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ORIGINAL ARTICLE

Moderate-Intensity Walking Training Improves Depressive Symptoms and Pain in Older Adults with Good Quality of Life: A Controlled Randomized Trial

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Abstract

Background: Walking training can be an adequate choice to improve physical and psychological conditions in the elderly. Studies have reported positive changes in the quality of life, depressive symptoms and pain. However, baseline characteristics of volunteers have been controlled, and some of previous studies have not investigated these parameters concomitantly.

Objectives: To assess the effects of moderate-intensity walking on quality of life, depressive symptoms and physical pain in physically active elderly individuals.

Methods: Sixty-nine subjects were recruited and allocated into two groups: training group (n = 40) and control group (n = 29). All were evaluated for quality of life, depressive symptoms and pain. Training group underwent 40 minutes of walking (50-70% of maximum heart rate), 3 days a week for 12 weeks. For statistical analysis, we used the Kolmogorov-Smirnov test, Student's t-test and Split-Plot ANOVA with Bonferroni post hoc, Pearson correlation. Significance level was set at 5%.

Results: After 12 weeks of training, depressive symptoms and physical pain significantly reduced in the training group (2.7 ± 2.4 to 1.9 ± 1.8 and 4.3 ± 3.1 to 2.8 ± 2.9, respectively) compared with baseline values, and remained unchanged in the control group. There was a positive, moderate correlation between depressive symptoms and pain (r = 0.30).

Conclusion: physically active elderly individuals with good quality of life show improved depressive symptoms after a short-term moderate-intensity walking training program. (Int J Cardiovasc Sci. 2019;32(6):553-562)

Keywords: Walking; Walking Speed; Quality of Life; Aged; Pain; Depression.

Introduction

The United Nations estimate that there will be 1.5 billion senior citizens in the world by 2050.[1] Aging process is a continuous and multidimensional phenomenon that generally leads to a decrease in independence and performance of daily life activities.[2-4] Quality of life (QOL) is one of the variables affected by aging, that may be differently described even by individuals living in similar conditions, including in terms of psychological aspects, as depressive symptoms.[3,5,6]

Despite the possible influence of several factors on the level of QOL, a worse QOL is observed in patients with high prevalence of depressive symptoms and increased physical pain. This phenomenon deserves attention, as these symptoms are associated with frailty, leading to a poor prognosis.[7]

Physical exercise is a powerful tool to prevent or at least delay the development of deleterious effects of aging.[8-10] Physical training can impact on both morphological and physical domains, causing an increase in muscle mass and strength, and improvement of cognitive and

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executive functions.[8,9] Besides, physical exercise can also act as a non-pharmacological treatment for chronic degenerative conditions, such as hypertension, diabetes mellitus and osteroporosis.[11]

Moderate-intensity aerobic exercise has been widely recommended for the elderly, due to considerable evidence suggesting it as a safe approach, able to control cardiovascular risks.[12,13] This is reinforced by the American College of Sports and Medicine (ACSM), which states that walking training can have these effects in elderly individuals, and should easily be included as part of their usual daily activities.[14,15]

Walking training has beneficial psychological and physical effects.[16-18] Studies have reported improvement in the QOL, depressive symptoms and physical pain in elderly subjects undergoing moderate-intensity aerobic exercise protocols.[19-22]

However, few studies have controlled baseline characteristics of volunteers, especially for QOL, pain and depressive symptoms.

The present study aimed to investigate the effects of moderate intensity walking training on depressive symptoms and physical pain in elderly individuals with a good quality of life.

Methods

Study design and ethical aspects

This is a prospective longitudinal study aiming at investigating the effects of a 12-week exercise program including moderate-intensity walking on depressive symptoms and physical pain in elderly individuals with a good quality of life.

All volunteers were instructed about the study and then signed the consent form. The study was approved and conducted according to the Ethics Committee of the University of Sao Paulo ethical standards (approval number 0562/11) and performed according to the Brazilian National Health Council resolution (196/96).

Patients

All patients were recruited from an elderly Community Center in São Paulo, Brazil. Inclusion criteria were: a) medical clearance from the assistant physician for participation in the study; b) age > 60 years; c) > 150 minutes per week of physical activity according to the International Physical Activity Questionnaire (IPAQ) recommendations;[23] d) a score between 1 and 7 in the Lequesne algofunctional index for hip and knee osteoarthritis,[24] and scores ≥ 40 in the World Health Organization Quality of Life (WHOQOL)-BREF and WHOQOL-OLD questionnaires. Exclusion criteria were absence of one or more evaluations, hormone replacement and/or psychotropic drugs, cardiovascular disease (acute myocardial infarction, stroke, peripheral artery disease and transient ischemic attack), metabolic diseases (type 1 or type 2 diabetes mellitus), pulmonary diseases (emphysema), psychiatric or neurologic diseases (Alzheimer's or Parkinson's disease), muscular disorders, skeletal disorders, comorbidities associated with higher risk of falls, clinical diagnosis of diseases associated with physical pain (low back pain) and response rates ≥ 5 in the short form of the Geriatric Depression Scale (GDS).

A total of 165 patients were invited to participate in the study; 96 were excluded: 22 declined to participate, 19 did not answer the invitations, and four had functional impairment. Therefore, 69 volunteers were considered eligible to participate in the study and were randomized by an assistant researcher, using a simple randomization system, a table of random numbers, and categorized in two groups – training group (TG; n = 40) and control group (CG; n = 29) (Figure 1). All volunteers were blinded to the intervention.

Assessments

All assessments were performed by an investigator who was blinded to the group. Participants were asked to refrain from exercise during the 96 hours before the measurement, and from consuming caffeinated, alcoholic and energy beverages. Although energy intake was not controlled, all volunteers were asked to maintain their usual diet during the study period. No volunteer participated in any other exercise program during the study.

All tests and experimental sessions were carried out at Unifesp Psychobiology Laboratory, under a controlled temperature between 22 and 24º C and relative humidity of 51%. All interviews were in-person and individualized. If the interviewee did not understand the question, the interviewer repeated it slowly, until three times.

WHOQoL-OLD and WHOQUoL-BREF

The WHOQOL is an instrument recommended to assess the QOL of elderly individuals. This questionnaire is composed of 24 items, organized in six major domains.

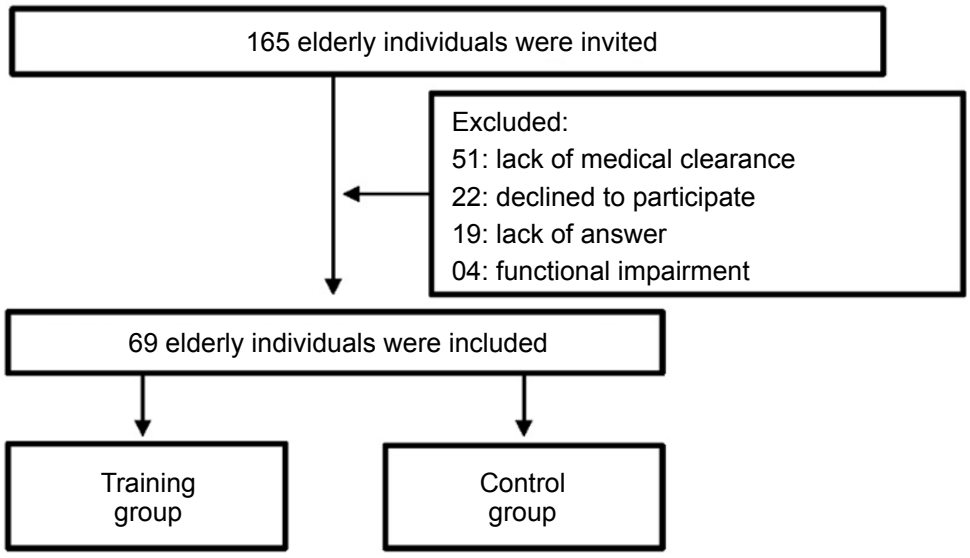

Figure 1 - Study flow chart.

The values of the six domains or the sum of the 24 questions may be combined to produce an overall score. However, there is no cut-off point, the greater the score, the better the QOL.[25]

Considering that the WHO recommends that the WHOQOL-OLD should not be administered alone,[25] we used the WHOQOL-BREF also. The WHOQOL-BREF is a short version of the WHOQoL-100, used in situations when the time available for application is short and when the number of respondents is large. The WHOQOL-BREF is composed of 26 questions, two of them related to QOL. The questions are organized in four domains: physical, psychological, social relationships and environment, and are positively correlated with the WHOQOL-100 overall score.[26]

Geriatric depression scale (GDS)

Depressive symptoms were assessed by the short version of the GDS, composed of 15 questions about feelings, and frequency of feelings in relation to life situations. The answers to the GDS questions are based on a binary code: yes or no.[27,28]

Visual analogue scale (VAS)

VAS is a widely used instrument to evaluate pain intensity in different populations, including the elderly. It contains a continuous scale consisting of a 10 cm horizontal line. The respondents place a line perpendicular to the VAS line at the point that represents their pain intensity. Quantification of pain intensity, volunteers were asked about the intensity of physical pain during the last week. A zero (0) means 'no pain' and a ten (10) means the worst pain imaginable. VAS score is positively associated with pain intensity.[29]

Incremental exercise test

Before the cardiac stress test, remained seated for 20 minutes. A resting electrocardiogram was performed to evaluate heart pressure, heart rate and lactate.

Then, incremental test was performed using an electronic treadmill (Life Fitness®, model 9700HR®, Fort Mill, Tennessee, USA), according to the modified Bruce protocol, composed of six stages of three minutes each, characterized by both speed (2.7-6.8 km/h) and slope (0-16º) increments.

The gases produced were analyzed during the incremental test using an analyzer (Cosmed®, Cosmed Quarker CPET®, Rome, Italy), previously calibrated, with a 3L syringe (flow calibration) and a standard gas mixture containing 4.9% CO_2 and 17.0% O_2 (gas calibration). Ventilation (VE), oxygen consumption (VO_2) and carbon dioxide production (VCO_2) were evaluated in the last 20 minutes of each 3-minute stage.

Heart rate (HR) was continuously measured (Oregon Scientific®, SE128®, Portland, Oregon, USA). Peak VO_2 and maximum HR (MaxHR) were recorded at physical exertion of patients.

All volunteers met two criteria for peak VO_2: a) respiratory exchange ratio (RER) ≥ 1.1; b) MaxHR at least equal to 90% of the maximum predicted for age, using the Jones equation (0.65 x age - 210). The electrocardiographic patterns were recorded and analyzed by a cardiologist during all the test.

Training group (TG)

The intensity, frequency and duration of the aerobic training sessions were conducted according to the ACSM and the American Heart Association (AHA) recommendations. Each participant underwent 36 walking sessions, which occurred three days a week for 12 weeks, with a minimum of 48 hours of recovery between the sessions. Each session consisted of five minutes of warm-up, which involved movements of the whole body; 30 minutes of continuous walking at moderate intensity – 50-70% of MaxHR, established at the stress test previously performed on the treadmill (Life Fitness®, model 9700HR®, Fort Mill, Tennessee, USA); finally, 5 minutes of smooth movements, stretching and breathing. A cardiac monitor (Oregon Scientific SE128®, Portland-Oregon), was used individually, according to the HR of each patient every three minutes in all sessions. Each session was conducted under supervision, which promoted safety and accuracy in prescribing individualized training (50-50% of MaxHR), and if necessary, adjusting for the training zone.

Control group (CG)

The CG continued their usual activities during the study period, without getting involved in exercise. Patients' follow-up was conducted by telephone every 15 days to assure that the protocol was being followed.

Statistical analysis

The Kolmogorov-Smirnov test was used to test data normality. Categorical data were expressed as frequency and percentage, whereas continuous data were described as mean and standard deviation. Between-group comparisons (TG x CG) were made at baseline using the unpaired Student's t-test. Within-group comparisons (pre-training vs post-training) and intergroup comparisons were conducted by the Split-Plot ANOVA, followed by the Bonferroni low or null correlation; post hoc test. The Pearson correlation coefficients (r) used in the study were: $0 < r < 0.25$: low or null correlation; $0.25 < r < 0.50$: weak correlation; $0.50 < r < 0.75$: moderate correlation; and $0.75 < r < 1.00$: strong or perfect correlation. The effect size (ES) was defined as mean Cohen's d greater than 0.2 and lower than 0.5; values between 0.5 and 0.8 were defined as good ES, and values equal to or greater than 0.8 were defined as a large ES.[30] Sample size was calculated considering an alpha error of 5%, statistical power of 90%, and a sample of 80 subjects. The level of significance was set at 5% ($p < 0.05$) and all analyzes were performed using the Statistical Package for the Social Sciences software, version 20.0. (IBM®, New York, New York, USA).

Results

Characteristics of the sample

Characteristics of the subjects at baseline are described in Table 1. As expected, all volunteers were elderly. Participants in both groups were classified as normal weight or overweight according to the body mass index (BMI) categories. On the other hand, all subjects had a very low to low cardiorespiratory fitness, as compared with the limits established for the elderly population.[31] The unpaired Student's t-test did not show any significant difference between the groups. All volunteers participated in 100% of sessions, and no adverse effect was observed during or after the training sessions.

Depressive symptoms and physical pain

Primary results are shown in Figures 2 and 3. There was a significant reduction in GDS in the TG after 12 weeks of walking training. In contrast both GDS and VAS remained unchanged in the CG (GDS = 3.0 ± 2.7 to 3.1 ± 2.4; p = 0.94; ES = - 0.03; VAS = 4.4 ± 3.2 to 4.2 ± 3.2; p = 0.68; ES = 0.06).

Quality of life and peak oxygen consumption

QOL (WHOQoL-OLD and WHOQoL-BREF) (Figure 4) and cardiorespiratory fitness (Table 2) were assessed as secondary outcomes. Regarding QOL, no difference was seen between the groups (TG [WHOQoL-OLD = 66.5 ± 14.0 % to 65.6 ± 15.9 %, (p = 0.94, ES = 0.06); WHOQoL-BREF = 67.8 ± 11.0 to 69.4 ± 10.8 (p = 0.21, ES = -0.14)] and CG [WHOQoL-OLD = 64.7 ± 12.3 to 63.2 ± 13.4,

Table 1 - Characteristics and questionnaire scores of participant in the beginning of the study

Variables	TG (n = 40)	CG (n = 29)	p value
Age (years)	68.2 (5.2)	65.3 (3.8)	0.57[a]
Body mass (kg)	73.4 (12.6)	67.7 (14.6)	0.08[a]
Height (cm)	1.61 (0.1)	1.57 (0.1)	0.69[a]
BMI (kg/m²)	28.5 (4.9)	27.3 (4.5)	0.28[a]
Peak VO_2 ($ml.kg^{-1}.min^{-1}$)	23.67 (5.2)	23.61 (4.9)	0.23[a]
GDS (rating)	2.7 (2.4)	3.0 (2.7)	0.89[a]
VAS (cm)	4.3 (3.1)	4.4 (3.2)	0.84[a]
WHOQOL-OLD (%)	66.5 (14.0)	64.7 (12.3)	0.84[a]
WHOQOL-BREF (%)	67.8 (11.0)	67.1 (10.6)	0.78[a]
Physical activity (min/sem)	215 (91.9)	280 (949.5)	0.45[a]

TG: training group; CG: control group; BMI: body mass index; GDS: geriatric depression scale; VAS: visual analogue scale; SD: standard deviation; a: unpaired Student's t test; WHOQOL: World Health Organization Quality of Life.

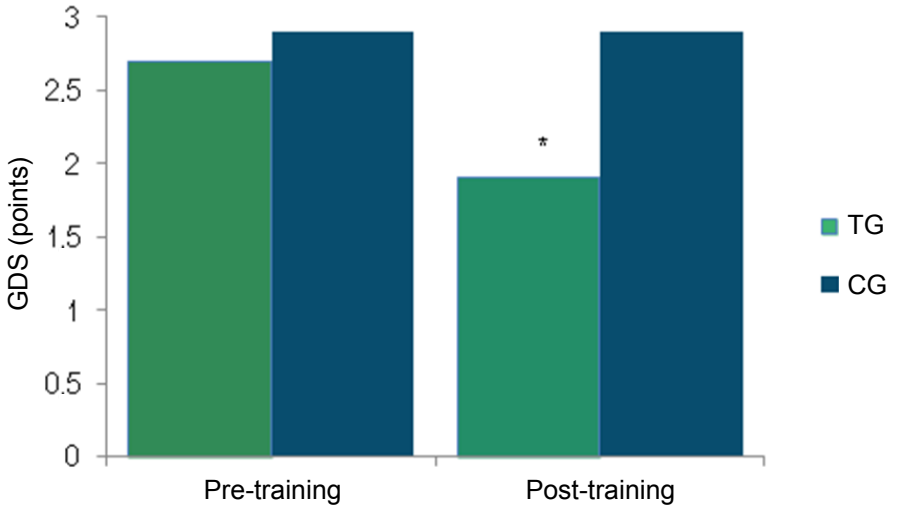

Figure 2 - Geriatric depression scale scores before and after 12 weeks of walking training.
GDS: geriatric depression scale; TG: training group; CG: control group; p = 0.04 (Student's t-test).*

(p = 0.52, TE = 0.11)]; WHOQoL-BREF = 67.1 ± 10.6 to 64.3 ± 11.9 (p = 0.16, ES = 0.24). Similarly, peak VO_2 did not show significant differences between the groups before and after the training: TG (23.67 ± 5.18 to 24.46 ± 5.62) and CG (23.61 ± 4.86 to 23.57 ± 4.65).

Correlation between depressive symptoms and physical pain

Figure 5 illustrates the results of the Pearson analysis. There was a positive, moderate correlation between GDS and VAS (r = 0.30; p = 0.05).

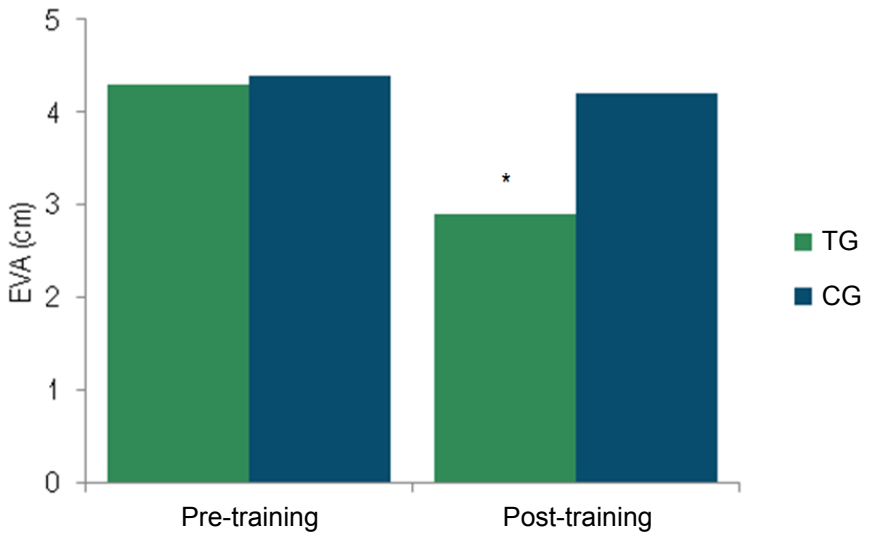

Figure 3 - Visual analogue scale scores before and after 12 weeks of walking training.
EVA: visual analogue scale; TG: training group; CG: control group; p = 0.006 (Student's t-test).*

Discussion

The main findings of the present study indicate that a moderate intensity, 12-week walking training reduces depressive symptoms and physical pain in elderly individuals. Interestingly, improvements seen occurred despite no change in QOL or aerobic fitness. Besides, Pearson correlation showed a significant association between depressive symptoms and pain score in TG.

Data of the present study are in agreement with the literature, since there is considerable evidence showing that different types of training can reduce depressive symptoms in patients with and without depression.[32] Nevertheless, it is of note that only some studies evaluated the effect of walking training on depressive symptoms of non-depressive patients. In fact, similarly to our study, in the study by Pereira et al.[21] elderly patients underwent a moderate-intensity (65-80% of MaxHR) walking training, carried out three days a week for 10 weeks. According to the authors, participants showed a significant reduction in depressive symptoms after exercise, Branco et al.[19] reported a 37.5% reduction in depressive symptoms in elderly individuals undergoing a long-term training period (6 months).

In another scenario, different from the data mentioned above, our study included physical pain as an outcome that could be associated with changes in depressive symptoms. In fact, this hypothesis is supported by many authors that indicated a strong association of physical pain with depressive symptoms, mainly in the context of chronic diseases (e.g., cancer).[20,33,34]

Our results showed that GDS and VAS scores were moderately correlated (r = 0.30), suggesting a relationship between effects of aerobic exercise on depressive symptoms and alleviation of symptoms, i.e., a probable analgesic effect of the trainings, leading to pain reduction in elderly individuals.[20,33,34]

It is worth mentioning that there is little evidence on the impact of physical training on depressive symptoms by pain alleviation, and most studies on the topic have been based on cross-sectional data and physical activity level. Sabiston et al.,[34] for example, observed that physical pain was positively associated with depressive symptoms, and that higher levels of exercise had an inhibitory effect on this association in elderly breast cancer patients.

Regarding the exercise protocol used in this study, volunteers of the study by Pennix et al.,[20] showed a reduction in physical pain and depressive symptoms after a moderate-intensity walking training. This corroborates our findings showing a significant hypoalgesia in response to walking training, since we observed a 35% reduction in overall pain in our volunteers. These results

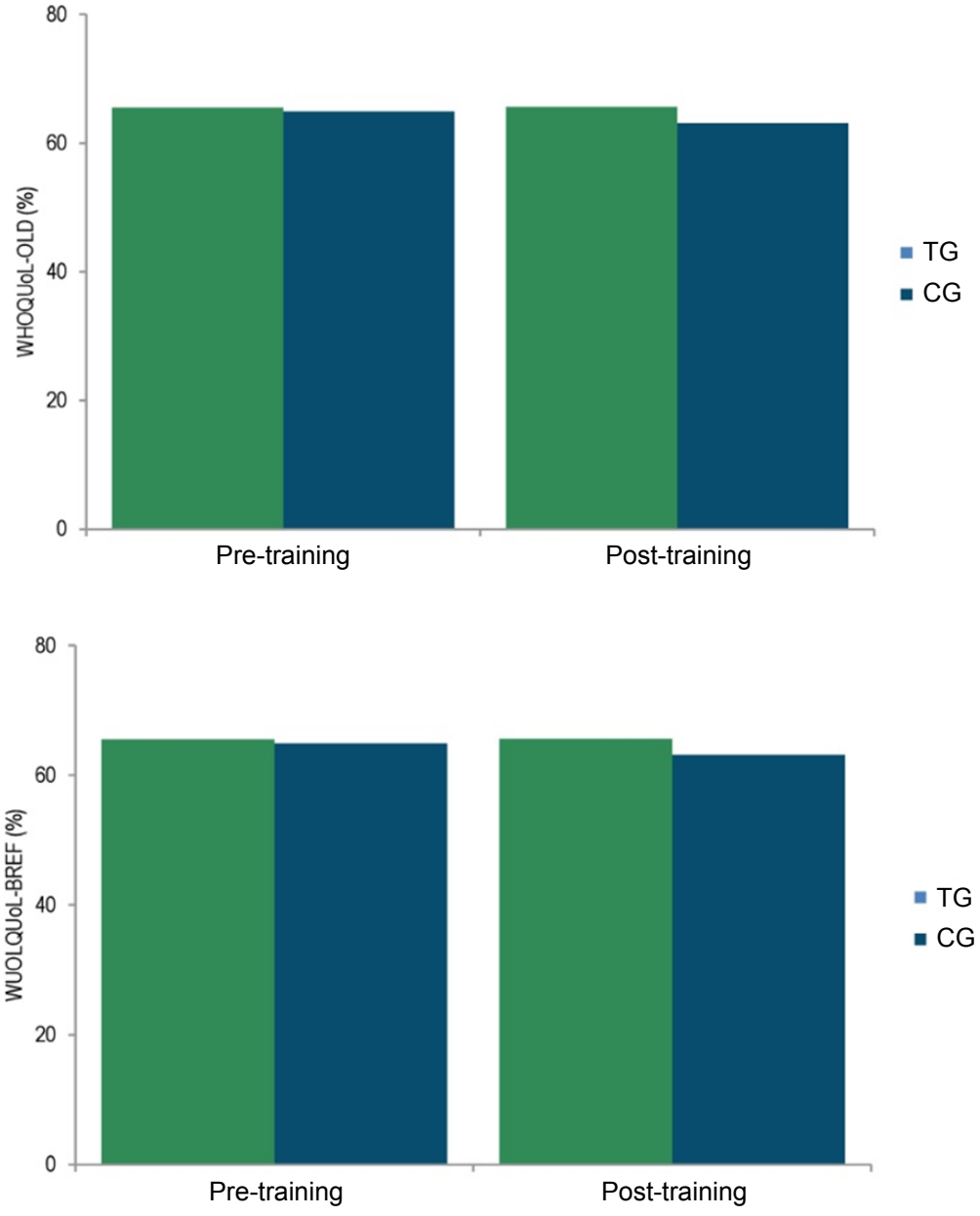

Figure 4 - Results of WHOQoL-OLD and WHOQoL-BREF before and after 12 weeks of walking training.
GDS: geriatric depression scale; VAS: visual analogue scale; TG: training group; CG: control group.

are supported by previous studies showing that aerobic exercise seems to increase pain threshold in response to several factors, including ischemic pain, compression and thermal stimulus.[35,36]

In addition, our findings seem to have a broad applicability in clinical practice, since evidence has shown that even healthy elderly subjects undergoing walking training can develop physical pain in an 18-month period. Therefore, our data suggest that a three-month program of moderate-intensity walking training has a protective role on chronic physical pain in healthy elderly individuals.[20,22,35] Interestingly, body pain and depressive symptoms are two domains of the WHOQoL-OLD and WHOQoL-BREF questionnaires. Nevertheless, although both parameters were reduced in response to our exercise protocol, QOL remained unchanged in the TG. In

Table 2 - Peak VO_2 prior to and after training period (12 weeks)

	Peak VO_2 ($ml.kg^{-1}.min^{1}$)		
Groups	**Pre-training**	**Post-training**	**p value**
Training	23.67 ± 5.18	24.46 ± 5.62	0.06[a]
Control	23.61 ± 4.86	23.57 ± 4.64	0.95[a]

Peak VO_2: maximum oxygen consumption; a: unpaired Student's t test.

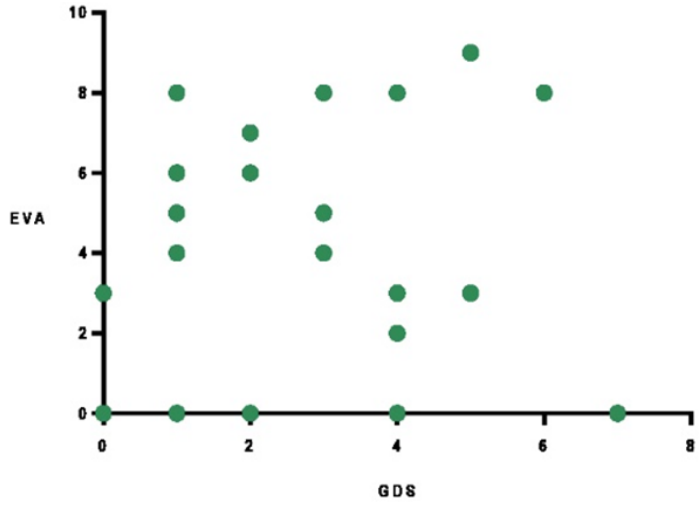

Figure 5 - Results of the intersection point between the geriatric depression scale (GDS) and the visual analogue scale (VAS).
GDS: geriatric depression scale; VAS: visual analogue scale; TG: training group; CG: control group.

contrast, several studies have shown an improvement in QOL of adults undergoing walking training protocols.[37-39] However, it is worth mentioning that these studies have involved patients with different comorbidities (e.g. hypertension, diabetes), without evaluating other covariates, such as body pain. Also, QOL has not been used as an inclusion criterion.

Although different methods were used in the studies, it is of note that our sample showed higher QOL scores (~ 65) compared with other studies,[37] limiting the effects of exercise on these parameters. Besides, evidence has suggested that physical function can be a determining factor in QOL.[38,40] Since aerobic capacity remained unchanged in the present study, it is possible to infer that this phenomenon is associated with the lack of changes in QOL scores.

Limitations

This study has some limitations that should be consider to contribute to a better inference from the data. First, the lack of specific physical examinations (muscle and fat mass) that could lead to a better understanding of the relationship between walking training and QOL, as well as the inclusion of other exercise groups, walking training strategies and exercise protocols.

Conclusions

Our findings indicate that a moderate-intensity walking training with three-month duration can improve depressive symptoms and physical pain in elderly individuals without necessarily changing QOL and aerobic fitness.

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Author contributions

Conception and design of the research: Alabarse SL, Coelho Júnior HJ, Asano RY, Luna Filho B, Oliveira Filho JA. Acquisition of data: Alabarse SL, Oliveira Filho JA. Analysis and interpretation of the data: Alabarse SL, Coelho Júnior HJ, Asano RY, Oliveira Filho JA. Statistical analysis: Alabarse SL, Coelho Júnior HJ, Luna Filho B, Oliveira Filho JA. Obtaining financing: Alabarse SL, Oliveira Filho JA. Writing of the manuscript: Alabarse SL, Coelho Júnior HJ, Asano RY, Santos WC, Oliveira Filho JA. Critical revision of the manuscript for intellectual content: Alabarse SL, Coelho Júnior HJ, Oliveira Filho JA. Supervision / as the major investigador: Alabarse SL, Oliveira Filho JA.

Potential Conflict of Interest

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

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade Federal de São Paulo under the protocol number 0562/11. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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EDITORIAL

Moderate Exercise Improves Depressive Symptoms and Pain in Elderly People

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Editorial related to the article: Moderate-Intensity Walking Training Improves Depressive Symptoms and Pain in Older Adults with Good Quality of Life: A Controlled Randomized Trial

By the year of 2050, it is estimated that approximately two billion people in the world will be older than 60 years.[1] Aging directly affects individuals' quality of life (QoL) due to reduced autonomy in daily life activities. In this context, psychological and physical aspects, such as depression and pain, impair the QoL of elderly individuals. Antidepressant medication is commonly used to treat depression, and physical exercise has been increasingly prescribed as therapeutic alternative to depression symptoms.[2] In addition, this non-pharmacological measure may have an analgesic effect as it attenuates the physical pain caused by the pathological process of aging.[3] In this regard, aerobic exercise, such as moderate-intensity walking seems to have a positive impact on anxiety/depression and on physical pain and has the potential to improve the QoL of elderly people according to an observational study conducted in South Korea.[4]

In the present issue of the International Journal of Cardiovascular Sciences, Alabarse et al.,[5] compare the effects of moderate-intensity walking on QoL, depressive symptoms, and physical pain in Brazilian elderly individuals. In this study, 69 individuals were recruited and allocated in two groups – training group (TG, n = 40) and CG, n = 29. The sample was composed of physically active individuals (> 150 minutes of physical activity per week), with a mean age of 68.2 ± 5.2 years and 65.3 ± 3.8 in the TG and in the CT, respectively (p = 0.57). Participants included in the TG performed moderate-intensity walking three times a week for 12 weeks. The CG was instructed to maintain their usual activities during the study period and were followed by telephone interview every 15 days. Exercise training protocol followed the American College of Sports and Medicine (ACSM) and the American Heart Association (AHA) guidelines and consisted of a five-minute warm-up using body movements, and 30 minutes of continuous, moderate-intensity walking. This was defined as 50-70% of the maximum heart rate (HRmax), established by the cardiopulmonary exercise testing (CPET). In the last five minutes, subjects performed low-intensity breathing and stretching exercises.

The authors found that both depressive symptoms and physical pain, measured by the Geriatric Depression Scale (GDS) and a Visual Analogue Scale (VAS), respectively, significantly decreased in the TG. For assessment of QoL, the authors used the World Health Organization Quality of Life (WHOQOL) BREF and OLD, and no difference was observed between the groups. Peak oxygen consumption (VO2peak), defined as a secondary outcome in the study, was not different after 12 weeks of intervention. There was a positive correlation between depressive symptoms and physical pain (r = 0.30).

In our opinion, the study presents interesting, clinically relevant results on the effects of moderate-intensity aerobic exercise in the fastest growing population in the world. However, the study has important limitations that should be addressed: 1) the exercise was prescribed based on the percent of HRmax (50-70%). If the HRmax were calculated using the equation proposed by Tanaka et al.,[6] in the TG, HRmax would be 160 beats per minute (bpm). This is to illustrate how training loads may be underestimated by an HRmax-based prescription (in this case, 50% = 80 bpm; 70% = 112 bpm). Thus, even in elderly subjects, 80 bpm would be close to the resting

Keywords

Aged; Antidepressive Agents/adverse effects; Comorbidity; Depressive Disorder/therapy; Frail Elderly; Physical, Activity.

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heart rate, and 112 bpm would possibly be within a subaerobic zone; 2) since a CPET was available, the exercise training could have be planned based on the velocities and heart rates of respective VO_2peak for both aerobic and anaerobic zones, or on the heart rates in the threshold and the interthreshold zone; 3) even if VO_2peak was not a primary outcome, in this type of experiment, it is always important to discuss the prescription of exercise, since the TG showed an increase in VO_2peak of 0.79 $mL.kg^{-1}.min^{-1}$ ($p = 0.06$), i.e., a small, non-significant increment, which may have been a mere consequence of an error in the prescription of exercise load based on the percentage of HRmax. We believe that the percentage of the heart rate reserve could have been used for the monitoring of the exercise training load, which would have considered the resting heart rate.[7] Besides, an alternative method to control exercise level is the "old" and useful Borg scale of perceived exertion, which was not used by the authors; finally, 4) the authors reported a moderate positive correlation ($r = 0.30$) between depressive symptoms and physical pain. In fact, a correlation of 0.30 is considered weak or meaningless.

However, despite the limitations mentioned above, the study has strengths that support its publication. One of the strengths is the authors' proposal to investigate the effects of exercise in a high-prevalence population, in terms of QoL, depressive symptoms and physical pain. Elderly individuals experience limitations in their daily activities, and this fact is generally associated with a reduction in QoL and worsening of depressive symptoms and pain. The study showed that an intervention consisted of 12-week aerobic exercise training improved these outcomes, which, in our understanding, is worthy of credit. Also, the initiative to develop an investigative study aimed at better understanding the mechanisms involved in health promotion should be applauded.

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ORIGINAL ARTICLE

Adverse Events and Risk Factors of Blood Transfusion in Cardiovascular Surgery: A Prospective Cohort Study

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Abstract

Background: Hemodilution, transoperative bleeding and cardiopulmonary bypass (CPB) are some of the factors associated with high transfusion rates in cardiac surgery.

Objective: To analyze the incidence of blood transfusion and early postoperative outcomes in cardiac surgery patients.

Methods: Cohort study of patients undergoing cardiac surgery in a university hospital, consecutively enrolled from May 2015 to February 2017. Data were prospectively collected and comparisons were made between two patients' groups: transfused and not transfused. Student's t-test, chi-square test, and logistic regression were used, and a p-value < 0.05 was considered significant.

Results: Among the 271 patients evaluated, 100 (37%) required transfusion in the transoperative (32.1%) and/or postoperative periods (19.5%). The following predictors of transfusion were identified by multivariate analysis: EuroScore II (OR 1.2); chronic kidney disease (CKD) (OR 3.2); transoperative bleeding ≥ 500 mL (OR 6.7); baseline hemoglobin (Hb) ≤ 10 g/dL (OR 11.5); activated partial thromboplastin time (aPTT) (OR 1.1) and CPB duration (OR 1.03). Transfusion was associated with prolonged mechanical ventilation (≥ 24h) (2.4% vs. 23%), delirium (5.9% vs. 18%), bronchopneumonia (1.2% vs. 16%), acute renal failure (3.5% vs. 25%), acute on CKD (0.6% vs. 8%), stroke or transient ischemic attack (1.8% vs. 8%), intensive care unit stay ≥ 72 h (36% vs. 57%), longer hospital stay (8 ± 4 days vs. 16 ± 15 days), as well as increased early mortality (1.75% vs. 15%).

