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EDITORIAL

Can Cardiopulmonary Exercise Test Contribute to Train Soccer Players?

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Soccer, which draws crowds and moves huge sums of money, has not been dissociated from science, being frequently approached in studies conducted by the academy or upon request of technical teams, aimed at optimizing the sports outcomes.

A training plan is used to prepare for the soccer competition and comprises purely physical, psychological, technical (p. ex.: pass, dribble, feint, leaps) and tactical components. In the preseason and during the competitive season, coaches measure and monitor different variables of the training.

The players of a soccer team, although having the same baseline physical fitness, face different physical challenges depending on their field position in the game. From the goalkeeper, exceptional capacity of instantaneous reaction, impulsion, flexibility and motor coordination, particularly of the upper limbs, are required. Field soccer players, however, must have good baseline aerobic conditioning associated with the capacity to repeatedly sprint during 2 to 4 seconds, every 90 seconds, covering distances that can range from 5 m to 40 m, in the case of lateral defenders and attackers, or be shorter, in the case of central-defenders and midfielders. During the 90 minutes of the game, elite soccer players walk or run approximately 10 km at a mean intensity similar to that achieved at the anaerobic threshold, with multiple explosive efforts, namely sprints, corresponding to as much as 11% of the distance covered during the game.[1]

The intermittent nature of soccer games requires the use of three types of energy substrates. The aerobic pathway supports the periods of walking or slow running (90% of game duration), while phosphocreatine and the anaerobic pathway are the sources of energy used in repeated explosive efforts, frequently carried out at a velocity superior to that achieved at the maximal effort of exercise testing and that the athlete will be able to repeat only after properly restoring the different energy substrates to the muscles.

The study by Souza e Silva et al.,[2] published in this IJCS issue, assessed, for the first time in athletes, the cardiorespiratory optimal point (COP) determined in a maximal cardiopulmonary exercise test (CPX), performed on a treadmill according to the ramp protocol in 198 soccer players of a major team of a Carioca club, between January 2005 and December 2016. They concluded that COP values do not differ according to the soccer players' field positions.

The COP is the minimum value of the ventilatory equivalent for oxygen (ratio between ventilation per minute and oxygen consumption: VE/VO_2) during a CPX. It represents the effort with the lowest ventilation per liter of oxygen consumed, considered the best integration point between respiration and circulation.

The COP occurs at the initial phase of the CPX, at 30 - 50% of maximal oxygen consumption, correlated with neither maximal oxygen consumption nor anaerobic threshold. It is easily determined in incremental tests, independently of the observer or the athlete's motivation, seeming useful for the assessment of healthy or ill individuals unable to achieve their maximum effort because of physical, psychological or other limitations.

This new parameter has shown an inverse relationship with all-cause mortality of healthy and ill individuals aged 40 to 85 years, as well as an ability to estimate mortality.[3]

In the discussion of their article, Souza e Silva et al.[2] hypothesized that the low COP values of those elite soccer players could represent a physiological advantage for sports practice, which, although logical, lacks confirmation.

Keywords

Exercise; Football / trends; Spirometry / methods; Athletic Performance.

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The consideration of COP, a parameter that occurs before the anaerobic threshold, to assess or guide the training of athletes, namely soccer players, raises doubts because the most intense and eventually discriminative efforts of soccer players occur at intensities close to the maximal effort.

Psotta et al.,[4] studying young soccer players, have reported that the ability to perform sets of 10 repeated sprints can be predicted based on the mean velocity obtained in a 20-m sprint and in a 2-km race, suggesting the need for high-level anaerobic and aerobic abilities to properly respond to the demands of the game.

Edwards et al.[5] have reported that training brings the values of oxygen consumption at the anaerobic threshold and at the ventilatory threshold close to the values of oxygen consumption at peak effort, but it does not change the latter, as if the maximal oxygen consumption had already been optimized. The values of oxygen consumption at the anaerobic threshold and at maximal effort specifically reflect the ability to perform aerobic efforts. The COP should be studied in the context of sports training to assess whether it identifies athletes with excellent aerobic capacity at submaximal level or whether it can assess and monitor training during the competitive season.

Regarding the possibility of parameters provided by an incremental and maximal CPX being capable of identifying the ability to sustain and repeat sudden and intense efforts in anaerobiosis and to recover rapidly, it seems more useful to focus on the parameters present close to the end of the exercise test, after overcoming the 2nd ventilatory threshold, which precedes the phase of exhaustion and defines the intensity of the effort the individual will be able to maintain during a few minutes, being useful to consider the load at which it occurs (e. g., the treadmill velocity).

In addition, it might be useful to study how long an individual can sustain exercise at high lactatemia levels (e.g. > 6 - 8 mmol) or high respiratory quotient (> 1.10), considering the training of soccer players or other sports practitioners with similar physical requirements.

This is a very interesting and challenging field of work and study for the scientific community, which continues committed to produce knowledge that might contribute to enhance the performance of athletes with access to new technologies.

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EDITORIAL

Is Cardiorespiratory Optimal Point Measured During the Maximal Cardiopulmonary Exercise Test a Relevant Indicator of Sports Performance?

