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EDITORIAL

The Heart of Physically Active Young Individuals can be Remodeled with an Intense 35-Week Military Training

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Physicians are educated and trained to treat diseases and save lives. This is particularly noticeable and valued among cardiologists. However, not every physician, living a busy professional life, manages to see the other "extreme". We quite often fall ill because we do not properly take care of our health, by failing to adopt a healthy lifestyle and to embrace the most recommended preventive strategies. It seems increasingly important to anticipate the disease and act to prevent it. In such context, the regular practice of physical exercise becomes a significant, if not the major priority. However, there is this natural clinical concern about "excessive" exercise practice, which would jeopardize the health and the physical integrity of the individuals. The study by our Portuguese and Swedish coleagues[1] published in this issue of the International Journal of Cardiovascular Sciences is worth reading.

Dinis et al.[1] have studied 76 young Portuguese individuals who had already achieved high levels of regular physical activity (> 10 hours/weeks) before entering a special military training program. That special training program consisted of 20 hours of different types of exercise practice at a purposely high intensity, divided into five days a week for 35 weeks. Because of the extremely rigorous characteristic of that special program, only 17 of those young individuals, all with previous experience on sports competition, managed to complete the 35-week training.

Keywords

Exercise; Exercise Movement Techniques; Aolescents; High-Intensity Internal Training; Atrial Remodeling/physiology ; Arrhythmias, Cardiac/diagnostic imaging.

The training caused several changes in the young participants, such as marked muscle mass gain and significant body fat loss, producing a very healthy body composition profile. As expected, mild reductions in heart rate and blood pressure at rest were observed when comparing the pre- and post-intervention mean values. However, the most relevant finding of that study was the significant left ventricular structural remodeling, identified by use of echocardiographic measurements taken before and after the special military training program, indicating that, even in physically fit young individuals with normal cardiac function, the heart can undergo morphofunctional adaptations of physiological nature, observed at rest.

The question posed by Dinis et al.[1] is certainly relevant and original, and its results contribute to the body of knowledge on exercise and sports cardiology. However, as in any study, some limitations exist, many of which have been reported by the authors. The first is the lack of a control group. However, with such obvious variations in the comparison between the pre- and post-training results, that limitation relates to the scientific methodology theory rather than to the practical and objective significance for the clinician. Nevertheless, it would have been advisable to perform a functional assessment of the aerobic and non-aerobic components of physical fitness,[2] and, exceptionally, a cardiopulmonary exercise test to quantify the changes in maximum oxygen consumption and anaerobic threshold resulting from the training, widening the range of possibilities of interpreting the functional implications of physical exercise practice on the cardiac remodeling reported by those authors. Another relevant point is that only 22% of the young participants completed the training. If such individuals can or cannot be classified as athletes, as the authors have, can be argued.[3] However,

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it would be more important to investigate whether any cardiac morphofunctional aspect obtained on the initial assessment could predict who would be able to complete such a rigorous physical training. Finally, a more detailed assessment of some other cardiac aspects, such as right ventricular function and structure[4] and the occurrence of arrhythmias (particularly the supraventricular ones), would be interesting.[5]

Briefly, Dinis et al.[1] are to be congratulated on the relevance of the subject studied and the results obtained, from which it is worth noting that more than 700 hours of high-intensity physical training for 35 weeks caused no morphostructural damage to the heart of healthy young individuals. Such data corroborate the increasingly prevalent impression that, at least from the cardiac viewpoint, it seems unlikely that healthy individuals can reach the true "over-exercise" point that can harm their hearts.[6] The truly deleterious factor for health is a sedentary lifestyle, and, thus, cardiologists and particularly those interested in exercise and sports cardiology should focus their attention and priority on sedentary individuals or those who exercise insufficiently or incompletely rather than on the extremely rare individuals who, due to a personal option, choose to exercise as much as four hours a day.

References

1. Dinis P, Dores H, Teixeira R, Moreno L, Mónico J, Cachulo MC, et al. Additional cardiac remodelling induced by intense military training in athletes. Int J Cardiovasc Sci. 2018; 31(3):209-217.
2. Araujo CG. Componentes aeróbico e não-aeróbicos da aptidão física: fatores de risco para mortalidade por todas as causas. Revista Factores de Risco. 2015;35(1):36-42.
3. Araujo CG, Scharhag J. Athlete: a working definition for medical and health sciences research. Scand J Med Sci Sports. 2016;26(1):4-7.
4. Scharhag J, Thunenkotter T, Urhausen A, Schneider G, Kindermann W. Echocardiography of the right ventricle in athlete's heart and hearts of normal size compared to magnetic resonance imaging: which measurements should be applied in athletes? Int J Sports Med. 2010;31(1):58-64.
5. Ricci C, Gervasi F, Gaeta M, Smuts CM, Schutte AE, Leitzmann MF. Physical activity volume in relation to risk of atrial fibrillation: a non-linear meta-regression analysis. Eur J Prev Cardiol.2018 Jan 1:2047487318768026 [Epub ahead of print]
6. Araujo CGS, Castro CLB, Franca JF, Souza-Silva CG. Aerobic exercise and the heart: discussing doses. Arq Bras Cardiol. 2017;108(3):271-5.

ORIGINAL ARTICLES

Metabolic Syndrome and Insulin Resistance by HOMA-IR in Menopause

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Abstract

Background: Metabolic syndrome is an important cardiovascular risk factor, and its prevalence increases after menopause. However, it is still uncertain whether menopause is an independent risk factor for metabolic syndrome. One of the pathophysiological basis for metabolic syndrome is insulin resistance, which can be calculated by the Homeostatic Model Assessment-Insulin Resistance (HOMA-IR) method, and the association between insulin resistance and menopause is little known.

Objective: To evaluate the association between metabolic syndrome and insulin resistance in menopausal women.

Method: Descriptive study, which evaluated 150 women, aged 40 to 65, treated at a Gynecology Outpatient Clinic of a tertiary public hospital, from May to December of 2013. The sample was divided into two groups: Group I, comprising women in the premenopausal period and Group II, comprising women in the post-menopausal period. The presence of metabolic syndrome and its components were evaluated, as well as occurrence of insulin resistance in both groups. The association of menopausal status and the assessed variables was assessed using the Mann-Whitney, Chi-square and Fisher's exact tests. The significance level was set at 5%. The statistical analysis was performed using STATA 12.0.

Results: Metabolic syndrome and its components were more prevalent in postmenopausal women. Postmenopausal women also had a higher prevalence of insulin resistance, but no statistical association was observed between the findings.

Conclusion: The menopausal status was not significantly associated with metabolic syndrome and insulin resistance. Insulin resistance was considered an independent risk factor for the development of metabolic syndrome only in the postmenopausal group. (International Journal of Cardiovascular Sciences. 2018;31(3)201-208)

Keywords: Metabolic Syndrome; Insulin Resistance; Menopause; Climacteric; Cardiovascular Diseases.

Introduction

Approximately 40 million women were menopausal in the United States in 2010 and there was an estimate of 60 million menopausal women by 2020.[1] In Brazil, 28% of the women (24.3 million) are over 40 years of age, and in the city of São Luís, state of Maranhão, the estimated female population in 2010 was 538,138, of which 39% was in the age group between 40 and 59 years.[2]

A set of cardiovascular risk factors related to visceral obesity and Insulin Resistance (IR) defines Metabolic Syndrome (MS),[3] which is established in the presence of three or more of the following components: glucose intolerance with fasting glycemia ≥ 100 mg/dL; abdominal obesity or greater amount of visceral fat, with waist circumference > 90 cm in men and > 80 cm in women; triglycerides ≥ 150 mg/dL; high-density lipoprotein (HDL) cholesterol < 40 mg/dL for men and < 50 mg/dL for women; current antihypertensive therapy or blood pressure >130 x 85 mmHg.

IR represents a decrease in the ability of insulin to stimulate glucose use. Pancreatic β-cells increase insulin production and secretion as a compensatory mechanism, while glucose tolerance remains normal. This has been pointed out as a collective health problem, affecting several age groups, especially menopausal-aged women.[4]

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The Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) index predicts the level of IR according to the glycemia and basal insulinemia. It has been widely used and represents one of the several alternatives for IR assessment, mainly because it is a simple, fast, easy to apply and low-cost method.[5]

The prevalence of MS and its association with IR in menopausal women is still poorly studied in our country. The identification of the main components of MS and their association with IR can be very useful in terms of public health, for instance, by allowing greater specificity for cardiovascular disease primary and secondary prevention actions.

The aim of this study was to evaluate the prevalence of MS, its components, and its association with IR in menopause.

Methods

This was a descriptive study, which evaluated 150 menopausal patients, aged 40 to 65 years, who agreed to participate in the study by signing the Free and Informed Consent form (FICF) at the Gynecology Outpatient Clinic of Hospital Universitário Materno Infantil of Universidade Federal do Maranhão, from May to December 2013. Patients who did not authorize their participation in the study; pregnant women; statin users; those who had undergone coronary angioplasty or myocardial revascularization, or those with a history of previous acute myocardial infarction; those who did not have information on the cause of menopause and the age at which it occurred; or cases of menopause caused by medical interventions (surgeries, radiotherapy or chemotherapy), were not included in the study. The patients were divided into two groups: Group I: premenopausal women and Group II: postmenopausal women.

The sociodemographic variables were: age (in full years), ethnicity, family income, schooling, marital status and occupation. Personal history data were also obtained (such as: date of last menstrual period, and time of menopause); comorbidities (Systemic Arterial Hypertension – (SAH), Diabetes Mellitus – (DM) and Cerebrovascular Accident – (CVA); daily use of medications and family history of coronary artery disease before age 60; and Information on social and life habits (regular physical activity, and the reporting of smoking status and alcohol intake).

The anthropometric variables were collected through a physical examination, including weight, height and Waist Circumference (WC). The WC measurement was made at the midpoint between the iliac crest and the lowest rib, using a simple fiberglass measuring tape with a latch (manufacturer: Sanny), in the orthostatic position, without clothes covering the chest and at the end of expiration.[6]

Blood pressure (BP) was obtained using the mean of two measurements, obtained through the standardized auscultatory method. Patients were classified according to the VI Brazilian Hypertension Guideline (VI Diretriz Brasileira de Hipertensão).[7] Participants who had a previous diagnosis of hypertension and/or used antihypertensive drugs were considered hypertensive, and those with a previous diagnosis of diabetes mellitus or undergoing treatment with hypoglycemic agents were considered diabetic, according to the consensus of the Brazilian Society of Endocrinology.[8]

The presence of MS was defined according to the criterion of Albert et al., which requires the presence of three or more of the following components: WC > 80 cm; systolic BP > 130 mmHg and/or diastolic BP > 85 mmHg or undergoing pharmacological treatment for arterial hypertension; fasting triglyceride levels > 150 mg/dL or undergoing pharmacological treatment for hypertriglyceridemia; HDL-cholesterol levels < 50 mg/dL or pharmacological treatment; fasting glycemia > 100 mg/dL or pharmacological treatment for hyperglycemia.

The biochemical tests were: fasting glucose, total cholesterol, HDL-cholesterol, triglycerides, urea, creatinine and glycated hemoglobin by the colorimetric method. All examinations were analyzed in the laboratory of Hospital Universitário Materno Infantil of Universidade Federal do Maranhão.

HOMA-IR was also calculated using the formula (insulin mUI/L x blood glucose mmol/L/22.5) to evaluate the insulin resistance (IR) of the participants. As reference values, HOMA-IR > 4.65 was used if Body Mass Index (BMI) was >28.9 kg/m^2 and HOMA-IR > 3.60 if BMI > 27.5 kg/m^2, according to Stern et al.[10]

The collection of anthropometric measures and blood samples after a 12-hour fasting was performed at the same time and according to this sequence.

Statistical analysis

Statistical analysis was performed using Fisher's exact test, Mann-Whitney and chi-square tests. A statistically

significant value of $p < 0.05$ was considered, using the STATA® software, version 12.0

This study is part of a larger project, entitled "Endothelial Dysfunction and Cardiovascular Risk Assessment in Menopausal Women", which was approved by the Research Ethics Committee (REC) of Hospital Universitário da Universidade Federal do Maranhão, under Opinion n. 182/11, according to Resolution 196/96 and its complementary regulations of the National Health Council (CNS/MS).

Results

A total of 150 women were evaluated, 75 in the premenopausal Group I and 75 in the postmenopausal Group II, aged 40 to 59 years, and mean age of 49.6 (± 6.7 years). Metabolic syndrome (MS) was diagnosed in 57 women (38%), of which 24 (32%) were premenopausal and 33 (44%) were postmenopausal women. There was no statistical difference between menopause and MS. When studying the association between MS components and menopausal status, higher mean values of blood pressure (BP), triglycerides, fasting glucose and waist circumference were found, as well as lower values of HDL-cholesterol in group II. The menopausal status was an independent risk factor only for the increase in BP and fasting glycemia (Table 1).

When evaluating the prevalence of IR calculated by the HOMA-IR Index, 28 participants had insulin resistance. In Group I, ten women (13.3%) had IR, while in Group II,

Table 1 – Distribution of metabolic syndrome components, according to the menopausal status, in women treated at a gynecology outpatient clinic. São Luís (MA), Brazil, 2015

Variables	General		Menopausal status				p value
			Premenopausal		Postmenopausal		
	n	%	n	%	n	%	
Arterial hypertension							**0.001***
No	100	66.67	60	80.00	40	53.33	
Yes	50	33.33	15	20.00	35	46.67	
Triglycerides							**0.212**
Normal	45	30.00	26	34.67	19	25.33	
High	105	70.00	49	65.33	56	74.67	
HDL cholesterol							**0.400**
Normal	93	62.00	49	65.33	44	58.67	
Low	57	38.00	26	34.67	31	41.33	
Fasting glucose							**0.031***
Normal	89	59.33	51	68.00	38	50.67	
Altered	61	40.67	24	32.00	37	49.33	
Waist circumference							**0.597**
No risk	47	31.33	25	33.33	22	29.33	
Risk	103	68.67	50	66.67	53	70.67	
Metabolic syndrome							**0.130**
Absent	93	62.00	51	68.00	42	56.00	
Present	57	38.00	24	32.00	33	44.00	

**p < 0.05, chi-square test.*

18 participants (24%) had IR, as shown in table 2. In this analysis, the menopausal status was once again not a direct predictor for the IR presence.

The study also assessed whether IR alone may be considered an independent risk factor for the development of MS and its components in both groups of assessed women. IR was statistically different from the increase in triglycerides and fasting glucose in the premenopausal group.

The study showed the association between the presence of IR and MS in both groups. The IR, calculated by the HOMA-IR index, differed from the statistically significant result in the presence of MS, only in the postmenopausal group, as shown in table 4.

Discussion

The prevalence of MS in women of different populations varies considerably. Differences in genetic profile, eating habits, physical activity level, age and lifestyle influence the prevalence of MS.[11] It is postulated that, among the several risk factors for the syndrome development, menopause is a direct predictor.[12] In our study, the prevalence of MS was 24% in premenopausal women and 44% in the postmenopausal group, with no statistically significant association. Figueiredo Neto et al.,[13] in a study carried out in the State of Maranhão, Brazil, using the National Cholesterol Education Program's (NCEP) criteria, found a prevalence of 24% in premenopausal women and 44.4% in postmenopausal ones, also without a statistically significant association. As for the study carried out by Ali et al.,[14] in Tunisia, with 2,680 women between 2004 and 2005, using NCEP criteria, they found a prevalence of 25.6% and 45.7% in the pre- and postmenopausal groups, respectively, with the menopausal status being an independent risk factor for the development of MS.

In our study, we evaluated the prevalence of MS components and the possible association with menopausal status. Among them, the most frequent in both groups was the increase in triglycerides, with a prevalence of 65.3% and 74.6% in the pre- and postmenopausal groups, respectively. After that, the increase in the waist circumference was the most often observed, with a frequency of 66.6% in the premenopausal period and 70.6% in the postmenopausal one. However, neither showed a statistical association with menopausal status. Cho et al.,[15] in a study carried out in South Korea, with 1,003 women, identified the increase in WC and the reduction in HDL-cholesterol as the most prevalent components of premenopausal MS, reaching 46.1% and 22.5%; respectively. In the postmenopausal period, the increase in WC was the most common (78.9%), followed by an increase in BP (40.6%).[15] Arthur et al.,[16] in a study carried out with African women, using the International Diabetes Federation (IDF) criteria, identified as the most prevalent factors in the premenopausal group the increase in WC (79%) and in BP (49.7%). Jouyandesh et al.,[17] based on the National Cholesterol Education Program – The Adult Treatment Panel III (NCEP-ATP III), studying 118 postmenopausal women from January 2011 to January 2012 at a clinic for menopause follow-up, found as the most prevalent components, once again, an increase in WC (64.3%) and BP (47.9%).[17] However, the authors suggest that the frequencies observed in the prevalence of MS components may vary among populations due to environmental, nutritional, economic and genetic diversity, characteristic of women in each area.

Table 2 – Prevalence of overall insulin resistance and according to the menopausal state in women treated in a Gynecology Outpatient Clinic. São Luís (MA), Brazil, 2015

Insulin resistance	General		Menopausal status				p value
			Premenopausal		Postmenopausal		
	n	%	n	%	n	%	
Absent	122	81.33	65	86.67	57	76.00	0.094
Present	28	18.67	10	13.33	18	24.00	

** $p < 0.05$, chi-square test.*

Table 3 – Statistically significant difference between HOMA-IR and metabolic syndrome and its components, according to menopausal status in women treated in a Gynecology Outpatient Clinic. São Luís (MA), Brazil, 2015

Variables	Premenopausal		Postmenopausal	
	HOMA-IR	p value*	HOMA-IR	p value*
	Mean ± Standard deviation		Mean ± Standard deviation	
Metabolic syndrome				
Absent	2.17 ± 1.15	0.1294	2.62 ± 1.77	0.0025*
Gift	3.16 ± 2.45		4.64 ± 3.27	
HDL cholesterol				
Normal	2.33 ± 1.32	0.7426	2.72 ± 1.76	0.0114*
Low	2.78 ± 2.30		4.39 ± 3.40	
Blood Pressure				
Normal	2.17 ±1.10	0.1751	3.04 ± 2.02	0.2470
Altered	3.20 ± 2.54		3.76 ± 3.15	
Waist circumference				
Normal	2.01 ± 1.28	0.0835	2.89 ± 2.45	0.0871
Cardiovascular risk	2.73 ± 1.87		3.63 ± 2.76	
Triglycerides				
Normal	1.65 ± 1.00	0.0001*	2.89 ± 2.28	0.2073
High	2.93 ± 1.86		3.59 ± 2.79	
Fasting glucose				
Normal	1.92 ± 1.02	< 0.0001*	2.73 ± 1.76	0.0531
Altered	3.69 ± 2.25		4.12 ± 3.24	

** p < 0.05, chi-square test.*

Furthermore, when we evaluated the association between the MS components and the menopausal status, we observed that the occurrence of menopause was considered an independent risk factor for the increase of both BP and blood glucose levels. Kim et al.[18], when studying 3,219 Korean women, found a statistically significant association only between the following syndrome components: WC, BP and triglycerides. Linet al.,[19] in a study developed in the northern region of Taiwan, with 597 women, based on NCEP criteria, demonstrated that menopause is a direct predictor for the development of four of the five MS components, including: WC, BP, triglycerides and HDL-cholesterol. Again, the authors believe that the divergent associations found in their study are consequences of the genetic, socioenvironmental and sociocultural differences of the studied populations.

It is known that MS has IR among its pathophysiological bases,[20] but for some time, the influence of menopause has been discussed on the onset of insulin resistance. To date, literature data are unclear regarding whether menopause is associated with increased IR, but evidence indicates that the role of aging and body fat redistribution (central adiposity) in IR increase in postmenopausal women is well established.[21] This study evaluated the presence of IR through the HOMA-IR index in pre- and postmenopausal women, as well as the association between the MS components with the HOMA-IR value, observing a

Table 4 – Association between insulin resistance and metabolic syndrome in premenopausal and postmenopausal women treated in a Gynecological Outpatient Clinic. São Luís (MA), Brazil, 2015.

Insulin Resistance	Premenopausal				p value*	Postmenopausal				p value
	Metabolic syndrome					Metabolic syndrome				
	Absent		Present			Absent		Present		
	n	%	n	%		n	%	n	%	
Absent	46	90.20	19	79.17	0.190	39	92.86	18	54.55	< 0.001†
Present	5	9.80	5	20.83		3	7.14	15	45.55	

** chi-square test; † p < 0.05 Fisher's exact test.*

prevalence of IR in 13.3% premenopausal and 24% postmenopausal women, with no statistically significant association. Lejsková et al.,[22] studying 909 pre- and postmenopausal women in the Czech Republic, found a slight increase in HOMA-IR values after menopause, but no significant association with menopausal status. These findings are corroborated by the study by Toth et al.,[23] which evaluated the association between menopausal status and insulin sensitivity through the direct and more reliable method to evaluate IR – the glycemic clamp – and demonstrated that menopause is not an independent risk factor for the development of IR.

The presence of IR was associated with the development of MS in the pre- and post-menopause, and it was observed that IR behaved as a direct predictor of MS only in the group of women who had already undergone the menopausal transition. This observation is consistent with what was found in the Czech study carried out by Lejsková et al.[22]. However, in a European study, the association occurred only in those women who already had a high HOMA-IR index in the reproductive period. These findings indicate that the menopausal transition alone did not result in an IR increase, and that the IR only determined MS in postmenopausal women.

This thesis is reinforced by the finding of Manco et al.[24] study, carried out in several European countries, with 523 participants, which analyzed IR in men and women of different ages. They observed that IR proportionally increases in both genders from middle age on, suggesting that menopause does not significantly affect IR.[24]

Among the components of the MS, the association with IR occurs in the premenopausal period only with elevated triglyceride levels and with altered glycemic levels. In the postmenopausal period, IR is an independent risk factor only for the reduction of HDL-cholesterol. No similar data were found in the recent articles on MS and IR for the studied population.

This study had as limitation a non-probabilistic sample with a relatively small number of assessed individuals, and further studies with larger sample sizes are necessary.

Conclusion

In the analyzed sample, menopause was not considered a risk factor for the development of metabolic syndrome, as well as for insulin resistance. However, the menopausal status was shown to be an independent risk predictor for fasting blood glucose and blood pressure components.

Insulin resistance was considered a risk factor for the development of metabolic syndrome only in the postmenopausal period.

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Author contributions

Conception and design of the research: Fonseca EJNC, Figueredo Neto JA. Acquisition of data: : Fonseca EJNC, Silva BL, Figueredo Neto JA, Rocha TPO, Melo JB, Andrade MVG, Sousa SMB, Lopes EJ, Lopes EJ. Analysis and interpretation of the data: Fonseca EJNC, Serra CB, Figueredo Neto JA. Statistical analysis: Fonseca EJNC, Nogueira IAL, Figueredo Neto JA. Obtaining financing: Fonseca EJNC, Nogueira IAL, Figueredo Neto JA, Melo JB. Writing of the manuscript: Fonseca EJNC, Figueredo Neto JA. Critical revision of the manuscript for intellectual content: Fonseca EJNC, Nogueira IAL, Figueredo Neto JA, Rocha TPO.

Potential Conflict of Interest

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

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Study Association

This article is part of the thesis of master submitted by Érika Joseth Nogueira da Cruz Fonseca, from Universidade Federal do Maranhão.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital Universitário da Universidade Federal do Maranhão under the protocol number 005900/2011-00. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

References

1. Gold EB, Crawford SL, Avis NE, Crandall CJ, Matthews KA, Waetjen LE, et al. Factors related to age at natural menopause: longitudinal analyses from SWAN. Am J Epidemiol. 2013;178(1):70-83. doi: 10.1093/aje/kws421.
2. Instituto Brasileiro de Geografia e Estatística (IBGE). Síntese de indicadores sociais: uma análise das condições de vida da população brasileira. [Internet]. 2010. [Acesso em 2015 jul 16]. Disponível em: http:www.ibge.gov.br/home/estatistica/populacao/condicoesde vida/indicadoresminimos/sinteseindicsociais2010/SIS_2010.pdf.3
3. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Clement JI, Donato KA, et al. Harmonizing the metabolic syndrome: a Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120(16):1640-5. doi: 10.1161/CIRCULATIONAHA.109.192644.
4. Gobato AO, Vasques AC, Zambon MP, Barros Filho AA, Hessel G. Metabolic syndrome and insulin resistance in obese adolescents. Rev Paul Pediatr. 2014;32(1):55-62. doi: http://dx.doi.org/10.1590/S0103-05822014000100010.
5. Vasques AC, Rosado LH, Alfenas RC, Geleneze B. Critical analysis on the use of the homeostasis hodel assessment (HOMA) indexes in the evaluation of the insulin resistance and the pancreatic beta cells functional capacity. Arq Bras Endocrinol Metab. 2008;52(1):32-9. doi: http://dx.doi.org/10.1590/S0004-27302008000100006.
6. Lainscak M, Haehling S, Anker SD. Natriuretic peptides and other biomarkers in chronic heart failure: from BNP, NT-pró BNP, and MR-pro ANP to routine biochemical markers. Int J Cardiol. 2009;132(3):303-11. doi: 10.1016/j.ijcard.2008.11.149.
7. Sociedade Brasileira de Cardiologia; Sociedade Brasileira de Hipertensão; Sociedade Brasileira de Nefrologia. [VI Brazilian Guidelines on Hypertension]. Arq Bras Cardiol. 2010;95(1 Suppl):1-51. PMID: 21085756. Erratum in: Arq Bras Cardiol. 2010;95(4):553.
8. Sociedade Brasileira de Diabetes.. Diagnóstico e classificação do Diabetes Mellitus do tipo 2. Consenso Brasileiro sobre Diabetes. [Acesso em 2015 jan 10]. Disponível em: http://www.c:/bvs/editavles/pdf/consensoSBD.doc.
9. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28(7):412-9. PMID: 3899825.
10. Stern SE, Williams K, Ferrannini E, DeFronzo RA, Bogardus C, Stern MP. Identification of individuals with insulin resistance using routine clinical measurements. Diabetes. 2005;54(2):333-9. PMID: 15677489.
11. Allal-Elasmi M, Taieb SH, Hsairi M, Zayani Y, Omar S, Sanhaji H, et al. The metabolic syndrome: prevalence, main characteristics and association with socio-economic status in adults living in Great Tunis. Diabetes Metab. 2010;36(3):204-8. doi: 10.1016/j.diabet.2009.11.009.
12. Mendes KG. Estado menopáusico e síndrome metabólica em mulheres no climatério atendidas em um ambulatório no Sul do Brasil [Dissertação]. Porto Alegre: Universidade Federal do Rio Grande do Sul; 2012.
13. Figueiredo Neto JA, Figueiredo ED, Barbosa JB, Barbosa Fde F, Costa GR, Nina VJ, et al. Metabolic syndrome and menopause: cross-sectional study in gynecology clinic. Arq Bras Cardiol. 2010;95(3):339-45. doi: http://dx.doi.org/10.1590/S0066-782X2010005000094.
14. Ali SB, Belfki-Benali H, Aounallah-Skhiri H, Traissac P, Maire B, Delpeuch F, et al. Menopause and metabolic syndrome in Tunisian women. BioMed Research International. 2014; Article ID 457131, 7 pages. doi: https://dx.doi.org/10.1155/2014/457131.
15. Cho GJ, Lee JH, Park HT, Shin JH, Hong SC, Kim T, et al. Postmenopausal status according to years since menopause as an independent risk factor for the metabolic syndrome. Menopause. 2008;15(3):524-9. doi: 10.1097/gme.0b013e3181559860.
16. Arthur FK, Adu-Frimpong M, Osei-Yeboah J, Mensah FO, Owusu L. The prevalence of metabolic syndrome and its predominant components among pre-and postmenopausal Ghanaian women. BMC Res Notes. 2013 Nov 8;6:446. doi: 10.1186/1756-0500-6-446.
17. Jouyandeh Z, Nayebzadeh F, Qorbani M, Asadi M. Metabolic syndrome and menopause. J Diabetes Metab Disord. 2013;12(1):1. doi: 10.1186/2251-6581-12-1

18. Kim HM, Park J, Ryu SY, Kim J. The Effect of menopause on the metabolic syndrome among Korean women: the Korean National Health and Nutrition Examination Survey, 2001. Diabetes Care. 2007;30(3):701-6. doi: 10.2337/dc06-1400.

19. Lin WY, Yang WS, Lee LT, Chen CS, Liu CS, Lin CC, et al. Insulin resistance, obesity and metabolic syndrome among non-diabetic pre and post-menopausal women in North Taiwan. Int J Obes (Lond). 2006;30(6):912-7. doi: 10.1038/sj.ijo.0803240.

20. Meirelles RM. Menopause and metabolic syndrome. Arq Bras Endocrinol Metab. 2014;58(2):91-6. doi: http://dx.doi.org/10.1590/0004-2730000002909.

21. Jou HJ, Huang HT. Metabolic syndrome: menopausal women and the health care challenge. Taiwan J Obstet Gynecol. 2009;48(3):205-9. doi: 10.1016/S1028-4559(09)60291-6. Erratum in: Taiwan J Obstet Gynecol. 2009;48(4):453.

22. Lejsková M, Alusík S, Suchánek M, Zecová S, Pitha J. Menopause: cluestering of metabolic syndomecomponentes and population changes in insulin resistance. Climateric. 2011;14(1):83-91. doi: 10.3109/13697131003692745.

23. Toth MC, Sites CK, Eltabbakh GH, Poehlman ET. Effect of menopausal status on insulin-stimulated glucose disposal. Diabetes Care. 2000;23(6):801-6. PMID: 10841000.

24. Manco M, Nolfe G, Calvani M, Natali A, Nolan J, Ferrannini E, et al; European Group for the Study of Insulin Resistance. Menopause, insulin resistance and risk factor for cardiovascular disease. Menopause. 2006;13(5):809-817. doi: 10.1097/01.gme.0000233492.38638.74.

ORIGINAL ARTICLE

Additional Cardiac Remodeling Induced by Intense Military Training in Competitive Athletes

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Abstract

Background: Cardiac remodeling depends on the intensity, duration, and training method.

Objective: To evaluate if the training performed in a Portuguese military special operations troop increases cardiac remodeling in a sample of young individuals who previously practiced competitive sports.

Methods: A prospective study involving 76 military candidates for military special operations, 45 of whom previously practiced at competitive level (> 10 hours per week). Of these military athletes, only 17 successfully completed the course. The evaluation was performed at 6 months intervals and included a complete clinical history, physical examination, vital signs, anthropometric data and echocardiographic evaluation. Statistical significance was considered when $p < 0.05$, with a 95% confidence interval.

Results: At the end of the course, there was a decrease in the percentage of fat mass (19.1 ± 3.3% vs. 13.1 ± 3.5%; $p < 0.01$), an increase in the percentage of lean mass (41.3 ± 2.1% vs. 44.4 ± 1.8%; $p < 0.01$), and decreased systolic and diastolic blood pressure and heart rate. Regarding cardiac remodeling, there was an increase in left ventricular diastolic diameter (49.7 ± 3.2 mm vs. 52.8 ± 3.4 mm; $p < 0.01$), an increase trend in left atrial volume (27.3 ± 4.5 mL/m² vs. 28.2 ± 4.1 mL/m²; $p = 0.07$) and increased left ventricular mass (93.1 ± 7.7 g/m² vs. 100.2 ± 11.4 g/m²; $p < 0.01$). Functional variables also changed, with an increase in S' (15 (13-16) cm/s vs. 17 (16-18) cm/s; $p < 0,01$) and a decrease in left ventricular ejection fraction (60 ± 6% vs. 54 ± 6%; $p < 0.01$).

Conclusion: Intense military physical training resulted in additional cardiac remodeling in athletes of competitive level, both structural and functional. (International Journal of Cardiovascular Sciences. 2018;31(3)209-217)

Keywords: Atrial Remodeling; Exercise; Athletes; Military Personnel.

Introduction

Since the 19th century, cardiac adaptations induced by physical exercise have been known. Henschen, in 1899, recognized cardiomegaly in long distance skiers through percussion of heart borders, concluding that this increase was related to cavity dilatation and wall hypertrophy of the left ventricle (LV), and that these changes resulted in physical benefits for the athletes.[1,2] With the evolution of complementary diagnostic means, mainly echocardiography, Morganroth et al.,[3] in 1975, developed the hypothesis that cardiac morphological changes depended on hemodynamic overload associated with physical exercise: dynamic exercise associated with eccentric hypertrophy due to volume overload, resulting in increased cardiac cavities by serial sarcomere addition; and static exercise associated with concentric hypertrophy due to pressure overload, with LV wall hypertrophy and parallel sarcomere addition.[3-5]

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Different sports and training methods result in varied cardiac remodeling patterns. A predominantly eccentric hypertrophy is expected to be found in a marathon runner, whereas concentric hypertrophy is expected in a weightlifter.[6] However, most of the sports practiced nowadays are influenced by the two components of the exercise (the dynamic and the static), and the adaptation these athletes may undergo is less predictable. The intensity, duration and frequency of physical exercise are characteristics that can determine different patterns of cardiac remodeling. High-intensity training is associated with more marked structural and functional changes.[7,8]

The aim of this study was to verify if there is additional cardiac remodeling in athletes of competitive level, when exposed to a high-intensity training protocol performed in a military course of special operations troops.

Methods

This was an observational and prospective study, which evaluated military personnel at the beginning and end of a course directed at special operations troops. The selected military personnel were candidates to complete the special operations troops course, the Portuguese Army Command (*Comando do Exército Português*). There were 76 candidates, of which 45 were previously athletes who competed in different modalities. Only 17 individuals successfully completed the course, all of them athletes. The evaluations were carried out between January and June 2016. In these evaluations, carried out at 6 months intervals, a complete clinical history including a medical questionnaire, physical examination, anthropometric evaluation and transthoracic echocardiogram (TTE) was performed. The evaluations were preceded by a rest interval of at least 12 hours. An electrocardiogram (ECG) was also performed in all participants as a cardiovascular screening method.

All subjects signed the Free and Informed Consent Form prior to participating in the study. The study protocol was authorized by the Ethics Committee of Faculdade de Medicina da Universidade de Coimbra (protocol reference 087/2015).

Characteristics of the study population

All military men who completed the course were previously considered competitive athletes. They practiced competitive physical exercises (> 10 hours a week), participating in regional and national competitions. Although this activity was not their main economic means of support, they all had benefits derived from their sports performance. The athletes maintained their level of physical performance in the different modalities until the first evaluation carried out by the researchers. The practiced modalities can be seen in Table 1. During the special operations course, they suspended the previous training, and the physical exercise performed by them was only the result of the training given in the military course.

Characteristics of military physical training in the special operations course

The special operations course consisted of one component of overall physical training and another of military physical training. In the overall physical training, the military was submitted to dynamic and static physical exercises, practicing several modalities such as athletics, team sports (soccer or basketball), swimming and combat sports (boxing, for instance).

The military physical training combined the physical education aspect adjusted to military specificities. For this purpose, the military performed dynamic exercises (long-distance running, long runs interspersed with sprinting and marching exercises), static (cargo transportation and weight lifting) and mixed exercises (steeplechase track, among other activities).

The special operations training program was carried out in two phases. The first one lasted 10 weeks, and the military were submitted to high-intensity exercise training, seeking to achieve approximately 77 to 95% of the maximal heart rate (HR),[9] with a frequency of five times a week and for an average of 4 hours daily, combining different types of exercise. The second phase lasted 15 weeks and included high-intensity exercises (approximately 77 to 95% of maximal HR), with periods of almost maximal or maximal intensity (> 96% of maximal HR),[9] five times a week, for an average of 4 hours a day, alternating different types of exercise.

Clinical evaluation

All participants underwent a clinical history and physical examination, including the analysis of cardiovascular risk factors (CVRF), pharmacological and dietary habits, hours of training during the military course and sports history.

Table 1 - Basal study sample characteristics

Basal sample characteristics	Military (n = 17)
Demographic characteristics	
Age, years	20 (20-24)
Male gender, %	17 (100)
Caucasian, %	17 (100)
Anthropometric characteristics	
Weight, kg	75.2 ± 7.8
Lean mass	41.3 ± 2.1
Fat mass, %	19.1 ± 3.3
SBP, mmHg	128 ± 10
DBP, mmHg	73 ± 7
HR, bpm	66 ± 12
Sports history	
Years of competition	7.4 ± 3.4
Hours of training/day, sports history	2.3 ± 0.6
Hours of training/day, military course	4.0 ± 0.5
Modalities practiced in the past	
Athletics	
5,000 and 10,000m long-distance runner	2
100 and 200m sprinter	2
Weight thrower	1
Soccer	4
Indoor soccer (*Futsal*)	2
Rugby	2
Canoeing	1
Swimming	1
Handball	1
Martial arts	1

SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate.

Anthropometric evaluation

The anthropometric evaluation was performed under the nursing team coordination, and the military personnel was evaluated through a full body digital scale with impedance (HBF510W, OMRON®), which allowed the assessment of body weight, percentage of fat mass (FM) and lean mass (LM) and height (using a tape measure). The systolic blood pressure (SBP) and diastolic blood pressure (DBP), as well as HR measurements were evaluated utilizing an arm blood pressure monitor (HEM 7113, OMRON®), according to the current recommendations.[10]

To predict the maximum HR, the indirect model was used, based on the equation Maximum HR = 220 – age. The following variables were calculated: variation (Δ) weight, ΔLM, ΔFM; ΔSBP, ΔDBP, ΔHR through the formula: [(final parameter - initial parameter)/initial parameter x 100].

Electrocardiographic evaluation

All 12-lead ECGs were performed by cardiopneumology technicians (electrocardiograph model 1200HR, NORAV®) and interpreted by two cardiologists according to the refined criteria,[11] of which one of them was blinded to the study conditions.

Echocardiographic evaluation

All TTEs (Vivid 7, GE Healthcare®) were performed by a cardiologist and reviewed by an echocardiography specialist blinded to the study conditions. The echocardiographic study was detailed, and echocardiographic windows were obtained according to the current recommendations of the European Society of Cardiology.[12,13] Data were digitally recorded for off-line analysis using the Echopac GE Healthcare software (Horton, Norway®). LV wall, interventricular septum (IVS) and LV posterior wall (LVPW) measurements, such as LV diastolic diameter (LVDD), were obtained at the parasternal long-axis window. The relative wall thickness (RWT) was calculated through the formula [(2 * LVPW)/LVDD].

The modified Simpson rule was used to determine the LV volumes and ejection fraction (LVEF) and left atrium (LA) volume. The results were indexed to the body surface area (BSA). LV mass was calculated using the Devereux's formula.[13]

Pulsed Doppler was acquired using a four-chamber apical window. Tissue Doppler images of the mitral and tricuspid annuli were obtained, and the E and e' waves were determined, as well as the S' wave velocity, respectively.

Two-dimensional echocardiography with speckle-tracking imaging was used to calculate the LV global

longitudinal strain (GLS). The images were acquired in apical four-, two- and three-chamber windows, with electrocardiographic monitoring. In the off-line mode, with dedicated software (EchoPAC 9.0, GE Healthcare®, Horten, Norway), myocardial tracking and subsequent conversion to Lagrangian were performed using a semiautomatic endocardial edge detection program. This system allowed manual corrections to be performed to ensure the correct tracing between the cavity and the LV wall. Using the three apical windows of four, two and three chambers, the regional longitudinal strain mean was calculated, so that, subsequently, it was possible to calculate the GLS mean. The exam quality was considered good when up to two segments were excluded and excellent when all segments were analyzed.

The following variables were calculated: ΔIVS, ΔLV mass, ΔRWT, ΔLVDD, ΔLA volume, ΔLVEF, ΔS', Delta of the Tricuspid Annular Plane Systolic Excursion (ΔTAPSE) and ΔGLS. The calculation of each of these variables was performed by the formula [(final parameter – initial parameter) / initial parameter x 100].

Figure 1 depicts the TTE of a military after the special operations course.

Statistical analysis

The distribution of the continuous variables was verified by the Kolmogorov-Smirnov test. The homogeneity of the individual variables was evaluated by the Levene test. Variables with normal distribution were expressed as mean and standard deviation, and paired Student's t-test with two-tailed analysis was used to compare groups. Variables with non-normal distribution were expressed as median and interquartile ranges, and the groups were compared using the paired Wilcoxon's test. Categorical variables were shown as frequency and percentage, and chi-square test and Fisher's test were used when appropriate.

A p value < 0.05 was considered statistically significant, with a 95% confidence interval. The software Statistical Package for Social Science (SPSS), version 20 (SPSS® Inc., Chicago, IL, USA) was used for the calculation and analysis of all data.

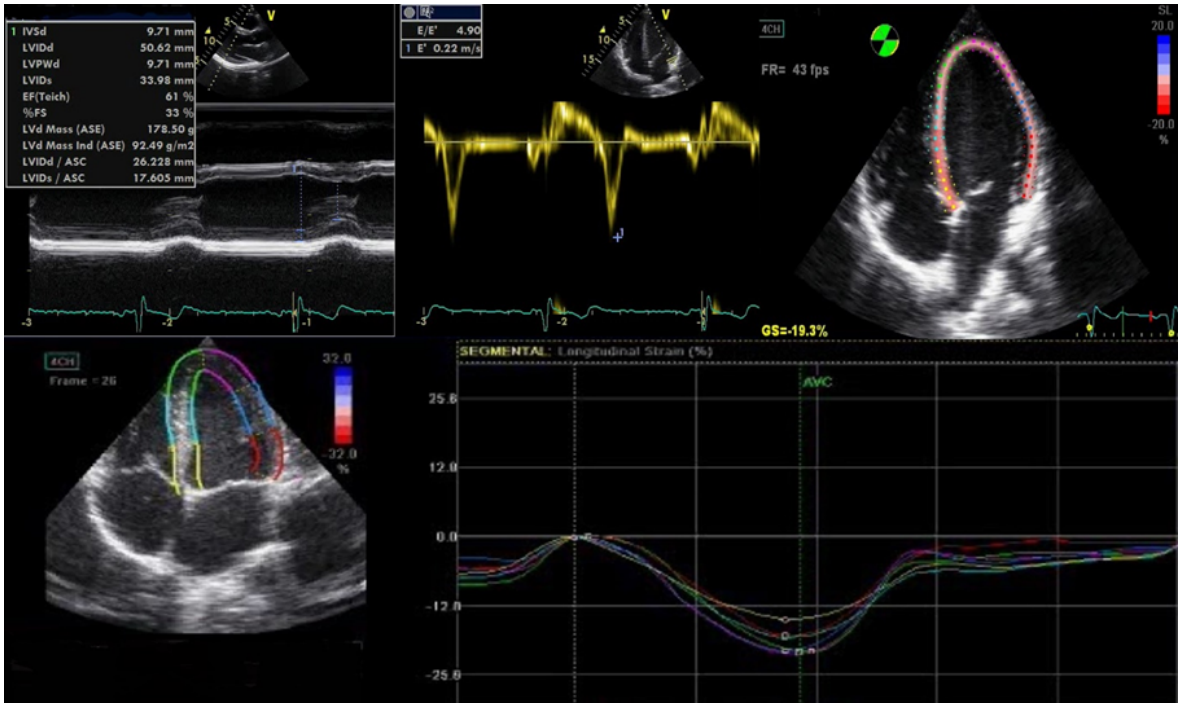

Figure 1 - Heart with left ventricular parietal thickness and dimension within limits considered to be normal, with supranormal values of diastolic function and normal global longitudinal strain.

Results

Population description

The sample characteristics, anthropometric data, the sports history and the different modalities practiced are shown in Table 1. The sample consisted of young Caucasian males, with a median age of 20 (20-24) years and body mass index (BMI) of 25.3 ± 2.7 kg/m^2.

Almost a fifth of the sample (20.6%) had at least one CVRF, with smoking being the most frequent (17.6%), followed by dyslipidemia (5.9%). None of the subjects included in the study had a family history of cardiovascular disease, hypertension or diabetes mellitus.

Anthropometric data variations

After the special operations course, the military had significant increase in body weight, with gain of LM and decrease in FM. There were also differences in relation to the blood pressure profile, with a decrease in mean SBP, DBP and HR (Table 2).

Electrocardiographic evaluation

All ECGs showed sinus rhythm and were considered normal or with only physiological alterations. The most prevalent physiological alteration was the early repolarization pattern (41.2%), followed by LV hypertrophy (29.4%), sinus bradycardia (17.6%) and incomplete right bundle branch block (17.6%).

Echocardiographic evaluation

The echocardiographic data are shown in Table 3. There was an increase, with statistical significance, in the left cavity dimensions, both in the LV diastolic diameter and in the LA volume, in addition to an increase in LV mass and a decrease in RWT. In the functional variables, there was reduction in the LVEF at rest and increase in the S' wave. Although the GLS did not show any significant differences, there was a tendency to decrease its absolute value.

Percentage differences between the beginning and end of the course

The differences in remodeling observed between the beginning and end of the special operations course in relation to anthropometric and echocardiographic data are shown in Figure 2. It was observed an increase in weight (3.1 ± 3.3%, $p < 0.01$) and LM (7.7 ± 4.1%, $p < 0.01$) and a decrease in FM (-30 ± 15.7%, $p < 0.01$). The pressure profile was altered with a decrease in SBP (-4.8 ± 3.0%, $p < 0.01$) and DBP (-8.6 ± 7.4%, $p < 0.01$). Among the echocardiographic findings, there was an increase in LV mass (10.2 ± 10.8%, $p < 0.01$) and LVDD (6.4 ± 14.3%, $p < 0.01$) and LA volume (10.6 ± 21.1%, $p = 0.02$), and a decrease in RWP (-7.0 ± 14.3%, $p = 0.05$). Functionally, there was a decrease in LVEF (-11.0 ± 12.8%, $p < 0.01$) and an increase in S' [13.3 (6.3-19.4)%; $p < 0.01$].

Discussion

In the present study, carried out in athletes undergoing a challenging military training program in a special operations course, additional cardiac remodeling was observed, as well as structural, functional and anthropometric changes.

Table 2 - Anthropometric data

Anthropometric data	Military (n = 17)		
	Initial	Final	p value
Weight, kg	75.2 ± 7.8	77.4 ± 6.6	< 0.01*
Lean mass, %	41.3 ± 2.1	44.4 ± 1.8	< 0.01*
Fat mass, %	19.1 ± 3.3	13.1 ± 3.5	< 0.01*
Systolic blood pressure, mmHg	128 ± 10	122 ± 7	< 0.01*
Diastolic blood pressure, mmHg	73 ± 7	66 ± 5	< 0.01*
Heart rate, bpm	62 (57-73)	60 (53-62)	< 0.01⁺

**Paired Student's t-test; ⁺Paired Wilcoxon test.*

Table 3 - Variation of echocardiographic parameters

Parameters	Military (n = 17)		
	Initial	Final	p value
Interventricular septum, mm	9.7 ± 1.0	9.9 ± 1.0	0.39*
Posterior wall, mm	9.7 ± 0.9	9.6 ± 0.8	0.39*
Left ventricular mass, indexed, g/m²	93.1 ± 7.7	100.2 ± 11.4	< 0.01*
Relative wall thickness	0.40 ± 0.1	0.36 ± 0.1	0.05*
Left ventricular diastolic diameter, mm	49.7 ± 3.2	52.8 ± 3.4	< 0.01*
Left ventricular systolic diameter, mm	33.2 ± 3.3	35.1 ± 2.6	0.04*
Left atrial volume (mL/m²)	27.3 ± 4.5	28.2 ± 4.1	0.07*
Left ventricular ejection fraction (%)	60 ± 6	54 ± 6	< 0.01*
Lateral E' (cm/s)	19 ± 3	19 ± 3	0.92*
E/E'	5.3 ± 1.0	5.3 ± 0.9	0.61*
S' (cm/sec)	15 (13-16)	17 (16-18)	< 0.01⁺
Tricuspid annular plane systolic excursion, mm	25 ± 4	26 ± 5	0.34*
Left ventricular longitudinal strain (%)	-21.3 ± 0.9	-20.5 ± 1.9	0.11*

**Paired Student's t-test; ⁺Paired Wilcoxon test.*

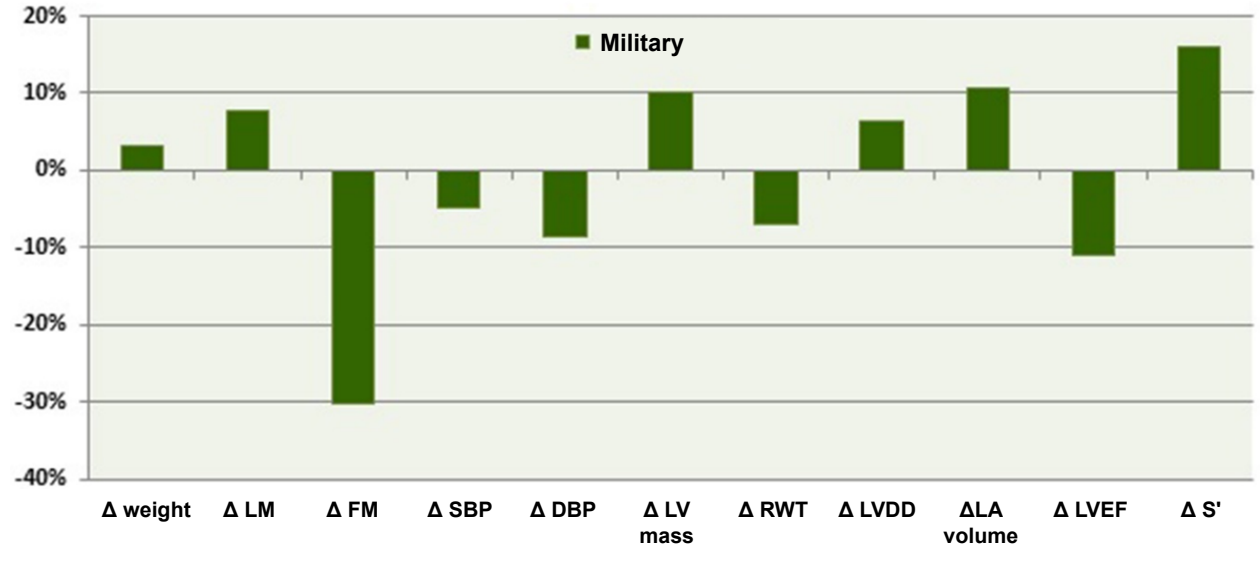

Figure 2 - Anthropometric and echocardiographic variables.