Conclusion: EuroScore II, CKD, major transoperative bleeding, preoperative Hb and aPTT values and CPB time were independent predictors of transfusion, which was associated with a higher rate of adverse outcomes, including early mortality. (Int J Cardiovasc Sci. 2019;32(6):565-572)

Keywords: Cardiac Surgical Procedures/mortality; Blood Transfusion; Intraoperative Care/adverse effects; Postoperative Complications/prevention and control; Risk assessment.

Introduction

Hemodilution, transoperative bleeding and cardiopulmonary bypass (CPB) are some of the factors associated with high transfusion rates in cardiac surgery.[1] The prevalence of patients undergoing cardiac surgery who receive blood components is unknown, with values varying from 10% to 95%.[2-4] Such diversity is partly due to different local practices and institutional protocols.

A Canadian retrospective study documented a red blood cell (RBC) transfusion rate ranging from 23.8% to 51.9%.[1] In another study, transfusion rates in coronary artery bypass grafting (CABG) varied from 26.5 to 71.3%.[5]

Moreover, as noted by Vonk et al.,[6] there was 28% reduction in RBC transfusion in the last 10 years, with non-significant change in the use of fresh frozen plasma (FFP) or platelets. In 2011, 50% and 60% of patients needed FFP and platelets, respectively.[6]

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If, in one hand anemia is an independent risk factor for morbidity and mortality by reducing oxygen supply, leading to ischemic injury,[7] on the other hand, the immune response caused by transfusion could be a potential harm factor.[8]

However, clinical trials such as TRACS[9] and TITRe 2,[10] which compared restrictive versus (vs) liberal RBC transfusion strategies, have shown non inferiority for a composite endpoint of 30-day all-cause mortality and severe morbidity [cardiogenic shock, acute respiratory distress syndrome or acute renal failure (ARF)] during the hospital stay (10% liberal vs. 11% restrictive),[9] as well as for infectious or ischemic events (35.1% vs. 33.0%).[10] RBC transfusion was an independent risk factor for 30-days clinical complications or death [hazard ratio (HR) for each unit transfused = 1.2; 95% confidence interval (CI) 1.1 – 1.4].[10]

Analyzing long-term results, the recent TRICS trial demonstrated that, in moderate-to-high risk for death patients, a restrictive transfusion strategy (hemoglobin < 7.5 g/dL intra or postoperatively) was non-inferior to a liberal strategy [hemoglobin < 9.5 g/dL in the intensive care unit (ICU) or < 8.5 g/dL in the non-ICU ward] in terms of death, myocardial infarction, stroke or new dialysis in 6-months (17.4% vs. 17.1%; 95% CI 0.87 – 1.18).[11]

Choosing between a liberal or a restrictive RBC transfusion strategy has been a major concern and, although clinical trials have supported more restrictive practices, some authors are still attempting to identify an "accurate" hemoglobin threshold for transfusion.[12]

In view of the clinical relevance and persistently high transfusion rates, we believe that recognition of modifiable risk factors and adverse events is the first step towards changing our daily practice.

Objectives

To analyze the incidence of blood transfusion in patients undergoing cardiovascular surgery in a tertiary university hospital in southern Brazil, between May 2015 and February 2017, as well as to analyze adverse events and risk factors associated with the transfusion.

Methods

Analysis of a prospective cohort of patients submitted to cardiovascular surgery, consecutively enrolled from May 2015 to February 2017. Patients were divided into two groups according to whether or not they received any blood products (RBC, FFP or platelets), and were followed until hospital discharge or up to 30 days after the procedure, in order to evaluate early postoperative adverse outcomes.

All patients older than 18 years old undergoing cardiovascular surgeries at *Hospital de Clínicas de Porto Alegre*, a tertiary university hospital in southern Brazil, were invited to participate in the study. Patients who did not agree to participate and those who did not sign the informed consent form were excluded. The project was approved by the research ethics committee of the *Hospital de Clínicas de Porto Alegre* (approval number: 15-0332). All procedures were in accordance with the ethical standards for human experimentation and with the 1975 Helsinki Declaration revised in 2008.

Mortality and other postoperative outcomes were considered early if they occurred before hospital discharge or up to 30 days after surgical intervention. The outcome "other infections" was considered positive if the patient had superficial (e.g. saphenectomy infection) or deep wound infection (e.g. osteomyelitis or mediastinitis), infective endocarditis, sepsis or bacteremia.

The use of anticoagulant or antiplatelet agents was considered recent if the patient received unfractionated heparin or low molecular weight heparin at therapeutic doses in the 24 hours preceding surgery, warfarin or clopidogrel in the last 5 days or non-vitamin K antagonist oral anticoagulants (NOACs) in the last 48 hours. No patient used any other anticoagulant medication.

Statistical analysis

Data were obtained by clinical interview or review of electronic medical records, stored in a service database and analyzed using the Statistical Package for Social Sciences (SPSS) 18.0 software.

Quantitative variables were described as mean (M) and standard deviation (SD) and qualitative variables as absolute number and percentages. Independent samples t-test was performed for continuous variables whereas the chi-square test was used to compare categorical variables. Normality test and non-parametric tests were not performed, since parametric tests are considered robust even for non-normal distributions and skewed data once the sample size is deemed sufficiently large (more than 40 individuals).[13-15]

In order to identify variables associated with outcomes, univariate analyses were performed. Then, variables with statistical significance were added to a multivariable logistic regression model. A bilateral p-value < 0.05 was considered significant.

Based on the study by Murphy et al.,[16] in which the observed 30-day mortality was 5% in those who received RBC and 1% in those who did not, a sample size of 164 patients was estimated considering an α value of 0.05 and a desired power of 0.80.

Results

Of the 271 patients evaluated, 100 (37%) required transfusion of some blood product during transoperative [87 (32.1%)] and/or postoperative periods [53 (19.5%)]. Baseline characteristics are shown in Table 1.

Transoperative bleeding ≥ 500 mL was observed in 11 patients who did not require transfusion (6.4%) and in 40 (40%) who required it. The other transoperative characteristics are presented in Table 2.

The type of transfusion stratified by the operative period is displayed in Table 3. Predictors of RBC transfusion in univariate and multivariate analyses are shown in Table 4.

Reintervention was indicated in 21 patients (7.7%), 11 (52.3%) of them due to increased postoperative bleeding or cardiac tamponade, all of them required blood transfusion. Patients who received blood transfusion presented higher early postoperative complication rates, as described in Table 5.

Discussion

Dilutional anemia, CPB-related thrombocytopenia, coagulation disorders due to medications, major surgery and hypothermia contribute to high rates of blood transfusion in cardiac surgery, despite a current trend for restrictive protocols.

In our sample of 271 patients, prospectively and consecutively enrolled, we observed a general transfusion rate of 37%; 28.8% of them required RBC, 22.1% platelets and 14.4% FFP, values similar to those in the literature.[1,5,6,9,10]

We emphasize that, in our hospital, decisions about transfusion are a jointly made by the surgical, anesthetic and intensive care teams, who try to follow the best current evidence, but also take into account their experience and understanding of each situation, making the numbers presented here closer to real life.

We observed that some preoperative characteristics were transfusion predictors, such as anemia and anormal coagulation tests [activated partial thromboplastin time (aPTT) and international normalized ratio (INR)], although platelet count was not.

Predictors of blood transfusion in our analyses were similar to the TRACS trial, which showed higher transfusion rates in patients with previous cardiac surgery (OR = 8.92; p = 0.04), longer duration of cardiopulmonary bypass (OR = 1.01; p = 0.03) and lower preoperative hemoglobin levels (OR = 0.51; p = 0.001),[9] and to Stevens et al.,[17] who reported as predictors: CKD, previous cardiac surgery, urgency surgery, ejection fraction, type of surgery, CPB duration, age and low body mass index, although the last two was not confirmed in our study.

We observed no difference in other infections rates, although higher bronchopneumonia rates have been observed in transfused patients, similarly to TRACS, TRITe2 and Horvath findings.[9,10,18] We also found longer ICU and hospital lengths of stay, prolonged need for mechanical ventilation, delirium, ARF, acute CKD, stroke and transient ischemic attack in transfused patients. A retrospective Brazilian study on patients with ischemic and valve diseases had already reported higher rates of respiratory infection (27.8% vs. 17.1%; p < 0.001), ARF (14.5% vs. 7,3%; p < 0.001), stroke (4.8% vs. 2.6%; p = 0.001) and longer hospital stay (13 ± 12.07 days vs. 9.72 ± 7.66 days; p < 0.001) in transfused patients, but no difference in mortality.[19]

Even though the baseline characteristics were significantly different between the two groups, with transfused patients sicker than not transfused patients, when analyzing transfusion-related mortality, adjusted for the main confounding factors (EuroScore II, age, cardiopulmonary bypass time ≥ 90 min, emergency or urgency surgery and combined surgery), we noticed that transfusion remained an independent predictor of mortality in multivariate logistic regression (OR 5.3; 95% CI 1.3 – 21; p < 0.001).

Therefore, we emphasize the importance of rethinking the almost routine decision on transfusion in cardiac surgery, taking into account that, even one unit of packaged RBCs, can worsen the postoperative outcomes.

Table 1 - Baseline characteristics of participants

Variable	Non-transfused (N = 171) Mean ± SD or N (%)	Transfused (N =100) Mean ± SD or N (%)	p-value
Age (years)	60.3 ± 13	63.3 ± 12.5	1.0
EuroScore II	2.6 ± 4	9.6 ± 12	< 0.001
Male	111 (65%)	56 (56%)	0.218
Caucasians	159 (93%)	89 (89%)	0.595
Weight (kg)	75 ± 14	73.2 ± 16.7	0.307
Height (cm)	165 ± 10	164 ± 10	0.547
Hypertension	129 (75%)	73 (73%)	0.914
Diabetes	54 (31.5%)	17 (17%)	0.683
Chronic kidney disease	13 (7.6%)	24 (24%)	< 0.001
Alcoholism	5 (3%)	5 (5%)	0.573
Smoking	31 (18%)	15 (15%)	0.642
Previous cardiac surgery	9 (5%)	16 (16%)	0.004
Previous myocardial infarction	45 (26%)	26 (26%)	1
Previous stroke	21 (12%)	16 (16.3%)	0.469
Oral anticoagulant or antiplatelet agent (recent use)	32 (18.7%)	28 (28%)	0.086
Left ventricular ejection fraction ≤ 30%	8 (4.7%)	15 (15%)	0.005
Preoperative laboratory values			
Hemoglobin (g/dL)	13.5 ± 1.4	11.8 ± 2.3	< 0.001
Hematocrit (%)	40 ± 3.7	35.7 ± 6.4	< 0.001
International normalized ratio	1.0 ± 0.2	1.3 ± 1.0	0.001
aPTT (s)	26 ± 3.4	30.5 ± 15	< 0.001
Urea (mg/dL)	45.2 ± 17	56 ± 27	< 0.001
Creatinine (mg/dL)	1.1 ± 0.4	1.5 ± 1.4	0.008
Platelet count (μL)	217.000 ± 55.000	210.000 ± 85.000	0.392

SD: standard deviation; N: number; EuroSCORE II: European System for Cardiac Operative Risk Evaluation; aPTT: activated partial thromboplastin time; independent samples t-test for continuous variables or chi-square test for categorical variables.

Since most of the risk factors for transfusion cannot be modified, such as surgery type and baseline chronic conditions, it is up to us to focus on those that can be modified or optimized. Thus, Likosky et al.,[8] suggested some strategies to reduce the risk of RBC transfusion, including mini circuits to reduce the prime volume (class I, level A), modified ultrafiltration (class I, level A), antifibrinolytic agents (class IIa, level B), centrifugation of salvaged blood (class IIa, level A), and a team for multidisciplinary blood management (class IIa, level B).[8]

Surgenor et al.,[7] suggested that the use of RBC transfusions in coronary artery bypass graft (CABG) surgery may be reduced by minimizing hemodilutional anemia with preoperative erythropoietin and iron, use of autologous transfusions, preservation of intravenous fluids, avoidance of blood loss, use of a transfusion

Table 2 - Intraoperative data in transfused and non-transfused patients

Variable	Non-transfused (N = 171) Mean ± SD or N (%)	Transfused (N = 100) Mean ± SD or N (%)	p-value
Urgency or emergency surgery	58 (34%)	61 (61%)	< 0.001
Combined surgery	23 (13.5%)	24 (24%)	0.003
Procedure			
Coronary artery bypass grafting	99 (58%)	45 (45%)	0.124
Aortic surgery	11 (6.5%)	13 (13%)	0.110
Valve surgery	64 (37.5%)	47 (47%)	0.168
Cardiopulmonary bypass time (min)	70 ± 22	104 ± 42	< 0.001
Cross-clamp time (min)	54 ± 22	87 ± 56	< 0.001
Transoperative bleeding (mL)	256 ± 153	562 ± 527	< 0.001

SD: standard deviation; independent samples t-test for continuous variables and chi-square test for categorical variables.

Table 3 - Types of transfusion (n = 271) by the time they were performed (transoperative or during intensive care)

	Red blood cell	Platelets	Fresh frozen plasma	Fibrinogen	Prothrombin complex
Transoperative N (%)	62 (23%)	56 (20%)	32 (11.8%)	12 (4.4%)	9 (3.3%)
During the intensive care unit stay N (%)	32 (12%)	10 (3.7%)	18 (6.6%)	-	-

threshold based on patients' physiological needs, achievement of patients' normothermia at the end of the procedure, avoidance of surgeries within 5 to 7 days of the clopidogrel use, performance of prompt coagulation testing to reduce delays in the diagnosis of reversible causes of bleeding.[7]

A recent review article by Patel and Murphy[20] reinforces the idea that transfusion decision should not be solely based on hemoglobin concentration. The authors report, as potential physiologic triggers, a mean arterial pressure < 60 mmHg (or < 70-80% of baseline), heart rate > 110-130 beats / min (or > 120-130% of baseline), new ST-segment depression or elevation of at least 0.1 mV in an electrocardiogram, new wall motion abnormality on transesophageal or transthoracic echocardiography, mixed venous oxygen partial pressure < 32 mmHg, oxygen extraction ratio > 40%, mixed venous oxygen saturation < 60%, or > 10% decrease in oxygen consumption (VO_2).[20]

Nowadays, thromboelastography (TEG) and thromboelastometry (ROTEM®) have been considered of great value in cardiac surgery. Kozek et al.,[21] reported that TEG or ROTEM-guided hemostatic therapy reduces the number of patients requiring RBC, FFP and platelet transfusions, providing a more restrictive strategy than that based on conventional laboratory testing.[21]

The present study has some limitations. This study aimed to report the rates and outcomes of transfusion in daily practice, in a real-life scenario, in which we are challenged by cases not always supported by guidelines' recommendations. Also, there are limitations intrinsic to cohort studies such as its observational nature, in addition to the fact that this was a single-center experience.

Conclusion

EuroScore II, chronic kidney disease, major transoperative bleeding, preoperative hemoglobin and

Table 4 - Predictors of transfusion in univariate and multivariate analyses

Univariate analysis			
Variable	**Odds ratio**	**95% confidence interval**	**p value**
Emergency or urgency surgery	3.1	1.8 – 5.2	< 0.001
Previous cardiac surgery	3.5	1.4 – 8.2	0.004
EuroScore II	1.2	1.1 – 1.3	< 0.001
Chronic kidney disease	3.9	1.9 – 8.1	< 0.001
Left ventricular ejection fraction ≤ 30%	3.5	1.4 – 1.8	0.005
Preoperative hemoglobin ≤ 10 g/dL	27	6.3 – 362	< 0.001
Preoperative INR	17.5	3.1 – 97	0.001
Preoperative aPTT	1.1	1.0 – 1.2	< 0.001
Preoperative urea	1.02	1.01 – 1.03	< 0.001
Preoperative creatinine	1.8	1.1 – 2.9	0.008
Combined surgery	2.6	1.3 – 5.0	0.003
Cardiopulmonary bypass time	4.8	2.8 – 8.2	< 0.001
Cross-clamp time	4.8	2.8 – 8.2	< 0.001
Transoperative bleeding ≥ 500 mL	9.6	4.6 – 20	< 0.001
Multivariate analysis			
EuroScore II	1.2	1.0 – 1.3	0.019
Chronic kidney disease	3.2	1.0 – 11	0.05
Preoperative hemoglobin ≤ 10 g/dL	11.5	1.0 – 121	0.04
Preoperative aPTT	1.1	1.0 – 1.2	0.012
Cardiopulmonary bypass time	1.03	1.01 – 1.06	0.004
Transoperative bleeding ≥ 500 mL	6.7	2.6 – 17	< 0.001

EuroSCORE II: European System for Cardiac Operative Risk Evaluation; INR: international normalized ratio; aPTT: activated partial thromboplastin time; P-value was obtained by logistic regression.

aPTT values and duration of cardiopulmonary bypass showed independent predictors for blood transfusion, which was associated with postoperative adverse outcomes, including early mortality.

Author contributions

Conception and design of the research: Tagliari AP, Cavazzola LT, Wender OCB. Acquisition of data: Tagliari AP, Silveira LMV, Souza AC, Gib MC, Freitas TM, Martins CB. Analysis and interpretation of the data: Tagliari AP, Kochi AN, Cavazzola LT, Wender OCB. Statistical analysis: Tagliari AP, Kochi AN. Writing of the manuscript: Tagliari AP, Silveira LMV, Kochi AN. Critical revision of the manuscript for intellectual content: Tagliari AP, Silveira LMV, Kochi AN, Souza AC, Gib MC, Freitas TM, Martins CB, Cavazzola LT, Wender OCB.

Potential Conflict of Interest

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

Table 5 - Early postoperative outcomes in transfused and non-transfused patients

Outcome	Non-transfused (N = 171) Mean ± SD or N (%)	Transfused (N = 100) Mean ± SD or N (%)	p value
Acute myocardial infarction	1 (0.6%)	3 (3%)	0.288
Delirium	10 (6%)	18 (18%)	0.003
Stroke or transient ischemic attack	3 (1.8%)	8 (8%)	0.029
Prolonged mechanical ventilation (≥ 24h)	4 (2.4%)	23 (23%)	< 0.001
Bronchopneumonia	2 (1.2%)	16 (16%)	< 0.001
Acute renal failure	6 (3.5%)	25 (25%)	< 0,001
Acute chronic kidney disease	1 (0.6%)	8 (8%)	< 0.001
New atrial fibrillation	27 (15.8%)	18 (18%)	0.759
Intensive care unit stay (days)	3.8 ± 3	7 ± 9	< 0.001
Hospital length of stay (days)	8 ± 4	16 ± 15	< 0.001
Other infections	14 (8.2%)	11 (11%)	0.57
Death	3 (1.8%)	15 (15%)	< 0.001

M: mean; SD: standard deviation; independent samples t-test for continuous variables and chi-square test for categorical variables.

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Hospital de Clínicas de Porto Alegre* under the protocol number 15-0332. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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EDITORIAL

Blood Transfusion in Cardiac Surgery: Less is More?

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Editorial related to the article: Adverse Events and Risk Factors of Blood Transfusion in Cardiovascular Surgery: A Prospective Cohort Study

Blood transfusion is one of the most common medical procedures,[1] and a major part of these are performed during cardiac surgeries. The incidence of perioperative transfusion in cardiac surgeries varies from 40 to 90%,[2] according to the complexity of the procedure and the protocols adopted in each institution.

The study by Tagliari et al.,[3] published in the International Journal of Cardiovascular Sciences, analyzed the use of blood transfusion and postoperative outcomes within 30 days in patients undergoing cardiac surgery in a Brazilian tertiary hospital between 2015 and 2017. In this prospective cohort, subjects were divided into those who received transfusion and those who did not. Patients most likely to receive blood transfusion were patients with previous cardiac surgery, longer time of cardiopulmonary bypass, chronic kidney disease recent use of oral anticoagulants and antiplatelet agents, left ventricular ejection fraction less than or equal to 30%, lower preoperative hemoglobin levels, and changes in coagulation, urea and creatinine tests. Patients in the transfused group had more severe disease than those in the non-transfused group, with more patients reoperated and taking medications that could interfere with blood coagulation, both factors associated with increased bleeding and need for transfusion. However, blood transfusion was an independent risk factor for mortality in multivariate analysis when adjusted for major confounders. Transfused patients had higher mortality, higher rates of bronchopneumonia and acute kidney injury, longer hospital stay and mechanical ventilation. The authors concluded that blood transfusion should be reconsidered in cardiac surgery, because even transfusion of a blood component unit was associated with a worse postoperative outcome. Since transfusion is one of the few modifiable factors that may worsen the prognosis of surgery, strategies to prevent transfusion should be encouraged. The main criticism about this study is that, as an observational one, had no possibility of randomization, with high chance of bias, which made it difficult to establish a causal relationship.

Finding the right balance between the risks and benefits of transfusion is a challenge that has been the subject of recent studies. Common complications of blood transfusion are described in Table 1;[4] these range from mild to severe and may even lead to death. The most common reactions, such as nonhemolytic fever and allergic fever, are self-limiting and mild in intensity. Acute hemolytic reaction is rare, but potentially fatal, and is associated with patient's misidentification. Transfusion-related acute lung injury (TRALI) is currently the leading cause of blood transfusion-related mortality. Together with transfusion-associated circulatory overload (TACO), TRALI causes respiratory dysfunction that adds morbidity to the patients' clinical condition, especially in the context of cardiac surgery. Immunomodulation and transmission of infectious agents are other potential complications of blood transfusion.

The combination of overuse of blood,[1] transfusion-related risks and limited availability of blood components stimulated the development of restrictive transfusion strategies and led to the development of patient blood management (PBM). PBM consists of a set of actions aimed at reducing the need for transfusion by encouraging detection and treatment of anemia before surgery, use of surgical techniques and several procedures focused on preservation of patient's own blood, use of medications that reduce bleeding, and discontinuation of others that may interfere with blood coagulation. PBM strategies are also aimed at reducing blood collection for

Keywords

Blood Transfusion/methods; Thoracic Surgery/complications; Risk Factors; Mortality; Perioperative Care.

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Table 1 - Frequency of acute blood transfusion reactions

Reaction	Characteristics	Frequency
Febrile non-Hemolytic Transfusion Reaction (FNHTR)	Unexplained fever with or without chills/rigors	1-3:100
Allergic	Urticaria, angioedema, dyspnea, shock	1:100-1:500 (minor) to 1:20,000-1:50,000 (severe)
Acute Hemolytic Reaction	Fever, rigors, chest/abdominal/low back pain, shock, hemoglobinuria	1:12,000 – 1:100,000
Bacterial Sepsis	Fever, chills, rigor, shock, nausea, respiratory distress	<1:10,000 – <1:250,000
Transfusion Associated Circulatory Overload (TACO)	Respiratory distress, nausea, anxiety, increased blood pressure, dyspnea, cough, onset within 6six hours of transfusion	1:100 – 1:1,000
Transfusion-related Acute Lung Injury (TRALI)	Severe dyspnea and cyanosis, respiratory failure within six hours of transfusion, absence of left atrial hypertension	<1:5,000

Adapted from Faed, J.[4]

laboratory tests, avoiding intraoperative hypothermia, and encouraging the use of point of care[6] techniques for screening and management of coagulopathies. Recent guidelines indicate the use of restrictive transfusion in many clinical and surgical conditions. The main pillars of PBM are summarized in Figure 1.[5]

In the context of cardiac surgery, Mazer et al.[7] demonstrated that, in medium to high-risk patients, restrictive transfusion strategies were not inferior to the liberal transfusion group regarding death from any cause, acute myocardial infarction, stroke, acute renal injury, and new-onset renal failure requiring dialysis

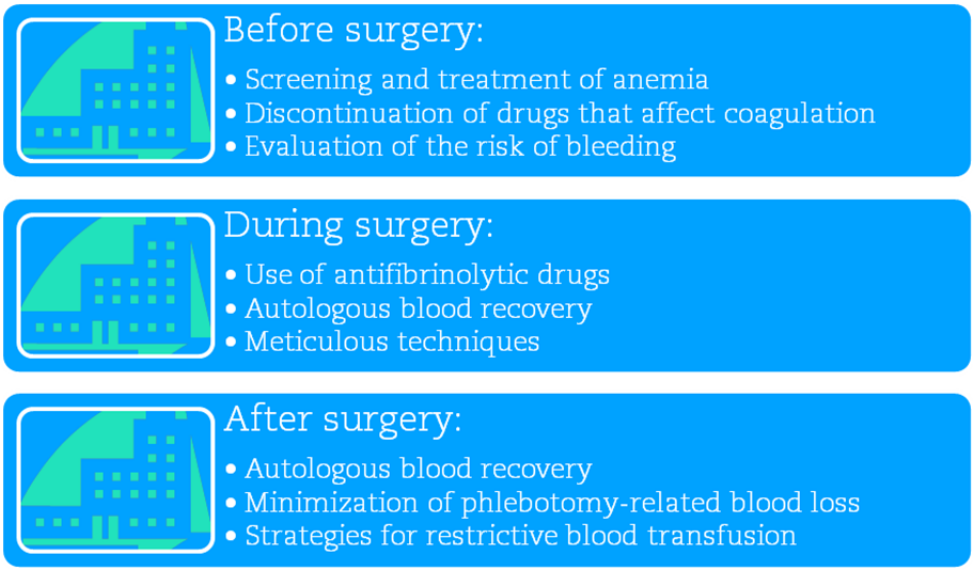

Figure 1 - Main actions in blood transfusion management.
Adapted from: Spahn D.R., Goodnough L.T.[5]

both in the immediate postoperative period[7] and within six months after surgery.[8] Likewise, Murphy e al.[9] concluded in their studies that there was no difference regarding postoperative complications and costs when using a restrictive or liberal threshold for transfusion. Also, in the TRICS III study,[7] more than half of the patients were older than 74 years old, demonstrating that restrictive transfusion protocols can also be used in the elderly population. The TRACS study,[10] conducted with a group of Brazilian patients in 2010, had already shown the non-inferiority of the restrictive transfusion strategy in patients undergoing cardiac surgery within 30 days.

Hensley et al.,[6] demonstrated that transfusion is more common in patients reoperated for cardiac surgery, despite the use of PBM. Dorneles et al.,[11] also found more infectious complications and acute kidney injury, and longer hospital stay in patients undergoing cardiac surgery who received blood transfusion. These results corroborate the findings of Tagliari et al.[3]

Unnecessary transfusion is a risk to the patient, in addition to increasing the cost of treatment and consuming limited financial resources that may not be available when needed.[6] Despite available guidelines, changes are slow in the real world. Many professionals are unaware of or do not adhere to current recommendations.[6] Guidelines can only bring benefits to patients when implemented,[2] and many transfusions are performed due to the ready availability of blood. Despite these setbacks, red blood cell transfusions have fallen worldwide, although this has not been seen in platelet and plasma concentrate transfusions.[12,13]

Considering the risks and benefits of blood transfusion, restrictive transfusion thresholds should be considered the standard for cardiac surgery, but attention should be paid to the peculiarities of each patient.

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ORIGINAL ARTICLE

Association Between Chocolate Consumption and Severity of First Infarction

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Abstract

Background: Cardiovascular diseases, such as acute myocardial infarction, are the main causes of death in the world. The flavonoids present in chocolate can have benefits for people who have risk factors to the development of cardiovascular diseases and have a coadjuvant effect on known therapies.

Objective: To analyze the association between chocolate consumption, severity of coronary lesions, risk factors and severity of the first infarction in patients attended at the Cardiology Institute of Santa Catarina and other hospitals in the State of Santa Catarina.

Methods: Subanalysis of the Catarina Heart Study cohort, evaluated 350 patients with first myocardial infarction. We evaluated clinical, echocardiographic, hemodynamic laboratorial variables. We used chi square test to evaluate qualitative variables, t student test in the case of parametric variables and U Mann Whitney test in non-parametric variables. We considered significant $p < 0,05$.

Results: Lower prevalence of hypertension (43.2% % vs. 62.3% p = 0.003), diabetes mellitus (13.5% vs. 25.7%, p = 0.027) and smoking (24.3% vs. 37.7%, p = 0.032) among those who consume chocolate. Higher use of alcohol (40.5% vs. 26.4%, p = 0.018) and drugs (9.5% vs. 3.3%, p = 0.023) among those who consumed chocolate. Among the patients who consumed chocolate, there was a negative correlation between amount consumed and Syntax (r = -0.296, p = 0.019).

Conclusion: There was association between chocolate consumption and lower prevalence of hypertension, diabetes and smoking. There was no association between amount of chocolate consumed and post-infarction ventricular function and TIMI frame count. Higher prevalence of alcohol and drug use among those who consume chocolate. Negative correlation between Syntax and the amount of chocolate consumed. (Int J Cardiovasc Sci. 2019;32(6):576-582)

Keywords: Cardiovascular Diseases/mortality; Myocardial Infarction/physiopathology; Flavonoids; Polyphenols; Cacao.

Introduction

Cardiovascular diseases (CVD) are the leading cause of death worldwide.[1] These include acute myocardial infarction (AMI) which, from 2008 to 2017, accounted for 813,982 hospital admissions in Brazil.[2]

There is evidence of the link between reduction of risks of cardiovascular events and chocolate consumption in larger amounts, as chocolate contains flavonoids.[3,4] Studies indicate that flavonoids present in cocoa or cocoa products have the potential to benefit people with risk factors for the development of CVD through different mechanisms, such as anti-inflammatory action.[5-8] This is of great importance, as AMI is also characterized as an inflammatory disease.[9]

However, aspirin and statins are the only medications that fight inflammation and are used in AMI.[9] The inclusion of a relatively high amount of high-flavonoid

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cocoa in the daily diet could reduce cardiovascular outcomes, make them less severe and improving the prognosis of patients after an AMI episode.

Chocolate, whose composition is rich in flavonoids, may have an adjuvant effect to ischemic disease therapies, mainly due to the anti-inflammatory action.[5-7] However, although there are indications that chocolate may decrease the occurrence of AMI events, there is no evidence that it may be associated with lower complexity of coronary lesions in patients with AMI or that AMI may be less severe. This study analyzes the association between chocolate consumption and the complexity of coronary lesions, as well as the risk factors for cardiovascular outcomes and the severity of first infarction.

Methods

This study is a subanalysis of the Catarina Heart Study[10] — a prospective cohort study that began in July 2016 that is intended to evaluate 1,426 patients by the year 2020 and proposes a follow-up of thirty days and one year. The patients selected were diagnosed as having the first AMI and were assisted at the Cardiology Institute of Santa Catarina and other hospitals in the State of Santa Catarina. Once the patients' consent was taken, they answered a questionnaire that included different clinical, laboratory, electrocardiographic, echocardiographic and angiographic variables from July 2016 to July 2018.

Inclusion criteria were minimum 18 years of age, presence of precordial pain suggestive of AMI associated with electrocardiogram with new ST-segment elevation at point J in two contiguous leads with ≥ 0.1 mv limits on all leads, in addition to the V2-V3 leads in which the following limits apply: ≥ 0.2 mv in men ≥ 40 years of age; ≥ 0.25 mv in men < 40 years of age, or ≥ 0.15 mV in women or the presence of precordial pain suggestive of AMI associated with elevation of troponin I or CK-MB above the 99th percentile of the upper reference limit. Exclusion criterion was the presence of previous AMI.

The primary endpoint of this study evaluated the association between chocolate consumption with severity, complexity and AMI complications. Secondary outcomes assessed the association between chocolate consumption and prevalence of classic cardiovascular risk factors and the correlation between chocolate consumption and variables associated with the complexity of coronary lesions and severity of infarction in patients who ate chocolate.

Measurement of chocolate consumption was done by asking the patients whether they had chocolate or not and the number of chocolate bites eaten per week. 43 grams were used as standard for each bite eaten, and the total consumption per week was divided by the days in order to evaluate the average consumption in grams per day.

To assess the severity and complexity of AMI, three variables were used: Syntax, Thrombolysis in Myocardial Infarction (TIMI) frame count and Left Ventricular Ejection Fraction (LVEF). The first variable is a score that considers the location, quantity and the respective repercussion of the lesions in the functioning of the coronary arteries, and the higher the Syntax index, the greater the complexity of coronary lesions.[11] The TIMI frame count evaluates the number of film frames from the beginning of the contrast injection to the range of the coronary artery end. It is an estimate of arterial perfusion performed after therapeutic management.[12] This variable was only applied for patients with AMI with ST-segment elevation. LVEF was estimated by transthoracic echocardiography within 72 hours after AMI.

Hypertension, diabetes mellitus and dyslipidemia were self-reported at the time of the study. Chocolate consumption was considered positive in those who ate it regularly, at least once a week. Patients with a positive family history were considered those who had first-degree relatives with coronary artery disease, women ≤ 65 years old and men ≤ 55 years old. Regarding the use of drugs and alcohol, any consumption of these substances was considered positive. As for relevant smoking, consumption of any tobacco at the time of the interview.

Statistical analysis

The current study sample was calculated as 158 patients with a power of 90% and alpha = 0.05 for a correlation of 0.35 between the consumption of chocolate per day in grams. Data were organized into a table and analyzed by the software SPSS 13.0. The qualitative variables were expressed using absolute and percentage numbers and evaluated using the chi-square test. Quantitative variables with normal distribution were presented as mean ± standard deviation and were evaluated using Student's t-test for independent samples, while quantitative variables with non-normal distribution were presented as median and interquartile range and were evaluated using Mann-Whitney's U test. Normality was evaluated using the Kolmogorov-Smirnov test. Among patients who consumed chocolate, the amount in grams

per day was correlated with the variables of AMI severity using Spearman's correlation. In this study, $p < 0.05$ was considered statistically significant.

The Catarina Heart Study was submitted to the Research Ethics Committee of *Instituto de Cardiologia de Santa Catarina* pursuant to Resolution 466/12, under the protocol 55450816.0.1001.0113. The patients were informed about the secrecy of the information collected in the questionnaire, and signed a consent form before applying the questionnaire.

Results

From July 2016 to July 2018, 350 patients aged 59.0 ± 11.0 years were evaluated. Most patients were males (64.0%) and hypertensive (58.3%). Regarding chocolate, 21.1% of the patients consumed it regularly, while Syntax presented a median value of 12.0 (6.0 — 19.0). The prevalence of diabetes mellitus in the interviewed population was 23.1% and the diagnosis of infarction with ST-segment elevation was delivered in 169 patients (48.0%). Median chocolate consumption among those who had chocolate was 21.5 grams per day. The other variables are presented in Table 1.

The study showed an association between chocolate consumption and the absence of systemic arterial hypertension: 43.2% of the patients who consumed chocolate were hypertensive, while 62.3% of those who did not eat the food had hypertension ($p = 0.003$). Likewise, there is a significant association between absence of diabetes mellitus and consumption of chocolate: 13.5% of patients who consume chocolate have the disease, while 25.7% of those who do not eat chocolate have diabetes, with $p = 0.027$. There was a higher prevalence of smokers among patients who did not consume chocolate (37.7%) compared to those who consumed chocolate (24.3%), with $p = 0.032$.

In addition, there was greater consumption of alcoholic beverages among those who consume chocolate (40.5%) compared to those who do not consume chocolate (26.4%), with $p = 0.018$. The group that used drugs was bigger among those who consumed chocolate (9.5%), compared to those who do not consume chocolate (3.3%), with $p = 0.023$. Dyslipidemia and family history of cardiovascular diseases were not associated with chocolate consumption. (Table 2).

Table 1 - Demographic, clinical and lifestyle characteristics of the study population

Variables	
Male sex - N (%)	224 (64.0)
Hypertension - N (%)	204 (58.3)
Diabetes mellitus - N (%)	81 (23.1)
Dyslipidemia - N (%)	120 (34.4)
Family history - N (%)	153 (43.7)
Smoking - N (%)	122 (34.9)
Alcohol - N (%)	103 (29.4)
Chocolate consumption - N (%)	74 (21.1)
ST-segment elevation infarction - N (%)	39 (50.6)
Age*	59.0 ± 11.0
Body mass index*	27.6 ± 5.0
Waist*	95.5 ± 13.8
Weight - median (AIQ)	74.0 (65.0 – 83.0)
Chocolate† - median (AIQ)	21.5 (6.1 – 56.8)
Syntax - median (AIQ)	12.0 (6.0 – 19.0)
TIMI frame - median (AIQ)	22.0 (14.0 – 34.0)

** = Mean ± standard deviation, † = Chocolate grams per day, only among those who consume chocolate.*

Table 2 - Association between chocolate consumption and risk factors

Variables	Chocolate consumption		p value
	Yes	No	
	n (%)	n (%)	
Hypertension	32 (43.2)	172 (62.3)	0.003
Diabetes mellitus	10 (13.5)	71 (25.7)	0.027
Dyslipidemia	23 (31.1)	97 (35.3)	0.500
Family history	39 (52.7)	114 (41.3)	0.079
Smoking	18 (24.3)	104 (37.7)	0.032
Alcohol	30 (40.5)	73 (26.4)	0.018
Drugs	7 (9.5)	9 (3.3)	0.023

The mean LVEF among those who consumed chocolate (48.7 ± 15.3) did not present any significant difference to those who did not consume chocolate (51.2 ± 13.0), with p = 0.228. The other variables are presented in Table 3.