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Cardiorespiratory fitness (CRF) is considered the gold standard for assessing aerobic performance among athletes and normal population and has recently been named as a clinical vital sign, being an essential indicator of cardiovascular and pulmonary function.[1] Cardiorespiratory fitness is associated with lower risk of non-fatal and fatal cardiovascular disease (CVD) events, with studies demonstrating a consistent, inverse association between CRF and mortality even after adjustment for the traditional risk factor burden.[2] Additionally, both maximal oxygen consumption (VO_2max) and VO_2 at ventilatory threshold (VT) have been associated with a reduced risk of adverse health outcomes.[1,3-5] A literature-based meta-analysis of 33 observational cohort studies has better delineated the relationship of CRF with CVD and all-cause mortality outcomes.[2] However, VO_2max and VT are often used to evaluate athletes' performance and to monitor their training responses. During the cardiopulmonary exercise test (CPX), many variables could be used to assess specific training responses to the cardiovascular, respiratory and musculoskeletal systems based on the analysis of submaximal and maximal responses to a progressively incremental exercise.

Modern CPX systems allow for the analysis of gas exchange at rest, during mild, moderate and maximal exercise levels, and during recovery and yield measures of VO_2, carbon dioxide output (VCO_2), and ventilation (VE).[6] These advanced computerized systems provide both simple and complex analyses of these data that are easy to retrieve and store, which makes CPX widely available. Oxygen uptake at VT, often referred to as the anaerobic threshold, is a variable assessed at submaximal level of CPX.[6] For majority of healthy individuals, the anaerobic threshold lies at exercise intensities between 50% and 75% of VO_2max, while in trained endurance athletes, it can reach intensities as high as 80% of VO_2max.[6]

Observing the oxygen ventilatory equivalents (the ratio between VE in l/min and VO_2 in l/min, VE/VO_2) in a given minute during CPX, it is possible to identify a U-shaped pattern with a clear minimal value. Ramos et al.[7] have named this minimal VE/VO_2, a dimensionless variable, as cardiorespiratory optimal point (COP) with age- and sex-reference data and suggested that COP reflects circulation-respiration integration and the most economical use of ventilation to obtain oxygen for the active tissues during exercise.

In this context, it is worthwhile to comment that VO_2max depends on performing a truly maximal exercise test. Although VT can be assessed at the submaximal level,[5] it also requires a more intense exercise level compared to the assessment of COP, and VT measurement may be hindered by the existence of several distinct criteria for its identification and/or characterization, because it cannot be accurately defined in all cases, limiting its use in both clinical practice and sports performance.

Applicability of the COP for the assessment of the athletes' exercise performance is potentially interesting.[8] In addition to the fact that, as a submaximal variable of CPX, the use of COP is particularly interesting for people unable to achieve a maximal CPX because of functional limitations. In the sports scenario, where

Keywords

Exercise; Respiratory Function Tests; Athletes; Cardiorespiratory Fitness; Athletic Performance.

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there are very limited opportunity or intention to have the athletes performing repeated maximal CPX during the competition season, COP could be a much easier and acceptable variable to be measured and followed along the season.[8] As previously described by the same research group,[9] the COP value increases with age and tends to be slightly higher in women, with associations being modest with other ventilation measures, suggesting an independent and potential contribution in the interpretation of the cardiorespiratory response at the CPX. Indeed, Ramos and Araujo,[9] have also showed that COP provides valuable information on the risk of all-cause mortality in middle-aged and older men and women. In healthy subjects with COP < 22, there were no deaths during the six-year follow-up suggesting that the lowest level of COP is an indicator of good prognosis. Over the years, one can consider that there is a worsening in VE and a reduction in VO_2max, i.e. variables directly involved in the calculation of the COP. However, it is possible that the decline in pulmonary ventilation is less significant or numerically important than the reduction in VO_2, thereby explaining the higher COP values in older individuals.[9]

The study published in this issue of the Int J Cardiovasc Sci by de Souza e Silva et al.[10] is the first one to describe the COP profile in athletes, as it was based on high-level soccer players undergoing CPX on a treadmill following the ramp protocol. They found that COP values did not significantly vary within the athlete's field position.[10] The absence of association with VO_2max and VT indicates that COP provides additional information on the top of conventional CPX parameters; however, it remains to be determined if this COP plays a significant role in terms of soccer performance and/or to the monitoring of the training responses along the competitive season. Notwithstanding, the information provided by this novel study[10] is original and it should be confirmed by future studies including the interpretation of the various CPX variables in athletes, especially for those participanting in very long endurance sport events, such as marathon or triathlon, situations in which the athlete performs at an exercise intensity that is below VT and likely closer to COP.

In conclusion, COP, defined as the lowest VE/VO_2 value in a given minute of CPX, has been associated with all-cause mortality in a population that is frequently seen for routine clinical exercise testing. COP is a reproducible and physiologically-based CPX variable. Additionally, the availability of age- and sex-reference data in a large sample of healthy subjects is an advantage compared to other CPX indices often obtained in a maximal CPX. The recent study by de Souza e Silva et al.[10] moves COP one step ahead by suggesting its potential use among adult professional soccer players. Future longitudinal studies are needed to confirm COP relevance and if its measurement would become a possible substitute for some other relevant CPX ventilatory variables, such as VT or VO_2max in athletes.

