevalence of Arrhythmogenic right ventricular cardiomyopathy (ARVC) and hypothesized that disqualifying athletes with a diagnosis or suspicion of that disease (or similar diseases) would be effective to reduce SD mortality at sports events.[10] These findings increased the discussion on the implementation of a specific algorithm that would make ECG mandatory in addition to anamnesis and physical examination as screening procedures for anyone engaging in a competitive and structured physical exercise program. Two years later and criticism aside, a classic study published by the same group of researchers tested the scheme and demonstrated it reduced SD cases by 89% in competitive activities involving young athletes in that country.[11] In fact, the PPE has been mandatory for more than two decades for every regulated amateur or professional athlete, with an Italian federal law that is adopted by all sports regulation entities.[12]

On the other hand, the joint procedure recommended by the American College of Cardiology (ACC) and the American College of Sports Medicine (ACSM) do not include a mandatory ECG, as argue that the annual incidence of SD in the United States is much lower than in Italy.[5] In addition, they reiterate that ECG's sub-optimal specificity for detecting anomalies in athletes may result in an excessive number of false-positive results.

In this regard, the overall consequences of a false-positive result[13] may lead to unnecessary over-investigation (e.g., echocardiography, cardiac resonance, among other examinations), with undesired financial and personal costs, or even disqualifications. However, contrary to the arguments of the American entities above, a cost-effectiveness analysis conducted by a Stanford group[14] pointed out that including ECG in the clinical examination would prevent 2.09 additional deaths per 1,000 athletes, with an estimated individual cost of U$ 89 per examination and a cost-effectiveness estimate of approximately U$ 43,000 per qualitiy-adjusted life years (QALY).

For Brazil, these data are particularly important, since the Ministry of Health is currently discussing, together with the National Congress and academic entities involved in the assessment of health technologies, the threshold of willingness to pay for added technology. Because until the present the cost per QALY of a new technology is unknown, we believe it is critical that decisions be made in Brazil based on knowledge of local statistics, which again reinforces the need for a national register of SD in young athletes to be properly conducted.

Why a National Register is Necessary

Because the etiology of SD in sports in young athletes is diverse, with regional and genetic influences, identifying the local prevalence is of utmost importance to make decisions based on evidence. For example, ethnicity has an effect on the incidence of SD in young athletes. In the US, an increased incidence of SD was found in black basketball and football players compared with other ethnic groups, most often due to hypertrophic cardiomyopathy (HCM).[15] Autopsy data from that country showed that that twice as many black athletes died from HCM as white athletes (20% vs. 10%).[16] Such information suggests a possible divergence in HCM presentation in different ethnic groups and that it may be more malignant in black individuals.

In fact, in at least 50% of the cases, HCM presents as an autosomal dominant monogenic disease. Its overall prevalence is traditionally estimated at 1:500 individuals,[17] but more recent data indicate that it may be even more frequent than previously established, which is corroborated by advances in genetic research.[18] In Brazil, the frequency of HCM is not solidly known. Here, it is our opinion that this disease is an example of the importance of ECG in the context of competitive athletes, as it can be suspected through this examination in a high percentage of cases. Moreover, changes in the ST segment, in the T wave, as well as the presence of pathological Q waves[19] can be warning signs based on which further exams (with a higher positive predictive value) can be requested in a context of greater pretest probability.

Once there is a diagnosis (clinical and/or molecular), septal ablation, myectomy, and/or an implantable cardioverter defibrillator (ICD) may be indicated. Likewise, but only in well-selected cases, disqualification may be the final outcome for the athlete's career.[20,21] In respect to the ethnicity of the Brazilian population, which is extremely mixed and with a high prevalence of blacks,[22] knowing the causes of SD in Brazilian athletes of this race seems to us very important to classify the risk for these individuals.