Among the patients who consumed chocolate, there was a negative correlation between the amount consumed and Syntax (r = -0.296, p = 0.019), characterizing a lower complexity of coronary lesions in patients consuming more chocolate. (Table 4).

Discussion

This study analyzed the complexity of coronary lesions and the severity of the first infarction with chocolate consumption. The data showed that, among patients who consume chocolate, there is a negative correlation between Syntax and the amount consumed, characterizing lower severity of coronary lesion in patients who had chocolate in larger amounts. In addition, there was a lower prevalence of hypertension, diabetes and smoking among those who consumed chocolate.

Table 3 - Association between chocolate consumption and quantitative variables

Variables	Chocolate consumption		p value
	Yes	No	
Age*	58.5 ± 11.6	59.2 ± 10.9	0.639
BMI*	27.9 ± 4.7	27.6 ± 5.1	0.624
Waist*	97.4 ± 14.8	95.0 ± 13.5	0.202
LVEF*	48.7 ± 15.3	51.2 ± 13.0	0.228
Weight†	74 (64.0–86.0)	74 (65.0 - 82.0)	0.386
Syntax†	14 (6.8 - 18.6)	11 (6.0 - 19.0)	0.778
TIMI frame†	28 (12.0 - 48.0)	20 (14.0 - 32.5)	0.360

** = Mean±standard deviation, † = Median (Interquartile range); BMI: Body mass index; FEVE: Left ventricular ejection fraction.*

Table 4 - Correlation between chocolate consumption and variables associated with coronary complexity and severity of infarction in patients who had chocolate

Variables	r	p value
LVEF*	-0.070	0.613
TIMI frame	0.131	0.499
Syntax	-0.296	0.019

** = Left ventricular ejection fraction.*

Similarities were found in the literature regarding the profile of the interviewed population, with a higher prevalence of males in patients affected by AMI.[13-17] In addition, it was found that most of these patients had hypertension as a risk factor for the cardiovascular event[13-16]. Regarding smoking, less than half of the population interviewed had this addiction, as also found in other publications.[14,15,17]

There was a lower prevalence of hypertension among those who consumed chocolate. This relationship has also been found in several other studies, which have shown reduced blood pressure with consumption of flavonoids, which are present in foods such as chocolate.[4,8,18,19] This association can be justified by the fact that flavonoids would improve endothelial function, since endothelial dysfunction is associated with hypertrophy and arterial wall stiffening.[18,20,21] One of the mechanisms of endothelial function improvement is the increased bioavailability of nitric oxide from the consumption of flavonoids, which results in a vasodilator effect and increases blood flow in the vessels, with consequent reduction in blood pressure levels.[22,23] Another important route of the benefits of flavonoids in reducing blood pressure is the inhibition of the angiotensin converting enzyme activity, as the formation of angiotensin II results in vasoconstriction and increased blood pressure, which increases the risk of cardiovascular outcomes.[23,24]

An association was also found between the use of alcohol and drugs with chocolate consumption, and a higher prevalence of consumption of these substances among patients have drink chocolate on a weekly basis. Some studies justify this relationship by the addictive characteristics of chocolate, which has compounds that can cause addiction, as in other substances, such as alcohol and other drugs.[25,26] Moreover, chocolate addiction also includes the typical stages of alcoholism and other drug addictions, such as relapse. At this stage, the individual goes back to having chocolate compulsively, without thinking about the adverse effects of exaggerated consumption, which further corroborates the additive effect of chocolate, which may prevail in those who are prone to addictive behaviors.[27] Another relevant point is that drugs, such as marijuana, are appetite stimulants, so they can increase the consumption of foods, including chocolate.[28,29]

There was also an association between chocolate consumption and lower prevalence of smoking, but this finding only seems to be coincidental.

An association between chocolate consumption and diabetes mellitus was also found. Studies suggest an inverse relationship between the prevalence of diabetes mellitus and chocolate intake.[8,30-33] Research studies have found that one of the mechanisms of this inverse relationship between chocolate and diabetes mellitus is the increased sensitivity to insulin caused by flavonoids, which helps to reduce blood glucose in the stream and can delay the onset of the disease.[34,35] An important point, reported in one of the studies analyzed, is that flavonoid consumption as a protective effect of diabetes mellitus should be recommended with caution. This is relevant because the study argues that large amounts of sugars and calories can be found in a number of cocoa products rather than high flavonoid content, which can generate a rebound effect, worsening the glycemic control of patients with type 2 diabetes mellitus.[36] Some authors believe that the beneficial effect of flavonoids also occurs in patients who already have established diabetes mellitus, reducing the risk of cardiovascular outcomes in these individuals, such as AMI.[19,20] However, it is relevant to express that patients who already have diabetes mellitus are advised not to consume sugars and, in this study, the patients interviewed already had the disease and, therefore, should eat less chocolate.

Among the patients who consumed chocolate, there was a negative correlation between Syntax and the amount of chocolate consumption. The median chocolate consumption among the patients was 21.5 grams per day. There is evidence that a daily dose of 80 mg could promote beneficial vascular outcomes.[18] There is also data showing an immediate improvement in coronary flow after consumption of 45 grams of chocolate with high cocoa content.[37] The correlation between higher amount of chocolate consumption and lower complexity of coronary lesions may be justified by the anti-inflammatory properties of the flavonoids present in chocolate.[5-7] Another important mechanism is the antioxidant action of flavonoids, which helps reducing free radicals and may result in coronary lesions of lower severity.[7,38] Also, a recent clinical trial has shown that chocolate with high cocoa content improves endothelial function (assessed through flow-mediated vasodilatation of the brachial artery) in patients with established coronary artery disease.[39] In addition to that, the beneficial effects of chocolate consumption are associated with lower mortality due to cardiovascular outcomes, which suggests lower severity of AMI in those who consume chocolate in higher amounts.[8,40] However, it was not possible to establish the exact amount of recommended consumption in order to reduce the severity of the cardiovascular outcome. It is worth noting that, although there was a negative correlation between the complexity of coronary lesions and the amount of chocolate consumed, there was no association between the amount consumed and other variables associated with severity, such as post-infarction ventricular function (LVEF) and coronary flow after primary angioplasty (TIMI frame count).

Regarding the limitations of this study, the comorbidities of patients and the risk factors for cardiovascular outcomes were evaluated at a single moment, which may compromise the cause-effect relationship. Variables such as alcoholism and smoking were self-reported, which could underestimate their prevalence. Also, some risk factors such as prior coronary artery bypass grafting or kidney disease requiring dialysis were not exclusion criteria and could influence the outcomes: however, the prevalence of these variables was less than 1% (data not shown). Type I error may have occurred in some findings, such as the association between chocolate consumption and lower prevalence of smoking. It was not possible to measure the proportion of cocoa present in the chocolate consumed. Another limitation of the study was the lack of income evaluation, since there could be a bias of contamination, since higher consumers of chocolate could be those with higher incomes and greater access to health services, even though the evaluation was performed exclusively in public hospitals. Besides, most patients interviewed were from a single hospital. These biases, however, do not invalidate the data found: literature data on the subject are still scarce and this evidence justifies new research studies such as clinical trials designed with adequate power to evaluate the association between chocolate consumption in patients with ischemic heart disease and the reduction of outcomes such as mortality.

Conclusion

There was an inverse association between chocolate consumption and hypertension, diabetes mellitus and smoking. There was also an association between

chocolate consumption and higher prevalence of drug and alcohol use. There was no association between the amount of chocolate consumed and post-infarction ventricular function (LVEF) and coronary flow after TIMI frame count. There was also a negative correlation between Syntax and the amount of chocolate consumed, suggesting lower severity of coronary lesion in patients who consumed chocolate in larger amounts.

Author contributions

Conception and design of the research: Duarte HM, Moreira DM, Silva RL, Fattah T. Acquisition of data: Duarte HM, Moreira DM, Silva RL, Fattah T. Analysis and interpretation of the data: Duarte HM, Moreira DM, Silva RL, Fattah T. Statistical analysis: Duarte HM, Moreira DM. Writing of the manuscript: Duarte HM, Moreira DM, Oliveira MCR, Jung R. Critical revision of the manuscript for intellectual content: Duarte HM, Moreira DM, Oliveira MCR, Jung R.

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 work of course conclusion submitted by Heloyse Martins Duarte, from *Universidade do Sul de Santa Catarina* (Unisul).

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Instituto de Cardiologia de Santa Catarina* (ICSC) under the protocol number 55450816010010113. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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EDITORIAL

Chocolate Consumption: Benefits in Cardiovascular Disease

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Editorial related to the article: Association Between Chocolate Consumption and Severity of First Infarction

The major risk factors for cardiovascular diseases (CVDs) are directly related to endothelial dysfunction, reduced bioavailability of nitric oxide, vasoconstriction, oxidative stress, and inflammation.[1] Several studies have been stimulating the use of non-pharmacological strategies to reduce these risk factors. In this sense, some nutrients and bioactive compounds in foods have demonstrated beneficial effects. Chocolate, for example, has gained attention for its content of cocoa, a polyphenols-rich food, and flavanols.[2]

In the paper entitled "Association between chocolate consumption and severity of first infarction", Duarte et al.,[3] found that patients with the first acute myocardial infarction (AMI) who consumed chocolate, showed a low Syntax index, indicating low complexity of coronary lesions. The authors also demonstrated a negative correlation between Syntax and the amount of chocolate consumed, and an association between chocolate consumption and absence of systemic arterial hypertension and diabetes. The cardioprotective effects of polyphenols present in chocolate have been studied, and a series of results supported the protective effects of cocoa and chocolate intake on CVDs. These protective effects are associated with vasodilation, improvement of endothelial function, platelet aggregation, increase in HDL and reduction in LDL levels.[4]

Recently, studies have demonstrated the relationship between gut microbiota and CVD, and it would be interesting to determine the possible effects of cocoa polyphenols on these microbioma. Flavanols are absorbed in the small intestine, metabolized in the liver and excreted in the urine.[5-8] A studied conducted in healthy individuals showed that consumption of a high-cocoa flavanol beverage significantly increased the growth of Lactobacillus spp. and Bifidobacterium spp. in comparison to a low cocoa flavanol drink,[6] promoting anti-inflammatory effects in these individuals.

Obesity is one of the main risk factors for CVDs. Experimental studies revealed that cocoa could reduce visceral adipose tissue and synthesis of fatty acids, enhance thermogenesis and appetite response, and increase the expression of adiponectin and glucose transporter.[4,9-11]

In conclusion, polyphenols present in chocolate seem to be a promising therapeutic strategy for CVD patients due to its activity in inflammatory modulation, endothelial dysfunction, gut microbiota, lipid status and obesity. In my point of view, further clinical studies are necessary to compare the best sources of polyphenols, chocolate or cocoa, and to determine the most effective way to offer these bioactive compounds to patients.

Keywords

Cardiovascular Diseases/mortality; Myocardial Infarction/ physiopathology; Flavonoids; Polyphenols; Chocolate.

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ORIGINAL ARTICLE

Left Atrial Size Contribution to the Predictive Capacity of Two Scores for Atrial Fibrillation in the Postoperative Period of Cardiac Surgeries

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Abstract

Background: Postoperative atrial fibrillation (POAF) is a common complication associated with undesirable outcomes; hence, the provision of appropriate tools is important to help identify patients at risk.

Objectives: To evaluate the predictive capacity of the $CHADS_2$ and CHA_2DS_2-VASc scores, alone and combined with left atrial (LA) size, for the onset of POAF in patients undergoing coronary artery bypass grafting and/or valvular surgery.

Methods: We performed a retrospective cohort study on 144 patients. A decision tree was used to identify the cut-off values of the $CHADS_2$ and CHA_2DS_2-VASc scores and LA size in order to calculate sensitivity, specificity, predictive-value positive (PVP), and predictive-value negative (PVN), in addition to regression models. The receiver operating characteristic (ROC) curve was used to estimate the accuracy of the models. The level of significance adopted was 5%.

Results: Patients who developed POAF were older (p = 0.050), had reduced left ventricular ejection fraction (p = 0.045), longer hospital length of stay (p = 0,018), but their mean $CHADS_2$ (p = 0.077) and CHA_2DS_2-VASc (p = 0.109) scores were similar to those of patients with no arrhythmia. LA size improved the predictive capacity of the $CHADS_2$ score, in terms of specificity and PVP, and of the CHA_2DS_2-VASc score, in terms of sensitivity and PVN. However, the $CHADS_2$ (OR = 1.198; CI95% = 0.859-1.156) and CHA_2DS_2-VASc (OR = 1.047; CI95% = 0.784-1.401) scores were not predictors of POAF, either alone or in combination with LA size (OR = 1.163; CI95% = 0.829-1.648 and OR = 1.065; CI95% = 0.795-1.433).

Conclusion: The $CHADS_2$ and CHA_2DS_2-VASc scores alone or in combination with LA size did not show good predictive capacity for POAF. (Int J Cardiovasc Sci. 2019;32(6):585-593)

Keywords: Atrial Fibrillation; Arrhythmias, Cardiac/complications; Postoperative Complications; Cardiac Surgical Procedures.

Introduction

Atrial fibrillation (AF) is cardiac arrhythmia resulting from grossly disorganized atrial electrical activity, due to multiple and continuous intra-atrial reentrant circuits, characterized by impaired atrial contraction, followed by absent atrial systole.[1] Certain pathological heart conditions, such as those evolving with structural changes, or surgical manipulation of the organ, may increase the risk of developing AF.[2] Arrhythmia occurs in about 30% of patients in the postoperative of coronary artery bypass graft surgery and in up to 60% of postoperative patients submitted to concomitant valvular surgery.[3,4]

The consequences of AF, especially when it is irreversible, are clearly associated with the risk of thromboembolic phenomena and mortality, affecting 11% of the elderly population, up to 30 days after the

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diagnosis.[5] In addition, cognitive changes, heart failure and worsened quality of life have been reported.[6,7]

Having tools for predicting the risk of developing AF in the postoperative period of cardiac surgery (POAF) may contribute to the implementation of measures designed to prevent and improve the monitoring of patients at risk. Different models have been tested to that end,[4,8,9] such as the $CHADS_2$ and CHA_2DS_2-VASc scores.[9-11]

Although these scores have been originally developed to assess the risk of thromboembolism in patients with AF, their items include risk factors for the onset of arrhythmia itself.[1,2,12] However, the results of studies that have evaluated the predictive capacity of the $CHADS_2$ and CHA_2DS_2-VASc scores in relation to POAF are controversial.[9,10,13]

Recently, a study demonstrated that left atrial (LA) size was the best variable to discriminate between patients with or without POAF.[14] To our knowledge, no study has assessed the contribution of LA size evaluation to the predictive ability of those scores. The objectives of this study were to verify the predictive capacity of the $CHADS_2$ and CHA_2DS_2-VASc scores for the onset of POAF in patients submitted to coronary artery bypass grafting and/or valvular surgery; and to assess the contribution of LA size to the predictive capacity of these scores.

Methods

This is a retrospective cohort study. Data were collected in the period from June 2017 to October 2017 at the Heart Institute of the Clinics Hospital of the School of Medicine of the University of São Paulo (INCOR-HC-FMUSP).

Population of interest and sample collection

The population of interest for this study included patients submitted to coronary artery bypass grafting and/or valvular surgery, either alone or in combination, during the year 2015.

The sample of the study was determined as 144 patients, considering an incidence of POAF as high as 50%, number of surgical procedures performed in 2015 at the institution, area of data collection and assuming type I error of 5%. We included medical records of patients aged 18 years or more, who had undergone coronary artery bypass grafting and/or valvular surgery. We excluded the medical records of patients diagnosed with pre- or intraoperative AF, from those who had undergone other types of associated surgeries or whose medical records were lacking information needed for the development of this study.

We located medical records for 1,225 individuals in the hospital's electronic records system. Out of these, 234 were excluded (188 belonged to patients with a diagnosis of pre-operative AF and 46, to patients who had undergone other surgical procedures concomitantly). The other medical records (n = 991) were revised and divided into two groups: with POAF (n = 148) and without POAF (n = 843) and, subsequently, they received codes which were used to draw the final sample.

In order to minimize the interference of external factors in this study, six medical records were chosen from the group with POAF and six from the group without POAF every month, for a total of twelve per month. The draw was carried out electronically (sorteador.com). Therefore, each group was composed of 72 patient records.

The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Ethics Committee in Research (approval number 1.957.400). The need for informed consent form was waived because all data were obtained from the patient records.

Variables

The clinical and demographic variables analyzed were: age, sex, skin color, smoking, $CHADS_2$ and CHA_2DS_2-VASc scores, preoperative echocardiographic data (left atrial size, left ventricle diastolic diameter and left ventricular ejection fraction), use of continuous medication in the preoperative period, intraoperative data (type of cardiac surgery, time of anesthesia, use of extracorporeal circulation (ECC) and the time of ECC); and postoperative data (POAF diagnosis, immediate postoperative laboratory tests, in the immediate postoperative, length of stay and death). Postoperative and POAF data were analyzed during the whole period of hospitalization. The onset of arrhythmia in the postoperative period, registered in electronic medical record system, was considered an episode of POAF.

$CHADS_2$ and CHA_2DS_2-VASc

The $CHADS_2$ score was proposed after scientific evidence suggest that certain factors other than AF contributed to the onset of thromboembolic phenomena in these patients.[5] The identification of the major factors associated with

thromboembolism culminated with the publication in 2001 of this risk score.[12] The main purpose was to identify outpatients at risk who could benefit from treatment with oral anticoagulants. $CHADS_2$, however, identifies high-risk patients. Nevertheless, due to the inherent risks of arrhythmia itself, as well as to the particular contribution of other risk factors for the onset of thromboembolism, the CHA_2DS_2-VASc score was proposed to identify real low risk patients who did not need anticoagulation.[5]

The $CHADS_2$ score consists of four items that count for one point each (congestive heart failure, age > 75 years and diabetes mellitus) and one item that counts as 2 points (stroke and transient ischemic attack). The total score ranges from zero to six points. Originally, the higher the score, the higher the risk of thromboembolic phenomena.[12]

The CHA_2DS_2-VASc score includes three additional factors (vascular disease, age 65-74 years and female gender); each additional factor counts as 1 point, while an age > 75 years was upgraded to two points. The total score ranges from zero to nine. Originally, the higher the score, the higher the risk of thromboembolic phenomena.[15]

Data analysis

Categorical variables were described by absolute and relative frequencies, and analyzed using Chi-square test and Fisher's exact test. Quantitative variables were described by using central tendency and dispersion measurements and Student's t-test. The cut-off values of the $CHADS_2$ and CHA_2DS_2-VASc sores and LA size were determined via decision tree. The predictive capacity of the scores alone and in combination with the LA size was determined by sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and logistic regression models. The assumption of normality of the scores was not tested, because they are discrete variables. The adjustment of the models was evaluated by the area under (AUC) the Receiver Operating Characteristic (ROC) curve. All analyses were performed using the statistical software R 3.4.3. The significance level adopted was 5%.

Results

We selected 144 medical records of patients submitted to coronary artery bypass grafting and/or valvular surgery in 2015, half of whom had developed POAF. The demographic and clinical characteristics of interest, registered in the preoperative period, are described in Table 1.

Although table 1 does not show statistically significant difference between patients with and without POAF, in relation to age, it is possible to consider that, clinically,

Table 1 - Demographic and clinical characteristics recorded in the postoperative period of patients with (n = 72) and without (n = 72) postoperative atrial fibrillation

	With POAF	Without POAF	p-value
Age, in years, mean (SD)	65.8 (10.7)	61.8 (13.3)	0.050*
Male gender, n(%)	44 (61.1)	47 (65.3)	0.604†
Skin color, n(%)			
White	61 (84.7)	61 (84.7)	0.678†
Other	11 (15.3)	9 (12.5)	
Not informed		2 (2.8)	
Active smoking, n(%)	9 (12.5)	12 (16.6)	0.478†
Preoperative echocardiographic data			
Left atrial size, in mm, mean (SD)	43.4 (6.6)	41.3 (6.3)	0.059*
LVDd, mm, mean (SD)	53.3 (7.7)	52.1 (7.0)	0.359*
LVEF %, mean (SD)	55.3 (12.4)	59.2 (10.6)	0.045*

POAF: postoperative atrial fibrillation; SD: standard deviation; LVDd: left ventricular diastolic diameter; (*) Student's t-test; (†) Pearson's chi-square test.

the age is associated with the onset of arrhythmia in the postoperative period (p = 0.050).

In relation to medication taken on a regular basis at home, the use of different classes was observed, among which, antihypertensives, antiarrhythmics, statins, antiplatelet agents, anticoagulants and diuretics. However, we only found statistically significant difference between patients with or without POAF in relation to the use of digitalis (0%, n = 0 vs 6.9%, n = 5, respectively; p = 0.026).

Laboratory tests results conducted in the preoperative period were not analyzed because they were not available for many patients. Table 2 describes the minimum and maximum values observed in laboratory tests results collected in the first 24 hours after surgery.

The other intra- and postoperative data of interest for this study are described in Table 3.

The $CHADS_2$ mean scores for patients with and without POAF were, respectively, 1.82+1.05 and 1.49+1.18 (p = 0.077). The CHA_2DS_2VASc mean scores, on the other hand, were, 3.38 + 1.53 and 2.96 + 1.56, in this sequence (p = 0.109). In order to evaluate the predictive capacity of these scores, alone or combined with LA size, we established the cut-off point of each score to better identify the patients who developed POAF (Chart 1).

Table 4 describes the predictive capacity of these scores, either alone or associated with LA size, to determine the onset of POAF.

Table 2 - Minimum and maximum values observed in the laboratory tests results conducted in the immediate postoperative period of patients with (n = 72) and without (n = 72) postoperative atrial fibrillation

	Minimum	p-value*	Maximum	p-value*
Magnesium, mEq/L, mean (SD)				
With AF	1.5 (0.4)	0.248	2.1 (0.5)	0.950
Without AF	1.6 (0.4)		2.1 (0.6)	
Potassium, mEq/L, mean (SD)				
With AF	3.8 (0.4)	0.251	4.4 (0.5)	0.780
Without AF	3.9 (0.9)		4.4 (0.9)	
Sodium, mEq/L, mean (SD)				
With AF	135.5 (3.2)	0.194	138.9 (3.7)	0.404
Without FA	136.6 (6.1)		139.6 (5.9)	
Calcium, mEq/L, mean (SD)				
With AF	1.15 (0.06)	0.406	1.25 (0.1)	0.984
Without AF	1.16 (0.06)		1.25 (0.1)	
CRP, mEq/L, mean (SD)				
With AF	8.4 (11.0)	0.019	111.1 (69.7)	0.099
Without AF	16.8 (27.4)		92.6 (64.1)	
Creatinine, mEq/L, mean (SD)				
With AF	1.0 (0.4)	0.277	1.4 (0.6)	0.601
Without AF	1.3 (1.6)		1.6 (1.7)	
Urea, mEq/L, mean (SD)				
With AF	38.1 (16.0)	0.840	48.0 (22.1)	0.210
Without AF	38.7 (18.5)		43.6 (19.8)	

SD: standard deviation; mEq/L: milliequivalents per liter; CRP: C-reactive protein; AF: atrial fibrillation; (*) Student's t-test.

Table 3 - Intra- and postoperative variables of patients with (n = 72) and without (n = 72) postoperative atrial fibrillation

	With POAF (n = 72)	Without POAF (n = 72)	p-value
Type of surgery, n(%)			
Coronary artery bypass grafting	36 (50.0)	35 (48.7)	
Valvular surgery	32 (44.4)	32 (44.4)	1.000*
Both	4 (5.6)	5 (6.9)	
ECC, n (%)	68 (94.4)	65 (90.2)	0.346†
Time of ECC, in hours, mean (SD)	1.4 (0.5)	1.5 (0.8)	0.726‡
Time of anesthesia, in hours, mean (SD)	7.2 (1.3)	7.3 (1.8)	0.640‡
Use of VAD in IPO, n (%)	71 (98.6)	72 (100.0)	1.000*
Total length of stay, in days, mean (SD)	17.8 (13.3)	12.6 (12.4)	0.018‡
Death, n (%)	3 (4.1)	10 (13.8)	0.042†

POAF: postoperative atrial fibrillation; SD: standard deviation; ECC: extracorporeal circulation; IPO: immediate postoperative period; VAD: vasoactive drug; (*) Fisher's exact test; (†)Pearson's chi-squared test; (‡) Student's t-test.

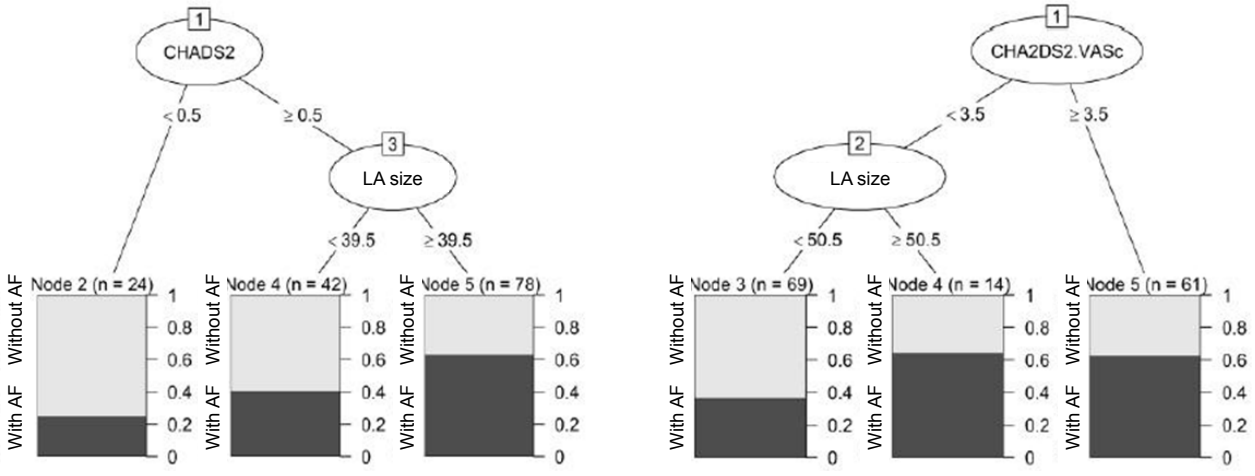

Chart 1 - Cut-off values for discrimination of patients with and without postoperative atrial fibrillation according to the $CHADS_2$ (A) and CHA_2DS_2-VASc (B) scores and left atrial size.

Tables 5 and 6 show logistic regression models of the $CHADS_2$ and CHA_2DS_2VASc scores alone and in association with left atrial size.

Chart 2 shows the ROC curve area for the scores alone or in association with LA size.

Discussion

The present study described the prediction capacity of the $CHADS_2$ and CHA_2DS_2VASc scores, alone or in association with LA size, to determine the onset of POAF

Table 4 - Sensitivity, specificity and positive and negative predictive values of $CHADS_2$ and CHA_2DS_2VASc scores, alone or in association with LA size, to determine atrial fibrillation following coronary artery bypass grafting and/or valvular surgery

	$CHADS_2 > 0.5$	$CHA_2DS_2VASc < 3.5$	$CHADS_2 > 0.5$ and LA > 39.5 mm	$CHA_2DS_2VASc < 3.5$ and LA > 50.5 mm
Sensitivity	91.7	52.8	68.1	65.3
Specificity	25.0	68.1	59.7	61.1
Predictive value positive	55.0	62.3	62.8	62.7
Predicitive value negative	75.0	59.0	65.1	63.8

LA: left atrial size.

Table 5 - Logistic regression model of the $CHADS_2$ score alone (Model 1) and in association with left atrial size (Model 2) for predicting the onset of postoperative atrial fibrillation following coronary artery bypass grafting and/or valvular surgery

		Odds ratio (CI 95%)	p-valor	AUC (CI 95%)
Model 1	$CHADS_2$	1.198 (0.859-1.156)	0.291	0.611 (0.518-0.714)
Model 2	$CHADS_2$	1.163 (0.829-1.648)	0.387	0.643 (0.552-0.733)
	LA size	1.049 (0.995-1.107)	0.078	

AUC: area under the curve; CI: confidence interval.

Table 6 - Logistic regression model of the CHA_2DS_2VASc score alone (Model 3) and in association with left atrial size (Model 4) for predicting the onset of postoperative atrial fibrillation following coronary artery bypass grafting and/or valvular surgery

		Odds ratio (IC 95%)	p-valor	AUC (CI 95%)
Model 3	CHA_2DS_2VASc	1.047 (0.784-1.401)	0.754	0.590 (0.497-0.683)
Model 4	CHA_2DS_2VASc	1.065 (0.795-1.433)	0.673	0.633 (0.542-0.724)
	LA size	1.052 (0.999-1.110)	0.061	

AUC: area under the curve; CI: confidence interval.

in patients undergoing myocardial revascularization surgery and/or valvular surgery. As far as we know, no other study had added the contribution of left atrial size to the prediction capacity of those scores. Having tools that allows us to predict the risk of POAF in an easy and reliable way is important because it could help identify patients at risk, who would benefit from more careful monitoring in the postoperative period, as well as, for the institution of prevention measures.

Patients with POAF were older compared to those who did not develop arrhythmia. Advanced age is, admittedly, a major risk factor for AF in patients in general[16,17] and in those undergoing cardiac surgery.[18,19] In fact, population aging, especially in emerging countries,

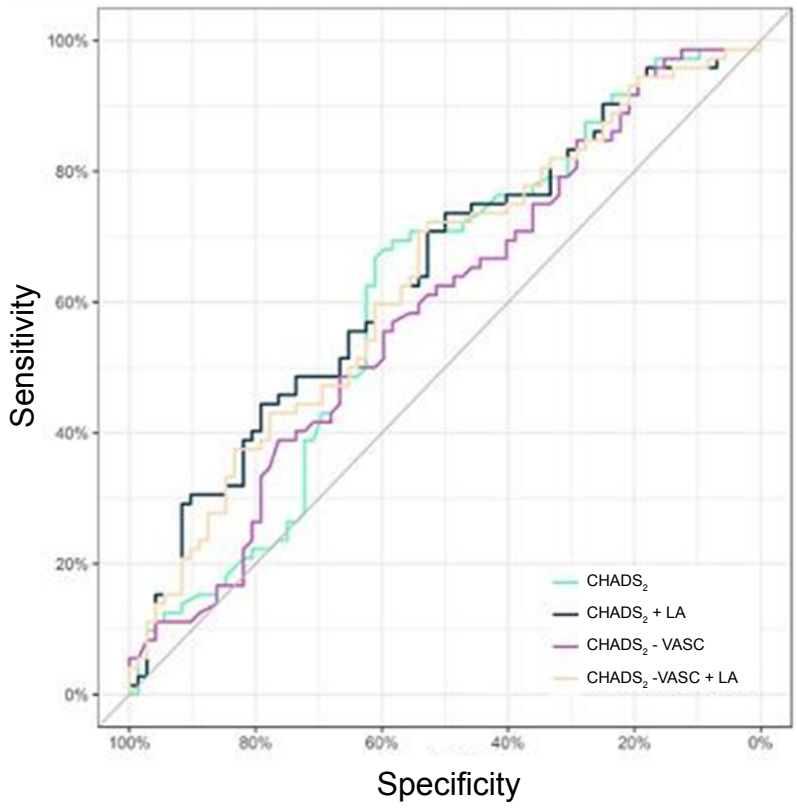

Chart 2 - Predictive ability of models constituted by the scores alone or in association with left atrial size to predict new-onset atrial fibrillation after coronary artery bypass graft surgery and/or valvular surgery.

will play an important role in changing the incidence of this type of arrhythmia in the general population, as well as in patients undergoing cardiac surgery.[5]

The mean ejection fraction in both groups was considered within normal limits, although LA size was slightly increased in both groups.[20] When AF is addressed in the context of heart failure, arrhythmia is more frequent in patients with normal ejection fraction, due to volume overload and pressured atrial chambers.[21] Atrial remodeling, caused by a structural rearrangement of myocardial fibers, is directly linked with the presence of AF.[21] Other authors have reported that LA size is associated with the occurrence of arrhythmia[2,4,9,22] and seems to be the best discriminant between postoperative patients who developed POAF and those who did not.[14] Considering the important role played by the LA in the physiopathology of AF, and the results of previous studies, we decided to test the predictive capacity of the scores alone and combined with this measure, even though no difference was observed between the groups with and without AF in relation to the size of this heart chamber. This will be further discussed below.

Regarding the use of continuous medication, comparison between the groups with and without AF showed that only the use of digitalis was different. Although this drug was prescribed with the aim of treating heart failure, its action on cell membranes and increased vagal tonus[5] could contribute to reduce the onset of POAF.

It is known that the risk to develop AF in the postoperative of cardiac surgery may vary depending on the type of surgery. In a multicenter study, the risk of POAF was higher in patients who had undergone coronary artery bypass grafting combined with valvular surgery (OR: 1.8; CI 95%: 1.2 - 2.7) or valve surgery alone (OR: 1.4; CI 95%: 1.1 - 1.9) compared with coronary artery bypass grafting surgery alone.[23] Although studies have associated the use of ECC with increased postoperative complications, among them, the occurrence of atrial fibrillation,[24] this study did not find significant differences

between the two groups. In addition, we did not observe any relation with the type of surgical procedure, nor in relation to the other intraoperative variables in the groups with and without POAF.

Several studies have demonstrated the association between arrhythmia and adverse postoperative outcomes.[23,25] A meta-analysis[23] with over 69 thousand patients showed that the length of stay was significantly higher among patients with and without POAF (11.0 vs 8.9 days, respectively; $p < 0.00001$). In coherence with the literature data, POAF patients, in this study, remained hospitalized for longer periods.

Nevertheless, mortality rates were higher among patients without POAF. These results were surprising, but some hypothesis can help us understand them. Short-term follow-up compared to other studies who had followed the patients after hospital discharge can contribute to decrease the number of new-onset and recurrent cases of POAF, as well as the number of deaths. In a meta-analysis, the recurrence rate of POAF ranged from 61% to 100% within two years.[26]

With respect to the estimation of the predictive capacity of the scores, the cut-off values of the $CHADS_2$ and CHA_2DS_2VASc scores that best discriminated patients with and without POAF were > 0.5 and < 3.5, respectively. In other words, patients would be at risk of developing POAF even if they had relatively few risk factors. In this situation, it is possible that the scores would not be very useful for identifying patients that should receive more intensive monitoring in the postoperative period or other prophylactic measures. Corroborating that perspective, the sensitivity of the $CHADS_2$ score increased, but specificity was extremely low; and for CHA_2DS_2VASc, they remained far below adequate.

When assessing the effect of LA size on the predictive capacity of these scores, although the sensitivity of the $CHADS_2$ score has decreased, all the other measures of specificity, PPV and NPV improved, but did not seem to be satisfactory. Similarly, for the CHA_2DS_2VASc score, in spite of a decrease in the specificity value, there was an improvement in all the other measures, which is not enough to ensure its adequacy.

Moreover, the regression models failed to show that the scores, alone or in association with the LA, are predictors of POAF. Therefore, it can be asserted that the models analyzed in this study are not good predictors of POAF. The literature is controversial regarding the determination of the predictive capacity of the $CHADS_2$ and CHA_2DS_2VASc scores.[8,9,10,13]

Some studies have shown that the risk of POAF increased as the $CHADS_2$ and CHA_2DS_2VASc scores increased, but they did not demonstrate their predictive capacity.[9,10] Recently, researchers[13] have analyzed the predictive capcity of different risk scores (Society of Thoracic Surgeons risk of mortality score, Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE)-AF score, POAF score and CHA_2DS_2VASc) and age for the new- onset of AF after coronary artery bypass graft operation. They noted that none of the variables analyzed performed well. The ROC area for CHARGE-AF was 0.6796 (CI 95%: 0.6672-0.6920), whereas for CHA_2DS_2VASc it was 0.5917 (CI 95%: 0.5782-0.6052). Different results were obtained in another study,[8] which showed good estimations on sensitivity (84.21), specificity (84.54) and negative predictive value (97.23) of the CHA_2DS_2VASc score to predict the risk of AF after coronary artery bypass, with a ROC area of 0.87.