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ORIGINAL ARTICLE

Cardiorespiratory Optimal Point in Professional Soccer Players: A Novel Submaximal Variable During Exercise

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Abstract

Background: Maximal oxygen consumption (VO_2max) and ventilatory threshold (VT) obtained during a cardiopulmonary exercise test (CPX) are used in the evaluation of athletes. However, the identification of these variables may sometimes be unreliable, which limits their use. In contrast, the cardiorespiratory optimal point (COP) is a submaximal variable derived from CPX with objective measurement and prognostic significance. However, its behavior in athletes is unknown.

Objective: To describe the behavior of COP in professional soccer players and its association with VO_2max and VT.

Methods: VO_2max, VT and COP were obtained retrospectively from 198 soccer players undergoing maximal treadmill CPX using ramp protocol. COP was defined as the lowest value of the ventilation/oxygen consumption ratio in a given minute of the CPX. The soccer players were stratified according to their field position: goalkeeper, center-defender, left/right-back, midfielder and forwarder. Continuous variables were compared using unpaired Student t test or ANOVA, or Mann-Whitney test or Kruskal-Wallis test depending on their distribution, and categorical variables were compared using chi-square test. Pearson correlation was used to test the association between COP and other ventilatory variables. A level of 5% was used for statistical significance.

Results: COP (mean ± SD) was 18.2 ± 2.1 and was achieved at a speed 4.3 ± 1.4 km.h^{-1} lower than that achieved at the VT. While VO_2max (62.1 ± 6.2 mL.kg^{-1}.min^{-1}) tended to be lower in goalkeepers ($p < 0.05$), the COP did not vary according to field position ($p = 0.41$). No significant association was observed between COP and VO_2max ($r = 0.032$, $p = 0.65$) or between COP and VT ($r = -0.003$, $p = 0.96$).

Conclusion: COP can be easily determined during submaximal exercise performed with incremental speed in soccer players and does not vary according to the athlete's field position. The absence of association with VO_2max and VT indicates that COP provides distinct and complementary information to these variables. Future studies are needed to determine the practical implications of COP in assessing athletes. (Int J Cardiovasc Sci. 2018;31(4)323-332)

Keywords: Exercise; Football / trends; Spirometry / methods; Bronchospirometry / methods; Athletic Performance.

Introduction

The cardiopulmonary exercise test (CPX) is a functional and noninvasive procedure used to assess the integration of the cardiovascular, respiratory and musculoskeletal systems based on the analysis of submaximal and maximal responses to exercise.[1] The information obtained from CPX is important to the prognostic assessment of healthy and unhealthy individuals,[2,3] and the measures of maximal aerobic power, represented by maximal oxygen consumption (VO_2max), and of ventilatory threshold (VT) are often used to assess and monitor athletes'

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training.[4-6] For example, soccer players with higher VO_2max are known to cover longer distances during a match,[7] and their mean exercise intensity during the match is approximately 75% of their VO_2max, similarly to the VT level of those players.[7,8]

However, limitations such as low reproducibility, different techniques and criteria for identification of both VO_2max and VT[9-13] hinder their routine use. In addition, mistakes in such measurements can jeopardize the planning of individualized trainings, impairing the athlete's performance improvement.[14]

In 2012, Ramos et al.[15] showed the minimum value of the ventilatory equivalent for oxygen (minimum VE/VO_2) during a CPX – the cardiorespiratory optimal point (COP) – and described its behavior, which, theoretically, represents the point of the best association or integration between the respiratory and cardiovascular systems. Based on the assessment of more than 600 healthy and non-athletes individuals aged aged between 23 and 73 years, those authors showed that COP tends to be higher in women and increases with age. In addition, studies conducted by that same group have shown that COP measurement is easy, objective and stable in CPX performed in adults,[16] supporting its potential use in physiological research and in clinical practice. Similarly to VO_2max and VT, COP proved to be an excellent predictor of all-cause mortality in healthy and unhealthy individuals aged between 40 and 85 years.[17]

So far, the behavior of COP in athletes is unknown. Thus, our objectives are: a) to describe the behavior of COP in professional soccer players; and b) to assess its association with VO_2max and VT.

Materials and Methods

Sample

This study analyzed retrospectively the data of 247 soccer players of the major team of a Rio de Janeiro club of the Brazilian Soccer Championship A series, who underwent a maximal CPX at a private Exercise and Sports Medicine clinic between January 2005 and December 2016. Of those, 198 players concomitantly meeting the following inclusion criteria were selected: a) to have undergone a treadmill CPX; b) to have completed a truly maximal CPX, which was not interrupted due to clinical reasons or lack of motivation; c) to have no history of cardiorespiratory diseases. Based on the information provided by the soccer players, they were categorized according to their predominant field positions: goalkeeper, center-defender, left/right-back, midfielder and forwarder.

Assessment protocol

Clinical assessment

Included clinical history and physical examination, as well as anthropometric, spirometric and resting 12-lead electrocardiographic data.