As for the causes of SD due to ion channel disturbance, genetic screening,[23] already included in the SBC's 2013 guidelines,[8] has been suggested as a possible strategy to help with prevention (note of the authors: when properly indicated), given the high contribution of the genetic factor for the event's occurrence.[24] given the high contribution of the genetic factor for the event's occurrence.[24] In fact, some malignant mutations are already known in genes that cause Long QT Syndrome (LQTS), Short QT Syndrome, Brugada Syndrome and catecholaminergic polymorphic ventricular tachycardia (CPVT).[25,26] Here, we would like to point out that although molecular mapping is accessible and technical improvement through new generation sequencing is available in our country, requesting it is still not part of our medical culture, even in more robust clinical scenarios (e.g., breast neoplasm screening and association with BRCA genes).[27] In fact, in order for medical entities to formally encourage its request in PPE, it is necessary to know prevalence so that the technology can be submitted to the health technology assessment (HTA) process, which is similar to the processes already performed for other clinical entities.[28]

The sport modality also has some bearing on the construction of a decision algorithm for PPE and SD prevention in young athletes. For example, in the United States, SD prevalence is higher in basketball and football.[29] In Europe, SD in young athletes is more frequent in field soccer players.[30]

General prevalence of SD in sports in young athletes;

Prevalence of SD in sports in young athletes by sports modality, socio-demographic status and ethnicity;

Annual absolute incidence of SD in sports;

Annual absolute incidence of SD in sports by sports modality, socio-demographic status and ethnicity;

Prevalence of possible causes of SD (e.g., necropsy report, causa mortis, etc.) with a survey of socio-demographic indicators and patient clinical history.

Figure 1 – *Suggestion of statistics to be surveyed by means of a national register of SD cases in competitive sports in young athletes. SD: sudden death.*

As a matter of curiosity, in combat sports, which involve high-energy trauma, or in sports involving interaction with high-speed artifacts (e.g., baseball), concerns with commotio cordis (a malignant arrhythmia triggered by direct trauma in the anterior thorax) must be present.[31]

Future Directions

As exposed above, we identified a few points still unknown which require priority examination in order to define tracking, prevention and national regulation strategies, all of which are essential for the HTA process; and which can be accessed through a genuinely Brazilian register (Figure 1).

We emphasize the central role of public research support agencies in Brazil for building a register. A call for projects specifically to that end seems to us appropriate, preferably for projects of a multicentric nature and with public sharing of data. So far, considering the lack interest on the part of independent researchers, the State has not yet expressed a position, nor has it facilitated the implementation of a viable strategy for a national register, which we consider a critical step.

Author contributions

Conception and design of the research; Acquisition of data; Analysis and interpretation of the data; Statistical analysis; Obtaining financing; Writing of the manuscript and Critical revision of the manuscript for intellectual content: Helal L, Ferrari F, Stein R.

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Case 6 – Woman with Ischemic Heart Disease Admitted due to Chest Pain and Shock

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A 67-year-old woman sought emergency medical care due to prolonged chest pain. In April 2009 the patient had prolonged chest pain and at that time she sought medical care. She was admitted at the hospital and diagnosed with myocardial infarction.

The patient had hypertension, diabetes mellitus, dyslipidemia and was a smoker.

During the patient's evolution, after the myocardial infarction, she was submitted to a coronary angiography in, which disclosed the presence of lesions with 70% obstruction in the right coronary, anterior descending and circumflex arteries. A left ventriculography revealed apical akinesia with signs of intracavitary thrombus in that region.

The echocardiogram (May 2009) disclosed ventricular dysfunction accentuated by diffuse hypokinesis, with a 28% left ventricular ejection fraction. Clinical and drug treatment was recommended to the patient.

The patient's evolution was asymptomatic until October 2009, when she had a cerebrovascular accident, with motor sequela.

On December 30, 2009, the patient had an episode of severe chest pain that lasted for one hour and she sought medical care.

At the physical examination, the heart rate (HR) was 100 beats per minute, blood pressure was 100/60 mmHg. Pulmonary assessment was normal. The heart examination disclosed a ++/ 6+ systolic murmur in the mitral area. The remainder of the physical examination was normal. The electrocardiogram (1h 19 min; Dec 30, 2009) showed sinus rhythm, HR of 103 bpm, PR interval of 122 ms, QRS duration of 159 ms, QT interval of 367 ms, and corrected QT of 480 ms.

There was left atrial overload, low voltage of the QRS complex in the frontal plane, probable inferior electrically inactive area, and left bundle branch block (Figure 1). Chest x-ray disclosed the presence of a large pleural effusion in the right hemithorax.