The present study has limitations relating to sample size and to the fact that this is a single-center study. Furthermore, the short follow-up period did not allow for the identification of new- onset and recurring AF after hospital discharge, which might have contributed to poor score performance in predicting arrhythmia, since the items of both scores take into account chronic conditions that can affect myocardial structure and stability in the long term after cardiac surgery.

Conclusion

The $CHADS_2$ and CHA_2DS_2-VASc scores alone were not good predictors of POAF in patients undergoing coronary artery bypass graft and/or valvular surgery in this study. Although LA size has improved the estimation of sensitivity, specificity, PPV and NPV, it was not enough to improve the predictive capacity of the scores.

Author contributions

Conception and design of the research: Silva NA, Butcher RCGS. Acquisition of data: Silva NA. Analysis and interpretation of the data: Silva NA, Butcher RCGS. Statistical analysis: Silva NA, Butcher RCGS. Writing of the manuscript: Silva NA, Butcher RCGS. Critical revision of the manuscript for intellectual content: Silva NA, Butcher RCGS.

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.

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EDITORIAL

Postoperative Atrial Fibrillation: The Challenge of Risk Prediction

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Editorial related to the article: Left Atrial Size Contribution to the Predictive Capacity of Two Scores for Atrial Fibrillation in the Postoperative Period of Cardiac Surgeries

Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice and is characterized by chaotic activation of the atrium, with f waves present on baseline electrocardiography. Postoperative atrial fibrillation (POAF) is a clinically important complication in patients who underwent heart surgery (coronary artery bypass grafting, or CABG surgery, or valvular surgery). The prevalence of POAF varies from 20 to 40%, with a peak incidence between days two and four after heart surgery.[1,2] Studies suggest that patients undergoing CABG alone have lower incidence of POAF (10 to 40%) compared with those undergoing CABG combined with heart valve replacement (62%).[3]

The most important risk factors associated with this condition are advanced age, heart failure, rheumatic heart disease, hypertension, previous history of AF, left atrial enlargement, chronic kidney failure, and chronic obstructive pulmonary disease (COPD).[4]

Although the POAF was initially recognized as a benign complication, several studies showed that AF in this circumstance is associated with higher mortality rates at short- and long-term follow-up.[5] The occurrence of POAF is associated with a significant increase in hospitalization time and overall costs.[1]

The $CHADS_2$ and CHA_2DS_2VASc scores are commonly used methods to predict the occurrence of thromboembolic events in AF patients. In 2014, Sareh et al.[6] reported that 344 (16.2%) out of a total of 2,120 patients developed de novo POAF during their primary hospitalization. $CHDAS_2$ score were calculated, and patients were grouped into three groups: low (0), intermediate (1) and high risk (≥ 2). A multivariate regression model was developed to account for known risk factors of AF. $CHADS_2$ score was a significant predictor of AF in multivariate regression analysis (adjusted odds ratio, 1.26; 95% confidence interval, 1.14-1.40). Compared with the low-risk group, the intermediate-risk and high-risk groups had a 1.73- and 2.58-fold increase in the odds of developing POAF, respectively ($p < 0.02$ and $p < 0.0001$). The authors concluded that patients with a $CHADS_2$ score of ≥ 2 have a higher probability of developing AF compared with those with a score of < 2. This scoring system could be used to develop a targeted prophylaxis strategy to reduce AF after cardiac surgery.[6]

In another recent study, Burgos et al.,[7] compared the performance of the CHA_2DS_2VASc, POAF, and HATCH scoring systems to predict new-onset atrial fibrillation after cardiac surgery. A total of 3,113 patients underwent cardiac surgery during the study period. Twenty-one percent (n = 654) had postoperative atrial fibrillation. The authors concluded that POAF, CHA_2DS_2-VASc, and HATCH scoring systems showed good discrimination and calibration to predict postoperative AF in cardiac surgery patients. Among them, the CHA_2DS_2-VASc score showed the best discriminative ability for postoperative AF, with the advantage of being easy to calculate, and hence a useful tool to identify low-risk patients during the preoperative period.

In this issue of the International Journal of Cardiovascular Sciences, Silva et al.,[8] evaluated the predictive capacity of the $CHADS_2$ and $CHAD_2DS_2VASc$ scores, alone or combined with left atrial (LA) size, for the onset of POAF in patients undergoing CABG and/or valvular surgery. They performed a retrospective

Keywords

Atrial Fibrillation/ physiopathology; Arrhytmias Cardiac/ complications; Postoperative Complications; Cardiac Surgery Procedures.

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cohort study on 144 patients and tried to identify the cut-off values of the $CHADS_2$ and CHA_2DS_2VASc scores and LA size to calculate sensitivity, specificity, predictive value positive (PVP), and predictive value negative (PVN), in addition to regression models. In this population, half developed POAF. In the POAF group, patients were older, had reduced left ventricular ejection fraction and longer hospital length of stay. However, the $CHADS_2$ and CHA_2DS_2VASc score alone or in combination with LA size did not show good predictive capacity for POAF. The results of the study by Silva et al.,[8] are in agreement with the findings observed in a recent meta-analysis[9] including 36,834 patients. The authors concluded that older age and history of heart failure were significant risk factors for POAF consistently, regardless of the design of the study included, i.e., whether prospective or retrospective.

It is worth mentioning that the study has several limitations, since it is a retrospective, single-center study, with a relatively small sample and based on data analysis. However, left atrial size is an important marker of AF and a potential predictor of POAF and needs to be evaluated in future studies.

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ORIGINAL ARTICLE

Heart Failure: An Overview of Morbidity and Mortality in Rio Grande do Sul

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Abstract

Background: Heart failure (HF) is the final pathway of most cardiac diseases. Although the prevalence of HF has increased, due to the ageing of the population, more comprehensive data have shown a reduction in the percentage of HF hospital admissions over the last years.

Objective: Assess the morbidity and mortality of HF patients in Brazil, Rio Grande do Sul and Porto Alegre.

Method: The study is a retrospective analysis of data from the Brazilian Unified Health System's (*Sistema Único de Saúde [SUS]*) Department of Informatics (DataSUS). We evaluated the incidence of HF hospital admissions, the average length of stay, hospital costs and sex ratio, during a ten-year period (2007 to 2016). Due to availability of the system, mortality rate and age range, the total duration of the study was nine years.

Results: Within this period, the percentage of hospitalizations for HF decreased. On the other hand, the length of stay increased in all regions studied. Mortality rates were in decline in all regions. Hospital costs showed an increase of 110.8%. HF was more prevalent in patients between the seventh and eighth decades of life, with men being more affected than women, except in Rio Grande do Sul.

Conclusion: We conclude that, in spite of the high costs of HF to healthcare providers, hospitalizations and mortality rates have shown a significant decline over the last years, which results from the advances in the treatment of this disease, through initiatives to improve patient education, engagement and planning in health care and self-care. (Int J Cardiovasc Sci. 2019;32(6):596-604)

Keywords: Heart Failure/physiopathology; Aging; Hospitalization; Plans Health; SUS- Unified Health System; Mortality; Morbidity.

Introduction

Heart failure is a burden for public health worldwide due to high mortality, readmission rates and considerable costs to healthcare services.[1] About 30% of patients need rehospitalization within 60 to 90 days.[2] HF is increasing in prevalence around the world as a result of population ageing. The projections indicate that by 2030, 46% of the population will be affected by HF.[3] In relation to the expenses, HF admissions accounted for 2.3% of the amount spent on healthcare services in Brazil in 2017.[4]

Although HF prevalence has increased, analysis of more comprehensive data on the situation of HF hospitalizations in Brazil, using data from DATASUS, showed a decrease in mortality rates in Brazil, especially in the South and Southeast regions.[5] This phenomenon seems to reflect an evolution in the treatment of the disease, including low-cost initiatives to improve treatment recommendations, patient education, engagement and post-discharge planning.[2] The impact of HF is expected to increase substantially, as a result of increased survival of CAD patients, in combination with population ageing.[6,7] This raises the need for registers to project, conduct and better understand this population of heterogeneous patients.

The BREATHE study presented data related to the South and Southeast regions of Brazil. The study analyzed the data from five centers in the South region, where 172

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patients were followed. This follow-up showed that the population affected by HF in the South region is older and the ischemic etiology predominates.[8] However, few studies have considered the morbidity and mortality due to HF in Rio Grande do Sul. This prevents a more comprehensive analysis of HF treatment and outcomes in that region. Nowadays, Rio Grande do Sul has large academic centers linked to hospital institutions, where publications related to the area of Cardiology are among the most published topics.

In this perspective, identifying the scenario of morbidity and mortality due to HF over the last years justifies and aids the planning and monitoring of actions focused on the patient, in the context of initiatives that aims at health promotion and reduction of readmissions. Thus, the objective of this study was to assess the evolution of morbidity and mortality in adult HF patients in Brazil, specifically in the state of Rio Grande do Sul and its capital Porto Alegre.

Method

This is a serious retrospective analysis, performed using public domain data. The scenario of the study is composed of the database of the Brazilian Unified Health System's (*Sistema Único de Saúde [SUS]*) Department of Informatics (DataSUS). The variables selected from the database were: regions (Brazil, Rio Grande do Sul and Porto Alegre), in-hospital morbidity (ICD-10 morbidity list, diseases of the circulatory system, heart failure (ICD-I50), mortality (proportional mortality), age range, average cost per admission, average length of stay and sex ratio. The ICD-10 included corresponds to the main Hospital Admission Authorization (AIH), in which the information on the reason for hospital admission is provided. The variables selected were collected from January 2007 to December 2016 and gathered in November 2017. Proportional mortality is the measure of importance of a specific cause of death in relation to all causes of death within the same population group.

The temporality (2007 to 2016) was defined in virtue of the availability of the data on DATASUS. The use of data from 2007 was intentional because, in the previous 10 years, multiprofessional follow-up strategies were assessed and implemented in that region. With the exception of the variables age range and mortality, temporal delimitation occurred from January 2008 to December 2016 and January 2007 to December 2015, respectively, due to unavailability of the system consulted (DATASUS).

The collection of these variables allowed for cross-checking of data, which were saved in the .csv format. Data analysis was temporal, through secondary data, which were organized in a new Microsoft Excel spreadsheet to enable descriptive statistics and graphical analysis.

Because this study deals with secondary data published by the Brazilian Ministry of Health (MS), there was no need for submission to the Research Ethics Committee, but all ethical precepts were followed according to the Resolution 466/2012, of the National Health Council.[9]

Results

Data will be presented according with the variables analyzed, and the percentages of HF admissions will be shown, followed by length of stay, cost, mortality, age range and sex. All variables will be considered by time series in accordance with the three regions studied.

Figure 1 shows the percentages of HF admissions from the total number of admissions due to diseases of the circulatory system. We can observe that, during the period investigated, there was a decrease in the percentages of admissions in the three regions. Moreover, we must highlight that the percentages for Porto Alegre are lower than those for RS and Brazil, where percentage change showed a decrease of 15%, 24% and 25%, respectively.

Considering age range, patients in their seventies had more hospitalizations in Brazil and in RS. In Porto Alegre, on the other hand, higher hospitalization percentages were observed in patients in their sixties, as shown in Figure 2.

When the sex ratio is calculated (males per 100 women), in which a ratio of 100 means there are equal numbers of males and females, if the ratio is above 100, it means there are more males than females; whereas a sex ratio below 100 indicates that there are more females than males. HF admission rates were higher among males, considering the data related to Brazil and Porto Alegre, where the sex ratio was of 117 males per 100 females admitted due to HF in 2016. On the other hand, in Rio Grande do Sul, there was a prevalence of women, with a ratio of 91 males per 100 females (Figure 3).

The average length of stay due to HF in Brazil was 6.1 days in 2007, reaching 7.4 in 2016, a percentage change

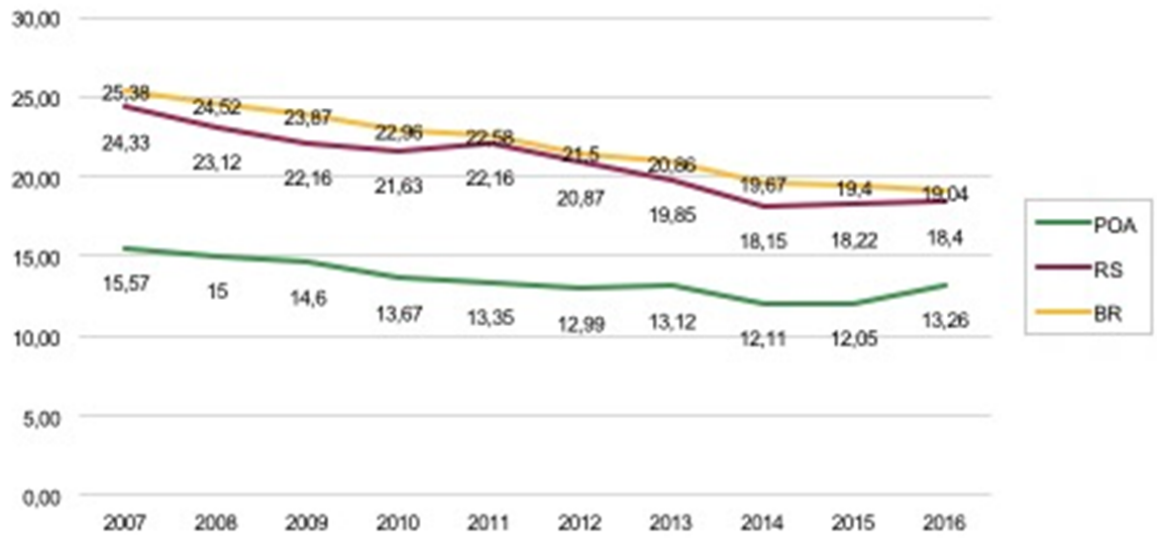

Figure 1 - Percentages of admissions for diseases of the circulatory system in Brazilian Unified Health System's (*Sistema Único de Saúde [SUS]*) due to HF in the period from 2007 to 2016 in Brazil, Rio Grande do Sul (RS) and Porto Alegre (POA).
Source: Elaborated by the author based on data obtained from DATASUS (2017).

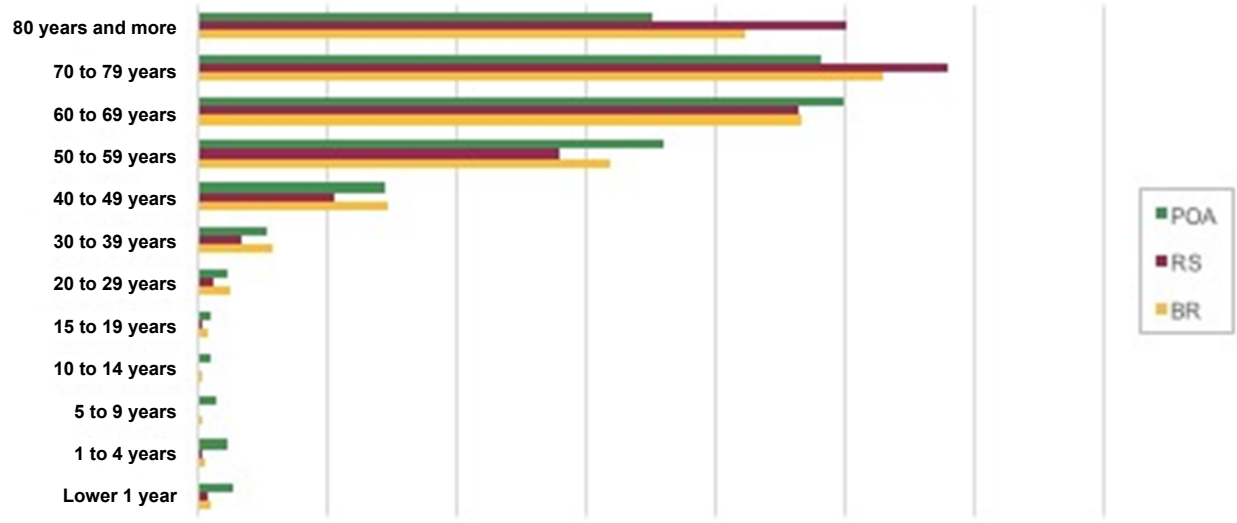

Figure 2 - Age range of patients admitted for heart failure in the period from 2008 to 2016 in Brazil, RS and Porto Alegre.
Source: Elaborated by the author based on data obtained from DATASUS (2017).

increase of 21%, whereas in Rio Grande do Sul, the hospital length of stay, in 2007, was 6.7 days and, in 2016, 7.5 days - a percentage change of 12%. In Porto Alegre, the average length of stay was 10.10, in 2007, and 10.06 days, in 2016, in which the percentage change was 5%. (Figure 4).

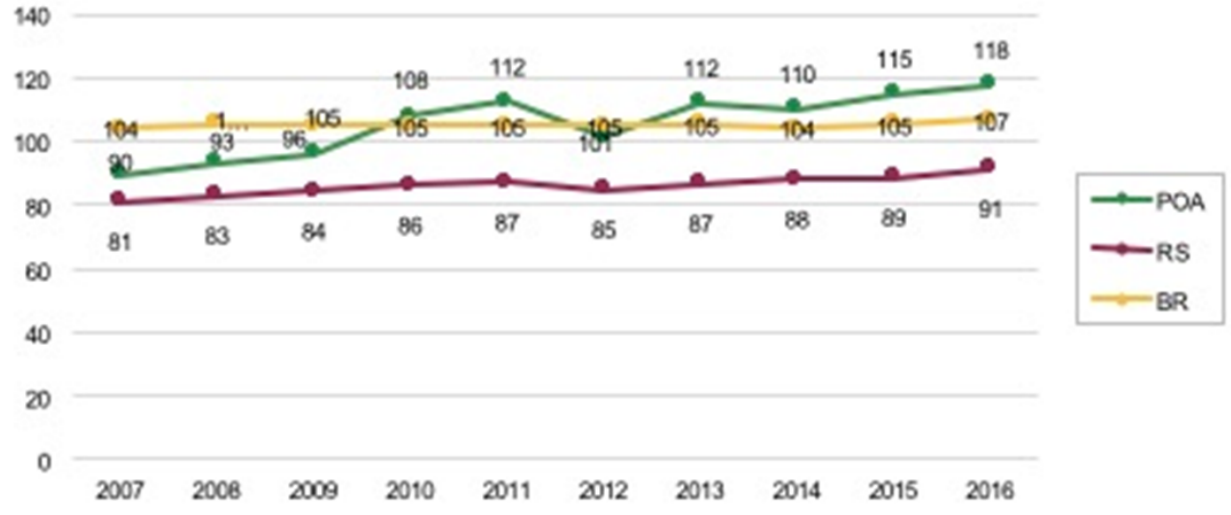

Figure 3 - Sex ratio (males per 100 women) of patients admitted due to heart failure in the period from 2007 to 2016 in Brazil, RS and Porto Alegre.
Source: Elaborated by the author based on data obtained from DATASUS (2017).

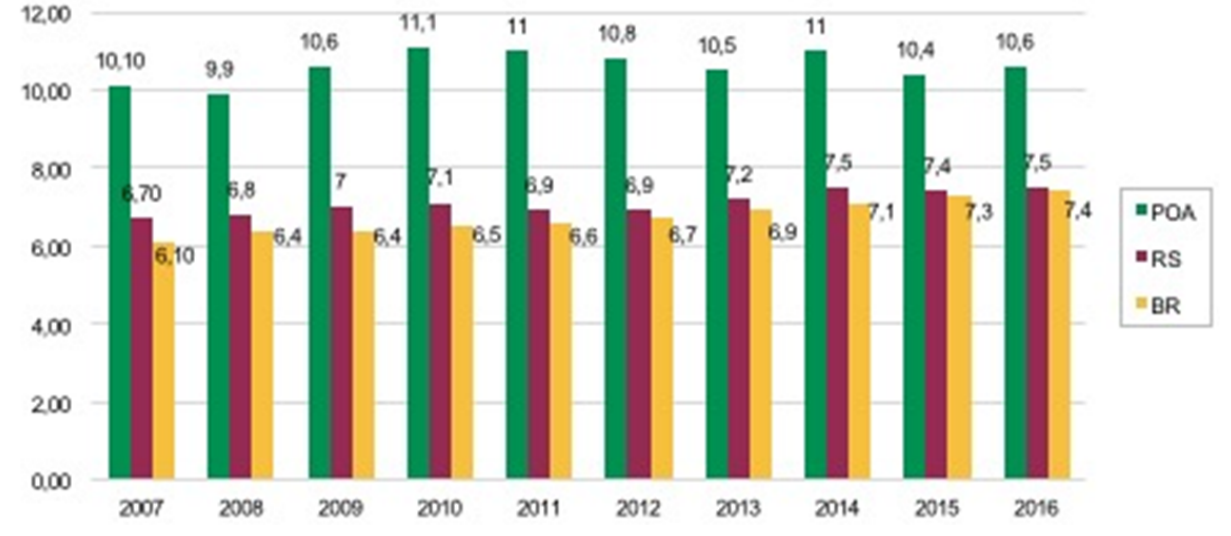

Figure 4 - Average length of hospital stay of HF patients in the period from 2007 to 2016 in Brazil, RS and Porto Alegre.
Source: Elaborated by the author based on data obtained from DATASUS (2017).

In relation to hospitalization costs, the average value per hospitalization was initially R$ 739.39, in 2007, reaching R$ 1,559.08 in 2016 in Brazil, with a percentage change increase of 97%. The corresponding values for Porto Alegre are higher in relation to the values found in the other regions, in which the initial value was R$ 1,047.74, in 2007, increasing to R$ 2,464.47, in 2016, with a percentage change increase of 135% (Figure 5).

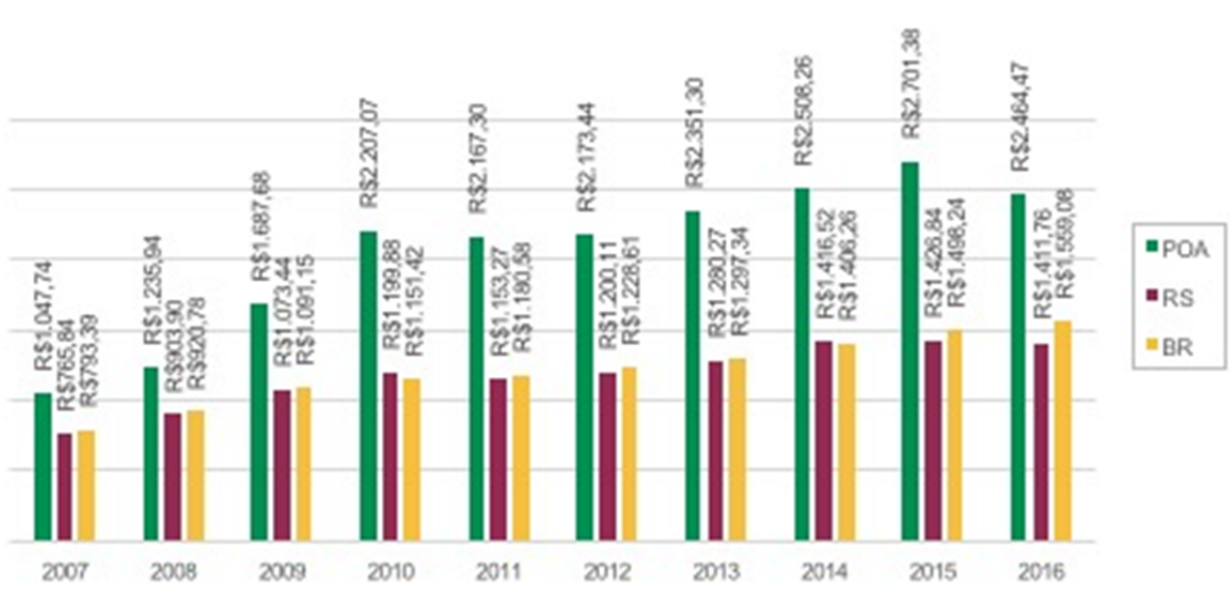

Figure 5 - Mean per-patient cost of an HF-related hospitalization in the period from 2007 to 2016 in Brazil, RS and Porto Alegre.
Source: Elaborated by the author based on data obtained from DATASUS (2017).

In the assessment of proportional mortality due to heart failure, all regions studied showed a reduction in in-hospital mortality. Rio Grande do Sul and Brazil showed a decrease in mortality rates to 25% and 19%, respectively. A more significant decrease was observed in Porto Alegre, where the percentage change reduced to 61%, during the period studied, as shown by Figure 6.

Discussion

This study presents an overview of the morbidity and mortality due to heart failure in the Unified Health System, over a 10-year period in Brazil, in Rio Grande do Sul and Porto Alegre. This overview shows, in general terms, a decrease in admissions and mortality rates due to heart failure over the years. Even though Porto Alegre has the longest length of hospital stay and, therefore, higher costs, it still presents the lowest admission rates and less mortality. The age range followed a similar trend in all regions. Finally, it is worth to mention that, over time, more men than women have been affected by HF, since there was a male predominance in two out of the three regions studied.

As for the percentage of admissions for diseases of the circulatory system, a decrease in HF hospitalizations was observed in Brazil in the period studied. This data suggests that the treatment of HF patients has been effective in the national territory. However, the BREATHE study shows that there is a considerable gap in HF treatment in Brazil, since treatments do not follow the guidelines currently published.[8] On the contrary, the decrease in the percentage of admission has an impact on the aspects that characterize HF as a chronic disease with high morbidity and mortality, since the decrease in admissions expresses an improvement in the assistance provided to the patients in the last years.

Similarly, data from Rio Grande do Sul and Porto Alegre suggest that local institutions are in consonance with the latest guidelines published. In addition, greater population access to medication and patient education about drug and non-drug treatment may explain the decrease in hospitalizations over the years. It is well known that adherence to treatment has an impact on the prognosis of HF patients.[10]

A previous study that assessed admissions for HF through the Global Health database and the World Health Organization (WHO) database showed that admissions due to HF account for 2.9% of admissions in developing countries, including Brazil. In low-income countries, HF admissions account for 31% of hospitalizations in public healthcare.[11] A previous study that assessed HF admissions for 12 years in Brazil reported that, even

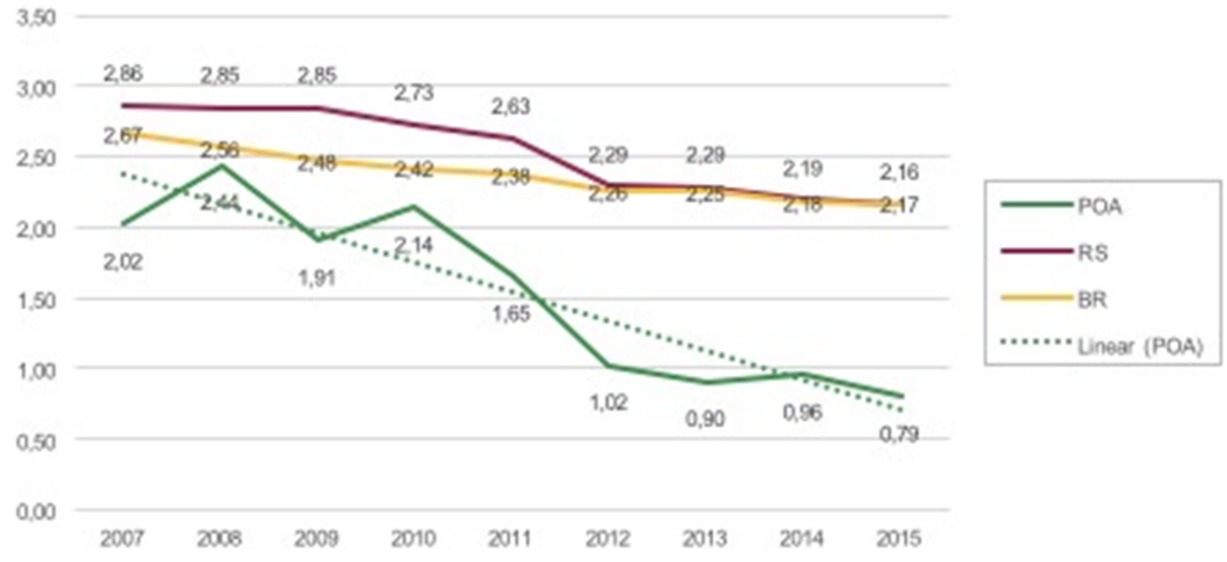

Figure 6 - Proportional mortality rates due to heart failure in the period from 2007 to 2015 in Brazil, RS and Porto Alegre.
Source: Elaborated by the author based on data obtained from DATASUS (2017).

though there was a decrease in HF hospitalizations in absolute numbers and a decrease in the relation of HF admissions and total admissions, the average length of stay and the mortality rate increased over time.[10]

Despite the predominant age range, the I Brazilian Registry of Heart Failure (BREATHE) reported a mean age of 64 years, with 73% of patients above the age of 75 years, in patients admitted with acute HF.[8] The same study showed a variation in the mean age in relation to Brazilian regions, with patients showing higher ages in the South and Southeast regions compared to patients in the North region (on average, 59 years of age).[8-12] Similarly, a pioneer study that portrayed the epidemiological profiles of patients admitted for decompensated HF between public and private hospitals in the city of Niterói, Rio de Janeiro, reported a mean age of 61.1 years in public hospitals.[13] Other studies published recently indicate a predominance of individuals in the eighth decade of life (70-79 years of age).[10,14,15]

Advanced age patients account for a significant fraction of the sample studied.[8] In Porto Alegre, the greatest number of HF admissions occurred in patients within the age range of 60 to 69 years. Data from Porto Alegre are similar to those from an international multicenter trial designed to assess HF patients in 388 centers in North America, Europe, Latin America and Asia, in which the mean age was 67 years.[16] In two previous studies that assessed HF patients in low-income countries, the mean age was 52 to 59 years.[11,17] Regional variation in age may be explained by differences in the prevalence of underlying risk factors, as well as living standards.[18]

It is estimated that HF will increase by 46% from 2012 to 2030, resulting in more than 8 million people over 18 years of age with HF. This ascending prevalence is a result of the growth in life expectancy, since HF affects mainly the elderly.[8]

Men have higher hospitalization rates for HF according to data from previous studies.[10,13,14,16,19] In this study, we observed a higher prevalence of males in all regions of Brazil and Porto Alegre. On the other hand, in Rio Grande do Sul, the sex ratio indicates an inversion, with a predominance of women, similar to a study carried out in a city of the state of Minas Gerais (Brazil), in which women accounted for 51% of admissions, in the period from 2010 to 2014.[20] Similarly, a previous study performed in public and private hospitals in the city of Niterói (Rio de Janeiro) reported 51% of female hospitalizations in private hospitals.[13] Analysis of global registries of HF patients indicated that 40% to 50% of HF patients are females, a group of patients traditionally under-represented in previous clinical trials. This is a remarkable observation, since female patients are unique in that they tend to be older at the time of initial diagnosis

and are more likely to have heart failure with preserved ejection fraction (HFpEF).[18] A previous study that assessed HF patients, according to age groups, showed an inversion in prevalence after the seventh decade of life, with a female prevalence. This fact can be explained due to women's higher life expectancy compared to men.[10]

The Ministry of Health attributed the higher rates of admissions among men to their greater vulnerability to diseases, especially to severe and chronic illnesses, and to the fact that they die earlier than women do. Regardless of the higher vulnerability and elevated mortality rates, men do not search for basic healthcare services, in the same proportion as momen.[21]

In relation to the length of stay, this study showed an increase in the period of hospitalization of HF patients, and the most expressive increase occurred in Brazil, with a variation of 21%. A previous study that assessed the average length of stay of adult HF patients in the National Health Service (SUS) in Brazil reported an average length of stay of 5.8 days, in 2001, reaching 6.6 days, in 2012, which represents an increase of 12.12%.[9] However, a study carried out in Niterói (Rio de Janeiro), in 2001, reported an average length of stay of 12.6 days in public hospitals and 8 days in private hospitals.[13] Similar data were found in previous global studies, reporting an average length of stay of 5 to 6 days in North America, Asia and Argentina.[11,18,22]

The present study found similar data, showing an increase in the length of stay in Brazil and RS. In Porto Alegre, we observed an increase in average length of stay throughout the period studied. This can be attributable to the higher number of hospitals and a greater offer in specialized centers and institutions linked to universities with a focus on teaching and research, providing qualified service in accordance with current guidelines, as well as a clear decrease in mortality rates, especially in Porto Alegre. Data equivalent to those from Porto Alegre are reported in previous studies, indicating 10 days of hospitalization in Western and Eastern Europe and low-income countries.[11,18]

Even with technological advances in the treatment of HF and in spite of the reduction in hospitalization rates, the average length of stay and hospital costs have increased, probably as a result of patients' clinical complexity.[10] A previous study that assessed the costs of heart failure-related hospitalizations in Brazil for 12 years showed a 132.8% increase in hospitalization costs in the period studied. The data obtained from this study also indicate an increase in the average cost per hospital admission. In Porto Alegre, the values are higher compared to the other regions studied, throughout the period considered, with a 135.2% increase in cost per hospitalization. These data should be correlated with the length of hospital stay, the percentage of admissions and mortality rates, which show an increase in length of stay and a decrease in admissions and mortality rates. Thus, we can conclude that the assistance provided to patients is related to better current practices, since in Porto Alegre patients had better clinical outcomes.

In 2016, in Brazil, the costs of HF-related hospitalizations were R$ 334 million, accounting for 2% of total hospitalization costs. For this reason, there is an increasing search for the implementation of prophylactic and preventive measures.[14]

In relation to mortality rates, a multicenter analysis performed in Brazil (BREATHE), showed that low treatment adherence accounts for a significant increase in morbidity, mortality and hospital costs.[8] However, the data obtained from this study show a decrease in in-hospital mortality rates throughout the 10 years studied. Porto Alegre showed a 61% decrease in mortality rates. Similarly, Brazil and Rio Grande do Sul had a decrease of 24.5% and 19%, respectively.

A previous study that assessed HF-related mortality in Brazil showed a 41% increase in mortality in the period from 2001 to 2012.[10] This increased mortality rate was associated with patient severity and with the fact that many patients with heart failure are elderly. Nevertheless, the data obtained from this study show a decrease in mortality due to HF, which can be attributable to the advances in treatment over the last years. It is well known that the use of proper medication, in combination with non-pharmaceutical measures, such as multidisciplinary follow-up and monitoring, provide significant benefits to clinical prognosis and consequently decreased morbidity and mortality.

Analysis of the results of the BREATHE study showed that 63% of the patients received guidelines on hospital discharge about the correct use of medications, whereas only 34.9% were advised about the diet to be followed at home and 16% were counseled about physical activity.[8]

It is well known that lack of adherence to pharmacological and non-pharmacological treatment are among the reasons for decompensated HF and consequent hospitalization.[13,19,23] In this context, follow-up by a multi-professional team after hospital discharge

is recommended to reduce morbidity and mortality and improve quality of life for HF patients. The aim of multidisciplinary management is to strengthen a health care system that provides a network of services for patients, in both hospital and ambulatory care settings. Disciplinary management programs are intended to improve the results through structured follow-up and patient education.[24] Educational programs are an important tool to improve the management of self-care by the multi-professional team specialized in the follow-up of patients with HF. However, it is difficult to identify the appropriate strategies and scenarios, since the interventions are heterogeneous, as well as the number of professionals involved, hindering the evaluation of results.[25]

It is important to mention that, because the data were collected from Hospital Admission Authorization (AIH) forms, through the DATASUS system, the assessment of other factors that can influence or clarify the causes of decompensation of HF that led to hospital admission were not analyzed due to limitations of the system.

Conclusions

The data presented showed the prevalence of heart failure-related hospitalization in the Brazilian Unified Health System (SUS), in RS and its capital, compared to national data. We observed a reduction in admission and mortality rates due to HF in all regions studied. The average length of hospital stay and hospital costs increased significantly over the period analyzed. Hospitalizations are prevalent among elderly in the seventh and eighth decades of life. Heart failure is a disease that affects both sexes, whose prevalence depends on the region studied. This is a timely moment to review the current management and to implement evidence-based measures in a controlled and monitored setting. Similarly, initiatives should be undertaken to improve quality of continuity of care.