Resting spirometry test

At least three maneuvers were carried out to determine the flow-volume curves using a pneumograph (SP-1 Spirometer, Schiller, Switzerland or KoKo, United States) periodically calibrated according to the protocol recommended by the North American and European guidelines.[18]

Maximal cardiopulmonary exercise test

The CPX were performed on a treadmill (ATL Master, Inbramed, Brazil) in a properly climatized room. All players underwent the same ramp protocol, at an initial velocity of 8.0 $km.h^{-1}$, with progressive increase of 0.1 $km.h^{-1}$ every 7.5 seconds, and without any inclination. All CPX were conducted by specialized physicians with large experience in assessing athletes, following a well-defined routine, mainly regarding the stimulus to achieve truly maximal exertion. CPX was considered maximal based on the physician's subjective assessment and other objective variables, such as: occurrence of VT, U-pattern ventilatory equivalent, and a 10-score in the 0-10 Borg scale.[19] During the CPX, the players were monitored continuously by use of a digital electrocardiograph (ErgoPC Elite versions 3.2.1.5 or 3.3.4.3 or 3.3.6.2, Micromed, Brazil), which measured heart rate (HR) on the electrocardiographic tracing in the CC5 or CM5 leads at the end of every minute.

Analysis of the expired gases

During the CPX, the expired gases were collected by use of a Prevent pneumograph (MedGraphics, United States) coupled to a mouth piece, with concomitant use of a nose clip. The expired gases were measured and analyzed with the VO2000 metabolic analyzer (MedGraphics, United States), which was calibrated with a 2L-serinje and with gases of known concentrations before the first assessment of the day, and this procedure was repeated when necessary. Pulmonary ventilation

(VE) and oxygen and carbon dioxide partial fractions were expressed every 10 seconds, and their mean values for each minute of CPX were then calculated.

Determining maximal oxygen consumption and ventilatory threshold

The VO_2max was considered the highest value at a given minute of CPX. The VT was visually determined as the point at which an interruption in VE's curve linearity and a sustained increment in VE/VO_2 ratio occurred, being described as the percentage of VO_2max at that velocity. In addition, the velocity and the VO_2 at which the VT occurred were recorded.

Determining the cardiorespiratory optimal point

The COP was obtained by identifying the lowest VE/VO_2 ratio at a given minute of CPX, being, thus, a non-dimensional value. In addition, the VO_2 and the running velocity in the ramp protocol at that point were recorded.

Statistical analysis

Data distribution was assessed by use of the Shapiro-Wilk normality test. Continuous variables with parametric distribution were expressed as mean ± standard deviation (SD), being compared by use of the unpaired Student t test or ANOVA and post-hoc Bonferroni test, when appropriate. Continuous variables with non-parametric distribution were expressed as median (interquartile range) and compared by use of Mann-Whitney test or Kruskal-Wallis test, when appropriate. Categorical variables were expressed as percentage of the frequency and compared by use of the chi-square test. The coefficients of variation of the variables COP, VT and VO_2max, obtained by the ratio between standard deviation and mean, were calculated. Pearson correlation was used to test the association between COP and other ventilatory variables. The statistical calculations were performed using the Stata14® software, adopting a significance level of 5%.

Ethical considerations

All soccer players underwent the assessment willingly, having read and signed the specific written informed consent before the CPX, and having authorized the use of their data for scientific research. The retrospective analysis of data was previously approved by the Ethics Committee on Research of the institution.

Results

Table 1 describes the major demographic characteristics, and the resting spirometry and CPX results of the soccer players. Age, weight, height and body mass index (BMI) ranged from 16 to 36 years, from 57.5 to 102.0 kg, from 163.3 to 196.3 cm, and from 19.3 to 29.6 $kg.m^{-2}$, respectively. COP, VT and VO_2max showed a parametric distribution ($p > 0.05$), with values ranging from 13.1 to 25.3, from 61.8 to 92.7% of VO_2max, and from 45.0 to 76.2 $mL.kg^{-1}.min^{-1}$, respectively. The coefficients of variation for COP, VT and VO_2max were 16.1%, 10.7% and 10.0%, respectively. On average, COP, VT and VO_2max occurred at the velocities of 10.0 ± 1.0, 14.3 ± 1.1, and 18.7 ± 0.9 $km.h^{-1}$, respectively ($p < 0.01$).

When stratified by their field positions during the match (Table 1), the only characteristics that differed were weight and height, with goalkeepers showing the highest values for both variables ($p < 0.01$). The BMI, however, was similar among the soccer players of different field positions ($p = 0.86$). Regarding CPX, goalkeepers achieved the lowest VO_2max values relative to their body weight ($mL.kg^{-1}.min^{-1}$) ($p = 0.01$) and reached the COP at a higher HR and percentage of VO_2max than the players of other field positions ($p < 0.01$). However, the values of COP ($p = 0.41$) and VT (% of VO_2max) ($p = 0.42$) did not differ according to the soccer players' field positions.

The coefficients of correlation between COP and VO_2max ($mL.kg^{-1}.min^{-1}$) and between COP and VT (% of VO_2max) were 0.032 ($p = 0.65$) and -0.003 ($p = 0.96$), respectively, evidencing the low association between those variables. Figure 1 shows those data.