Keywords

Myocardial Ischemia; Myocardial Infarction; Chest Pain; Cardiac Catheterization;Thromboembolism; Shock, Cardiogenic

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The laboratory tests showed hemoglobin 13 g/dL, hematocrit 40%, MCV 91 fL, leukocytes 12,400/mm^3 (66% neutrophils, 1% eosinophils, 1% basophils, 19% lymphocytes and 13% monocytes), 421,000/mm^3, total cholesterol 228 mg/dL, HDL-cholesterol 35 mg / dL, LDL-cholesterol 162 mg/dL, triglycerides 157 mg/dL, CK-MB mass 5.63 ng / mL, Troponin I 0.21 ng/mL, urea 33 mg/dL, creatinine 0.66 mg/dL, sodium 137 mEq/L, and potassium 3.4 mEq/L. Venous blood gasometry showed pH 7.46, pCO_2 39.3 mmHg, pO_2 36.3 mmHg, O_2 saturation 62.7%, bicarbonate 27.7 mEq/L and base excess 4.1 mEq/L.

Approximately two hours after hospital admission, she had seizures and cardiac arrest with pulseless electrical activity, reversed in 5 min.

The electrocardiogram after the cardiac arrest (4:18 am; Dec 30, 2009) showed a HR of 64 bpm, absence of P waves, and left bundle branch block. The QRS complex alteration, in relation to the previous tracing, was a positive QRS complex in the V6 lead (Figure 2).

She had a new cardiac arrest 20 min later, which was also reversed. After half an hour, a new episode of cardiac arrest occurred, which was irreversible, and the patient died (5:45 am; Dec 30, 2009).

Clinical aspects

This patient is a 67-year-old woman with cardiovascular risk factors and ischemic cardiomyopathy, with severe left ventricular systolic dysfunction. Cardiac catheterization disclosed multivessel coronary disease and apical akinesis with an intracavitary thrombus. During outpatient follow-up, clinical treatment was chosen, possibly influenced by the patient's clinical status, as well as the characteristics of the coronary anatomy.

The indication of surgical treatment with myocardial revascularization in patients with coronary heart disease with heart failure and severe left ventricular systolic dysfunction is still debatable, but recent data from the STICH study suggest a long-term survival benefit in patients undergoing myocardial revascularization.[1]

During follow-up in October 2009, the patient had a clinical picture suggestive of a cerebrovascular accident that may have been of atherothrombotic origin due to the multiple cardiovascular risk factors or of cardioembolic origin, associated with intracavitary thrombi.

In December 2009 the patient was admitted to the emergency room with acute chest pain. She had mild tachycardia and borderline systolic blood pressure of 100 mmHg. The electrocardiogram showed sinus tachycardia, left atrial overload and left bundle branch block.

In patients with acute chest pain and electrocardiogram with acute or undetermined left bundle branch block,

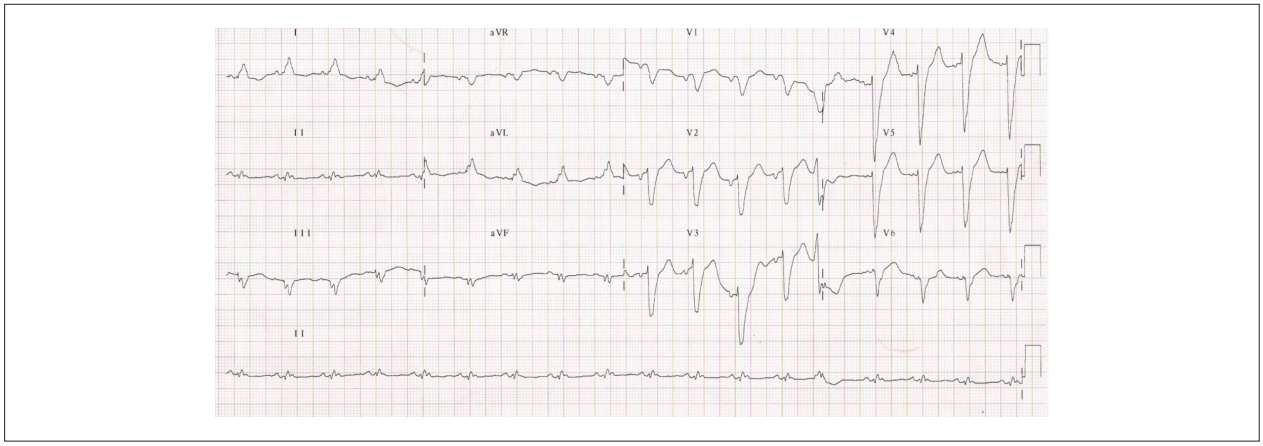

Figure 1 – *Electrocardiogram - Sinus rhythm, low voltage of the QRS complex in the frontal plane, electrically inactive area in the inferior wall and left bundle branch block.*