Author contributions

Conception and design of the research: Nicolao CZ, Paz AA, Linch GFC, Rover M, Souza EN. Acquisition of data: Nicolao CZ, Ferreira JB, Paz AA, Linch GFC. Analysis and interpretation of the data: Nicolao CZ, Ferreira JB, Paz AA, Linch GFC, Rover M, Souza EN. Statistical analysis: Nicolao CZ, Paz AA, Linch GFC, Souza EN. Obtaining financing: Nicolao CZ. Writing of the manuscript: Nicolao CZ, Ferreira JB, Paz AA, Linch GFC, Rover M, Souza EN. Critical revision of the manuscript for intellectual content: Nicolao CZ, Linch GFC, Rover M, Souza EN.

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.

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International Journal of Cardiovascular Sciences. 2019;32(6):605-606

EDITORIAL

The Burden of Heart Failure in Brazil: Are we Providing Better Care or Just more Expensive Care?

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Editorial related to the article: Heart Failure: An Overview of Morbidity and Mortality in Rio Grande do Sul

Heart failure is one of the leading causes of cardiovascular morbidity and mortality and affects 0.5 to 2% of the population,[1] with significant costs for the healthcare system.[2] In 2012, heart failure accounted for over 270,000 hospitalizations in Brazil, corresponding to a cost of more than 170 million US dollars.[3] The knowledge of the profile of heart failure patients and treatment outcomes is crucial for the development of health policies and interventions aimed at reducing costs, morbidity and mortality.

In this issue, Nicolao et al.,[4] published a retrospective analysis of data from the Brazilian public health system (DataSUS), evaluating morbidity, mortality, and costs related to heart failure in adult patients, considering three geographic dimensions: the state of Rio Grande do Sul, its capital Porto Alegre city, and Brazil.[4] A ten-year period was selected, January 2007 to November 2017. Heart failure accounted for over one-quarter (25.38%) of the hospitalizations in the public health system in Brazil in 2007, with a reduction to 19.4% in 2017, with similar trends in Rio Grande do Sul state (18.4%) and Porto Alegre city (13%). Most patients were older than 40 years, with an increasing incidence of heart failure until the age of 79. There was an increase in the sex ratio, towards male, for patients admitted due to heart failure, mainly in Porto Alegre. Hospital length of stay increased in about one day, from 6.4 to 7.4 days in Brazil and from 6.7 to 7.5 in Rio Grande do Sul. However, in Porto Alegre, hospital length of stay differed from the other series, reaching 10.1 days in 2007, and with a slight increase to 10.6 days in 2017. The costs of heart failure hospitalization increased in all series, and it was more costly in Porto Alegre than in Brazil and Rio Grande do Sul state. Finally, mortality rate reduced over time from 2.67% to 2.17% in Brazil and from 2.86% to 2.16% in Rio Grande do Sul. Porto Alegre showed a greater reduction, from 2.02% to 0.79%. Taken together, these findings might reflect on more heart failure patients referrals to tertiary centers in Porto Alegre.

This study has some limitations. First, since it analyzes data obtained from a national database, it relies on the correct completion of the authorization for hospital admission form. Additionally, it does not contemplate patients diagnosed with heart failure during hospitalization. This method does not allow us to understand the reasons of the changes in hospitalizations, length of stay and mortality rates, or whether these reductions were associated with changes in etiology, rate of optimal medical treatment and public policies. An analysis of individual data would be needed to answer these questions.

The BREATHE study revealed that heart failure etiology differs among Brazilian regions.[5] In Rio Grande do Sul state, ischemic cardiomyopathy was the most common etiology, with comparable rates of Brazil, although hypertensive etiology was about 63% more prevalent than in the rest of the country. Bocchi et al.,[5] also highlighted these discrepancies, since hypertension as the cause of HF ranged from 7% to 25% in some series.[6] In addition, Chagas disease affects 42% of HF patients in

Keywords

Heart Failure/physiopathology; Heart Failure/mortality; Epidemiology; Hospitalization; Unified Health System; Health Systems Plans; Mortality & Morbidity.

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the Central-West region, but only 2% in the South.[5] In a continental country like Brazil, there are also important discrepancies in terms of access to public health system and educational levels between states. These findings help understand differences in hospitalization and mortality rates between Rio Grande do Sul state and Brazil. Complex cases are usually referred to the largest hospitals in Rio Grande do Sul, located in Porto Alegre, which may explain the longest length of stay and highest costs in this city. The city has three public hospitals with heart failure and transplant teams, which may promote better care and lower mortality rate. The authors also showed that the increase in costs over time occurred in parallel to a decrease in mortality, and that might reflect improvement in quality of care. It is not known whether costs increased due to greater investment in health system or to economic inflation.

Only about two-thirds of patients in Brazil receive guideline-based treatment on hospital discharge.[3] Public policies are needed to increase the rate of guideline-based treatment in heart failure patients not only in Brazil but also in Latin America. Our continent has the highest rates of mortality (8.2 events per 100 patients-year) in comparison with others, such as the Western Europe, with 4.8 events per 100-patients year.[7] The recent incorporation of sacubitril/valsartan to the list of medications available in the Brazilian public health system may have a positive impact on the outcome rates in the next decade, but still, there is a lot of work to be done. Control of Chagas disease vector, treatment of hypertension according to recent guidelines, and lower obesity/physical inactivity rates are important goals to be achieved to reduce the burden of heart failure in our country. In addition, a better care during the vulnerable phase after hospital discharge could help avoid readmissions.

In conclusion, the authors showed that trends in heart failure have changed in the last decade. Although the cost of heart failure has increased, hospitalization and mortality rates decreased over time, especially in Porto Alegre city. By knowing these regional differences, a more organized network could be built to offer more specialized care to the sickest patient. There is an urgent need for more studies on the epidemiology of cardiovascular disease and heart failure in Brazil and its regions, to optimize the provision of funds and development of policies to improve the care provided to these patients and outcomes achieved. So far, the lower mortality rates observed point towards a better, not just more expensive, care.

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ORIGINAL ARTICLE

Effect of Hospital Accreditation Process in Outcomes of Patients with Acute Coronary Syndrome

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Abstract

Background: Hospital accreditation has as goal the standardization of patient care, aiming quality improvement. On 2015, a cardiology reference hospital was evaluated and got level 3 from ONA in care given to Acute Coronary Syndrome (ACS) patients.

Objetive: To compare length of stay (LOS) at Coronary Care Unit (CCU) and the total LOS at the hospital of ACS patients before and after ONA 3 accreditation. Other clinical outcomes were also analyzed.

Methods: Systematic and prospective registry of admitted ACS patients at CCU, whose population was divided into pre-accreditation (period 1) and post-accreditation (period 2). Descriptive analysis was performed. For statistical analysis the Mann-Whitney test, chi-squared, Fisher's exact test and Multiple Linear Regression were performed. P value was considered statistically significant when < 0,05.

Results: 372 patients were admitted with ACS, 186 in period 1, of which 47 (25,3%) with ST segment Elevation Myocardial Infarction (STEMI), and 186 in period 2, of which 70 (37,6%) with STEMI. The mean age was 65,9 years (± 12,2). About the CCU LOS, there was a reduction from 3 (IQR: 2-4) to 2,5 days (IQR: 2-4; p value = 0,088). Regarding the hospital LOS, there was also a reduction from 8 (IQR: 5-12,25) to 6 days (IQR:4-11; p value = 0,004). Analyzing the type of ACS, there was a significant reduction only at the hospital LOS in non-STEMI patients: 8 to 6 days (p value = 0,001). Other hospitalization length of stay and clinical outcomes did not present a significant reduction in the comparison.

Conclusion: After the ONA 3 accreditation, there was a reduction of hospital LOS. There were no significant differences in the other outcomes analyzed. (Int J Cardiovasc Sci. 2019;32(6):607-614)

Keywords: Hospital Accreditation; Consensus; Acute Coronary Syndrome; Data Interpretation, Statistical; Coronary Care Units.

Introduction

Institutions that offer health services face challenges in improving safety and quality[1-4], and it is therefore critical that a global organization be in place for all sectors to work in a systematic way[1,5]. Constant evaluation of this system proves to be useful to ensure its smooth operation[3,6]. Hospital quality certification has then emerged. It is a process of continuing professional education that helps to encourage perfecting through multidisciplinary procedures that improve patient hospitalization and ensure lower rates of in-hospital complications.[3,6-8]

Hospital accreditation programs, which are forms of certification in many parts of the world have proven to be a method that assists in the evolution of the quality of health services, besides serving as an external validation of the service[1-3,9,10]. These programs analyze many criteria, ranging from hospital infrastructure to teaching and

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research and patient care service[6]. In Brazil, we have the National Accreditation Organization (ONA) that follows the standards established by the Ministry of Health[1], where the institution is evaluated and receives a classification ranging from level 1 to 3, which represents accreditation with excellence.[3,11]

Several studies have analyzed the positive effects of the process and have found that there was a reduction in the length of hospital stay, improved management of preventable outcomes, reduction of hospital mortality, and it helps to create internal protocols.[12-15]

Coronary artery disease (CAD) is the most frequent cause of death in the world, consisting of approximately 13% of all causes of mortality.[16,17] Acute coronary syndrome (ACS) in Brazil represents an important cause of hospitalization and acute myocardial infarction is the second leading cause of death in the country.[18,19] These data demonstrate the importance of adequate management of ACS, especially with regards to the creation of guidelines.[20]

The length of stay in both the Intensive Care Unit and at the hospital is an important parameter of quality and better prognosis for the patient, where a decrease of this time is related to reduced hospital costs with the patient and a lower rate of complications, such as lower readmission rates, death or infection (such as mechanical ventilation-related pneumonia, central venous catheter infection or urinary tract infection related to bladder catheter use).[21]

In a reference Cardiology hospital in Salvador, Bahia, ACS was considered the main line of care in the ONA 3 accreditation process, held in December 2015.

The primary outcome of this study was the comparison between length of stay at the Coronary Care Unit and hospital stay of patients with ACS before and after ONA 3 accreditation. Secondly, the impact of accreditation on clinical outcomes was analyzed.

Methods

Study design and population

This is a prospective observational registry that consecutively included patients diagnosed with Acute Coronary Syndrome hospitalized at the Coronary Care Unit (CCU) of Hospital Santa Izabel (HSI) — Salvador/BA from February 2015 to August 2016. *Santa Casa de Misericórdia da Bahia* — HSI is a tertiary philanthropic hospital that underwent ONA 3 accreditation (excellence) in December 2015 and successfully achieved this goal. The study population was divided into two groups: Period 1 (Pre-accreditation: before December 1, 2015) and Period 2 (Post-accreditation: as of December 1, 2015).

All patients with diagnostic confirmation of acute coronary syndrome (including unstable angina, ST-segment elevation acute myocardial infarction — STEMI — and non-ST-segment elevation acute myocardial infarction — non-STEMI) met the inclusion criteria, as well as patients receiving drug and/or interventional treatment for acute coronary syndrome at Hospital Santa Izabel. Patients readmitted after elective interventional treatment of previous acute coronary syndrome were excluded.

The data were collected prospectively through a structured electronic medical record of the coronary care unit by a team specifically involved in the collection, completed by the unit's attending physician, always with the possibility of rediscussing some topic with the physician. In summary, the variables include socio-demographic and clinical aspects, in addition to admission, evolution and outcomes.

Statistical analysis

A descriptive analysis of the frequencies of variables was performed using IBM SPSS Statistics 14.0.

Initially, the Kolmogorov-Smirnov test of normality was performed to find out whether the variables had a normal or non-normal distribution pattern and, from this, the statistical tests and the most adequate description of each variable were defined.

The variables were described using measures of central tendency (mean, median) and dispersion (standard deviation, interquartile range) when continuous and by absolute and relative frequencies, for the categorical variables.

Comparisons of clinical outcomes between the pre- and post-accreditation periods were performed using the chi-square test (X^2) or Fisher's exact test when the sample number was < 5. The Mann-Whitney test was used to compare the time of hospitalization at the coronary care unit and hospital admission between the two periods, since non-parametric variables were involved.

In addition, multivariate analysis was performed by multiple linear regression to find out where the hospital accreditation process was an independent predictor of length of hospital stay and length of stay at the CCU, controlling for relevant confounding factors in the

context of acute coronary syndrome (age, sex, type of ACS, systemic arterial hypertension, diabetes mellitus, dyslipidemia, previous infarction and prior coronary artery bypass grafting surgery).

The differences observed in all statistical tests (non-parametric and linear regression) were considered significant when the probability (p) of type I error was < 0.05.

Results

A total of 372 patients were included in the study, of which 186 in period 1 (pre-accreditation) and 186 in period 2 (post-accreditation). Of the total, 117 (31.5%) were patients diagnosed with ACS with ST-segment elevation and 255 (68.5%) were diagnosed as non-ST-segment elevation ACS.

In period 1, 47 (25.3%) patients with ST-segment elevation and 139 (74.7%) with non-ST-segment elevation were admitted and, in period 2, 70 (37.6%) patients with ST-segment elevation and 116 (62.4%) patients with non-ST-segment elevation were admitted.

Male sex was the most prevalent one, with 211 (56.7%) patients; 110 (29.6%) were from the public health system — SUS; and, as for the medical history, the most prevalent comorbidities were systemic arterial hypertension — SAH, totaling 299 (80.4%) patients, and dyslipidemia, with 187 (50.3%) patients. (Table 1)

The average age was 65.9 (± 12,2), with minimum age of 14 and maximum of 95.

Regarding the length of hospital stay, in the total period of the study, the median CCU length of stay was 3 (IQR = 2 - 4) and the hospital length of stay was 7 days (IQR = 5 - 11.75). In period 1, the median was 3 days (IQR = 2 - 4) for the CCU length of stay and 8 days for the hospital length of stay (IQR = 5 - 12.25). In period 2, the median was 2.5 days for the CCU length of stay (IQR = 2 - 4) and 6 days for hospital length of stay (IQR = 4 - 11).

By analyzing the median variation between the CCU length of stay and the hospital length of stay between the pre- and post-accreditation periods, it was found that the reduced hospital length of stay in the general sample was statistically significant at p = 0.004. (Table 2)

In the analysis of subgroups, the median remained with a tendency of reduction, but only the decrease in hospital length of stay of non-STEMI was relevant, with p = 0.001. (Table 2)

Table 1 - Prevalence and comparison of sociodemographic characteristics and presence of comorbidities between pre- and post-accreditation periods in a reference cardiology service. Salvador-Bahia, 2018

Variable	General* (n = 372)	Pre-accreditation* (n = 186)	Post-accreditation* (n = 186)	p value
STEACS (%)	117 (31.5)	47 (25.3)	70 (37.6)	0.01
Male (%)	211 (56.7)	111 (59.7)	100 (53.8)	0.250
Health insurance (%)	262 (70.4)	134 (72)	128 (68.8)	0.495
SAH (%)	299 (80.4)	152 (81.7)	147 (79)	0.514
Diabetes mellitus (%)	159 (42.7)	78 (41.9)	81 (43.5)	0.753
Previous AMI (%)	110 (29.6)	46 (24.7)	64 (34.4)	0.041
Previous coronary artery bypass grafting surgery (%)	36 (9.7)	19 (10.2)	17 (9.1)	0.726
Dyslipidemia (%)	187 (50.3)	108 (58.1)	79 (42.5)	0.003
Previous stable angina (%)	78 (21)	39 (21)	39 (21)	1.000
Previous heart failure (%)	30 (8.1)	16 (8.6)	14 (7.5)	0.703
Previous angioplasty (%)	82 (22)	40 (21.5)	42 (22.6)	0.802

(*) Absolute frequencies; Absolute numbers and percentages on the total sample. Chi-square test; STEACS: ST-segment elevation acute coronary syndrome; SAH: systemic arterial hypertension; AMI: acute myocardial infarction.

Table 2 - Comparison of the median length of stay at the CCU and hospital stay in the pre- and post-accreditation periods at a reference cardiology service. Salvador-Bahia, 2018

Variable	Pre-accreditation	Post-accreditation	p value
CCU length of stay			
General (median, IQR)	3 (2-4)	2.5 (2-4)	0.088
STEACS (median, IQR)	3 (2-4)	2 (2-4)	0.052
Non-STEACS (median, IQR)	3 (2-4)	3 (2-4)	0.427
Hospital length of stay			
General (median, IQR)	8 (5-12.25)	6 (4-11)	0.004
STEACS (median, IQR)	8 (5-10)	7 (4.75-12.50)	0.734
Non-STEACS (median, IQR)	8 (5-14)	6 (4-10)	0.001

Mann-Whitney test; IQR: interquartile range; CCU length of stay: length of stay in the Coronary Care Unit; STEACS: ST-segment elevation acute coronary syndrome; Non-STEACS: non-ST-segment elevation acute coronary syndrome.

Regarding the secondary outcomes, it was found that the type of clinical outcome most commonly presented in the sample was cardiorespiratory arrest (CRA) of any type, evolving to death or not (29 patients — 7.8%), followed by death (26 patients — 7%). Comparing the two periods, period 1 had a higher number of deaths than period 2 (14 and 12, respectively), but this data did not reach statistical relevance. (Table 3)

By cross-comparing the data, it was found that mortality and cardiogenic shock were variables that showed a decrease in the number of cases between the pre- and post-accreditation period, but this data did not reach any statistical significance. Reinfarction, CRA (resulting in death or not) and combined outcomes showed an increase in the absolute number of cases in the comparison between the two periods analyzed, but this difference did not present a significant p-value. (Table 3)

By analyzing the clinical outcomes correlated to the types of ACS, it was found that some outcomes increased and others decreased in frequency in the comparison between the pre- and post-accreditation periods, but this change is not statistically relevant. (Table 3)

In the multivariate analysis by multiple linear regression, controlling for the variables of age, sex, systemic arterial hypertension, diabetes mellitus, dyslipidemia, previous acute myocardial infarction, previous coronary artery bypass grafting and type of ACS, the post-accreditation period was an independent predictor of reduced time of hospitalization ($p = 0.041$; $B = 2.081$; $\beta = 0.105$).

By doing the same analysis for the hospitalization time at the coronary care unit, we found that accreditation was not an independent predictor of this change in length of stay ($p = 0.834$ $B = 0.086$; $\beta = 0.011$).

Discussion

The accreditation process has a positive impact on the standardization of care offered to patients, generating a flow that results in faster and more effective practices, contributing to a better patient prognosis.[22]

At Hospital Santa Izabel, where this study was conducted, the hospital accreditation process resulted in better health care processes and had a strong impact on the pursuit of patient safety. With regard to acute coronary syndromes (ACS), its line of care was devised by conducting analyses before the patient arrived at the hospital until their follow-up after discharge. Mortality and bleeding outcomes were established as indicators of the line of care, and these outcomes were adjusted by the GRACE score and the CRUSADE score obtained on admission to the coronary care unit. A set of measures were planned and implemented at the different phases of the line of care, such as taking joint actions with the Municipal Health Department and SAMU (Mobile Emergency Care Service), aiming at improving the time to the implementation of reperfusion in ST-segment elevation acute myocardial infarction. Another relevant aspect was the construction of a therapeutic plan for

Table 3 - Comparison of the frequencies of outcomes between the pre- and post-accreditation periods in a reference cardiology service. Salvador-Bahia, 2018

Variable	Pre-accreditation* (n = 186)	Post-accreditation* (n = 186)	p value
Death			
General (%)	14 (7.5)	12 (6.4%)	0.684[a]
STEACS (%)	3 (1.6)	7 (3.8%)	0.738[b]
Non-STEACS (%)	11 (5.9)	5 (2.7%)	0.237[a]
Reinfarction			
General (%)	5 (2.7)	11 (5.9%)	0.125[a]
STEACS (%)	1 (0.5)	5 (2.7%)	0.399[b]
Non-STEACS (%)	4 (2.1)	6 (3.2%)	0.519[b]
Cardiogenic shock			
General (%)	8 (4.3)	6 (3.2%)	0.586[a]
STEACS (%)	2 (1.1)	4 (2.1%)	1[b]
Non-STEACS (%)	6 (3.2)	2 (1.1%)	0.298[b]
CRA (death or not)			
General (%)	14 (7.5)	15 (8.1%)	0.847[a]
STEACS (%)	3 (1.6)	9 (4.8%)	0.357[b]
Non-STEACS (%)	11 (5.9)	6 (3.2%)	0.382[a]
Combined unfavorable outcomes	20 (10.7)	24 (12.9%)	0.521[a]

(*) Absolute frequencies. P values regarding the tests: a Chi-square test, b Fisher's exact test; STEACS: ST-segment elevation acute coronary syndrome; Non-STEACS: non-ST-segment elevation acute coronary syndrome; CRA: cardiorespiratory arrest.

each patient. The plan guides the therapeutic project of each area (nursing, physiotherapy, clinical practice, psychology, etc.), whose goals are always based on the pursuit of improvements of clinical results based on humanized practice. From the ONA 3 accreditation process, all prescriptions for the patients of the ACS line of care were then analyzed by the clinical pharmacist, who interacts directly with the medical team, by signaling nonconformities, risks and suggestions.

In this study, regarding the demographic characteristics of the sample, a higher mean age was found, with a difference of about 10 years, compared with the studies of Eagle et al.[15] and Chen et al.[23] which analyzed the impact of the evaluation of hospital services based on the standardization of these services. Moreover, this study has found a lower incidence of ACS in women and a higher prevalence of SAH compared to the results of the two studies mentioned above.[15,22] There was also a higher prevalence of diabetes mellitus and previous angioplasty; approximately the same prevalence of previous acute myocardial infarction; and a lower prevalence of patients with heart failure compared to patients from the study of Chen et al.[22] It can be assumed that, because the population sample of Salvador has more comorbidities than the population analyzed by Eagle et al.[15] and Chen et al. al.[22], the patients in the sample may be associated with earlier infarction, since a considerable difference was observed between the mean ages of the patients in this study and those of the other authors cited.

The hospitalization times at the Coronary Care Unit and at the hospital were analyzed and a tendency of reduced medians has been found. As for the total sample and that of patients with non-ST-segment elevation ACS, there was a significant reduction in the length of

hospital stay. Patients with ST-segment elevation also had a reduced length of hospital stay, but this data did not present any statistical significance.

In a multicenter study conducted by Sack et al.[24] in 73 hospitals, the quality of care offered and the patient's satisfaction with their hospitalization in accredited and non-accredited hospitals were analyzed.[24] The population considered was more comprehensive, excluding only obstetric patients and pediatric patients. As a result, it was found that the median length of hospital stay in accredited hospitals tended to be lower, but with no statistical relevance.[24] In the sample of this study, the population was more specific, and the reduction in hospital length of stay may be associated with a better systematization of care for these patients, which was confirmed in this study through a multivariate linear regression. Furthermore, it can be assumed that, with improved care, with protocols established and fulfilled, the patient presents more favorable conditions for early discharge. Also, regarding the length of stay, a study conducted by Falstie-Jensen et al.[9] also found that patients hospitalized in accredited hospitals had a shorter hospital stay,[9] which is consistent with this study.

Regarding the outcomes analyzed, in the current study, it can be seen that the tendency related to cardiogenic shock was a reduction in the sample studied and an increase in patients with STEMI. Regarding mortality, there was a decrease in this variable both in the sample as a whole and in patients with non-ST-segment elevation, but without statistical significance. In the analysis of subgroups, there was an increase in the number of deaths in patients with ST-segment elevation. Compared to the Eagle[15] study, it can be seen that the patients analyzed in the United States showed an increase in the number of cases of cardiogenic shock and that mortality decreased significantly.[15]

One possibility to be raised to increase the number of deaths of patients with STEMI is that there were more admissions of more severe patients in the second period analyzed. According to Greenfield et al.[14] by undergoing a quality assessment such as the hospital accreditation process, the institution tends to receive more patients with more serious disorders[14], possibly due to the recognition of the effectiveness of the service offered.

Another issue to be emphasized is that the results on mortality obtained in this analysis should be interpreted carefully. In a study conducted by Williams et al.[25] in 2005, a dissociation was found between the variable in-hospital mortality of patients with acute myocardial infarction and the other variables analyzed. These other variables were more associated with the quality of the service offered to the patient, and an improvement was perceived after the hospital evaluation process. The authors pointed out that previous studies reported a lower sensitivity of the clinical outcomes to the detriment of quality parameters with regard to the protocols established at the hospital.[25] In-hospital mortality refers to the management of a specific patient and does not necessarily shows the ineffective outcome of all other procedures of care provided during hospitalization.[25] Due to this, the number of deaths is not considered a good parameter in assessing the impact of the accreditation process.

Regarding the other variables of clinical outcomes, there was an increase in reinfarction and CRA, especially in patients with ST-segment elevation, but without significance. In 2015, Falstie-Jensen et al.[9] studied the relationship between accredited hospitals and acute readmission (up to 30 days), considering all patients admitted to the hospital, and it was found that patients seen in institutions certified as accredited institutions did not present any difference comparing with non-accredited hospitals.[9] Given that reinfarction can be considered a factor that would lead to acute readmission, this cause may be included in the context of the study.

Limitations

This study has some limitations. Firstly, it includes data from a single hospital, with a relatively small sample. In addition, it is not possible to evaluate the secondary outcomes satisfactorily, since the sample size is not so big. Moreover, it was impossible to have a control group in parallel to the study, since it was conducted in two distinct periods, and the motivation of the team may imply different results. However, note that the motivation of the team is one of the benefits of the accreditation process. Another limitation was that the data of this study were secondary and were derived from medical records, although the researchers made sure they conducted an active search for any information that might be missing or doubtful.

Conclusions

In conclusion, after the ONA 3 accreditation process, there was a reduction in hospital stay. There were no significant differences in the frequency of hospital mortality or combined clinical outcomes, as well as in the length of hospital stay at the CCU.

Author contributions

Conception and design of the research: Leite CD, Pereira TC, Freitas MP, Tinôco NLW, Pereira FG, Menezes RVLV, Feitosa-Filho GS. Acquisition of data: Leite CD, Pereira TC, Freitas MP, Tinôco NLW, Pereira FG, Menezes RVLV, Andrade MQS, Vilas Boas SPRV. Analysis and interpretation of the data: Leite CD, Tinôco NLW, Pereira FG, Menezes RVLV, Andrade MQS, Vilas Boas SPRV, Feitosa-Filho GS. Statistical analysis: Leite CD, Tinôco NLW, Pereira FG, Menezes RVLV, Andrade MQS, Vilas Boas SPRV, Feitosa-Filho GS. Writing of the manuscript: Leite CD, Barbosa PJB, Feitosa-Filho GS. Critical revision of the manuscript for intellectual content: Leite CD, Pereira TC, Freitas MP, Tinôco NLW, Pereira FG, Menezes RVLV, Andrade MQS, Vilas Boas SPRV, Barbosa PJB, Feitosa-Filho GS.

Potential Conflict of Interest

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

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital Santa Izabel under the protocol number 41496815.7.0000.5520. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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ORIGINAL ARTICLE

The Influence of Seasonal Temperature Variation on Blood Pressure Behavior

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Abstract

Background: Hypertension in Brazil affects 32.5% of the population, accounting for 50% of deaths due to cardiovascular disease. The correct measurement and interpretation of blood pressure are essential for attaining an adequate disease diagnosis and management.

Objective: To verify the correlation between the seasonal temperature variation during 2016 and blood pressure variation in 902 patients of a private Cardiology Service in the city of Porto Alegre/RS.

Method: A total of 902 ambulatory blood pressure monitoring (ABPM) results were analyzed in 2016. Pearson's Correlation Coefficient was used to correlate blood pressure levels with the values of temperature and relative air humidity; the Kolmogorov-Smirnov and Shapiro-Wilk tests were adopted for significance values, assuming an alpha error < 0.05 and a 95% confidence interval. The Analysis of Variance compared the 902 ABPM results with the continuous variables obtained for this study.

Results: No statistically significant differences were found when the blood pressure values obtained from the 902 ABPM results were correlated with the minimum, mean and maximum values of temperature and relative air humidity, and also when each of the continuous variables obtained for this study were compared with these same pressure measurements.

Conclusion: Despite the great variation in temperature and relative air humidity throughout the year in the region, there was no significant influence on the systemic arterial pressure in the study population. New comparative studies in the same population with different thermal variations may provide further clarification on this subject. (Int J Cardiovasc Sci. 2019;32(6):615-622)

Keywords: Blood Pressure; Climate Change; Risk Factors; Risk Assessment; Seasons; Humidity.

Introduction

According to data obtained from the 7th Brazilian Guideline of Arterial Hypertension, Arterial Hypertension (AH) in Brazil affects 32.5% of the adult population (36 million), and more than 60% of this population consists of elderly individuals. This condition contributes directly or indirectly to 50% of deaths from cardiovascular disease, and for this reason it is considered a public health problem. Due to this fact, the correct measurement and interpretation of systemic arterial pressure are essential for the adequate diagnosis and management of hypertension.[1]

Risk factors such as age, overweight and obesity, socioeconomic factors, excessive salt intake, chronic and high consumption of alcoholic beverages and sedentary lifestyle effectively contribute to the development of AH. The influence of climatic factors (seasonality, temperature, relative air humidity and others) as a risk factor for AH development is not well established. Few studies have been carried out to verify the influence of temperature variation throughout the year on the development of arterial hypertension, but this correlation is still unclear and requires further studies.[1-4] Amoah et al.,[5] reported that an increase in the sympathetic system activity is correlated with higher blood pressure readings

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during winter and that blood pressure decreases in summer due to blood vessel dilation, associated with loss of salt and water through perspiration, so that lower BP values are recorded during that season.

Considering that the city of Porto Alegre, capital of the state of Rio Grande do Sul, Brazil, is characterized by quite different climatic conditions during the year, the aim of the present study was to verify the correlation between the seasonal variation of temperature and relative humidity of the air during the year 2016 and the systemic arterial pressure variation in a sample assessed through ambulatory blood pressure monitoring (ABPM) of 902 patients from a private Cardiology Service of the aforementioned city.

Methods

This was a retrospective longitudinal study of a convenience sample, in which we analyzed 902 results of patients submitted to ABPM, after indication of their attending physicians, from January to December 2016, in a private Cardiology Service in the city of Porto Alegre/RS.

The sample consisted of individuals older than 18 years of age, of both genders, divided into three groups: the first group included all 902 patients in the sample; the second group included 186 patients using one or more antihypertensive drugs of different classes, and the third group included 716 patients who did not use any type of antihypertensive medication. We analyzed the diagnostic and follow-up examinations of all patients who underwent ABPM at the clinic during the specified period. A Cardios ABPM device was used. The values for systolic and diastolic blood pressure levels were obtained from the respective ABPM of each individual, and the daily values for temperature and relative humidity of the air were obtained from INMET (National Institute of Meteorology) website from December to January 2016 and were divided by the four seasons of the year (summer, fall, winter and spring).

Statistical analysis

The collected data were organized into a database using the software Statistical Package for Social Sciences (SPSS).[22] For the continuous variables, mean, standard deviation and 95% confidence intervals were used, as well as minimum and maximum values of each variable after assessment of their normality using the Shapiro-Wilks test.

Pearson's Correlation Coefficient was applied to correlate the mean awake systolic and diastolic blood pressure (MASBP/MADBP) and the mean resting systolic and diastolic blood pressure (MRSBP/MRDBP), minimum (MIN SBP) and maximum (MAX SBP) systolic blood pressure, 24-hour mean systolic and diastolic blood pressure (24HMSBP/24HMDBP), systolic and diastolic dipping in relation to the minimum, mean and maximum temperature values, and relative humidity of the air stratified by the users of antihypertensive medication (Table 2) or non-use of medication (Table 3).

The analysis of variance (one-way ANOVA) was applied to compare the levels of SBP obtained in ABPM, age, temperature and relative humidity between the 4 seasons of the year 2016.

For statistical significance, an alpha error < 0.05 and a 95% confidence interval were admitted.

Results

The results of 902 ABPM from different individuals were included in the study. The data obtained regarding the mean, standard deviation and 95% confidence interval, as well as minimum and maximum values of the patient's age, the results related to the systolic and diastolic blood pressure levels, temperature and relative humidity are shown in Table 1.

No significant associations were found when the variables obtained through ABPM were correlated with the minimum, mean and maximum values of temperature and relative air humidity, both in group 2, which used antihypertensive medications and in group 3, which did not use antihypertensive medications (Table 2 and Table 3, respectively).

Also, no significant differences were found when all three patient groups (total of patients, users and non-users of antihypertensive drugs) were compared with each of the continuous obtained variables – age, minimum, mean and maximum values of MASBP, MADBP, MRSBP, MRDBP, MIN SBP, MAX SBP, 24HMSBP, 24HMDBP, systolic and diastolic dipping, temperature and relative humidity (Table 4) (Figures 1 and 2).

Discussion

Hypertension is an important factor for cardiovascular morbidity and mortality, being an independent risk factor for myocardial infarction, chronic kidney disease,

Table 1 - Values obtained in the ABPM of 902 patients (January to December / 2016)

	Mean ± SD (95%CI)	Minimum value	Maximum value
Age	57.47 ± 15.429	18	94
MASBP	129.12 ± 12.940	94	185
MADBP	81.56 ± 10.745	51	118
MRSBP	116.73 ± 14.643	82	174
MRDBP	68.81 ± 10.364	43	105
MAX SBP	163.95 ± 21.566	114	255
MIN SBP	102.72 ± 12.435	68	152
24HMSBP	126.14 ± 12.641	93	180
24HMDBP	78.54 ± 10.210	50	115
Systolic dipping	9.50 ± 7.766	-27	28
Diastolic dipping	15.52 ± 9.215	-16	42
Maximum temperature	23.929 ± 5.930	13.0	39.0
Minimum temperature	14.759 ± 5.191	3.0	25.4
Mean temperature	18.493 ± 5.281	8.0	29.0
Relative air humidity	77.149 ± 10.164	49.2	97.25

ABPM: ambulatory blood pressure monitoring; SD: standard deviation; CI: confidence interval; MASBP/MADBP: mean awake systolic and diastolic blood pressure; MRSBP/MRDBP: mean resting systolic and diastolic blood pressure; MAX SBP/MIN SBP: maximum and minimum systolic blood pressure; 24HMSBP/24HMDBP: 24H mean systolic and diastolic blood pressure.

ischemic and hemorrhagic strokes, and premature death. It should not be treated alone, and the approach should include lifestyle changes (LSC) for these patients and the use of antihypertensive medications. In Brazil, it is considered a public health problem, requiring public policy strategies aimed at preventing the development of AH.[1-3] In a study entitled ELSA-BRASIL - Longitudinal Study of Adult Health (*Estudo Longitudinal de Saúde do Adulto*)[6] carried out between 2008 and 2010, involving 15,105 individuals between the ages of 35 and 74, the authors found almost 36% of hypertensive individuals in the study population, corroborating the fact that AH is a serious problem, requiring early intervention and prevention measures. Guimarães et al.,[7] in an ecological time-series study on mortality due to cardiovascular diseases in Brazil, observed that there was a reduction in mortality coefficients from ischemic heart disease and cerebrovascular disease in Brazil between 1980 and 2012, but the regions that showed the highest coefficients for both conditions were the southeast and south regions, which draws attention to the region in which the present study was carried out.

Several studies have addressed and shown the association of risk factors such as age,[8-9] socioeconomic factor,[10] obesity,[11-14] sedentary lifestyle,[14] excessive intake of salt[13,15,16] and alcoholic beverages[17] with the development of AH. Moreira et al.,[8] in a cohort study carried out in the city of Porto Alegre, involving 1,089 individuals aged 40 to 49 years, concluded that age and waist-to-height ratio are independent factors for hypertension and that the incidence of hypertension in Brazil tends to be higher than in developed countries. Picon et al.,[9] in a meta-analysis, also reports that the prevalence of hypertension in the elderly in Brazil is quite high; therefore, both authors corroborate that the age factor has influence on blood pressure behavior.

In the study by Bassanesi et al.,[10] also carried out in Porto Alegre, premature mortality (between 45 and 64 years of age) from cardiovascular diseases was 163% higher in districts located in the worst socioeconomic quartile compared to those located in the best quartile. In this same study, almost half of the mortality from cardiovascular diseases before the age of 65 years was associated with poverty and socioeconomic factors.