Discussion

During an exercise training with progressive intensity increase up to the voluntary maximum, the relationship between VE and VO_2 is nonlinear,[20] and the curve that illustrates that relation has a U shape, suggesting higher ventilatory efficiency (lower VE/VO_2) at submaximal exercise levels when compared to rest and to the highest exertion intensities. Based on that, COP was described as the lowest VE/VO_2 value at a given minute during an incremental exercise, representing the time point with the lowest amount of ventilation per liter of oxygen to be consumed, which is the best integration of the relationship between circulation and respiration.[15] Recent studies have shown the clinical applicability of the COP for the diagnostic and prognostic assessment

Table 1 - Major demographic characteristics and results of maximal cardiopulmonary exercise test on treadmill of professional soccer players

Variables*	Total (n = 198)	Goalkeeper (n = 13)	Left/right-back (n = 27)	Center-defender (n = 32)	Midfielder (n = 76)	Forwarder (n = 50)	p value
Characteristics							
Age (years)	23 (21 - 27)	22 (19 - 24)	26 (21 - 28)	22 (21 - 26)	23 (21 - 28)	24 (10 - 27)	0.35
Weight (kg)	76.7 ± 7.6	85.1 ± 4.7	74.3 ± 6.2	80.7 ± 5.4	74.1 ± 7.6[β]	77.3 ± 7.6[β]	< 0.01
Height (cm)	179.2 ± 6.4	187.5 ± 4.1	175.5 ± 4.2	184.3 ± 3.8	176.5 ± 6.0[β]	180.0 ± 5.8	< 0.01
Body mass index ($kg.m^{-2}$)	23.9 ± 1.8	24.2 ± 1.1	24.1 ± 1.7	23.8 ± 1.6	23.8 ± 1.8	23.9 ± 2.1	0.86
HR at rest (bpm)	59 (53 - 66)	62 (57 - 66)	57 (51 - 62)[a]	61 (53 - 65)	61 (54 - 66)	57 (52 - 66)	0.15
SBP at rest (mm Hg)	130 ± 10	130 ± 8	130 ± 14	129 ± 7	129 ± 11	131 ± 10	0.92
DBP at rest (mm Hg)	70 ± 9	72 ± 7	71 ± 11	70 ± 8	70 ± 9	71 ± 9	0.95
Resting spirometry							
FEV1 (L)	4.31 (3.94 - 4.69)	4.74 (4.35 - 5.04)	4.16 (3.96 - 4.41)	4.44 (4.13 - 5.00)[$]	4.24 (3.79 - 4.61)[β]	4.41 (3.90 - 4.71)[β,#,€]	< 0.01
% of predicted FEV1	98.5 (90.8 - 105.6)	101.9 (93.9 - 105.3)	96.7 (93.5 - 104.8)	98.5 (88.6 - 105.8)	98.5 (91.6 - 105.0)	100.8 (87.3 - 107.0)	0.99
FVC (L)	5.05 ± 0.68	5.70 ± 0.68	4.83 ± 0.50	5.23 ± 0.66	4.94 ± 0.62[β]	5.05 ± 0.75[β,€,#]	< 0.01
% of predicted FVC	96.2 ± 10.5	100.5 ± 10.8	95.7 ± 8.4	94.0 ± 10.3	97.0 ± 10.0	95.6 ± 12.1	0.38
FEV1/FVC ratio (%)	86.0 ± 5.3	83.1 ± 5.6	87.3 ± 4.1[a]	87.6 ± 5.3[a]	85.4 ± 5.1[c]	85.8 ± 5.9	0.05
CPX							
Duration (min)	13.0 (13.0 - 14.0)	13.0 (13.0 - 14.0)	14.0 (13.0 - 14.0)	13.0 (13.0 - 14.0)[b]	14.0 (13.0 - 14.0)	13.0 (13.0 - 14.0)[b]	0.09
Maximal RER	1.10 (1.06 - 1.15)	1.09 (1.06 - 1.13)	1.09 (1.05 - 1.15)	1.13 (1.07 - 1.16)	1.11 (1.06 - 1.15)	1.10 (1.06 - 1.14)	0.59
Maximal HR (bpm)	192 ± 9	194 ± 8	187 ± 7	194 ± 10[$]	192 ± 10[$,€]	192 ± 8[$,€,#]	0.01
Maximal VE ($L.min^{-1}$)	123.2 (113.1 - 133.2)	129.8 (122.6 - 135.2)	123.1 (112.8 - 133.7)	125.4 (113.7 - 136.0)	121.7 (111.6 - 129.9)[a]	122.9 (113.9 - 134.4)	0.30
Maximal velocity ($km.h^{-1}$)	18.8 (18.4 - 19.2)	18.4 (18.0 - 19.2)	19.2 (18.4 - 19.5)	18.5 (17.9 - 19.2)[b]	18.8 (18.4 - 19.2)	18.6 (18.4 - 19.2)[b]	0.13
COP (lowest VE/VO_2)	18.2 ± 2.1	19.1 ± 2.2	18.7 ± 2.1	17.9 ± 2.5	18.1 ± 2.2	18.2 ± 1.9[β]	0.41
Time to reach COP (min)	2.0 (2.0 - 3.0)	3.0 (2.0 - 4.0)	2.0 (2.0 - 3.0)	2.0 (2.0 - 3.0)	2.0 (2.0 - 2.5)[a]	2.0 (2.0 - 2.0)[a,c]	0.07
Velocity at the COP ($km.h^{-1}$)	9.6 (9.6 - 10.4)	10.4 (9.6 - 11.2)	9.6 (9.6 - 10.4)	9.6 (9.6 - 10.4)	9.6 (9.6 - 10.0)[a]	9.6 (9.6 - 9.6)[a,c]	0.07
HR at the COP (bpm)	132 (122 - 142)	142 (134 - 148)	131 (122 - 138)	139 (128 - 152)[$]	131 (121 - 140)[$]	128 (121-137)[β,#]	< 0.01