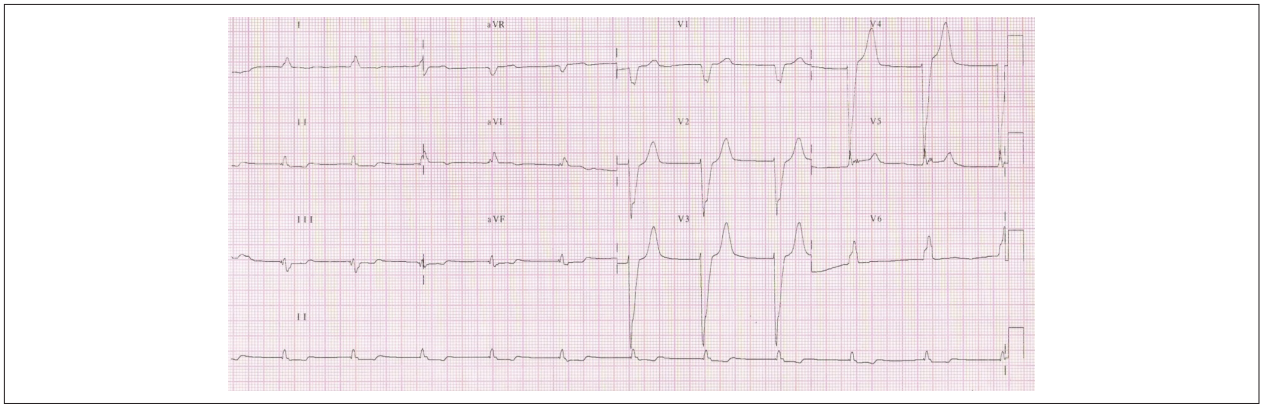

Figure 2 – *Electrocardiogram - Sinus rhythm, left bundle branch block and positive T waves on an also positive derivative of the QRS complex.*

the possibility of acute myocardial infarction should be considered, especially in case of hemodynamic instability. Criteria such as those proposed by Sgarbossa et al.,[2] and Smith et al.,[3] modified by other authors can contribute to the diagnostic accuracy improvement in this context.[2,3] However, one should consider that the occurrence of left bundle branch block is more commonly a marker of previous structural heart disease.

The patient had a cardiorespiratory arrest with pulseless electrical activity (PEA) within a short time after hospital admission. In cases of acute myocardial infarction, PEA can occur in patients with severe ventricular dysfunction and cardiogenic shock and/or mechanical complications such as rupture of the left ventricular free wall with cardiac tamponade, papillary muscle rupture and / or severe dysfunction and acute interventricular septal defect.

Other conditions should be considered in patients with acute chest pain who present with rapid clinical deterioration such as aortic dissection and pulmonary thromboembolism. The chest x-ray showed a massive pleural effusion in the right hemithorax, although this finding was not readily apparent at the physical examination. In this patient, pleural effusion may be due to chronic heart failure decompensation but may also be associated with other conditions, such as rheumatologic diseases, tuberculosis or pleural carcinomatosis due to neoplasias. The last two conditions mentioned here are not uncommon in patients with chronic heart diseases.