Regarding vital signs, there was a decrease in mean SBP, DBP and HR at rest. This fact is due to the decrease in the activation of the sympathetic nervous system and the increase of the parasympathetic system at rest in the individuals submitted to the training.[14,15] As for the anthropometric data, a mean increase in body weight was observed, with an increase in LM and marked reduction in FM. At the beginning of the training program, the military had FM values considered above the desirable for their age and gender,[16] and these values decreased to levels considered appropriate after the military training program. The decrease in FM is related to the increase in intensity and/or duration of training,[17] also demonstrated in this study.

The cardiac adaptations were compatible with eccentric cardiac remodeling. There was a significant increase in LV dimensions and mass, and tendency to increase the LA volume. It is known that cardiac remodeling resulting from physical exercise is related to the increase and harmonious hypertrophy of the cardiac cavities, also influencing the right cavities.[17,18] During the special operations course, the percentage of military personnel with eccentric hypertrophy (RWT < 0.42 and LVMI > 115g/m^2)[19] practically doubled (from 5.9% to 11.8%). The verified changes result from the training intensity, frequency and method. Although the special operations training program consists of dynamic and static exercises, the dynamic training predominates. Frequency and intensity are other factors that contribute to high cardiac output, with corresponding volume overload and cardiac chamber dilatation.[20]

At the functional level, there was a decrease in LVEF, which agrees with what has been previously described.[21-23] This occurs because athletes submitted to intense and prolonged exertion may show a slight decrease in resting LVEF. Several factors may contribute to this phenomenon, such as the athletes' ability to significantly increase LVEF during exercise at the expense of increased LV diastolic dimensions, which, through the Frank-Starling mechanism, is associated with increased preload, more effective diastolic filling and lower LV systolic volume, allowing a considerable increase in ejection volume.[22] Another possible explanation is that LVEF represents an estimate of LV function and not directly of myocardial contractility, which may underestimate its capacity when submitted to intense exertion. Also, the mathematical formula used to calculate LVEF (100 x ejection volume/LVDD) in hearts with increased cavities underestimates LV performance.[22] In this study, despite the verified adaptations, one can say the latter were within ranges considered normal (none of the military had LVEF < 50% at the initial or final evaluations). However, after the military training program, 12 individuals (approximately 70% of the population) had LVEF at rest between 50 and 55%.

Myocardial GLS was studied using the speckle-tracking technique, and it was verified that the military had values within the ranges considered normal. There was a decrease in the absolute value of GLS, but it did not reach a statistically significant difference, probably due to the small sample size. This parameter may be important to differentiate left ventricular hypertrophy associated with exercise and disease, namely hypertrophic cardiomyopathy, since values of myocardial mechanics, within normal values, suggest physiological alterations.[24-26]

The literature on cardiac remodeling resulting from physical exercise in athletes is vast,[27-30] but the existing bibliography in the military population is smaller. The authors did not find in the literature a study that addressed cardiovascular variations in competitive athletes when submitted to an intense military training program. Particularly in Portugal, in the Army special operations group, this is the first study that associated the military physical exercise training with the cardiovascular remodeling resulting from it.

Limitations

The present study has some limitations. The first is the small sample assessed. The great physical and mental demands of this type of training mean that the number of individuals who successfully finish it is a small one. The second is the absence of a control group, and the fact that the individuals who dropped out of the course were not re-evaluated, to compare their results with the ones that finished the military training. The third limitation is the fact that the individuals were not further evaluated with aerobic physical fitness indicators, cardiopulmonary exercise test, and muscle strength tests, before and at the end of the course, to evaluate the real impact of training on the heart and gains in physical and functional capacity. The cardiopulmonary exercise testing would be important to more accurately determine the training range based on maximal HR. Fourth, the quantification of unprogrammed training practiced by the individuals during the special operations course, very common in this context, limits the more objective determination of this variable, which is probably underestimated. During the course, these individuals are permanently involved

in activities and evaluations in which the physical component is central, in addition to conventional or scheduled physical exercise practice. Fifthly, the study protocol did not include the hydration level assessment of the evaluated individuals to verify whether it was similar at both moments of the evaluation and, finally, although they denied taking any stimulants, this fact was not proven either.

Conclusion

Intense military physical training causes additional cardiac remodeling in athletes of competitive level, both structural and functional. The characteristics of the physical exercise are conditioning factors of cardiac remodeling, and should be considered during the evaluation of these individuals.

Author contributions

Conception and design of the research: Dinis P, Dores H, Teixeira R. Acquisition of data: Dinis P, Moreno L, Mónico J, Bergman M, Lekedal H. Analysis and interpretation of the data: Dinis P. Statistical analysis: Dinis P. Writing of the manuscript: Dinis P, Dores H, Teixeira R. Critical revision of the manuscript for intellectual content: Dinis P, Dores H, Teixeira R, Cachulo MC, Cardoso J, Gonçalves L.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Faculty of Medicine of the University of Coimbra under the protocol number 087/2015. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

References

1. Henschen S. Skilanglauf und skiwettlauf: Eine Medizinische Sportstudie. Mitt Med Klin Upsala (Jena). 1899;2:15-8.
2. Maron BJ, Pelliccia A. The heart of trained athletes: cardiac remodeling and the risk of sports, including sudden death. Circulation. 2006;114(15):1633-44. doi: 10.1161/CIRCULATIONAHA.106.613562.
3. Morganroth J, Maron BJ, Henry WL, Epstein SE. Comparative left ventricular dimensions in trained athletes. Ann Intern Med. 1975;82(4):521-4. doi: 10.7326/0003-4819-82-4-521.
4. Dores H, Freitas A, Malhotra A, Mendes A, Sharma S. The hearts of competitive athletes: An up-to-date overview of exercise-induced cardiac adaptations. Rev Port Cardiol. 2015;34(1):51-64. doi: 10.1016/j.repc.2014.07.010.
5. Paterick TE, Gordon T, Spiegel D. Echocardiography: profiling of the athlete's heart. J Am Soc Echocardiogr. 2014;27(9):940-8. doi: 10.1016/j.echo.2014.06.008.
6. Grazioli G, Sanz M, Montserrat S, Vidal B, Stiges M. Echocardiography in the evaluation of athletes. F1000Res. 2015 Jun 15;4:151. doi: 10.12688/f1000research.6595.1.
7. Arbab-Zadeh A, Perhonen M, Howden E, Peshock RM, Zhang R, Adams-Huet B, et al. Cardiac remodeling in response to 1 year of intensive endurance training. Circulation. 2014;130(24):2152-61. doi: 10.1161/CIRCULATIONAHA.114.010775.
8. Kemi OJ, Haram PM, Loennechen JP, Osnes JB, Skomedal T, Wisloff U, et al. Moderate vs. high exercise intensity: differential effects on aerobic fitness, cardiomyocyte contractility, and endothelial function. Cardiovasc Res. 2005;67(1):161-72. doi: https://doi.org/10.1016/j.cardiores.2005.03.010.
9. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al; American College of Sports Medicine. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc. 2011;43(7):1334-59. doi: 10.1249/MSS.0b013e318213fefb.
10. Mancia G, Fagard R, Narkiewicz, Redón J, Zanchetti A, Bohm M, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology. J Hypertens. 2013;31(7):1281-357. doi: 10.1097/01.hjh.0000431740.32696.cc.
11. Sheikh N, Papadakis M, Ghani S, Zaidi A, Gati S, Adami PE, et al. Comparison of electrocardiographic criteria for the detection of cardiac abnormalities in elite black and white athletes. Circulation. 2014;129(16):1637-49. doi: 10.1161/CIRCULATIONAHA.113.006179.
12. Evangelista A, Flachskampf F, Lancellotti P, Badano L, Aguilar R, Monaghan M, et al; European Association of Echocardiography. European Association of Echocardiography recommendations for standardization of performance, digital storage and reporting of echocardiographic studies. Eur J Echocardiogr. 2008;9(4):438-48. doi: 10.1093/ejechocard/jen174.
13. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28(1):1-39.e14. doi: 10.1016/j.echo.2014.10.003.

14. Aubert A, Seps B, Beckers F. Heart rate variability in athletes. Sports Med. 2003;33(12):889-919. PMID: 12974657.

15. Fernandes T, Oliveira M. Eccentric and concentric cardiac hypertrophy induced by exercise training: microRNAs and molecular determinants. Braz J Med Biol Res. 2011;44(9):836-47. doi: http://dx.doi.org/10.1590/S0100-879X2011007500112.

16. American College of Sports Medicine. (editor). ACSM's health-related physical fitness assessment manual. 4th ed. Baltimore: Lippincott Williams & Wilkins; 2013. ISBN: 978-1-4511-568-0.

17. Zaidi A, Ghani S, Sharma R, Oxborough D, Panoulas VF, Sheikh N, et al. physiological right ventricular adaptation in elite athletes of African and Afro-Caribbean origin. Circulation. 2013;127(17):1783-92. doi: 10.1161/CIRCULATIONAHA.112.000270.

18. Ujka K, Bruno RM, Catuzzo B, Bastiani L, Tonacci A, D'angelo G, et al. Right cardiac chambers remodeling in marathon and ultra-trail athletes detected by speckle tracking echocardiography. Eur Heart J Cardiovasc Imaging. 2016;17(suppl_2):ii45-ii48. doi: 10.1093/ehjci/jew236.003.

19. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al; American Society of Echocardiography's Nomenclature and Standards Committee; Task Force on Chamber Quantification; American College of Cardiology Echocardiography Committee; American Heart Association; European Association of Echocardiography, European Society of Cardiology. Recommendations for cardiac chamber quantification. Eur J Echocardiogr. 2006;7(2):79-108. doi: 10.1016/j.euje.2005.12.014.

20. Pluim BM, Zwinderman AH, van der Laarse A, van der Wall EE. The athlete's heart. A meta-analysis of cardiac structure and function. Circulation. 2000;101(3):336-44. doi: https://doi.org/10.1161/01.CIR.101.3.336.

21. Abernethy WB, Choo JK, Hutter AM Jr. Echocardiographic characteristics of professional football players. J Am Coll Cardiol. 2003;41(2):280-4. doi: 10.1016/S0735-1097(02)02633-5.

22. Galderisi M, Cardim N, D'Andrea A, Bruder O, Cosyns B, Davin L, et al. The multi-modality cardiac imaging approach to the athlete's heart: an expert consensus of the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015;16(4): 353. doi: 10.1093/ehjci/jeu323.

23. Gilbert CA, Nutter DO, Felner JM, Perkins JV, Heymsfield SB, Schlant RC. Echocardiographic study of cardiac dimensions and function in the endurance-trained athlete. Am J Cardiol. 1977;40(4):528-33. doi: https://doi.org/10.1016/0002-9149(77)90067-4.

24. Beaumont A, Grace F, Richards J, Hough J, Oxborough D, Sculthorpe N. Left ventricular speckle tracking-derived cardiac strain and cardiac twist mechanics in athletes: a systematic review and meta-analysis of controlled studies. Sports Med. 2017;47(6):1145-70. doi: 10.1007/s40279-016-0644-4.

25. Galanti G, Stefani L, Mascherini G, Di Tante V, Tonncelli L. Left ventricular remodeling and the athlete's heart, irrespective of quality load training. Cardiovasc Ultrasound. 2016;14(1):46. doi: 10.1186/s12947-016-0088-x.

26. Caselli S, Montesanti D, Autore C, Di Paolo FM, Pisicchio C, Squeo MR, et al. Patterns of left ventricular longitudinal strain and strain rate in Olympic athletes. J Am Soc Echocardiogr. 2015;28(2):245-53. doi: 10.1016/j.echo.2014.10.010.

27. Sharma S, Maron BJ, Whyte G, Firoozi S, Elliott PM, Mckenna WJ. Physiologic limits of left ventricular hypertrophy in elite junior athletes: relevance to differential diagnosis of athlete's heart and hypertrophic cardiomyopathy. J Am Coll Cardiol. 2002;40(8):1431-6. doi: https://doi.org/10.1016/S0735-1097(02)02270-2.

28. Basavarajaiah S, Boraita A, Whyte G, Wilson M, Carby L, Shah A, et al. Ethnic differences in left ventricular remodeling in highly-trained athletes: relevance to differentiating physiologic left ventricular hypertrophy from hypertrophic cardiomyopathy. J Am Coll Cardiol. 2008;51(23):2256-62. doi: 10.1016/j.jacc.2007.12.061.

29. Pelliccia A, Culasso F, Di Paolo F, Maron BJ. Physiologic left ventricular cavity dilatation in elite athletes. Ann Intern Med. 1999;130(1):23-31. doi: 10.7326/0003-4819-130-1-199901050-00005.

30. Abergel E, Chatellier G, Hagege AA, Oblak A, Linhart A, Ducardonnet A, et al. Serial left ventricular adaptations in world-class professional cyclists: implications for disease screening and follow-up. J Am Coll Cardiol. 2004;44(1):144-9. doi: 10.1016/j.jacc.2004.02.057.

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ORIGINAL ARTICLE

Correlation Between the Complexity of Coronary Lesions and High-Sensitivity Troponin Levels in Patients with Acute Coronary Syndrome

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Abstract

Background: Cardiovascular diseases are the leading cause of death in Brazil. Biochemical markers have diagnostic and prognostic importance in acute coronary syndromes (ACSs), with troponin as the preferred biomarker. Studies have already demonstrated a positive relationship between increased levels of high-sensitivity troponin (hsTn) and prognosis. However, few studies have correlated hsTn levels with the complexity of coronary lesions.

Objectives: To compare hsTn levels with the complexity of coronary lesions according to the SYNTAX score, and to correlate the levels of this biomarker with the TIMI and GRACE scores in patients with ACS.

Methods: Retrospective, cross-sectional study with 174 patients with ACS. The correlation between variables was assessed by the nonparametric Spearman's rank correlation, and statistical analysis was performed by the SPSS program, with a significance level of 5%.

Results: Mean age was 63 years, and most patients were women (52.9%), hypertensive, non-diabetic and non-smokers. Nineteen percent of the patients had STEMI, 43.1% NSTEMI, and 36.8% unstable angina. Most were in Killip 1 (82.8%). Median hsTn was 67 pg/mL. Median risk scores were 3, 121 and 3 in the TIMI, GRACE and SYNTAX scores, respectively. There was a correlation of hsTn with SYNTAX ($p < 0.001$, $r = 0.440$), TIMI ($p < 0.001$, $r = 0.267$) and GRACE ($p = 0.001$, $r = 0.261$) scores.

Conclusion: A positive linear correlation was found of hsTn levels with the complexity of coronary lesions, and with the TIMI and GRACE clinical scores. (International Journal of Cardiovascular Sciences. 2018;31(3)218-225)

Keywords: Acute Coronary Syndrome; Troponin; Cardiovascular Diseases / Mortality; Myocardial Infarction; Hospitalization / Economy.

Introduction

Cardiovascular diseases (CVDs) are the main cause of death in Brazil, generating high costs of hospitalizations every year.[1] According to the World Health Organization, there were 214.2 deaths per 100,000 inhabitants from CVDs in Brazil in 2012, with higher prevalence among men.[2]

Acute myocardial infarction (AMI) is one of the main causes of death and disability worldwide.[3] According to the third international definition of AMI, published in 2012, AMI occurs when there is evidence of myocardial necrosis in a clinical context of acute myocardial ischemia.

The importance of biochemical markers in both diagnosis and prognosis of acute coronary syndromes (ACSs) has been well documented.[4] Cardiac troponin has been considered the best biomarker for AMI diagnosis since 2000, when a redefinition of myocardial infarction was published.[5] High-sensitivity troponin (hsTn) assay, as compared with the first generations of troponin assays,

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shows higher analytical sensitivity enabling precise quantification of low troponin concentrations. Therefore, hsTn can exclude AMI earlier than other less sensitive, conventional markers. However, its indiscriminate use may lead to false positive results while contributing with few additional cases of ischemia.[6]

Prognostic evaluation of ACSs includes clinical, laboratory and anatomical criteria. One of the anatomical criteria is the SYNTAX score, which has been established to evaluate the complexity of coronary lesions diagnosed by coronary angiography. SYNTAX score is a comprehensive angiographic rating system derived from anatomical features and coronary lesion.[7]

Several studies have consistently demonstrated a positive relationship between increased hsTn and the prognosis of patients with ACSs.[8] Nevertheless, few studies have evaluated the relationship between hsTn and the complexity of angiographic coronary lesions.[9]

In light of this, the aim of the present study was to correlate hsTn levels with the complexity of coronary lesions according to the SYNTAX score in patients admitted for ACSs. Considering the prognostic value of this biomarker, we will also compare this hsTn levels with previously validated risk scores, the GRACE and TIMI scores.

Methods

This was a retrospective, cross-sectional, analytical study using convenience sampling, and collection of secondary data from medical records. From January to June 2013, 211 patients with suspicion of ACS (AMI and unstable angina) were admitted to the emergency department of Maria Aparecida Pedrossian University Hospital. Among these patients, 174 had the diagnostic confirmed and underwent coronary angiography during hospitalization, and hence considered eligible for the study.

The myocardial necrosis markers and respective reference values used in this institution are: hsTn > 14 pg/mL and CKMB (mass) > 3.8 ng/mL in women and 6.7 ng/mL in men. Patients' highest troponin levels were considered for the analysis of correlation between troponin and lesion complexity. For the diagnosis of unstable angina, we considered: pain or discomfort in the chest, epigastrium, mandible, shoulder, back or upper limbs, with onset at rest, and of early or progressive onset.[10]

Anatomical complexity of coronary lesions was classified by the SYNTAX score, using a validated calculator available at http://www.syntaxscore.com. The score evaluates the number, localization, extension and morphology of lesions. Patients with scores lower than 22 were considered at low risk, patients with scores from 23 to 32 were considered at moderate risk, and those with scores higher than 32 were considered at high risk. All tests were revised and the score rated by the same experienced hemodynamic technician.

TIMI and GRACE clinical scores were used for risk stratification of the included patients. GRACE score was calculated using the electronic calculator available at http://www.outcomes-umassmed.org/ GRACE/ acs_risk/acs_risk_content.html. Patients with a score lower than 109 were considered at low risk; patients with a score between 109 and 140 were considered at intermediate risk, and those with scores higher than 140 were considered at high cardiovascular risk.

Patients were considered diabetic if they met one of the following criteria, according to the Brazilian Diabetes Society Guidelines:[11] previous diagnosis of the disease and use of glucose-lowering agents; patients without a previous diagnosis of the disease with fasting glucose levels equal to or greater than 126 mg/dL, plasma glucose level after a 75 g glucose load equal to or greater than 200 mg/dL, casual glucose level equal to or greater than 200 mg/dL associated with classical symptoms (polyuria, polydipsia, unexplained weight loss), or glycated hemoglobin levels higher than 6.5%.[11] Patients who reported smoking a cigarette in the year prior to the study, and those who had quit smoking less than 30 days were considered smokers.

Inclusion criteria were: patients older than 18 years with a confirmed diagnosis of ACS according to the Third Universal Definition of Myocardial Infarction.[3] Patients who had not undergone a coronary angiography during hospitalization were excluded from the study.

The study was approved by the research ethics committee of the Federal University of Mato Grosso do Sul (approval number 51783415.1.0000.0021).

Statistical analysis

Linear correlations of hsTn levels with TIMI, GRACE and SYNTAX scores were assessed by the nonparametric Spearman correlation coefficient, since the data did not pass the Shapiro-Wilk test for normality. The other results were described using descriptive statistics or in tables

and graphics. Quantitative variables were expressed as median and interquartile range, and categorical variables as relative and absolute frequency. Statistical analyses were performed using the SPSS software version 24.0, and statistical significance was set at 5%.[12]

Limitations

- Small number of patients;

- Some of the medical records data were missing, which made the exact calculation of the GRACE and TIMI prognostic score impossible; data of family history were also missing in 35.6% of the medical records. Most medical records did not contain patients' body weight or time of symptom onset, which were required for TIMI calculation in patients with ST-segment elevation myocardial infarction (STEMI). No patient was rated because of missing body weight, since, from our experience, for most patients, body weight must have been greater than 67 kg. However, all patients were rated for 'time of symptom onset', since due to a failure in the city's control system, most patients have been suffering pain for more than 4 hours when admitted to the service. For this reason, some patients may have received a score higher than they actually had, since some characteristics may have not been properly rated.

- Patients with previous myocardial revascularization were not included in the analysis using the SYNTAX score, since this instrument does not consider the history of bypass.

- Lack of standardization in the time of blood collection for troponin measurement, as well as lack of some measurements due to structural and operational problems of the service. This limitation may have influenced the detection of the peak concentration of this biomarker.

Results

Patients' age varied from 37 to 92 years, and most patients were women, hypertensive, non-diabetic and non-smokers. Only 20.7% (n = 36) of patients had a positive history of CAD. Forty percent of the patients used acetylsalicylic acid (ASA) at the moment of the event, and most of them reported episodes of severe angina, without ST-segment depression in electrocardiography. Electrocardiographic changes other than ST-segment elevation or depression were not considered for analyses.

Of the 174 patients evaluated, 19.0% (n = 33) had the diagnosis of STEMI, 43.1% (n = 75) had non ST-segment elevation myocardial infarction (non-STEMI), and 36.8% (n = 64) had unstable angina. Most patients were in Killip class I at admission. These results and the distribution of patients by history of diseases and Killip classification are described in Table 1.

Results of quantitative clinical variables (vital data, biochemical and risk parameters) are described in Table 2. Median hsTn was 67 pg/mL.

There was a significant moderate, positive linear correlation between hsTn levels and SYNTAX score ($p < 0.001$, $r = 0.440$) (Figure 1). In addition, a significant but weak positive linear correlation was found of hsTn levels with TIMI score ($p < 0.001$, $r = 0.267$), and GRACE score ($p = 0.001$, $r = 0.261$) (Figures 2 and 3, respectively).

Discussion

The relationship between altered hsTn and the prognosis of ACS patients has been consistently demonstrated in previous studies. However, few studies have correlated hsTn levels with the complexity of coronary lesions in patients undergoing coronary angiography.[9] Similarly, few studies comparing troponin levels with well-established clinical prognostic scores, such as TIMI and GRACE, have been found in the literature.

Our results indicate that there is a significant, positive moderate linear correlation of hsTn levels with the complexity of coronary lesions evaluated by the SYNTAX scoring system. These findings may be explained by the fact that zero point has been assigned to many patients (n = 65/174), and many patients have not been rated because of the history of myocardial revascularization in SYNTAX score. In contrast, although patients with STEMI were the minority (33/174), they showed higher severity, and consequently higher hsTn levels (mean 3.073 pg/dL). However, we also included patients with unstable angina, who did not show increased hsTn levels, which may have caused a decrease in the mean value. For these reasons, despite positive, the importance of this correlation may be questioned.

In the study by Altun et al.,[9] involving 287 patients, a linear correlation of hsTn levels with the complexity of coronary lesions measured by the SYNTAX score was also reported, but with lower statistical power ($r = 0.327$) compared with our study ($r = 0.440$). The authors established a cut-off point for hsTn, above which the severity of coronary lesions was higher (high SYNTAX scores). This is a relevant conclusion, considering the

Table 1 - Age, history of diseases and Killip classification in patients diagnosed with acute coronary syndrome, who underwent cardiac catheterization

Variable	Median (IQR) or % (n)
Age (years)	63.5 (16.5)
Sex	
Female	52.9 (92)
Male	47.1 (82)
SAH	
No	11.5 (20)
Yes	88.5 (154)
Diabetes Mellitus	
No	60.3 (105)
Yes	39.7 (69)
STEMI	
No	81.0 (141)
Yes	19.0 (33)
Non-STEMI	
No	56.3 (98)
Yes	43.1 (75)
Missing information	0.6 (1)
Unstable angina	
No	62.6 (109)
Yes	36.8 (64)
Missing information	0.6 (1)
Smoking	
No	66.7 (116)
Yes	25.3 (44)
Missing information	8.0 (14)
Family history	
No	43.7 (76)
Yes	20.7 (36)
Missing information	35.6 (62)
ASA	
No	47.1 (82)
Yes	42.5 (74)
Missing information	10.3 (18)
Severe angina	
No	19.0 (33)
Yes	78.2 (136)
Missing information	2.9 (5)
ST depression	
No	86.8 (151)
Yes	6.9 (12)
Missing information	6.3 (11)
Killip	
1	82.8 (144)
2	15.5 (27)
3	1.7 (3)

IQR: Interquartile range; SAH: systemic arterial hypertension; ASA: acetylsalicylic acid; STEMI: ST-segment elevation myocardial infarction; ST: ST-segment.

Table 2 - Results of quantitative clinical variables (vital data, biochemical and risk parameters) in patients with acute coronary syndrome, who underwent cardiac catheterization

Variable	Median (IQR)
Heart rate (bpm)	80 (21)
SBP (mmHg)	130 (33)
Ejection fraction (%)	59 (21)
Total cholesterol (mg/dL)	181 (72)
Non-HDL cholesterol (mg/dL)	133 (68)
HDL (mg/dL)	43 (18)
LDL (mg/dL)	106 (68)
Triglycerides (mg/dL)	127 (86)
Troponin (pg/mL)	67 (38)
Creatinine (mg/dL)	1 (1)
CRP	7 (16)
Killip (points)	1 (0)
TIMI (points)	3 (2)
GRACE (points)	121 (43)
SYNTAX (points)	3 (12)

IQR: Interquartile range; SBP: systolic blood pressure; CRP: C-reactive protein; HDL: high density lipoprotein; LDL: low density lipoprotein.

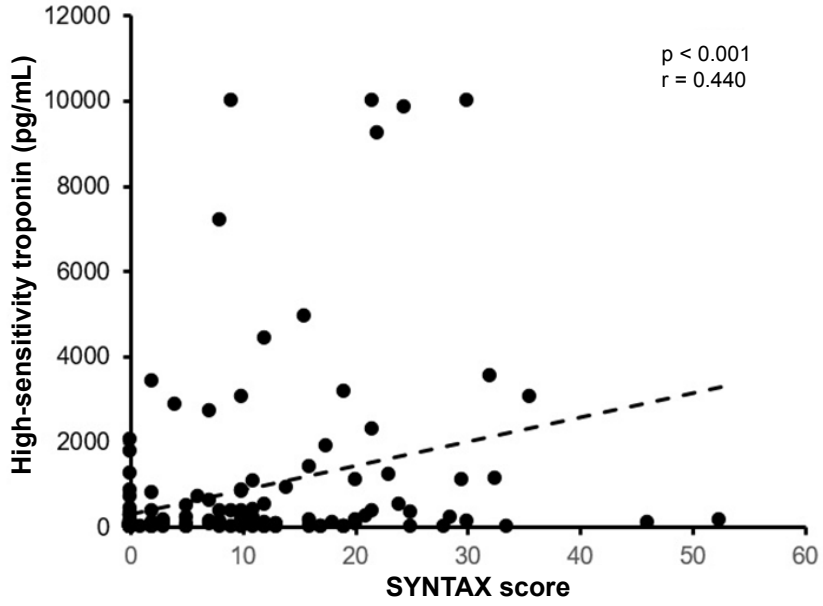

Figure 1 - Scatter plot showing a significant moderate, positive linear correlation between high-sensitivity troponin levels and SYNTAX score. Each plot represents one patient. Dashed line represents the linear regression. P-value of Spearman rank correlation test, and "r" is the linear correlation coefficient.

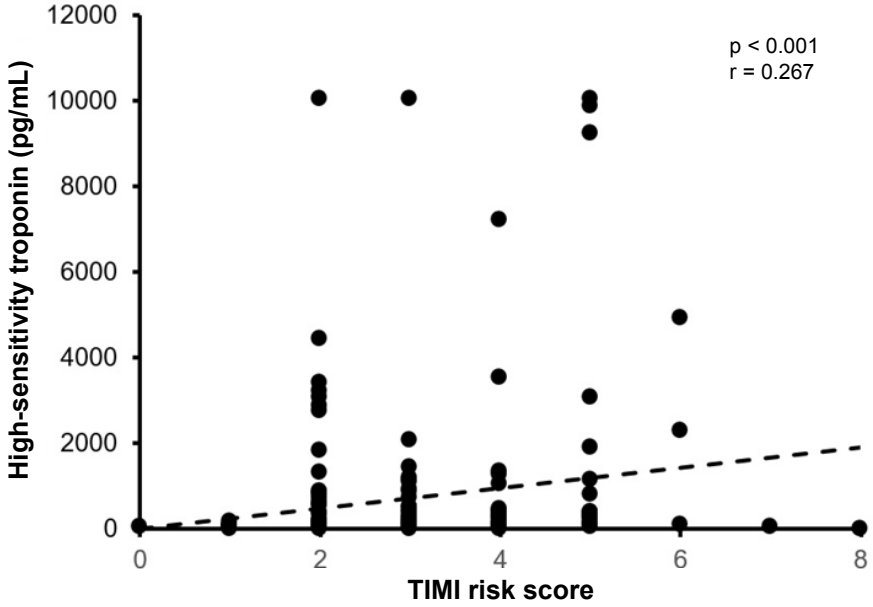

Figure 2 - Scatter plot showing a significant weak, positive linear correlation between high-sensitivity troponin levels and TIMI risk score. Each plot represents one patient. Dashed line represents the linear regression. P-value of Spearman rank correlation test, and "r" is the linear correlation coefficient.

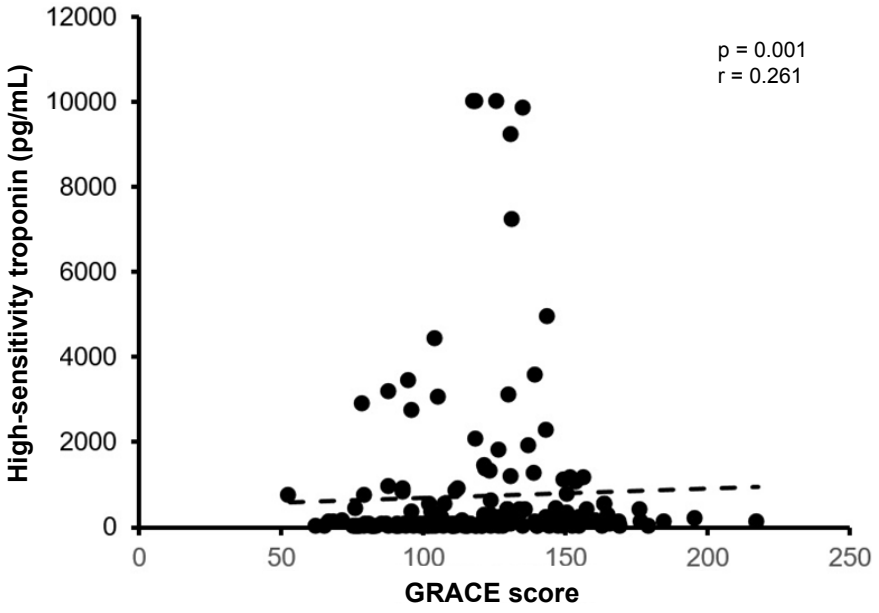

Figure 3 - Scatter plot showing a significant weak, positive linear correlation between high-sensitivity troponin levels and GRACE score. Each plot represents one patient. Dashed line represents the linear regression. P-value of Spearman rank correlation test, and "r" is the linear correlation coefficient.

high sensitivity of the troponin used in our study, and the possibility of increased hsTn levels in conditions other than ACSs, such as sepsis, stroke, among others.

Although previous studies on the subject have compared troponin levels with the severity of coronary lesions, neither hsTn nor the SYNTAX score for evaluation of the severity of these lesions was used in these studies. One example was the Brazilian study by Faria RC.[13] The author compared the levels of troponin I with the severity of coronary lesions, which was measured by characteristics of the lesions in cardiac catheterization or changes in coronary circulation. In this study, although the author found no statistically significant correlation between increased troponin I levels and lesion severity or coronary circulation, the protein levels were correlated with a higher number of obstructive lesions and the presence of thrombus.[13]

In addition, in our study, hsTn levels were correlated with GRACE and TIMI clinical prognostic scores. The linear correlation between these parameters, despite weak, suggests a worse prognosis of patients with higher levels of this biomarker.

Median GRACE and TIMI scores (121 and 3, respectively) found in our population indicated an intermediate risk in these patients, whose hsTn levels were 4 times the upper limit of normal range (cut-off point: 14 pg/dL).

In a similar study by Biener et al.,[14] rising and falling changes of hsTn at admission were correlated with GRACE risk score, aiming to evaluate whether these changes would improve the prognostic performance of the score. The authors suggested that a GRACE score ≥ 140 points and hsTn admission values above the 99th percentile are reliable indicators of adverse cardiovascular events in hospitalized patients with suspicious of ACS. Nevertheless, neither rising nor falling hsTn kinetic changes seemed to add prognostic information.[14]

Although we did not evaluate the presence of kinetic changes or the possibility of future cardiovascular events, we found slightly increased hsTn levels associated with intermediate GRACE score values. The linear relationship, despite weak, may also suggest a worse prognosis in these patients.

With respect to TIMI score, we also found some studies that directly compared it with troponin. Gomes et al.,[15] for example, evaluated the relative contribution of hsTn to the final risk classification of patients with ACS without ST-segment elevation, previously evaluated by the TIMI score, and found that hsTn contributed to their

reclassification to a higher risk. O´Donoghue et al.,[16] after evaluating several biomarkers, concluded that troponin T was associated with higher TIMI scores. Although the authors did not use hsTn in their study, these data corroborate our findings.

Therefore, there is a correlation between hsTn and the complexity of lesions quantified by the anatomical SYNTAX score in ACS patients, and a correlation of this biomarker with the prognostic clinical scores GRACE and TIMI. Thus, despite the limitations in blood collection for troponin measurements, and late admission of patients to the emergency department, troponin was shown to be a biomarker capable of predicting intermediate levels of risk score and higher complexity of coronary lesions, indicating a worse prognosis. Additional studies, including larger samples and the follow-up of future cardiovascular events, are needed to better evaluate and, if possible, to identify the cut-off point for hsTn, indicative of a worse prognosis.

Although it was not the aim of the present study, LDL-cholesterol levels were not very increased, as the study population was classified as intermediate risk. Even with borderline cholesterol levels, patients had acute coronary event, which highlights the importance of other associated risk factors.

In addition, although this parameter was not measured in the whole sample due to insufficient data, increased c-reactive protein levels were found in our population (reference value < 5 mg/dL in our institution). This indicates a higher inflammation status, which has been well correlated with increased risk for acute coronary events.

Conclusion

The present study found a significant moderate positive liner correlation between hsTn levels and the complexity of coronary lesions evaluated by the SYNTAX score. Besides, a weak correlation was found between this biomarker and the TIMI and GRACE clinical prognostic scores.

Author contributions

Conception and design of the research: Cardoso MR, Silva Junior DG. Acquisition of data: Cardoso MR, Ribeiro EA, Rocha Neto AM. Analysis and interpretation of the data: Cardoso MR, Silva Junior DG, Ribeiro EA, Rocha Neto AM. Statistical analysis: Cardoso MR, Silva Junior DG. Writing of the manuscript: Cardoso MR. Critical revision of the manuscript for intellectual content: Silva Junior DG.

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

References

1. Instituto Brasileiro de Geografia e Estatística. (IBGE). Pesquisa Nacional de Saúde 2013: Percepção do estado de saúde, estilos de vida e doenças crônicas. Rio de Janeiro; 2014.
2. World Health Organization. (WHO). Global health observatory data repositor: cardiovascular disease, deaths per 100 000, 2012. [Accessed in 2015 Sept 22]. Available from: http://apps.who.int/gho/data/ node.main.A865CARDIOVASCULAR?lang=en
3. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al; Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction. Third universal definition of myocardial infarction. Circulation. 2012;126(16):2020-35. doi: 10.1161/CIR.0b013e31826e1058.
4. Piegas LS, Timerman A, Feitosa GS, Nicolau JC, Mattos LA, Andrade MD, et al. V Diretriz da Sociedade Brasileira de Cardiologia sobre tratamento do infarto agudo do miocárdio com supradesnível do segmento ST. Arq Bras Cardiol. 2015;105(2):1-105. doi: http://dx.doi.org/10.5935/abc.20150107.
5. Thygesen K, Alpert JS, Antman E, Bassand JP. Myocardial infarction redefined - A consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction. J Am Coll Cardiol. 2000;36(3):959-69. PMID: 10987628. Erratum in: J Am Coll Cardiol 2001 Mar 1;37(3):973.
6. Maznyczka A, Kaier T, Marber M. Troponins and other biomarkers in the early diagnosis of acute myocardial infarction. Postgrad Med J. 2015;91(1076):322-30. doi: 10.1136/postgradmedj-2014-133129.

7. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention. 2005;1(2):219-27. PMID: 19758907.

8. Bonaca M, Sabatine M, Dalby A, Spinar J, Murphy AS, Jarolil P, et al. Prospective evaluation of the prognostic implications of improved assay performance with a sensitive assay for cardiac troponin I. J Am Coll Cardiol. 2010;55(19):2118-24. doi: 10.1016/j.jacc.2010.01.044.

9. Altun B, Turkon H, Tasolar H, Beggı H, Altun M, Temız A, et al. The relationship between high-sensitive troponin T, neutrophil lymphocyte ratio and SYNTAX Score. Scand J Clin Lab Invest. 2014;74(2):108-15. doi: 10.3109/00365513.2013.860619.

10. Cesar LA, Ferreira JF, Armaganijan D, Gowdak LH, Mansur AP, Bodanese LC et al; Sociedade Brasileira de Cardiologia. Guideline for stable coronary artery disease. Arq Bras Cardiol. 2014;103(2 Suppl 2):1-56. doi: http://dx.doi.org/10.5935/abc.2014S004.

11. Milech A, Angelucci AP, Golbert A, Matheus A, Carrilho AJ, Ramalho AC, et al. Diretriz da Sociedade Brasileira de Diabetes 2015 – 2016. São Paulo: AC Farmacêutica; 2016.

12. Rowe P. Essential statistics for the pharmaceutical sciences. Chichester (Engl): John Wiley & Sons Ltda; 2007.

13. Faria RC. Troponina como indicador de gravidade angiográfica em pacientes com síndrome coronariana aguda sem supradesnível de segmento ST. Rev SOCERJ. 2005;18(5):443-4.

14. Biener M, Mueller M, Vafaie M, Jaffe AS, Katus HA, Giannitsis E. Prognostic performance of high-sensivity cardiac troponin T kinetic changes adjusted for elevated admission values and the GRACE score in an unselected emergency department population. Clin Chim Acta. 2014;435:29-35. doi: 10.1016/j.cca.2014.04.007.

15. Gomes BF, Rau BS, Abitbol RA, Taets GG, Filho CF, Tura BR, et al. Contribuição relativa da troponina ultrassensível na classificação de risco pelo Timi Risk Score em pacientes com síndrome coronariana aguda sem supra de ST. Rev Bras Cardiol. 2011;24(5):277-81.

16. O´Donoghue ML, Morrow DA, Cannon CP, Jarolim P, Desai NR, Sherwood MW, et al. Multimarker risk stratification in patients with acute myocardial infarction. J Am Heart Assoc. 2016;5(5). pii: e002586. doi: 10.1161/JAHA.115.002586.

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ORIGINAL ARTICLE

Heart Failure: Correlation between Anthropometric Parameters, Body Composition and Cell Integrity

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Abstract

Background: Knowledge about phase angle and its use as a prognostic determinant in patients with heart failure is still scarce.

Objective: To evaluate the correlation between anthropometric indicators, cardiac function and cell integrity in patients with heart failure with reduced ejection fraction.

Methods: This was a cross-sectional study that evaluated patients with heart failure with reduced ejection fraction by anthropometry and bioelectrical impedance analysis. Chi-square test and Student's t test were used to analyze differences, and Pearson's linear correlation was used to evaluate associations, using $p < 0.05$ to indicate statistical significance.

Results: We evaluated 41 subjects aged 30-74 years, of which 34 were men (82.9%). Mean phase angle was higher among women (7.1%), but significant differences between men and women were found only for body fat percentage. Phase angle correlated with body mass index ($r = 0.44$, $p = 0.004$) and there was a trend of correlation of the phase angle with waist-to-height ratio ($r = 0.29$, $p = 0.06$) and the left ventricular ejection fraction ($r = 0.29$, $p = 0.07$).

Conclusions: Phase angle showed a good correlation with body mass index and showed a trend of correlation with the left ventricular ejection fraction, supporting the obesity paradox and the prognostic importance of this marker. Further studies on the applicability of the phase angle in the prognosis of these patients are still needed. (International Journal of Cardiovascular Sciences. 2018;31(3)226-234)

Keywords: Heart Failure; Body Composition; Obesity; Stroke Volume; Body Mass Index.

Introduction

Systemic arterial hypertension (SAH) and coronary artery disease (CAD) are common causes of heart failure (HF). One of their main risk factors is obesity, which causes several adverse effects to health, particularly to cardiovascular health.[1]

According to the International Diabetes Federation (IDF),[2] although increased body mass index (BMI) may lead to these conditions, excessive abdominal fat, estimated by waist circumference (WC), is the main indicative of metabolic syndrome. Therefore, central body fat has been increasingly recognized as an independent risk for cardiovascular disease (CVD).[3]

On the other hand, in established HF, mild to moderate overweight has been associated with a substantial increase in survival as compared with normal weight individuals, the so called "obesity paradox".[1,4] One of the several theories that may explain such paradox is the fact that excessive adipose tissue provides greater storages that may exert a protect role against disease-related metabolic changes that may lead to cardiac cachexia. Cardiac cachexia is a syndrome that involves progressive weight loss and changes in body composition, bearing a devastating prognosis for HF patients.[4]

Besides, most data related to this paradox identify obesity by BMI,[4] which although is the most widely used method in nutritional assessment, does not clearly reflect

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individual's body composition, and has a relatively low sensitivity in predicting excessive body fat.[5] In this context, other nutritional assessment methods may be used, such as densitometry by dual-energy X-ray absorptiometry (DXA) and computed tomography (CT). These methods, however, although more accurate, are also more costly and complex.[6]

When these recommended methods are not available, some anthropometric measures and indexes seem to be good alternatives for estimating body composition. In addition to WC, the conicity index (C-index), proposed by the World Health Organization (WHO) to evaluate obesity and body fat distribution is of equal importance.[7] Also, waist-to-height ratio (WHtR), which is based on the assumption that for each height, there is an acceptable level of fat stored in the upper body, has also a good relationship with central body fat.[8]

Bioelectrical impedance analysis (BIA) has also been widely used, especially due to the high data processing speed, its non-invasiveness, easiness of use and relatively low cost. BIA provides estimates of fat mass and fat-free mass components using predictive equations, and of phase angle (PA).[9,10]

Left ventricular ejection fraction (LVEF) is another parameter to be evaluated in these patients due to its prognostic importance. Its reduction is associated with lower survival, and distinction of HF patients with (HFREF) and without reduced ejection fraction is increasingly required because of different clinical manifestations and forms of treatment for each case.[11]

Therefore, due to the association between obesity and cardiovascular changes, assessment of HFREF by methods that estimate not only total fat, but also central fat, is extremely relevant. Besides, the applicability of PA in HF has not been well established in the literature.

Thus, the aim of the present study was to evaluate the relationship between anthropometric indicators, cardiac function and cell integrity in HFREF.

Methods

This was a cross-sectional study of patients treated at the Heart Failure Outpatient Center of Pedro Ernesto University Hospital.

A convenience sample was used, and HFREF of both sexes, aged from 18 to 74 years were considered eligible. Exclusion criteria were patients with clinical evidence of edema and ascites, amputee patients and patients using pacemakers. Patients with a BMI lower than 16 kg/m^2 or greater than 34 kg/m^2 were also excluded, because estimation of body composition by most of BIA predictive equations using these BMI values is not considered reliable.[12] We also excluded patients who did not meet the standardized BIA protocol, and those with a higher percentage of extracellular water compared with intracellular water, indicating a water imbalance that had not been identified at the physical exam,[9] and patients with an electrocardiography performed longer than one year before the date of the anthropometric assessment.

Outcome measures were: sex, age, LVEF (electrocardiography), etiology of the disease, functional class (New York Heart Association, NYHA),[13] comorbidities, previous myocardial revascularization surgery (MRS), valve replacement, stent implantation, acute myocardial infarction (AMI), and anthropometric parameters (body mass, kg; height, m; WC, cm; BMI, kg/m^2; WHtR and C index), measured by one trained examiner.

Body mass was measured using a digital medical scale (Welmy®) with maximum capacity of 200 kg at the nearest 0.1kg. Height was measured to the nearest 0.1 cm using a wall mounted stadiometer (Sanny®, 220 cm). Measurements were performed as proposed by Lohman et al.[14]

WC was measured using an inelastic tape at the nearest 0.1 mm, according to the IDF criteria.[15] Patients were divided into the following groups – WC ≥ 80 cm and < 80 cm for women; WC ≥ 90 cm and < 90 cm for men.

WHtR was calculated by dividing WC (cm) by height (cm), and the cutoff points adopted were 0.52 for men and 0.53 for women. C-index was obtained according to the equation proposed by Valdez,[16] with the cutoff points of 1.25 and 1.18 for men and women, respectively. The WHtR and the C-index cutoff points indicating an increased coronary risk were defined based on the study by Pitanga and Lessa.[17]

Nutritional diagnosis was determined by BMI, which was calculated by dividing body mass by height squared and classified according to the WHO criteria.[18]

Body composition and cell integrity were evaluated by tetrapolar BIA (Biodynamics 450®), according the Brazilian Medical Association criteria.[12] BIA results of PA and body fat percentage (BF%) were used for analyses. For BF% classification, we used the cutoff points of 25% for men and 32% for women.[19]

The study was approved by the Research Ethics Committee of the institution (approval number 47828915.3.0000.5259). All patients were informed about the study's purpose, and signed an informed consent form before being included, as volunteers, in the study.

Statistical analysis

Normality of the variables was tested by the Kolmogorov-Smirnov test. Descriptive statistics was used for characterization of the sample. Continuous variables were expressed as mean and standard deviation (±SD); the Student's t-test and the Pearson correlation were used to analyze differences and correlations between independent samples, respectively. Categorical variables were expressed as percentage, and associations between them were analyzed by the chi-square test or the Fisher's exact test. Analyzes were performed using the STATA 14 softwae, and statistical significance was set at $p < 0.05$.

Results

In the present study, 41 volunteers of both sexes (n = 34, 82.9% were men) aged 61 ± 10.8 years were studied.

The most common comorbidity was SAH (n = 33; 80.5%), followed by DM (n = 21, 51.2%), chronic kidney disease (n = 3; 7.3%) and chronic obstructive pulmonary disease (n = 3, 7.3%).

With respect to HF classification, NYHA functional class I was the most prevalent (n = 18, 43.9%), and 34.1% (n = 14) of patients had ischemic HF. Eighteen (43.9%) patients had previous AMI, 14.6% (n = 6) had previous MRS, 9.8% (n = 4) had previous valve replacement, and 21.9 (n = 9) had previous stent implantation. No differences were found between men and women, except for the prevalence of DM, which was higher in women (n = 6, 85.7%) than men (n = 15, 44.1%) (Table 1).