Cont. Table 1 - Major demographic characteristics and results of maximal cardiopulmonary exercise test on treadmill of professional soccer players

Variables*	Total (n = 198)	Goalkeeper (n = 13)	Left/right-back (n = 27)	Center-defender (n = 32)	Midfielder (n = 76)	Forwarder (n = 50)	p value
VO_2 at the COP ($mL.kg^{-1}.min^{-1}$)	31.8 (29.0 - 34.6)	33.6 (31.0 - 33.7)	32.2 (28.6 - 35.7)	33.1 (30.9 - 35.6)	31.3 (28.2 - 34.4)[c]	31.3 (33.8 - 29.7)[c]	0.10
%VO_2max at the COP	51.4 (46.4 - 55.8)	57.0 (53.3 - 59.3)	48.4 (45.1 - 54.7)	55.9 (51.2 - 59.2)[$]	51.0 (44.2 - 54.3)[ß]	50.7 (45.9 - 54.0)[ß,#]	< 0.01
Time to reach the VT (min)	7.9 ± 1.4	8.1 ± 0.9	8.1 ± 1.3	7.3 ± 1.3[b]	8.0 ± 1.6[c]	7.8 ± 1.3	0.06
Velocity at the VT ($km.h^{-1}$)	14.3 ± 1.1	14.5 ± 0.7	14.5 ± 1.0	13.8 ± 1.1[b]	14.4 ± 1.2[c]	14.3 ± 1.0	0.06
HR at the VT (bpm)	169 (160 - 178)	178 (168 - 181)	165 (162-169)[a]	172 (160 - 178)[b]	167 (160 - 177)[a]	166 (160 - 178)[a]	0.08
VO_2 at the VT ($mL.kg^{-1}.min^{-1}$)	46.8 ± 5.0	45.3 ± 2.5	47.9 ± 4.7	45.5 ± 4.5	46.7 ± 6.1	47.4 ± 4.0	0.25
%VO_2max at the VT	75.5 ± 5.7	77.3 ± 4.3	74.7 ± 4.8	76.1 ± 6.3	74.7 ± 6.2	76.0 ± 5.4	0.42
VO_2max ($L.min^{-1}$)	4.75 ± 0.52	4.98 ± 0.35	4.74 ± 0.35	4.82 ± 0.43	4.63 ± 0.60[a]	4.81 ± 0.53	0.09
VO_2max ($mL.kg^{-1}.min^{-1}$)	62.1 ± 6.2	58.6 ± 3.6	64.2 ± 6.5	59.8 ± 4.8$	62.6 ± 6.8[ß]	62.5 ± 5.8[ß,#]	0.01

** Data expressed as median (interquartile range) or mean ± standard deviation according to the distribution of the variables. The results were compared by use of the unpaired Student t test, ANOVA, Mann-Whitney test, Kruskal-Wallis test or chi-square test, according to the characteristics of the variables. [$]No statistically significant difference as compared to the goalkeeper group (p > 0.05). [#]No statistically significant difference as compared to the midfielder group (p > 0.05). [ß]No statistically significant difference as compared to the left/right-back group. [€]No statistically significant difference as compared to the center-defender group. [a]There was a statistically significant difference as compared to the goalkeeper group (p < 0.05). [b]There was a statistically significant difference as compared to the left/right-back group (p < 0.05); [c]There was a statistically significant difference as compared to the center-defender group (p < 0.05). FVC: forced vital capacity; HR: heart rate; VT: ventilatory threshold; SBP: systolic blood pressure; DBP: diastolic blood pressure; COP: cardiorespiratory optimal point; RER: respiratory exchange rate; CPX: cardiopulmonary exercise test; VE: ventilation; FEV1: forced expiratory volume in the first second; VO_2max: maximal oxygen consumption.*

of the cardiorespiratory interaction of both healthy individuals and those with chronic diseases; in addition, by being a submaximal variable of CPX, the use of COP is particularly interesting for patients unable to achieve a maximal CPX because of functional limitations (eg, peripheral obstructive arterial disease, orthopedic disorders) or because of their fear of achieving peak exertion (eg, patients with panic syndrome),[17,21] as well as for athletes during the competition season.[22] For example, the COP bears an inverse relationship with all-cause mortality in healthy and ill individuals aged from 40 to 85 years, having, thus, prognostic value and being a new possibility for mortality risk assessment.[17] Based on those observations, it is worth trying to expand the applicability of COP to other scenarios. In theory, one might assume that for athletes of modalities with high aerobic demands, such as soccer, low COP values can represent a physiological advantage, especially when occurring at relatively high velocities. Because the aerobic demands vary according to the field position during the match, the opportunity to compare a large number of elite soccer players tested in standard conditions can contribute to better understand the meaning and the potential applicability of COP in sports. The present study is an original contribution because it is the first to describe the COP behavior in athletes, in particular, high-level adult soccer players submitted to a CPX on a treadmill following the ramp protocol.