Additionally, massive pleural effusions may coexist, in some conditions, with pericardial involvement and consequent cardiac tamponade.[4] Pleural effusion may also be present in patients with acute aortopathies, such as dissection of the aorta and aortic ulcer with associated rupture, but usually the most frequent effusion is located in the left pleural space as a consequence of the aortic anatomy. **(Dr. Hilda Sara Montero Ramirez)**

Main hypothesis: Acute myocardial infarction complicated by cardiogenic shock. **(Dr. Hilda Sara Montero Ramirez)**

Differential diagnoses: Cardiac tamponade, Pulmonary thromboembolism and Dissection of the aorta. **(Dr. Hilda Sara Montero Ramirez)**

Necropsy

The heart weighed 422 g and showed increased volume, with cross-sections (short axis of the ventricles) disclosing a

Anatomopathological Correlation

healed transmural myocardial infarction in the left ventricular anterior and septal walls. There was wall thinning and fibrosis, with antero-apical aneurysm and thrombus at the apex (Figure 3). Signs of a previous systemic thromboembolism, with previous renal and cerebral infarctions were also found, with the latter being a cavitated infarction affecting the temporal and occipital regions of the left cerebral hemisphere.

The aorta and coronary arteries showed marked atherosclerotic involvement, with ulcerated plaques in the aorta and obstructions > 70% in the initial and middle thirds of the anterior interventricular branch of the left coronary artery and between 50 and 70% in the circumflex branch of the same artery and in the right coronary artery. Signs of congestive heart failure were found in the lungs and liver.

The terminal cause of death was pulmonary thromboembolism on the right, with infarction organization at the pulmonary base (Figure 4). The right pleura showed fibrin deposits and the histological analysis showed acute fibrinous pleuritis (Figure 5). There was also pleural effusion on the right (500mL of citrine-colored fluid) **(Prof. Dr. Vera D. Aiello)**.

Anatomopathological diagnoses

- Ischemic heart disease with healed transmural infarctions in the anterior wall and ventricular septum and anteroseptal aneurysm.
- Apical thrombus in the left ventricle.
- Systemic and coronary atherosclerosis of moderate to high degree.
- Previous infarctions in the kidneys and in the temporal and occipital cortex of the left cerebral hemisphere.
- Pulmonary thromboembolism on the right, with recent pulmonary infarction.
- Acute fibrinous pleuritis on the right, with pleural effusion (500mL) **(Prof. Dr. Vera D. Aiello)**

Comments

The patient described herein sought emergency care with chest pain and was known to have ischemic heart disease. The clinical investigation for acute infarction was inconclusive and the patient died less than 24 hours after hospital admission.

Necropsy showed previous infarctions and signs of congestive heart failure. We found no evidence of a recent infarction and attributed the chest pain to the finding of a recent pulmonary thromboembolism on the right, with pulmonary infarction and acute fibrinous pleuritis.

In a study carried out at our institution, which assessed the agreement between clinical diagnoses and necropsy findings, the greatest discrepancy occurred in cases of pulmonary thromboembolism (34.1%).[5] **(Prof. Dr. Vera Demarchi Aiello)**

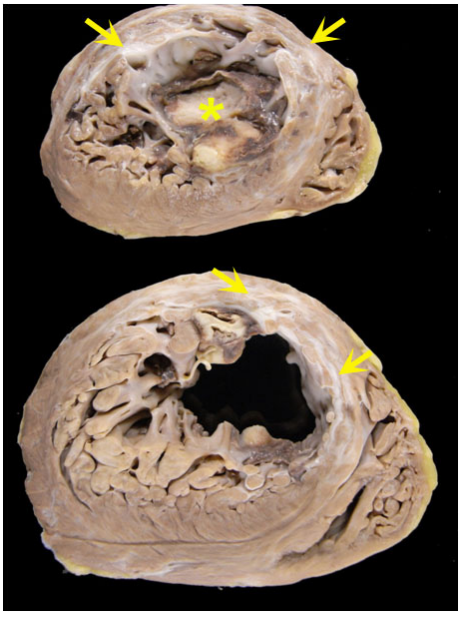

Figure 3 – *Cross-sections of the heart at the level of the ventricles (short axis) showing previous transmural infarctions in the anterior and septal walls (arrows). These same places show thinning of the wall and, localized slight dilatation (aneurysm). There is also a cavitary thrombus in the ventricular apex (asterisk).*