Regarding the anthropometric variables, BF% was significantly lower in men (mean of 27.2%) than women (mean of 35.8%). No differences were found in the other anthropometric parameters between men and women. PA (7.1° ± 1.4), estimated by BIA, and LVEF (37.4%) were higher in women than men, with no significant difference though. Clinical and anthropometric characteristics of the study population are described in Table 2.

Mean BMI was 26.4 ± 3.6 Kg/m², with no difference between men (26.4 ± 3.4 Kg/m²) and women (26.5 ± 4.8 Kg/m²) (Table 2). Most participants were overweight (41.5%), followed by normal weight (39.0%) and obese subjects (19.5%).

Anthropometric indicators of obesity (Table 3) showed that 61.8% of men and 57.1% of women were overweight/obese, and 100% of women and 91.2% of men were at increased risk according to the C-index (totaling 92.7% of the study population). According to WC, 82.4% of men and 85.7% of women were at increased risk, and 76.5% of men had increased WHtR. With respect to BF%, 67.7% of men and 71.4% of women were obese. No statistically significant difference in any of the indicators was found between men and women.

Table 4 shows the correlation between obesity anthropometric indicators, PA and LVEF of the studied population. BMI showed a significant positive correlation with C-index, WC, WHtR, BF%, and PA; there was a positive significant correlation of C-index with WC, WHtR and BF%, a positive significant correlation of WC with BF% and WHtR, and between WHtR and BF%. The strongest correlations were observed of BMI with WC (r = 0.84) and WHtR (r = 0.83), of C index with WC (r = 0.80) and WHtR (r = 0.81), and between WC and WHtR (r = 0.85). PA showed a significant correlation with BMI and a marginal correlation with WHtR (r = 0.29, 0.06) and LVEF (r = 0.29, p = 0.07).

Discussion

Some studies have demonstrated the relationship of excess weight with left ventricular hypertrophy and concentric and eccentric remodeling, and with diastolic dysfunction followed by long-term systolic dysfunction,[20,21] indicating a direct effect of body composition on cardiovascular system.

In this context, anthropometric assessment is crucial in the clinical practice, since an early diagnosis of obesity and an adequate intervention contribute to improve patients' quality of life and prevent the worsening of health.[22] Borné et al.[23] investigated 26,653 individuals aged 45-73 years and showed that increased BMI, WC and BF% increased the risk of hospitalization for HF, and that this risk was even greater with combined exposure to both increased BMI and WC.

In our study, mean BMI was 26.4 ± 3.4 Kg/m², and most patients (41.5%) were overweight. Gastelurrutia et al.[24] evaluated HFREF and patients without reduced ejection fraction and identified that 42% of patients were overweight and 27% were obese. Although BMI has been used as an important indicator of body composition in epidemiologic studies, individual BMI values should be interpreted with caution.[10] Different from the general population, in HF patients, BMI is inversely correlated

Table 1 – Comorbidities, heart failure etiology, New York Heart Association (NYHA) functional class, previous acute myocardial infarction and previous surgeries by sex in the study population (n = 41)

	Men (n=34)	Women (n=7)	Total (n=41)	p-value*
	n (%)	n(%)	n(%)	
Comorbidities				
SAH	27 (79.4)	6 (85.7)	33 (80.5)	0.7
DM	15 (44.1)	6 (85.7)	21 (51.2)	0.04
CKD	2 (5.9)	1 (14.3)	3 (7.3)	0.4
COPD	3 (8.8)	0 (0.0)	3 (7.3)	0.4
HF etiology				
Ischemic	12 (35.3)	2 (28.6)	14 (34.1)	0.7
Non-ischemic	22 (64.7)	5 (71.4)	27 (65.9)	
FC (NYHA)				
I	16 (47.1)	2 (28.6)	18 (43.9)	
II	11 (32.3)	2 (28.6)	13 (31.7)	0.2
III	7 (20.6)	2 (28.6)	9 (22.0)	
IV	0 (0.0)	1 (14.2)	1 (2.4)	
AMI				
Yes	16 (47.1)	2 (28.6)	18 (43.9)	0.4
No	18 (52.9)	5 (71.4)	23 (56.1)	
Surgery				
MRS	6 (17.6)	0 (0.0)	6 (14.6)	0.2
VR	3 (8.8)	1 (14.3)	4 (9.8)	0.7
Stent implantation	8 (23.5)	1 (14.3)	9 (21.9)	0.6

**comparison between men and women. SAH: systemic arterial hypertension; DM: diabetes mellitus; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; HF: heart failure; FC: functional class; AMI: acute myocardial infarction; MRS: myocardial revascularization surgery; VR: valve replacement*

with mortality and rehospitalization.[25] However, some studies have shown that not only BMI but also other anthropometric variables should be used in the assessment of HF patients, for a better assessment of body compartments and central obesity.[24,26]

BIA has been currently validated to estimate body composition and nutritional status in healthy individuals, and in several clinical conditions, including malnutrition and chronic diseases.[9] The validity of its use in HF patients has been questioned, since the method is known to be influenced by the amounts of body fluids, and to not be appropriate for situations of altered hydration of tissues.[12,25] Therefore, in our study, we used standardization criteria for BIA; only stable patients participated in the study, and those with altered hydration were excluded.[12] According to BF% measured by this method, 67.7% of men and 71.4% of women were identified as obese, corresponding to the majority (68.3%) of the study population.

Central obesity indicators are positively correlated with the amount of visceral adipose tissue and cardiometabolic disorders.[25] Our subjects had excess central adiposity according to all indicators studies (WC, C-index and WHtR). Similar findings were

Table 2 – Clinical and anthropometric variables of the study population, by sex

Variables	Men (n = 34)	Women (n = 7)	Total (n = 41)	p-value *
	Mean (±SD)	Mean (±SD)	Mean (±SD)	
Age (years)	60.5 (11.3)	63 (8.7)	61 (10.8)	0.29
BMI (Kg/m²)	26.4 (3.4)	26.5 (4.8)	26.4 (3.6)	0.48
WC (cm)	96.8 (11.4)	93.6 (13.0)	96.3 (11.6)	0.26
WHtR	0.57 (0.06)	0.61 (0.1)	0.57 (0.07)	0.05
C-index	1.32 (0.09)	1.35 (0.08)	1.32 (0.09)	0.22
BF%	27.2 (4.3)	35.8 (4.6)	28.7 (5.4)	< 0.001
PA (°)	6.7 (1.0)	7.1 (1.4)	6.8 (1.1)	0.18
LVEF (%)	34.5 (8.6)	37.4 (7.3)	35.0 (8.4)	0.21

**comparison between men and women. SD: standard deviation; BMI: body mass index; C-index: conicity index; WC: waist circumference; WHtR: waist-to-height-ratio; BF%: body fat percentage; PA: phase angle; LVEF: left ventricular ejection fraction*

Table 3 – Obesity anthropometric indicators in the study population by sex

Variables	Men	Women	Total	p-value*
	n(%)	n(%)	n (%)	
BMI				
Normal weight	13 (38.2)	3 (42.9)	16 (39.0)	0.09
Overweight/obesity	21 (61.8)	4 (57.1)	25 (61.0)	
C-index				
Normal	3 (8.8)	0 (0.0)	3 (7.3)	0.4
Increased	31 (91.2)	7 (100.0)	38 (92.7)	
WC				
Normal	6 (17.6)	1 (14.3)	7 (17.1)	0.8
Increased	28 (82.4)	6 (85.7)	34 (82.9)	
WHtR				
Normal	8 (23.5)	2 (28.6)	10 (24.4)	0.8
Increased	26 (76.5)	5 (71.4)	31 (75.6)	
BF%				
Normal	11 (32.3)	2 (28.6)	13 (31.7)	0.8
Obesity	23 (67.7)	5 (71.4)	28 (68.3)	

**comparison between men and women. BMI: body mass index; C-index: conicity index; WC: waist circumference; WHtR: waist-to-height-ratio; BF%: body fat percentage.*

Table 4 – Correlation between obesity anthropometric indicators, phase angle and left ventricular ejection fraction

	BMI	C-index	WC	WHtR	BF%	PA
BMI						
C-index	(0.46)					
p-value	0.002					
WC	(0.84)	(0.80)				
p-value	< 0.001	< 0.001				
WHtR	(0.83)	(0.81)	(0.85)			
p-value	< 0.001	< 0.001	< 0.001			
BF%	(0.36)	(0.38)	(0.32)	(0.53)		
p-value	0.02	0.01	0.04	< 0.001		
PA	(0.44)	(-0.01)	(0.22)	(0.29)	(0.06)	
p-value	0.004	0.95	0.17	0.06	0.7	
LVEF	(0.17)	(0.12)	(0.15)	(0.17)	(0.23)	(0.29)
p-value	0.29	0.47	0.34	0.29	0.15	0.07

BMI: body mass index; C-index: conicity index; WC: waist circumference; WHtR: waist-to-height-ratio; BF%: body fat percentage; PA: phase angle; LVEF: left ventricular ejection fraction

reported in the study by Quirino et al.[27] showing that mean WC and WHtR values were higher than recommended in both men and women.

Regarding the analysis of associations between anthropometric variables, Gomes et al.[28] found a positive significant correlation between BMI and WC. Colombo et al.[29] showed that BMI had a positive significant correlation with BF%, obtained by the sum of skinfold thickness measures, and both BMI and BF% had a significant correlation with WC. These correlations were found in our study also.

Lobato et al.,[30] found correlations between BMI and WC, and positive significant correlations of WC with WHtR and C-index, and between WHtR and C-index. In the study by Mendes et al.,[31] involving patients with diabetes mellitus (DM), obesity and/or SAH, BMI was positively correlated with BF% ($p < 0.001$) and C-index ($p = 0.009$).

Studies on C-index and WHtR as coronary risk predictors have been carried out in the Brazilian population and demonstrated the importance of these indicators in diagnostic assessment of patients.[15,17]

We also obtained PA measures using BIA. These parameters have been increasingly used as a diagnostic tool in the clinical practice. In our study group, mean PA was 6.8° ± 1.1, with greater values in women (7.1° ± 1.4), but not significantly different than men. In healthy individuals, these values can vary from 4 to 10 degrees.[9] When increased, PA may be associated with greater amounts of intact cell membranes, indicating adequate health status, whereas low PA values suggest worsening of disease and cell death.[9] PA cutoff points vary between diseases – in HIV-infected patients, a PA lower than 5.3° was associated with a unfavorable prognosis,[32] whereas lower survival rates were found in advanced cancer patients with PA lower than 4.4°.[33]

With respect to HF, Colín-Ramírez et al.[34] investigated a cohort of 389 HF patients in Mexico city and demonstrated that PA is a good prognostic indicator. A PA lower than 4.2° was more strongly associated with mortality (even after adjusting for age), serum hemoglobin and presence of DM. Another study reported a significant reduction in PA values in HF patients as compared with healthy controls (5.5° *vs*. 6.4°).[35]

Colín-Ramirez et al.[34] demonstrated the prognostic value of PA in HF patients, and showed that a lower PA was associated with markers of malnutrition, such as decreased BMI, worsening of functional class and kidney failure.

In the study by Tajeda et al.,[36] a lower PA (4.32°) was associated with changes in glomerular filtration rate and cardiac troponin T levels. Martínez et al.[37] showed that a lower PA was associated with worsening of functional class (from III to IV), even after adjusting for age and sex, and that PA values were significantly lower in patients with preserved systolic function. Colín-Ramírez et al.[38] evaluated patients with systolic and diastolic HF and observed that those with volume overload and anemia had reduced PA values, and such reduction was associated with thyroid disorders in the study by Silva-Tinoco et al.[39]

In the present study, PA had a significant correlation with BMI and a marginal significant correlation with WHtR and LFEV. Therefore, the higher the BMI and WHtR, the higher the PA, indicating that excess weight and body fat could be a protective factor for HF patients, corroborating the results of previous studies on the obesity paradox.[1,4] Besides, the correlation between LVEF and PA supports the use of the latter as a prognostic indicator of HF.

The main limitation of this study was the sample size, as a larger sample size could result in stronger correlations between the variables and yield more definite results.

Conclusion

In our study, most patients had excessive total and central body fat, and correlations of BMI and C-index with WC and WHtR, and of WHtR with WC were found. Besides, there was a trend of correlation of WHtR and LVEF with PA, and a correlation between PA and BMI. We thereby demonstrate a possible example of obesity paradox. Also, we highlight the need for further studies on the use of PA in HFREF, to establish PA cutoff points and enable their application as a prognostic parameter in this population.

Author contributions

Conception and design of the research: Faria TC, Giannini DT, Gasparini PVF, Rocha RM. Acquisition of data: Faria TC. Analysis and interpretation of the data: Faria TC, Giannini DT, Gasparini PVF, Rocha RM. Statistical analysis: Giannini DT. Writing of the manuscript: Faria TC, Giannini DT, Gasparini PVF, Rocha RM. Critical revision of the manuscript for intellectual content: Giannini DT, Gasparini PVF, Rocha RM.

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 Pesquisa da Universidade do Estado do Rio de Janeiro under the protocol number 47828915.3.0000.5259. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

References

1. Lavie CJ, Alpert MA, Arena R, Mehra MR, Milani RV, Ventura HO. Impact of obesity and the obesity paradox on prevalence and prognosis in heart failure. JACC Heart Fail. 2013;1(2):93-102. doi: 10.1016/j.jchf.2013.01.006.
2. The IDF consensus worldwide definition of metabolic syndrome. International Diabetes Federation, 2006 [Acesso em 2015 maio 10]. Disponível em: http://www.idf.org.
3. Tankó LB, Bagger YZ, Alexandersen P, Larsen PJ, Claus Christiansen C. Central and peripheral fat mass have contrasting effect on the progression of aortic calcification in postmenopausal women. Eur Heart J. 2003;24(16):1531-7. PMID: 12919778.
4. Gupta PP, Fonarow GC, Horwich TB. Obesity and the obesity paradox in heart failure. Can J Cardiol. 2015;31(2):195-202. doi: 10.1016/j.cjca.2014.08.004.
5. Lavie CJ, Milani RV, Ventura HO, Romero-Corral A. Body composition and heart failure prevalence and prognosis: getting to the fat of the matter in the "obesity paradox". Mayo Clin Proc. 2010;85(7):605-8. doi: 10.4065/mcp.2010.0333.
6. Rezende F, Rosado L, Franceschinni S, Rosado G, Ribeiro R, Marins JC. Revisão crítica dos métodos disponíveis para avaliar a composição corporal em grandes estudos populacionais e clínicos. Arch Latino Am Nutr. 2007;57(4):327-34.

7. Christmann AC, Zanelatto C, Semchechem CC, Novello D, Schiessel DL. Perfil de risco de doenças cardiovasculares e estado nutricional de idosos ativos de Guarapuava – Paraná. UNOPAR Cient Ciênc Biol Saúde. 2013;15(ESP):349-56.

8. Ho SY, Lam TH, Janus ED; Hong Kong Cardiovascular Risk Factor Prevalence Study Steering Committee. Waist to stature ratio is more strongly associated with cardiovascular risk factors than other simple anthropometric indices. Ann Epidemiol. 2003;13(10):683-91. PMID: 14599732.

9. Eickemberg M, Oliveira CC, Roriz AK, Sampaio LR. Bioelectric impedance analysis and its use for nutritional assessments. Rev Nutr Campinas. 2011;24(6):883-93.

10. Guedes DP. Clinical procedures used for analysis of the body composition. Rev bras cineantropom desempenho hum. 2013;15(1):113-29. doi: http://dx.doi.org/10.5007/1980-0037.2013v15n1p113.

11. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012 (version 2012). Rev Port Cardiol. 2013;32(7-8):641.e1-641.e61.

12. Associação Brasileira de Nutrologia. Sociedade Brasileira de Nutrição Parenteral e Enteral. Projeto Diretrizes: utilização da bioimpedância para avaliação da massa corpórea. 2009. p. 1-13.

13. The Criteria Committee of the New York Heart Association. Diseases of the heart and blood vessels: Nomenclature and criteria for diagnosis. 6th ed. Boston (Mass): Little Brown; 1964.

14. Lohman TG, Roche AF, Martorell R. Anthropometric standardization reference manual. Champaign (IL): Human Kinetics Books; 1991.

15. Pitanga FJ, Lessa I. Waist-to-height ratio as a coronary risk predictor among adults. Rev Assoc Med Bras. 2006;52(3):157-61. doi: http://dx.doi.org/10.1590/S0104-42302006000300016.

16. Valdez R. A simple model-based index of abdominal adiposity. J Clin Epidemiol. 1991;44(9):955-6. PMID: 1890438.

17. Pitanga FJ, Lessa I. Anthropometric indexes of obesity as an instrument of screening for high coronary risk in adults in the city of Salvador – Bahia. Arq Bras Cardiol. 2005;8(1):26-31. doi: http://dx.doi.org/10.1590/S0066-782X2005001400006.

18. World Health Organization. (WHO). Obesity preventing and managing the global epidemic. Report of a WHO consultation on obesity. Geneve; 1998.

19. Lohman TG. Advances in body composition assessment. Champaign, IL: Human Kinetics Publishers; 1992.

20. Neeland IJ, Gupta S, Ayers CR, Turer AT, Rame JE, Das SR, et al. Relation of regional fat distribution to left ventricular structure and function. Circ Cardiovasc Imaging. 2013;6(5):800-7. doi: 10.1161/CIRCIMAGING.113.000532.

21. Reis JP, Allen N, Gibbs BB, Gidding SS, Lee JM, Lewis CE, et al. Association of the degree of adiposity and duration of obesity with measures of cardiac structure and function: the CARDIA Study. Obesity (Silver Spring). 2014;2(11):2434-40. doi: 10.1002/oby.20865.

22. Moyer VA; U.S. Preventive Services Task Force. Screening for and management of obesity in adults: U.S. preventive services task force recommendation statement. Ann Intern Med. 2012;157(5):373-8. doi: 10.7326/0003-4819-157-5-201209040-00475.

23. Borné Y, Hedblad B, Essén B, Engström G. Anthropometric measures in relation to risk of heart failure hospitalization: a Swedish population-based cohort study. Eur J Public Health. 2012;24(2):215-20. doi: 10.1093/eurpub/cks161.

24. Gastelurrutia P, Lupón J, Domingo M, Ribas N, Noguero M, Martinez C, et al. Usefulness of body mass index to characterize nutritional status in patients with heart failure. Am J Cardiol. 2011;108(8):1166-70. doi: 10.1016/j.amjcard.2011.06.020.

25. Schommer VA, Vogel P, Marcadenti A. Antropometria, composição corporal e prognóstico em pacientes com insuficiência cardíaca. Rev Soc Cardiol Est RG Sul. 2015;28:1-7.

26. Puig T, Ferrero-Gregori A, Roig E, Vazquez R, Gonzalez-Juanatey JR, Pascual-Figal D, et al; REDINSCOR Researchers. Prognostic value of body mass index and waist circumference in patients with chronic heart failure (Spanish REDINSCOR Registry). Rev Esp Cardiol (Engl Ed). 2014;67(2):101-6. doi: 10.1016/j.rec.2013.06.022.

27. Quirino CS, Maranhão RV, Giannini DT. Metabolic syndrome among patients enrolled in a cardiac rehabilitation program. Rev Bras Cardiol. 2014;27(3):180-8.

28. Gomes MN, Maciel MG, Torres RS, Barbosa SN. Relação entre variáveis antropométricas, bioquímicas e hemodinâmicas de pacientes cardiopatas. Int J Cardiovasc Sci. 2015;28(5):392-9.

29. Colombo RC, Aguillar OM, Gallani MC, Gobatto CA. Obesity in patients with myocardial infarction. Rev Latino-Am Enfermagem. 2003;11(4):461-7. doi: http://dx.doi.org/10.1590/S0104-11692003000400008.

30. Lobato TA, Torres RS, Guterres AS, Mendes WA, Maciel AP, Santos FC, et al. Anthropometric indicators of obesity among patients with acute myocardial infarction. Rev Bras Cardiol. 2014;27(3):203-12.

31. Mendes WA, Carmin SE, Pinho PM, Silva AC, Machado LM, Araújo MS. Relationship between anthropometric variables and pressure/lipid profiles in adults with chronic non-communicable diseases. Rev Bras Cardiol. 2012;25(3):200-9.

32. Schwenk A, Beisenherz A, Römer K, Kremer G, Salzberger B, Elia M. Phase angle from bioelectrical impedance analysis remains an independent predictive marker in HIV-infected patients in the era of highly active antiretroviral treatment. Am J Clin Nutr. 2000;72(2):496-501. PMID: 10919947.

33. Lee SY, Lee YJ, Yang JH, Kim CM, Choi WS. The Association between phase angle of bioelectrical impedance analysis and survival time in advanced cancer patients: preliminary study. Korean J Fam Med. 2014;35(5):251-6. doi: 10.4082/kjfm.2014.35.5.251.

34. Colín-Ramírez E, Castillo-Martínez L, Orea-Tejeda A, Vázquez-Durán M, Rodríguez AE, Keirns-Davis C. Bioelectrical impedance phase angle as a prognostic marker in chronic heart failure. Nutrition. 2012;28(9):901-5. doi: 10.1016/j.nut.2011.11.033.

35. Doesch C, Suselbeck T, Leweling H, Fluechter S, Haghi D, Schoenberg SO, et al. Bioimpedance analysis parameters and epicardial adipose tissue assessed by cardiac magnetic resonance imaging in patients with heart failure. Obesity (Silver Spring). 2010;18(12):2326-32. doi: 10.1038/oby.2010.65.

36. Orea-Tejeda A, Sánchez-González LR, Castillo-Martínez L, Valdespino-Trejo A, Sánchez-Santillán RN, Keirns-Davies C, et al. Prognostic value of cardiac troponin T elevation is independent of renal function and clinical findings in heart failure patients. Cardiol J. 2010;17(1):42-8. PMID: 20104456.

37. Castillo Martínez L, Colín Ramírez E, Orea Tejeda A, Asensio Lafuente E, Bernal Rosales LP, Rebollar González V, et al. Bioelectrical impedance and strength measurements in patients with heart failure: comparison with functional class. Nutrition. 2007;23(5):412-8. doi: 10.1016/j.nut.2007.02.005.

38. Colín-Ramírez E, Castillo-Martínez L, Orea-Tejeda A, Asensio Lafuente E, Torres Villanueva F, Rebollar González V, et al. Body composition and echocardiographic abnormalities associated to anemia and volume overload in heart failure patients. Clin Nutr. 2006;25(5):746-57. doi: 10.1016/j.clnu.2006.01.009

39. Silva-Tinoco R, Castillo-Martínez L, Orea-Tejeda A, Orozco-Gutiérrez JJ, Vázquez-Díaz O, Montaño-Hernández P, et al. Developing thyroid disorders is associated with poor prognosis factors in patient with stable chronic heart failure. Int J Cardiol. 2011;147(2):e24-5. doi: 10.1016/j.ijcard.2009.01.012.

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Original Article

ORIGINAL ARTICLE

Low to Moderate Alcohol Consumption and Myocardial Ischemia on Exercise Stress Echocardiography

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Abstract

Background: The impact of alcohol consumption on the development of myocardial ischemia remains uncertain. Studies diverge whether low to moderate alcohol consumption provides cardioprotection or whether it is a risk factor for myocardial ischemia.

Objective: To study the relationship between low to moderate alcohol consumption and myocardial ischemia on exercise stress echocardiography (ESE).

Methods: Cross-sectional study with 6,632 patients with known or suspected coronary artery disease undergoing ESE between January/2000 and December/2015. The patients were divided into two groups: G1, composed of 2,130 (32.1%) patients whose report showed maximal consumption of 1 drink per day on average for women or of 2 drinks per day for men; G2, composed of individuals denying any alcohol consumption. For comparing between the groups, Student t test was used for quantitative variables, and chi-square test or Fisher exact test, for categorical variables. The significance level adopted was $p < 0.05$. Logistic regression was also used to evaluate independent risk factors for myocardial ischemia.

Results: G1 had a higher number of men (77.1%; $p < 0.001$), lower mean age (54.8 ± 10.3 years old; $p < 0.001$) and higher frequency of myocardial ischemia on ESE ($p = 0.014$). Age, male sex, dyslipidemia, systemic arterial hypertension, diabetes mellitus, smoking and family history were independently associated with myocardial ischemia on ESE. Independent association between low to moderate alcohol consumption and myocardial ischemia on ESE (OR 0.96; 95%CI: 0.83 to 1.11) was not observed. However, age, male sex, smoking and dyslipidemia were associated with alcohol consumption.

Conclusion: Low to moderate alcohol consumption was not an independent predictor of myocardial ischemia on ESE. Nevertheless, we observed a predominance of the male sex, dyslipidemia and smoking habit, important predictors of myocardial ischemia, in the group of alcohol consumers. (International Journal of Cardiovascular Sciences. 2018;31(3)235-243)

Keywords: Alcoholic Beverages; Alcohol Drinking; Risk Factors; Coronary Artery Disease; Echocardiography, Stress.

Introduction

Coronary artery disease (CAD) remains the leading cause of morbidity and mortality worldwide.[1,2] In Brazil, that scenario is not different, because cardiovascular diseases account for more than one third of the deaths annualy.[3] Thus, one of the most frequent challenges in daily cardiology practice is the early assessment of CAD. Such investigation implies a substantial and growing burden to health systems, especially considering the characteristics of the Brazilian population, of which approximately two thirds use the Brazilian Unified

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Health System. Therefore, it is mandatory to identify high-risk groups that would benefit from further investigation, and low-risk groups that would not require additional investigative procedures.[4,5]

There are numerous effects of alcohol consumption, most of which are harmful to health.[6,7] While its influence on deaths from external causes and on morbidity and mortality due to neoplasms is often reported,[8] the impact of low to moderate alcohol consumption on the prognosis of CAD remains uncertain.[6,8] Recent studies have described moderate alcohol consumption as cardioprotective,[7-11] although that association has been questioned.[12-15]

The definition of moderate alcohol consumption varies widely (from 5 to 60 grams of ethanol per day); however no more than one drink daily of alcoholic beverage for women and up to two drinks daily for men are commonly considered moderate alcohol consumption.[10-11] More specifically, one drink of alcoholic beverage can be defined as approximately 330 mL of common beer, 100 mL of wine, or 30 mL of distilled beverage.[16]

Stress echocardiography is a well-established non-invasive test to assess myocardial ischemia in patients with suspected or known CAD, to determine its diagnosis and prognosis, and to aid in therapeutic decision-making.[17] Exercise stress echocardiography (ESE) is the first choice for patients with preserved physical capacity, being safer and more versatile than pharmacological stress echocardiography.[18]

This study was aimed at assessing the relationship between low to moderate alcohol consumption and the presence of myocardial ischemia on ESE.

Methods

This analytical and descriptive cross-sectional study was carried out from January 2000 to December 2015.

Patients

The convenience sample consisted initially of 10827 patients with suspected and/or established CAD, who underwent ESE at the accredited Echocardiography Laboratory (ECOLAB) of the São Lucas Hospital and Foundation (*Instituto Qualisa de Gestão - IQG)*, in Aracaju city, Sergipe State. All patients older than 25 years referred to the service were included in this study, except for those who refused to participate. Of those, 27 patients were excluded due to their average intake of more than one drink of alcoholic beverage daily for women and more than two drinks for men. In addition, 4,168 individuals did not report the frequency of consumption, resulting in a final sample of 6,632 patients. The isolated or combined indications for ESE were: assessment of chest pain; preoperative assessment for non-cardiac surgery; positive exercise test (ET) for myocardial ischemia in patients at low risk for CAD; negative ET for myocardial ischemia in patients at intermediate risk for CAD; arrhythmia during ET; stratification of previously established CAD; and risk stratification after acute coronary syndrome.

The study patients were divided into two groups according to their frequency of alcoholic beverage intake as follows: G1 - 2,130 (32.1%) patients reporting a maximum daily consumption of one drink (women) or two drinks (men); and G2 - 4,502 (67.9%) individuals reporting no alcohol intake.

Clinical characteristics

The clinical data were collected and recorded during an interview conducted before the ESE, by use of a standard questionnaire assessing: weight; height; symptoms, such as dyspnea and chest pain; medications; risk factors for CAD; family or personal history of heart disease; and data regarding previous CAD, such as acute myocardial infarction, and percutaneous and surgical myocardial revascularization. In addition, the results of previous laboratory and cardiovascular tests were recorded.

Alcohol consumption was quantified by use of self-report as follows: low to moderate alcohol consumption, consisting of a maximum daily intake of two drinks of alcoholic beverage for men, and of one drink for women. One drink of alcoholic beverage can be defined as approximately 330 mL of common beer, 100 mL of wine, or 30 mL of distilled beverage.[10,16] Based on those parameters and on the reports in the interview, the average daily consumption for each patient was estimated.

Obesity was defined as a body mass index greater than 30 kg/m². Hypercholesterolemia was defined as total cholesterol serum levels greater than 200 mg/dL (after 12-hour fasting), while hypertriglyceridemia, as triglyceride serum levels greater than 150 mg/dL (after 12-hour fasting) or use of lipid-lowering agents (statins and/or fibrates).

Systemic arterial hypertension was identified in the presence of systolic blood pressure ≥ 140 mm Hg and/

or diastolic blood pressure ≥ 90 mm Hg, measures taken on the upper limb, at rest and under ideal conditions, and repeated and confirmed, or when antihypertensive agents were used.

Diabetes mellitus was identified in the presence of: fasting glycemia ≥ 126 mg/dL; or glycemia ≥ 200 mg/dL after 2 hours of oral glucose overload (75g); or random glycemia ≥ 200 mg/dL associated with classic symptoms of hyperglycemia; or use of oral hypoglycemic agents.

Exercise stress echocardiography

The protocol consisted initially in performing a 12-lead electrocardiogram (ECG) and a resting echocardiography after clinical investigation. Then, ET was performed on a treadmill, and, right after, new echocardiographic images were acquired.

All patients were submitted to the standard Bruce or Ellestad protocol during ET. Heart rate was monitored continuously, and the patients were encouraged to achieve their peak physical effort. For metabolic calculations, maximum oxygen consumption at peak exercise (VO_2max) was obtained indirectly by use of the formula: $VO_2max = 14.76 – 1.379t + 0.451t^2 - 0.012t^3$, where t is the duration of ET in minutes.[19] Load was expressed in metabolic equivalents, where 1 MET corresponds to 3.5 mL/kg·min of inhaled VO_2 at rest.20 During ET, the individuals were continuously monitored by use of 3-lead ECG.

The electrocardiographic ischemic changes during exercise were horizontal or descending ST-segment depressions ≥ 1 mm for men, and ≥ 1.5 mm for women, at 0.08 second from J point.[21]

The ET was performed in an ergonomically designed environment with a continuously trained team, at a reference hospital in cardiology, accredited for specific assessment. The suspension of beta-blockers three days before the ET is recommended routinely, while the other usual drugs are maintained.

The ET was performed with a Hewlett Packard/Phillips SONOS 5500 device until 2012, and, from that year on, with a Phillips IE-33 device, abiding by the technical aspects classically described by Schiller et al.[22] The two-dimensional echocardiographic images were obtained in parasternal and apical acoustic windows, at rest and immediately after exertion, with the patient lying in the left lateral decubitus position and simultaneous electrocardiographic recording.

Left ventricular segmental wall motion was assessed by an experienced level III echocardiographer, as recommended by the American Society of Echocardiography.[23] Left ventricular segmental wall thickening was quantitatively assessed at rest and after exertion by use of the model of 16 segments graded as: 1, normal; 2, hypokinetic; 3, akinetic; 4, dyskinetic. The left ventricular wall motion score index (LVWMSI) was calculated at rest and during exertion as the addition of the scores of each of the 16 segments divided by the number of segments assessed at a given time. A LVWMSI of 1 corresponds to normality, between 1.1 and 1.6 represents mild dysfunction, and between 1.61 and 2, moderate dysfunction. Values greater than 2 represent significant dysfunction.22 The difference between the LVWMSI at exertion and at rest is the ΔLVWMSI. The development of a new wall motion change or worsening of the existing dyssynergy (ΔLVWMSI ≠ 0) was considered indicative of myocardial ischemia.

Statistical analysis

The quantitative variables were described as mean and standard deviation. According to the assumption of sample normality, assessed by use of the Kolmogorov-Smirnov test, the quantitative variables were assessed by use of Student *t* test for independent groups. For the categorical variables, absolute frequency and percentage were used. To compare the characteristics of categorical variables between the two groups, chi-square test or Fisher exact test, when more appropriate, was used.

To assess the association between the variable outcome (myocardial ischemia on ESE) and the associated factors, logistic regression was performed with backward-Wald method. To enter the initial model, all variables with $p < 0.25$ were admitted, while to remain in the model, $p < 0.05$ was adopted. The variables were entered into and removed from the model manually, depending on meeting the assumption. The Statistical Package for the Social Sciences (SPSS), version 22.0 (Chicago, IL), was used in the statistical analysis.

Ethical aspects

This study abided by the ethical principles that regulate human experimentation, and all patients provided written informed consent. This study was approved by the Committee in Ethics and Research of the Sergipe Federal University (CAAE 1818.0.000.107-06).

Results

This study assessed 6,632 patients, 3,257 (49.1%) of the male sex, mean age of 57.6 ± 11.1 years (25 - 98 years). Low to moderate alcohol consumption (G1) was reported by 2,130 individuals (32.1%), while 4,502 (67.9%) individuals (G2) reported no alcohol intake.

In G1, 21.8% of the patients showed positive results for myocardial ischemia on ESE, with a statistically significant relationship between low to moderate alcohol consumption and myocardial ischemia, as compared to G2.

Clinical characteristics of the groups

In G1, there were a higher relative frequency ($p < 0.001$) of male individuals, lower mean age and higher percentage of smokers. Regarding the other sociodemographic characteristics, G1 showed a significantly ($p < 0.001$) higher educational level, higher abdominal circumference values and lower frequency of sedentary lifestyle as compared to G2 (Table 1).

The major clinical variables that associated with myocardial ischemia on ESE are shown in Table 2. Of the major clinical findings, only history of sedentary lifestyle and diagnosis of obesity were not significant on univariate analysis for the presence of myocardial ischemia.

Echocardiographic and exercise test characteristics of the groups

The G2 showed a higher number of patients without evidence of myocardial ischemia on ESE. Fixed myocardial ischemia was the most frequent type found in G1. Greater sizes of the aorta and left atrium were observed in G1, while G2 showed a higher frequency of diastolic dysfunction. Of the ET variables, ST-segment depression and chronotropic insufficiency were more frequent in G1 and in G2, respectively (Table 3).

Logistic regression analysis

The multivariate analysis by use of logistic regression of the clinical data available showed that age, male sex, diabetes mellitus, systemic arterial hypertension, dyslipidemia, smoking habit and family history were independently associated with myocardial ischemia (Table 4). When assessing those confounding factors of the model, there was no association between low to moderate alcohol consumption and myocardial ischemia on ESE.

Table 1 - Clinical characteristics of patients consuming a low to moderate amount of alcohol (G1) or none (G2), submitted to exercise stress echocardiography

Variables	G1 (n = 2,130)	G2 (n = 4,502)	p*
Male sex	1,643 (77.1%)	1,614 (35.9%)	< 0.001
Age	54.8 ± 10.3	59.0 ± 11.3	< 0.001
Previous symptoms			
Asymptomatic	1,088 (52.3%)	1,808 (41.2%)	
Typical chest pain	135 (6.5%)	290 (6.6%)	< 0.001
Atypical chest pain	762 (36.6%)	2,034 (46.4%)	
Dyspnea	103 (4.9%)	269 (6.1%)	
Obesity	509 (24%)	991 (22.1%)	0.088
Weight	78.3 ± 14.2	70.7 ± 14.0	< 0.001
Height	1.68 ± 0.09	1.61 ± 0.09	< 0.001
Abdominal circumference	96.6 ± 11.9	93.3 ± 12.4	0.001
Systemic arterial hypertension	1,269 (59.8%)	2,786 (62%)	0.078
Diabetes mellitus	274 (12.9%)	542 (12.1%)	0.339
Dyslipidemia	1,185 (55.8%)	2,457 (54.7%)	0.414
Smoking habit	157 (7.4%)	140 (3.1%)	< 0.001
Family history	1,252 (58.9%)	2,671 (59.5%)	0.690
Physical activity			
None	997 (49.9%)	2,408 (56.9%)	
Active	985 (49.3%)	1,789 (42.3%)	< 0.001
Athlete	18 (0.9%)	34 (0.8%)	
Old infarction	113 (5.5%)	191 (4.4%)	0.049
Recent infarction	8 (0.4%)	10 (0.2%)	0.258
Revascularization	122 (5.9%)	215 (4.9%)	0.092
Angioplasty	174 (8.5%)	312 (7.2%)	0.064
Stent	122 (5.9%)	214 (4.9%)	0.084

(*) The qualitative variables were calculated by use of Pearson chi-square test, and the quantitative variables, by use of Student t test for independent samples, according to the normality assumption of the sample.

In addition, age, male sex, smoking habit and dyslipidemia associated with low to moderate alcohol consumption (Table 5).

Table 2 - Univariate analysis of the clinical parameters associated with the presence of myocardial ischemia on exercise stress echocardiography

Variables	Odds Ratio	95% CI	p*
Alcohol consumption	1.15	1.01-1.30	0.035
Male sex	1.69	1.50 - 2.90	< 0.001
Age	1.03	1.02-1.03	< 0.001
Obesity	1.02	0.88-1.18	0.76
Diabetes mellitus	1.99	1.70-2.35	< 0.001
Systemic arterial hypertension	2.16	1.88-2.47	< 0.001
Dyslipidemia	2.25	1.98-2.56	< 0.001
Smoking habit	1.79	1.39-2.31	< 0.001
Family history	1.82	1.59-2.07	< 0.001
Sedentary lifestyle	1.07	0.94-1.21	0.285

CI: confidence interval. (*) The qualitative variables were calculated by use of Pearson chi-square test, and the quantitative variables, by use of Student t test for independent samples, according to the normality assumption of the sample.

Table 3 - Echocardiographic and exercise test characteristics of patients consuming a low to moderate amount of alcohol (G1) or none (G2), submitted to exercise stress echocardiography

Variables	G1 (n = 2,130)	G2 (n = 4,502)	p*
Ischemia			
None	1,666 (78.2%)	3,621 (80.4%)	
Induced	195 (9.2%)	430 (9.6%)	0.014
Fixed	211 (9.9%)	359 (8%)	
Fixed and induced	58 (2.7%)	91 (2%)	
Aorta	3.3 ± 0.4	3.1 ± 0.4	< 0.001
Left atrium	3.9 ± 0.4	3.8 ± 0.4	< 0.001
E wave velocity	68.4 ±15.1	70.9 ± 17.1	0.778
E' wave velocity	8.0 ± 4.1	7.6 ± 2.3	0.140
E/E' ratio	9.3 ± 2.8	10.0 ± 3.6	0.347
Ejection fraction	67% ± 6.4	67% ± 6.5	0.133
LVWMSI at rest	1.02 ± 0.09	1.01 ± 0.08	0.246
LVWMSI on exertion	1.03 ± 0.09	1.02 ± 0.09	0.459
Diastolic function			
Normal	294 (17.4%)	473 (13.6%)	
Relaxation deficit	851 (50.3%)	1,918 (55.1%)	0.001
Pseudonormal	540 (31.9%)	1,075 (30.9%)	
Restrictive	8 (0.5%)	17 (0.5%)	
ST-segment depression	1,355 (64.1%)	2,793 (62.5%)	< 0.001
Left bundle-branch block	66 (3.1%)	183 (4.1%)	0.054
Simple arrhythmias	539 (25.3%)	1,309 (29.1%)	0.001
Severe arrhythmias **	4 (0.2%)	16 (0.4%)	0.245
NSVT	-	2 (< 0.1%)	0.330
Atrial fibrillation	1 (0.1%)	2 (0.1%)	0.999
Ventricular extrasystole	63 (3.8%)	105 (3.2%)	0.242
Supraventricular extrasystole	19 (1.1%)	43 (1.3%)	0.654
Supraventricular tachycardia	4 (0.2%)	8 (0.2%)	0.999
Chronotropic insufficiency	160 (7.5%)	440 (9.8%)	0.003

LVWMSI: left ventricular wall motion score index; NSVT: non-sustained ventricular tachycardia; (**) Ventricular tachycardia or ventricular fibrillation. (*) The qualitative variables were calculated by use of Pearson chi-square test, and the quantitative variables, by use of Student t test for independent samples, according to the normality assumption of the sample.

Discussion

Low to moderate alcohol consumption related with myocardial ischemia on ESE, but was not an independent predictor of positivity on that test. The literature is controversial about the association between alcohol consumption and ischemic heart diseases. The effect of alcohol on patients with myocardial ischemia has been reported as protective in a daily alcohol intake of up to one drink[6,7] or two drinks.[9,10] Other studies have reported alcohol consumption as a risk factor for myocardial ischemia at an average consumption of at least one drink daily[13] or at any daily amount.[12,14] Divergences and lack of correlation between myocardial

Table 4 - Multivariate logistic regression with clinical parameters associated with the presence of myocardial ischemia on exercise stress echocardiography

Variables	Odds Ratio	95% CI	p
Alcohol consumption	0.94	0.81-1.01	0.463
Male sex	1.83	1.62-2.09	< 0.001
Age	1.02	1.02-1.03	< 0.001
Diabetes mellitus	1.52	1.28-1.80	< 0.001
Systemic arterial hypertension	1.55	1.34-1.79	< 0.001
Dyslipidemia	1.84	1.61-2.1	< 0.001
Smoking habit	2.03	1.55-2.64	< 0.001
Family history	1.69	1.47-1.93	< 0.001

CI: confidence interval.

Table 5 - Multivariate logistic regression with clinical parameters associated with low to moderate alcohol consumption

Variables	Odds Ratio	95% CI	p
Myocardial ischemia à ESE	0.96	0.83-1.11	0.603
Male sex	5.88	5.21-6.63	< 0.001
Age	0.97	0.96-0.97	< 0.001
Smoking habit	2.73	2.11-3.54	< 0.001
Dyslipidemia	1.51	1.02-1.29	0.017

ESE: exercise stress echocardiography; CI: confidence interval.

ischemia and alcohol intake evidenced in certain studies can be explained by individual differences inherent in genetic characteristics.[11]

Roerecke and Rehm6 in a systematic review, have assessed 44 observational studies relating ischemic heart diseases to low to moderate alcohol consumption, between 1980 and 2010, in a total of 957,684 participants. Those authors have shown that, although there is some confirmed cardioprotective association, substantial heterogeneities remain unexplained and the confidence intervals were relatively wide, particularly between one and two drinks of alcoholic beverage daily. Therefore, the cardioprotection related to alcohol intake has been described as an association that cannot be assumed, even when assessing the level of alcohol consumption.

The variables male sex, dyslipidemia and smoking habit - independent predictors of low to moderate alcohol consumption in the present study - also showed a close relationship with myocardial ischemia. In accordance with the literature, greater frequency of alcohol intake is observed among men[7,13] and together with the smoking habit,[13,14] widely identified as risk factors for myocardial ischemia.[17] Perissinotto et al.[24] have evidenced higher serum levels of LDL cholesterol and total cholesterol among the elderly whose alcohol intake was moderate, as in the present study, although that consumption has been reported as inversely associated with dyslipidemia.[11,14]

The literature lacks ET and echocardiography data related to low to moderate alcohol consumption, and significant differences were evidenced in the present study. Statistical significance was observed in the relationship between alcohol consumption and larger size of the aorta and left atrium, as well as with the higher frequency of ST-segment depression and lower frequency of diastolic dysfunction and chronotropic insufficiency.

Regarding the limitations of this study, those inherent in any observation study stand out, in which the variables not measured can contribute to the statistical differences between the groups. In addition, distinct intervals of alcohol intake could not be accurately quantified, and neither could the duration of alcohol consumption, the type of alcoholic beverage used and the previous history of that habit.

Conclusion

Low to moderate alcohol consumption showed not to be an independent predictor of the presence of myocardial ischemia on ESE. In the group of alcohol consumers, there were more individuals of the male sex, dyslipidemic and smokers, which are important predictors of myocardial ischemia.

Author contributions

Conception and design of the research: Fontes VJB, Oliveira JLM. Acquisition of data: Fontes VJB, Souto MJS, Conceição FMS, Telino CJCL, Silveira MS,

Dória JAS, Matos CJO, Oliveira JLM. Analysis and interpretation of the data: Fontes VJB, Souto MJS, Sousa ACS, Melo EV, Conceição FMS, Telino CJCL, Silveira MS, Dória JAS, Matos CJO, Oliveira JLM. Statistical analysis: Melo EV. Writing of the manuscript: Fontes VJB, Souto MJS, Sousa ACS, Melo EV, Conceição FMS, Telino CJCL, Matos CJO, Oliveira JLM. Critical revision of the manuscript for intellectual content: Fontes VJB, Souto MJS, Sousa ACS, Melo EV, Conceição FMS, Telino CJCL, Matos CJO, Oliveira JLM. Supervision / as the major investigador: Oliveira JLM.

Potential Conflict of Interest

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

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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 Sergipe under the protocol number CAAE 1818.0.000.107-06. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

References

1. Moran AE, Forouzanfar MH, Roth GA, Mensah GA, Ezzati M, Murray CJ, et al. Temporal trends in ischemic heart disease mortality in 21 world regions, 1980 to 2010: the global burden of disease 2010 study. Circulation. 2014;129(14):1483-92. doi: 10.1161/CIRCULATIONAHA.113.004042.
2. Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics - 2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2009;119(3):480-6. doi: 10.1161/CIRCULATIONAHA.108.191259. Erratum in: Circulation. 2009;119(3):e182.
3. Brasil. Ministério da Saúde. [Internet]. Secretaria Executiva. Datasus. Informações de Saúde. Morbidade e informações epidemiológicas. [Citado 2014 maio 24]. Disponível em: http://www.datasus.gov.br.
4. Araújo AC, Santos BF, Oliveira JL, Calasans FR, Pinto IM, Oliveira DP, et al. Physical stress echocardiography: prediction of mortality and cardiac events in patients with exercise test showing ischemia. Arq Bras Cardiol. 2014;103(5);418-25. doi: http://dx.doi.org/10.5935/abc.20140144.
5. Alves AA. Valor prognóstico da ecocardiografia sob estresse pela dobutamina e adenosina associada à perfusão miocárdica em tempo real em pacientes com doença arterial coronariana suspeita ou confirmada. [Tese]. São Paulo: Universidade de São Paulo (USP); 2010.
6. Roerecke M, Rehm J. The cardioprotective association of average alcohol consumption and ischaemic heart disease: a systematic review and meta-analysis. Addiction. 2012;107(7):1246-60. doi: 10.1111/j.1360-0443.2012.03780.x.
7. Rehm J, Baliunas D, Borges G, Graham K, Irving H, Kehoe T, et al. The relation between different dimensions of alcohol consumption and burden of disease: an overview. Addiction. 2010;105(5):817-43. doi: 10.1111/j.1360-0443.2010.02899.x.
8. Bruegger-Andersen T, Poenitz V, Snapinn S, Dickstein K; OPTIMAAL study group. Moderate alcohol consumption is associated with reduced long-term cardiovascular risk in patients following a complicated acute myocardial infarction. Int J Cardiol. 2009;133(2):229-32. doi: 10.1016/j.ijcard.2007.12.046.
9. Klatsky AL. Alcohol and cardiovascular health. Physiol Behav. 2010;100(1):76-81. doi: 10.1016/j.physbeh.2009.12.019.
10. Rimm EB, Moats C. Alcohol and coronary heart disease: drinking patterns and mediators of effect. Ann Epidemiol. 2007;17(5):S3-7. doi: http://dx.doi.org/10.1016/j.annepidem.2007.01.002
11 Movva R, Figueredo VM. Alcohol and the heart: to abstain or not to abstain? Int J Cardiol. 2013;164(3):267-76. doi: 10.1016/j.ijcard.2012.01.030.
12. Fillmore KM, Stockwell T, Chikritzhs T, Bostrom A, Kerr W. Moderate alcohol use and reduced mortality risk: systematic error in prospective studies and new hypotheses. Ann Epidemiol. 2007;17(5 Suppl):S16-23. doi: 10.1016/j.annepidem.2007.01.005.
13. Zhou X, Li C, Xu W, Hong X, Chen J. Relation of alcohol consumption to angiographically proved coronary artery disease in Chinese men. Am J Cardiol. 2010;106(8):1101-3. doi: 10.1016/j.amjcard.2010.06.012.
14. Roy A, Prabhakaran D, Jeemon P, Thankappan KR, Mohan V, Ramkrishna L, et al; Sentinel Surveillance in Industrial Populations Study Group. Impact of alcohol on coronary heart disease in Indian men. Atherosclerosis. 2010;210(2):531-5. doi: 10.1016/j.atherosclerosis.2010.02.033.
15. Mostofsky E, Chalhal HS, Mukamal KJ, Rimm EB, Mittleman MA. Alcohol and immediate risk of cardiovascular events: a systematic review and dose-response meta-analysis. Circulation. 2016;133(10):979-87. doi: 10.1161/CIRCULATIONAHA.115.019743.
16. U.S. Department of Agriculture and U.S. Department of Health and Human Services [Internet]. 2015–2020 Dietary Guidelines for Americans, 2015. 8th ed., Appendix 9. [Cited in 2016 Sept 19]. Available from: http://health.gov/dietaryguidelines/2015/guidelines/appendix-9/.
17. Cesar LA, Ferreira JF, Armaganijan D, Gowdak LH, Mansur AP, Bodanese LC et al; Sociedade Brasileira de Cardiologia. Guideline for stable coronary artery disease. Arq Bras Cardiol. 2014;103(2 Suppl 2):1-56. doi: http://dx.doi.org/10.5935/abc.2014S004.
18. Andrade SM, Telino CJ, Sousa AC, Melo EV, Teixeira CC, Teixeira CK, et al. Low prevalance of major events adverse to exercise stress echocardiography. Arq Bras Cardiol. 2016;107(2):116-23. doi: 10.5935/abc.20160096.
19. Lauer MS, Francis GS, Okin PM, Pashkow FJ, Snader CE, Marwick TH. Impaired chronotropic response to exercise stress testing as a predictor of mortality. JAMA. 1999;281(6):524-9. PMID: 10022108.