The COP has advantages related to its determination and measurement when compared to VO_2max and VT, the two major variables of CPX used to assess the performance of athletes. Obtaining a true VO_2max

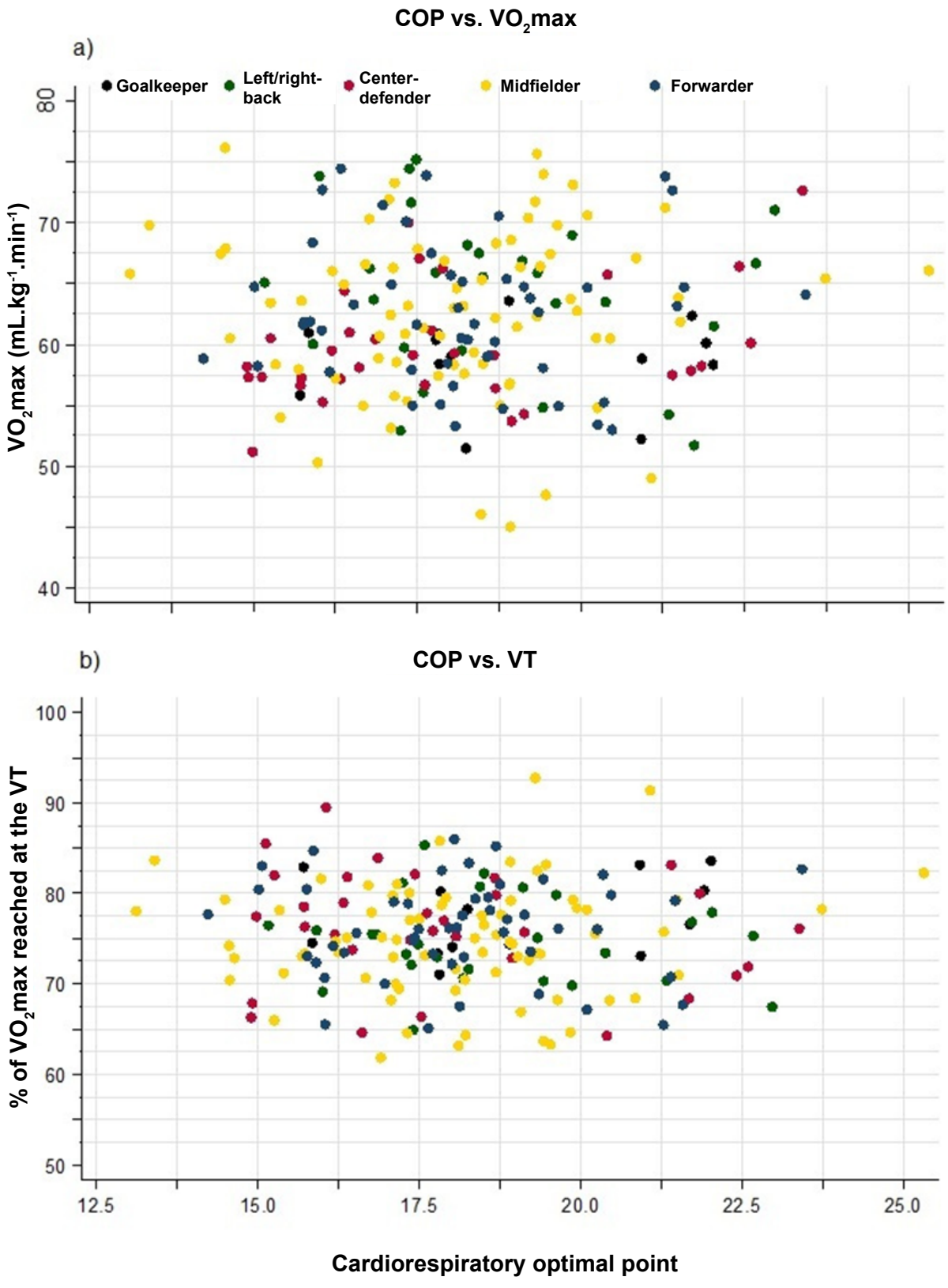

Figure 1 - Diagram of dispersion between variables: a) cardiorespiratory optimal point (COP) and maximal oxygen consumption (VO_2max); and b) COP and percentage of VO_2max reached at the ventilatory threshold (VT).

suggests the existence of a plateau in the VO_2 curve, which is not always possible, and it can vary according to the CPX protocol used and the gas sampling or collection interval.[10,11] In addition, VO_2max depends on performing a truly maximal exercise test, whose determination criteria vary in the literature, being subjective to a certain extent. On the other hand, although the VT does not require a maximal test, it requires a more intense exercise than COP does, and VT measurement is hindered by the existence of several distinct criteria for its identification and/or characterization, which, in a significant percentage of cases, cannot be obtained, limiting its use in clinical practice and sports.[13] In addition, although both VO_2max and VT can be detected automatically with commercial software, the methods available for that have been developed from varied definitions and algorithms, implying the need for its review by at least one experienced observer, making those measures subjective and widening the potential of high inter- and intraobserver variability.[23,24] In contrast, COP is easily determined from the identification of the lowest value of the VE/VO_2 ratio for each minute of CPX, not depending, thus, on the interpretation and experience of the observer, and relying on a relatively small effort, because it occurs at relatively low exercise intensities, before the VT.