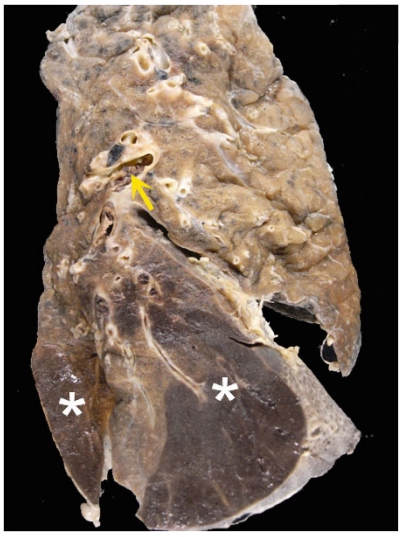

Figure 4 – *Right lung cross-section at its long axis showing the presence of thromboembolism in the central branch of the pulmonary artery (arrow). At the base, there are two triangular areas (asterisks) where the parenchyma is homogeneous and reddish in color, corresponding to recent pulmonary infarctions.*

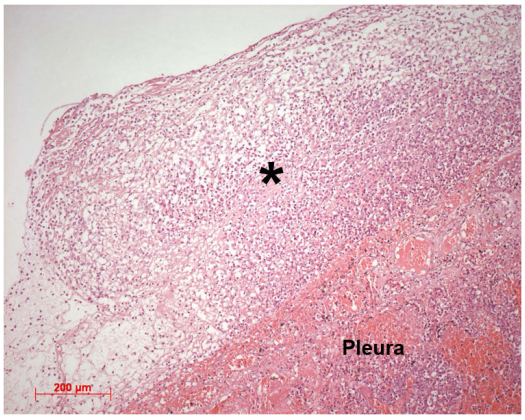

Figure 5 – *Photomicrography of the right pleura showing neutrophilic exudate on the surface (asterisk), characterizing acute pleuritis. Hematoxylin-eosin staining, objective magnification = 10X.*

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Myocarditis with Cardiogenic Shock as the First Manifestation of Systemic Lupus Erythematosus

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Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease with multisystemic and autoimmune characteristics. It is the most common systemic autoimmune disease, occurring mainly in women between 20 and 40 years old, with a female-to-male ratio of 10:1. Even though the kidneys are classically considered the main organ affected by SLE, cardiomyopathy is one of the complications more frequently associated with morbidity and mortality in SLE patients.[1] Cardiovascular impairment can be highly variable in terms of the affected structures and, in severe cases, may lead to cardiogenic shock.

In 2012, the Systemic Lupus International Collaborating Clinics (SLICC) published new criteria for SLE classification, aiming to optimize the diagnosis of cardiovascular impairment. However, cardiovascular disturbances are not part of the SLICC, even though there is such a high prevalence of cardiovascular disturbances in this population.[2]

Case report

A 30-year-old Caucasian woman with a three-year history of arterial hypertension, who was an irregular user of captopril, sought medical attention due to a one-week history of dyspnea and chest pain. The patient presented with cold and clammy skin, dyspnea, hypotension, and tachycardia and was afebrile. A resting electrocardiogram (ECG) showed ST-segment elevation in all derivations. She was admitted for thrombolysis with streptokinase at the original hospital and was then transferred to the Tertiary Clinical Hospital. The patient was admitted to our emergency department on mechanic ventilation and was hemodynamically unstable and receiving norepinephrine.

A chest X-ray revealed cardiomegaly and pulmonary congestion; a transthoracic echocardiogram showed mild to moderate pericardial effusion, with diffuse hypokinesia of the left ventricle and significant systolic impairment with a left ventricular ejection fraction of 30%, as determined by the Teichholz method; the coronary angiography did not show any coronary lesions. Cardiac enzymes such as troponin and CKMB were elevated.

There was no recent history of infection. Additionally, blood cultures were negative three times, and serology for HIV was nonreactive.

The patient was diagnosed with myopericarditis, and hemodynamic support was provided with dobutamine, norepinephrine, and an intra-aortic balloon pump (IABP). Later, on the tenth day of hospitalization, the patient also showed signs of knee arthritis, altered consciousness and anisocoria.

A computed tomography scan of the brain demonstrated multiple areas of cortical and subcortical hypodensity (Figure 1) and a brain arteriography showed a vasculitis pattern in the cerebral arteries. Antinuclear (ANA) and anti-DNA antibody tests were positive.