20. Whaley MH, Brubaker PH, Otto R. (eds.). ACSM's guidelines for exercise testing and prescription. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2007.

21. Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, et al; American College of Cardiology / American Heart Association Task Force on Practice Guidelines. Committee to Update the 1997 Exercise Testing Guidelines. ACC / AHA 2002 guideline update for exercise testing: summary article. A report of the American College of Cardiology / American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). J Am Coll Cardiol. 2002;40(8):1531-40. PMID: 12392846. Erratum in J Am Coll Cardiol 2006;48(8):1731.

22. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. Recommendations for quantitation of the left ventricle by two dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr. 1989;2(5):358-67. PMID: 2698218.

23. Pellikka PA, Nagueh SF, Elhendy AA, Kuehl CA, Sawada SG. American Society of Echocardiography Recommendations for Performance, Interpretation and Application of Stress Echocardiography. J Am Soc Echocardiogr. 2007;20(9):1021-41. doi: 10.1016/j.echo.2007.07.003.

24. Perissinotto E, Buja A, Maggi S, Enzi G, Manzato E, Scafato E, et al. Alcohol consumption and cardiovascular risk factors in older lifelong wine drinkers: the Italian Longitudinal Study on Aging. Nutr Metab Cardiovasc Dis. 2010;20(9):647-55. doi: 10.1016/j.numecd.2009.05.014.

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ORIGINAL ARTICLE

Association of Respiratory Mechanics with Oxygenation and Duration of Mechanical Ventilation After Cardiac Surgery

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Abstract

Background: Mechanical ventilation (MV) and extracorporeal circulation (ECC) are associated with a decline in pulmonary mechanics that may affect gas exchange.

Objective: To evaluate the impact of pulmonary mechanics on MV duration and gas exchange in the postoperative period of cardiac surgery.

Methods: This was a cohort study in patients undergoing cardiac surgery. All patients underwent evaluation of pulmonary mechanics (static compliance and airway resistance) and arterial blood gas analysis upon admission to the intensive care unit (ICU) and were followed up until extubation and hospital discharge.

Results: The study included 50 patients (46 women, 52%) with a mean age of 57.5 ± 13.5 years. The MV duration was 7.7 ± 3.0 hours, static compliance was 35.5 ± 9.1 cm H_2O, resistance was 6.0 ± 2.3 cm H_2O, mean length of ICU stay was 2.9 ± 1.1 days, and oxygenation index was 228.0 ± 33.4 mmHg. No significant correlation was found between MV duration and static compliance ($p = 0.73$), but a strong correlation was found between static compliance and gas exchange ($r = 0.8$ and $p < 0.001$).

Conclusion: Pulmonary mechanics have a strong correlation with gas exchange and a weak correlation with MV duration after cardiac surgery. (International Journal of Cardiovascular Sciences. 2018;31(3)244-249)

Keywords: Respiration, Artificial; Oxygenation; Thoracic Surgery; Cardiac Surgical Procedures; Postoperative Care.

Introduction

Cardiac surgery is a form of treatment for coronary and myocardial pathologies aimed at increasing the patient's survival and quality of life. However, this type of surgery is associated with deleterious effects on the main body systems, such as the cardiovascular, central nervous, digestive, renal, and respiratory systems.[1] In this context, pulmonary complications emerge as an important cause of increased morbidity and mortality during the postoperative period.[2]

Patients undergoing cardiac surgery remain under mechanical ventilation (MV) in the immediate postoperative period until properly awaken and presenting good respiratory and hemodynamic stability.[3,4] In some cases, the hospital stay may be even longer, and the patient may remain in the hospital for several days, often due to a requirement for vasoactive drugs.

Complications caused by cardiac surgery lead to multifactorial changes in pulmonary function, including alveolar collapse, decreased functional residual capacity, secretion retention, and decreased cough effectiveness.[5,6]

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Physical therapy prescribed correctly during the preoperative and postoperative periods of cardiac surgery provides major benefits for patients with heart disease and may reduce substantially the occurrence of complications during these periods. With these potential benefits, the inclusion of physical therapists becomes fundamental in the hospital environment. However, there is scarce information in the literature regarding the impact of changes in respiratory mechanics on the duration of invasive MV (IMV) and whether this would increase the duration of stay in the intensive care unit (ICU).

Based on these considerations, this study aimed to evaluate the association between respiratory mechanics with oxygenation and duration of IMV and ICU hospitalization in patients in the postoperative period of cardiac surgery.

Methods

This was a prospective cohort study conducted with patients admitted to the *Instituto Nobre de Cardiologia / Santa Casa de Misericórdia* in the period between February and June 2016. The study was approved by the Research Ethics Committee at *Faculdade Nobre* (CAAE 51208115.1.0000.5654), and all patients signed an informed consent form in the preoperative period.

The inclusion criteria were individuals of both genders, aged 18 years or older, undergoing cardiac surgery (coronary-artery bypass grafting [CABG], aortic and/or mitral valve replacement, and correction of cardiac disease), who underwent sternotomy and extracorporeal circulation (ECC) under IMV in the immediate postoperative period. The exclusion criteria were: (a) hemodynamic instability requiring vasopressors at high concentration, (b) nonevaluable respiratory mechanics (for example, interaction with the MV), (c) progression to death during the ICU period, (d) sedation required for more than 48 hours, (e) absence of arterial catheter for collection of blood sample, and (f) refusal to participate in the research and to sign the informed consent form.

Patients who met the inclusion criteria were evaluated at the moment of admission to the ICU, soon after leaving the operating room. After receiving the initial support from the health care team, the physiotherapist on call evaluated the ventilatory mechanics and obtained from the ventilator (Vela, Viasys Healthcare, Critical Care Division, Palm Springs, CA, USA) the values related to peak and plateau pressure, static compliance of the respiratory system, and airway resistance.

During this evaluation, the patients remained in the supine position with the bed-head raised to a minimum of 30º while still under the effect of the surgical anesthesia, receiving ventilation at a controlled volume mode (6 mL/kg) with an inspiratory flow of 40 L/min, respiratory rate of 15 mpm, pause duration of 1 second, fraction of inspired oxygen (FiO_2) of 100%, and positive end-expiratory pressure (PEEP) of 5 cm H_2O. To calculate the static compliance, we used the formula tidal volume / (plateau pressure - PEEP) and to calculate resistance, the formula (peak pressure - plateau pressure) / flow.

Immediately after evaluating the ventilatory mechanics, the physician on call collected a sample of arterial blood through a catheter inserted into the radial artery. The sample was analyzed with a blood gas analyzer and the results related to arterial oxygen pressure (PaO_2) and FiO_2 were recorded. Levels of PaO_2 were divided by those of FiO_2, yielding the oxygenation index.

After these assessments, the patients continued to receive support according to the routine procedures of the unit, including the maintenance of strategies for weaning and decisions about the patient's discharge to the ward. The researchers refrained from interfering with the decisions and were limited to taking notes about the IMV duration (from ICU admission to extubation) and ICU stay.

Statistical analysis

The analysis was performed using SPSS 20.0, and the data are represented as mean and standard deviation. Normality was tested with the Kolmogorov-Smirnov test. Categorical variables were analyzed with the chi-square test and numerical variables (IMV duration, length of ICU stay, static compliance, resistance, and gas exchange) with Pearson's correction test. P values < 0.05 were considered statistically significant.

Results

Between February and June 2016, a total of 64 patients were hospitalized to undergo cardiac surgery. Of these, 14 were excluded from the study due to nonevaluable ventilatory mechanics (10 patients) or for refusing to sign the informed consent (4 patients). Therefore, we included 50 patients (52% women) with a mean age of 57.5 ± 13.5 years, who underwent cardiac surgery at *Instituto Nobre de Cardiologia / Santa Casa de Misericórdia em Feira de Santana*, Bahia (Brazil).

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Table 1 presents the characteristics of the patients included in the study.

The mean static compliance was 35.5 ± 9.1 cm H_2O, the mean airway resistance was 6.0 ± 2.3 cm H_2O, and the mean duration of ICU stay was 2.9 ± 1.1 days.

No significant correlation was found between IMV duration with static compliance and resistance (p = 0.73 and p = 0.51, respectively) (Table 2).

Table 3 shows the static compliance and resistance as functions of the duration of hospitalization in the ICU, analyzed with the Spearman test. No statistically significant relationship was observed (p = 0.83 and p = 0.98, respectively).

On the other hand, a strong correlation was observed between static compliance and gas exchange (228.0 ± 33.4, r = 0.8, p < 0.001) (Figure 1).

Discussion

The results of this study show that ventilatory mechanics (static compliance and resistance) had no influence on the IMV duration and length of ICU stay. However, static compliance presented a strong correlation with gas exchange in the postoperative period of cardiac surgery.

For Arcênio et al.,[7] both anesthesia and certain surgeries predispose patients to changes in respiratory mechanics, pulmonary volumes, and gas exchange. Cardiac surgery, which is considered a large procedure, can trigger in the postoperative period respiratory changes related to several factors, including pulmonary and cardiac function in the preoperative period, use of ECC, and degree of sedation.

According to Badenes et al.,[8] cardiac surgery associated with MV in the postoperative period causes significant structural and functional changes at a pulmonary level due to the inflammatory process that is also associated

Table 1 - Clinical, demographic, and surgical data of the patients who underwent cardiac surgery

Variables	Mean/SD	N (%)
Age (years)	57 ± 13	
Gender		
Male		24 (48)
Female		26 (52)
Type of surgery		
CABG		37 (74)
Valve replacement		12 (24)
Correction of congenital malformations		1 (2)
ECC duration (minutes)	72 ± 22	
MV duration (hours)	8 ± 3	
PaO_2/FiO_2	228.0 ± 33.4	
Successful weaning		50 (100)

SD: standard deviation; N: number of patients; CABG: coronary-artery bypass grafting; MV: mechanical ventilation; ECC: extracorporeal circulation; PaO_2: arterial oxygen pressure; FiO_2: fraction of inspired oxygen.

Table 2 - Analysis of the ventilatory mechanics and duration of invasive mechanical ventilation (IMV) in patients undergoing cardiac surgery

Variable	
Static compliance (cm H_2O)	35.5 ± 9.1
IMV duration (hours)	8 ± 3
p[a]	0.73
Resistance (cm H_2O)	6.0 ± 2.3
IMV duration (hours)	8 ± 3
p*	0.51

*Data are presented as mean ± standard deviation. *Pearson's test.*

Table 3 - Analysis of the ventilatory mechanics and duration of hospitalization in the intensive care unit (ICU) in patients undergoing cardiac surgery

Variable	
Static compliance (cm H_2O)	35.5 ± 9.1
Duration of ICU stay (days)	2.9 ± 1.1
p*	0.83
Resistance (cm H_2O)	6.0 ± 2.3
Duration of ICU stay (days)	2.9 ± 1.1
p*	0.98

*Data are presented as mean ± standard deviation. *Spearman test.*

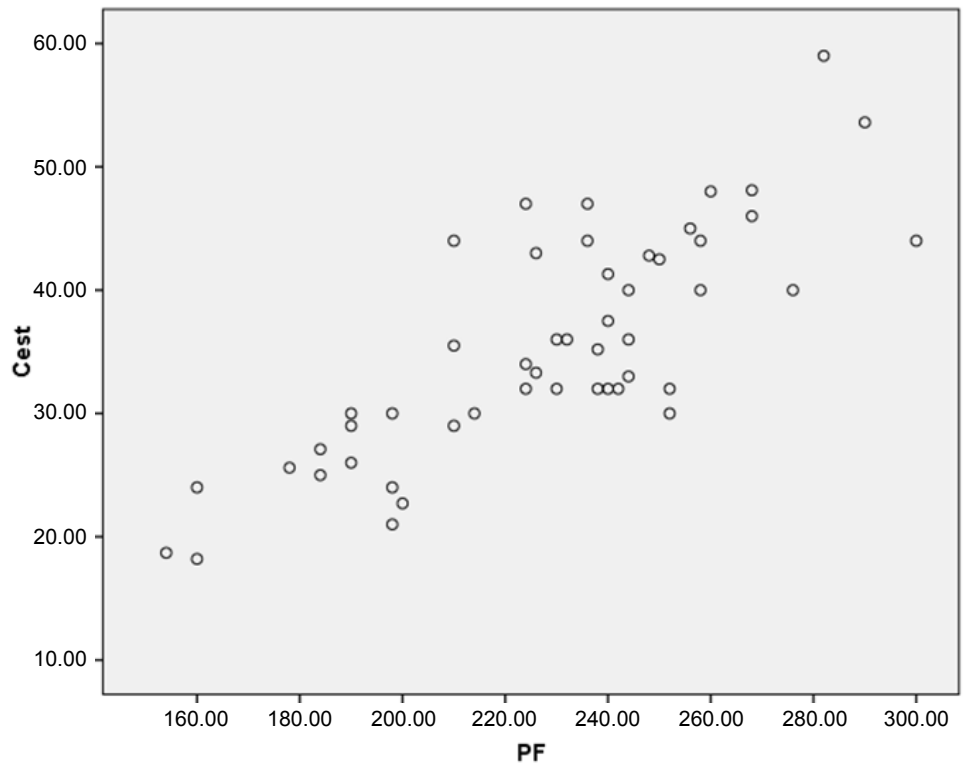

Figure 1 - Correlation between static compliance and gas exchange.

with the ECC, leading to reduced compliance of the respiratory system. In the present study, it was not possible to assess the parameters of pulmonary function prior to surgery.

Taking into consideration the pulmonary decline that occurs after cardiac surgery, Auler Jr et al.[9] investigated the effect of PEEP on respiratory mechanics in patients submitted to cardiac revascularization. The authors applied different PEEP levels (0, 5, 10, and 15 cm H_2O) and demonstrated that with increases in positive pressure, there were decreases in airway resistance and elastance. It is worth mentioning that in the present study, all patients had the PEEP previously set at 5 cm H_2O and a low resistance was also observed with a mean of 6 cm H_2O.

Another factor that may increase the length of stay of the patient in the IMV and in the ICU is the intraoperative ECC duration. Canver & Chanda[10] verified that ECC might be an independent factor for postoperative respiratory insufficiency, which consequently increases the duration of IMV and ICU stay. In an attempt to reduce the impact of ECC on the pulmonary function, Figueiredo et al.[11] evaluated 30 patients in the postoperative period of CABG to verify the impact of continuous positive airway pressure (CPAP) on gas exchange during ECC and showed that there was no lasting improvement with the use of ECC at 10 cm H_2O.

The causes of unsuccessful weaning in patients undergoing cardiac surgery are mainly related to the presence of cardiac dysfunction and prolonged ECC duration. The ECC duration is one of the main factors to delay MV weaning after cardiac surgery, due to the important physiological disorder caused by the inflammatory response to the extracorporeal circuit.[12] In a study conducted by Nozawa et al.,[12] static pulmonary compliance was altered in patients undergoing cardiac surgery, showing values below the normal range, but this parameter was not sensitive enough to identify the prognosis of the patients in regards to MV weaning. Airway resistance was increased in all patients; however, no significant difference was observed between the patients who progressed to MV independence and those who evolved to weaning failure.

In relation to gas exchange, the present study found that the lower the static compliance, the lower the

oxygenation index. Rodrigues et al.[13] assessed 942 patients in order to verify the factors associated with dysfunctional exchanges after cardiac surgery and observed that the presence of pneumonia, cardiac arrhythmia, and hemotherapy correlated with such dysfunction. Other authors have demonstrated that the body mass index and smoking may be associated with hypoxemia, which in turn is associated with a decline in pulmonary compliance.[14,15]

As an alternative to correct this decline in pulmonary compliance, Lima et al.[16] investigated the impact of different levels of PEEP on gas exchange in patients undergoing CABG. The authors evaluated 78 individuals divided into three groups according to PEEP level (5, 8, and 10 cm H_2O) and observed that changes in PEEP level do not interfere in the exchanges. When the authors analyzed the group that received a PEEP of 5 cm H_2O (an identical level to that used in the present study), they observed a mean value of 320.5 ± 65.0 mmHg, whereas in the current study, the mean value was 228.0 ± 33.4 mmHg.

The limitations of the present study include the lack of information regarding the comorbidities presented by the patients included in the analysis. Another limitation was the lack of information about static compliance, resistance, and gas exchange in the preoperative period.

Conclusion

Based on the findings of this study, we conclude that pulmonary mechanics correlate strongly with gas exchanges and weakly with the duration of MV in the postoperative period of cardiac surgery.

Author contributions

Conception and design of the research: Oliveira LFL, Queiroz TC, Santana VLL, Cordeiro ALL. Acquisition of data: Oliveira LFL, Queiroz TC, Santana VLL. Analysis and interpretation of the data: Cordeiro ALL, Melo TA. Statistical analysis: Cordeiro ALL, Melo TA. Writing of the manuscript: Oliveira LFL, Queiroz TC, Santana VLL, Cordeiro ALL. Critical revision of the manuscript for intellectual content: Melo TA, Guimarães AR, Martinez BP.

Potential Conflict of Interest

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

Sources of Funding

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References

1. Umeda IIK. Manual de fisioterapia na reabilitação cardiovascular. São Paulo: Editora Manole; 2006. ISBN: 852041477x.
2. Padovani C, Cavenaghi OM. Alveolar recruitment in patients in the immediate postoperative period of cardiac surgery. Rev Bras Cir Cardiovasc. 2011;26.1:116-21. doi: http://dx.doi.org/10.1590/S0102-76382011000100020.
3. Barbosa e Silva MG, Borges DL, Costa Mde A, Baldez TE, Silva LN, Oliveira RL, et al. Application of mechanical ventilation weaning predictors after elective cardiac surgery. Braz J Cardiovasc Surg. 2015;30(6):605-9. doi: 10.5935/1678-9741.20150076.
4. Gonçalves JQ, Martins RC, Andrade AP, Cardoso FP, Melo MH. Weaning from mechanical ventilation process at hospitals in Federal District. Rev Bras Ter Intensiva. 2007;19(1):38-43. http://dx.doi.org/10.1590/S0103-507X2007000100005
5. Hachenberg T, Tenling A, Rothen HU, Nyström SO, Tyden H, Hedenstierna G. Thoracic intravascular and extravascular fluid volumes in cardiac surgical patients. Anesthesiology. 1993;79(5):976-84. PMID: 8239016.
6. Babik B, Asztalos T, Petak F, Deak Z, Hantos Z. Changes in respiratory mechanics during cardiac surgery. Anesth Analg. 2003;96(5):1280-7. PMID: 12707120.
7. Arcênio L, Souza M, Bortolin B, Fernandes A, Rodrigues A, Evora P. Pre- and postoperative care in cardiothoracic surgery: a physiotherapeutic approach. Rev Bras Cir Cardiovasc. 2008;23(3):400-10. doi: http://dx.doi.org/10.1590/S0102-76382008000300019.
8. Badenes R, Lozano A, Belda FJ. Postoperative pulmonary dysfunction and mechanical ventilation in cardiac surgery. Crit Care Res Pract. 2015;2015:420513. doi: 10.1155/2015/420513.
9. Auler JO Jr, Carmona MJ, Barbas CV, Saldiva PH, Malbouisson LM. The effects of positive end-expiratory pressure on respiratory system mechanics and hemodynamics in postoperative cardiac surgery patients. Braz J Med Biol Res. 2000;33(1):31-42. http://dx.doi.org/10.1590/S0100-879X2000000100005.
10. Canver CC, Chanda J. Intraoperative and postoperative risk factors for respiratory failure after coronary bypass. Ann Thorac Surg. 2003;75(3):853-7. PMID: 12645706.

11. Figueiredo LC, Araújo S, Abdala RC, Abdala A, Guedes CA. CPAP at 10 cm H2 O during cardiopulmonary bypass does not improve postoperative gas exchange. Rev Bras Cir Cardiovasc. 2008;23(2):209-15. http://dx.doi.org/10.1590/S0102-76382008000200010

12. Nozawa E, Kobayashi E, Matsumoto ME, Feltrim MI, Carmona MJ, Auler Júnior JO. Assessment of factors that influence weaning from long-term mechanical ventilation after cardiac surgery. Arq Bras Cardiol. 2003;80(3):301-5. doi: http://dx.doi.org/10.1590/S0066-782X2003000300006.

13. Rodrigues CD, Moreira MM, Lima NM, Figueiredo LC, Falcão AL, Petrucci Junior O, et al. Risk factors for transient dysfunction of gas exchange after cardiac surgery. Braz J Cardiovasc Surg. 2015;30(1):24-32. doi: http://dx.doi.org/10.5935/1678-9741.20140103.

14. Santos NP, Mitsunaga RM, Borges DL, Costa MA, Baldez TE, Lima IM, et al. Factors associated to hypoxemia in patients undergoing coronary artery bypass grafting. Rev Bras Cir Cardiovasc. 2013;28(3):364-70. doi: http://dx.doi.org/10.5935/1678-9741.20130056.

15. Oliveira DC, Oliveira Filho JB, Silva RF, Moura SS, Silva DJ, Egito ES, et al. Sepsis in the postoperative period of cardiac surgery: problem description. Arq Bras Cardiol. 2010;94(3):332-6. doi: http://dx.doi.org/10.1590/S0066-782X2010000300012.

16. Lima RO, Borges DL, Costa MA, Baldez TE, Silva MG, Sousa FA, et al. Relationship between pre-extubation positive end-expiratory pressure and oxygenation after coronary artery bypass grafting. Rev Bras Cir Cardiovasc. 2015;30(4):443-8. doi: 10.5935/1678-9741.20150044.

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ORIGINAL ARTICLE

Spatial Analysis and Mortality Trends Associated with Hypertensive Diseases in the States and Regions of Brazil from 2010 to 2014

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Abstract

Background: Systemic Arterial Hypertension (SAH) represents the most relevant worsening factor and one of the major risk factors for cardiovascular diseases.

Objectives: To analyze trends in the mortality rate associated with hypertensive diseases in Brazil from 2010 to 2014, for states as well as regions.

Methods: An epidemiological study was performed from aggregate data obtained in populational strata. Cartographic data of the Brazilian territory in "shapefile" were provided by IBGE. Records of mortality associated with arterial hypertension were obtained in DATASUS, through notifications filtered by category I.10 of the International Classification of Diseases (ICD-10). The criterion of statistical significance was a two-tailed p-value < 0.05.

Results: The increase in age was progressively associated with an increase in the mean number of deaths related to hypertensive diseases between the years 2010 and 2014. In the age groups between 50-59 years, 60-69 years, 70-79 years and 80 or more years, the mean and standard deviation for the mortality rate were, respectively: 15.11% (35.35); 24.14% (55.34); 35.07% (81.03) and 57.87% (139.08). The overall mortality rate per 10,000 inhabitants varied between the regions: north (1.25); northeast (2.69); center-west (2.06); southeast (2.48) and south (2.04).

Conclusions: The mortality rate associated with hypertensive diseases was higher in the southeastern and northeastern states of Brazil, and remained stable between 2010 and 2014. Increased age and brown color were predictors of higher mortality. (International Journal of Cardiovascular Sciences. 2018;31(3)250-257)

Keywords: Cardiovascular Diseases / mortality; Hypertension / epidemiology; Hypertension / etiology; Ethnicity and Health; Stroke; Epidemiologic Studies.

Introduction

Cerebrovascular diseases have been classified among those with the greatest impact in terms of morbimortality.[1] Among the major cardiovascular risk factors, systemic arterial hypertension (SAH) represents the most relevant worsening factor, requiring health actions in order to minimize the factors of impact that are determinant for the populations' health.[2]

The global prevalence of arterial hypertension was 22%, in 2014, in adults aged 18 years and over.[3] SAH is characterized by increased blood pressure levels (≥ 140 and / or 90 mmHg), in which the clinical condition can be caused by several reasons and may be worsened by other risk factors, such as dyslipidemia, abdominal obesity, glucose intolerance, diabetes mellitus (DM), in addition to other modifiable factors, socioeconomic determinants and inadequate access to health care.[3,4]

Several studies point to the influence of ethnic aspects in the emergence of hypertensive diseases.[5] Often it is difficult to dissociate the role represented by an ethnic group of the socioeconomic factors simultaneously active.[6] In Brazil, cerebrovascular mortality rates were higher in black people, followed by brown and white people.[7]

About 32.6% of adults and more than 60% of elderly people suffer from high blood pressure in Brazil, which

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contributes direct or indirectly to 50% of deaths due to cardiovascular diseases (CVD).[4] In low- and medium-income countries, where treatment and control are lower than in developed countries, it is estimated that the prevalence of HBP-related diseases is of about 80%.[8] The impact of this illness reflects in high costs for the Brazilian Unified National Health System (SUS), with an annual treatment cost of approximately US$ 398.9 million, that is, about 1.43% of overall healthcare expenditures.[9]

The objective of this research is to estimate the impact of arterial hypertension in the Brazilian territory in a period of five years. For such purpose, we analyzed trends in mortality rates associated with hypertensive diseases in Brazil, between 2010 and 2014, stratified according to skin color and age group, both for states and regions.

Methods

An epidemiological study was performed from aggregate data obtained in population strata and combined with a spatial analysis.

Data regarding the organization of the Brazilian territory, including the coordinates and the estimated population for the years studied, were taken from the Brazilian Institute of Geography and Statistics (IBGE) website in shapefile format.[10,11]

Epidemiological information regarding mortality due to arterial hypertension was obtained from the Ministry of Health database, DATASUS.[12] These data refer to notifications from the Mortality Data System (SIM).[13] Deaths were filtered by category I.10 of the International Classification of Diseases (ICD-10). Then, the aggregate data were obtained per year, state, sex, age and skin color.

The selection of the analysis period, between 2010 and 2014, occurred due to the following reasons. First, because we consider that more recent analysis provides greater reliability in data collection, due to progressive improvements in the process of computerization with technological advances. Second, because it potentially portrays the transition scenario resulting from the introduction of losartan, an effective antihypertensive drug, which has been distributed free of charge by the "Popular Pharmacy Program" since 2010, and became in 2014 the most demanded medication in units of the Unified Health System (SUS), including in the countryside of Brazil.[14,15]

However, one must consider that the program's effect may occur unevenly across the regions, which would potentially influence the analysis. Finally, the end of the period under consideration, the year of 2014, arose from the fact that it is the most recent date available in DATASUS to obtain vital statistics all over the Brazilian territory.

The selected variables were year, sex, age, skin color, state, region and number of deaths. Since it is a chronic illness, the selected age groups used to calculate the rate of mortality associated with arterial hypertension were as follows: 50-59 years; 60-69 years; 70-79 years; 80 or more years. This calculation was computed for the twenty-six Brazilian states and the Federal District. The variable "skin color" basically portrays the skin color and ethnic traits, based on the death certificate data, and may be classified as "white", "yellow", "brown", "black", "indigenous" or "ignored".

Statistical analysis

The categorical variables were presented as absolute number and percentage. The numerical variables were presented as average and standard error. Regression models (Poisson and negative binomial) for analyzing countable data have been used in longitudinal studies to estimate future mortality rates. Due to overdispersion, negative binomial regression was preferred. The estimate of the "effect size" was adjusted to sex, age groups, skin color, country region and year, and presented in the form of incidence rate ratio (IRR) and confidence intervals at 95%.

In order to minimize distortions resulting from spatial and temporal differences between the populations, random-effect models included annual population estimates for each state as an "exposition" factor, that is, the coefficient was restricted, producing an IRR equal to 1, with standard error (virtually) zero, adjusting the calculation for the other coefficients. In order to select the model that provides the best predictive adequacy, the Akaike information criterion (AIC) was used. For the spatial analysis, the "spmap" command was used to draw choropleth maps containing the Brazilian states and the Federal District, and representing the distribution of mortality rates associated with arterial hypertension in quintiles. Statistical significance was considered as a two-tailed p value < 0.05. The statistical calculations and the spatial analysis were conducted in Stata, version 14.2 (College Station, Texas, USA).

Ethnical aspects

Since these were public data, and there were no elements of identification of the individuals studied, there was no need to use an informed consent term.

Results

The progressive increase in age was associated with an increase in the mean number of deaths related to hypertensive diseases between the years 2010 and 2014. In the age groups between 50-59 years, 60-69 years, 70-79 years and 80 or more years, the mean and standard deviation for the mortality rate were, respectively: 15.11% (35.35); 24.14% (55.34); 35.07% (81.03) and 57.87% (139.08).

In the graphic representation of the binomial regression model extended to longitudinal data (Figure 1), adjusted to age, higher incidence rate ratios can be observed in the southeast and northeast regions, compared to the south, north and center-west regions.

According to IBGE's population estimates for each year and state,[11] the global mortality rate related to hypertensive diseases was calculated per 10,000 inhabitants, between 2010 and 2014, which varied between regions: north (1.25); northeast (2.69); center-west (2.06); southeast (2.48) and south (2.04). Table 1 shows the numbers per year and region.

It is possible to observe clearly, on the map of Brazil, the regions with the highest mortality rates related to hypertensive diseases in the year of 2014, as well as the regions with the lowest rates (Figure 2).

The analysis per state showed that Rio de Janeiro had the highest mean, with 3.66% of deaths associated with hypertensive diseases in the year of 2010, progressively decreasing until the year 2014, with a mean of 3.02% in that same year. On the other hand, in the years 2011, 2012, 2013 and 2014, the state of Piauí had the highest death average compared to the other states, with 3.80%, 3.58%, 3.87% and 3.61%, respectively (Table 2). The highest death rates occurred in the southeastern and northeastern regions of Brazil.

In the period of 2010 to 2014, The Federal District presented mortality rates similar to the state of Goiás, except for the year 2012, which showed one of the lowest death rates in the country.

A predictive model for fatality rates was estimated (Table 3). There were no sex differences in mortality, when adjusted to the other predictors. In relation to the

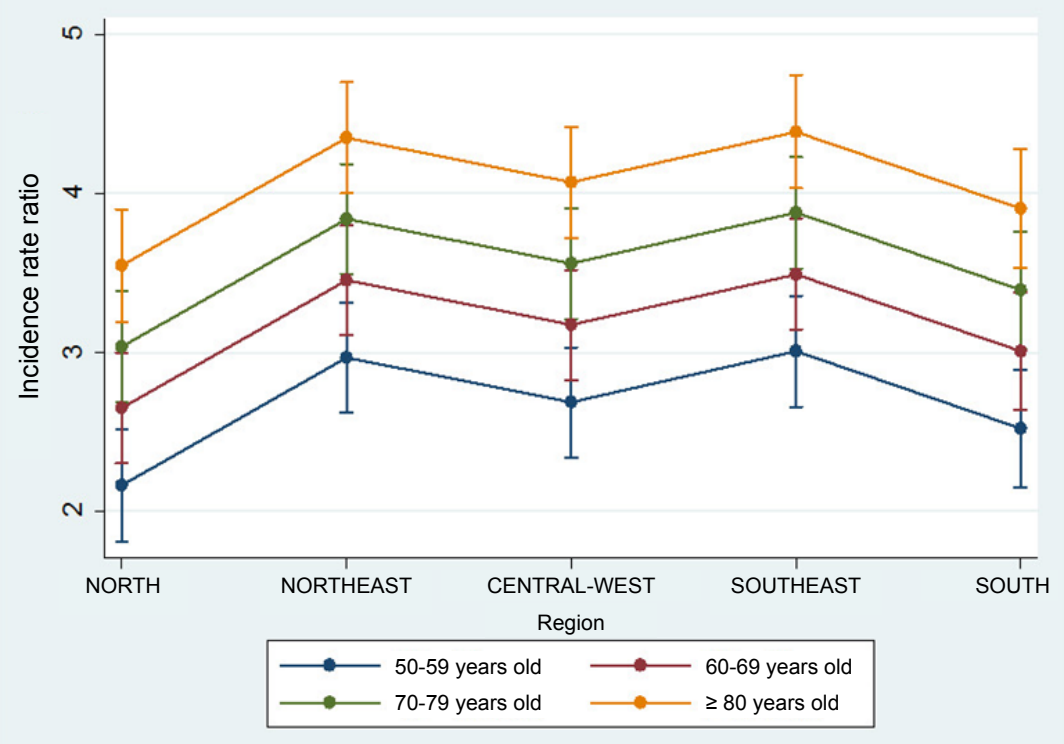

Figure 1 - Graphical representation of the binomial regression model extended for longitudinal data, with incidence rate ratio adjusted to age group and in accordance with Brazilian regions, in the period from 2010 to 2014.

Table 1 - Annual mortality rate associated with hypertensive diseases in Brazil, adjusted to 10,000 inhabitantes (average and standard error), between 2010 and 2014

Year	North		Northeast		Central-West		Southeast		South	
	Deaths	SE	Deaths	SE	Deaths	SE	Deaths	SE	Deaths	SE
2010	1.12	0.02	2.67	0.02	2.02	0.04	2.52	0.05	1.96	0.02
2011	1.38	0.02	2.77	0.02	2.11	0.05	2.57	0.05	2.12	0.02
2012	1.31	0.02	2.02	0.02	2.09	0.04	2.52	0.04	2.02	0.02
2013	1.17	0.03	2.77	0.03	2.09	0.04	2.41	0.04	2.06	0.02
2014	1.26	0.01	2.56	0.02	2.03	0.04	2.39	0.03	2.06	0.02

SE: standard error.

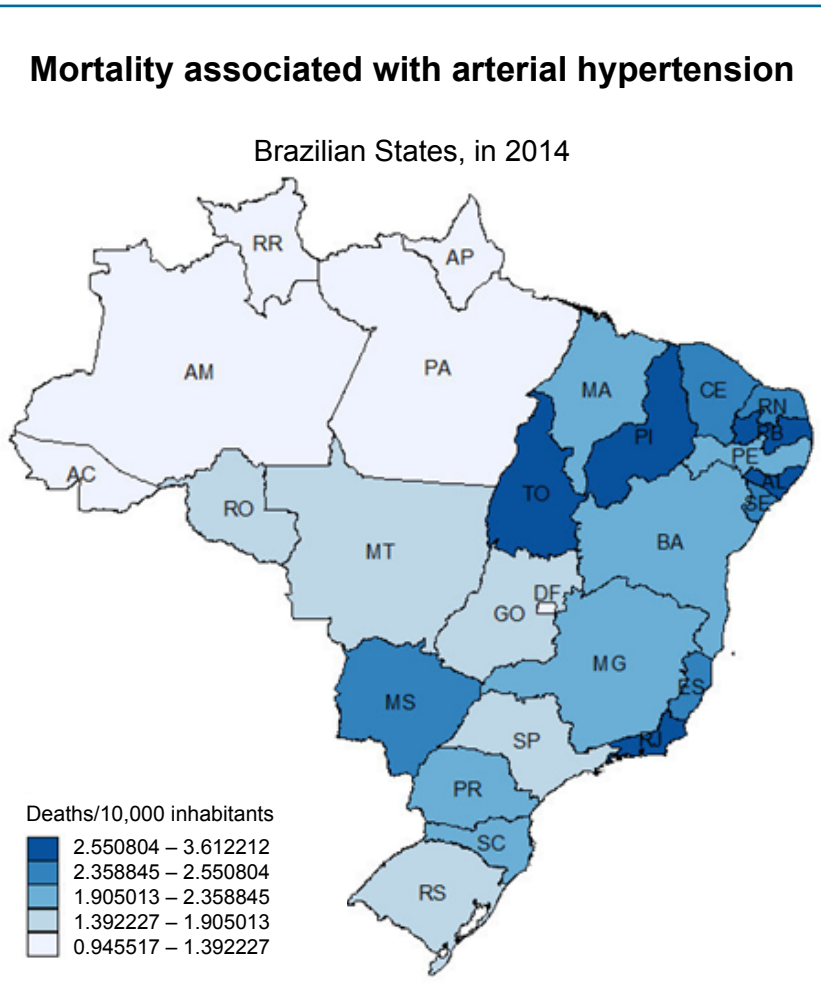

Figure 2 - Choropleth map of Brazil, referring to deaths per 10,000 inhabitants associated with hypertensive disease, in the year 2014.

Table 2 - Average of deaths related to hypertensive diseases per 10,000 inhabitants in each Brazilian state, between 2010 and 2014

State	2010	2011	2012	2013	2014
Acre	1.20	1.63	1.62	1.39	1.39
Alagoas	2.64	2.81	2.87	2.98	2.64
Amapá	0.61	1.02	0.80	0.71	0.95
Amazonas	1.00	0.98	0.99	1.06	1.02
Bahia	2.27	2.24	2.33	2.35	2.33
Ceará	2.60	2.85	2.48	2.66	2.49
Distrito Federal	1.13	1.30	0.99	1.10	1.08
Espírito Santo	2.32	2.62	2.64	2.42	2.55
Goiás	1.43	1.52	1.77	1.69	1.81
Maranhão	2.00	2.13	1.97	2.11	2.07
Mato Grosso	2.22	2.13	1.97	2.11	2.07
Mato Grosso do Sul	2.39	2.68	2.74	2.83	2.52
Minas Gerais	2.26	2.36	2.40	2.29	2.29
Pará	1.05	1.21	1.27	1.27	1.30
Paraíba	3.10	3.26	3.26	3.23	2.88
Paraná	2.26	2.47	2.26	2.35	2.36
Pernambuco	2.41	2.44	2.29	2.18	2.13
Piauí	3.51	3.80	3.58	3.87	3.61
Rio de Janeiro	3.66	3.52	3.37	3.23	3.02
Rio Grande do Norte	2.22	2.54	2.34	2.56	2.44
Rio Grande do Sul	1.80	1.96	1.99	1.93	1.91
Roraima	1.07	1.65	1.62	1.54	1.29
Santa Catarina	1.81	1.92	1.81	1.89	1.92
São Paulo	1.82	1.79	1.69	1.70	1.69
Sergipe	3.31	2.88	3.12	3.02	2.49
Tocantins	2.91	3.01	2.74	2.72	2.84
Rondônia	1.79	1.78	1.71	1.67	1.63

Table 3 - Longitudinal analysis using a negative binomial model, having as dependent variable the number of deaths associated with hypertensive diseases, and as predictors "age group", "sex", "color", "region" and "year", adjusted to the annual population estimate for each location, between 2010 and 2014

Deaths	IRR	95% CI		p-value
Sex				
Female (reference)	-	-	-	-
Male	1.03	0.99	1.08	0.158
Age group				
50 – 59 years old (reference)	-	-	-	-
60 – 69 years old	1.63	1.53	1.73	< 0.0001
70 – 79 years old	2.40	2.25	2.55	< 0.0001
≥ 80 years old	3.99	3.76	4.26	< 0.0001
Color				
White (reference)	-	-	-	-
Black	0.27	0.25	0.29	< 0.0001
Brown	1.28	1.20	1.36	< 0.0001
Yellow	0.01	0.00	0.01	< 0.0001
Indígenous	0.01	0.01	0.01	< 0.0001
Ignored	0.13	0.12	0.14	< 0.0001
Region				
Southeast (reference)	-	-	-	-
North	0.43	0.40	0.47	< 0.0001
Northeast	0.96	0.90	1.03	0.237
Central-West	0.73	0.67	0.78	< 0.0001
South	0.61	0.57	0.67	< 0.0001
Year				
2010 (reference)	-	-	-	-
2011	106	0.99	1.14	0.112
2012	1.00	0.94	1.08	0.898
2013	0.96	0.90	1.03	0.267
2014	0.96	0.90	1.03	0.261

IRR: incidence rate ratio; CI: confidence interval.

age groups, the greater the age, the greater the risk of death associated with systemic arterial hypertension. Skin color, taking "whites" as reference group, indicated greater association between hypertensive diseases and mortality in "browns", and lower association in "blacks", "yellows", "indigenous" and in the cases in which this variable was "ignored". It should be stressed that the total number of "indigenous" and "yellows" added to the "ignored" group corresponded to less than 6%. "Blacks" represented less than 12% of the "brown", "white" and "black" groups, with the vast majority among the "whites".

Since this is not an ethnical study, but still taking into account that skin color, as stated in the death certificate, has been considered a relevant data in the development of public health policies, the inclusion of this predictor has been less useful in producing racial inferences, than in adjusting this data to the other predictors and establishing iterative algorithms. In addition, it was observed that the models that include the variable "skin color", compared to the models that exclude this predictor, in addition to presenting predictors with similar IRRs, also achieved convergence in less time and provided lower AIC values, which indicates higher adequacy from a statistical point of view.

Taking the southeast region as a reference, due to its highest development level and public policies applied for longer, there was no statistical difference compared to the northeast region, and the other regions presented a lower incidence rate ratio than the southeast Brazil.

The predictive model showed that there was no significantly statistical difference in the incidence rate ratio of mortality between the years, when adjusted to the other predictors. Similarly, sex differences had no influence. High-age group, brown skin and southeast and northeast regions were predictors of the greatest mortality during the period under study.

Discussion

An epidemiological study was carried out based on aggregate data, obtained in population strata. Therefore, in order to avoid the "ecological fallacy", the applicability of the results cannot be extended to the individual level, to the doctor's practice level, but only to state, regional and national levels.

Since the data were collected from public organizations, which, in turn, came from constant notifications in death certificates, the outline of this article does not include methodological elements able to test their veracity. This also applies to the matter of item selection in the death certificates, which may potentially present differences related to preferences in each state or region to highlight, more or less often, hypertension as a relevant cause of death.

The number of deaths associated with hypertensive diseases is related with the increase in age, as can be observed in this study. The impact of this illness tends to aggravate, since the elderly population increases every year, corresponding nowadays to 15% of the world's population. World projections indicate that this population will continue to increase, and it is estimated that this number may nearly double to 30% by the year 2050. This demands special attention to the development of measures that can help prevent and control hypertensive diseases.[16]

In another study, this time about the prevalence of arterial hypertension, the south and southeast regions of Brazil presented higher rates, compared to the other regions: 25% (95% CI: 23.8 - 26.1) and 25% (95% CI: 23.5 - 26.5), respectively.[17] However, the present study focused on mortality rates associated with hypertensive diseases, and the regions with the highest rates were the northeast and the southeast. Although this issue is beyond the scope of the present research, it is speculated that the discrepancy between higher prevalence and lower mortality in the south could result from more intensive application of therapeutic strategies, both in health care and drug provision.

An opposite phenomenon could be observed in a northeastern state. This study showed that the state of Piauí presented, for four consecutive years, the highest mortality rate associated with hypertensive diseases. Nevertheless, a research conducted with elderly people in 2013, in the same state, indicated that the prevalence of SAH in this population is 40.2%, below than expected for that age group, whose prevalence is 68% among the population over 60 years of age.[4,18] Once again, speculatively speaking, but still beyond the scope of this research, this finding could be a result of obstacles to health care and access to medications.

These considerations are mainly intended to formulate hypotheses that remain to be analyzed in future research.

Death rates associated with hypertensive diseases were higher among the brown population in Brazil,

compared to blacks, something that might have been influenced by eventual subjectivity in skin color identification and due to the predominance of miscegenation in Brazil.[19] There are still few studies conducted in South America on the higher prevalence of arterial hypertension in blacks, with most scientific information concerning ethnicity coming from studies carried out in the United States.[20]

Several limitations arise from this type of study, which deals with aggregate data. For example, we cannot rule out the possibility of having occurred increased notifications, on the one hand, and hypertension control improvement, on the other hand, something that would generate an apparent constancy of the illness in the time series analysis of the data. However, from a methodological point of view, the research design sought to adjust the analysis for eventual influences of both temporal and geographic factors in the same region or state.

It is also important to highlight that we used the data considered more relevant for the elaboration of public policies nowadays, something that reflects in the planning, execution and evaluation of health actions towards the combat of the diseases of greatest impact in Brazil.[21] Therefore, the implementation of Pharmaceutical Assistance by the Ministry of Health´s department has arisen as a major impact resource to reduce mortality due to non-transmitted chronic diseases, including arterial hypertension.[9]

Nevertheless, based on the information available on mortality associated with hypertensive diseases in public registries, and by submitting these data to a complex evaluation, corroborated by several analytical models, the absence of major reduction in mortality rates in the period of five years suggests that it is necessary, among other measures, to broaden the pharmacological scope of free distribution drugs and enhance healthcare programs.

Conclusion

Death rates associated with hypertensive diseases were higher in the southeastern and northeastern Brazil, compared to the other regions. This rate did not show significant alterations between the years 2010 and 2014, when assessed in relation to the same state and region of Brazil. Other predictors of higher rates of mortality were brown skin color and increase in age. Public health policies, concerning medical care for hypertensive patients and prevention of complications, must be preferably applied in the states with the highest rates.

Author contributions

Conception and design of the research: Santos MAA. Acquisition of data: Santos MAA. Analysis and interpretation of the data: Santos MAA. Statistical analysis: Santos MAA. Writing of the manuscript: Santos MAA, Prado BS, Santos DMS. Critical revision of the manuscript for intellectual content: Santos MAA, Prado BS, Santos DMS.

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

References

1. Guimarães RM, Andrade SS, Machado EL, Bahia CA, Oliveira MM, Jacques FV. Regional differences in cardiovascular mortality transition in Brazil, 1980 to 2012. Rev Panam Salud Publica. 2015;37(2):83-9.
2. Andrade SS, Rizzato S, Scalioni A, Landmann C, Malta DC. Self-reported hypertension prevalence in the Brazilian population: analysis of the National Health Survey, 2013. Epidemiol Serv Saúde. 2015;24(2):297-304.
3. World Health Organization (WHO). Global status report on noncommunicable diseases. Geneva; 2014.
4. Malachias MV, Souza WK, Plavnik FL, Rodrigues CI, Brandão AA, Neves MF, et al; Sociedade Brasileira de Cardiologia. 7a Diretriz Brasileira de hipertensão arterial. Arq Bras Cardiol. 2016;107(3 supl 3):1-83.
5. Thorpe RJ Jr, Bowie JV, Smolen JR, Bell CN, Jenkins ML Jr, Jackson J, et al. Racial disparities in hypertension awareness and management: are there differences among African Americans and Whites living in similar social and healthcare resource environments? Ethn Dis. 2014;24(3):269-75.
6. Judd SE, Kleindorfer DO, McClure LA, Rhodes JD, Howard G, Cushman M, et al. Self-report of stroke, transient ischemic attack, or stroke

symptoms and risk of future stroke in the reasons for geographic and racial differences in stroke (REGARDS) study. Stroke. 2013;44(1):55-60.

7. Lotufo PA, Bensenor IJ. [Race and stroe mortality in Brazil]. Rev Saude Publica. 2013;47(6):1201-4.

8. Chor D, Pinho Ribeiro AL, Sá Carvalho M, Duncan BB, Andrade Lotufo P, Araújo Nobre A, et al. Prevalence, awareness, treatment and influence of socioeconomic variables on control of high blood pressure: results of the ELSA Brasil Study. PLoS One. 2015;10(6):e0127382.

9. Oliveira PA, Menezes FG. Atenção farmacêutica a pacientes hipertensos. Revista Eletrônica de Farmácia. 2013;10(1):51-68.

10. Instituto Brasileiro de Geografia e Estatística. (IBGE). [Internet]. Organização do território, malhas territoriais e municipais em 2015 [Acesso em 2017 jan 20]. Disponível em: ftp://geoftp.ibge.gov.br/organizacao_do_territorio/malhas_territoriais/malhas_municipais/mun icipio_2015/Brasil/BR/.

11. Instituto Brasileiro de Geografia e Estatística. (IBGE). [Internet]. Estimativas da população residente no Brasil e unidades da federação com data de referência em 1º de julho de 2011. [Acesso em 2017 jan 20]. Disponível em: http://www.ibge.gov.br/home/estatistica/populacao/estimativa2011/tab_Brasil_UF.pdf

12. Brasil. Ministério da Saúde [Internet]. Departamento de Informática do SUS. Datasus. Informações de Saúde. Estatísticas vitais. [Acesso em 2016 dez 10]. Disponível em: http://www2.datasus.gov.br/DATASUS/index.php?area=0205.