Regarding the association between obesity / sedentary lifestyle and AH, there are many studies on this subject.[11-14] Galve et al.,[14] reported that excess weight and sedentary lifestyle are among the leading causes of hypertension in both developed and developing countries.

Salt intake is considered to be one of the main causes of elevated blood pressure according to Trieu et al.,[15] and Frohlich et al.,[16] and its restriction can prevent cardiovascular and renal injuries. Regarding alcohol abuse, Briassoulis et al.,[17] concluded in a meta-analysis that its excessive intake, regardless of gender, also greatly increases the risk of AH.

Regarding the influence of climate / temperature on blood pressure behavior, the studies, mainly in Brazil, are scarce. Worldwide, the vast majority of studies was carried out in China, with large population samples.

Table 2 - Values obtained from 186 ABPM in group 2 (patients taking antihypertensive medications) – Pearson's Correlation Coefficient

Pearson's Correlation Coefficient	Maximum temperature	Minimum temperature	Mean temperature	Relative air humidity
MASBP	-.081	-.072	-.078	.069
MADBP	-.043	.022	.001	-.037
MRSBP	.063	.073	.078	-.123
MRDBP	.065	.117	.111	-.105
MAX SBP	-.038	-.062	-.053	-.042
MIN SBP	-.027	-.004	-.012	-.058
24HMSBP	-.024	-.011	-.014	-.093
24HMDBP	.000	.072	-.051	-.054
Systolic dipping	-.193	-.192	-.209	.113
Diastolic dipping	-.175	-.165	-.186	.127

ABPM: ambulatory blood pressure monitoring; MASBP/MADBP: mean awake systolic and diastolic blood pressure; MRSBP/MRDBP: mean resting systolic and diastolic blood pressure; MAX SBP/MIN SBP: maximum and minimum systolic blood pressure; 24HMSBP/24HMDBP: 24H mean systolic and diastolic blood pressure.

Table 3 - Values obtained from 716 ABPM in group 3 (patients without antihypertensive medication) - Pearson's Correlation Coefficient

Pearson's Correlation Coefficient	Maximum temperature	Minimum temperature	Mean Temperature	Relative air humidity
MASBP	-.158	-.188	-.191	.001
MADBP	-.113	-.134	-.137	.029
MRSBP	-.033	-.030	-.041	-.028
MRDBP	-.042	-.042	-.050	.035
MAX SBP	-.154	-.187	-.189	.008
MIN SBP	-.127	-.121	-.140	-.008
24HMSBP	-.145	-.155	-.168	.017
24HMDBP	-.089	-.103	-.107	.019
Systolic dipping	-.138	-.172	-.162	-.028
Diastolic dipping	-.083	-.100	-.097	.001

ABPM: ambulatory blood pressure monitoring; MASBP/MADBP: mean awake systolic and diastolic blood pressure; MRSBP/MRDBP: mean resting systolic and diastolic blood pressure; MAX SBP/MIN SBP: maximum and minimum systolic blood pressure; 24HMSBP/24HMDBP: 24H mean systolic and diastolic blood pressure.

Regarding the pathophysiology, Amoah et al[5] states that an increase in sympathetic tonus during winter increases BP levels, whereas vasodilation and loss of salt and water through summer perspiration causes BP levels to decrease. In 2013, in a study carried out in China, the authors[18] concluded that blood

Table 4 - Values obtained at the ABPM in the 3 groups of patients (January to December / 2016) - Analysis of variance

ANOVA	Group 1 (n = 902)*	Group 2 (n = 186)†	Group 3 (n = 716)‡
Age	.477	.172	.501
MASBP	.000	.738	.000
MADBP	.013	.476	.012
MRSBP	.552	.265	.402
MRDBP	.485	.119	.496
MAX SBP	.003	.727	.001
MIN SBP	.053	.553	.006
24HMSBP	.002	.610	.000
24HMDBP	.073	.202	.081
Systolic dipping	.006	.151	.020
Diastolic dipping	.204	.377	.337
Maximum temperature	.000	.000	.000
Minimum temperature	.000	.000	.000
Mean temperature	.000	.000	.000
Relative air humidity	.000	.000	.000

ABPM: ambulatory blood pressure monitoring; MASBP/MADBP: mean awake systolic and diastolic blood pressure; MRSBP/MRDBP: mean resting systolic and diastolic blood pressure; MAX SBP/MIN SBP: maximum and minimum systolic blood pressure; 24HMSBP/24HMDBP: 24H mean systolic and diastolic blood pressure; (*) total group of patients; (†) group of patients taking antihypertensive medications; (‡) group of patients without antihypertensive medications.

pressure levels are strongly and inversely associated with external temperature and suggest that seasonal variations in blood pressure should be considered in the patients' assessment. In another study, carried out in a rural area of China, in which more than 57,000 individuals between 30 and 79 years old participated, Su et al.,[19] also concluded that a lower external temperature is strongly associated with higher mean arterial pressure and the prevalence of hypertension, as well as poorer control of hypertension, and that this factor should be considered when performing population studies of hypertension.

Yang et al.,[20] in a sample of 23,000 Chinese individuals with a history of cardiovascular disease, showed that there is an increase in blood pressure and cardiovascular mortality in winter. They concluded that careful monitoring and a more aggressive treatment are needed to decrease blood pressure during the cold months and reduce mortality from cardiovascular causes in high-risk individuals.

Lewington et al.,[21] and Wang et al.,[22] carried out surveys with population samples of more than 500,000 and 430,000 individuals, respectively, with the first study sample consisting of individuals from several Chinese rural regions, and the second one of patients from a university hospital linked to Zhejiang University (Zhejiang University School of Medicine). The authors of both studies also concluded that a low external temperature increases blood pressure levels, and similarly, suggest that the seasonal variation in blood pressure should be considered in the patients' clinical assessment.

In an American study, Amoah et al.,[5] recently investigated the seasonal variation of blood pressure monitoring but correlated the control of blood pressure levels with the use of electronic equipment in the different climatic seasons, and concluded this control is performed cyclically, being higher during the winter period. However, they did not report the results of this variation in absolute numbers of blood pressure.

In Brazil, there have been some studies that associated seasonal temperature variation with gestational hypertension,[4,23] symptoms of stroke,[24,25] respiratory diseases,[26] epistaxis[27] and others that investigated the association between climate and mortality from different diseases in elderly individuals.[28] Only one study[29] approached the subject, when it investigated the effect of water temperature on cardiovascular responses: heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) during exercise at different temperatures (29° C, 33° C and 37° C). The authors found a HR increase and DBP decrease at 37º C; they did not find a significant effect on SBP. At the end, they suggest that, when therapeutic swimming pools are used for water-walking exercises, the choice of the water temperature should be considered as a way to decrease cardiovascular stress.

Studies that are similar to the present work, assessing the temperature seasonal variation in association to blood pressure behavior, were not found. This fact indicates the need for further investigations, since studies with large population bases, such as the Chinese studies, have shown that temperature variation does in fact influence blood pressure behavior.

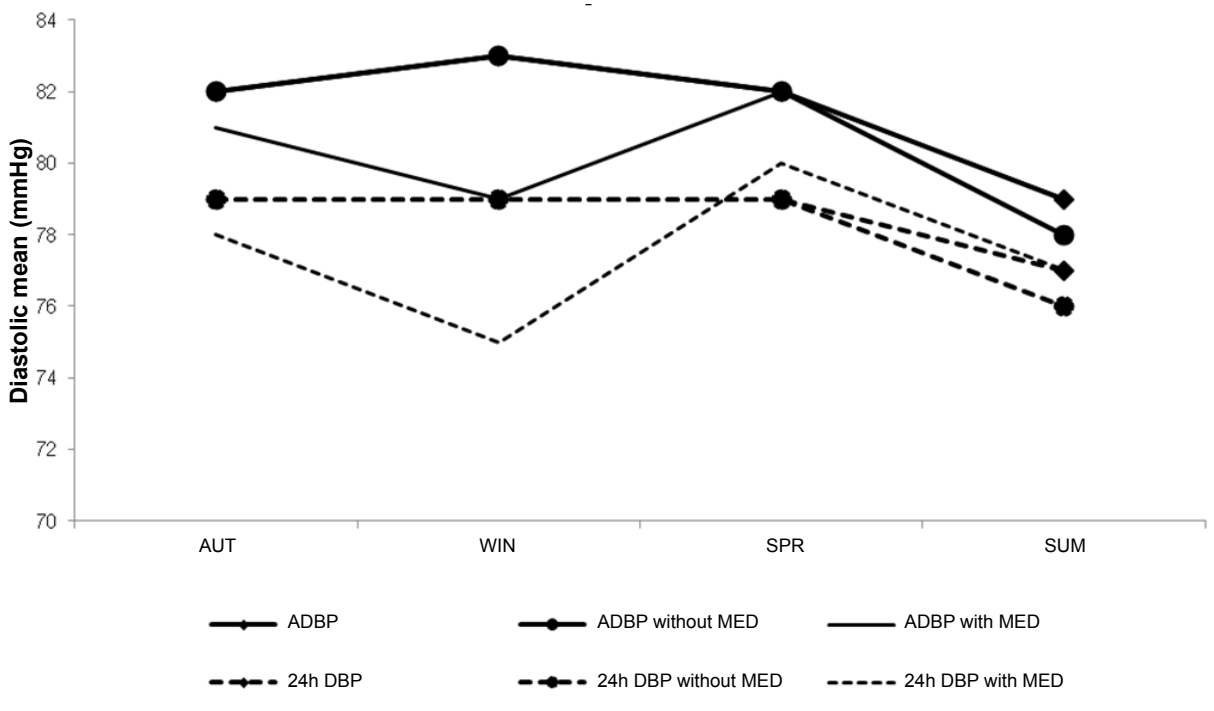

Figure 1 - Mean diastolic blood pressures at ABPM compared between the climatic seasons in the total group and according to antihypertensive drug use (January to December / 2016).
ADBP: awake diastolic blood pressure; ADBP with MED.: awake diastolic blood pressure with medication; ADBP without MED: awake diastolic blood pressure without medication; 24h DBP: 24-hour diastolic blood pressure in the entire group.

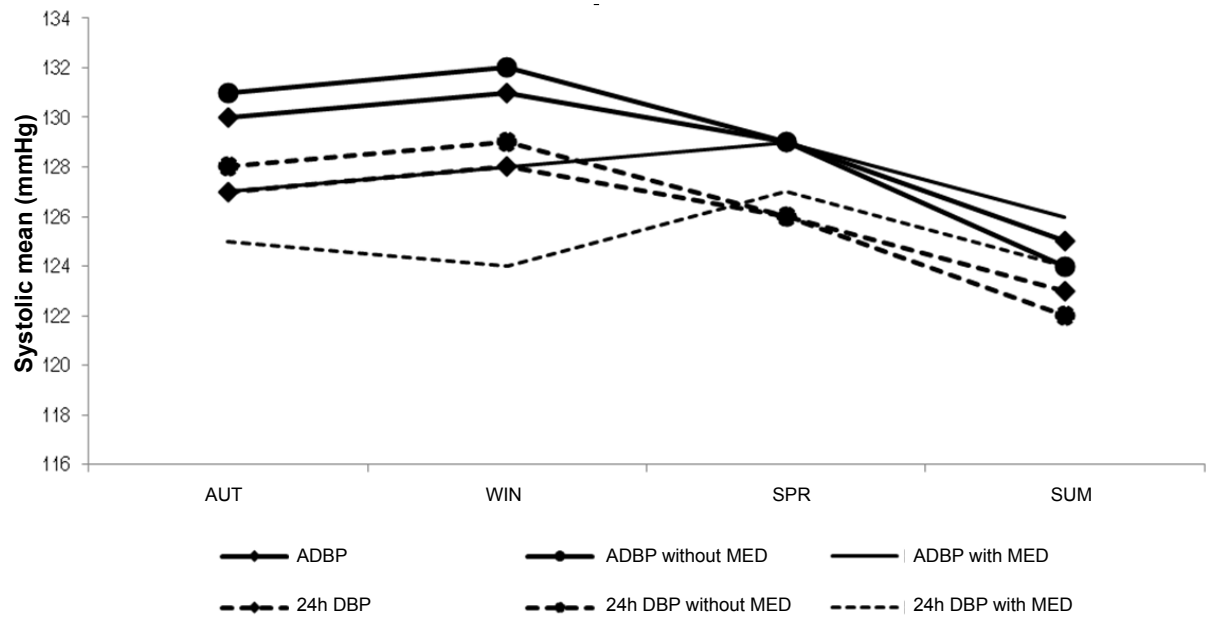

Figure 2 - Mean systolic pressures at ABPM compared between climatic seasons in the entire group and according to antihypertensive drug use (January to December / 2016).
ASBP: awake systolic blood pressure; ASBP with MED.: awake systolic blood pressure with medication; ASBP without MED: awake systolic blood pressure without medication; 24h SBP: 24-hour systolic blood pressure in the entire group; 24-h SBP without MED: 24-hour SBP without medication.

This study has limitations, as it consists of a population sample that had exams requested according to the attending physicians' individual criteria and no evaluation of other risk factors for AH, such as weight, ethnicity and family history of SAH.

Conclusion

The influence of climatic factors on blood pressure behavior is still controversial. There are not enough data in Brazil and in its South region because the studies related to the subject are scarce or nonexistent.

With four well-defined climatic seasons, mean air temperature and relative humidity in Porto Alegre show great variation throughout the year; however, this variation did not show a significant influence on systemic arterial pressure behavior in the assessed population. New comparative studies carried out in the same population with different thermal variations can provide further clarification on this subject.

Author contributions

Conception and design of the research: Escosteguy JR, Beskow M, Van Der Sand CR. Acquisition of data: Escosteguy JR, Beskow M, Van Der Sand CR. Analysis and interpretation of the data: Van Der Sand CR. Statistical analysis: Van Der Sand CR. Writing of the manuscript: Escosteguy JR, Beskow M, Van Der Sand CR. Critical revision of the manuscript for intellectual content: Escosteguy JR, Van Der Sand CR.

Potential Conflict of Interest

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

Sources of Funding

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Study Association

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

Ethics approval and consent to participate

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

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ORIGINAL ARTICLE

Nutritional Status, Lifestyle and Lipid Profile in Vegetarians

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Abstract

Background: Vegetarian diets have been linked to reduced risk of chronic noncommunicable diseases, since they positively modulate biochemical parameters, particularly those related with glycemic control and lipemia, and considered as potential strategy for weight control.

Objective: To compare the nutritional status, lifestyle and lipid profile of adult vegetarians with omnivores in a sample of individuals in the city of São Paulo.

Methods: This was a cross-sectional study. Anthropometric, biochemical and lifestyle variables were compared between vegetarians and omnivores. A significance level of 5% was considered for all analyses.

Results: Vegetarians were more likely to practice physical activity (64.3% vs 42.5%, p = 0.056) and consuming dietary supplements (48.1% vs 20.5%, p = 0.012). There was no statistically significant difference for the variables: age, sex, triglycerides, total cholesterol and low-density lipoprotein between the two groups. Vegetarians had significantly lower weight [60.8 kg (56.7 – 69.4) vs 71.1 kg (58.0 – 75.4), p = 0.038], BMI [22.4 kg/m2 (20.9 – 23.8) vs 24.6 kg/m2 (21.7 – 26.1), p = 0.001], and waist circumference [(81.8 ± 8.2 vs 87.8 ± 10.9 cm, p = 0.003)], and higher high-density lipoprotein (54.88 ± 14.44 vs 47.30 ± 12.27 mg /dL p = 0.008) than omnivores.

Conclusion: Compared with omnivores, vegetarians had a better nutritional status, with lower BMI and waist circumference, significantly higher levels of plasma lipoprotein high-density, and healthier lifestyle. (Int J Cardiovasc Sci. 2019;32(6):623-634)

Keywords: Diet, Vegetarian; Chronic Disease; Dyslipidemias; Lipoproteins; ife Style; Epidemiology; Body Weight and Measures.

Introduction

Assessment of nutritional status is made by anthropometry, biochemical tests and evaluation of dietary intake, which altogether, determine whether individuals have "normal" status or are at risk of malnutrition. The evaluation of nutritional status plays an important role as it has an inverse relationship with the incidence of non-communicable diseases (NCDs), including obesity, type 2 diabetes mellitus (DM2), cardiovascular diseases (CVDs), systemic arterial hypertension (SAH) and some cancers.[1] The close relationship between obesity and life style (physical inactivity and poor-quality diet) make this modifiable component the main target of weight control strategies.

Healthy eating is considered eating habits that promote health and that should be guided and encouraged from childhood to adult life.[2] In this context, vegetarian diets may be advantageous as a nutritional strategy not only to promote healthy eating habits but also to help in the treatment and prevention of obesity.[3] According to the Brazilian Vegetarian Society (SVB), a vegetarian is an individual who exclude all kinds of

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meat, poultry and fish from their diet, and may include or not dairy products and eggs.[4]

In the last 30 years, several researches have reported important and measurable benefits of vegetarian diets, especially of well-planned diets followed by individuals living in places where vegetable foods are highly available. Under these conditions, vegetarians can enjoy good health, with body mass index (BMI)[5] and plasma cholesterol levels[6] within healthy ranges,[6] in addition to increased serum levels of antioxidants,[7] low prevalence of obesity, cardiovascular diseases,[8] type 2 diabetes mellitus,[9] systemic arterial hypertension,[10] metabolic syndrome,[11] colon polyps,[12] many types of cancer,[8] and increased life expectancy.[13] There is much evidence that a vegetarian diet can be recommended for the prevention and treatment of cardiovascular diseases[14] and even as a therapeutic alternative for diabetes,[15] hypertension[16] and obesity.[17]

Vegetarian diets offer nutritional benefits, including lower levels of saturated fat, cholesterol and animal protein, as well as higher levels of carbohydrates, dietary fiber, magnesium, potassium, folate, antioxidant vitamins and other bioactive compounds. However, vegans may have a deficient intake of vitamin B-12, calcium, vitamin D and omega-3 fatty acid.[18] The marginal intake of some nutrients does not prevent these diets from being recommended, based on strong scientific evidence showing that the health benefits of these diets exceed potential risks.[19]

Studies comparing body weight of vegetarians and non-vegetarians have shown that those who follow a vegetarian diet tend to have lower weight.[5]

Therefore, it seems that the main characteristic of vegetarian diets, i.e., the exclusion of meat or reduction of its consumption, when combined with a high nutrient density, plays an important role in maintenance of a healthy nutritional status. Thus, the expansion of the study of vegetarian diets may lead to more efficient strategies for weight control, development of healthy habits and consequent reduction of NCDs. The aim of this study was to assess and compare the nutritional status, by means of anthropometric and biochemical parameters, of a sample of adult vegetarians and omnivores from the same population in São Paulo, Brazil.

Methods

This was a cross-sectional study. Calculation of the sample size (non-probabilistic, convenience sampling) was based on the test of the difference of means of BMI, described in a previous study involving a similar population.[20] BMI was chosen because the variable encompasses a large number of individuals, thereby increasing the power of the sample. Fifty-eight individuals in each group would be necessary for statistically significant results (Student's t-test), with 80% power and level of significance of $\alpha = 0.05$. We studied adults (≥ 18 years and < 60 years) of both sexes. A total of 198 individuals were first selected, and then we excluded women using oral contraceptives (in attempt to establish a hormonal profile), and individuals using antidepressants, anti-hypertensive drugs, beta-blockers or vasodilators. Ninety-six individuals (56 vegetarians and 40 omnivores) were included in the study.

In general, studies comparing the effects of vegetarian diet on health in relation to omnivore diet have not considered different types of vegetarian diets. Rather, the authors have reported differences between exposed and non-exposed to vegetarian diets, or between vegetarians and omnivores.[14] The exceptions in this regard are population-based, longitudinal, cohort studies that involve large sample populations and hence allow a stratified analysis by the type of vegetarian diet. In the present study, we opted to dichotomize the study group as vegetarians and omnivores and to compare the nutritional status and life style between these groups.

For recruitment of vegetarian volunteers (Figure 1), we contacted the SVB, which supported and publicized the study. An e-mail was sent to the addresses registered in the SVB database of more than 2,000 individuals (omnivores and vegetarians), who were invited to participate in the study. The message contained an electronic address to which the volunteers willing to participate in the study could make contact.

Those interested in participating got their first visit scheduled by e-mail; they also published the call for participation on online social medias. After the first interview, vegetarians who met the inclusion criteria were invited via e-mail to the second phase of the study (collection of blood samples).

Omnivores were recruited through advertisement of the study in social medias and in universities, based on the same flowchart of vegetarians (Figure 2).

The first stage of data collection comprised: explanation of the study; explanation of the informed consent form; administration of the questionnaire containing sociodemographic data, lifestyle information and assessment of the nutritional status, with measurement

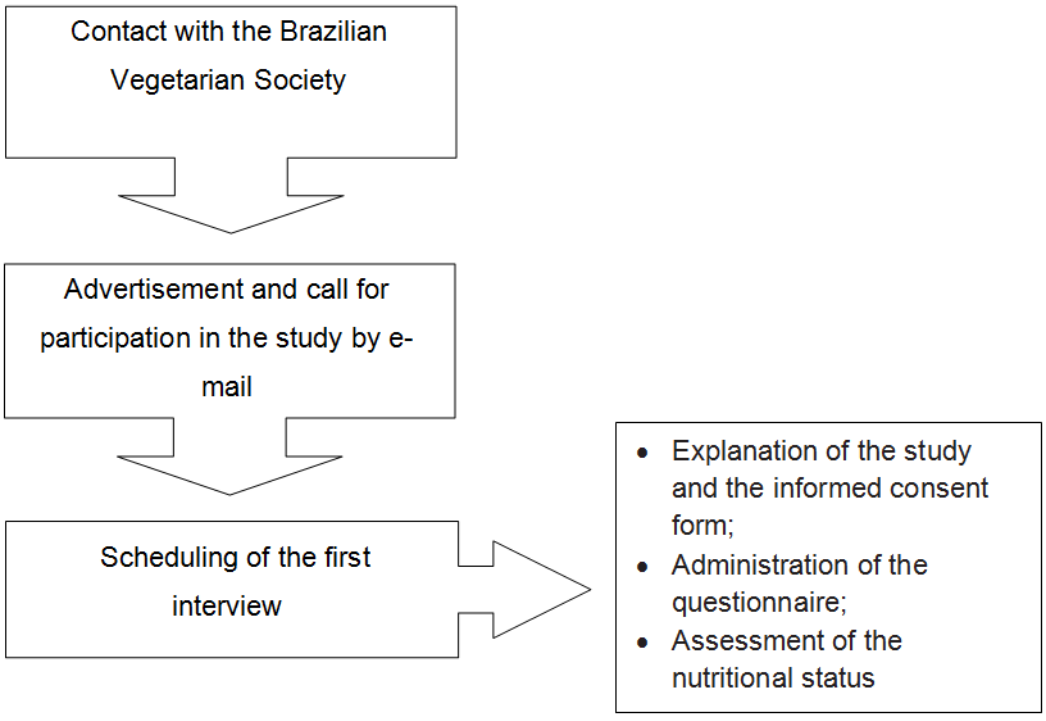

Figure 1 - Recruitment process of vegetarians for participation in the study.

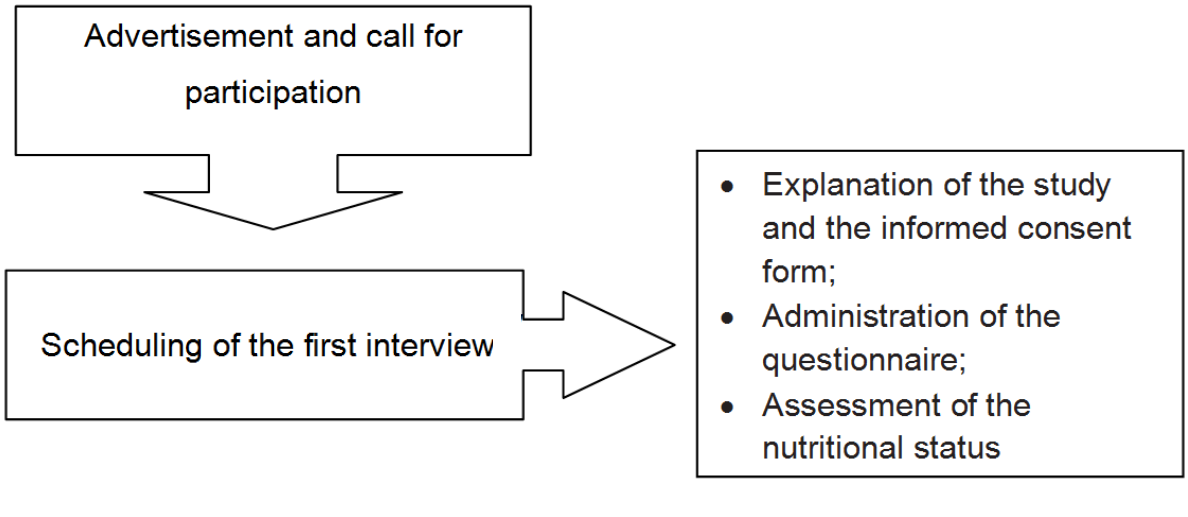

Figure 2 - Recruitment process of omnivores for participation in the study.

of weight, height and waist circumference (WC). After application of the exclusion criteria, participants included had blood samples collected for laboratory analysis.

Vegetarianism: participants were classified by the type of vegetarian diet or eating practices by self-report; they were asked if they considered themselves

semivegetarians, ovo-lacto vegetarians, vegans or omnivores. In addition, they were asked which food items they excluded from their diets (fish, red meat, poultry, eggs and dairy) based on the SVB definition of the diet types. Individuals classified as vegetarians (or subgroups), were also asked the reasons for becoming a vegetarian and how long they had been following this type of diet.

Sociodemographic and clinical variables: participants were asked about their age (in years), educational attainment, marital status and health conditions (presence of any disease at the interview).

Life style variables: practice of physical exercise (physically active or inactive), according to the International Physical Activity Questionnaire (IPAQ), smoking habits (yes or no), number of meals/day (three or less meals/day; more than three meals/day); sleeping hours (eight or less hours/day/ more than eight hours/day) and use of vitamins and supplements (yes or no).

Variables of nutritional status: nutritional status was assessed by BMI. For weight measurement, volunteers were asked to stand in the middle of the platform of an electronic scale (Welmy®, model R-110, 150 kg capacity and 100 g accuracy). Height was measured using a portable stadiometer (Estad® - Alturexata, 0.35 m – 2.13 m). All measurements were made with participants barefoot and wearing light clothes.[21] For analysis of body composition, WC was measured at the level of the umbilicus, using a non-elastic, retractable tape (Sanny®). Nutritional status was classified according to the WHO classification for BMI[21] individuals were classified as normal or altered nutritional status if they had a BMI of 18.5 – 24.9 kg/m^2 or > 24.9 kg/m^2, respectively. WC was classified according to the risk of obesity-related complications, by gender. A WC ≤ 80 cm for women and < 94 cm for men was considered normal, and a WC > 80 cm for women and > 94 cm for men considered altered or indicator of risk.[1]

Biochemical variables: for biochemical analysis, concentrations of total cholesterol (TC) and cholesterol fractions were measured using the automated enzymatic method. All procedures were conducted in a clinical analysis laboratory. The following cut-off values were used to classify the variables as normal or altered – TC > 200 mg/dL, LDL-c > 100 mg/dL, HDL- cholesterol < 40 mg/dL for men and < 50 mg/dL for womenm and triglycerides (TG) > 150 mg/dL.

Statistical analysis

Statistical analysis was performed using the SPSS software version 20.0. Sociodemographic data, characteristics of vegetarian diet, lifestyle data and data of nutritional status were expressed as proportion and mean ± standard deviation. Normality of data distribution was tested by the Kolmogorov-Smirnov test, and the chi-squared test used to compare differences in proportions. Comparisons of means were performed using the Student's t-test for normally distributed variables or the Mann-Whitney test for variables without normal distribution. Data were not matched, since only one measure was taken from the sample unit, and the study had a cross-sectional design, with no intervention. Continuous variables with normal distribution (WC, TC, HDL, LDL) were expressed as mean and standard deviation, whereas those without a normal distribution (weight, BMI, glycemia, insulin, HOMA-IR, TG) were expressed as median and interquartile range (1st quartile and 3rd quartile). Categorical variables (type of diet, sex, educational attainment, smoking status, marital status, physical activity, number of meals per day, number of sleeping hours, vitamins/supplements intake) were presented as absolute numbers and percentages. The level of significance was set at 5%.

Ethical aspects

The present study was approved by the Ethics Committee of the University of Sao Paulo School of Public Health (approval number 2260).

Results

Ninety-six volunteers were studied, 56 vegetarians and 40 omnivores. Most of participants were women (n = 60, 63%), adults (33.2 years ± 7.1 years), with high educational attainment (n = 66, 69% with higher education and postgraduate study), non-smokers (n = 91, 96%), and lived with a partner (n = 54, 56%). Despite a high percentage of sedentary individuals (n = 43, 45%), median BMI was 22.7, 21.3 – 25.0 kg/m^2 (i.e., normal) and participants were considered healthy, since 70% of them did not have any disease at the interview. Table 1 describes the general characteristics of the study population.

Tables 2 and 3 present descriptive data of both groups (vegetarians and omnivores), stratified by sex.

Table 1 - General characteristics of the study population

Variables		n (%)
Type of diet	Vegetarian	56 (58.3)
	Omnivore	40 (41.7)
Sex	Male	36 (37.5)
	Female	60 (62.5)
Educational attainment	Completed high school	9 (9)
	Some superior education	21 (22)
	Superior or postgraduate education	66 (69)
Smoker	Yes	4 (4)
	No	91 (96)
Marital status	With a partner	54 (56)
	Without a partner	42 (44)
Physical activity	Active	53 (55)
	Inactive	43 (45)
Age (years) (m ± DP)		33.5 + 7.2
BMI (kg/m^2) (median (1st Q – 3rd Q);		22.7 (21.3 – 25.0)*

** BMI: body mass index; 1st Q: first quartile; 3rd Q: third quartile.*

To identify possible differences in life style between vegetarians and omnivores, categorical variables, physical activity data, sleeping hours number of meals, smoking habit and use of vitamin were compared between the two groups using the chi-square test (Table 4).

The use of vitamins and dietary supplements was more frequent among vegetarians than omnivores (48.1% vs 20.5%, p = 0.012). Also, although not statistically significant, the practice of exercise was more frequent in vegetarians than in omnivores (64.3% vs 42.5%, p = 0.056).

Comparisons of anthropometric and biochemical variables are summarized in Table 5. No statistically differences were found for age, sex, smoking habits, practice of physical activity, sleeping hours, number of meals per day, TC, LDL-c and TC. However, significant differences were found between the groups for WC (p = 0.003), BMI (p < 0.001), use of vitamins and supplements (p = 0.012), glycemia (p = 0.004), body weight (p = 0.038), insulin (p = 0.035) and HDL-c (p = 0.008).

Although statistically differences were found for anthropometric and biochemical variables between the groups, mean BMI, and glucose and HDL-c levels are within recommended ranges. To increase the power of the analysis, the variables were then categorized into normal and altered (reference values described in Methods). Thus, statistically significant differences between vegetarians and omnivores were found for WC (p = 0.004), BMI (p = 0.002) and HDL-c (p = 0.034) (Table 6).

Discussion

In the present study, we found that the use of vitamins and supplements is significantly higher among vegetarians than omnivores (48.1% vs 20.5%, p = 0.012) and, although not statistically significant, a higher number of vegetarians are physically active compared with non-vegetarians. The percentages of individuals with BMI, WC and HDL-c within normal ranges were also higher among vegetarians, indicating lower cardiovascular risk in this group. Although mean glucose levels were found within normal ranges in both groups, the lower values in the vegetarian group suggests higher insulin sensitivity. While 8.9% of vegetarians showed an altered WC, this percentage was nearly four times greater in omnivores (35%).

Table 2 - Sociodemographic and lifestyle data of vegetarians and omnivores, stratified by sex

Variables			Vegetarians		Omnivores	
			Female	Male	Female	Male
			Mean ± SD or n (%)	Mean ± SD or n (%)	Mean ± SD or n (%)	Mean ± SD or n (%)
	Sex		33 (59)	23 (41)	27 (68)	13 (32)
	Age		35.1 ± 7.3	31.9 ± 7.7	33.5 ± 7.3	32.5 ± 6.3
Sociodemographic	Educational attainment	Completed high school; some higher education	5 (9)	5 (9)	13 (33)	8 (20)
		Completed higher school; postgraduate degree	28 (50)	18 (32)	14 (35)	5 (12)
	Marital status	Without partner	20 (36)	17 (30)	11 (27)	6 (15)
		With partner	13 (23)	6 (11)	16 (40)	7 (18)
Life style	Physical activity	Inactive	20 (36)	17 (30)	21 (53)	11 (27)
		Active	13 (23)	6 (11)	6 (15)	2 (5)
	Smoker	No	32 (57)	21 (37)	25 (64)	13 (33)
		Yes	1 (2)	2 (4)	1 (3)	0 (0)
	Number of meals	< 3 meals	6 (11)	6 (11)	5 (13)	2 (5)
		4 or more meals	27 (48)	17 (30)	22 (55)	11 (27)
	Sleeping hours	< 8 hours	28 (50)	20 (36)	24 (60)	11 (28)
		> 8 hours	5 (9)	3 (5)	3 (7)	2 (5)
	Vitamins / supplements	No	15 (28)	13 (24)	20 (51)	11 (28)
		Yes	17 (31)	9 (17)	7 (18)	1 (3)

Considerable research on the effects of a vegetarian diet has been done with seventh-day Adventists, whose practices include refraining from eating meat.[22] So far, three cohort studies involving seventh-day Adventists have been conducted in the USA. The Adventist Health Study-1 (AHS-1) collected data from approximately 34,000 non-Hispanic Californian Adventists on fatal and non-fatal events.[23] The study provided important information, showing that obesity was less prevalent among vegetarians, and, similar to our study, the most common diet followed by vegetarians was the ovo-lacto vegetarian diet. The Adventist Health Study-2 (AHS-2), started in 2002, is a cohort prospective study involving more than 96,000 seventh-day Adventists, 52% of them vegetarians. The most common diet also was the ovo-lacto-vegetarian diet (28%), followed by semi-vegetarians (16%) and vegans (8%).[24] The study has reported some important results, including the relationship between vegetarianism and lower risk for diabetes,[25] hypertension[26] and obesity.[27]

There has been much debate on the mechanisms underlying the beneficial effects of vegetarian diets. Petterson et al.[26] highlighted that the lower incidence of hypertension among vegetarians in the AHS-2 study is due to the lower BMI in this group. Another cohort study (the EPIC-Oxford investigation) recruited 65,500 adults (20-89 years old); 51.8% were omnivores, 28.8% ovo-lacto-vegetarians, 15.5% semi-vegetarians and 3.9% vegans. Mean BMI was higher in non-vegetarian men (24.2 kg/m^2), in line with our results (see Table

Table 3 - Nutritional status and biochemical data of vegetarians and omnivores stratified by sex

Variables		Vegetarians		Omnivores	
		Female	Male	Female	Male
Nutritional status	Weight (mean [1st Q – 3rd Q])	59.0 (54.8 – 61.3)	71.4 (61.3 – 78.4)	63.5 (52.7 – 73.5)	73.6 (69.7 – 83.4)
	Height (Mean ± SD)	1.63 ± 0.07	1.75 ± 0.08	1.61 ± 0.06	1.76 ± 0.08
	BMI (Median [1st Q – 3rd Q])	22.1 (20.7 – 22.8)	22.9 (20.9 – 24.8)	24.5 (21.5 – 27.3)	25.2 (23.0 – 25.8)
	WC (Mean ± SD)	78.2 ± 5.63	87.1 ± 8.61	85.3 ± 10.39	92.9 ± 10.34
Biochemical data	TC (Mean ± SD)	177.7 ± 34.14	160.0 ± 36.26	175.4 ± 30.45	177.2 ± 40.35
	LDL-c (Mean ± SD)	100.4 ± 24.4	99.0 ± 30.6	106.7 ± 27.9	112.5 ± 30.2
	HDL-c (Mean ± SD)	61.7 ± 14.35	45.1 ± 7.20	50.7 ± 12.25	40.2 ± 9.05
	TG (Median [1st Q – 3st Q])	69.0 (58.0 – 96.0)	86 (70.0 – 104.0)	78.0 (61 – 95)	116.0 (86.0 – 161.0)
	CI 1 (Mean ± SD)	2.94 ± 0.54	3.63 ± 1.03	3.61 ± 0.91	4.50 ± 0.92
	CI 2 (Mean ± SD)	1.67 ± 0.41	2.26 ± 0.86	2.20 ± 0.75	2.86 ± 0.70
	Glycemia (Median [1st Q – 3rd Q])	78.0 (75.0 – 82.0)	84.0 (80.0 – 89.0)	85.0 (81.0 – 88.0)	87.0 (83.0 – 89.0)
	Insulin (Median [1st Q – 3rd Q])	4.2 (2.4 – 5.3)	5.8 (4.9 – 7.8)	6.8 (4.6 – 9.5)	5.4 (4.1 – 7.5)
	HOMA-IR (Median [1st Q – 3rd Q])	0.8 (0.6 – 1.0)	1.2 (1.0 – 1.7)	1.4 (0.9 – 1.9)	1.2 (1.0 – 1.7)

BMI: body mass index; WC: waist circumference; TC: total cholesterol; LDL: low density lipoprotein; HDL-c: high-density lipoprotein; TG: triglycerides; CI: Castelli's index; HOMA – IR: Homeostasis model assessment of insulin residence; 1st Q: first quartile; 3rd Q: third quartile.