After the diagnosis of lupus myocarditis was made, on the twelfth day of hospitalization, the patient was started on immunosuppressive therapy with methylprednisolone (1 g intravenously once daily for three consecutive days) and later with cyclophosphamide (0.6 g/m^2 intravenously once a month). There was significant clinical improvement, and a repeated transthoracic echocardiogram showed complete resolution of all changes. The patient remained asymptomatic, and on the twenty-eighth day was discharged from the hospital for outpatient clinical follow-up on 25 mg of captopril twice daily, 30 mg of diltiazem twice daily, 20 mg of omeprazole once daily, 70 mg of prednisone once daily and 250 mg of chloroquine once daily.

Discussion

SLE is a chronic inflammatory multisystemic autoimmune disease with complex characteristics that affects mainly women, of which onset usually occurs between the ages of 16 and 55 years-old; it has a variable frequency in the general population, with an incidence of 1:200 in black women.[1]

Recently, the diagnostic criteria for SLE, collectively called the SLICC, have been revised and increased to a total of 17 criteria, from the 11 criteria of the previous 1997 classification.[2]

To diagnose SLE according to the new recommendations, four or more criteria must be met, and at least one must be clinical, whereas one must be immunological.[1]

In our patient, the diagnosis was confirmed due to the presence of serositis, neurological symptoms, and positive ANA and anti-DNA antibody testing (Table 1).

Although cardiovascular impairment is very common in patients with SLE, with a prevalence of up to 40-50% in

Keywords

Myocarditis; Shock, Cardiogenic; Lupus Erythematosus, System; Heart Failure; Echocardiography.

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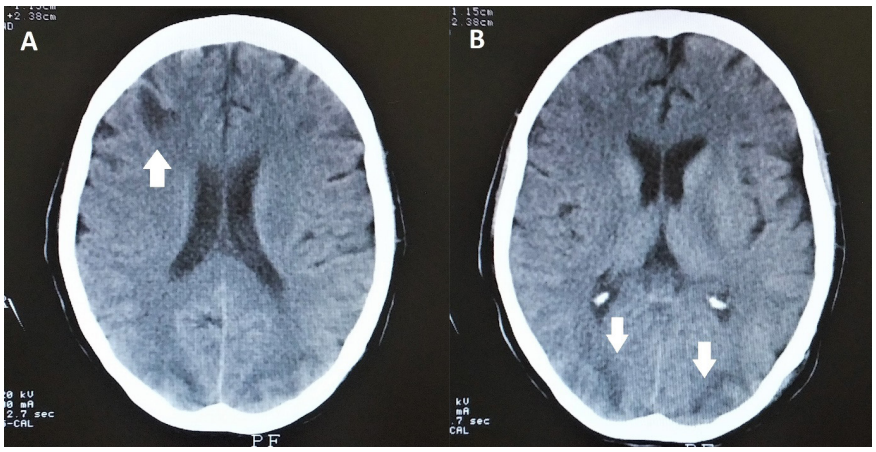

Figure 1 – *Computed tomography of the brain showing, in both A and B panels, hypodensity areas compatible with lacunar infarcts caused by vasculitis.*

Table 1 – Clinical and immunological criteria of the SLICC (Petri et al. 2012)[2]

CLINICAL CRITERIA	IMMUNOLOGICAL CRITERIA
1. Acute Cutaneous Lupus	1. ANA
2. Chronic Cutaneous Lupus	2. Anti-dsDNA
3. Oral ulcers	3. Anti-Sm
4. Nonscarring alopecia	4. Antiphospholipid Antibody
5. Synovitis involving >2 joints	5. Low Complement
6. Serositis	6. Direct Coombs Test
7. Renal manifestations	
8. Neurological Manifestations	
9. Hemolytic anemia	
10. Leukopenia/Lymphopenia	
11. Thrombocytopenia	

postmortem studies, it is not part of the new diagnostic criteria; it is considered only associated damage due to long-term disease.[1-5] It may manifest as pericarditis, myocarditis, Libman-Sacks endocarditis, pulmonary arterial hypertension or coronary artery disease; coronary artery disease is the most prevalent one, due to the inflammatory process of the disease itself together with the use of corticosteroids, which are commonly employed in the treatment of lupus.[6]

Due to the several impairment sites, the clinical manifestations may be quite variable and may range from asymptomatic or oligosymptomatic to cardiogenic shock, in the most severe cases of myocarditis.

In general, patients with lupus myocarditis are usually asymptomatic, with symptoms present in only approximately 5 to 10% of patients.[3] However, severe heart failure may be the first manifestation of the disease.