13. Brasil. Ministério da Saúde. Sistema de Informações sobre Mortalidade – SIM. Consolidação da base de dados de 2011. Brasília; 2013.

14. Silva RM, Caetano R. "Farmácia Popular do Brasil" Program: characterization and evolution between 2004 and 2012. Cienc Saude Colet. 2015;20(10):2943-56.

15. Amorim ME, Ferreira MR, Oliveira SA, Fernandes CK. Programa Farmácia Popular no Brasil em uma drogaria de São Luís de Montes Belos (GO). Revista Faculdade Montes Belos (FMB). 2015;8(1):1-13.

16. Coelho Júnior HJ, Sampaio RA, Gonçalvez IO, Aguiar SS, Palmeira R. Cutoffs and cardiovascular risk factors associated with neck circumference among community-dwelling elderly adults: a cross-sectional study. Sao Paulo Med J. 2016;134(6):519-27.

17. Malta DC, Santos NB, Perillo RD, Szwarcwald CL. Prevalence of high blood pressure measured in the Brazilian population, National Health Survey, 2013. Sao Paulo Med J. 2016;134(2):163-70.

18. Oliveira Neto JG, Carvalho DA, Moura GG, Monteiro MM, Lopes KD, Martins MC. Pressão arterial e perfil socioeconômico de idosos atendidos na estratégia saúde da família de Floriano-Piauí. Rev Saúde Públ Santa Cat. 2014,7(2):17-28.

19. Menezes TN, Oliveira EC, Fischer MA, Esteves GH. Prevalence and control of hypertension in the elderly: a population study. Rev Port Saúde Pública. 2016;34(2):117-24.

20. Task Force of the Latin American Society of Hypertension. Guidelines on the management of arterial hypertension and related comorbidities in Latin America. J Hypertens. 2017;35(8):1529-45.

21. Marinho F, Passos VM, França EB. New century, new challenges: changes in the burden of disease profile in Brazil, 1990-2010. Epidemiol Serv Saude. 2016,25(4):713-24.

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ORIGINAL ARTICLE

Epidemiological Characteristics and Mortality Predictors in Patients Over 70 Years Submitted to Coronary Artery Bypass Grafting

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Abstract

Background: Coronary artery disease is the leading cause of death worldwide, with age being an independent risk factor for mortality in patients submitted to surgical revascularization.

Objective: To evaluate the mortality risk predictors in patients older than 70 years submitted to myocardial revascularization.

Methods: This is a retrospective cohort study of a cardiac surgery database. Logistic regression was used to assess independent death predictors.

Results: A total of 372 patients submitted to surgical revascularization from 2004 to 2012 were assessed. The main cardiovascular risk factor was hypertension, followed by diabetes mellitus. Mortality at 30 days was 19.35%. The presence of peripheral vascular disease (OR: 2,47), emergency surgery (OR: 4,86) and combined valve procedure (OR: 3,86) were independent predictors of death.

Conclusion: The surgical procedure in elderly patients showed a higher mortality than in the general population. Peripheral vascular disease, emergency surgery and combined valve procedures increased the risk of death in these patients. (International Journal of Cardiovascular Sciences. 2018;31(3)258-263)

Keywords: Coronary Artery Disease / surgery; Myocardial Revascularization; Hypertension; Diabetes Mellitus; Aged.

Introduction

Cardiovascular disease is currently one of the main causes of hospitalization in Brazil in the general population, being the main cause of hospitalization in elderly patients.[1]

With the advent of new technologies for the treatment of cardiovascular disease, the survival of the patient with heart disease increases and, with aging, other comorbidities, such as hypertension, diabetes, kidney failure and cognitive dysfunction appear.[2,3]

With the aging process, the cardiovascular system itself shows physiological changes, such as progressive increase in systolic blood pressure, reduction of aerobic capacity and of reflex responses of the autonomic nervous system.[4]

The aging process alone increases the patient's cardiovascular risk, either by the Framingham and SCORE risk score evaluation, which are used in asymptomatic patients, or by assessing the prevalence of coronary heart disease using the Diamond score.[5,6]

In patients with coronary disease, age is an important predisposing risk factor for future events, both in acute coronary disease scores, such as GRACE, as well as in preoperative risk assessment, such as the EuroSCORE.[7,8]

There are still doubts related to the predictive factors of surgical death, defined as death occurring within 30 days

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of the surgical procedure, in the Brazilian population of patients aged 70 years or older.

The aim of our study was to evaluate the epidemiological characteristics of patients undergoing coronary artery bypass grafting at a specialized hospital of the Brazilian Unified Health System (*Sistema Único de Saúde* - SUS), and to analyze the risk predictors of surgical death and complications inherent to the procedure.

Methods

Retrospective cohort of the cardiac surgery database of Instituto Nacional de Cardiologia, in Rio de Janeiro (RJ), of patients operated from December 2004 to March 2012.

This database included demographic, clinical, laboratory, echocardiographic and angiographic variables of the preoperative, intraoperative and immediate postoperative periods at the Intensive Care Unit (ICU) and the late postoperative period at the infirmary, totaling 327 variables, in addition to vital status at 30 days. In the present study, we assessed the demographic, clinical, laboratory, echocardiographic and angiographic data of the patient's preoperative period and the need for combined valve surgery, considering the type of evolution (discharge vs. death within 30 days of the procedure). Angina pectoris was classified according to the Canadian Class Society (CCS) criteria.[9]

The institutional Research Ethics Committee authorized the performance of this study, approval number 0117/110906.

Statistical analysis

Statistical analysis was performed by recording the frequencies, the means and their respective standard deviations, or the median and quartiles, when appropriate. Student's *t* test was used to compare the outcome groups, when the variables showed a normal distribution, or Mann-Whitney U test, when normality was not observed. For dichotomous variables, chi-squared or Fisher's exact test were applied, as appropriate. To study the association between the independent variables and the outcome, two-phase multivariate logistic regression was used and the variables that had $p < 0.20$ in the first stage were included in the final stage. The StataCorp 14 program (by StataCorp LP) was used. It was considered an alpha value of 0.05. All tests were two-tailed.

Results

The epidemiological characteristics are shown in table 1. There were 372 patients, most of them males, with a median age of 74.26 years and a mean body mass index of 26.2 kg/m². Regarding the risk factors, the patients had systemic arterial hypertension (93.2%), diabetes (29.0%) and were current smokers (4.3%). Even with a mean creatinine level within the normal range, patients had decreased creatinine clearance. The mortality rate of the study population was 19.35% (72 patients) at 30 days.

Table 1 - Demographic and clinical characteristics of the study population

Characteristic	
Age, years (median and interquartile range)	74.26 (71.77-77.08)
Men	67.2
Body mass index	26.2 ± 4.1
Systemic arterial hypertension	93.2
Diabetes Mellitus	29.0
Smoking	4.3
Previous acute myocardial infarction	19.4
Previous stroke	5.3
Creatinine clearance	51.77 (42.38-61.86)
Creatinine	1.1 (1.0-1.38)
Previous coronary artery bypass grafting	2.1
Previous percutaneous coronary angioplasty	9.1
Angina	80.9
Unstable angina	27.6
Stable angina	72.4
Left main coronary artery lesion	41.9
Proximal anterior descending artery lesion	62.0
Trivascular	75.0
Ejection fraction	62.0 (49.0-69.0)
NYHA functional class III or IV	9.2
Death at 30 days	19.3

Results expressed in median (interquartile range), percentage or mean ± median. NYHA: New York Heart Association.

In the univariate analysis (Tables 2 and 3), the following were markers of surgical death: emergency surgery, combined valvular surgery, previous surgery, peripheral vascular disease, NYHA functional class III/IV, increased left atrial diameter, lower preoperative statin use, increased need for preoperative nitrate use, moderate/severe aortic regurgitation, moderate/severe aortic stenosis, and moderate/severe tricuspid regurgitation.

The multivariate analysis was performed in two stages and, in the final stage, the presence of peripheral vascular disease, the need for emergency surgery and the combined procedure with valve replacement were found to be independent predictors of death (Tables 4 and 5).

Discussion

The objective of coronary artery bypass grafting is to correct myocardial ischemia resulting from coronary artery obstruction, aiming at relieving symptoms, improving quality of life and allowing the patient to return to work, as well as increasing life expectancy.[9]

It is a revascularization method with higher percentage of complete revascularization and reduction of anginal episodes. In contrast, there is a longer hospital length of stay and a higher incidence of complications during surgical hospitalization, which makes this surgery a second alternative for patients requiring revascularization.[9]

The epidemiological characteristics of patients submitted to coronary artery bypass grafting show that most patients are males, with a mean age of 60 years, arterial hypertension as the most prevalent risk factor and preserved left ventricular function.[10,11]

However, elderly patients have a greater number of comorbidities, when compared to younger patients. In addition to these comorbidities, the elderly's

Table 2 - Univariate analysis of surgical mortality by the presence of categorical variables potentially predictive of surgical death

Variable	Death (%)	Survivor (%)	p-value
Combined surgery	40.00	15.82	< 0.001
NYHA Functional class III or IV	38.24	17.26	0.003
Emergency surgery	40.91	18.00	0.004
Use of statins in the preoperative period	16.84	30.43	0.017
Peripheral vascular disease	30.16	17.12	0.018
Previous surgery	31.37	17.35	0.019
Moderate/severe tricuspid regurgitation	60.00	18.44	0.019
Moderate/severe aortic regurgitation	38.89	18.07	0.029
Moderate/severe mitral regurgitation	34.78	17.93	0.040
Moderate/severe aortic stenosis	32.81	16.03	0.002
Nitrates in the preoperative period	33.33	17.99	0.051
Beta-blocker in the preoperative period	32.81	28.57	0.056
Male gender	17.60	22.95	0.220
Diabetes	15.74	20.91	0.253
Left main coronary artery lesion	18.59	19.52	0.822

NYHA: New York Heart Association.

Table 3 - Univariate analysis of surgical mortality by the presence of continuous variables potentially predictive of surgical death

Variable	Survivor	Death	p-value
Left atrial dimension, cm	3.91 (3.84-3.98)	4.13 (3.94-4.32)	0.0129
Body mass index, kg/m^2	26.11 (25.72-26.50)	26.80 (25.36-28.24)	0.3162
Age, years	74.15 (71.73-7.08)	74.81 (72.16-77.23)	0.3505
Left ventricular ejection fraction, %	58.77 (57.12-60.43)	55.76 (51.62-59.90)	0.7250
Pulmonary artery systolic pressure, mmHg	35.50 (32.11-38.89)	39.83 (33.97-45.68)	0.9114

Table 4 - Multivariate analysis of surgical death predictors in the initial stage

Factor	Odds ratio	Standard error	95%CI	p-value
Emergency surgery	4.4952	2.5857	1.4559-13.879	0.009
Peripheral vascular disease	2.5038	0.9111	1.2271-5.1091	0.012
Left atrial dimension	1.4488	0.3623	0.8874-2.3655	0.138
Combined surgery	2.1760	1.2039	0.7357-6.4358	0.160
Previous surgery	1.6740	0.6984	0.7390-3.7925	0.217
Moderate/severe tricuspid regurgitation	3.1501	3.1348	0.4479-22.152	0.249
Beta-blocker in the preoperative period	0.6536	0.2706	0.2903-1.4715	0.304
Moderate/severe aortic stenosis	1.4779	0.7335	0.5587-3.9096	0.431
Statins in the preoperative period	0.8023	0.3059	0.3800-1.6941	0.564
NYHA III-IV	1.3249	0.6894	0.4777-3.6742	0.589
Nitrates in the preoperative period	1.2760	0.8513	0.3451-4.7179	0.715
Moderate/severe aortic regurgitation	0.9405	0.5882	0.2761-3.2041	0.922

95% CI: 95% confidence interval; NYHA: New York Heart Association.

Table 5 - Multivariate analysis of the factors predicting surgical death in the final stage

Factor	Odds ratio	Standard error	95%CI	p-value
Combined surgery	3.8651	1.2871	2.0123-7.4236	< 0.001
Emergency surgery	4.8608	2.3881	1.8558-12.732	0.001
Peripheral vascular disease	2.4773	0.8218	1.2931-4.7463	0.006

95% CI: 95% confidence interval.

circulatory system has alterations caused by the aging process, such as increased arterial stiffness, diastolic function worsening and greater extent of coronary artery disease.[12-14]

Compared to younger patients, elderly ones have higher mortality in relation to revascularization – be it surgical or percutaneous. However, in comparison with percutaneous revascularization, the long-term benefits of undergoing surgery are better for the elderly, especially in relation to greater symptomatic relief and the less need for new revascularizations.[15]

Several studies have shown that age leads to an increased risk of death. Santos et al. observed that patients over 65 years of age have a 2.3-fold higher risk of death than younger patients; Rocha et al. compared patients older and younger than 70 years, and found a mortality rate of 8.9% in the older patients and 3.6% in the younger patients – this cohort did not involve patients submitted to the combined surgery, which is an important predictor of mortality.[16,17]

Contrarily, Aikawa did not identify an impact on the mortality in older patients (> 65 years) (5.8% vs. 2.0%), but identified a higher rate of postoperative complications in the elderly, when compared to the younger patients (30% vs. 14%).[14]

We already have reports of surgical series involving octogenarians submitted to isolated myocardial revascularization procedures, showing that these patients have a higher risk of developing in-hospital death; however, when compared with patients who undergo

elective surgery or those with fewer comorbidities, the risk is similar to that of younger patients.[18,19]

The mortality among older patients was much higher than that assessed in the general population, according to a previous study performed by our group. The assessment of all patients showed an index of 10.3%, compared to 22.3% in the current cohort. However, when we compare it with some cohorts of patients over 70 years of age, one observes very similar mortality rates.[10,20]

Regarding the predictors of mortality, it is known that emergency surgery in the elderly has a negative impact on prognosis in the postoperative evolution of patients, with a risk of death up to 55-fold higher in some series.[21]

The presence of peripheral atherosclerotic disease is closely related to age and the highest number of risk factors for coronary disease. Associated with this, there have been reports that graft quality is worse in these patients. The PREVENT IV study demonstrated that patients with peripheral vascular disease have a 3.3-fold increased risk of death, infarction or new revascularization in 5 years, but without an impact in the first 30 days after surgery. This fact is supported by two other studies that demonstrated that the impact of peripheral vascular disease lies in the long term. However, none of these studies have studied only the elderly population, a fact that may explain why the combination of advanced age with peripheral vascular disease shows a worse prognosis than isolated peripheral vascular disease in the postoperative period of coronary artery bypass grafting.[22-24]

When making comparisons with other populations, one needs to keep in mind some peculiarities of the assessed patients. Our patients were from the Brazilian Unified Heath System (SUS), which, for the most part, have a more unfavorable socioeconomic condition than those from the private health care network and from other countries, in addition to having less access to specialized care.[25]

Conclusion

The predictors of surgical death in the septuagenarians of this assessed sample were the need for emergency surgery, combined valvular procedure and the presence of peripheral vascular disease.

Author contributions

Conception and design of the research: Azevedo VMP, Xavier RMA, Chaves RBM. Acquisition of data: Azevedo VMP, Xavier RMA, Chaves RBM. Analysis and interpretation of the data: Kaufman R, Azevedo VMP, Sá RMG, Geller M, Xavier RMA, Chaves RBM, Castier MB. Statistical analysis: Kaufman R, Azevedo VMP, Geller M. Writing of the manuscript: Kaufman R, Azevedo VMP, Sá RMG, Xavier RMA, Chaves RBM, Castier MB. Critical revision of the manuscript for intellectual content: Kaufman R, Azevedo VMP, Castier MB.

Potential Conflict of Interest

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

Sources of Funding

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Instituto Nacional de Cardiologia* under the protocol number 0117/110906. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

References

1. Brasil. Ministério da Saúde. Datasus. [Internet]. Banco de dados do Sistema Único de Saúde. [Acesso em 2015 jun 18]. Disponível em: http://www.datasus.org.br
2. Grundy EMD. The epidemiology of aging. In: Tallis RC, Fillit HW. (editors). Brocklehurst's textbook of geriatric medicine and gerontology. Philadelphia: Elsevier Science Ltd; 2003. p. 3-20.
3. Schramm JM, Oliveira AF, Leite IC, Valente JG, Gadelha AM, Portela MC, et al. Epidemiological transition and the study of burden of disease in Brazil. Ciênc Saúde Coletiva 2004;9(4):897-908. doi: http://dx.doi.org/10.1590/S1413-81232004000400011.
4. Fechine BR, Trompieri NO. Processo de envelhecimento: as principais alterações que acontecem com o idoso com o passar dos anos. Rev

Cient Int. 2012;20(1):106-132. doi: http://dx.doi.org/10.6020/1679-9844/2007.

5. Xavier HT, Izar MC, Faria Neto JR, Assad MH, Rocha VZ, Sposito AC, et al; Sociedade Brasileira de Cardiologia. [V Brazilian Guidelines on Dyslipidemias and Prevention of Atherosclerosis]. Arq Bras Cardiol. 2013;101(4 Suppl 1):1-20. doi: http://dx.doi.org/105935/abc20135010.

6. Cesar LA, Ferreira JF, Armaganijan D, Gowdak LH, Mansur AP, Bodanese LC et al; Sociedade Brasileira de Cardiologia. Guideline for stable coronary artery disease. Arq Bras Cardiol. 2014;103(2 Suppl 2):1-56. doi: http://dx.doi.org/10.5935/abc.2014S004.

7. Roques F, Nashef SA, Michel P, Gauducheau E, deVincentiis C, Baudet E, et al. Risk factors and outcome in European cardiac surgery: analysis of the EuroSCORE multinational database of 19030 patients. Eur J Cardiothorac Surg. 1999;15(6):816-22. PMID: 10431864.

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

9. Hueb W, Soares PR, Gersh BJ, César LA, Luz PL, Puig LB, et al. The medicine, angioplasty, or surgery study (MASS-II): a randomized, controlled clinical trial of three therapeutic strategies for multivessel coronary artery disease: one-year results. J Am Coll Cardiol. 2004;43(10):1743-51. doi: 10.1016/j.jacc.2003.08.065.

10. Kaufman R, Kuschnir MC, Xavier RM, Santos MA, Chaves RB, Müller RE, et al. Perfil epidemiológico na cirurgia de revascularização miocárdica. Rev Bras Cardiol. 2011;24(6):369-76.

11. Cruz LC, Kaufman R, Azevedo VM, Militão RC, Schneider F, Treml FT, et al. Análise das metas terapêuticas na prevenção secundária de DAC após CRM. Rev Bras Cardiol. 2012;25(4):309-12.

12. Scott BH, Seifert FC, Grimson R, Glass PS. Octogenarians undergoing coronary artery bypass graft surgery: resource utilization, postoperative mortality, and morbidity. J Cardiothorac Vasc Anesth. 2005;19(5):583-8. doi: 10.1053/j.jvca.2005.03.030.

13. Graham MM, Ghali WA, Faris PD, Galbraith PD, Norris CM, Knudtson ML; Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) Investigators. Survival after coronary revascularization in the elderly. Circulation. 2002;105(20):2378-84. doi: https://doi.org/10.1161/01.CIR.0000016640.99114.3D.

14. Aikawa P, Cintra AR, Leite CA, Marques RH, da Silva CT, Afonso Mdos S, et al. Impact of coronary artery bypass grafting in elderly patients. Rev Bras Cir Cardiovasc. 2013;28(1):22-8. doi: http://dx.doi.org/10.5935/1678-9741.2013000.

15. Mullany CJ, Mock MB, Brooks MM, Kelsey SF, Keller NM, Sutton-Tyrrell K, et al. Effect of age in the Bypass Angioplasty Revascularization Investigation (BARI) randomized trial. Ann Thorac Surg. 1999;67(2):396-403. doi: https://doi.org/10.1016/S0003-4975(98)01191-6.

16. Santos CA, Oliveira MA, Brandi AC, Botelho PH, Brandi Jde C, Santos MA, et al. Risk factors for mortality of patients undergoing coronary artery bypass graft surgery. Rev Bras Cir Cardiovasc. 2014;29(4):513-20. doi: 10.5935/1678-9741.20140073.

17. Rocha AS, Pittella FJ, Lorenzo AR, Barzan V, Colafranceschi AS, Brito JO, et al. Age influences outcomes in 70-year or older patients undergoing isolated coronary artery bypass graft surgery. Rev Bras Cir Cardiovasc. 2012;27(1):45-51. doi: http://dx.doi.org/10.5935/1678-9741.20120008.

18. Alexander KP, Anstrom KJ, Muhlbaier LH, Grosswald RD, Smith PK, Jones RH, et al. Outcomes of cardiac surgery in patients > or = 80 years: results from the National Cardiovascular Network. J Am Coll Cardiol. 2000;35(3):731-8. doi: https://doi.org/10.1016/S0735-1097(99)00606-3.

19. Wang W, Bagshaw SM, Norris CM, Zibdawi R, Zibdawi M, MacArthur R. Association between older age and outcome after cardiac surgery: a population-based cohort study. J Cardiothorac Surg. 2014 Nov 18;9:177. doi: 10.1186/s13019-014-0177-6.

20. Almeida FF, Barreto SM, Couto B, Starling CE. Predictive factors of in-hospital mortality and of severe perioperative complications in myocardial revascularization surgery. Arq Bras Cardiol. 2003;80(1):41-50. doi: http://dx.doi.org/10.1590/S0066-782X2003000100005.

21. Guimarães IN, Moraes F, Segundo JP, Silva I, Andrade TG, Moraes CR. Risk factors for mortality in octogenarians undergoing myocardial revascularization surgery. Arq Bras Cardiol. 2011;96(2):94-8. doi: http://dx.doi.org/10.1590/S0066-782X2011005000008.

22. Harskamp RE, Alexander JH, Schulte PJ, Jones WS, Williams JB, Mack MJ, et al. Impact of extracardiac vascular disease on vein graft failure and outcomes after coronary artery bypass surgery. Ann Thorac Surg. 2014;97(3):824-30. doi: 10.1016/j.athoracsur.2013.09.099.

23. Chu D, Bakaeen FG, Wang XL, Dao TK, LeMaire SA, Coselli JS, et al. The impact of peripheral vascular disease on long-term survival after coronary artery bypass graft surgery. Ann Thorac Surg. 2008;86(4):1175-80. doi: 10.1016/j.athoracsur.2008.06.024.

24. vanStraten AH, Firanescu C, Soliman H, Tan ME, TerWoorst JF, Martens EJ, et al. Peripheral vascular disease as a predictor of survival after coronary artery bypass grafting: comparison with a matched general population. Ann Thorac Surg. 2010;89(2):414-20. doi: 10.1016/j.athoracsur.2009.11.036.

25. Gomes WJ, Mendonça JT, Braile DM. Cardiovascular surgery outcomes: oportunity to rediscuss medical and cardiological care in the Brazilian Public Health System. Rev Bras Cir Cardiovasc. 2007;22(4):3-4. doi: http://dx.doi.org/10.1590/S0102-76382007000400002.

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ORIGINAL ARTICLE

Use of GATED-SPECT for Ventricular Desynchronization Evaluation in Patients with Heart Failure Submitted to Cardiac Resynchronization Therapy

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Abstract

Background: Approximately 20 to 40% of patients with heart failure do not respond to cardiac resynchronization therapy (CRT). To improve patient selection, phase analysis by myocardial perfusion scintigraphy (GSPECT) was developed.

Objectives: To evaluate the clinical and scintigraphic response of patients with heart failure (HF) submitted to CRT using GSPECT.

Method: This was an interventional study that included consecutive patients assessed by GSPECT four weeks prior to CRT implantation and six months after it for comparison. These patients also answered the Minnesota Living with Heart Failure Questionnaire (MLHFQ). The categorical variables were compared using Fisher's exact test and chi-square test, whereas Student's t-test was used for numerical variables. The level of statistical significance was set at 5%. The scintigraphic variables analyzed were left ventricular ejection fraction, end-systolic volume, end-diastolic volume, left ventricular mass, standard deviation and bandwidth, as well as QRS duration and the Minnesota Quality of Life Questionnaire score. The presence of mechanical dyssynchrony was defined as standard deviation > 43º.

Results: Nine patients were included in the study. After the cardiac resynchronization therapy, there was a significant improvement ($p < 0.05$) in the end-systolic volume (206 ± 80 mL vs. 158 ± 108 mL), QRS (180 ± 18 ms vs. 120 ± 9 ms), left ventricular mass (248 ± 65 g vs. 193 ± 52 g) and Minnesota Quality of Life Questionnaire score (63 ± 16 vs. 34 ± 20). All patients with scintigraphic criteria of mechanical dyssynchrony showed clinical improvement. Two patients had only electrical dyssynchrony and did not achieve significant clinical improvement, although they showed QRS duration reduction.

Conclusion: GSPECT was able to differentiate patients with isolated electrical dyssynchrony from those with associated mechanical dyssynchrony, through the intraventricular dyssynchrony parameters. The cardiac resynchronization therapy is associated with the improvement of both mechanical and electrical dyssynchrony. Pre-implantation GSPECT showed that patients with associated electrical and mechanical dyssynchrony had a better response to cardiac resynchronization therapy than those with isolated electrical dyssynchrony. (International Journal of Cardiovascular Sciences. 2018;31(3)264-273)

Keywords: Heart Failure; Cardiac Resynchronization Therapy; Myocardial Perfusion Imaging / scintigraphy; Stroke Volume; Artery Coronary Disease / physiopathology; Myocardial Infarction.

Introduction

In the United States, approximately 550,000 new cases of Heart Failure (HF) are diagnosed each year, totaling 5 million Americans with the disease. Therefore, decompensated HF is responsible for more than 1 million hospitalizations per year.[1] The estimated direct and indirect costs for HF in 2011, in the United States, were US$ 215 billion, and this figure is expected to reach US$ 804 billion in 2020.[2] The Brazilian Registry of Heart

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Failure (BREATHE) has shown that 60% of the cases admitted to hospitals with HF are due to a reduction in the left ventricular systolic function.[3]

The cardiac resynchronization therapy (CRT) comprises an implantable device capable of synchronic stimulation of the left ventricle (LV) walls, improving cardiac performance and ejection fraction (EF). It has shown to be effective in restoring the synchronic contraction of the interventricular septum with the LV posterolateral wall, contributing to a reduction in neurohumoral activation and consequent reverse remodeling.[4] CRT is a well-established treatment for morbidity and mortality reduction in HF.[5]

The current criteria for CRT implantation, recommended by the European Society of Cardiology[6] with Class I and Level of Evidence A for CRT implantation, are: New York Heart Association (NYHA) functional class II and III with sinus rhythm, LVEF < 35%, QRS width > 150 ms or 120 to 150 ms with Ventricular Electrical Dyssynchrony (ED) by Left Bundle Branch Block (LBBB).

Despite the benefit observed with the use of CRT, there is still a high rate of nonresponders (between 20 and 40%).[7-11] Patients with coronary artery disease and patients with acute myocardial infarction (AMI) are less likely to show a good response to the resynchronizer implantation and a lower chance of undergoing reverse remodeling.[12] Therefore, it becomes necessary to improve patient selection for CRT, considering not only the ED criteria, which would be QRS enlargement (> 150 ms) and LBBB, but also the presence of mechanical desynchronization (MD), according to scintigraphic criteria.

The aim of our study was to assess the clinical and scintigraphic responses of patients with HF submitted to CRT using the phase analysis based on the gated-Single Photon Emission Computed Tomography (GSPECT).

Methods

We performed a prospective intervention study that included consecutive patients (age > 18 years) according to the following inclusion criteria: NYHA functional class II to IV, despite receiving optimal medical treatment according to the guidelines,[6] in sinus rhythm, LVEF < 35%, QRS width > 150 ms or 120 to 150 ms with ventricular dyssynchrony (presence of LBBB). Patients with CRT indication, who signed the Free and Informed Consent Form, were invited to participate in the study.

The patients were referred from the Cardiology Outpatient Clinic of Hospital Universitário Antônio Pedro and the Electrophysiology Outpatient Clinic of Instituto Estadual de Cardiologia Aloysio de Castro. All patients were submitted to GSPECT within 4 weeks prior to CRT implantation and 6 ± 1 month after implantation for comparison. These patients also answered the Minnesota Living with Heart Failure Questionnaire (MLHFQ) and underwent a speckle-tracking echocardiography before and 6 months after implantation, to obtain the EF and end-systolic volume (ESV) variables, with all these evaluations being carried out in a single day, at Hospital Universitário Antônio Pedro.

This study is part of a multinational research project, funded by the International Atomic Energy Agency, which evaluates the use of GSPECT in finding the best left ventricular segment for resynchronizer electrode implantation. This study is being carried out in several countries, aiming at following patients with CRT indication.[12]

Exclusion criteria were: death before completing the follow-up period; severe illness with risk of death in the following 6 months; acute coronary syndromes; CABG surgery or percutaneous coronary intervention in the 3 months before enrollment and within 6 months after CRT implantation.

Patients were submitted to GSPECT at rest in the supine position after intravenous administration of the 99mTc-sestamibi radiotracer (RPH, Brazil). The administered activity was 10 to 20 mCi (adjusted by weight 0.2 mCi/kg). The waiting time between the injection and image acquisition was 40 to 60 minutes. Patients received fatty foods after the injection to minimize liver uptake.

The Millenium MPR gamma-camera (GE, Milwaukee, USA) was used, and the images were processed through the Xeleris 3.0 workstation. Ventricular function analysis was performed using the Emory Cardial Toolbox™, version 3.0 2012 (Syntermed, USA), which generated values of LVEF, ventricular volume and LV mass. Quantitative analyses and image processing were performed using the SyncTool™ software, which was developed for the evaluation of LV MD by GSPECT.[13] The phase analysis technique can transform the four-dimension images (three spatial planes and time) into two-dimensional paired images. The computer program generates an analysis of the cardiac contraction sequence (phase). Each pixel of the cardiac images has its own cycle of contraction and relaxation, having a characteristic temporal association (phase) in relation to the R wave. Based on the phase histogram, the software calculates five quantitative indices: PP (Peak Phase), SD (Standard Deviation), HBW

(Histogram Bandwidth), S (Skewness) and K (Kurtosis). Potential benefits of the phase analysis technique include its wide availability, automation and reproducibility.[14]

All patients in the study were considered as having ED according to the inclusion criteria (QRS width > 150 ms or 120 to 150 ms with ventricular dyssynchrony). MD was defined by the GSPECT phase analysis using the cut-off value SD > 43° and HBW > 135°.

Patients who responded to the therapy were defined as having three of the following four criteria: improvement of one functional class; increase of at least 5% of LVEF; reduction of at least 15% of the ESV; and a 5-point increase in the MLHFQ score.

This project was submitted to the Research Ethics Committee of Hospital Universitário Antônio Pedro through the Brazil platform, being approved under number 884,844, on November 25, 2014.

Statistical analysis

Statistical analysis was performed using the Excel program (2010, Microsoft Corporation) and the software Statistical Package for Social Sciences (SPSS), version 21.0 (2012, IBM Corporation), with data shown as means and standard deviations. The One-Sample Kolmogorov-Smirnov test was performed to confirm data normality. The categorical variables were compared using Fisher's exact test and chi-square test and, as for the numerical variables, the Student's t-test was used. The linear correlation between the continuous variables was used for the calculation of Pearson's linear correlation coefficient. The phase analysis histogram was generated by the Syntool ECT software and correlated with the QRS duration, using Pearson's linear correlation coefficient calculation. The level of statistical significance was set at 5%.

Results

Fifteen patients were recruited from July 2014 to October 2016. Of these, nine were included in the study, as they were able to complete the exams 6 months after the resynchronizer implantation. The reasons for non-inclusion were: death (two patients died in the fifth month after implantation, one due to heart disease decompensation and another due to severe pneumonia); technical problems (one patient was unable to undergo CRT because of an intraventricular thrombus and another showed no adherence to treatment); loss of follow-up (one patient lost contact with the team); and protocol withdrawal (one patient refused to repeat the scintigraphy 6 months after the implantation).

The patients were followed for up a mean time of 193 ± 16 days. All patients underwent anamnesis, MLHFQ, 6-minute Walk Test (6MWT), speckle-tracking echocardiography, and myocardial perfusion scintigraphy before and after implantation, according to the protocol.

The basal general characteristics of the patients included in the study are shown in table 1.

The patients had pre-implantation electrocardiograms with controlled heart rate (beta-blocked) and enlarged QRS, with a mean of 214 ± 17 ms – all with LBBB morphology. In the 6MWT, the average distance traveled was 341 ± 77 m. High values of the Minnesota score (63 ± 16) were observed, showing a higher frequency of symptoms in patients.

Table 2 shows the scintigraphic parameters of systolic function and basal left ventricular mass of the patients included in the study.

Table 3 shows the basal scintigraphic parameters of the phase analysis related to the ventricular synchrony. Two patients did not have MD, according to the scintigraphic criterion (SD > 43°), but only ED.

Table 4 shows patients' clinical response after the cardiac resynchronizer implantation. It was observed that NYHA functional class decreased for all patients with FC > III, with two patients with NYHA IV showing a decrease to NYHA III, and only one FC III patient did not show FC improvement, with statistical significance by Fisher's exact test. There was a statistically significant reduction in the MLHFQ scores, which, despite being subjective, showed a marked improvement in patients' symptoms, with quality of life improvement. Regarding the 6-minute Walk Test, there was an increase in the distance covered, a decrease in the Borg index (subjective dyspnea score) and in the dyspnea assessed by the examiner, although not statistically significant.

In table 5, the findings of imaging methods in relation to desynchronization were compared. The scintigraphic values of ventricular function (LVEF, EDV, ESV and LV mass) and the values that evaluated dyssynchrony (PP, HBW, SD, S and K) were analyzed. There was a statistically significant reduction in mean systolic volume and LV mass after CRT, due to probable post-resynchronization reverse remodeling.

Several correlations of the dyssynchrony scintigraphic parameters with electrocardiographic findings were performed aiming to demonstrate the

Table 1 - Basal general characteristics

Characteristics	n = 9
Age, years	62.4 ± 8
Body mass index, kg/m²	27.3 ± 5.5
Female gender	6
Diabetes Mellitus	5
Hypertension	7
Dyslipidemia	6
Smoking	0
Previous coronary disease	6
Previous infarction	5
CABG surgery	2
Percutaneous Coronary Intervention	1
NYHA functional class	
II	2
III	5
IV	2
Beta-blocker	9
Angiotensin-converting enzyme inhibitor	3
Angiotensin-receptor blocker	5
Acetylsalicylic acid	2
Diuretics	9
Statins	3
Mineralocorticoid-receptor antagonist	6
Digoxin	4

Results expressed as number or mean ± standard deviation. NYHA: New York Heart Association.

Table 2 - Scintigraphic parameters of basal ventricular function of patients included in the study

Patients	LVEF (%)	EDV (mL)	ESV (mL)	Mass (g)
1	38	287	178	233.5
2	23.5	161	123	175
3	28	143.5	102.5	169
4	35	225.5	146.5	213.5
5	26	210	154	200
6	26.5	325	238	274.5
7	31.5	483.5	333.5	378.5
8	30.5	375.5	260	294
9	26	432	320.5	302.5
Mean ± SD	29.4 ± 4.5	293 ± 112.9	206 ± 80.2	248.9 ± 65

LVEF: left ventricular ejection fraction; EDV: end-diastolic volume; ESV: end-systolic volume; SD: standard deviation.

association between QRS duration and the presence of dyssynchrony. Figure 1 analyzes QRS duration with the SD values of the phase histogram. It was known that the higher the SD (SD > 43°), the higher the intraventricular dyssynchrony. Likewise, a QRS > 130 ms was associated with a higher probability of dyssynchrony. The association of both parameters was directly proportional. When analyzed with HBW, it was also observed that the longer the QRS duration, the greater its value. This demonstrates that HBW and SD were also directly associated, as both increased with QRS enlargement and the presence of dyssynchrony.

SD and HBW values were higher for responders than for non-responders, and the difference between HBW in both groups was statistically significant (Figure 2).

Discussion

The present study evaluated dyssynchrony at pre and post-implantation of CRT through GSPECT. CRT had a positive impacted on functional capacity, MD and ED of patients with advanced HF and LBBB and demonstrated the use of GSPECT to identify patients with a higher probability of responding to CRT.

GSPECT is a useful tool for assessing systolic function in patients submitted to perfusion studies by adding diagnostic and prognostic information without additional exposure to radiation.[15] Technological evolution has allowed phase analysis to be employed in GSPECT studies, providing significant data regarding ventricular synchrony.[13] Trimble et al.[16] used the technique of phase analysis in myocardial perfusion scintigraphy, comparing patients with left ventricular dysfunction with patients with LBBB or right bundle branch block, patients with pacemakers and controls for the evaluation of MD. The parameters of phase analysis were able to identify the subgroups according to the degree of ED.[16] Our findings confirm, as those by Trimble et al.,[16] the feasibility of using myocardial perfusion scintigraphy

Table 3 - Scintigraphic parameters of the pre-implantation synchronization of the resynchronizer

Patient	PP	SD	HBW	S	K
1	110	61.08	171	2.96	9.34
2	118	74.04	160	4.09	5.15
3	105.5	22.41	58.5	3.15	10.37
4	153	46.77	146	2.36	5.54
5	191.5	57.74	203	2.31	6.00
6	109	49.26	129	2.99	11.83
7	44.5	15.91	35.5	3.32	10.27
8	131.5	85.71	257	2.09	5.13
9	81	69.93	134.5	1.72	2.82
Mean ± SD	116 ± 39	53 ± 21	144 ± 64	2.7 ± 0.7	7.4 ± 3

PP: peak phase; SD: standard deviation; HBW: histogram bandwidth; S: skewness; K: Kurtosis; SD: standard deviation.

Table 4 - Clinical response before and after cardiac resynchronizer implantation

Variables	Pre-resynchronization	Post-resynchronization	p value
NYHA Functional Class			
II	2	7	
III-IV	7	2	0.015*
MLHFQ	63.6 ± 17.5	34.1 ± 20.5	0.006†
6-minute Walk Test			
Distance covered, m	342.7 ± 82.2	376.6 ± 84.0	0.314**
Borg index	3.1 ± 1.8	1.2 ± 1.3	0.023†
Dyspnea	2.4 ± 2.0	0.89 ± 0.93	0.049†

Fisher's exact test; † paired t-test. MLHFQ: Minnesota Living with Heart Failure Questionnaire.

with phase analysis, as well as the fact that it can be used in patients with HF and CRT indication.

The pathophysiological basis for the resynchronizer implantation is the correction of a mechanical disorder secondary to an altered LV activation due to LBBB. The presence of LBBB is a sign of electrical abnormality and has been the main criterion for the selection of patients to undergo CRT.[17] However, the current criteria used to indicate CRT are still imperfect, as a group of 20 to 40% of patients does not respond to treatment.[18,19] Bleeker et al.[20] compared the echocardiogram with QRS duration for MD evaluation, and found that 30 to 40% of the patients with QRS duration > 120 ms did not have mechanical desynchronization, suggesting that there is an association between the findings of non-response to CRT and absence of MD.[20] MD was not necessarily associated with ED, as evidenced by the absence of MD in patients with QRS duration > 120 ms.[20] This finding was also demonstrated in the present study, in which 22% of patients with clinical indication for CRT (and QRS duration > 150 ms) did not show electrocardiographic criteria for MD. These patients did not show clinical improvement after CRT implantation.

The use of imaging methods to identify desynchronization has been validated;[16] however, its routine use as a support tool for the selection of patients for CRT remains a topic to be studied, such as the study of Henneman et al.,[21] who evaluated patients with CRT indication through GSPECT and observed a 29% rate of nonresponders after 6 months of therapy – comparable to the 22% observed in the present study. In the study by Henneman et al.,[21] the responders had significantly higher dyssynchrony parameters compared to non-responders (HBW of 175° vs. 117°; and SD of 56° vs. 37°, respectively). These values are close to those found in our results (HBW of 177° vs. 76° and SD of 62° vs. 36°, respectively), confirming that the presence of MD identified at GSPECT is a strong predictor for CRT response.[21] Henneman et al.[21] derived, from the sample of 42 patients, cut-off values of the scintigraphic parameters to indicate the presence of MD and to predict good response to CRT in patients with HF: HBW > 135° and SD > 43°.[21]

Table 5 - Statistical analysis of the pre and post-implantation resynchronizer findings between scintigraphy and echocardiography parameters, using Student's t-test, considering p values < 0.05 as statistically significant

Scintigraphy	Pre-implantation	Post-implantation	p value
Ejection fraction, %	29.4	33.89	0.32
End-diastolic volume, mL	293.7	231.1	0.08
End-systolic volume, mL	206.2	158	0.05
Mass, g	249	193.9	0.02
PP	116	114	0.94
SD	53.66	45.8	0.53
HBW	143.8	130.3	0.68
S	2.78	3.28	0.27
K	7.38	15. 35	0.17

PP: peak phase; SD: standard deviation; HBW: histogram bandwidth.

Medical therapy decision-making should always focus on treatments that lead to changes in clinical outcomes, rather than just changes in imaging or laboratory tests. Thus, more than ventricular function improvement, the aim of this study was to select an ideal patient, who shows a reduction in morbidity and mortality after CRT. Recent studies have demonstrated that the phase analysis parameters are markers of adverse prognosis, as observed by Al Jaroudi et al.,[22] who evaluated 144 patients with chronic renal failure and had higher mortality at 2 years in those with HBW ≥ 62° – a value well below that of the study by

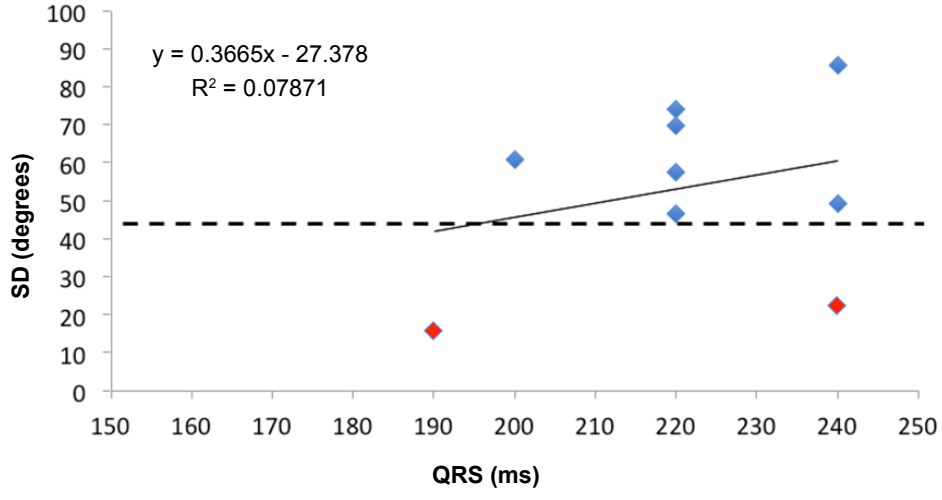

Figure 1 - Correlation between pre-implantation QRS duration and pre-implantation standard deviation (SD).

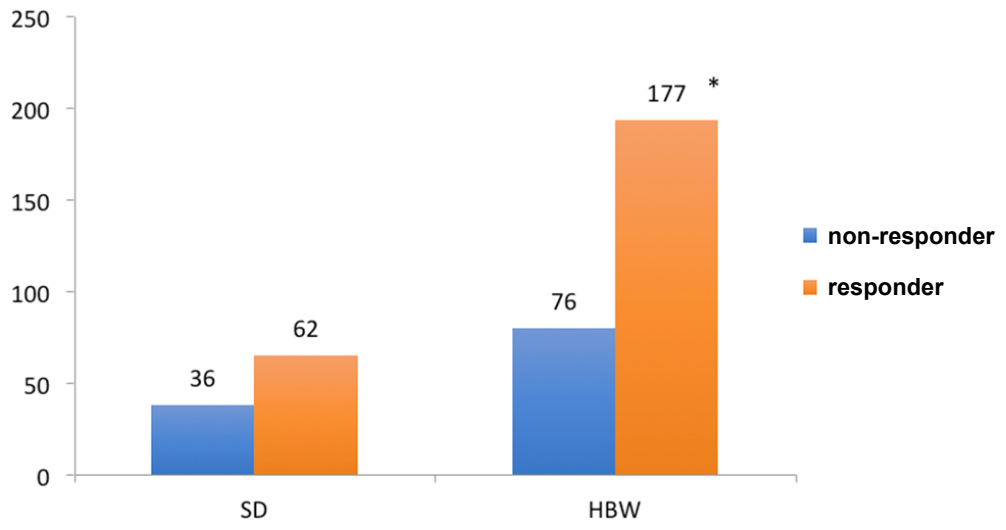

Figure 2 - Distribution of mean SD and HBW before implantation of the cardiac resynchronization therapy, according to the clinical response to implantation. *Chi-square test, with p = 0.03.

Henneman et al.,[21] but already showing some degree of desynchronization.

The subgroup of patients with end-stage renal disease was also extensively studied by Aggarwal et al.,[23] who followed 828 patients with normal EF for 5 years. It was observed that values of SD ≥ 21° or HBW ≥ 56° were associated with worse survival in 5 years. Thus, they also demonstrated that LV desynchronization through phase analysis (GSPECT) provides prognostic value in end-stage renal failure.[23]

A relatively recent study by Zafrir et al.[24] had a significant impact on desynchronization assessment and its association with cardiac mortality, by following 787 patients who underwent GSPECT in a single center for several clinical reasons.[24] These patients were followed for 18.3 ± 6.2 months for cardiac events, and it was verified that SD had the capacity to predict cardiac mortality, and that with every 10° increment, it became an independent predictor of mortality (p = 0.04). Our study did not have data on adverse clinical outcomes in the long term, but ventricular function improvement has been used in several situations, as a valuable surrogate outcome.

Studying clinical outcomes specifically in patients with HF, Al Jaroudi et al.[22] assessed dyssynchrony in patients with an implantable cardioverter defibrillator (ICD) and showed that the higher the SD and the HBW, the higher the incidence of cardiopulmonary arrest or appropriate shock by the ICD.[23] The value of SD > 50° was a predictor of death or appropriate shock by the ICD. More recently, Zafrir et al.,[24] assessing 143 patients with HF and ICD indication, showed a higher rate of events when they also had DM evidenced by SD > 60°.[25] These authors suggest that patients referred to a defibrillator implantation should receive associated CRT when they have SD > 60°.[25]

New studies have addressed the combination of GSPECT parameters to create a MD gradation, using, in addition to HBW and SD, the K and S parameters. Aguadé-Bruix et al.[26] employed a combination of these four parameters and observed that 12% of patients with CRT indication do not have any abnormal phase parameters[26]. Perhaps the study of these combined parameters can increase the sensitivity and specificity of the technique for CRT indication.

In summary, the findings of the present study, together with the growing literature in the area, support that phase analysis by GSPECT is considered a clinically useful tool, to be used both in the assessment of patients in specific subgroups of high cardiovascular risk (end-stage chronic renal failure, hypertensive patients, patients with ICDs) and in the selection of patients with CRT indication.

Study limitations

The main study limitation was the small number of patients, which limited the statistical analysis. Despite the small sample size, statistical significance was observed in parameters that corroborate previous studies in the dyssynchrony area. Another study limitation was the absence of a control group with ventricular dysfunction without CRT. From the ethical point of view, it is not possible to maintain patients with CRT indication as controls, considering the impact of this treatment on mortality and its broad indication recommended in several guidelines.[6] The study had a short follow-up period (6 months) using secondary outcomes, such as left ventricular function, rather than clinical outcomes such as death, HF progression or hospitalization.

Conclusion

The study of phase analysis by GSPECT was able to differentiate patients with isolated electrical dyssynchrony from those with associated mechanical dyssynchrony, through the intraventricular dyssynchrony parameters. The cardiac resynchronization therapy is associated with the improvement of both the mechanical desynchronization (improvement of desynchronization parameters through the phase analysis) and electrical dyssynchrony (QRS interval reduction at the electrocardiogram). Thus, because of the pre-implantation GSPECT assessment, it was possible to verify that patients with associated electrical and mechanical dyssynchrony showed better response to cardiac resynchronization therapy than those with isolated electrical dyssynchrony.

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Author contributions

Conception and design of the research: Wiefels CC, Nascimento EA, Alves CR, Ribeiro FB, Ribeiro ML, Mesquita CT. Acquisition of data: Wiefels CC, Nascimento EA, Alves CR, Ribeiro FB, Fernandes FA, Ribeiro ML, Mesquita CT. Analysis and interpretation of the data: Wiefels CC, Nascimento EA, Alves CR, Ribeiro FB, Fernandes FA, Ribeiro ML, Mesquita CT. Statistical analysis: Wiefels CC, Nascimento EA, Alves CR, Mesquita CT. Obtaining financing: Ribeiro ML, Mesquita CT. Writing of the manuscript: Wiefels CC, Nascimento EA, Alves CR, Ribeiro FB, Fernandes FA, Ribeiro ML, Mesquita CT. Critical revision of the manuscript for intellectual content: Wiefels CC, Mesquita CT.