Table 4 - Comparison of life style between vegetarians and omnivores

Variables		Vegetarians	Omnivores	p-value
		n (%)	n (%)	
Number of meals/day	< 3 meals/day	12 (22.2)	7 (17.5)	0.761
	> 3 meals/day	42 (77.8)	33 (82.5)	
Sleeping hours	< 8 hours	48 (85.7)	35 (87.5)	1.000
	> 8 hours	8 (14.3)	5 (12.5)	
Smoker	Yes	3 (5.4)	1 (2.6)	0.883
	No	53 (94.6)	38 (97.4)	
Physical activity	Yes	36 (64.3)	17 (42.5)	0.056
	No	20 (35.7)	23 (57.5)	
Supplements	Yes	26 (48.1)	8 (20.5)	0.012*
	No	28 (51.9)	31 (79.5)	

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

Table 5 - Comparison of anthropometric and biochemical parameters between vegetarians and omnivores

Variables	Vegetarians	Omnivores	p-value
	Mean ± SD or median (1st Q – 3rd Q)	Mean ± SD or median (1st Q – 3rd Q)	
Weight (kg)	60.8 (56.7 - 69.4)	71.1 (58.0 - 75.4)	0.038*[b]
WC (cm)	81.8 ± 8.2	87.8 ± 10.9	0.003*[a]
BMI (kg/m²)	22.4 (20.9 - 23.8)	24.6 (21.7 - 26.1)	0.001*[b]
Glycemia (mg/dL)	81.0 (78.0 - 85.0)	85.0 (82.5 – 89.0)	0.004*[b]
Insulin (Uu/mL)	5.1 (3.6 - 6.8)	6.4 (4.4 - 9.2)	0.035*[b]
HOMA-IR	1 .0 (0.8 - 1.4)	1.3 (0.9 - 1.8)	0.021*[b]
TC (mg/dL)	170.4 ± 35.8	176.0 ± 33.5	0.447[a]
HDL-c (mg/dL)	54.9 ± 14.4	47.3 ± 12.3	0.008*[a]
LDL-c (mg/dL)	99.8 ± 26.9	108.6 ± 28.4	0.127[a]
TG (mg/dL)	71.0 (63.5 - 99.0)	84.5 (67.0 – 122.0)	0.104[b]

**p < 0.05. [a]: Student's t-test (mean ± standard deviation); [b]: Mann-Whitney test (median [1st Q – 3rd Q]. 1st Q: first quartile; 3rd Q: third quartile; WC: waist circumference; BMI: body mass index; TC: total cholesterol; HDL-c: high density lipoprotein; LDL: low density lipoprotein; TG: triglycerides.*

3). It has been suggested that vegetarians and vegans usually adopt eating habits that are consonant with healthy eating recommendations and may offer advantages in terms of weight control, prevention of hypertension, and ultimately lower mortality from NCDs.[28] In addition, an association between a BMI > 27.5 kg/m² and a lower incidence of deaths from cardiovascular diseases was reported.[29]

With respect to weight control as a strategy for health protection, in a cohort study, Rosell et al.[30] evaluated weight gain in vegetarian and non-vegetarian individuals over a five-year period. Using logistic regression adjusted by mean age, the authors observed that the lowest weight gain was seen among semi-vegetarian, vegetarian and vegan women and those who, during follow-up, changed to a diet with no animal food. Philipps et al.[31] observed for 6 months individuals who had recently become vegetarian; at the end of the follow-up period, significant changes were found in the percentage of body fat, biceps and triceps skinfolds and WC.

Analysis of data from the Australian Longitudinal Study on Women's Health, which included 9,113 women aged between 22 and 27 years revealed a prevalence of 3% and 10% of vegetarians and semi-vegetarians (consumed fish or poultry), respectively. Compared with non-vegetarians, vegetarians and semi-vegetarians were leaner according to BMI and tended to exercise more.[32]

Data from the American population-based study NHANES 1994-2000 suggested that vegetarian diets naturally lead to weight loss and weight control,[31,33] have higher nutrient density (nutrient/kcal), higher whole-grain content, lower saturated fatty acids and lower salt. On the other hand, the study also showed that vegetarians consumed a less calories per day (mean of 363 kcal/day) than omnivores. One may presume that vegetarians have a healthier life style regardless of dietary factors, including lower prevalence of smoking and sedentary habits, and higher intake of vitamins and dietary supplements. This "health consciousness",[30,32] combined with the substitution of animal-derived foods with vegetable foods would promote a more efficient weight control, indicated by lower BMI and WC,[10,27,30] and consequently lower cardiovascular risk.[26,27]

Visceral fat deposition makes the abdominal visceral obesity a greater risk factor for cardiovascular disease and disturbances in glycemia-insulin homeostasis compared with generalized obesity. It is also associated with hypertension, dyslipidemias, fibrinolysis and progression of atherosclerosis.[33]

Table 6 - Comparison of nutritional status variables (dichotomized into "normal" and "altered") between vegetarians and omnivores

Variables		Vegetarians	Omnivores	Total	Chi-square test (p)
		n (%)	n (%)	n (%)	
BMI	Normal	49 (87.5)	23 (57.5)	72 (75)	0.002*
	Altered	7 (12.5)	17 (42.5)	24 (25)	
WC	Normal	51 (91.1)	26 (65.0)	77 (80.2)	0.004*
	Altered	5 (8.9)	14 (35.0)	19 (19.8)	
Glycemia (mg/dL)	Normal	51 (91.1)	37 (92.5)	88 (91.7)	1.000
	Altered	5 (8.9)	3 (7.5)	8 (8.3)	
TC (mg/dL)	Normal	45 (80.4)	33 (82.5)	78 (81.3)	1.000
	Altered	11 (19.6)	7 (17.5)	18 (18.8)	
HDL-c (mg/dL)	Normal	41 (73.2)	20 (50.0)	61 (63.5)	0.034*
	Altered	15 (26.8)	20 (50.0)	35 (36.5)	
LDL (mg/dL)	Normal	22 (39.3)	17 (42.5)	39 (40.6)	0.916
	Altered	34 (60.7)	23 (57.5)	57 (59.4)	
TG (mg/dL)	Normal	53 (94.6)	34 (85.0)	87 (90.6)	0.214
	Altered	3 (5.4)	6 (15.0)	9 (9.4)	

*$p < 0.05$. *BMI: body mass index; WC: waist circumference; TC: total cholesterol; HDL-c: high density lipoprotein; LDL: low density lipoprotein; TG: triglycerides.*

A study on estimated prevalence of nutritional status categories among adults, residents of the city of São Paulo, based on self-reported information on weight and height from a population-based inquiry revealed important findings.[34] The prevalence of overweight and obesity in this population was 34.3% and 13.2%, respectively, indicating the need for an intervention, particularly due to the influence of obesity as a risk factor for severe complications.[34] These results are in accordance with VIGITEL,[35] which reported a prevalence of overweight among Brazilian men and women of 54.7% and 47.4%, respectively. This same study reported a 51% of overweight and 18% of obesity in the state of Sao Paulo in both sexes.

Therefore, studies on nutritional strategies with significant positive effects on reducing obesity should guide clinical practices aimed at obesity prevention and weight control. Although there are few Brazilian studies evaluating the metabolic effects of vegetarian diets, there is a consensus that this eating pattern is associated with lower BMI, TG, TC and LDL-c compared with an omnivore diet.[20]

Regarding CVDs, a meta-analysis investigated the mortality rate from CVDs and cancer among vegetarians and omnivores. Mortality rate from CVDs and cancers was lower in vegetarians in seven cohort studies.[8,29] Analysis of mortality data from these cohorts showed that the distribution of deaths from CVDs between vegetarians and omnivores were not significantly different; however, one must consider the mild and moderate protective effects of vegetarian diets on CVDs must be considered.

In Brazil a study that compared nutritional awareness between vegetarians and omnivores showed that vegetarians followed a more balanced diet in terms of adequacy in the number of servings from each food group.[36]

In addition, data from the Brazilian Family Budget Enquiry37 showed that individuals aged from 19 to 59 years showed the highest prevalence of inadequate inatake of vitamin D, E, A and C, calcium and magnesium.

Mean dietary fiber intake was 22 g per day, lower than the recommended value of 25 g/day according to the Brazilian Ministry of Health. The low fiber intake may be explained by a diet based on refined cereals and low intake of fruits, vegetables and whole cereals. In this context, potential benefits of a well-balanced vegetarian diet would be of value, due to its main characteristic of low or no consumption of animal meat combined with increased intake of vegetable foods.[37]

Population-based studies have showed that, compared with an omnivore diet, vegetarian diets have higher nutrient density.[38] The concept of nutrient density is defined by Phillip et al.[2] as the amount of nutrient (g or mg) divided by the total of calories. Vegetarians consume fewer calories and higher amounts of fibers, vitamins A, C and E, thiamin, riboflavin, folate, calcium, magnesium, iron and potassium.[28,38]

The correct intake of all food groups may also normalize plasma lipid and lipoprotein levels, and for this reason, vegetarians are more likely to have normal lipid levels. A recent study by Najjar et al.[39] showed that a plant-based diet has a favorable effect on lipid levels and reduces inflammatory markers and other atherogenic lipoproteins and particles. The authors showed that the levels of HDL-c were significantly higher in vegetarians than in omnivores; it is known that increased HDL-c levels are associated with reduced relative risk for CVDs.[39]

A meta-analysis involving 4,177 individuals was conducted to compare the effects of vegetarian and omnivore diets on HDL-c.[40] Different from what was expected from the authors, vegetarian diets did not alter plasma HDL-c [standardized mean difference (SMD) = 0.02 mmol/l; 95% confidence interval (CI): 20.19 to 0.22 mmol/l]. In Asia and Latin America countries, no significant differences in HDL-c levels were found between vegetarians and omnivores (SMD = 20.09 mmol/l; 95% CI: 20.43 to 0.25 mmol/l), and in Europe and North America countries, plasma HDL-c was also not different between the two diets (SMD = 0.09 mmol/l; 95% CI: 20.19 to 0.36 mmol/l). So far, available studies in Brazil are not sufficient to support these conclusions.

In our study, the higher levels HDL-c in vegetarians compared with omnivores may have been associated with the practice of exercise, which was more frequent in this group, in addition to the absence of smoking habits and higher consumption of monounsaturated fatty acids in this group (not forgetting the genetic predisposition). However, this study was focused on assessing the nutritional status rather than food intake of participants.

Other studies involving vegetarian individuals have reported contradicting results. A study with Buddhist vegetarians showed significantly higher BMI and body fat in these individuals compared with omnivores.[38] The authors attributed this finding to their habits of consuming fried foods, common to the Asian cooking style.

In scientific literature, contradictory findings are as important as conclusive ones, as they may encourage new way of thinking and hypothesis formulation, leading to advances in scientific knowledge. Therefore, it is erroneous to think that the adoption of a vegetarian diet will necessarily promote improvements in biochemical parameters. Factors like ethnicity, culture, among others, may exert an important influence on following a so-called 'healthy' diet.

This study has some limitations that deserve to be mentioned. Since this was a cross-sectional study, both exposure and outcomes were collected at the same time point. For this reason, neither temporal or a causal relationship between the events could be established, nor could we determine whether the results were influenced by facts of the past. Also, regarding the use of nutritional supplements, since we did not evaluate their nutritional composition, the possibility that they constituted a confounding factor cannot be ruled out. Another possible confounding factor that may have influenced HDL-c levels was the practice of physical exercise by vegetarians.

Conclusion

The findings of this study indicated that, compared with omnivores, vegetarians have better nutritional status, with lower BMI and WC. Vegetarians were also more likely to practice exercise and showed significantly lower levels of HDL-c.

Author contributions

Conception and design of the research: Pimentel CVMB, Philippi ST, Teodorov E. Acquisition of data: Pimentel CVMB, Simomura VL. Analysis and interpretation of the data: Pimentel CVMB, Philippi ST, Simomura VL, Teodorov E. Statistical analysis: Pimentel CVMB, Simomura VL. Obtaining financing: Pimentel CVMB, Teodorov E. Writing of the manuscript: Pimentel CVMB. Critical revision of the manuscript for intellectual

content: Pimentel CVMB, Philippi ST. Supervision / as the major investigador: Pimentel CVMB, Philippi ST.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Universidade de São Paulo – Faculdade de Saúde Pública* under the protocol number 2260. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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REVIEW ARTICLE

New 2018 ACC/AHA Guidelines on Cholesterol Management: Key Changes and Implications

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During the American Heart Association (AHA)'s scientific sessions held in November 2018, the new ultisociety Guideline on the Management of Blood Cholesterol[1] was presented to the cardiology community emphasizing some previous key recommendations and new concepts in atherosclerotic cardiovascular disease (ASCVD) prevention. The main updates of these guidelines are:

1) a new 10-y risk ASCVD categorization for adults 40 to 75 years of age and a lifetime risk estimation in young patients;

2) upgrading of non-statin therapies for LDL-cholesterol lowering treatment;

3) use of LDL-c thresholds (and not only of percental reduction) to consider intensification of therapy;

4) time of blood collection to measure lipid levels;

5) inclusion of the coronary artery calcium (CAC) score in the decision-making process in the management of intermediate-risk patients.

A healthy lifestyle including an anti-atherogenic diet, physical activity, weight control and not smoking remains the cornerstone for cardiovascular prevention. Regardless of pharmacological treatment used, these habits are important at all ages, and are some of the key recommendations for ASCVD prevention.

About the treatment with lipid-lowering drugs, statins remain as the first-choice agents. However, ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have gained attention as add-on drugs in a more aggressive approach for low-density lipoprotein cholesterol (LDL-c) reduction. Ezetimibe, a cholesterol absorption inhibitor, is the most commonly used drug in combination with statins, contributing for an additional 15-30% reduction in LDL-c levels.

Considerable changes have been made in lipid-lowering therapy with the use of monoclonal antibodies that inhibit PCSK9, such as evolocumab and alirocumab. Based on studies showing an 1.5% absolute risk reduction in composite ASCVD outcomes in a follow-up of 2.2-2.8 years, these new drugs are now recommended and should be included to therapy if lipid targets are not met after maximally tolerated doses of statin and ezetimibe. Recommendations are detailed below:

- Established ASCVD: high-intensity statin should be indicated aiming at a ≥ 50% LDL-c reduction (and LDL-c < 70 mg/dl in those at very high ASCVD risk – Table 1). If this target is not achieved, ezetimibe should be added followed by PSCK9 inhibitors. The rationale is based on the findings that support the safety of extremely low LDL levels, and that, for LDL-c levels, "lower is better".[2]

- Primary prevention (Figure 1)

- 10-year ASCVD risk calculation: the 10-y risk of ASCVD (calculated by the pooled cohort equation - PCE) is now categorized as:

a. low (< 5%) – lifestyle changes are indicated;

b. borderline (5% –< 7.5%) – the initiation of moderate-intensity statin therapy is recommended in selected cases;

c. intermediate (7.5% –< 20%) – this is one of the main updates of the guideline. In the presence of risk-enhancing factors, it is suggested to start a moderate-intensity statin in this new group (Table 2). In addition, if the need for statin therapy by the patient remains uncertain (a common situation), the CAC score may

Keywords

Cardiovascular Diseases/ prevention and control; Lifestyle Physical, Activity; Weight Loss; Diet, Atherogenic; Cholesterol, Dietary.

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Table 1 - Established ASCVD and High-Risk Factors

Major ASCVD
ACS within the past 12 months
History of MI (other than recent ACS event listed above)
History of ischemic stroke
Symptomatic peripheral arterial disease
High-Risk Conditions
Age ≥ 65 y
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
Diabetes mellitus
Hypertension
CKD (eGFR 15-59 mL/min/1.73 m^2)
Current smoking
Persistently elevated LDL-C (LDL-C ≥100 mg/dl) despite maximally tolerated statin therapy and ezetimibe
History of congestive HF

ABI: indicates ankle-brachial index; ACS: acute coronary syndrome; ASCVD: atherosclerotic cardiovascular disease; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HF: heart failure; LDL: low-density lipoprotein cholesterol; and MI, myocardial infarction.

be a reasonable tool for assessing the risk of ASCVD in these patients. Since the CAC score is the tool that best adds predictive value of cardiovascular outcomes to risk calculators,[3] its use is recommended by the most recent guidelines when drug treatment is not well defined.

Thus, in case of a CAC score of 1 to 99 Agatston units, introduction of pharmacological therapy should be individualized, particularly in those ≥ 55 years of age.[4] Also, in any patient with CAC ≥ 100 Agatston or ≥ 75th percentile (regardless of the CAC score), statin therapy should be introduced. On the other hand, in individuals with a CAC of zero, statin therapy may be withheld or delayed, considering the very low incidence of cardiovascular events observed in this population.[5]

d. high risk (≥ 20%) – as recommended in the previous statement, high-intensity statin is indicated aiming at reducing LDL-c levels by ≥50%.

- Specific Situations

- Severe hypercholesterolemia (LDL-c ≥190 mg/dl): high-intensity statins are indicated, with not need for risk calculation. Ezetimibe should be added if LDL-c reduction is ≤ 50% or remains ≥ 100 mg/dl. This group, composed mostly of people with familial hypercholesterolemia, received special attention due to the high rate of cardiovascular events, corresponding to 3-4-fold higher risk compared with other individuals with the same LDL-c levels.

- Diabetes: patients aged 40-75 years old with diabetes should be treated with moderate-intensity statin and, in case of a 10-y ASCVD risk ≥ 20%, high-intensity statin should be added.

These updated recommendations highlight a more personalized approach, with a follow-up of lipid profile for up to 20 years-old, with reassessment every 4-6 years. If pharmacological therapy is implemented, a closer follow-up is recommended to check LDL-c levels, safety and adherence. Regarding young adults (20 to 39 years of age), it is crucial to exclude secondary causes of hypercholesterolemia, as hypothyroidism (TSH), obstructive liver disease, renal disease and nephrosis, as well as dietary and medication-related dyslipidemia. Also, as mentioned before, intensive lifestyle change is strongly indicated due to its potential to reduce ASCVD risk. For young adults with persistent hypercholesterolemia (LDL-c levels above 160-189 mg/dL), it is recommended to consider risk-enhancing factors in the decision on whether to prescribe statins. For all patients with LDL-c ≥ 190 mg/dl, treatment should be conducted as previously described in "severe hypercholesterolemia" section.

Lifestyle therapies are also pivotal in the management of children and adolescents with abnormal lipid values, aiming to treat obesity and other ASCVD risk factors. Also, this helps to identify individuals who would clearly benefit from statins,6 especially among those with persistent LDL-c ≥ 190 mg/dl (or LDL-c ≥ 160 mg/dl with familial hypercholesterolemia). Due to the very early atherogenic process in familial hypercholesterolemia, children and adolescents with a family history of early ASCVD or severe hypercholesterolemia should be evaluated for lipid profile as early as age of 2 years. Once hypercholesterolemia is detected, a comprehensive family screening is recommended to detect familial forms of hypercholesterolemia.

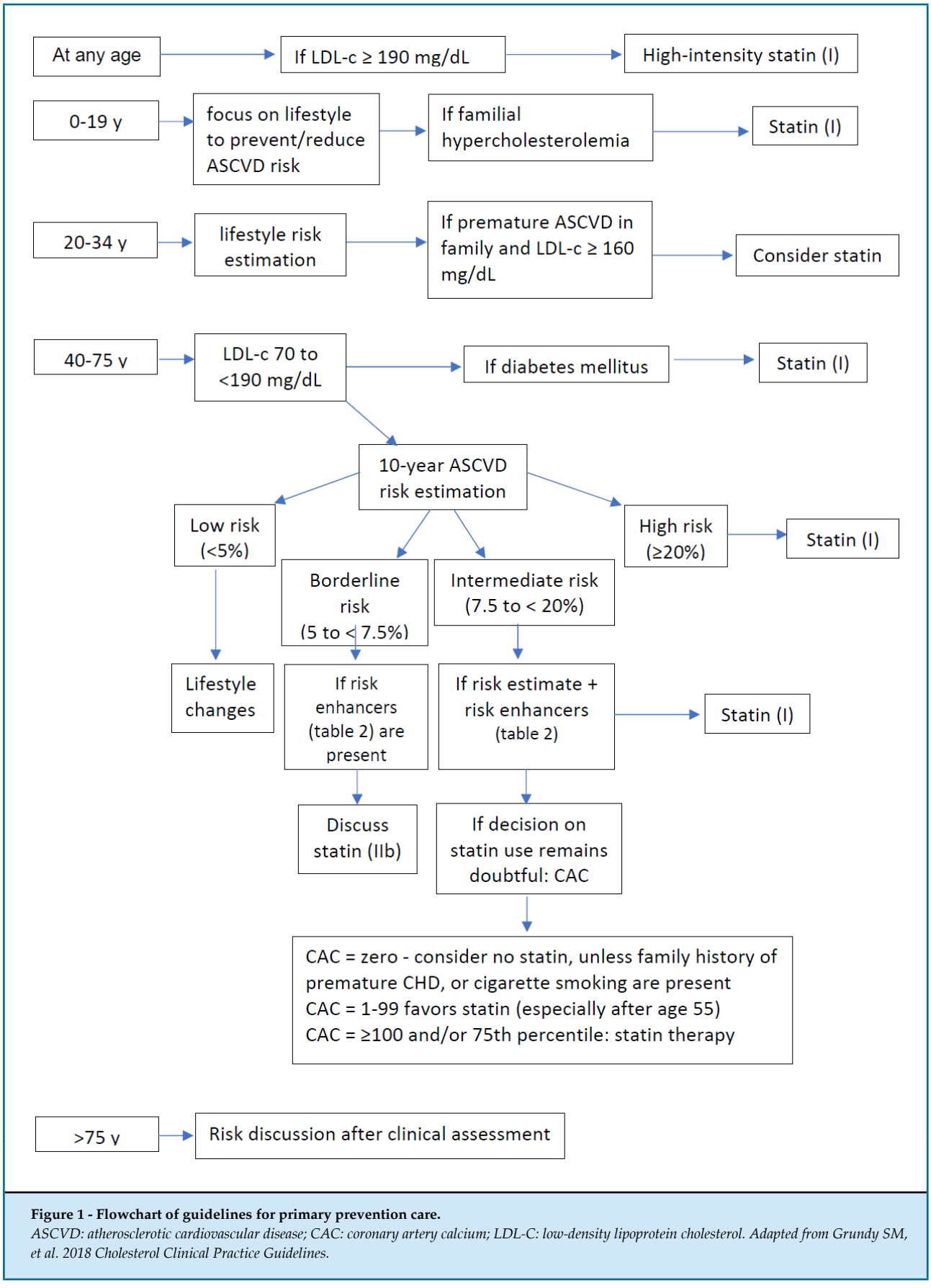

Figure 1 - Flowchart of guidelines for primary prevention care.
ASCVD: atherosclerotic cardiovascular disease; CAC: coronary artery calcium; LDL-C: low-density lipoprotein cholesterol. Adapted from Grundy SM, et al. 2018 Cholesterol Clinical Practice Guidelines.

Table 2 - Risk-Enhancing Factors

- Family history of premature ASCVD - (men < 55 years; women < 65 years)
- Primary hypercholesterolemia (LDL-C 160-189 mg/dl; non-HDL-C 190-219 mg/dl
- Metabolic syndrome
- Chronic kidney disease (eGFR 15- 59 ml/min per 1.73 m^2)
- Chronic inflammatory conditions: psoriasis, rheumatoid arthritis (RA) or human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS)
- History of premature menopause (before age 40) and history pre-eclampsia at pregnancy
- High-risk ethnicities (e.g. South Asian)
- Lipid/Biomarkers:
  a. Persistently elevated, primary hypertriglyceridemia (≥ 175 mg/dl);
  b. If measured:
    - High-sensitivity C-reactive protein ≥ 2.0 mg/L
    - Lp(a) ≥ 50 mg/dL or ≥ 125 nmol/L
    - Apo B ≥ 130 mg/dL
    - ABI < 0.9

AIDS: acquired immunodeficiency syndrome; ABI: ankle-brachial index; apoB: apolipoprotein B; ASCVD: atherosclerotic cardiovascular disease; eGFR: estimated glomerular filtration rate; HDL-c: high-density lipoprotein cholesterol; HIV: human immunodeficiency virus; LDL-c: low-density lipoprotein cholesterol; Lp(a): lipoprotein (a); and RA: rheumatoid arthritis.

In conclusion, even though the clinical risk stratification followed by selective use of preventative pharmacological interventions is still the main strategy of primary prevention, these new guidelines allow individualization of treatment by complementary risk stratification, new therapies and facilitation of patient involvement in a shared decision making process.

Author contributions

Conception and design of the research: Generoso G, Bittencourt MS. Acquisition of data: Generoso G, Bittencourt MS. Analysis and interpretation of the data: Generoso G, Bittencourt MS. Writing of the manuscript: Generoso G, Bittencourt MS. Critical revision of the manuscript for intellectual content: Generoso G, Bittencourt MS.

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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.

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VIEWPOINT

Challenges and Opportunities in the use of Ionizing Radiation for Cardiovascular Diseases

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Introduction

Cardiovascular diseases are the leading cause of global death, accounting for 31% of deaths in 2015 according to the World Health Organization (WHO). Three-quarters of these deaths occurred in low- and middle-income countries.[1] In Brazil, in 2011, there were approximately 350,000 deaths of cardiovascular origin, becoming the most important cause of death since the epidemiological transition of the 60's.[2] The diagnosis in the early stages and the management of more severe cases are among the most important methods in the fight against cardiovascular diseases. Imaging procedures with ionizing radiation has a major role in this area.

According to data from public outpatient health services of the Brazilian Unified Health System (SUS, *Sistema Único de Saúde*) (Figure 1),[3] in the last 10 years, the number of procedures performed for evaluation of cardiovascular diseases using ionizing radiation has increased (73% in nuclear medicine, 18% in interventional radiology and 12% in cardiac catheterization), except for conventional radiology, in which a decreased has been seen (-58%). These numbers, however, underestimate the number of tests performed with the general population, since diagnostic methods such as coronary angiotomography have not been incorporated into the SUS yet, and the time for inclusion of new techniques to public health care is much higher than to supplementary health care.

Keywords

Cardiovascular Diseases/mortality; Nuclear Medicine; Diagnostic, Imaging;/methods; Nuclear Energy; Air Ionization/radiation effects; Radiation/protection.

Although the benefits are undeniable, the increased use of procedures with ionizing radiation results in a greater potential risk for patients, who may undergo 8 to 10 procedures in a single year, and for workers, who may be exposed to radiation for more than 40 hours of work a week.

Studies in the United States have shown that the estimated effective dose of radiation due to medical imaging procedure for an individual increased five times from 0.6 mSv/year in 1987 to 3.2 mSv/year in 2006, surpassing the natural sources of radiation (Figure 2).[4] For instance, the exposure for medical purposes in 2006 would be comparable to 160 chest x-ray examinations per person per year.[5]

The technological progress is a constant in this market, valued at billions of dollars. New methods and applications have quickly emerged, requiring that health professionals from all areas be involved in continuing education processes for the rational use of radiation.

However, studies have already shown that those responsible for requesting examinations and performing procedures involving ionizing radiation have very low knowledge of the principles of radiation protection.[6,7] It is common to observe the unfamiliarity with the principles of radioprotection by health professionals and even situations of unjustifiable fear when mentioning the use of radioactive elements.

Requirements of radiation protection

Cardiologists and health professionals should generally be aware of the basic requirements for radiation protection (Justification, Optimization and Limitation of Individual Dose), as defined by the

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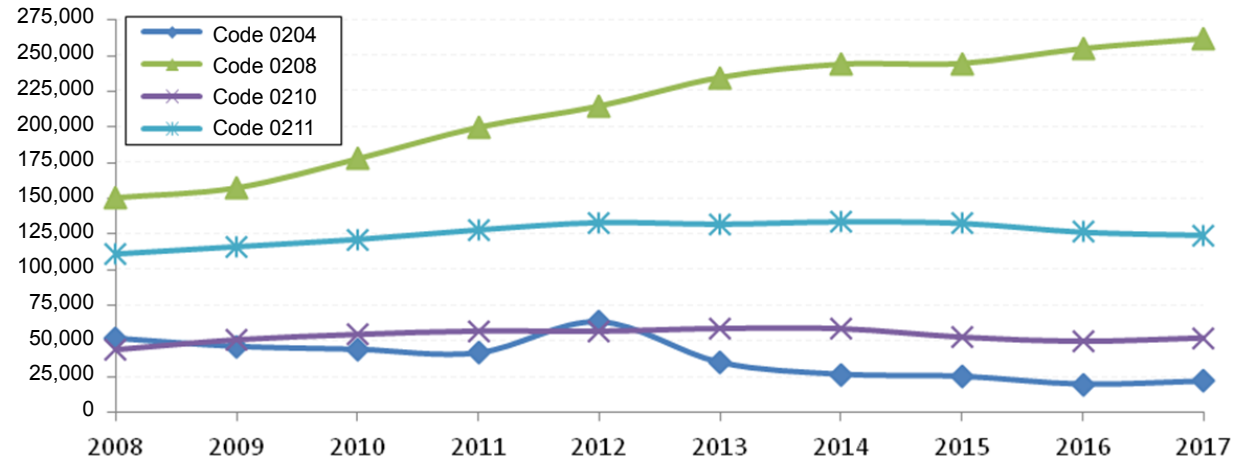

Figure 1 - Evolution of the number of procedures with ionizing radiation in the Brazilian Unified Health System (SUS). Codes of procedures: 0204 (Conventional Radiology), 0208 (Nuclear Medicine), 0210 (Interventional Radiology) e 0211 (Cardiac Catheterization).
Source: DATASUS – Portal da Saúde[3]

Brazilian National Commission for Nuclear Energy (CNEN, from Portuguese: *Comissão Nacional de Energia Nuclear*) regulation NN-3.01[8] and presented in Table 1. Poor understanding of these concepts and of the risks involved can lead to failures across the chain of decisions and increase the potential risks for patients and workers.

Risk assessment and biological effects of radiation

Risk assessment involves the understanding of specific factors of each technique such as: the type of radiation, the intensity or quantity used, the time of exposure and possible effects. Recently, a consensus paper was published, the result of a task force of the American College of Cardiology, which reviewed

Table 1 - Basic requirements for radiation protection

Justification	No practice or source associated with this practice is accepted by CNEN, unless the practice produces benefits to exposed individuals or to society sufficient to compensate for the corresponding detriment, taking into account social and economic factors, among other relevant factors. Medical exposures must be justified considering the diagnostic and therapeutic benefits they will produce in relation to corresponding detriment, taking into account the risks and benefits of available alternative techniques that do not involve exposure.
Optimization	Related to the exposures caused by a particular source associated with a practice, radiation protection should be optimized so that the magnitude of individual doses, the number of exposed persons, and the likelihood of exposures occurring remain as low as reasonably achievable, taking into account economic and social factors. In case of medical exposures of patients, the medical optimization of radiation protection should be understood as the application of the dose of radiation necessary and sufficient to achieve the intended purposes.
Limitation	The normal exposure of individuals should be restricted in such a way that neither the effective dose nor the equivalent dose in the organs or tissues of interest, caused by the possible combination of exposures originated from authorized practices, exceeds the specified dose limit except to special circumstances authorized by CNEN. These dose limits do not apply to medical exposures.

Source: CNEN regulation 3.01 - Basic Guidelines for Radiation Protection[8]

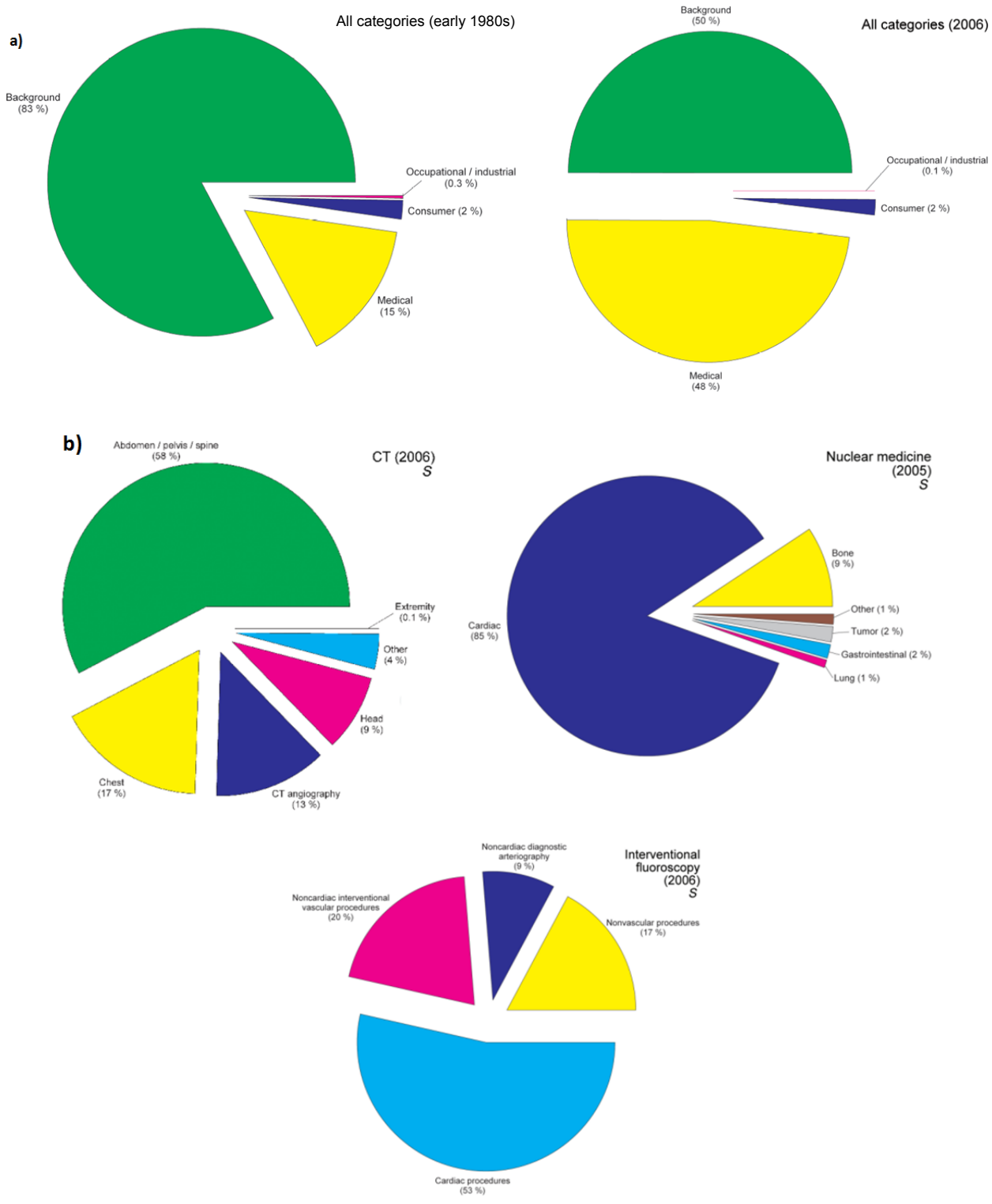

Figure 2 - a) Comparison of the effective dose per individual of the American population in 1980 and 2006. b) Distribution of the collective dose by application and by type of examination.
Source: Adapted from NCRP Report no. 160[4]

concepts, best practices and their effectiveness in Cardiovascular imaging.[5] Biological factors such as the sensitivity of irradiated tissues, the biodistribution of radioactive material (when administered or absorbed), age, gender and even health condition of the individuals are important.