Cardiogenic shock in lupus patients may have several etiologies, such as coronary artery disease, drug-induced cardiotoxicity (e.g., antimalarial drugs), pericarditis with cardiac tamponade, and valvular insufficiency secondary to valvular destruction, among other causes.[6]

A definitive diagnosis is made through anatomopathological analysis of an endomyocardial biopsy, which is not necessary in most cases. The endomyocardial biopsy has low sensitivity since the myocardial pattern may be focal in many situations.[5] Thus, clinical suspicion combined with epidemiology, individual history and symptoms continue to be essential for diagnosis.

Inflammatory markers associated with the disease may be elevated in cases of myocarditis, along with reduction in serum complement levels. Among all the markers, the presence of anti-DNA antibodies has been associated with lupus myocarditis.[3] An elevation in myocardial necrosis markers can occur; however, it is not related to clinical severity.[7,8]

The treatment of cardiogenic shock secondary to SLE begins with the same supportive treatment that is usually employed for patients with severe heart failure, regardless of the etiology.[2,4,5] Thus, patients are usually started on inotropic drugs, vasodilators and vasopressors, and in patients who are refractory to the conventional clinical approach, mechanical support is required. The most common mechanical support, partly due to its availability, is an intra-aortic balloon pump; however, new devices for circulatory assistance may be used based on need.

Specific treatments for patients with severe left ventricular dysfunction associated with lupus myocarditis include high-dose corticosteroids; in some situations, such as in this patient, this involves pulse therapy with methylprednisolone, and other immunosuppressants (cyclophosphamide, azathioprine) or immunoglobuolins.[2,3,5,7] However, the currently used treatments are not supported by scientific findings from controlled studies, due to the difficulty in performing such studies because of the rarity of this kind of presentation.

An early and precise diagnosis allows the implementation of an aggressive treatment of lupus myocarditis and leads to better outcomes, including the resolution of left ventricular systolic

dysfunction, which may occur in up to 89% of cases within 6 months, according to reports in the literature[3]. However, an episode of lupus myocarditis seems to be a marker of worse prognosis in patients with systemic lupus erythematosus. In addition, perhaps cardiovascular manifestations should be included in future diagnostic criteria for SLE.

Author contributions

conception and design of the research: Rebelato JB; acquisition of data and writing of the manuscript: Rebelato JB, Silveira CFSMP, Valadão TFC, Reis FM; analysis and interpretation of the data: Rebelato JB, Silveira CFSMP, Valadão TFC, Reis FM, Bazan R, Bazan SGZ; critical revision of the manuscript for intellectual contente: Bazan R, Bazan SGZ.

Potential Conflict of Interest

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

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Study Association

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

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Anxiety and Depression and their Association with Low Quality of Life in Patients with Metabolic Syndrome

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Dear Editor,

We read the article entitled "Lifestyle Intervention on Metabolic Syndrome and its Impact on Quality of Life: A Randomized Controlled Trial", by Saboya et al.[1] with great interest and would like to contribute with some suggestions.

Firstly, regarding the method. There are no reports about the blinding of the evaluators, both for the interviews and for body mass index and waist circumference measurements. This is a factor considered a high risk of bias by the "Cochrane Collaboration's tool for assessing risk of bias"[2] since the interviewers, even unconsciously, may influence the responses and their view of the participants.

Secondly, regarding the results. The researchers reported that the quality of life of patients with metabolic syndrome is affected not only by the clinical picture but is also significantly affected by the presence of depression and anxiety.[1] The prevalence of depression and anxiety was 41.7% and 22.2%, respectively, and these data are not associated with the metabolic syndrome components.

Anxiety and depression have often been associated with metabolic syndrome, as well as other non-transmissible chronic diseases, due to the limiting characteristic the disease has on the individuals' lives. The present study did not demonstrate this association, perhaps due to the sample size, which was too small for a study with so many stages and variables for assessment.

The substantial loss of subjects may have compromised the results. Most studies[3,4] that associate metabolic syndrome with depression and anxiety, and also evaluate these patients' quality of life, have a larger sample size.

Keywords

Depressive Disorder; Stress, Physiological; Depression; Metabolic Syndrome; Quality of Life.

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