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 Antônio Pedro under the protocol number 884.844. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

References

1. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation. 2009;119(14):e391-479.
2. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al; American Heart Association Statistics Committee; Stroke Statistics Subcommittee. Heart disease and stroke statistics 2016 Update: A Report From the American Heart Association. Circulation. 2016;133(4):e38-360.
3. Albuquerque DC, Souza JD, Bacal F, Rohde LE, Bernardez-Pereira S, Berwanger O, et al; Investigadores Estudo BREATHE. I Brazilian Registry of Heart Failure - clinical aspects, care quality and hospitalization outcomes. Arq Bras Cardiol. 2015;104(6):433-42.
4. Wells G, Parkash R, Healey JS, Talajic M, Arnold JM, Sullivan S, et al. Cardiac resynchronization therapy: a meta-analysis of randomized controlled trials. CMAJ. 2011;183(4):421-9.

5. Rossi A, Rossi G, Piacenti M, Startari U, Panchetti L, Morales MA. The current role of cardiac resynchronization therapy in reducing mortality and hospitalization in heart failure patients: a meta-analysis from clinical trials. Heart Vessels. 2008;23(4):217-23.

6. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129-200.

7. Cubillos-Garzon LA, Casas JP, Morillo CA, Bautista LE. Congestive heart failure in Latin America: the next epidemic. Am Heart J. 2004;147(3):412-7.

8. Abraham WT, Hayes DL. Cardiac resynchronization therapy for heart failure. Circulation. 2003;108(21):2596-603.

9. Leclercq C, Kass DA. Retiming the failing heart: principles and current clinical status of cardiac resynchronization. J Am Coll Cardiol. 2002;39(2):194-201.

10. Auricchio A, Stellbrink C, Sack S, Block M, Vogt J, Bakker P, et al. The Pacing Therapies for Congestive Heart Failure (PATH-CHF) study: rationale, design, and endpoints of a prospective randomized multicenter study. Am J Cardiol. 1999;83(5B):130D-135D.

11. Bleeker GB, Kaandorp TA, Lamb HJ, Boersma E, Steendijk P, De Roos A, et al. Effect of posterolateral scar tissue on clinical and echocardiographic improvement after cardiac resynchronization therapy. Circulation. 2006;113(7):969-76.

12. International Atomic Energy Agency (IAEA). IAEA Annual Report 2013. Vienna (Austria); 2013. [Acesso em 2017 fev 9]. Disponível em: <https://www.iaea.org/About/Policy/GC/GC58/GC58Documents/English/gc58-3-att1_en.pdf>.

13. Chen J, Garcia EV, Folks RD, Cooke CD, Faber TL, Tauxe EL, et al. Onset of left ventricular mechanical contraction as determined by phase analysis of ECG-gated myocardial perfusion SPECT imaging: development of a diagnostic tool for assessment of cardiac mechanical dyssynchrony. J Nucl Cardiol. 2005;12(6):687-95.

14. Reis CW, Nascimento EA, Ribeiro ML, Dias FB, Wanderley AP, Batista LA, et al. Applicability of myocardial perfusion scintigraphy in the evaluation of cardiac synchronization. Arq Bras Cardiol: Imagem cardiovasc. 2017;30(2):54-63.

15. Chen J, Garcia EV, Bax JJ, Iskandrian AE, Borges-Neto S, Soman P. SPECT myocardial perfusion imaging for the assessment of left ventricular mechanical dyssynchrony. J Nucl Cardiol. 2011;18(4):685-94.

16. Trimble MA, Borges-Neto S, Honeycutt EF, Shaw LK, Pagnanelli RJ, Chen J, et al. Evaluation of mechanical dyssynchrony and myocardial perfusion using phase analysis of gated SPECT imaging in patients with left ventricular dysfunction. J Nucl Cardiol. 2008;15(5):663-70.

17. Poole JE, Singh JP, Birgersdotter-Green U. QRS duration or QRS morphology what really matters in cardiac resynchronization therapy. J Am Coll Cardiol. 2016;67(9):1104-17.

18. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, et al; European Society of Cardiology (ESC); European Heart Rhythm Association (EHRA). 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Europace. 2013;15(8):1070-118.

19. Abraham WT, Hayes DL. Cardiac resynchronization therapy for heart failure. Circulation. 2003;108(21):2596-603.

20. Bleeker GB, Schalij MJ, Molhoek SG, Verwey HF, Holman ER, et al. Relationship between QRS duration and left ventricular dyssynchrony in patients with end-stage heart failure. J Cardiovasc Electrophysiol. 2004;15(5):544-9.

21. Henneman MM, Chen J, Dibbets-Schneider P, Stokkel MP, Bleeker GB, Ypenburg C, et al. Can LV dyssynchrony as assessed with phase analysis on gated myocardial perfusion SPECT predict response to CRT? J Nucl Med. 2007;48(7):1104-11.

22. AlJaroudi, W, Aggarwal, H, Venkataraman R, Heo J, Iskandrian AE, Hage FG. Impact of left ventricular dyssynchrony by phase analysis on cardiovascular outcomes in patients with end-stage renal disease. J Nucl Cardiol. 2010;17(6):1058-64.

23. Aggarwal H, AlJaroudi WA, Mehta S, Mannon R, Heo J, Iskandrian AE, et al. The prognostic value of left ventricular mechanical dyssynchrony using gated myocardial perfusion imaging in patients with end-stage renal disease. J Nucl Cardiol. 2014;21(4):739-46.

24. Zafrir N, Nevzorov R, Bental T, Strasberg B, Gutstein A, Mats I, et al. Prognostic value of left ventricular dyssynchrony by myocardial perfusion-gated SPECT in patients with normal and abnormal left ventricular functions. J Nucl Cardiol. 2014;21(3):532-40.

25. Zafrir N, Bental T, Strasberg B, Solodky A, Mats I, Gutstein A, et al. Yield of left ventricular dyssynchrony by gated SPECT MPI in patients with heart failure prior to implantable cardioverter-defibrillator or cardiac resynchronization therapy with a defibrillator: Characteristics and prediction of cardiac outcome. J Nucl Cardiol. 2017;24(1):122-9.

26. Aguadé-Bruix S, Romero-Farina G, Candell-Riera J, Pizzi MN, García-Dorado D. Mechanical dyssynchrony according to validated cut-off values using gated SPECT myocardial perfusion imaging. J Nucl Cardiol. 2016 Nov 1. [Epub ahead of print].

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ORIGINAL ARTICLE

Acute Effect of Manual Lymphatic Drainage on Natriuresis and Lipolysis in Young Women

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Abstract

Background: The importance of scientific validation of supporting techniques to various treatments is unquestionable. In this context, the influence of manual lymphatic drainage (MLD) on natriuresis and lipolysis and its interaction with oral contraceptives still need to be investigated.

Objectives: To evaluate the acute effect of MLD on natriuresis and lipolysis in young women using or not oral contraceptives.

Methods: Twenty-nine non-users of oral contraceptives and 29 oral contraceptive users, self-reported healthy, sedentary, normal weight women were enrolled. Analyses were conducted on two different days – control (C), without therapeutic intervention and MLD day. Four urine samples were collected at 60-minute intervals. MLD was performed in lower limbs and abdomen for 45 min following the Leduc method. Urinary flow rate and urinary sodium, glycerol and atrial natriuretic peptide excretion were analyzed. Data normality was tested by the Shapiro-Wilk test. Data without normal distribution were expressed as median and interquartile range (25%-75%), while normally distributed data were expressed as mean ± standard error. Mann-Whitney test was used for unpaired data and Wilcoxon test for paired data. Data with normal distribution were evaluated by the unpaired t-Student test. Statistical significance was set at 5%.

Results: One MLD session had an acute effect on both groups, increasing natriuresis in non-users of oral contraceptives and glycerol and atrial natriuretic peptide excretion in oral contraceptive users.

Conclusion: Oral contraceptives influence the effect of MLD on natriuresis. (International Journal of Cardiovascular Sciences. 2018;31(3)274-281)

Keywords: Musculoskeletal Manipulations; Natriuresis; Lipolysis; Lymphatic System.

Introduction

Manual lymphatic drainage (MLD) was created by the Danish physician Dr. Emil Vodder in 1936 as a supporting therapy, later established as the gold standard for the treatment of lymphedema.[1] However, based on beauty standards currently imposed by society, many women undergo some types of treatments that have no scientific basis for their well-being. In this context, MLD has become a popular procedure among healthy individuals to reduce body size, and performed by individuals without knowledge about lymphatic system physiology or pathophysiology.

Lymphatic system has a crucial role in maintaining fluid balance in the body, macromolecular homeostasis, lipid absorption and immune function. However, the effect of MLD on other systems has been poorly investigated.[1]

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In women, water and electrolyte balance is influenced by ovarian hormones, whose receptors are located in reproductive tissues and in those involved in body fluid regulation, such as hypothalamus, cardiovascular system and renal tubules. These hormones affect capillary dynamics, by increasing renal sodium reabsorption and influencing plasma volume.[2,3] Stachenfeld & Taylor[4] showed that estradiol increased plasma volume by its effect on capillary endothelial permeability, decreasing the outflow of proteins and water, without affecting extracellular fluid volume. Estrogen can affect capillary filtration and permeability, be it by direct action on capillary endothelium or indirectly by compounds like the atrial natriuretic peptide (ANP) and nitric oxide.[4]

ANP is an important hormone stored in secretory granules of atrial cells, contributing to water-electrolyte balance. Its secretion depends on atrial distension caused by an increase in venous return, mechanical distension or hypernatremia, which lead to increased natriuresis combined with osmotic diuresis and vasodilation, relaxation of vascular smooth muscle of small arteries, arterioles and metarterioles, and hypotension. Besides, ANP inhibits renin, aldosterone and vasopressin release; it exerts a strong vasodilating action in the kidneys, contributing to increased blood flow and glomerular filtration rate, resulting in natriuresis and increased urine flow.[5] In adipocytes, ANP induces lipolysis via cyclic guanosine monophosphate (cGMP), resulting in activation of protein kinase G type I (GK-I), and degradation of triglycerides by perilipin A and hormone-sensitive lipase (HSL).[6]

Nelson et al.[7] examined plasma concentration of glycerol and its urinary excretion in 12 young, healthy, trained men. The authors found that plasma glycerol peak concentration coincided with its peak in urinary excretion. Krupek et al.[8] evaluated urinary glycerol before and after twelve sessions of MLD in 3 young healthy women. Urinary glycerol was not increased in this study.

Data on the effects of MLD on natriuresis and lipolysis are scarce and conflicting. Our aim was to assess the acute effect of MLD on natriuresis and lipolysis in young women using or not oral contraceptives.

Material and methods

According to the regulations of researches involving human subjects (resolution number 466/2012, Brazilian National Health Council), the study was approved by the Research Ethics Committee of the School of Medical Sciences/University of Campinas (CAAE: 24537613.2.0000.5404), Brazilian Registry of Clinical Trials -45c8br. All participants signed the informed consent form.

Sample size was calculated based on a pilot study. GraphPad Statmate software, version 2 was used for calculation of 95% confidence interval and power of 80%. Thus, for statistical power of the sample be considered relevant, 30 volunteers per group would be necessary. This calculation was performed by Prof. Maria Imaculada de Lima Monteselo, specialist in the area. Twenty-nine women, non-users of oral contraceptives (nOCPu 21.5 ± 0.6 years BMI 21.3 ± 0.5 kg/m^2) and 29 oral contraceptive users (OCPu 21.4 ± 0.5 years, BMI 21.8 ± 0.4 kg/m^2), sedentary (international physical activity questionnaire, IPAQ-v8),[9] self-reported as healthy, and taking no medications except for OCP were enrolled. Women of the nOCPu group were included in luteal phase of menstrual cycle, whereas women of the OCPu group in the "rest period" from the OCP.

All procedures were performed with volunteers at rest, in supine position, without fluid ingestion in a temperature-controlled room (22-24ºC) and relative humidity between 40 and 60% in the morning. For maintenance of resting metabolism, all volunteers received a standardized diet composed of one Brazilian nut, one nut, two apricots and six almonds without salt or sugar added.

MLD procedure

MLD was performed by the same physiotherapist as proposed by Leduc and Leduc10 Volunteers underwent a 45-minute session on abdomen and lower limbs.[11] Participants had previously received instructions for the procedure.

First, in the abdomen, MLD of axillary lymph nodes was done by 10 strokes (clearing motions). Anterior abdominal wall was drained to two directions – the region above the umbilicus was drained toward the axilla, whereas the region below umbilicus was drained toward the inguinal lymph nodes – and thereby the inguinal lymph nodes were drained before the lower abdominal region. Following drainage of axillary and inguinal regions, 10 movements in each region were performed, beginning from the region closer to corresponding lymph nodes toward distal region. And finally, another movement in the opposite direction, i.e., from the distal toward proximal lymph nodes followed by 10 strokes on axillary lymph nodes were performed.

In the lower limbs, drainage of inguinal lymph nodes was started by 10 strokes to evacuate the lymph. With the hands contacting the skin, a pressure was put to promote the flow of the lymph towards internal iliac lymph nodes, followed by 10 strokes in each region, from proximal to distal thigh to direct the flow of the lymph to the internal saphenous vein. Ten strokes were performed on the knees, aimed at cleaning popliteal lymph nodes, by dividing the area in two regions (upper and lower). Then, drainage of legs and thighs was performed, promoting lymph to drain toward the anterointernal part of the leg. In the ankles, 10 strokes in the retromalleolar region were made, directing the lymph to the leg, which was repeated on the feet. At the end of the procedure, a clearing motion was performed from the foot to the upper part of the leg, followed by 10 motions on popliteal lymph nodes and one motion toward upper thigh. The procedure was finished by 10 strokes on inguinal lymph nodes.

Urine collection and assessment of urine composition

Urine was collected at four-time points with 60-minute intervals – -60, 0, 60 and 120 minutes. Urine samples were collected using 1000mL beakers in a water closet available by the experiment room. Volunteers were instructed to completely empty the bladder for correct assessment of urine flow. The sample collected at -60min aimed at excluding potential influence of dietary or climate factors on the results. This protocol was followed on two days – one (control) day without therapeutic intervention and one day of MLD, performed between urine collection at 0 and 60 minutes[11] (Figure 1).

Urinary excretion of the following compounds was calculated from urinary flow rate (mL/min): sodium, by titration with silver nitrate (mM/min), glycerol (mmol/min) by colorimetric assay (LABORCLIN, SP); and ANP (pg/min) by ELISA (USCNLife Science Inc., Houston, EUA).

Statistical analysis

Statistical analysis was performed using GraphPadPrism 5.0 software (Inc, La Jolla, CA, USA). Normal distribution was tested by the Shapiro-Wilk test. Data without normal distribution were expressed as median and interquartile range (25%-75%), whereas those with normal distribution as mean ± standard error. For data without normal distribution, the Mann-Whitney test and Wilcoxon test were used for unpaired (different "n") and paired (same "n") data, respectively, and normally distributed data were analyzed by the unpaired t-test. Statistical significance was set at 5%.

Results

In within-group analysis, on both days (control and MLD), initial values (0 min) in the nOCPu group showed increased urinary flow rate without changes in sodium or glycerol excretion. The same analysis showed that there were no statistical differences in OCPu between days. However, between-group comparison showed that, at the beginning of the study, urinary flow rate on both days and sodium excretion on control day were lower in OCPu than nOCPu (Table 1).

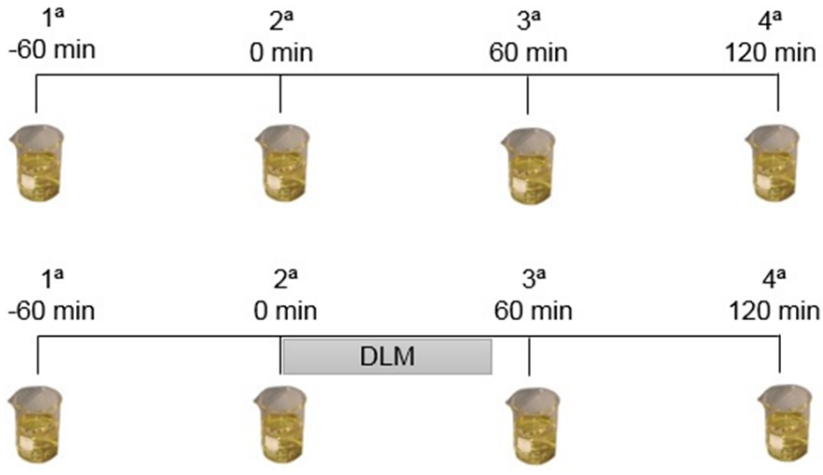

Figure 1 - Urine collection schedule on day without therapeutic intervention (Control) and on day with manual lymphatic drainage (MLD).

Table 1 - Urinary composition in young women, users (OCPu) or not (nOCPu) of oral contraceptives on manual lymphatic drainage (MLD) day or control (C) day at baseline

Urinary flow rate	nOCPu		OCPu		Between-group analysis		Within-group analysis	
	C	MLD	C	MLD	P* C	P# MLD	P$ nOCPu	P$ OCPu
Urine (mL/min)	0.70(0.47-1.35)	1.20(0.70-1.93)$	0.51(0.33-0.75)*	0.70(0.40-1.00)#	0.048	0.006	0.034	0.177
Sodium (mM/min)	140(110.50-184.20)	185.40±100.00	113.30(78.05-149.50)*	161.10±87.10	0.027	0.329	0.414	0.097
Glycerol (μmol/min)	0.01(0.007-0.035)	0.014(0.007-0.02)	0.04(0.01-0.15)*	0.09(0.01-0.14)#	0.014	0.004	0.595	0.945
ANP (pg/min)	0.79(0.33-2.71)	1.91(0.57-3.94)	2.45(1.21-2.86)	2.38(1.63-4.92)	0.064	0.146	0.214	0.324

Normal distribution was tested by the Shapiro-Wilk test. Data without normal distribution were expressed as median and interquartile range (25%-75%), whereas those with normal distribution as mean ± standard error. For normally distributed data, the Mann-Whitney test was used for unpaired data (different "n") and the Wilcoxon test for paired data (same "n"). The unpaired t-test was used for data that failed to pass the normality test. Significance level was set at 5%. ANP: atrial natriuretic peptide.

Urinary flow remained unchanged in nOCPu on both days. However, on control day, OCPs showed an increase in this parameter over time. On MLD day, although urinary flow increased from 0 to 60min, no difference was observed between 120 min and 60 minutes (Table 2).

Urinary excretion of sodium increased in nOCPu group on control day only at 120 minutes; however, on MLD day, this increase occurred at 60 min, indicating an acute effect of the therapy on sodium in the body. At 0 on control day, sodium urinary excretion was lower in OCPu

Table 2 - Urinary flow rate in young women, users (OCPu) or not (nOCPu) of oral contraceptives (OCPu) on manual lymphatic drainage (MLD) day or control (C) day at 0, 60 and 120 minutes

		0	60	120	P** 60 vs 0	P# 120 vs 0	P& 120 vs 60
nOCPu	C	0.70(0.47-1.35)	1.00(0.70-1.31)	1.00(0.69-1.47)	0.06	0.32	0.38
	MLD	0.70(0.49-1.90)	1.20(0.70-1.93)	1.20(0.59-1.40)	0.08	0.86	0.15
OCPu	C	0.51(0.33-0.75)*	0.83(0.58-1.47)**	1.18(0.84-1.80)#&	0.0001	0.0001	0.01
	MLD	0.70(0.40-1.00)	1.30(0.69-2.25)**	1.40(0.96-1.80)#	0.0001	0.0009	0.56
Between-group analysis	P* C	0.04	0.51	0.19			
	P MLD	0.27	0.75	0.07			
Within-group analysis	nOCPu	0.18	0.32	0.91			
	OCPu	0.29	0.13	0.94			

Normal distribution was tested by the Shapiro-Wilk test. Data without normal distribution were expressed as median and interquartile range (25%-75%), whereas those with normal distribution as mean ± standard error. For normally distributed data, the Mann-Whitney test was used for unpaired data (different "n") and the Wilcoxon test for paired data (same "n"). The unpaired t-test was used for data that failed to pass the normality test. Significance level was set at 5%.

as compared with the nOCPu group. An increase in this parameter was observed on both study days, suggesting that MLD had no effect on this variable (Table 3).

Glycerol excretion did not change in nOCPu on both study days, and on control day, values of this variable were greater at 0 for OCPu as compared with nOCPu. Although glycerol excretion increased over time in the OCPu group on control day, it was greater in the OCPu group (Table 4).

ANP values in nOCPu at 60 min were higher than in OCPu. MLD increased ANP excretion in OCPu only (Table 5).

Discussion

One strength of the protocol proposed in this study was a "control" day, to demonstrate that changes occurring after the MLD were actually caused by the procedure.

When control day of both groups was compared, no difference in urinary excretion was found. Graugaard-Jensen et al.[12] investigated 8 healthy, young women with regular menstrual cycle in low and high estrogen phases. The author showed that hormone levels had no effect on urinary excretion. In addition, although urinary excretion did not change between the two time-points, the authors observed a tendency towards sodium retention when estrogen was high.

Based on our protocol, nOCPu responded to MLD with increased sodium excretion and nOCPu with increased urinary excretion when compared with nOCPu, suggesting an acute effect of this technique on natriureis, and hence on urine composition.

Camargo et al.[11] showed that one MLD session promoted an increase in urinary excretion with unaltered sodium excretion or urinary osmolarity in OCP non-users. On the other hand, OCP users were not sensitive to the acute effect of the therapy. These findings suggest an underlying hormonal regulation of these mechanisms. Increased estrogen and progesterone levels were found in OCP users, even though the exact mechanism of these hormones on water-electrolyte balance is still unclear.[2,4,13]

Stachenfeld & Taylor[4] investigated the effects of gonadotropin-releasing hormone (GnRH) administration, combined or not with 17 beta-estradiol (transdermal patches, 0.1 mg/day) in young, healthy, non-smoking women. The authors found that 17 beta-estradiol caused a reduction in urinary osmolarity by concentration of vasopressin in the plasma at baseline. Stachenfeld & Keefe[3] found that estrogen and progesterone in young, healthy women caused little change in water and sodium regulation, suggesting that these hormones affect allostasis. These investigators reported a reduction in osmotic threshold and increase in plasma vasopressin, without changes in urinary free water, indicating that

Table 3 - Urinary sodium excretion in young women, users (OCPu) or not (nOCPu) of oral contraceptives on manual lymphatic drainage (MLD) day or control (C) day at 0, 60 and 120 minutes

		0	60	120	P** 60 vs 0	P# 120 vs 0	P& 120 vs 60
nOCPu	C	140(110.50-184.20)	202.90±113.40	194.70(148.50-244.20)#	0.07	0.04	0.97
	MLD	185.40±100.00	200.00(109.70-329.40)**	203.00±93.13	0.02	0.26	0.24
OCPu	C	113.30(78.05-149.50)*	198.20±87.13**	210.00(166.90-333.90)#&	0.0001	0.0001	0.001
	MLD	161.10±87.10	199.80(138.70-313.60)**	237.60(193.70-331.60)#	0.0001	0.0001	0.08
Between-group analysis	P* C	0.02	0.86	0.10			
	P MLD	0.39	0.82	0.06			
Within-group analysis	nOCPu	0.53	0.21	0.90			
	OCPu	0.05	0.19	0.91			

Normal distribution was tested by the Shapiro-Wilk test. Data without normal distribution were expressed as median and interquartile range (25%-75%), whereas those with normal distribution as mean ± standard error. For normally distributed data, the Mann-Whitney test was used for unpaired data (different "n") and the Wilcoxon test for paired data (same "n"). The unpaired t-test was used for data that failed to pass the normality test. Significance level was set at 5%.

Table 4 - Urinary glycerol excretion in young women, users (OCPu) or not (nOCPu) of oral contraceptives on manual lymphatic drainage (MLD) day or control (C) day at 0, 60 and 120 minutes

		0	60	120	P** 60 vs 0	P# 120 vs 0	P& 120 vs 0
nOCPu	C	0.02(0.01-0.03)	0.01(0.01-0.06)	0.02(0.01-0.07)	0.91	0.62	0.52
	MLD	0.01(0.01-0.02)	0.03(0.01-0.08)	0.02(0.01-0.07)	0.10	0.19	0.80
OCPu	C	0.05(0.02-0.15)*	0.10(0.04-0.31)*	0.17(0.06-0.56)*#	0.05	0.01	0.23
	MLD	0.09(0.01-0.15)%	0.12(0.03-0.32)%	0.17(0.07-0.44)%#	0.10	0.01	0.38
Between-group analysis	P* C	0.01	0.0001	0.0001			
	P MLD	0.0049	0.0012	0.0001			
Within-group analysis	nOCPu	0.59	0.14	0.72			
	OCPu	0.94	0.86	0.91			

Normal distribution was tested by the Shapiro-Wilk test. Data without normal distribution were expressed as median and interquartile range (25%-75%), whereas those with normal distribution as mean ± standard error. For normally distributed data, the Mann-Whitney test was used for unpaired data (different "n") and the Wilcoxon test for paired data (same "n"). The unpaired t-test was used for data that failed to pass the normality test. Significance level was set at 5%.

Table 5 - Urinary atrial natriuretic peptide excretion in young women, users (OCPu) or not (nOCPu) of oral contraceptives on manual lymphatic drainage (MLD) day or control (C) day at 0, 60 and 120 minutes

		0	60	P** 60 vs 0
nOCPu	C	0.79(0.33-2.71)	1.10(0.54-3.71)	0.45
	MLD	1.91(0.57-3.94)	1.72(0.88-4.79)	0.87
OCPu	C	2.45(1.21-2.86)	4.05(1.90-6.63)*	0.05
	MLD	2.38(1.63-4.92)	7.67±5.48%**	0.03
Between-group analysis	P* C	0.06	0.0047	
	P% MLD	0.14	0.0054	
Within-group analysis	nOCPu	0.21	0.24	
	OCPu	0.32	0.13	

Normal distribution was tested by the Shapiro-Wilk test. Data without normal distribution were expressed as median and interquartile range (25%-75%), whereas those with normal distribution as mean ± standard error. For normally distributed data, the Mann-Whitney test was used for unpaired data (different "n") and the Wilcoxon test for paired data (same "n"). The unpaired t-test was used for data that failed to pass the normality test. Significance level was set at 5%.

OCP inhibits renal sensitivity to vasopressin, requiring higher hormone production to obtain the same effects. This is corroborated by our results in OCPu on both days, suggesting that OCP induces greater sensitivity to central osmoreceptors. We believe that resting and temperature-controlled conditions in our study prevented water loss from the body surface, resulting in dilution in the extracellular compartment and inhibitory stimulus of vasopressin, which, in turn, promoted an increase in urinary excretion in the OCPu group.

Increased venous return is one of the stimulus for ANP release by atrial cells. ANP exerts its biological

function by binding into receptors located in renal tubules and in the glomerular zone of the adrenal glands, inhibiting sodium reabsorption by decreased renin secretion, resulting in lower production of angiotensin II, aldosterone and vasopressin.

Graugaard-Jensen et al.[12] reported that changes in endogenous estrogen have no effects on plasma ANP levels. In contrast, in our study, women of the OCPu had higher estrogen levels and greater urinary ANP excretion.

According to Schlueter et al.,[6] ANP lipolytic effect occurs via GMPc formation, which induces triglyceride degradation. However, MLD did not affect urinary excretion of ANP or glycerol, suggesting that venous return promoted by this procedure was not sufficiently effective to stimulate ANP and exert a lipolytic effect readily observable in the urine.

Our data corroborate those found by Krupek et al.[8] These authors reported that 12 sessions of MLD had no effect on urinary glycerol excretion in 3 healthy, young women. However, different from our study, the authors investigated the chronic effect rather than the acute effect of MLD.

One limitation of our study was the fact that urine collection was carried out in the mornings, which limited the participation of many eligible volunteers.

Conclusion

One session of MLD promoted an acute effect on natriuresis in women not taking OCP and glycerol and ANP secretion in OCP users by increasing these parameters.

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Author contributions

Conception and design of the research: Grassi-Kassisse DM, Pires-de-Campos MSM. Acquisition of data: Camargo EAM, Souza AL, Marcorin DM, Rodrigues LL, Crege DRXO, Ishizu LY. Analysis and interpretation of the data: Camargo EAM, Borghi F, Grassi-Kassisse DM, Pires-de-Campos MSM. Statistical analysis: Camargo EAM, Borghi F, Grassi-Kassisse DM, Pires-de-Campos MSM. Obtaining financing: Grassi-Kassisse DM, Pires-de-Campos MSM. Writing of the manuscript: Camargo EAM, Borghi F, Silva PC, Grassi-Kassisse DM, Pires-de-Campos MSM. Critical revision of the manuscript for intellectual content: Camargo EAM, Borghi F, Silva PC, Grassi-Kassisse DM, Pires-de-Campos MSM. Supervision / as the major investigador: Camargo EAM, Grassi-Kassisse DM, Pires-de-Campos MSM.

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

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References

1. Williams A. Manual lymphatic drainage: exploring the history and evidence base. Br J Community Nurs. 2010;15(4):S18-24. doi: 10.12968/bjcn.2010.15.Sup5.78111.
2. Stachenfeld NS. Sex hormone effects on body fluid regulation. Exerc Sport Sci Rev. 2008;36(3):152-9. doi: 10.1097/JES.0b013e31817be928.
3. Stachenfeld NS, Keefe DL. Estrogen effects on osmotic regulation of AVP and fluid balance. Am J Physiol Endocrinol Metab. 2002;283(4):E711-21. doi: 10.1152/ajpendo.00192.2002.
4. Stachenfeld NS, Taylor HS. Progesterone increases plasma volume independent of estradiol. J Appl Physiol (1985). 2005;98(6):1991-7. doi: 10.1152/japplphysiol.00031.2005.

5. Hodes A, Lichtstein D. Natriuretic hormones in brain function. Front Endocrinol (Lausanne). 2014 Nov 28;5:201. doi: 10.3389/fendo.2014.00201.

6. Schlueter N, de Sterke A, Willmes DM, Spranger J, Jordan J, Birkenfeld AL. Metabolic actions of natriuretic peptides and therapeutic potential in the metabolic syndrome. Pharmacol Ther. 2014;144(1):12-27. doi: 10.1016/j.pharmthera.2014.04.007.

7. Nelson JL, Harmon ME, Robergs RA. Identifying plasma glycerol concentration associated with urinary glycerol excretion in trained humans. J Anal Toxicol. 2017;35(9):617-23. PMID: 22080901.

8. Krupek T, Oliveira LP, Moraes LR, Vizoni SL. Laboratory analysis of post-lymphatic drainage urine. Revista Saúde e Pesquisa. 2012;5(1):75-85.

9. Matsudo S, Araújo T, Marsudo V, Andrade D, Andrade E, et al. International physical activity questionnaire (IPAQ): study of validity and reability in Brazil. Rev Bras Ativ Fis Saúde. 2001;6(2):5-18. doi: http://dx.doi.org/10.12820/RBAFS.V.6N2P5-18.

10. Leduc A, Leduc O. Drenagem linfática: teoria e prática. São Paulo: Manole; 2007.

11. Camargo EA, Marcorin DM, Silva BD, Helleno LG, Gomes-Marcondes MC, Grassi-Kassisse DM, et al. Composição urinária de homens e mulheres após drenagem linfática manual. Fisioterapia Brasil. 2015;16(2):148-54.

12. Graugaard-Jensen C, Hvistendahl GM, Frøkiær J, Bie P, Djurhuus JC. The influence of high and low levels of estrogen on diurnal urine regulation in young women. BMC Urol. 2008 Nov 19;8:16. doi: 10.1186/1471-2490-8-16.

13. Sancho B, Guerra-Tapia A. [Oral contraceptives in dermatology]. Actas Dermosifiliogr. 2017;100(6):445-55. PMID: 19709548.

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REVIEW ARTICLE

Accuracy of Impedance Cardiography in Acute Myocardial Infarction: A Literature Review

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Introduction

Hemodynamic monitoring of individuals with acute myocardial infarction, for evaluation of progression and prognosis of the patient's clinical picture, has been studied for years.

The Swan-Ganz catheter is an invasive hemodynamic monitoring measurement, indicated for clinical situations, such as acute heart failure (e.g. acute myocardial infarction, complicated by progressive hypotension or cardiogenic shock); mechanical complications of acute myocardial infarction; right ventricular infarction; refractory congestive heart failure; pulmonary hypertension.[1]

Although there are indications, there is no consensus among them, since there is an enormous amount of work published on the clinical use of the Swan-Ganz catheter, but with doubtful methodology, allowing controversies regarding its true indications. Moreover, some authors have even published test results correlating the use of the Swan-Ganz catheter with increased mortality.[1,2]

Electrical impedance cardiography (ICG) or thoracic bioimpedance, among other forms of monitoring, is a noninvasive method for the estimation of hemodynamic variables. The method assumes that the thorax is a homogeneous fluid cylinder, composed of blood tissue, air and organs, with a specific resistance, and thus measures the electrical resistance at high frequencies with low steady current amplitude (1.5 mA, 86 KHZ) generated by external sensors and electrodes (in the thoracic and cervical regions) that capture instantaneous voltage changes.[3]

The device behaves according to Ohm's law: when a steady current is applied to the thorax, the voltage changes are directly proportional to the impedance changes. The total thoracic impedance, named baseline impedance (Z), is the sum of the impedance of all thoracic components (adipose tissue, heart, lung, skeletal muscle, vascular tissue, bones and air).[4]

The electrodes sense the Z change resulting from the pulsatile blood flow through the descending aorta during systole and diastole. Over time, this alteration has a direct impact on the left ventricular contractility. The alteration of Z is converted to stroke volume and cardiac output values using mathematical algorithms. The other hemodynamic variables are measured or calculated from the ICG data and provided on a continuous and real-time basis.[3,4]

Major studies demonstrate the efficacy of this method, making possible an early evaluation of heart failure, treatment guidelines in hypertension and monitoring of hemodynamic performance in acute myocardial infarction and in the postoperative of cardiac surgery. Normally, these hemodynamic measurements would be obtained for only the most critically-ill patients, such as Swan-Ganz catheter monitoring. However, due to the risk, discomfort, and cost of invasive procedures, bioimpedance is considered safer and more economical.[4]

Impedance cardiography has been an attractive alternative for determining body composition, since

Keywords

Myocardial Infarction / physiopathology; Data Accuracy; Hemodynamics; Cardiography, Impedance; Electric Impedance.

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it is a noninvasive, portable, easy to handle and has good reproducibility and, therefore, is viable for clinical practice and epidemiological studies. Impedance cardiography has been increasingly used as a prognostic indicator in acute myocardial infarction.[3]

Objectives

- To verify the accuracy of the use of impedance cardiography in patients with acute myocardial infarction.

- To compare the indications of the impedance cardiography with the Swan-ganz catheter in patients with acute myocardial infarction.

Method

It was a descriptive, retrospective research, based on a quantitative approach, conducted by means of literature review. For the survey of articles in the literature, a search was conducted in the following databases: Latin American and Caribbean Literature in Heath Sciences (LILACS), Medical Literature Analysis and Retrieval Sistem on-line (Medline), Cumulative Index to Nursing & Allied Health Literature (CINAHL) and COCHRANE LIBRARY.

The electronic search was guided by the PICO strategy. The PICO acronym stands for: Patient, Intervention, Comparison and Outcomes.[5] Table 1 presents the components of the PICO strategy.

The collection of data occurred in the period from January to August 2015. The following controlled descriptors were used to find the articles in databases: myocardial infarction, cardiography impedance, catheterization, Swan Ganz, invasive hemodynamic monitoring and hemodynamics. The composition of the sample met the inclusion criteria: Articles in Portuguese, English and Spanish; Articles that compared bioimpedance cardiography and invasive hemodynamic monitoring; Population: adult patients (aged older than 18 years) in critical condition; Articles published between 2005 and 2015. And as exclusion criteria: Articles not available in full-text; Studies conducted with animals; Articles that compared bioimpedance cardiography with other methods; Revision articles. For data collection, an instrument was developed composed of data related to the journal (title, area, database, country, language, year of publication), the authorship (number of authors, profession of the authors) and to the study (place of research, sample identification, design, type of participants, type of publication, results and conclusions).

In the search, 108 articles were found in MEDLINE (02 articles were added due to similarity), 126 in CINAHL, 11 in LILACS, and 62 in COCHRANE, totaling 307 articles in an initial sample.

Following the eligibility criteria, 259 (84.36%) articles were excluded. A dynamic reading of the 48 (15.63%) remaining articles was taken, and 38 (12.37%) articles were excluded since they were related to heart failure or compared bioimpedance cardiography with other methods. 10 articles were absorbed from the initial sample in order to develop this study.

Table 1 - Components of the PICO* strategy

P	Patient with acute myocardial infarction
I	Impedance Cardiography
C	Swan-Ganz catheter
O	Hemodynamic variables

**Adapted from Lima, 2009.[6]*

Results

Ten articles were selected for review, among which eight (80%) were found in the Medline database and two (20%) in Cochrane. The USA and Lithuania were the countries that most published on the proposed outcome, totaling 60% of the results. It was found no indexed publication in Brazilian journals (Chart 1).

It was shown that 80% of the articles were developed by doctors, 10% by nurses and 10% by professionals of both categories (Chart 2).

Discussion

In accordance with this study's objective, which refers to the identification of the accuracy of impedance cardiography compared to the Swan-Ganz catheter, this revision was concerned to elect clinical trial articles, considering their scientific magnitude to the scientific society, in addition to checking the journal's origin and its scientific relevance.

Impedance cardiography (ICG) is a reliable method for hemodynamic monitoring in cases of acute myocadial infarction without complications.[7]

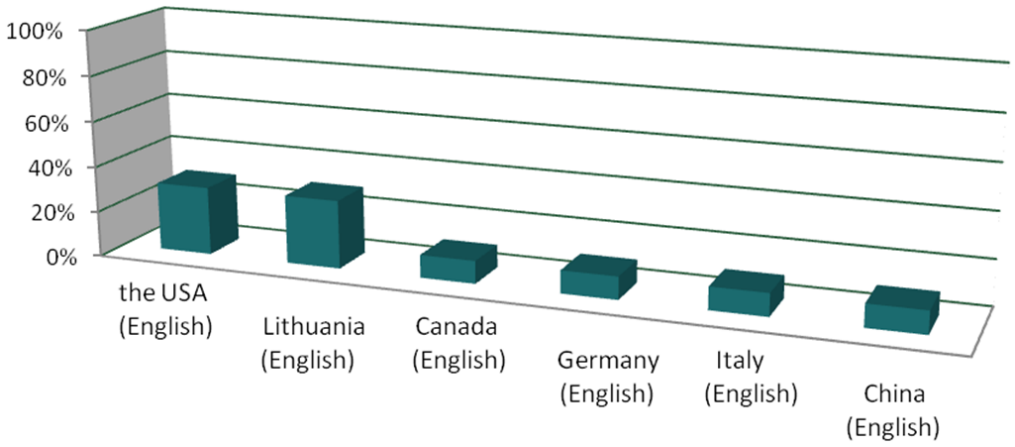

Chart 1 - *Characterization of the country and language of publication of articles.*

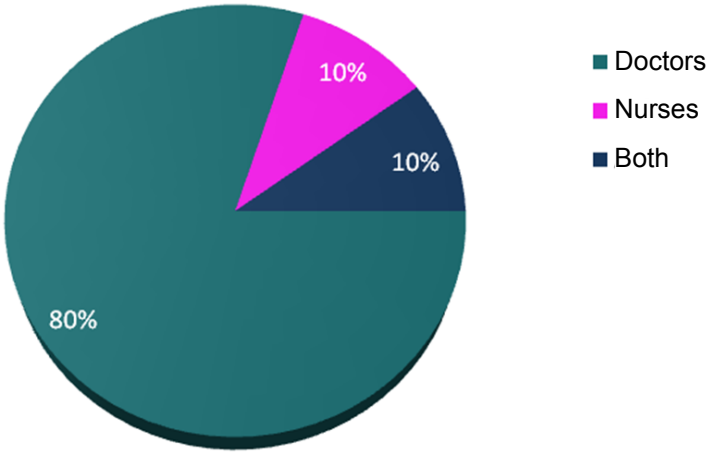

Chart 2 - *Distribution of articles according to the author's professions.*

The comparison of cardiac output (CO) accuracy determined by bioimpedance, thermodilution, and the Fick method led to the conclusion that the three techniques are not interchangeable in a heterogeneous population of critically ill patients. Measurements of CO by thermodilution were more significant than by bioimpedance. However, for each subject, the bioimpedance method varies less than the thermodilution method varies.[8]

ICG could decrease the need for placement of a pulmonary artery catheter in critically ill patients in coronary care units (CCU). The benefits of pulmonary artery catheter (PAC) may not justify the risks associated with invasive hemodynamic monitoring, such as the potential for infection and other complications associated with a catheter. Although ICG does not provide pulmonary artery pressure, it does provide reliable and reproducible measures of cardiac index, stroke volume, systemic vascular resistance, and other hemodynamic parameters. Clinicians utilizing ICG believe it aids medical decision-making and improves patient outcomes in coronary care units, and in the comparison of average hospital cost, it was found PAC 2165$ / ICG 34$ per procedure.[9]

ICG data could reflect the early cardiac functions of AMI patients, but the accuracy of ICG in evaluating cardiac

Chart 3 - Description of Results

Author	Year	Results	Conclusions
Braždžionytė and Macas[7]	2007	Compared statistically, in 34 patients, based on graphical techniques and simple calculations, two methods: the Swan-Ganz (recognized and accepted as a "Gold standard" for hemodynamic monitoring) and impedance cardiography (newly introduced method). It was presented an alternative approach, suggested by DG Altman and JM Bland, for cardiac output measurement simultaneously in patients with acute myocardial infarction.	Bland-Altman analysis is an alternative approach for evaluation of agreement between two methods for clinical measurement. According to data, it is a noninvasive technique. Impedance cardiography is a reliable method for hemodynamic monitoring in cases of acute myocardial infarction without complications.
Engoren and Barbee.[8]	2005	Determined the accuracy of cardiac output (CO) assessment through bioimpedance, thermodilution and Fick methods. In a sample of 46 patients, 15 used the Flick method. Mean (SD) cardiac output in all patients was 6.3 (2.2) L/min by thermodilution and 5.6 (2.0) L/min by bioimpedance. In the 15 patients in whom all 3 methods were used, mean cardiac output was 6.0 (1.7) L/min by thermodilution, 5.3 (1.7) L/min by bioimpedance, and 8.6 (4.5) L/min by the Fick method.	The determinations of CO using the three techniques are not interchangeable in a heterogenous population of critically ill patients. Measurements of cardiac output by thermodilution were significantly greater than by bioimpedance. But for each subject, the bioimpedance method varied less than the thermodilution method varied.
Silver et al.[9]	2005	The hypothesis was that ICG could decrease the need for placement of a pulmonary artery catheter in critically ill patients in coronary care units (CCU). After evaluating the need for hemodynamic monitoring of 107 patients admitted to the CCU, 14 were judged to have indications, and all patients were monitored by ICG. ICG parameters were provided to the attending physician who then decided whether pulmonary artery catheter insertion was still necessary. 10/14 patients (71%) were monitored only by bioimpedance and clinicians reported that the information was helpful in 10/10 patients (100%; 95% confidence interval, 74.1%–100.0%). ICG can replace the pulmonary artery catheter in coronary care unit and clinicians utilizing ICG believe it aids medical decision-making and improves patient outcomes.	The benefits of pulmonary artery catheter (PAC) may not justify the risks associated with invasive hemodynamic monitoring, such as the potential for infection and other complications associated with a catheter. Although ICG does not provide pulmonary artery pressure, it does provide reliable and reproducible measures of cardiac index, stroke volume, systemic vascular resistance, and other hemodynamic parameters. Total Procedure Cost – PAC 2165$ / ICG – 34$
Chen et al.[10]	2014	Evaluated with impedance (ICG) the cardiac function of 99 acute myocardial infarction patients. Blood was obtained for the detection of BNP, NT-proBNP and troponin, followed by ICG, which measured: Thorax fluid capacity (TFC); pre-ejection period (PEP); left ventricular ejection fraction (LVEF); cardiac output (CO); stroke index (SI); stroke volume (SV); systemic vascular resistance (SVR); systemic vascular resistance index (SVRI); cardiac index (CI); end-diastolic volume (EDV); systolic time ratio (STR). All these patients underwent ICG and echocardiography 2 days after surgery. The results indicate that NT-proBNP and BNP are associated with SVR, SVRI, PEP and STR, independently ($P < 0.05$). Troponin was associated with SVR and SVRI ($p < 0.05$).	ICG data could reflect the early cardiac functions of AMI patients, but the accuracy of ICG in evaluating cardiac functions should be combined with detection of blood NT-proBNP, BNP and cTnT and echocardiography.

Cont. Chart 3 - Description of Results

Author	Year	Results	Conclusions
Ablonskytė-Dūdonienė et al.[5]	2012	Due to ICG, it was possible to offer an integrated analysis with electrocardiogram to help identify the patients at risk of serious adverse events after ST-segment. All-cause or cardiac mortality and in-hospital recurrent ischemia, recurrent nonfatal MI, and need for revascularization were considered as serious adverse events. A greater risk of cardiac death was observed within a 5-year period after STEMI.	A greater risk of cardiac death was observed within a 5-year period after STEMI. An integrated analysis of electrocardiogram and impedance cardiogram helps estimate patient's risk of adverse outcomes after STEMI.
Braždžionytė and Macas[11]	2006	Hemodynamic evaluation in patients with acute myocardial infarction (AMI) is crucial. The management of the intra-aortic balloon (IAB) in patients with cardiogenic shock can be made by the invasive Swan-Ganz method. However, noninvasive methods, such as impedance cardiography (ICG), can also have a place in monitoring these patients. The study aimed to evaluate the possibility of applying a noninvasive method in the hemodynamic monitoring during AMI complicated by cardiogenic shock, managed by an intra-aortic balloon. A total of 16 patients were selected; anterior AMI was diagnosed in 68.75% of them, inferior in 25% and circular in 6.25%. Primary angioplasty was successfully performed in 43.75% of the patients; unsuccessfully, in 1 patient, who died within the first 18 hours. Half of patients underwent cardiac surgery within the first two weeks. Mortality rate was 68%. A total of 109 paired measurements were carried out in 16 patients in accordance with different IABP stages. Monitoring of cardiac output, cardiac index, systemic vascular resistance and systolic volume were compared by the two methods, every 12 hours.	Significant correlation of cardiac output values was observed between the impedance cardiography and the Swan-Ganz technique during intra-aortic balloon use. Noninvasive evaluation of hemodynamic indices by continuous monitoring of impedance cardiography during acute myocardial infarction complicated by cardiogenic shock and managed by an intra-aortic balloon is a reliable method for further application.
Fuller[12]	2006	The study examined the use of impedance cardiography to stimulate cardiac output in critically ill patients in the intensive care unit. Cardiac output was measured, concurrently, in 61 patients with a pulmonary artery catheter (PAC) and impedance cardiography (ICG).	The study has found a low correlation between PAC and ICG in critically ill patients, with 95% confidence interval, but the exclusion of patients with valve regurgitation and adjustment for hematocrit and skinfold thickness improved agreement. The support of clinicians for the introduction of any new technology is as important as the accuracy and reliability of that technology. Only with such support can impedance cardiography be accepted. The use of bioimpedance led to a 71% reduction in PAC usage in critically ill patients.
Keuhne et al.[13]	2013	Fifteen postinfarction patients, with symptomatic heart failure and akinetic or dyskinetic segment were included in the study. During the implantation of a cardiac resynchronization therapy (CRT) device, stroke volume was measured via impedance cardiography. It has shown an advantage over the pulmonary artery catheter because it is a simple method for measuring daily hemodynamic data of patients.	Impedance cardiography is a valid parameter to estimate stroke volume and to guide optimization of CRT timing in postinfarction patients.