Among the various ways of estimating the exposure of individuals to ionizing radiation, the absorbed dose (which is a measure of the energy deposited by the radiation in an exposed tissue through interaction with its molecular constituents) and the effective dose (estimated sum of absorbed doses for each organ weighted by the sensitivity to radiation and the type of radiation) are the main concepts when the objective is the evaluation of the potential biologicl effects in the diagnosis by image. These effects can be separated into deterministic and stochastic.

The occurrence of deterministic effects is rare in the diagnostic routine due to the type and the amount of radiation used. Also referred today as tissue reactions, these effects are characterized by having a minimum dose below which they probably will not occur. In practice, the most observed reactions are skin lesions from prolonged exposures or from excessive radiation use such as invasive procedures guided by X-ray Fluoroscopy.[5,9]

Stochastic effects are the most relevant for cardiology and should always be considered, although they do not represent a high risk of damages. Even in very low doses of radiation, indirect interactions (through free radicals) and direct interactions with DNA can generate mutations. Experimental difficulties have limited a precise evaluation of the effects of low doses, an unanswered research question, and limits and recommendations have been established based on data obtained from the extrapolation of large nuclear accidents and researches with human cells.[10] We are not used to dealing with probabilistic concepts and, therefore, we seek unique values for our decision making. According to the lifelong risk model presented in the Biological Effects of Ionizing Radiation VII,[10] one person in 100 is expected to develop life-long cancer due to a single dose of 100 mSv above background radiation levels, while 42 people would develop cancer from other causes (Figure 3). Similarly, 1 person in 1,000 would result in a single dose of 10 mSv.

In general, among professionals working with radiation, those involved with interventional techniques and, to a lesser degree, those who are involved in manipulation of radionuclides or with ergometry are the most exposed to risks.[5]

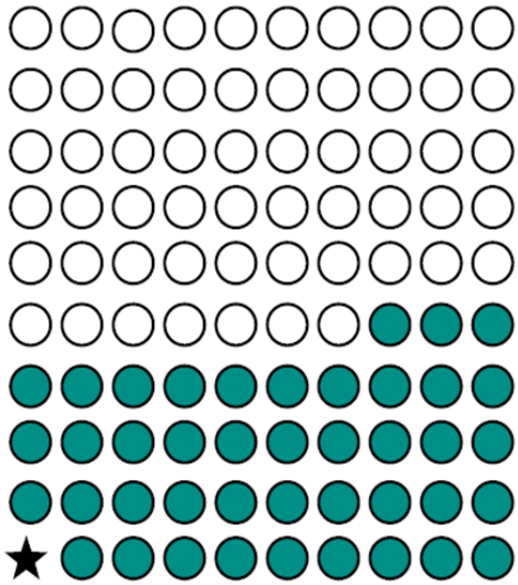

Figure 3 - Expectation of developing cancer due to a single dose of 100 mSv.
Source: BEIR VII[10]

Dose reductions: initiatives and advances

Aware of the current role of ionizing radiations in health care and of the perspective for growth in applications and indications, several initiatives have recently been developed mainly by the International Atomic Energy Agency (IAEA).

The 2012 International Conference on Radiation Protection in Medicine held in Bonn, Germany, resulted in the Bonn Call for Action that published the 10 main actions considered essential for the strengthening of radiation protection in medicine in the decade that would come.[11]

In 2017, a new edition of the Conference held at the IAEA headquarters reinforced its importance. Among the actions are: to increase the implementation of the principles of justification and optimization, to strengthen the role of manufacturers and the education of health professionals, to increase the availability of information on occupational and medical exposures, and to nurture increased dialogue on risk-benefit of radiation.

The IAEA also promotes training and courses, and the development of tools and applications. The QUANUM (Quality Management Audits in Nuclear Medicine

Practice) methodology was developed to guide quality audits of nuclear medicine practices and audit groups were trained in a number of countries. A research with the experience and the impact in a Brazilian Hospital was published recently.[12]

Coordinated researches such as the INCAPS study are also part of global initiatives to improve practices. It investigated the application of eight good practices in 308 Nuclear Medicine Services in 65 countries. Only 45% of them showed a satisfactory index.[13] Subsequently, a similar study performed in healthcare centers in Brazil reported an even lower number, 25% with satisfactory index, and a correlation between a higher level of qualification of the service and presence of an interdisciplinary team, resulting in more appropriate and precise indications of tests involving ionizing radiation.[14]

International alliances supported by WHO and the IAEA, such as the Image Gently, Image Wisely, EuroSafe, LatinSafe, Canada Safe Imaging, ArabSafe, AfroSafe and others, have made relevant contributions in the standardization of procedures, information production and dissemination of radiation protection.

Knowledge as one of the pillars of radiological safety

The global impact and the growth of cardiovascular diseases, the greater number of medical applications, and consequently, of the radiation doses to patients and workers, the constant technological advances and the complexity regarding the use of ionizing radiations for health care make it clear that the understanding of the concepts and responsibilities is critical for the continued growth of the benefits and mitigation of risks and potential effects.

The Bonn Call for Action 10 actions are a step towards this direction and the consensus of the American College of Cardiology and four other societies is even more direct suggesting that specialists have the responsibility to understand the basics of radiation protection first to make appropriate choices and after to conduct optimized procedures. The publication also suggests that this topic should be part of the training and certification of physicians.[5]

In Brazil, there are similar initiatives to international ones in radiology, but not in nuclear medicine. In many cases, concerns about radiation protection are still restricted to the legal obligations established by the CNEN and the Brazilian Health Regulatory Agency.

The safe future of the field is linked to the recognition of the value of multidisciplinary teams and of the quality of professional training. However, there are no specific certifications for radiology technicians and technologists, pharmacists and nurses in Brazil. On the other hand, medical physicists are considered specialists in nuclear medicine or in radiology when approved for this title by the Brazilian Association of Medical Physics. However, these professionals usually do not get support from the community for the certification. In addition, despite legal difficulties, the maintenance of expertise certificates should be tied to the continuing education of specialists. Finally, patients' care is the main objective and the involvement of patients in medical and therapeutic decisions, considering accepted risks and benefits has increased, and needs to be fostered with knowledge.

Author contributions

Conception and design of the research: Fernandes AF, Mesquita CT. Acquisition of data: Fernandes AF. Analysis and interpretation of the data: Fernandes AF, Mesquita CT. Writing of the manuscript: Fernandes AF. Critical revision of the manuscript for intellectual content: Fernandes AF, Mesquita CT, Oliveira A, Santos AASMD.

Potential Conflict of Interest

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CASE REPORT

Physical Exercise for Active Skin Ulceration Secondary to Peripheral Arterial Occlusive Disease

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Introduction

Peripheral arterial occlusive disease (PAOD) is a chronic, initially subclinical, and characteristically inflammatory disease that mainly affects the carotid arteries and lower limbs.[1,2]

When in the lower limbs, it causes intermittent claudication, associated with a shortened leg gait, cyanotic extremities and decreased muscular force associated with sarcopenia below the obstruction site. At more advanced stages, it can cause ulcerations that are difficult to heal, due to the decrease in blood flow. The final stage of pathophysiology is completed with a trophic lesion and consequent amputation of the affected limb, leading to a decrease in the quality of life and to functional limitations in activities of daily living.[3] This results in increased costs generated by the treatment and impaired productive capacity of these patients.[3,4]

Chronic systemic arterial hypertension (SAH), diabetes, smoking, and dyslipidemia are the four main triggers of atherosclerotic disease. Usually individuals with lower-limb PAOD are associated with one or more of these four factors. Therefore, all patients with one of these four factors should be investigated for the presence of PAOD.[2,3]

Keywords

Peripheral Arterial Disease/complications; Skin Ulcer/complications; Risk Factors; Exercise; Intermittent Claudication; Sarcopenia.

One of the most efficient ways to diagnose lower-limb PAOD is through the Ankle-Brachial Index (ABI), where the systolic blood pressure in the ankle is divided by the systolic blood pressure of the arm. A result < 0.9 means a diagnosis of PAOD, even in the absence of specific symptoms.[4]

The nosological diagnosis of lower-limb PAOD is based on pain-free walking time. The Fontaine classification is the most commonly used one. It is divided into four stages: I - asymptomatic (presence of PAOD without symptoms); IIa - claudication above 200 meters and IIb - claudication below 200 meters; III - pain at rest; and stage IV - trophic lesion and consequent amputation of part of the affected limb.[4]

The maximum walking tolerance test is used for both the diagnosis and classification of lower-limb PAOD as the basis for treatment of this condition, since a cardiovascular and metabolic rehabilitation (CMR) program, using treadmill walking, is considered the treatment that shows the best cost-benefit relation for this disease.[5,6]

Therefore, this report aims at describing how a CMR program using a treadmill improved the clinical and functional condition and stimulated the healing of a heel skin ulceration in a patient with lower-limb PAOD.

Case report

IAS, a 65-year-old female patient, whose weight was 55 kilos, and height, 1.62 meters, entered the Cardiovascular

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Rehabilitation Service of the URMEC Clinic in Santo Antônio de Jesus, BA, Brazil in December 2014, diagnosed with PAOD. The arteriography disclosed 100% of occlusion in the popliteal, anterior and posterior tibial arteries of the right lower limb.

According to the medical report, the patient was submitted to coronary artery bypass grafting (CABG) with three grafts: distal third of the posterior descending artery, proximal third of anterior descending artery and circumflex artery. She had been diagnosed with systemic arterial hypertension 15 years ago and type II diabetes mellitus for 8 years, with both conditions under pharmacological treatment. She had osteopenia in the pelvic region and in the head of the femur. She reported symptoms of chronic fatigue at moderate exertion, compatible with functional class II heart failure during the anamnesis.

The physical examination disclosed diffuse sarcopenia, mainly in the upper and lower limbs, blood pressure of 180/100 mmHg. She had an ulceration in the posterior side of the right heel in progress for 24 months, undergoing topical pharmacological treatment (Papain and Chlorhexidine). For the skin ulcer treatment, the patient also reported that she had undergone physical therapy sessions (32 sessions) with laser, microcurrent and 3MHZ ultrasound. She did not show any signs of pulmonary congestion and cyanosis of the extremities. These findings corroborated the idea of a good prognosis for the heart failure, since it was characterized as non-congestive and warm.

The 24-hour ambulatory blood pressure monitoring (ABPM) showed mean BP of 160/90 mmHg with absence of nocturnal dipping. The fasting laboratory tests showed: triglycerides 276 mg/dL, high-density lipoprotein (HDL) of 41 mg/dL, low-density lipoprotein (LDL) of 58 mg/dL, total cholesterol of 154 mg/dL and glycemia of 172 mg/dL.

At the end of the evaluation, the patient's main complaint was ambulation difficulty, due to the heel ulceration and the difficulties caused by this condition when performing the activities of daily living.

She was receiving treatment with the following drugs: NPH insulin, 25 IU/mL at 8 AM and 20 IU/mL at 8 PM; Metformin, 500 mg at 8 AM and 12 PM; Olmesartan, 40 mg at 8 AM; Indapamide, 1.5 mg at 8 AM, Manidipine, 20 mg at 8 AM; Atorvastatin, 80 mg at 7 PM; Clopidogrel, 75 mg at 7 PM; and Vitamin D, 1,200 IU twice a week.

Based on the patient's complaints and the possibilities of the exercise program, the aims of the study were: 10-20% reduction in the fasting glycemia and glycated hemoglobin values; normalization of fasting triglyceride values; reduction of 5 to 10 mmHg in SBP and 5 mmHg in DBP; increase in functional capacity by at least 20%; skin ulceration healing; increased tolerance to walking. An eight-month projection was estimated to reach the goals.

Cardiovascular and Metabolic Rehabilitation Protocol

The patient started the CMR by performing neuromuscular exercises for the upper and lower limbs, arm cycle ergometer for upper body training and inspiratory muscle training (IMT).

In the first month, the neuromuscular exercises were performed twice a week on alternate days (Mondays and Wednesdays), with the exercises for upper limbs being performed on the first day and those for lower limbs on the second day. The exercises comprised two sets of 20 repetitions with a 2-minute interval between sets, with loads based on Borg's rating of perceived exertion (RPE) scale between 9 and 11. After the first month, the neuromuscular exercise schedule was readjusted to two sets of 12 repetitions with loads that stimulated a Borg scale score between 12 and 15. The load progression occurred monthly until the end of the treatment, which lasted six months.

At the same session, after the neuromuscular exercises, the arm cycle ergometer training was performed for 20 minutes using a passive interval approach (active for five minutes followed by two minutes of passive rest). The load was also based on the Borg scale, being the first and second sets performed with Borg score between 9 to 11 and the last 3 with Borg between 12 and 14. The arm cycle ergometer was used until the third month of treatment.

The IMT was performed at home with 30% of PImax in 30 daily repetitions carried out in sets of 10 repetitions, seven days a week. The IMT load was readjusted weekly, which persisted until the end of the first three months of treatment. After the third month, the IMT was performed with no more progressive loads.

After three months, a gel insole was manufactured for the ulcerated heel, which contained an orifice at the ulceration site allowing the treadmill training. Therefore, the arm cycle ergometer training was replaced by the treadmill at the beginning of the fourth month of

treatment. For the treadmill use, a maximum walking tolerance test, described by Petto et al., was applied at a velocity of 1.5 km/h on a treadmill without inclination. The maximum walking tolerance road was reached at 280 seconds (4 minutes and 7 seconds).

The training was prescribed based on this test. The first two sets were performed with 60% and, the last four, with 80% of the maximum walking tolerance obtained at the test (280 seconds) at a speed of 1.5 km/h, the same speed used in the test. This totaled 1,232 seconds of walking, approximately 4.5 times the total time obtained at the walk tolerance test. The test was performed monthly for the increase in time and speed employed for the training, which lasted three months.

Therefore, the total time of CMR was six months, with the first three months being dedicated to neuromuscular exercises for upper and lower limbs, arm cycle ergometer and IMT, twice a week. In the last three months, the cycle ergometer was replaced by the ergometric treadmill and CMR started to be performed three times a week.

It is important to note that the pharmacological treatment, laser therapy, ultrasound and microcurrent for the ulceration healing were maintained from the beginning to the end of the CMR.

Results

Table 1 shows the evolution of the metabolic variables after the CMR. The great improvement in the patient's lipid profile and fasting glycemia can be observed, factors that positively contribute to the clinical and functional improvement of patients with PAOD. The reduction in the glycated hemoglobin levels demonstrates the glycemic control improvement throughout the CMR program.

This figure shows that the heel ulceration was healed, after the three-month treadmill training. No ulceration improvement was seen in the first three months of CMR. In addition to the ulceration healing, the patient improved her treadmill performance, being able to carry out uninterrupted walks at a speed of 5.5 km/h for 30 minutes.

It is worth emphasizing that this gain probably occurred due to the blood flow improvement in the affected limb, caused by the opening of the collateral circulation and angiogenesis (formation of new capillaries), therefore promoting ulceration healing and walking performance improvement.

Table 1 - Evolution of laboratory variables pre- and post-cardiovascular rehabilitation (six months)

Variables	Pre-CR	Post-CR	Normal values
Triglycerides (mg/dL)	276	119	< 150 mg/dL
HDL (mg/dL)	41	51	> 50 mg/dL
LDL (mg/dL)	58	39	< 130 mg/dL
Total cholesterol (mg/dL)	154	114	< 200 mg/dL
Glycemia (mg/dL)	172	130	< 100 mg/dL
Glycated hemoglobin (%)	9.8	7.8	Between 4.0 and 5.6%
Creatinine (mg/dL)	1.5	1.5	Between 0.6 and 1.1 mg/dL

HDL: high-density lipoprotein; LDL: low-density lipoprotein; CR: cardiovascular rehabilitation.

In addition to these improvements, the patient after six months of treatment was able to reduce drug dose for hypertension (Manidipine), diabetes mellitus (NPH and metformin) and dyslipidemia (atorvastatin).

Discussion

Physical exercise has been increasingly becoming significant in the treatment of peripheral vascular diseases because it is a non-invasive method, it has a positive impact on the quality of life and functional status, in addition to being a low-cost and high-effectiveness treatment.[7]

Locatelli et al.,[8] report that a physical exercise program that combines treadmill walking with neuromuscular exercises (resistance exercises with weights) is the one that significantly increases the maximum pain-free walking distance in patients with lower-limb PAOD and intermittent claudication. That occurs because walking training stimulates the opening of collateral circulation and also angiogenesis.[9]

These two mechanisms are the main responsible ones for the improvement in the perfusion of the affected region, reducing ischemia and its consequences. Specifically in this reported case, the ulceration healing was due mainly to the improved blood irrigation, which

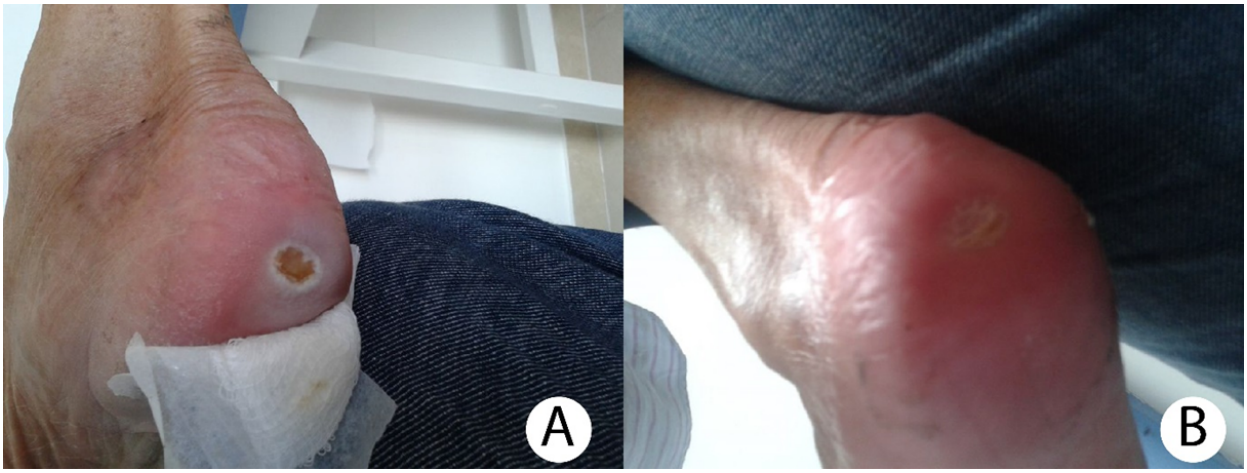

Figure 1 - Skin ulceration before and after the CMR.

favors the entire tissue healing process. Additionally, CMR resulted in improved glycemia and lipid control, a condition that favors the ulceration healing and controls the evolution of the atherosclerotic disease.[7]

Strongly corroborating this hypothesis, Murphy et al.,[5] carried out a study in which 111 subjects with lower-limb PAOD were randomized into three groups. A group received only pharmacological treatment, a group underwent coronary artery bypass grafting in the region affected by PAOD plus pharmacological treatment and a group that underwent a supervised walking training plus pharmacological treatment. The authors found that after a six-month period, the exercise group increased walking tolerance more than the CABG group and the medication group. The same result was identified in the questionnaire that was applied in this study and investigated the limitation that claudication brings to activities of daily living. It was concluded that, of the three treatments, the supervised walking exercise was the best treatment option, considering the cost-benefit ratio.

However, despite evidence such as this and cases such as the one reported herein, there are few patients with lower-limb PAOD who are referred to CMR services to undergo a specific and supervised treatment.

A study carried out in 2002 by Nunes et al.,[3] reported that more than 180 people a year are amputated because of lower-PAOD in the city of Salvador, state of Bahia, Brazil. There are reports in the literature that support the idea that a CMR program could in many cases avoid amputation. A study published in 2011[1] reports the case of a patient with lower-limb PAOD that avoided amputation after undergoing a supervised treadmill walking program. Such evidence suggests that other patients with lower-limb PAOD may benefit from CMR.

It is also interesting to note that in the case reported herein, before the patient underwent the CMR, she had already undergone unsuccessful physical therapy with laser, ultrasound and microcurrent sessions for the ulceration healing. She had also been undergoing two years of topical pharmacological treatment with no positive response. However, when the pharmacological treatment was associated with CMR and physical therapy, the ulceration healing was attained. It should be noted in this case the fact that the CMR program, using treadmill walking as the main exercise type, was crucial for the patient's clinical and functional improvement and ulceration healing and how the interdisciplinary interaction is essential to optimize the treatment of lower-limb PAOD.

Physical exercise is fundamental for the control of two of the main modifiable risk factors for the development of lower-limb PAOD - diabetes mellitus and dyslipidemia. According to Conte et al.,[6] the main modifiable risk factors for PAOD are dyslipidemia, diabetes mellitus and smoking. Therefore, the visible metabolic improvement in this case, both in triglyceride and plasma lipoprotein levels, as well as glycemia, also favored the patient's clinical and functional improvement. Brandão et al.,[2] reported that each 10% reduction in total cholesterol

levels resulted in a reduction of up to 15% in the risk of mortality due to cardiovascular diseases.

The evidence currently available in the literature is enough to routinely refer patients with lower-limb PAOD to CMR services before having them submitted to more invasive procedures, such as revascularization or angioplasty. The interdisciplinary treatment should be the first option, as it increases the chance of clinical and functional condition improvement, reduces the administration of drugs and prevents surgical treatment and amputations in this population.

Conclusion

According to this case report, a supervised exercise program on a treadmill combined with neuromuscular exercises was effective in the healing process of the lower-limb PAOD-related skin ulcer and in the control of the modifiable risk factors that lead to this condition, such as diabetes mellitus and dyslipidemia. This report also aims to encourage more health professionals to prioritize interdisciplinary treatment by referring their patients with PAOD to supervised physical exercise programs.

Author contributions

Conception and design of the research: Petto J, Farias JBF, Rosa EA. Acquisition of data: Petto J, Almeida FOB. Analysis and interpretation of the data: Petto J, Sacramento MS, Almeida FOB, Farias JBF, Rosa EA. Statistical analysis: Petto J, Sacramento MS. Writing of the manuscript: Petto J, Sacramento MS. Critical revision of the manuscript for intellectual content: Petto J, Farias JBF, Rosa EA.

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

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Universidade Estadual de Feira de Santana* under the protocol number 0033.059.000-11. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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CASE REPORT

Fourteen Years' Survival After Batista Operation: The Short History of a Long Journey

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Abstract

A 41-year-old man with end-stage heart failure due to nonischemic dilated cardiomyopathy was submitted to the Batista procedure as an alternative to heart transplantation. With surgery, the patient showed progressive clinical amelioration, achieving long-term stable NYHA functional class II, despite gradual dilation of the heart chambers. Persistent atrial fibrillation appeared on the last year of life, his clinical condition deteriorated, and the patient died 14 years, four months, and 13 days after the operation. To the best of our knowledge this seems to be the longest reported survival for a patient submitted to Batista operation.

Introduction

Heart failure (HF) is one of most severe diseases affecting man, showing high morbidity and mortality. Once HF is diagnosed, survival is around 50% and 10% at 5 and 10 years, respectively. One of the main causes of heart failure is dilated cardiomyopathy (DCM), which is one of the main indications for heart transplant (HT). Historically, however, the potential benefits of HT have been very limited due to shortage of suitable donors, several contraindications, high financial costs and mortality due to infection, neoplasms, allograft rejection and other complications.[1-2] Meanwhile, a considerable proportion of patients die annually while on the waiting list and only a small proportion of candidates can benefit from a new heart.[1-2]

To overcome such limitations, in the mid-1990s, the Brazilian surgeon Randas Batista and coworkers created an innovative and radical operation, named partial left ventriculectomy (also referred to as PLV, Batista operation and Batista procedure) to treat patients with end-stage heart failure as an alternative to HT.[3] By using an original concept based on Laplace's law, where ventricular wall stress = intracavity pressure x radius/2 x wall thickness, the rationale for the procedure was that, by reducing the dilated ventricular cavity, a normalization of chamber volume/mass ratio could be re-established. Then, they postulated that a decrease in tension on the left ventricular wall through volume reduction could decrease wall stress and myocardial consumption of oxygen, resulting in systolic function improvement.

The initial results obtained with the PLV generated tremendous enthusiasm among surgeons worldwide and more than 70 centers, at least 20 in Japan, performed the surgery in the 1990´s. At that time, several centers in Brazil adopted the surgery and the I Brazilian Guidelines for Cardiac Transplantation recognized PLV as an alternative to HT.[1] However, the prestige of PLV began to decline at 2001's when a report from the Cleveland Clinic Foundation demonstrated perioperative failures that could preclude its widespread use.[4] At the same time, however, this study emphasized that, due to its possible beneficial effects, the Batista surgery could be employed in situations that do not allow a transplant or as a biological bridge to a new heart. Meanwhile in Japan, ventricular restoration surgery, including more a refined

Keywords

Heart Failure/physiopathology; Partial Left ventriculectomy; Cardiac Surgery; Ventricular Dysfunction, Left/surgery; Cardiomyopathy, Dilated/surgery.

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Batista procedure, remains alive and has been considered a good non-transplant option for selected patients with end-stage DCM. Curiously, in relation to United States, the Batista procedure was not completely discontinued, considering that in the period of 2008-2014 it was applied in 401 patients but has been decreasing over time and is now employed in a limited number of selected patients.[5]

Few cases of very long-term survival with PLV have been reported in the medical literature to date, in which patients were clinically well at the time of the publication and the longest reported survival is a 68-year-old woman who was alive 13 years after the operation that, coincidentally, was the first PLV applied in Korea.[6]

Clinical case

A 41-year-old man with a six-month history of progressive HF due to nonischemic DCM was hospitalized for clinical treatment, receiving bed rest, fluid restriction, diuretics, cardiac glycoside, ACE inhibitor (ACEI) (captopril), heparin and pentoxifylline, with transient improvement. He had no history of diabetes, hypertension, angina and myocardial infarction. His coronary angiography was normal and serologic testing for Chagas disease, cytomegalovirus, hepatitis virus A, B, C, E and HIV infection all were negative. Despite treatment optimization, his clinical condition rapidly deteriorated and end-stage heart failure was diagnosed, necessitating inotropic therapy with dobutamine. The patient was listed for cardiac transplant. However, the heart of the problem was that, due to the shortage of organs and serious logistic difficulties at that time, the Batista surgery was offered as the last effort to save his life. An informed consent was obtained from the patient for the surgery.

The procedure was carried out in August 1998. The operation was performed under normothermic standard cardiopulmonary bypass and the technique used was based on that originally described by Batista and colleagues.[3] In simple terms, the procedure consisted of resection of a large slice of the posterolateral LV wall, beginning from the apex to near the mitral annulus, preserving the papillary muscles and subsequent ventriculorraphy. It is interesting to note that right ventriculectomy was also performed at the same time, because of the large right ventricular dilatation. Concomitant mitral and tricuspid repairs were performed. The postoperative course was uneventful.

Pre-and postoperative transthoracic echocardiography data are summarized in Table 1. One month after the operation, the echocardiographic examination showed significant improvement: the left atrial and ventricular sizes as well as right ventricular dimensions were reduced, LV ejection fraction increased, while pulmonary arterial systolic pressure declined. Trivial tricuspid and mitral regurgitation remained after surgery. The patient achieved NYHA class-II, remaining under optimized medication with furosemide, ACEI, spironolactone, B-blocker (carvedilol) and digoxin. The nutrition was improved, and the patient gradually recovered his normal weight.

Although at six months after the procedure the heart chambers were redilated, the patient still continued to maintain good clinical condition. Thirteen years after the operation the transthoracic echocardiogram and the cardiac MRI showed enlargement of the heart chambers, atrioventricular valve regurgitation and severe ventricular systolic dysfunction (Figures 1-A, 1-B, 2-A and 2-B). The clinical condition deteriorated only in the last year of his life, after the development of persistent atrial fibrillation, requiring several hospitalizations.

Discussion

Despite modern treatment of patients with advanced DCM, the morbi-mortality rates continue to be high and

Table 1 - Pre-and postoperative echocardiographic data

		Postop		
Variable	Preop	1 month	6 months	13 years
LA (cm)	5.7	4.1	6.0	6.4
LVSD (cm)	6.9	4.9	5.9	6.8
LVDD (cm)	7.4	5.9	6.5	7.4
SV (ml)	42	60	43	40
RVD (cm)	3.5	2.7	3.3	3.7
LVEF (%)	14	35	20	17
PASP (mmHg)	50	37	65	59

LA: left atrium; LVSD: left ventricular systolic diameter; LVDD: left ventricular diastolic diameter; SV: systolic volume; RVD: right ventricular diameter; LVEF: left ventricular ejection fraction; PASP: pulmonary artery systolic pressure.

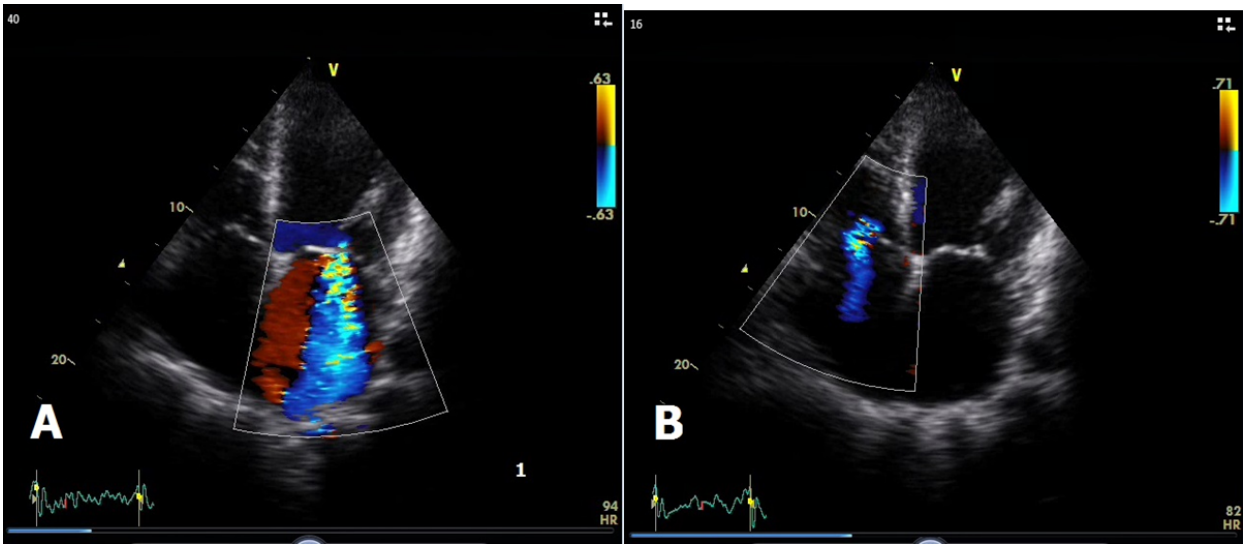

Figure 1 - Transthoracic echocardiogram showing dilated chambers, severe mitral regurgitation (A) and mild tricuspid incompetence (B).

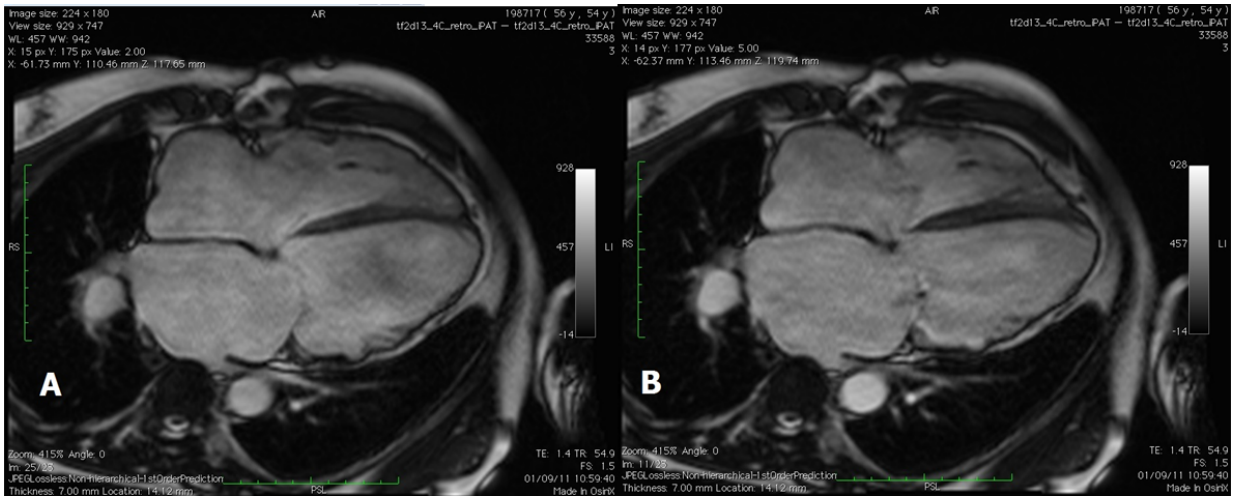

Figure 2 - Cardiac MRI: long axis views at diastole (A) and systole (B), showing dilated heart chambers, wall thinning and severe ventricular systolic dysfunction.

patients with poor responses to medical therapy may need surgical options, including HT and mechanical circulatory support. Non-transplant cardiac strategy for treatment of advanced DCM, such as the Batista procedure, has been applied to hundreds of people worldwide as an alternative or as bridge to HT.

Although the procedure were drastically reduced after 2001 in most countries, it is significant that, since

PLV creation, several recent reports about its success rates have appeared, revealing a renewed interest on the subject.[5,7-10]

Patients with advanced DCM under clinical therapy may have poor quality of life and unfavorable long-term prognosis, with or without ventricular volume reduction surgery, but it is also significant that many patients submitted to Batista procedure has lived for months or years, with much better clinical status and cardiac function than before. In our opinion, PLV can still be performed in selected patients with advanced heart failure, refractory to pharmacological therapy, when heart transplant is not available.

It is important to note that patients submitted to PLV were compared in the literature with patients undergoing heart transplantation. There is no direct comparison of PLV with optimized clinical treatment, since the optimized clinical treatment failure is necessary for surgery indication. Only patients who remain very symptomatic with optimized clinical treatment or those who are inotropic-dependent have been indicated for treatment with PLV as an alternative to cardiac transplantation. In our patient, clinical treatment optimization was attempted to the maximum extent possible, but he remained refractory and dependent on inotropes, in what is now classified as INTERMACS 3.

In our patient, the subsequent cardiac chamber redilation, the progression of mitral regurgitation over time and the decrease in ventricular function were all potential significant adverse factors for a favorable long-term outcome. However, it is extraordinary that, despite such limitations, he lived for 14 years, four months and 13 days after the operation. Possible explanations for the long-term survival would be the optimization of pharmacological therapy (he did not tolerate the use of beta-blockers and only reduced doses of ACEI were used before the surgery), as well as nutritional adjustment in the postoperative period (his weight at the time of surgery was 39 kg and after 1 year he reached 67 kg, compensated). In addition, the right ventriculectomy and the correction of the mitral-tricuspid regurgitation were factors that probably contributed to a favorable outcome.

Conclusion

This is a rare case of long-term survival of a patient with advanced heart failure, who was submitted to partial left ventriculectomy. Since the patient did not tolerate optimized clinical therapy, necessitating inotropic support, partial biventriculectomy and concomitant mitral and tricuspid repair were applied, resulting in a favorable outcome, allowing the patient to present excellent clinical recovery and an exceptional long-term survival.

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Author contributions

Conception and design of the research: Almeida Junior GLG, Jazbik W, Morgado JV, Almeida GLG. Acquisition of data: Almeida Junior GLG, Jazbik W, Morgado JV. Analysis and interpretation of the data: Almeida Junior GLG, Morgado JV, Almeida GLG. Writing of the manuscript: Almeida Junior GLG, Almeida GLG. Critical revision of the manuscript for intellectual content: Almeida Junior GLG, Morgado JV, Almeida GLG.

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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.

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