Piepoli et al.[14]	2010	It used impedance cardiography, and not the pulmonary artery catheter, to assess stroke volume, in post-MI patients, and the use of bone marrow stem cells to improve cardiac function.	The study showed the beneficial effect of stem cells usage in post-MI patients with depressed LV function.
Albert[15]	2006	Comparison between hemodynamic variables: **Cardiography impedance** Stroke volume / stroke index; cardiac output / cardiac index; systemic vascular resistance; left cardiac work / left cardiac work index. Other contractility parameters: - Systolic time ratio; Pre-ejection period; Left ventricular ejection time; Velocity index; Thoracic fluid content. **Pulmonary Artery Catheter** - Stroke volume / stroke index; cardiac output / cardiac index; left cardiac work / left cardiac work index; systemic vascular resistance and peripheral vascular resistance index; pulmonary vascular resistance and pulmonary vascular resistance index; pulmonary artery pressure; right atrial pressure..	Impedance cardiography provides contractility data that can increase traditional hemodynamic information. Current measure systems that measure thoracic impedance to electrical current are user friendly, easy to apply and safe. The use of impedance cardiography may enlarge the relationships between hemodynamic and cardiovascular parameters and circulation disorders that may subsidize patient care.

functions should be combined with detection of blood NT-proBNP, BNP and cTnT and echocardiography.[10]

The use of ICG made it possible to offer an integrated analysis with electrocardiogram to help identify the patients at risk of serious adverse events after ST-segment. All-cause or cardiac mortality and in-hospital recurrent ischemia, recurrent nonfatal MI, and need for revascularization were considered as serious adverse events. A greater risk of cardiac death was observed within a 5-year period after STEMI.[5]

Significant correlation of cardiac output values was observed between the impedance cardiography and the Swan-Ganz technique during intra-aortic balloon (IAB) usage. Noninvasive evaluation of hemodynamic indices by continuous monitoring of impedance cardiography during acute myocardial infarction complicated by cardiogenic shock and managed by an intra-aortic balloon is a reliable method for further application.[11]

There is a low correlation between PAC and ICG in critically ill patients, but the exclusion of patients with valve regurgitation improves the results. The use of ICG led to a 71% reduction in PAC usage in critically ill patients. The support of clinicians for the introduction of any new technology is as important as the accuracy and reliability of that technology. Only with such support can impedance cardiography be accepted.[12]

Impedance cardiography is a valid parameter to estimate stroke volume and to guide optimization of CRT timing in postinfarction patients. It has shown an advantage over the pulmonary artery catheter because it is a simple method of measuring daily hemodynamic data of patients.[13]

Impedance cardiography, similarly to the pulmonary artery catheter, measures stroke volume, and in post-MI patients, it was possible to show the beneficial effect of stem cells usage in patients with depressed LV function using ICG, without the need for an invasive method.[14]

Impedance cardiography provides contractility data that can increase traditional hemodynamic information. Current measure systems that measure thoracic impedance to electrical current are user friendly, easy to apply and safe. The use of impedance cardiography may enlarge the relationships between hemodynamic parameters and cardiovascular and circulation disorders that may subsidize patient care. Comparison between hemodynamic variables:

Cardiography impedance - Stroke volume / stroke index; cardiac output / cardiac index; systemic vascular resistance; left cardiac work / left cardiac work index. Other contractility parameters: - Systolic time ratio; Pre-ejection period; Left ventricular ejection time; Velocity index; Thoracic fluid content.

Pulmonary Artery Catheter - stroke volume; stroke index; cardiac output; cardiac index, left cardiac work; left cardiac index; systemic vascular resistance and peripheral vascular resistance index; pulmonary vascular resistance and pulmonary vascular resistance index; pulmonary artery pressure; right atrial pressure.[15]

Conclusion

ICG has shown to be a reliable method for hemodynamic monitoring in cases of acute myocardial infarction without complications. This method enlarges the relationships between hemodynamic/cardiovascular parameters and circulation disorders that may subsidize patient care.

It is emergent that we understand the importance of assisting the client based on clinical evidence. Our knowledge about the pathology and its hemodynamic repercussions assures the appropriate diagnosis identification, allowing the implementation of client care with quality and safety.

Author contributions

Conception and design of the research: Silva LS, Lima DVM. Acquisition of data: Silva LS. Analysis and interpretation of the data: Silva LS, Reis FF, Silva MES. Writing of the manuscript: Silva LS, Reis FF, Silva MES. Critical revision of the manuscript for intellectual content: Silva LS, Lima DVM.

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

References

1. Pereira Jr GA, Marson F, Ostini FM, Antoniazzi P, Gomide M, Basile-Filho A. Monitorização hemodinâmica invasiva. Medicina, Ribeirão Preto. 1998;31(3):380-99.
2. Robin ED. The cult of the Swan-Ganz catheter. Overuse and abuse of pulmonary flow catheters. Ann Intern Med. 1985;103(3):445-9. doi: 10.7326/0003-4819-103-3-445.
3. Mehta Y, Arora D. Newer methods of cardiac output monitoring. World J Cardiol. 2014;6(9):1022-9. doi: 10.4330/wjc.v6.i9.1022.
4. Villacorta H, Albuquerque DC. Cardiografia por bioimpedância transtorácica: uma nova abordagem no manuseio de pacientes com insuficiência cardíaca. Rev SOCERJ. 2006;19(6):516-22.
5. Ablonskytė-Dūdonienė R, Bakšytė G, Čeponienė I, Kriščiukaitis A, Drėgūnas K, Ereminienė E. Impedance Cardiography and heart rate variability for long-term cardiovascular outcome prediction after myocardial infarction. Medicina (Kaunas). 2012;48(7):350-8. PMID: 23032907.
6. Lima DV, Lacerda RA. Hemodynamic oxygenation effectsduring the bathing of hospitalized adult patients critically ill: systematic review. Acta Paul Enferm. 2010;23(2):278-85. doi: http://dx.doi.org/10.1590/S0103-21002010000200020.
7. Braždžionytė J, Macas A. Bland-Altman analysis as an alternative approach for statistical evaluation of agreement between two methods for measuring hemodynamics during acute myocardial infarction. Medicina (Kaunas). 2007;43(3):208-14. PMID: 17413249.
8. Engoren M, Barbee D. Comparison of cardiac output determined by bioimpedance, thermodilution, and the Fick method. Am J Crit Care. 2005;14(1):40-5. PMID: 15608107.
9. Silver MA, Cianci P, Brennan S, Longeran-Thomas H, Ahmad F. Evaluation of impedance cardiography as an alternative to pulmonary artery catheterization in critically ill patients. Congest Heart Fail. 2004;10(2 Suppl 2):17-2. doi: 10.1111/j.1527-5299.2004.03410.x.
10. Chen SJ, Gong Z, Duan QL. Evaluation of heart function with impedance cardiography in acute myocardial infarction patients. Int J Clin Exp Med. 2014;7(3):719-27. PMID: 24753769.
11. Braždžionytė J, Macas A. Impedance cardiography for aortic balloon counterpulsation impact assessment on patients hemodynamics during acute myocardial infarction. Medicina (Kaunas). 2006;42(11):904-13. PMID: 17172792.
12. Fuller HD. Improving the accuracy of impedance cardiac output in the intensive care unit: comparison with thermodilution cardiac output. Congest Heart Fail. 2006;12(5):271-6. doi: 10.1111/j.1527-5299.2006.05755.x.
13. Keuhne M, Bocchiardo M, Neagele H, Schaer B, Lippert M, Sticherling C, et al. Noninvasive monitoring of stroke volume with resynchronization devices in patients with ischemic cardiomyopathy. J Card Fail. 2013;19(8):577-82. doi: 10.1016/j.cardfail.2013.06.005. doi: 10.1016/j.cardfail.2013.06.005.
14. Piepoli MF, Vallisa D, Arbasi M, Cavanna L, Cerri L, Mori M, et al. Bone marrow cell transplantation improves cardiac, autonomic, and functional indexes in acute anterior myocardial infarction patients (Cardiac Study). Eur J Heart Fail. 2010;12(2):172-80. doi: 10.1093/eurjhf/hfp183.
15. Albert NM. Bioimpedance cardiography measurements of cardiac output and other cardiovascular parameters. Crit Care Nurs Clin North Am. 2006;(18)195-202. doi: 10.1016/j.ccell.2006.01.008.

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REVIEW ARTICLE

Clinical Usefulness of Cystatin C to Assess the Prognosis of Acute Coronary Syndromes: A Systematic Review and Meta-Analysis

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Abstract

Cystatin C is used as a marker of renal function and has been shown to be promising for evaluating the prognosis of acute coronary syndromes (ACSs). To evaluate the prognostic value of cystatin C in patients with ACSs. The articles were searched using PubMed, Web of Science and Scielo databases. Observational cohort studies that evaluated the association between increased cystatin C and the development of cardiovascular events and mortality in patients with ACSs were included. Only studies that evaluated similar outcomes, studies that compared the highest with the lowest quartiles of cystatin C, and studies that performed multivariate analysis that included glomerular filtration rate or serum creatinine, were included in the meta-analysis. Methodological quality of the articles was assessed using the Newcastle-Ottawa Scale questionnaire for cohort studies. After applying the eligibility criteria, 17 studies were included in the systematic review. All included studies reported a significant association between higher levels of cystatin C and outcomes. The meta-analysis demonstrated that elevated levels of cystatin C are associated with increased risk of cardiovascular mortality or non-fatal myocardial infarction in patients with ACSs, and such association is independent of renal function [OR = 1.65 (1.464 – 1.861), $p < 0.001$]. Among the studies included, 4 have good quality and 13 have excellent methodological quality.The systematic review and meta-analysis demonstrated that there is a significant association between increased cystatin C levels and the development of cardiovascular events and mortality in patients with ACSs.

Keywords

Acute Coronary Syndrome / Physiopathology; Cystatin C; Prognosis, Biomarkers.

Introduction

Cystatin C is a protein belonging to cystatin superfamily of human cysteine protease inhibitors, which is composed of 12 proteins.[1] It is produced at a constant rate by nucleated cells. Due to its low molecular weight (13-kDa) and basic isoelectric point, cystatin C is removed from the bloodstream by glomerular filtration, reabsorbed and catabolized by tubular epithelial cells.[2] Serum cystatin C has been used as a marker of renal function, and suggested as a better endogenous marker of glomerular filtration rate (GFR) compared with serum creatinine.[2,3] The protein is able to detect small reductions in GFR, enabling the early diagnosis of renal dysfunction.[4]

Some studies have demonstrated that increased levels of cystatin C in patients with acute coronary syndrome (ACS) are associated with increased risk for cardiovascular events, cardiovascular death and overall mortality, indicating that cystatin C is a promising prognostic marker of ACSs.[5-7] However, due to lack of scientific evidence of its prognostic value, cystatin C has not been used in clinical practice.

Few systematic reviews[8] or meta-analysis[9-11] have been performed on the theme, and none of them has included exclusively ACS patients. Therefore, it is of great importance the development of a systematic review and a meta-analysis on this subject in order to compile and analyze the results of currently available

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studies. In light of this, this systematic review and meta-analysis aimed to assess the prognostic value of cystatin C in patients with ACS.

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.[12]

Search strategy

An electronic search was conducted in Medline via PubMed, Web of Science and Scielo databases. Descriptors were determined using the Medical Subject Headings (MeSH) for the search in PubMed and Web of Science, and the Health Sciences Descriptors for Scielo database. The search was conducted until 30 May, 2016.

The search strategy in Pubmed and Web of Science included the term "cystatin C" and its variations, combined with all variations of the term "acute coronary syndrome", using the connector word "AND". The search strategy in Scielo included the term "cystatin C" combined with all variations of the term "acute coronary syndrome", using the connector word "AND".

Eligibility criteria

Articles written in English, Portuguese or Spanish that met these eligibility criteria were included:

- Study design: observational cohort studies.
- Study population: patients with ACS - unstable angina, ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI) - with increased baseline cystatin C levels.
- Exposure: increased cystatin C levels.
- Clinical outcome: cardiovascular events or mortality evaluated by odds ratio / relative risk and / or differences between the proportions of patients with higher and lower levels of cystatin C.

The following events were considered cardiovascular events: acute myocardial infarction, need for revascularization, stroke, recurrent angina, unstable angina, heart failure and cardiovascular death.

Article selection

After exclusion of duplicate articles, articles published until 30 May 2016 that met the eligibility criteria were selected. The articles were selected by two independent investigators in two steps: in the first step, analysis of the title and abstracts was performed; in the second step, the articles selected in the previous step were read in full.

Data extraction from the articles

The following information was extracted from each article: type of ACS, diagnostic method for ACS, number of patients, patients' age range; time of follow-up, outcome measures, method for cystatin C measurement, patients' kidney function (normal or not), GFR or serum creatinine, patients' classification by cystatin levels, variables included in the multivariate analysis, results (frequency of cardiovascular events, cardiovascular death or all-cause mortality and / or odds ratio).

Evaluation of the methodological quality of the articles

Methodological quality of the articles included in the systematic review was assessed by two reviewers. The Newcastle-Ottawa Scale (NOS)[13] for cohort studies was used, which also included the following evaluation categories - cohort selection, comparability of cohorts and outcome. A maximum of one star can be attributed to the categories selection of the cohorts and outcome, a maximum of two stars can be attributed to comparability of the cohorts, such that quality of the studies can be awarded up to nine stars. Articles awarded 5 or 6 stars were considered of good methodological quality, and those awarded 7 stars were considered of excellent methodological quality.

Meta-analysis

In this meta-analysis, we included only studies that analyzed similar outcomes, studies that compared the fourth quartile with the first quartile of cystatin C, and studies that performed multivariate analysis (which included, among other variables, GFR or serum creatinine). Odds ratio and 95% confidence interval adjusted by multivariate analysis and heterogeneity between studies were analyzed by the I2 test. The studies were considered homogeneous when I2 was greater than 50% and p-value was lower than 0.10. Odds ratio was calculated using the fixed or the random effect model in case of homogeneity or heterogeneity, respectively. The Comprehensive Meta-Analysis (CMA) software version 3 was used for statistical analysis.

Results

In the initial search, 640 articles were identified, and 17 were included in this systematic review (Figure 1).

The studies that met the eligibility criteria were published between 2004 and 2015; characteristics of these studies are described in Table 1. The studies included patients with ACS, 29.4% (n = 5) of them included STEMI patients only, 17.7% (n = 3) evaluated only patients with NSTEMI, 23.5% (n = 4) analyzed patients with unstable angina, STEMI and NSTEMI, and 17.7% (n = 3) examined patients with unstable angina and NSTEMI, and 11.7% (n = 2) evaluated patients with NSTEMI and STEMI. Among the studies evaluated, 35.3% (n = 6) used the recommended diagnostic criteria,[14] whereas 41.2% (n = 7) did not use these criteria; 23.5% (n = 4) did not report the criteria used.

Sample size of these studies varied from 71 to 16,401 patients; it was greater than 1,000 in 23.5% of the studies (n = 4);[2] between 200 and 1,000 in 52.9% (n = 8) of the studies, and lower than 200 in 29.4% (n = 5) of the studies. Age of the study groups ranged from 31 to 82 years. Mean follow-up period was 15 months, varying from 1 month to 5 years. Patients were followed for 1-6 months in 35.3% (n = 6) of the studies and for more than 6 months in 64.7% (n = 11).

In 52.9% (n = 9) of the studies, outcome measures were all-cause mortality and non-fatal cardiovascular events; 41.2% (n = 7) of them evaluated cardiovascular death and non-fatal cardiovascular events, and one study (5.9%)[3] analyzed all-cause mortality only.

The methods for cystatin C measurement were immunonephelometry (41.2% [n=7]), immunoturbidimetry (41.2% [n = 7]), immunofluorimetry (5.9% [n = 1]) and immunoenzymatic assay (5.9% [n = 1]), and one study (5.9%) did not report the method used.

In 88.2% (n = 15) of the studies, patients with normal and altered kidney function were included, whereas 11.8% (n = 2) of the studies included patients with normal kidney function only. Kidney function was assessed mostly by GFR (82.4% [n = 14]), followed by serum creatinine (17.6% [n = 3]).

Classification criteria of patients, the variables included in the multivariate analysis and results of each study are described in Table 2. In 14 (82.3%) studies, patients were classified by cystatin levels, in 7 (41.2%) by quartiles, in 3 (17.6%) by tertiles. Two studies (11.8%) adopted the cutoff point to prevent cardiovascular events, one (5.9%) study used the median values of cystatin C levels, another study used the reference value of the cystatin C measurement method (immunonephelometry), whereas 3 (17.6%) studies did not make this classification.

Most studies (88.2%, n = 15) performed multivariate analysis; 58.8% (n = 10) of them included, among other variables, GFR or serum creatinine in this analysis. On the other hand, five studies (29.4%) included other variables than GFR or serum creatinine.

All studies included in this systematic review assessed the association between increased cystatin C and outcome measures using odds ratio or relative risk and found a significant association between them. A significant association was found of increased cystatin C with cardiovascular events or all-cause mortality in 47.1% (n = 8) of the studies, with cardiovascular events or cardiovascular mortality in 17.6% (n = 3), with cardiovascular events in 17.6% (n = 3) and with cardiovascular death or all-cause mortality in 17.6% (n = 3).

In addition, 35.3% (n = 6) of the studies compared the proportion of patients with increased cystatin C levels who had outcomes with those who did not. This proportion was significantly greater for cardiovascular events in 2 (11.8%) studies, for cardiovascular events or all-cause mortality in two (11.8%), and for cardiovascular events or cardiovascular death in one study (5.9%). Only one (5.9%) study did not report a statistically significant difference between the proportions of patients with increased cystatin C levels who developed cardiovascular events or cardiovascular death in comparison with those with lower cystatin C levels who developed these outcomes.

Analysis of the methodological quality of the studies is described in Table 3, with the criteria for assignment of the stars described in detail in the legend. Four (23.5%) studies showed good methodological quality and 13 (76.5%) showed excellent methodological quality.

Only 5 studies compared the fourth and the first quartile of cystatin C and performed multivariate analysis, including GFR and serum creatinine in this analysis. Of these, only 2 evaluated similar outcomes (cardiovascular death, non-fatal myocardial death), and thereby were included in the meta-analysis (Figure 2). Since the studies were heterogeneous (I2 < 0,001 e p = 0,621), the odds ratio was calculated using the random effect model. Results of the meta-analysis (OR = 1.65 [1.464 – 1.861], p < 0.001) indicate a significant association between increased levels of cystatin C and the risk of cardiovascular death or non-fatal myocardial infarction in ACS patients.

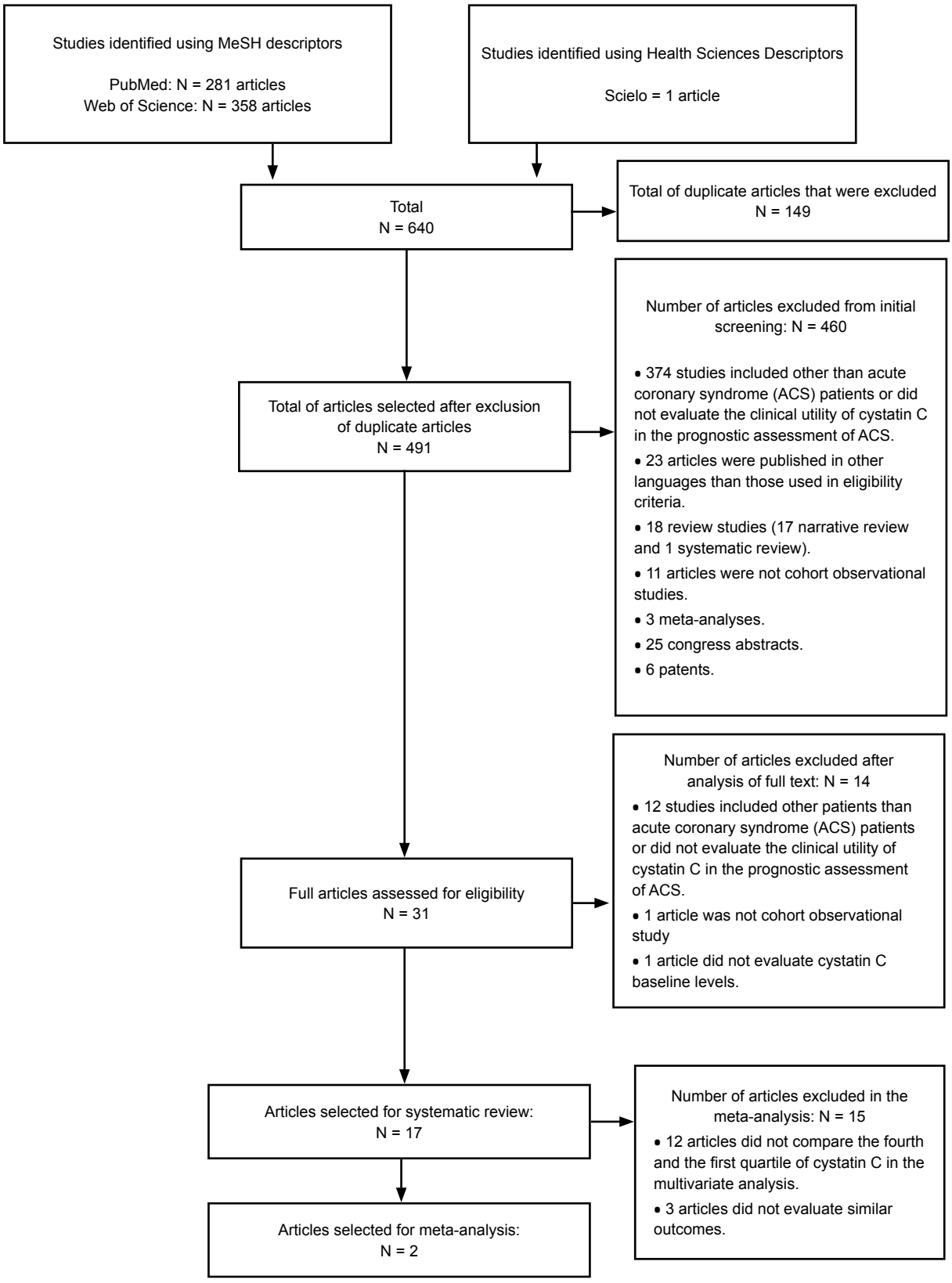

Figure 1 - Flowchart of the articles selected for systematic review and meta-analysis.

Table 1 - Characteristics of the selected studies

Author/ Year	Type of acute coronary syndrome	Diagnostic method for acute coronary syndrome	Number of patients / Age range (years)	Time of follow-up / Outcome measure	Method of cystatin C measurement	Inclusion of patients with normal kidney function only	GFR of patients (mL/ min/1,73m²) or serum creatinine
Studies included only in the systematic review and meta-analysis							
Tonkin et al., 2015[15]	Unstable angina, NSTEMI, STEMI	NI	9014 / 31-75	5 years / Cardiovascular death, non-fatal infarction	Immunoturbidimetry	Yes	GFR = 69 (60-80)
Akerblom et al., 2012[16]	NSTEMI, STEMI	NSTEMI: at least two of these criteria: change in ST segment; increase in cardiac marker levels; presence of one of the risk factors. STEMI: at least two of the following criteria: ST segment elevation in ECG; recent left bundle branch block; intention to perform primary PCI.	16401 / 57 (51-64) (1st quartile) 59 (52-67) (2nd quartile) 63 (56-71) (3rd quartile) 70 (61-76) (4th quartile)	12 months / Cardiovascular death, non-fatal infarction	Immunoturbidimetry	No	GFR = 82,6
Studies included only in the systematic review							
Tang et al., 2015[17]	STEMI	Chest pain > 30 min, ST segment elevation in ECG; recent left bundle branch block; increase in cardiac markers	108 / 58.8 ± 9.8 (cystatin C < 1.36 mg/L) 65.9 ± 11.3 (cystatin C ≥ 1.36 mg/L)	6 months / Cardiovascular death, non-fatal infarction, need of revascularization, stroke and CHF	Immunoturbidimetry	No	GFR = 81.6 ± 22.5 (cystatin C ≥ 1.36 mg/L) GFR = 99.5 ± 20.8 (cystatin C < 1.36 mg/L) p = 0.01
Fu et al., 2013[18]	Unstable angina, NSTEMI, STEMI	NI	660 / 81.74 ± 2.54 (group with diabetes) 81.99 ± 2.21 (group without diabetes)	28 months / All-cause mortality, myocardial infarction, need of revascularization	NI	No	GFR = 68.67 (55.97–82.14) (with DM) GFR = 72.55 (63.08-81.74) (without DM) p = 0.106
Akgul et al., 2013[19]	STEMI	Chest pain > 30 min, ST segment elevation in ECG	475 / 62.8 ± 13.1 (3rd quartile) 52.3 ± 10.5 (1st and 2nd quartiles)	1 month / Cardiovascular death, non-fatal infarction, need of revascularization	Immunoturbidimetry	No	GFR = 70.6 ± 24.3 (cystatin C > 1.12 mg/L) GFR = 98.1 ± 22.8 (cystatin C ≤ 1.12 mg/L) p < 0.001

Widera et al., 2013[20]	Unstable angina, NSTEMI	Unstable angina: increased levels of cardiac troponin. NSTEMI: increased levels or cardiac troponin, signs of ischemia in ECG, CAD, at least one 50% coronary stenosis	1146/ 74 (68-80) (with cardiac event) 69 (59-76) (without cardiac event)	6 months/ All-cause mortality, non-fatal infarction	Immunoturbidimetry	No	Serum creatinine (mg/dL) = 1.20(0.90-1.65) (with cardiac event) Serum creatinine (mg/dL) = 0.93 (0.79-1.13) (without cardiac event) p < 0.001
Manzano -Fernández et al., 2012[21]	Unstable angina, NSTEMI	Chest pain ≥ 10 min within 72 hours before hospital admission and/or ST segment deviation or increased cardiac markers	226/ 58 ± 11 (1st quartile) 64 ± 10 (2nd quartile) 71 ± 10 (3rd quartile) 76 ± 7 (4th quartile)	At least 12 months/ All-cause mortality	Immunonephelometry	No	GFR = 92.1 ± 25.7 (1st quartile) GFR = 85.9 ± 19.8 (2nd quartile) GFR = 77.8 ± 14.2 (3rd quartile) GFR = 54.8 ± 16.8 (4th quartile) p ≤ 0.001
Ristiniemi et al., 2012[22]	NSTEMI	NI	245/ 62 (10.9) (1st tertile) 69 (9.5) (2nd tertile) 76 (8.8) (3rd tertile)	12 months/ All-cause mortality non-fatal infarction	Immunofluorescence	No	GFR = 76 (17.4) (1st tertile) GFR = 62 (15.2) (2nd tertile) GFR = 44 (15.5) (3rd tertile) p < 0.0001
Silva et al., 2012[23]	STEMI	Chest pain at rest > 30 min, ST segment elevation in ECG or left bundle branch block	151/ 61 ± 12	12 months/ All-cause mortality, non-fatal infarction	Immunonephelometry	No	GFR = 96.9 ± 37.1 (no death or infarction) GFR = 80.9 ± 25.3 (death or infarction) p > 0.05
Sun et al., 2012[24]	Unstable angina, NSTEMI, STEMI	NI	660 patients/ 62.5 ± 10.5 (with cardiac event) 59.9 ± 10.6 (without cardiac event)	At least 12 months/ All-cause mortality, non-fatal infarction, need of revascularization, CHF, recurrent chest angina, stroke	Immunoturbidimetry	No	GFR = 96.00 (with cardiac event) GFR = 104.08 (without cardiac event) p = 0.057
Kaski et al., 2010[25]	Unstable angina, NSTEMI	Chest pain at rest > 5 min, and ≥ 1 of these criteria: signs of myocardial ischemia in ECG, CAD and/ or myocardial revascularization with PCI or bypass surgery; increased cardiac troponin	610/ 67.2 ± 10.9 (with cardiac event) 64.5 ± 11.3 (without cardiac event)	12 months/ All-cause mortality, non-fatal infarction	Immunonephelometry	No	GFR = 74 (58-87) (with cardiac event) GFR = 78 (64-94) (without cardiac event) p = 0.05

Cont. Table 1 - Characteristics of the selected studies

Author/ Year	Type of acute coronary syndrome	Diagnostic method for acute coronary syndrome	Number of patients / Age range (years)	Time of follow-up / Outcome measure	Method of cystatin C measurement	Inclusion of patients with normal kidney function only	GFR of patients (mL/ min/1,73m²) or serum creatinine
Taglieri et al., 2010[6]	NSTEMI	Chest pain and at least one of the following criteria: signs of myocardial ischemia in ECG; increased cardiac markers; history of CAD	525/ 58 (50-66) (1st quartile) 63 (53-70) (2nd quartile) 68 (59-74) (3rd quartile) 72 (67-67) (4th quartile)	12 months/ Cardiovascular death, non-fatal infarction, unstable angina	Immunonephelometry	No	GFR = 92.3 (80.2-107.4) (1st quartile) GFR = 84.0 (74.9-97.3) (2nd quartile) GFR = 75.1(62.6-89.8) (3rd quartile) GFR = 59.1(47.5-72.9) (4th quartile) p < 0.001 (4th quartile x 1st, 2nd and 3rd quartile)
Derzhko et al., 2009[26]	STEMI	Chest pain > 20 min, ST segment elevation in ECG, increased cardiac troponin	150/ 56.99 ± 11.3	6 months/ CHF, non-fatal infarction, unstable angina, all-cause mortality	Immunonephelometry	No	Serum creatinine (mg/dL) (general) = 1.02 ± 0.17
Ichimoto et al., 2009[7]	STEMI	Chest pain > 30 min, ST segment elevation in ECG, CK-MB levels twice greater than upper normal limit	71/ 61.9 ± 10.4 (cystatin C < 0.96 mg/L) 66.5 ± 12.6 (cystatin C ≥ 0.96 mg/L)	Approximately 6 months/ All-cause mortality, non-fatal infarction, need of revascularization, stroke, CHF	Immunoturbidimetry	No	Serum creatinine (mg/dL) = 0,93 ± 0,22 (cystatin C ≥ 0,96 mg/L) Serum creatinine (mg/dL) = 0,72 ± 0,14 (cystatin C < 0,96 mg/L) p < 0,01
Kilic et al., 2009[27]	Unstable angina, NSTEMI, STEMI	Increased cardiac markers and at least one of these criteria: chest pain; development of pathological Q waves in ECG; signs of ischemia in ECG; PCI; pathological findings of AMI	160/ 59 ± 10 (without cardiovascular events) 61 ± 10 (with cardiovascular events)	12 months/ Cardiovascular death, non-fatal infarction, recurrent angina	Immunoenzymatic assay	Yes	GFR = 80 ± 31 (with cardiac events) GFR = 92 ± 35 (without cardiac events) p = 0,03

García Acuña et al., 2009[28]	NSTEMI, STEMI	At least two of these criteria: chest pain: signs of ischemia in ECG; increased cardiac markers	203 / 59.21 ± 12.26 (cystatin C ≤ 0.95 mg/L) 72.49 ± 10.69 (cystatin C > 0.95 mg/L)	Approximately 6 months / Heart failure, no-fatal infarction, cardiovascular death	Immunonephelometry	No	Patients with cystatin C > 0.95 mg/L had a higher frequency of GFR < 60 and a lower frequency of GFR > 90 in comparison with patients with cystatin C levels ≤ 0,95 mg/L p = 0,001
Windhausen et al., 2009[5]	NSTEMI	Chest pain with increasing intensity or at rest, increased levels of cardiac troponin, and one of these criteria: signs of ischemia in ECG; CAD	1128 / 57 ± 10 (1st tertile) 62 ± 10 (2nd tertile) 67 ± 9 (3rd tertile)	3 years (infarction) and 4 years (death) / All-cause mortality, non-fatal infarction	Immunonephelometry	No	GFR = 102 (87-118) (1st tertile) GFR = 87 (75-103) (2nd tertile) GFR = 68 (56-82) (3rd tertile) p < 0,001

CK-MB: Creatine kinase isoenzyme MB; CAD: Coronary artery disease; ECG: Electrocardiogram; AMI: acute myocardial infarction; CHF: congestive heart failure; NI: not informed; NSTEMI: non-ST segment elevation myocardial infarction, PCI: percutaneous coronary intervention; STEMI: ST segment elevation myocardial infarction; GFR: glomerular filtration rate.

Discussion

The current study aimed to assess the association between increased levels of cystatin C and the development of cardiovascular events and mortality in patients with ACS by a systematic review and meta-analysis. All studies included in the systematic review found a significant association between increased cystatin C levels and the outcome measures by odds ratio or relative risk, which was confirmed in the meta-analysis. Some studies also compared the proportion of patients with increased cystatin C levels who developed or not outcomes, and only one study showed no statistically significant difference. Therefore, results of the studies included in this systematic review and meta-analysis indicate a significant association between increased cystatin C levels and the development of cardiovascular events and mortality in ACS patients.

The mechanism responsible for this association has not been fully elucidated. However, a possible mechanism is based on the fact that cystatin C is a more sensitive marker for kidney dysfunction, capable to detect small reductions in GFR,[4] and a pre-clinical status of kidney dysfunction, which cannot be detected by serum creatinine or creatinine-based GFR.[29] Some studies have shown that the presence of mild-to-moderate kidney failure is an important risk factor for the development of cardiovascular events and mortality.[30-32] Thus, patients with increased cystatin C levels could have a mild kidney dysfunction, which could contribute to increased risk of cardiovascular events and worse prognosis.

Another possible mechanism is related to inflammation associated with the atherogenic process, since some studies have suggested that increased cystatin C levels are associated with inflammation and atherosclerosis.[32] Inflammatory cytokines and atherosclerosis stimulate the production of lysosomal cathepsins,[32] such as cathepsin S that seems to contribute to disruption of atherosclerotic plaque.[33] Since cystatin C is a cathepsin inhibitor,[32] increased cystatin C levels may be associated with inhibition of these cathepsins involved in atherosclerotic plaque disruption, contributing to the development of cardiovascular events.

Although all studies included in this review had good or excellent methodological quality, evaluated by the NOS,[13] they also showed some limitations. Only two studies (11.8%) included exclusively patients with normal kidney function. Nevertheless, most studies (88.2%, n = 15) performed a multivariate analysis, and more than half (58.8%, n = 10) included GFR or serum creatinine, which gives greater credibility to results. After adjustment for these and other risk factors, a

Table 2 - Classification of patients, variables included in the multivariate analysis and results of the selected studies

Author/ Year	Classification of patients according to cystatin C levels	Variables included in the multivariate analysis	Results
Studies included in the systematic review and meta-analysis			
Tonkin et al., 2015[15]	1st quartile (< 0.72 mg/L) 2nd quartile (0.72-0.81 mg/L) 3rd quartile (0.81-0.93 mg/L) 4th quartile (> 0.93 mg/L)	Age; sex; DM; current smoking; total cholesterol; triglycerides; fasting glycemia; acute coronary syndrome; hospitalization for unstable angina; History of coronary revascularization; systolic arterial pressure, history of hypertension; atrial fibrillation; GFR; BMI; level of dyspnea; level of angina; white blood cell count; peripheral arterial disease; use of aspirin; history of stroke.	Risk of cardiovascular events or death Univariate analysis: 2nd quartile x 1st quartile: OR = 1.30 (1.07-1.59) 3rd quartile x 1st quartile: OR = 1.33 (1.08-1.63) 4th quartile x 1st quartile: OR = 1.75 (1.41-2.18). p < 0.001 Multivariate analysis: 2nd quartile x 1st quartile: OR = 1.27 (1.05-1.54) 3rd quartile x 1st quartile: OR = 1.31 (1.08-1.58) 4th quartile x 1st quartile: OR = 1.64 (1.36-1.99). p < 0.001
Akerblom et al., 2012[16]	1st quartile (< 0.68 mg/L) 2nd quartile (0.68-0.83 mg/L) 3rd quartile (0.83-1.01 mg/L) 4th quartile (≥1.01 mg/L)	Age; female sex; weight; smoking; hypertension; DM; MI; CHF; non-hemorrhagic stroke; peripheral artery disease; CKD; acute coronary syndrome without ST segment elevation; acute coronary syndrome with ST segment elevation; use of aspirin; use of glycoprotein IIb/IIIa inhibitors; use of beta-blockers, use of ACE inhibitor, angiotensin receptor blockers, or both; use of statin; use of proton-pump inhibitors; coronary angiography; primary PCI for acute coronary syndrome with ST segment elevation; other PCIs before index event; myocardial revascularization; serum creatinine	Risk of cardiovascular events or cardiovascular death: Multivariate analysis of STEMI patients: 2nd quartile x 1st quartile: OR = 1.10 (0.86-1.42) 3rd quartile x 1st quartile: OR = 1.23 (0.96-1.58) 4th quartile x 1st quartile: OR = 1.81 (1.43-2.29) Multivariate analysis of NSTEMI patients: 2nd quartile x 1st quartile: OR = 0.94 (0.74-1.18) 3rd quartile x 1st quartile: OR = 1.19 (0.96-1.47) 4th quartile x 1st quartile: OR = 1.55(1.26-1.90)
Studies included in the systematic review			
Tang et al., 2015[17]	Cystatin C < median (< 1.36 mg/L) Cystatin C ≥ median (≥ 1.36 mg/L)	Angiography without reflux; ST segment resolution < 30%; IMR > 33.7 U after PCI; serum cystatin C ≥ median; peak CK-MB; baseline LVEF; left ventricular remodeling.	Proportion of patients who developed cardiovascular events or cardiovascular death: 18.5% (cystatin C ≥ median) x 13.0% (cystatin C < median). p = 0.43 Proportion of patients who developed CHF: 18.5% (cystatin C ≥ median) x 5.6% (cystatin C < median). p = 0.022 Risk for CHF: Univariate analysis: cystatin C ≥ median x cystatin C < median: OR = 4.54 (3.51 – 7.82). p < 0.001 Multivariate analysis: cystatin C ≥ median x cystatin C < median: OR = 3.85 (2.82 – 5.96). p = 0.005

Fu et al., 2013[18]	1st quartile (< 1.23 mg/L) 2nd quartile (1.23-1.43 mg/L) 3rd quartile (1.44-1.82 mg/L) 4th quartile (1.83-5.12 mg/L)	NA	Risk of all-cause mortality: Univariate analysis: 2nd quartile x 1st quartile: OR = 1.31 (1.23-1.43) 3rd quartile x 1st quartile: OR = 1.59 (1.44-1.82) 4th quartile x 1st quartile: OR = 2.23 (1.83-5.12) p = 0.0001
Akgul et al., 2013[19]	1st and 2nd tertile (≤ 1.12 mg/L) 3rd tertile (> 1.12 mg/L)	Age; female sex; DM; hypertension; current smoking; Killip class > 1; anemia at admission; KF; lesion in three cardiac vessels; unsuccessful PCI; LVEF < 40%; use of tirofiban; serum creatinine > 1.5 mg/dL.	Proportion of patients who developed cardiovascular events: 21.4% (3rd tertile) x 8.5% (1st and 2nd tertile). p < 0.001 Risk of cardiovascular death: Univariate analysis: 3rd tertile x 1st and 2nd tertiles: OR = 5.9 (2.6-13.3). p < 0.001 Multivariate analysis: 3rd tertile x 1st and 2nd tertiles: OR = 4.66 (1.3-16.6). p = 0.017
Widera et al., 2013[20]	Without classification	NA	Risk of cardiovascular event or all-cause mortality: Univariate analysis: Log (cystatin C): OR = 1.9 (1.6-2.3)
Manzano -Fernández et al., 2012[21]	1st quartile (< 0.79 mg/L) 2nd quartile (0.79-0.91 mg/L) 3rd quartile (0.92-1.13 mg/L) 4th quartile (1.14-2.55 mg/L)	BTP; serum cystatin C; serum creatinine; GFR; hemoglobin, anterior acute coronary syndrome without ST-segment elevation; GRACE risk score.	Risk of all-cause mortality Univariate analysis: 2nd quartile x 1st quartile: OR = 1.89 (0.35-10.3) 3rd quartile x 1st quartile: OR = 2.41 (0.47-12.4) 4th quartile x 1st quartile: OR = 7.87 (1.78-34.9) p = 0.004 Multivariate analysis: 2nd quartile x 1st quartile: OR = 1.85 (0.34-10.1) 3rd quartile x 1st quartile: OR = 1.98 (0.38-10.4) 4th quartile x 1st quartile: OR = 6.32 (1.40-28.6) p = 0.014
Ristiniemi et al., 2012[22]	1st tertile (< 0.96 mg/L) 2nd tertile (0.96-1.21mg/L) 3rd tertile (> 1.21 mg/L)	Age > 65 years; BMI (median > 27,1 kg/m²); sex; CHF; hypertension; previous MI; current smoking; DM; family history of CVD	All-cause mortality rate: 18% (3rd tertile) x 10% (2nd tertile) x 4% (1st tertile). p < 0.012 Proportion of cardiovascular events: 35% (3rd tertile) x 20% (2nd tertile) x 12% (1st tertile). p < 0.0012 (3rd tertile x 1st tertile) Risk of all-cause mortality: Univariate analysis: 3rd tertile x 1st tertile: OR = 2.19 (1.27-3.77). p = 0.0046 Multivariate analysis 3rd tertile x 1st tertile: OR = 2.19 (1.28-3.78). p = 0.0046 Risk of cardiovascular events: Univariate analysis: 3rd tertile x 1st tertile: OR= 1.86 (1.31-2.65). p = 0.0005 Multivariate analysis 3rd tertile x 1st tertile OR = 1.75 (1.22-2.51). p = 0.0024

Cont. Table 2 - Classification of patients, variables included in the multivariate analysis and results of the selected studies

Author/ Year	Classification of patients according to cystatin C levels	Variables included in the multivariate analysis	Results
Silva et al., 2012[23]	1st, 2nd and 3rd quartiles (< 0.84 mg/L) 4th quartile (≥ 0.84 mg/L)	Serum cystatin C ≥ 0,84 mg/L; creatinine ≥ 1,10 mg/dL; GFR ≤ 71,1 mL/min/1,73 m²; urea ≥ 52,25 mg/dL; uric acid ≥ 6,3 mg/dL; NT-proBNP ≥ 688,5 pg/mL; EF ≤ 40%.	Risk of all-cause mortality: Univariate analysis 4th quartile x 1st quartile: OR = 8.5 (1.71-42.15). p= 0.009 Risk of all-cause mortality or reinfarction: Univariate analysis: 4th quartile x 1st quartile: OR = 3.40 (1.23-9.39). p = 0.018 Multivariate analysis 4th quartile x 1st quartile: OR = 3.89 (1.23-12.31). p = 0.021
Sun et al., 2012[24]	1st quartile (< 1.02 mg/L) 2nd quartile (1.02-1.16 mg/L) 3rd quartile (1.17-1.34 mg/L) 4th quartile (≥1.35 mg/L)	Age; sex; DM; hypertension; serum creatinine; GFR; LVEF; serum troponin; number of arteries affected; implanted stents	Proportion of patient who developed cardiovascular events or all-cause mortality: 29.68% (4th quartile); 15.29% (3rd quartile); 9.10% (2nd quartile); 4.67% (1st quartile). p < 0.001 Risk of cardiovascular events or all-cause mortality: Multivariate analysis: 3rd quartile x 1st quartile: OR = 3.930 (1.306-11.829). p = 0.015 4th quartile x 1st quartile: OR = 6.380 (2.171-18.751). p = 0.001
Kaski et al., 2010[25]	Without classification	CHF; previous CVD; TIMI risk score	Risk of cardiovascular events or all-cause mortality: Multivariate analysis: OR = 2.15 (0.93-4.92)
Taglieri et al., 2010[6]	1st quartile (< 0.81 mg/L) 2nd quartile (0.81-0.92 mg/L) 3rd quartile (0.93-1.10 mg/L) 4th quartile (≥1.11 mg/L)	Age; sex; heart rate; BMI; hypertension; hypercholesterolemia; statin therapy; HDL cholesterol; hemoglobin; DM; smoking; myocardial revascularization; previous stroke ; TIMI risk score; troponin levels; CHD during hospitalization; RCP; PCI; administration of clopidogrel; creatinine levels at admission; GFR; serum cystatin C.	Proportion of patient who developed cardiovascular events or all-cause mortality 50% (4th quartile); 44% (3rd quartile); 37% (2nd quartile); 26 % (1st quartile). p < 0.044 Risk of cardiovascular events: Univariate analysis: 3rd quartile x 1st quartile: OR = 1.73 (1.08-2.81). p = 0.027 4th quartile x 1st quartile: OR = 1.88 (1.17-3.02). p = 0.009 Multivariate analysis: 3rd and 4th quartiles x 1st quartile: OR = 1.66 (1.07-2.57). p = 0.025
Derzhko et al., 2009[26]	Without classification	Age; sex; BMI; concomitant DM and hypertension; LDL cholesterol; HDL cholesterol; multivessel disease; left anterior descending artery infarction; mitral insufficiency; time of reperfusion; use of ACE inhibitor, use of ß-blocker and statin, baseline levels of the biomarkers CRP, cystatin C, NT-proBNP and troponin	Risk of cardiovascular events or all-cause mortality: Multivariate analysis: OR = 2.98 (1.21-7.40). p= 0.008

Ichimoto et al., 2009[7]	Cystatin C ≥ 0.96 mg/L Cystatin C < 0.96 mg/L	Killip class ≥ 2; time elapsed from hospital admission to angioplasty; cystatin C ≥ 0,96 mg/L; previous MI; increased creatinine; age.	Risk of cardiovascular events or all-cause mortality: Multivariate analysis: Cystatin C ≥ 0.96 mg/L: OR = 2.17 (1.07-6.98). p = 0.04
Kilic et al., 2009[27]	Patients with cystatin C > 1,051 ng/mL who developed fatal or non-fatal cardiovascular events Patients with cystatin C > 1,051 ng/mL who did not develop fatal or non-fatal cardiovascular events	Female sex; previous hypertension; previous DM; smoking; previous use of ACE inhibitor; previous use of diuretics; EF; creatinine clearance; fasting glycemia; log cystatin C; log BNP	Proportion of patients cystatin C > 1051 ng/mL who developed or not fatal and non-fatal cardiovascular events: 67% x 30% (developed cardiovascular events X did not develop cardiovascular events). p < 0.001 Risk of fatal and non-fatal cardiovascular events Univariate analysis: Log (Cystatin C): RR = 9.25 (3.94-21.6). p = < 0.001 Multivariate analysis: Log (Cystatin C): RR = 9.43 (4-21.8). p = < 0.001
García Acuña et al., 2009[28]	Cystatin C > 0.95 mg/L Cystatin C ≤ 0.95 mg/L	Age; EF; serum cystatin C; hs-CRP; TFG.	Risk of cardiovascular events or cardiovascular death: Multivariate analysis: RR = 1,91 (1,03-3,53), p = 0,03
Windhausen et al., 2009[5]	1st tertile (< 0.86 mg/L) 2nd tertile (0.86-1.01 mg/L) 3rd tertile (> 1.01 mg/L)	Age > 65 years; sex; hypertension; DM; smoking; hypercholesterolemia; history of CAD; history of MI; PCI or myocardial revascularization; use of aspirin; use of beta-blockers; use or ACE inhibitors before randomization; NT-proBNP ≥ 1170 ng/L in men and ≥ 2150 ng/L in women; CRP ≥ 10 mg/L; cardiac troponin ≥ 0,3 μg/L; ST segment deviation ≥ 0,1 mV in ECG ad admission.	Risk of mortality death: Univariate analysis: 2nd tertile x 1st tertile: OR = 1.81 (0.89-3.67) 3rd tertile x 1st tertile: OR = 4.07 (2.16-7.66). p < 0.001 Multivariate analysis: 2nd tertile x 1st tertile: OR = 1.41 (0.68-2.94) 3rd tertile x 1st tertile: OR = 2.04 (1.02-4.10). p = 0.004 Risk of cardiovascular event: Univariate analysis: 2nd tertile x 1st tertile: OR = 1.26 (0.67-2.35) 3rd tertile x 1st tertile: OR = 2.06 (1.17-3.63). p = 0.01 Multivariate analysis: 2nd tertile x 1st tertile: OR = 1.32 (0.70-2.50) 3rd tertile x 1st tertiile: OR = 1.95 (1.05-3.63). p = 0.04

BNP: B-type natriuretic peptide; CK-MB: Creatine kinase isoenzyme MB; CAD: Coronary artery disease; CVD: cardiovascular disease; DM: Diabetes mellitus; CKD: Chronic kidney disease; ECG: Electrocardiography; EF: ejection fraction; LVEF: left ventricular ejection fraction; HDL: high-density lipoprotein; CHF: congestive heart failure; PCI: percutaneous coronary intervention; ACE: angiotensin-converting-enzyme; MI: myocardial infarction; BMI: body mass index; IMR: Index of microcirculatory resistance; KF: kidney failure; LDL: low density lipoprotein; NA: not applicable; NT-proBNP: N-terminal pro–B-type natriuretic peptide; BTP: beta-trace protein; CRP: C reactive protein; GFR: glomerular filtration rate; hs-CRP: high-sensitivity C reactive protein. CKD: chronic kidney disease.

significant association was found between increased cystatin C levels and the development of cardiovascular events and mortality, suggesting that such association is independent of patients' kidney function. However, 7 studies did not include GFR or serum creatinine in the multivariate analysis or did not perform this analysis. Iin this case, a poor patient prognosis may result from kidney dysfunction rather from increased cystatin C levels, since several studies have demonstrated that kidney dysfunction is associated with cardiovascular events and mortality.

Only studies that performed multivariate analysis including GFR or serum creatinine were included in this meta-analysis. We found that the association between

Table 3 - Assessment of the studies' quality according to the Newcastle-Ottawa Scale

Author/Year	Selection			Comparability	Outcomes			Total points
	1	2	3	4	5	6	7	8	
Tonkin et al., 2015[15]	*	*	*	-	**	*	*	*	8
Akerblom et al., 2012[16]	*	*	*	-	**	*	*	*	8
Tang et al., 2015[17]	*	*	*	-	*	*	*	*	7
Fu et al., 2013[18]	*	*	-	-	-	*	*	*	5
Akgul et al., 2013[19]	*	*	*	-	**	*	-	*	7
Widera et al.,2013[20]	*	-	*	-	-	*	*	*	5
Manzano-Fernández et al., 2012[21]	*	*	*	-	**	*	*	*	8
Ristiniemi et al., 2012[22]	*	*	*	-	*	*	*	*	7
Silva et al., 2012[23]	*	*	*	-	**	*	*	*	8
Sun et al., 2012[24]	*	*	*	-	**	*	*	*	8
Kaski et al., 2010[25]	*	-	*	-	*	*	*	*	6
Taglieri et al., 2010[6]	*	*	*	-	**	*	*	*	8
Derzhko et al., 2009[26]	*	-	*	-	*	*	*	*	6
Ichimoto et al., 2009[7]	*	*	*	-	**	*	*	*	8
Kilic et al., 2009[27]	*	*	*	-	**	*	*	*	8
García Acuña et al., 2009[28]	*	*	*	-	**	*	*	*	8
Windhausen et al., 2009[5]	*	*	*	-	*	*	*	*	7

1- Representativeness of the exposed cohort: all studies were awarded one star, since the exposed cohort was somewhat representative of the average; 2 - Selection of the non-exposed cohort: in the studies that were awarded one star, the non-exposed cohort was drawn from the same community as the exposed cohort; in the studies that did not receive any star, no comparison was performed between patients exposed to high cystatin C levels and those who were not exposed; 3 - Ascertainment of exposure: studies that performed the measurement of cystatin C levels and informed which method was used were awarded one star, whereas no star was assigned if the study performed the measurements but did not inform the method used. 4- Demonstration that outcome of interest was not present at start of study: no study received a star, since patients had one of the outcome measures (acute coronary syndrome) in the beginning of the study; 5 - Comparability of cohorts on the basis of the design or analysis: studies that performed multivariate analysis, which included GFR or serum creatinine, among other variables, were awarded two stars; studies that performed multivariate analysis, which included variables other than GFR or serum creatinine, were awarded one star, whereas no star was awarded to studies that did not perform a multivariate analysis. 6 - Assessment of outcome; all studies were awarded one star, since assessment of outcome was performed independently, by the physicians. 7-Period of follow-up (long enough for outcomes to occur): studies in which patients were followed for at least 6 months were awarded one star, and studies in which patients were followed for less than 6 months received no star. 8 - Adequacy of follow up of cohorts: studies in which at least 90 of patients were followed until the end of the study or those with no description of significant losses were awarded one star.

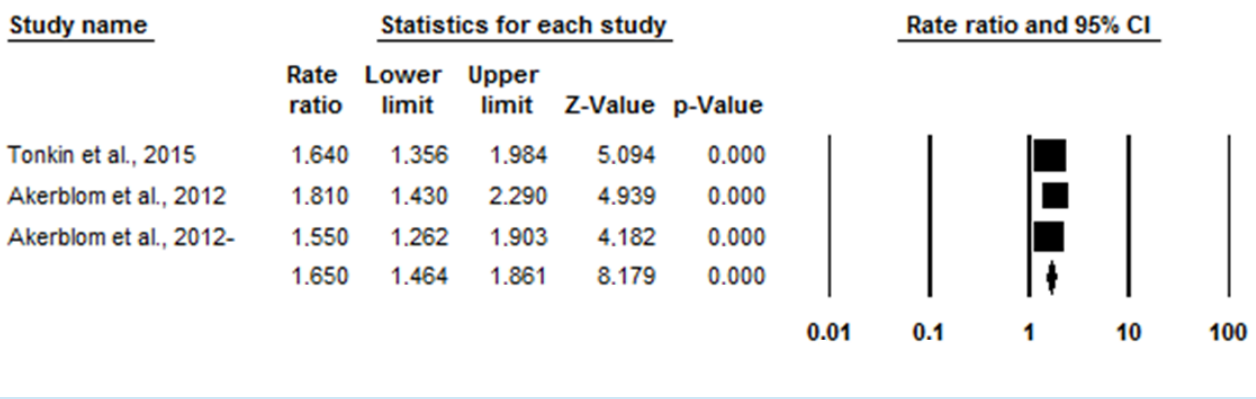

Figure 2 - Meta-analysis of the studies investigating the association between increased cystatin C levels and the development of cardiovascular death or non-fatal infarction by the comparison of the fourth and the first quartiles of cystatin C.

increased cystatin C levels and the risk for cardiovascular death or non-fatal myocardial infarction is independent of patient's kidney function.

Analysis of the studies that classified patients according to cystatin C tertiles or quartiles showed that patients with higher cystatin C levels were also older, which results from a progressive, physiological decrease in GFR associated with aging.[34] However, 58.8% (n = 10) of the studies included age in the multivariate analysis, including the two studies included in the meta-analysis, indicating that the association between increased cystatin C levels and worse cardiovascular prognosis is independent of age.

All studies assessed patients' kidney function, and most of them (82.4%, n = 14) (including the two studies included in the meta-analysis) used GFR, which is a better marker of kidney function than serum creatinine.[35] Serum creatinine levels may be affected by several factors like muscle mass, age, sex, and hence, it is not specific for assessment of kidney function.[32] Besides, increases in serum creatinine occur only when there is a decrease greater than 50% in glomerular ultrafiltration, and thereby is not considered a sensitive marker for assessment of kidney function.[36] Determination of GFR by calculation of creatinine clearance or equations based in serum creatinine levels may mitigate or eliminate these limitations.[36] The most common equations used to estimate GFR are the Cockcroft & Gault, MDRD and CKD-EPI equations, which include clinical and demographic variables in place of physiological factors known to affect creatinine serum concentrations.[37]

Classification of patients according to cystatin C levels was heterogeneous in the studies. A considerable number of these studies (58.8%) classified patients in quartiles or tertiles, which may have influenced the results. It is easier to obtain a correlation of increased cystatin C levels with poor prognosis when patients in the fourth quartile or third tertile (who have higher levels of cystatin C) are compared with patients in the first quartile or first tertile (whose cystatin C levels are decreased) than in comparison between patients with cystatin C levels above and below reference/median values. Nevertheless, classification of cystatin C levels in quartiles and tertiles is of greater clinical value, since it may be used in the determination of cutoff points above which the risk of cardiovascular events and mortality is significantly greater. Therefore, only studies in which patients were classified by cystatin C quartiles, and higher quartiles were compared with lower quartiles were included in the meta-analysis.

Immunonephelometry and immunoturbidimetry are the most used methods of cystatin C determination,[38] which has been confirmed in this systematic review, since 84.2% (n = 14) of the studies used these methods for cystatin C measurement, and only 3 studies used other methods or did not mention the method used. Immunonephelometry and immunoturbidimetry are the methods of choice for determination of cystatin C levels in body fluids due to their high accuracy, convenience, automation, in addition to being simple and fast for daily routine.[38] Besides, immunonephelometry has been suggested as a better method than immunoturbidimetry

for its high sensitivity in detecting smaller immune aggregates, and monitoring an increase in light intensity against a low background signal, which gives the method a theoretical edge.[38] Although a lack of standardization of the methods may affect the results reported in different studies, the fact that most studies used immunonephelometry and immunoturbidimetry may indicate high reliability of the results. In addition, all studies included in the meta-analysis used these methods for cystatin C measurement.

The predominant type of ACS was NSTEMI followed by STEMI and unstable angina. STEMI involves a total coronary obstruction and hence a more critical cardiovascular event than NSTEMI and unstable angina.[39] A well-established diagnosis of AMI should take into consideration all recommended criteria, that consist in increased levels of myocardial necrosis markers (preferably troponin or CK-MB mass) combined with at least one of the following parameters: symptoms suggestive of ischemia (chest pain), pathological Q-wave in ECG, significant changes in ST segment or T-wave inversion, new left bundle branch block, loss of viable myocardium, changes in segmental ventricular contractility in imaging tests, and intracoronary thrombus in angiography. Unstable angina is diagnosed by the same criteria, except for myocardial necrosis markers, which are not increased.[14] Some studies (23.5%) did not report the criteria used (i.e., it was not possible to determine whether these criteria were used or not), and 7 studies (41.2%) did not use these criteria, which may yield an incorrect diagnosis of ACS, and variations in the groups of patients included in these studies.

A study performed in 2009 demonstrated that STEMI is associated with increased short-term mortality risk, whereas NSTEMI is associated with increased long-term mortality risk.[40] All studies evaluated mortality, either alone or in combination with cardiovascular events, requiring a longer period of follow-up. Among the studies included in this systematic review, only one (5.9%) had a follow-up period shorter than six months; however, despite that, a significant association between increased levels of cystatin C and cardiovascular events or mortality was reported. Both studies included in the meta-analysis had a follow-up period longer than 12 months.

Four studies (23.5%) had a sample size greater than 1,000, which may increase their statistical power. Although 5 studies (29.4%) had a sample size smaller than 200, these studies also reported a significant association of cystatin C and the outcomes. The only study that did not find any significant difference between the frequencies of patients who developed cardiovascular events or cardiovascular death and of those who did not develop these outcomes, found a significant association between the proportion of patients with and without congestive heart failure. Sample size of this study was smaller than 200; patients were followed for 6 months and classified by median cystatin C, which may have contributed for the results of cardiovascular events and cardiovascular mortality.

Although this systematic review and meta-analysis has demonstrated a significant association between increased cystatin C levels and a worse prognosis of ACS, some limitations should be considered. First, the search was restricted to Medline via PubMed, Web of Science and Scielo databases; second, only articles published in English, Portuguese and Spanish were included in this study; finally the small number of articles included in the meta-analysis due to high variability of analyses between the studies.

Conclusion

Despite the limitations of the studies included in this systematic review, they demonstrated, using a prospective design, a significant association between increased cystatin C and the development of cardiovascular events and mortality in patients with ACSs. Such association was confirmed by the meta-analysis, and shown to be independent of renal function evaluated by serum creatinine or GFR. Therefore, cystatin C is a useful marker in the prognosis assessment of ACSs and can be used in combination with currently available markers.

Author contributions

Conception and design of the research: Martucheli KFC, Domingueti CP. Acquisition of data: Martucheli KFC, Domingueti CP. Analysis and interpretation of the data: Martucheli KFC, Domingueti CP. Statistical analysis: Martucheli KFC, Domingueti CP. Writing of the manuscript: Martucheli KFC. Critical revision of the manuscript for intellectual content: Domingueti CP. Supervision / as the major investigador: Domingueti CP.

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Ethics approval and consent to participate

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

References

1. Filler G, Bökenkamp A, Hofmann W, Le Bricon T, Martínez-Brú C, Grubb Al. Cystatin C as a marker of GFR – history, indications, and future research. Clin Biochem. 2005 Jan;38(1):1-8. doi: 10.1016/j.clinbiochem.2004.09.025.
2. Laterza OF, Price CP, Scott MG. Cystatin C: an improved estimator of glomerular filtration rate? Clin Chem. 2002;48(5):699-707. PMID: 11978596.
3. Dharnidharka VR, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. Am J Kidney Dis. 2002;40(2):221-6. doi: 10.1053/ajkd.2002.34487.
4. Coll E, Botey A, Alvarez L, Poch E, Quinto L, Saurina A, et al. Serum cystatin C as a new marker for noninvasive estimation of glomerular filtration rate and as a marker for early renal impairment. Am J Kidney Dis. 2000;36(1):29-34. doi: 10.1053/ajkd.2000.8237.
5. Windhausen F, Hirsch A, Fischer J, van der Zee PM, Sanders GT, van Straalen JP, et al; Invasive versus Conservative Treatment in Unstable Coronary Syndromes (ICTUS) Investigators. Cystatin C for enhancement of risk stratification in non-ST elevation acute coronary syndrome patients with an increased troponin T. Clin Chem. 2009;55(6):1118-25. doi: 10.1373/clinchem.2008.119669.
6. Taglieri N, Fernandez-Berges DJ, Koenig W, Consuegra-Sanchez L, Fernandez JM, Robles NR, et al; SIESTA Investigators. Plasma cystatin C for prediction of 1-year cardiac events in Mediterranean patients with non-ST elevation acute coronary syndrome. Atherosclerosis. 2010;209(1):300-5. doi: 10.1016/j.atherosclerosis.2009.09.022.
7. Ichimoto E, Jo K, Kobayashi Y, Inoue T, Nakamura Y, Kuroda N, et al. Prognostic significance of cystatin C in patients with ST-Elevation myocardial infarction. Circ J. 2009;73(9):1669-73. doi: https://doi.org/10.1253/circj.CJ-08-0943
8. Ferraro S, Marano G, Biganzoli EM, Boracchi P, Bongo AS. Prognostic value of cystatin C in acute coronary syndromes: enhancer of atherosclerosis and promising therapeutic target. Clin Chem Lab Med. 2011;49(9):1397-404. doi: 10.1515/CCLM.2011.607.
9. Bi M, Huang Z, Li P, Cheng C, Huang Y, Chen W. The association between elevated cystatin C levels with myocardial infarction: a meta-analysis. Int J Clin Exp Med. 2015;8(11):20540-7. PMID: 26884971.
10. Lee M, Saver JL, Huang WH, Chow J, Chang KH, Ovbiagele B. Impact of elevated cystatin C level on cardiovascular disease risk in predominantly high cardiovascular risk populations: a meta-analysis. Circ Cardiovasc Qual Outcomes. 2010;3(6):675-83. doi: 10.1161/CIRCOUTCOMES.110.957696.
11. Li R, Hao P, Chen Y, Zhang Y. Association of cystatin C level and cardiovascular prognosis for patients with preexisting coronary heart disease: a meta-analysis. Chin Sci Bull. 2014;59(5-6):539-45.
12. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group preferred reporting items for systematic reviews and meta- analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097. doi: 10.1371/journal.pmed.1000097.
13. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis [Internet]. Ottawa Hospital Research Institute. Canada: University of Ottawa, Department of Epidemiology and Commuunity Medicine. 2017 [Access in 2017 21 Feb]. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
14. Nicolau JC, Timerman A, Marin-Neto JA, Piegas LS, Barbosa CJ, Franci A, et al; Sociedade Brasileira de Cardiologia. [Guidelines of Sociedade Brasileira de Cardiologia for unstable angina and non-ST-segment elevation myocardial infarction (II edition, 2007) 2013-2014 update]. Arq Bras Cardiol. 2014;102(3 Suppl 1):1-61. doi: http://dx.doi.org/10.5935/abc.2014S001.
15. Tonkin AM, Blankenberg S, Kirby A, Zeller T, Colquhoun DM, Funke-Kaiser A, et al; LIPID study investigators. Biomarkers in stable coronary heart disease, their modulation and cardiovascular risk: The LIPID biomarker study. Int J Cardiol. 2015 Dec 15;201:499-507. doi: 10.1016/j.ijcard.2015.07.080.
16. Akerblom Å, Wallentin L, Siegbahn A, Becker RC, Budaj A, Buck K, et al. Cystatin C and estimated glomerular filtration rate as predictors for adverse outcome in patients with ST-elevation and non-ST-elevation acute coronary syndromes: results from the Platelet Inhibition and Patient Outcomes study. Clin Chem. 2012;58(1):190-9. doi: 10.1373/clinchem.2011.171520.
17. Tang L, Fang ZF, Zhou SH, Tai S, Ahmed S, Huang F, et al. Association of serum Cystatin C levels with myocardial perfusion and cardiac functional recovery in patients with anterior wall ST elevation myocardial infarction treated with primary coronary intervention. Heart Vessels. 2015.31(9):1456-66. doi: 10.1007/s00380-015-0764-z.
18. Fu Z, Xue H, Guo J, Chen L, Dong W, Gai L, et al. Long-term prognostic impact of Cystatin C on acute coronary syndrome octogenarians with diabetes mellitus. Cardiovasc Diabetol. 2013 Nov 1;12:157. doi: 10.1186/1475-2840-12-157.
19. Akgul O, Uyarel H, Ergelen M, Pusuroglu H, Gul M, Turen S, et al. Predictive value of elevated cystatin C in patients undergoing primary angioplasty for ST-elevation myocardial infarction. J Crit Care. 2013;28(5):882.e13-20. doi: 10.1016/j.jcrc.2013.03.004.
20. Widera C, Pencina MJ, Bobadilla M, Reimann I, Guba-Quint A, Marquardt I, et al. Incremental prognostic value of biomarkers beyond the GRACE (Global Registry of Acute Coronary Events) score and high-sensitivity cardiac troponin T in non-ST-elevation acute coronary syndrome. Clin Chem. 2013;59(10):1497-505. doi: 10.1373/clinchem.2013.206185.
21. Manzano-Fernández S, López-Cuenca Á, Januzzi JL, Parra-Pallares S, Mateo-Martínez A, Sánchez-Martínez M, et al. Usefulness of ß-trace protein and cystatin c for the prediction of mortality in non ST-segment elevation acute coronary syndromes. Am J Cardiol. 2012;110(9):1240-8. doi: 10.1016/j.amjcard.2012.06.027.
22. Ristiniemi N, Lund J, Tertti R, Christensson A, Ilva T, Porela P, et al. Cystatin C as a predictor of all-cause mortality and myocardial infarction in patients with non-ST-elevation acute coronary syndrome. Clin Biochem. 2012;45(7-8):535-40. doi: 10.1016/j.clinbiochem.2012.02.012.
23. Silva D, Cortez-Dias N, Jorge C, Marques JS, Carrilho-Ferreira P, Magalhães A, et al. Cystatin C as prognostic biomarker in ST-segment elevation acute myocardial infarction. Am J Cardiol. 2012;109(10):1431-8. doi: 10.1016/j.amjcard.2012.01.356.

24. Sun TW, Xu QY, Yao HM, Zhang XJ, Wu Q, Zhang JY, et al. The predictive value of plasma Cystatin C for acute coronary syndrome treated with percutaneous coronary intervention. Heart Lung. 2012;41(5):456-62. doi: 10.1016/j.hrtlng.2012.04.007.

25. Kaski JC, Fernández-Bergés DJ, Consuegra-Sánchez L, Fernández JM, García-Moll X, Mostaza JM, et al. A comparative study of biomarkers for risk prediction in acute coronary syndrome—results of the SIESTA (Systemic Inflammation Evaluation in non-ST-elevation Acute coronary syndrome) study. Atherosclerosis. 2010;212(2):636-43. doi: 10.1016/j.atherosclerosis.2010.06.026.

26. Derzhko R, Plaksej R, Przewlocka-Kosmala M, Kosmala W. Prediction of left ventricular dysfunction progression in patients with a first ST-elevation myocardial infarction--contribution of cystatin C assessment. Coron Artery Dis. 2009;20(7):453-61.

27. Kilic T, Oner G, Ural E, Yumuk Z, Sahin T, Bildirici U, et al. Comparison of the long-term prognostic value of cystatin C to other indicators of renal function, markers of inflammation and systolic dysfunction among patients with acute coronary syndrome. Atherosclerosis. 2009;207(2):552-8. doi: 10.1016/j.atherosclerosis.2009.05.015.

28. García Acuña JM, González-Babarro E, Grigorian Shamagian L, Peña-Gil C, Vidal Pérez R, López-Lago AM, et al. Cystatin C provides more information than other renal function parameters for stratifying risk in patients with acute coronary syndrome. Rev Esp Cardiol. 2009;62(5):510-9. doi: 10.1016/S1885-5857(09)71833-X.

29. Shlipak MG, Katz R, Sarnak MJ, Fried LF, Newman AB, Stehman-Breen C, et al. Cystatin C and prognosis for cardiovascular and kidney outcomes in elderly persons without chronic kidney disease. Ann Intern Med. 2006;145(4):237-46. doi: 10.7326/0003-4819-145-4-200608150-00003.

30. Mann JF, Gerstein HC, Pogue J, Bosch J, Yusuf S. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. Ann Intern Med. 2001;134(8):629-36. doi: 10.7326/0003-4819-134-8-200104170-00007.

31. Muntner P, He J, Hamm L, Loria C, Whelton PK. Renal insufficiency and subsequent death resulting from cardiovascular disease in the United States. J Am Soc Nephrol. 2002;13(3):745-53. PMID: 11856780.

32. Taglieri N, Koenig W, Kaski JC. Cystatin C and cardiovascular risk. Clin Chem. 2009;55(11):1932-43. doi: 10.1373/clinchem.2009.128397.

33. Sukhova GK, Shi GP, Simon DI, Chapman HA, Libby P. Expression of the elastolytic cathepsins S and K in human atheroma and regulation of their production in smooth muscle cells. J Clin Invest. 1998;102(3):576-83. doi: 10.1172/JCI181.

34. Finney H, Bates CJ, Price CP. Plasma cystatin C determinations in a healthy elderly population. Arch Gerontol Geriatr. 1999;29(1):75-94. doi: https://doi.org/10.1016/S0167-4943(99)00025-4.

35. Nunes GL. Avaliação da função renal em pacientes hipertensos. Rev Bras Hipertens. 2007;14(3):162-6.

36. Kirsztajn GM. Avaliação do ritmo de filtração glomerular. J Bras Patol Med Lab. 2007;43(4):257-64. doi://http://dx.doi.org/10.1590?S1676-24442007000400007.

37. Bastos MG, Kirsztajn GM. Chronic kidney disease: importance of early diagnosis, immediate referral and structured interdisciplinary approach to improve outcomes in patients not yet on dialysis. J Bras Nefrol. 2011;33(1):93-108. doi: http://dx.doi.org/10.1590/S0101-28002011000100013.

38. Mussap M, Plebani M. Biochemistry and clinical role of human cystatin C. Crit Rev Clin Lab Sci. 2004;41(5-6):467-550. doi: 10.1080/10408360490504934.

39. Libby P. Mechanisms of acute coronary syndromes and their implications for therapy. N Engl J Med. 2013;368(21):2004-13. doi: 10.1056/NEJMra1216063.

40. Chan MY, Sun JL, Newby LK, Shaw LK, Lin M, Peterson ED, et al. Long-term mortality of patients undergoing cardiac catheterization for ST-elevation and non-ST-elevation myocardial infarction. Circulation. 2009;119(24):3110-7. doi: 10.1161/CIRCULATIONAHA.108.799981.

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CASE REPORT

Hemochromatosis: Reversible Cause of Heart Failure

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Introduction

GCW, age 33, presents acute heart failure (HF), amenorrhea and darkening of the skin. Three months after this initial situation, the patient is referred to a large cardiology centre and is submitted to HF screening, and the suspicion of hemochromatosis is promptly raised. This disease affects the heart in only 15% of cases. It has been shown that early recognition and intervention may change the prognosis. This is a diagnosis that should be considered in all cases of HF screening since it is easy to diagnose and its treatment can drastically change the prognosis of the disease.

Hereditary hemochromatosis (HH) is a genetic disease of iron metabolism characterized by increased intestinal absorption and progressive accumulation of it in different organs.[1] HH is the most common autosomal disease in Caucasians, particularly those with Nordic or Celtic ancestors, affecting one in each 220-250 individuals.[2] According to the mutations found, HH can be classified as: Hemochromatosis associated with HFE (classical hemochromatosis) and hemochromatosis not associated with HFE: Hereditary hemochromatosis due to mutation at the receptor 2 of transferrin-TfR2, juvenile hemochromatosis (hemojuvelin mutation - HJV gene and hepcidin mutation - HAMP gene), ferroportin disease and African iron overload. The vast majority (80-85%) of HH cases that have northern European ancestors are associated with HFE, while 10-15% of HH cases are not associated with HFE.[3]

Keywords

Heart Failure; Hemochromatosis / genetics; Iron Metabolism Disorders; Phlebotomy; Indicators of Morbidity and Mortality.

Cardiac involvement, despite being a low-incidence complication (15%), is the main cause of morbidity and mortality, presenting 1-year survival after diagnosis without treatment.[4]

It is a significant and potentially reversible cause of heart failure which mainly involves diastolic dysfunction and increased susceptibility to arrhythmias and terminal HF, and has a varied spectrum of symptoms.

It was demonstrated that early recognition and intervention can alter the course of the disease. Biochemical markers and tissue biopsy have traditionally been used to diagnose and guide the therapy. More recent diagnostic modalities, such as cardiac MRI, are noninvasive and can assess the quantitative loading of cardiac iron. Phlebotomy and chelating drugs are the main current treatments. Other treatments are being investigated.[5]

Case report

A 33-year-old Caucasian female worker from Alto Jequitiba, Minas Gerais, presented amenorrhea for 3 years and darkening of the skin for 1 year. Progressive dyspnea report for 3 months, associated with gastric fullness, ascites, lower limb edema, orthopnea and NYHA III functional class. Referred to the National Institute of Cardiology for follow-up and etiological investigation.

At the examination she had grayish skin changes, she said she could see her skin more tanned in the last year, but she related it to the fact that she used to work under the sun. In addition to regular heart rhythm in 3 times with presence of 4th accessory sound and symmetrical lower limb edema.

As an initial propaedeutic, the following exams were performed: Ferritin 6073 ng/ml (VR: 20-200 ng/ml), Serum iron 342 mcg/dL (VR: 60 A 180 mcg/dL), Transferrin Saturation 101% VR: 20 to 40%).

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With the suspicion of heart disease caused by iron deposition due to the results of laboratory tests and physical examination, complementary tests were performed to close the diagnosis. Magnetic resonance imaging by the T2* method was suggestive of myocardial and hepatic iron deposition (Figure 1). The pre-treatment cardiac MRI showed a time of T2* 13.0 ms (N: > 20 ms) and an estimated MIC (Miocardial Iron Concentration) of 2.0 mg/g (N: < 1.1 mg/g). After treatment the time of T2* was 17.0 ms, with MIC estimated at 1.3 mg/g. This result was confirmed by endomyocardial biopsy.

Research continued with the exclusion of secondary causes of hemochromatosis and the genetic analysis that excluded HH related to the HFE gene. In conjunction with the clinical data the case is suggestive of Juvenile Hemochromatosis.

The established treatment based on weekly phlebotomies in association with the use of oral and parenteral iron chelators, as well as conventional beta-blocker, ACE inhibitor, spironolactone and furosemide therapy. After 6 months of outpatient follow-up, the patient presented improvement of the functional capacity and improvement of the echocardiographic parameters (figure 2).

Discussion

The main diagnostic hypothesis is non-classical hemochromatosis, or not linked to the HFE gene, the juvenile type being the most compatible with the clinical picture presented. Juvenile HH is characterized by early accumulation of iron in the body, with manifestations between the 2nd and 3rd decades of life. The manifestations include hypogonadotrophic hypogonadism, heart disease, cirrhosis, diabetes, arthropathy and skin pigmentation. It is characterized by rapid accumulation of iron in the body, early onset, with manifestations of iron overload between the second and third decades of life (15-20 years of age) and functional impairment of affected organs before 30 years of age. Cardiac manifestations with heart failure and arrhythmias are early and are important causes of death.[6]

Cardiomyopathy due to iron overload, whether caused by hemochromatosis or not, is a disease that should always be considered as soon as begins the diagnosis of patients with heart failure. The patient described above manifested the disease with a classic picture of congestive heart failure and already presented a significant iron deposition burden on the heart. Although the disease was no longer at an early stage, the natural history of the disease was modified and there was regression of iron accumulation as well as improvement of ventricular function.

It is worth mentioning that cardiac MRI using the T2* method was established as a diagnostic method as well as a method for risk stratification in these patients. It can also be used to follow the response to the treatment of the disease.[7]

Iron overload cardiomyopathy is a potentially lethal but treatable disease when diagnosed and treated early in its course. Despite the low incidence of heart disease associated with iron overload in the general population, it is a cardiopathy with potential for treatment and reversal, and its screening tests are easy to perform and inexpensive. Therefore, iron, ferritin and transferrin saturation should be part of the initial propaedeutic routine of patients with dilated cardiomyopathy.

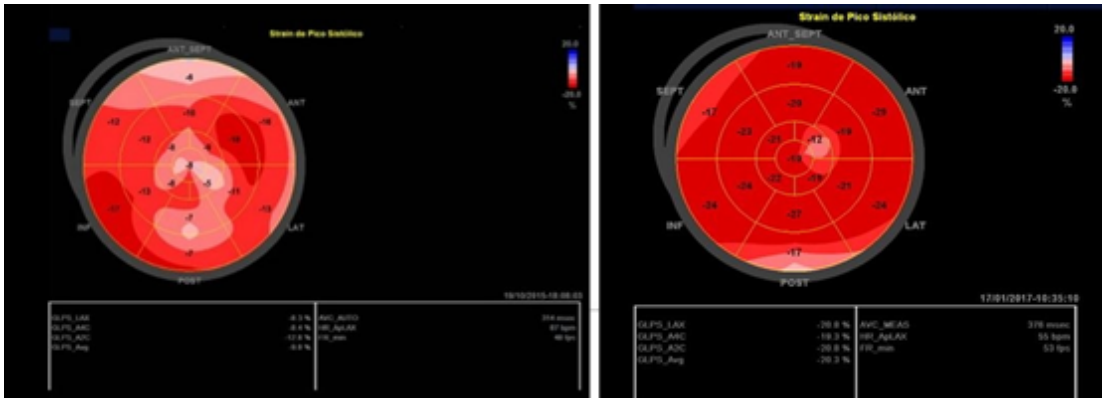

Figure 1 – *Echocardiogram by Strain method: First image shows left ventricular systolic dysfunction demonstrated by the value of -9.8 obtained by the global LV Strain. Second image performed after treatment shows recovery of LV systolic function demonstrated by the Strain value of -20.8.*

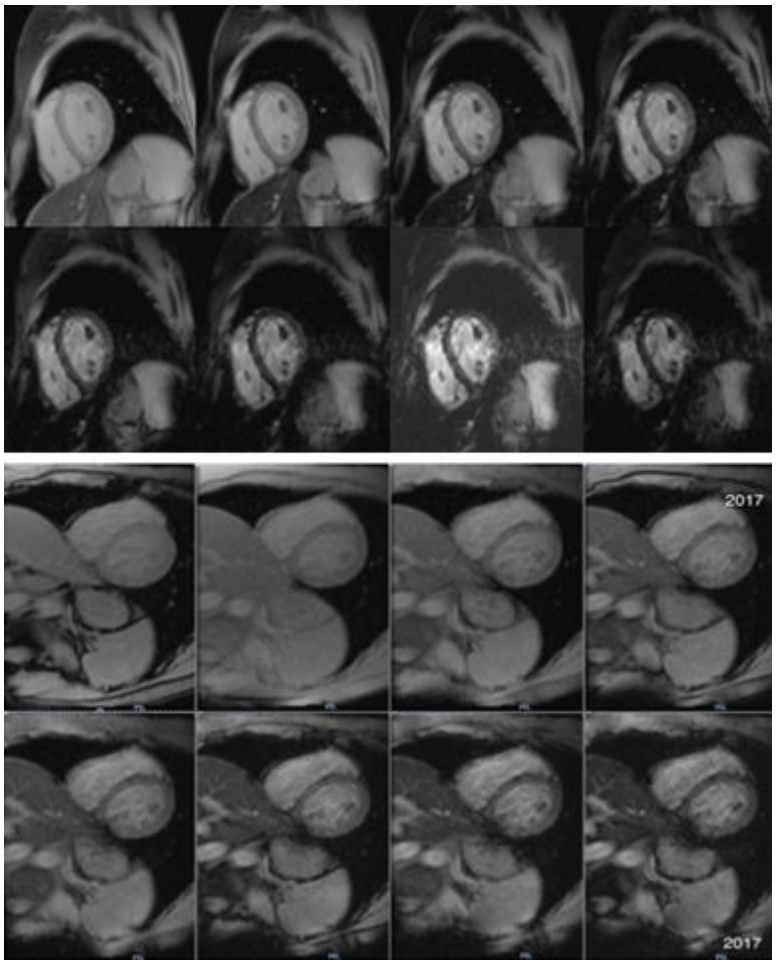

Figure 2 – *Cardiac Magnetic Resonance by T2* method: First image shows iron myocardial deposition feature and the second image shows improvement after treatment.*

Author contributions

Conception and design of the research: Iglesias CPK, Duarte PVF, Miranda JSS. Acquisition of data: Iglesias CPK, Miranda JSS. Analysis and interpretation of the data: Iglesias CPK, Duarte PVF, Miranda JSS, Machado LG, Andrade CRA. Statistical analysis: Iglesias CPK. Obtaining financing: Iglesias CPK. Writing of the manuscript: Iglesias CPK, Duarte PVF, Machado LG, Andrade CRA. Critical revision of the manuscript for intellectual content: Iglesias CPK, Duarte PVF, Miranda JSS, Machado LG, Andrade CRA.

Potential Conflict of Interest

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References

1. Powell LW, George DK, McDonnell SM, Kowdley KV. Diagnosis of hemochromatosis. Ann Intern Med. 1998;129(11):925-31. PMID: 9867744.
2. Merryweather-Clarke AT, Pointon JJ, Sherman JD, Robson KJ. Global prevalence of putative haemochromatosis mutations. J Med Genet. 1997;34(4):275-8. PMID: 9138148.
3. Bacon BR, Adams PC, Kowdley KV, Powell LW, Tavill AS; American Association for the Study of Liver Diseases. Diagnosis and management of hemochromatosis: practice guidelines by the American Association for the Study of Liver Diseases. Hepatology. 2011;54(1):328-43. doi: 10.1002/hep.24330.
4. Gulati V, Harikrishnan P, Palaniswamy C, Aronow WS, Jain D, Frishman WH. Cardiac involvement in hemochromatosis. Cardiol Rev. 2014;22(2):56-68. doi: 10.1097/CRD.0b013e3182a67805.
5. Gujja P, Rosing DR, Tripodi DJ, Shizukuda Y. Iron overload cardiomyopathy, better understanding of an increasing disorder. J Am Coll Cardiol. 2010;56(13):1001-12. doi:10.1016/j.jacc.2010.03.083.
6. Martinelli AL. Hemocromatose hereditária: muito além do HFE. In: Programa de Educação Médica Continuada. São Paulo: Sociedade Brasileira de Hepatologia. s.d. p. 1-8.
7. Kremastinos DT, Farmakis D. Iron overload cardiomyopathy in clinical practice. Circulation. 2011;124(20):2253-63. doi: 10.1161/CIRCULATIONAHA.111.050773.

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CASE REPORT

Hypertrophic Cardiomyopathy, All Phenotypes in one

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Introduction

Hypertrophic cardiomyopathy (HCM) is an intrinsic myocardial disorder characterized by cardiac hypertrophy (wall thickness ≥ 15 mm), that is not explained by conditions of pressure overload (eg, hypertension, severe aortic stenosis).[1] HCM is the most common genetic primary cardiomyopathy, with a prevalence estimated to be about one in 500 adults in the general population.[2]

More than 450 mutations have been identified in the 20 genes that cause different phenotypes. In most cases, HCM is associated with sarcomere protein gene mutations, and exhibits multiple phenotypic expressions. We present a case that combines all phenotypes.[3]

Case Report

A 58-year-old hypertensive woman was admitted to the coronary care unit because of acute heart failure syndrome. The patient denied chest discomfort, illicit drug use or previous disease. The patient noted progressive dyspnea, abdominal swelling, edema of both legs and weight gain. Bilateral edema, ascites, jugular venous distention and (a 3-sound) gallop rhythm were evident on physical examination. The electrocardiogram (ECG) showed sinus rhythm, low QRS amplitude and a pseudoinfarction pattern (Figure 1). The echocardiogram depicted global severe hipokinesis with preservation of lateral wall motion, and increased wall thickness with left chamber enlargement. Moderate pericardial effusion was also present. A continuous infusion of loop diuretics was administered.

Keywords

Cardiomyopathy, Hypertrophic; Heart Failure; Cardiomegaly; Heart Transplantation.

Thyroid hormones, iron tests and free light chain proteins were negative. Coronary angiography showed normal coronary arteries.

Cardiac magnetic resonance revealed maximal wall thickness of 15 mm, left ventricular (LV) mass 262 g and LV mass index 178 g/m², LV diastolic volume 194 mL, LV systolic volume 167 mL and ejection fraction 14%. A marked, diffuse transmural late gadolinium enhancement was also detected (Figure 2. A-F) (Video 1).

With the picture of severe congestive heart failure in addition to an inverse relationship of ECG amplitude with wall thickness, an infiltrative cardiomyopathy was suspected. Right heart catheterization showed high filling pressures and low cardiac output, and endomyocardial biopsy showed diffuse fibrosis without specific changes. As the patient became refractory to optimal medical treatment, she underwent orthotopic heart transplantation. She recovered uneventfully and biopsy of the explanted heart was positive for HCM, showing severe interstitial fibrosis and extensive foci of myocyte disarray affecting the LV (Figure 2.G).

Discussion

HCM is a heterogeneous disease in terms of both genetics and phenotypes. For instance, it has been reported that distribution of hypertrophy in hypertrophic cardiomyopathy by troponin T gene differs no only among families but also within families.[4]

The information available about the genotype - phenotype correlation in HCM is sparse.

Sometimes HCM exhibits a "restrictive phenotype" characterized by restrictive filling and minimal or no left ventricular hypertrophy, which resembles idiopathic restrictive cardiomyopathy.[5]

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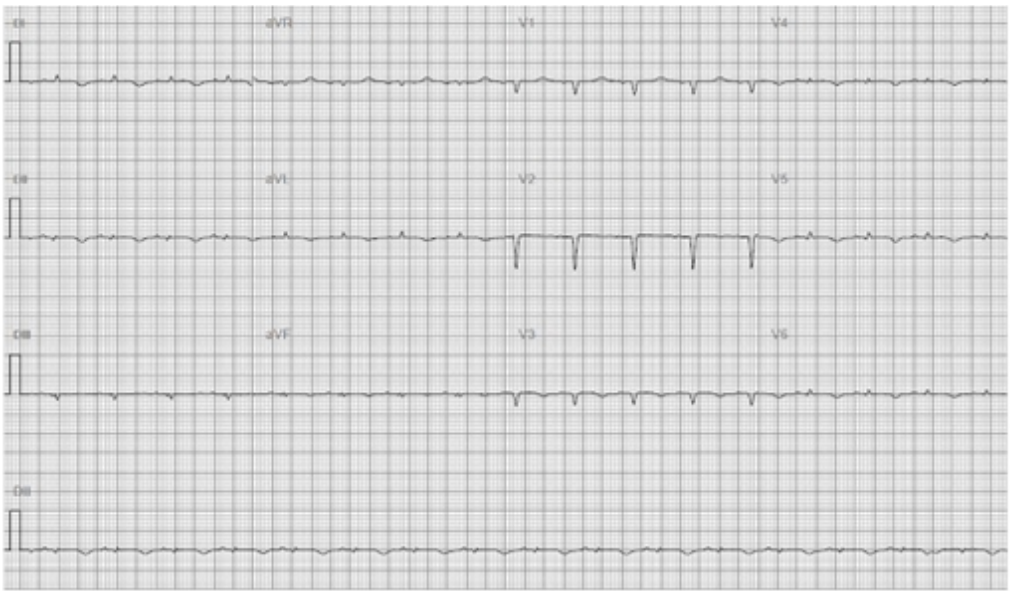

Figure 1 – *The electrocardiogram (ECG) showed sinus rhythm, low QRS amplitude and a pseudoinfarction pattern.*

A smaller number of patients with HCM (5-10%) will progress to an end-stage form of the disease that is characterized by LV dilation, wall thinning and systolic dysfunction.[6] Despite the absence of systemic disease, the relationship between increased wall thickness, low ECG amplitude and severe diastolic dysfunction favors the diagnosis of a restrictive cardiomyopathy. Gadolinium enhancement was also typical for cardiac amyloidosis. In addition, there was no history of familial cardiac disease. Although endomyocardial biopsy even ruled out the diagnosis of cardiac amyloidosis, it also failed to confirm HCM, probably because the right ventricle was less affected.

In this case, we reported increased left ventricular dimensions, depressed systolic function, ventricular hypertrophy and restrictive physiology, which are typical of a dilated, restrictive, hypertrophic phenotype. It is known that multiple genetic mutations can be present in the same person, which might explain the combination of three different features in this case.

There is no similar case report in the literature.

The limitation of this report is that we could not perform genetic testing as it is not currently available at our institution. In addition to the HCM diagnosis provided by biopsy it would have been of great value to know the specific gene mutation in order to puzzle out this "intriguing phenotype".

Author contributions

Conception and design of the research: Arias AM, Arenaza DP, Pizarro R, Marenchino RG, Garagoli F, Rivello HG, Belziti C. Acquisition of data: Arias AM, Arenaza DP, Pizarro R, Marenchino RG, Garagoli F, Rivello HG, Belziti C. Analysis and interpretation of the data: Arias AM, Arenaza DP, Pizarro R, Marenchino RG, Garagoli F, Rivello HG, Belziti C. Statistical analysis: Arias AM, Arenaza DP, Pizarro R, Marenchino RG, Garagoli F, Rivello HG, Belziti C. Writing of the manuscript: Arias AM, Arenaza DP, Pizarro R, Marenchino RG, Garagoli F, Rivello HG, Belziti C. Critical revision of the manuscript for intellectual content: Arias AM, Arenaza DP, Pizarro R, Marenchino RG, Garagoli F, Rivello HG, Belziti C.

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.

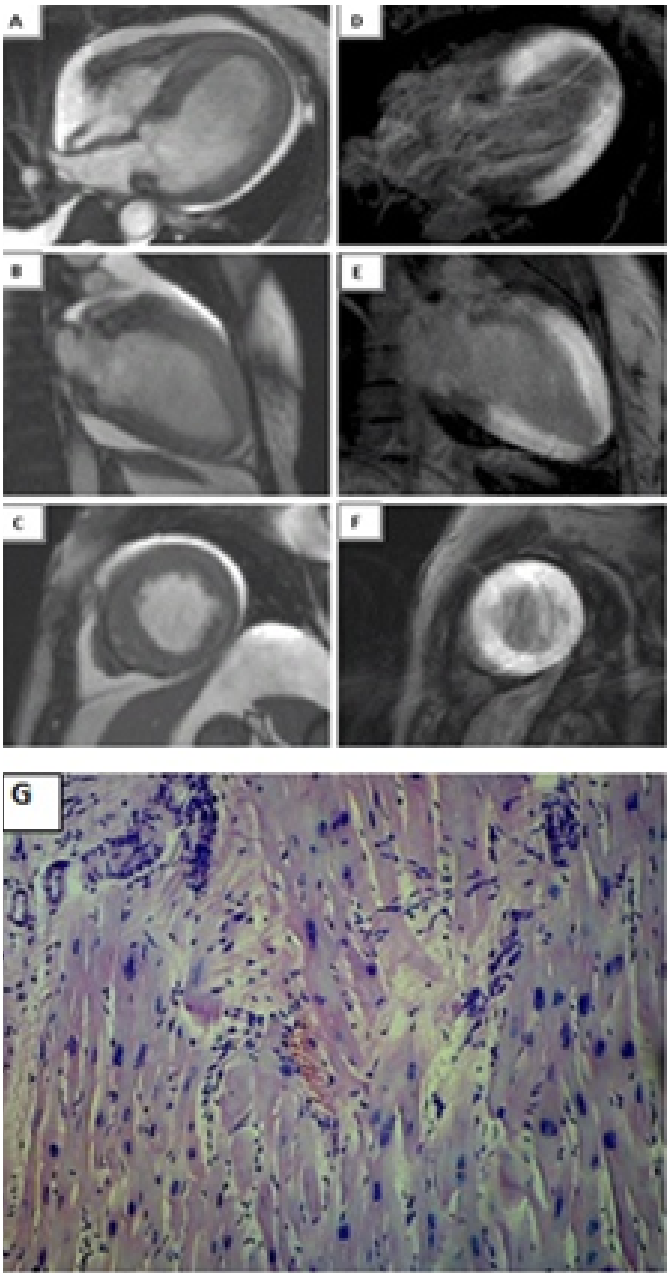

Figure 2 – *Cardiovascular magnetic resonance shows increased left ventricular volume and wall thickness on cine images acquired in 4-chamber (A), long axis (2-chambers) (B) and medial short axis (C) views. Diffuse and transmural late gadolinium enhancement is showed (D, E, F) with preservation of basal segments. (G) Endomyocardial biopsy showed myocyte disarray.*

References

1. Task Force Members. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the task force for the diagnosis and management of hypertrophic cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J. 2014; 35(39): 2733–79. DOI: 10.1093/euheartj./Orgv-Ejehu284.

2. Lipshultz SE, Sleeper LA, Towbin JA, lowe AM, Cox GF, Lurie PR, et al. The incidence of pediatric cardiomyopathy in two regions of the United States. N Engl J Med. 2003;348(17):1647-55. DOI: 10.1056/NEJM.oa21715.

3. Ho CY, Charron P, Richard P, Garolami F, Van Spaendonck-Zwarts KY, Pinto Y. Genetic advances in sarcomeric cardiomyopathies: state of the art. Cardiovasc Res 2015; 105: 397–408. DOI: 10.1093/cv/cvv025.

4. Anan R, Shono H, Kisanuki A, Arima S, Nakao S, Tanaka H. et al. Patients with familial hypertrophiccardiomyopathy caused by a Phe110Ile missense mutation in the cardiactroponin T gene have variable cardiac morphologies and a favorableprognosis. *Circulation.*1998;98(5):391–7. PMID:9714088.

5. Kubo T, Gimeno JR, Bahl A, Steffenson U, Osman E, Thaman R, et al.Prevalence, Clinical Significance,and Genetic Basis of Hypertrophic Cardiomyopathy With Restrictive Phenotype. J Am Coll Cardiol 2007;49(25):2419–26. DOI: 10.1016/jack.2007.02061.

6. Harris JK, Spirito P, Maron MS, zenovich AG, Formisano F, Lesser JR, et al. Prevalence, clinical profile, and significance of left ventricular remodeling in the end-stage phase of hypertrophic cardiomyopathy.Circulation. 2006;114(3):216 –25. DOI: 10.1161./CIRCULATIONAHA.105.583.500.

NEWS

Calendar

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De 9 a 12 de Maio de 2018
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http://sociedades.cardiol.br/ba/congresso2018/default.asp

Congresso Sociedade de São Paulo de Cardiologia (SOCESP)
De 31 de Maio a 2 de Junho de 2018
Transamerica Expo Center (SP)
http://www.socesp2018.com.br/

Congresso Brasileiro de Insuficiência Cardíaca - DEIC 2018
De 28 a 30 de junho de 2018
Goiânia (GO)
http://www.deic2018.com.br/

XXXVIII Congresso Norte-Nordeste de Cardiologia / XXIII Congresso Paraibano de Cardiologia
De 2 a 4 de Agosto de 2018
Centro de Convenções do Hotel Tambaú (PB)
http://sociedades.cardiol.br/nn/congresso.html

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De 9 a 11 de Agosto de 2018
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XXX Congresso da SBC/ES
De 16 a 18 de Agosto de 2018
http://sociedades.cardiol.br/es/

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De 14 a 16 de setembro de 2018.
CICB - Centro Internacional de Convenções do Brasil (DF)
http://cardio2018.com.br/

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De 12 a 13 de outubro de 2018
Florianópolis (SC)
http://departamentos.cardiol.br/decage2014/

XXV Congresso Nacional do SBC/DERC
De 25 a 27 de Outubro de 2018
Costão do Santinho Resort
http://departamentos.cardiol.br/sbc-derc/2016/

XXV Congresso Brasileiro de Cardiologia e Cirurgia Cardiovascular Pediátrica
De 31 de Outubro a 3 de Novembro de 2018
http://departamentos.cardiol.br/sbc-dcp/2010/default.asp

XV Congresso do Departamento de Hipertensão Arterial da SBC
De 01 a 02 de novembro de 2018
Salvador (BA)
http://departamentos.cardiol.br/sbc-dha/

XXV Congresso Brasileiro de Cardiologia e Cirurgia Cardiovascular Pediátrica
De 1 a 3 de novembro de 2018
Maceió (AL)
https://pebmed.com.br/event/xxv-congresso-brasileiro-de-cardiologia-e-cirurgia-cardiovascular-pediatrica/

XXXV Congresso Brasileiro de Arritmias Cardíacas
De 22 a 24 de Novembro de 2018
Centro de Convenções, Goiânia, GO
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