Regarding the COP of the soccer players assessed, some findings are worth noting: 1- as expected, COP was obtained at lower percentage of VO_2max and velocity than those at the VT; 2- similarly to VT, but opposite to VO_2max, COP did not differ according to the different field positions of the soccer players; 3- no significant association was observed between COP and the variables VO_2max and VT; and 4- the coefficient of variation of oxygen consumption at the time of the COP was greater than that observed at the VT and VO_2max. It is interesting to point out that, on average, the COP values found for the soccer players were below the 50th percentile of the values found for healthy male non-athletes of the same age group in a previous study,[15] and that only eight (4%) soccer players had COP over 22, considered the cutoff point for optimal clinical prognosis,[17] suggesting that those soccer players have a privileged circulation-respiration interaction, probably more economic at the submaximal exercise. However, it is worth noting that the COP values described for non-athletes were obtained from a CPX performed on a lower limb cycle ergometer, with an individualized ramp protocol. Thus, the description of COP in different exercise modalities and protocols should be approached in future studies, because there is evidence that the behavior of some variables obtained in CPX differ depending on the ergometer and protocol used.

The running velocity on the treadmill and the exercise intensity represented by the percentage of VO_2max at which the soccer players assessed in this study reached the COP (10.0 ± 1.0 km.h^{-1} and 51.3 ± 8.7%, respectively) were lower than the values obtained at the VT by soccer players assessed in other studies, even when compared to those of players of lower athletic performance, who are expected to reach an earlier VT. For example, according to Ziogas et al.,[25] soccer players of the first, second and third Greek division submitted to a CPX in the pre-season period reached the VT at a mean velocity of 13.2, 12.6 and 12.3 km.h^{-1}, respectively. Boone et al.,[26] however, assessing 289 soccer players of the first Belgian division, have reported mean running velocities on the treadmill at the VT ranging from 12.7 ± 1.4 in goalkeepers to 14.4 ± 0.7 km.h^{-1} in center-defenders. Regarding the exercise intensity, Impellizzeri et al.[27] and Helgerud et al.[28] have reported that junior soccer players reached the VT at a mean percentage of VO_2max greater than 80%. Considering that the running velocity and the exercise intensity at which the VT is reached reflect the training status of the soccer players, future studies should assess whether COP is also useful to differentiate the physical performance of athletes.

When comparing the soccer players according to their field positions, goalkeepers, midfielders, left/right-backs, center-defenders and forwarders did not differ regarding the COP. Manari et al.,[29] comparing the VT and the VO_2max of 450 European elite soccer players of different field positions, have found no differences regarding the VT, similarly to our study's findings regarding VT and COP. However, similarly to our study's findings, VO_2max was lower in goalkeepers. Tonessem et al.,[30] assessing 1,545 male soccer athletes, have found small to moderate differences in VO_2max according to the athlete's field position, with greater values in the midfielders, followed, in decreasing order, by the defense athletes, forwarders and goalkeepers. Similarly, Balikian et al.,[31] assessing 25 professional soccer players, have found lower mean VO_2max values of goalkeepers (52.68 mL.kg^{-1}.min^{-1}) as compared to the mean values of soccer players of other field positions. However, in contrast to our study's findings, the mean velocity at which the players reached the VT differed according to their field position, being lower for goalkeepers (12.66 km.h^{-1}) and higher for left/right-

backs (14.33 km.h^{-1}) and midfielders (14.11 km.h^{-1}). Nevertheless, it is worth noting that the heterogeneity of the methods used to measure VT hinders the comparison of the results between the studies.

Finally, the COP failed to show a linear association with the variables VT and VO_2max. Ramos et al.[15] have not only described a moderate association with VO_2max (-0.47) and VT (-0.42), but have also observed that the combination of COP and VO_2max adds more prognostic information to all-cause mortality than each variable in isolation.[17] Such findings suggest a possible independence and complementarity of COP regarding VO_2max and VT, which could contribute with additional information to the interpretation of the relationship between the cardiovascular and respiratory systems during a CPX. Thus, one can speculate that the submaximal variables – COP and VT – might better reflect the energetic demands of a soccer match in the current context, in which the differences in distance and in percentage of time spent in intense efforts are less evident in soccer players of different field positions.

The present study has some limitations in addition to those already mentioned. The CPX analyzed were limited to those performed in the pre-season period, not allowing us to assess the COP behavior in different training periods of the soccer players. In addition, this study only assessed male adult elite soccer players, which limits the extrapolation of the results to female soccer players, other age groups, different technical levels and other sport modalities.

Conclusion

The present study described the COP behavior and its absence of association with VO_2max and VT of male adult elite soccer players. Thus, future studies are required to assess whether COP can provide additional and relevant information to other sport contexts.

Author contributions

Conception and design of the research: de Souza e Silva CG, Castro CLB, Franca JF, Bottino A, Myers J, Araújo CGS; Acquisition of data: Castro CLB, Franca JF, Araújo CGS; Analysis and interpretation of the data, Statistical analysis and Writing of the manuscript: de Souza e Silva CG, Araújo CGS; Critical revision of the manuscript for intellectual content: Castro CLB, Franca JF, Bottino A, Myers J, Araújo CGS.

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 Suprema - Faculdade de Ciências Médicas e da Saúde de Juiz de Fora under the protocol number 0218/11. 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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ORIGINAL ARTICLE

Comparison between Myocardial Ischemia Evaluation by Fractional Flow Reserve and Myocardial Perfusion Scintigraphy

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Abstract

Background: Moderate coronary artery lesions can be, or not, responsible for myocardial ischemia. The functional analysis of these lesions can be performed by invasive and noninvasive methods.

Objective: To compare the functional analysis of moderate coronary lesions by fractional flow reserve and myocardial perfusion scintigraphy.

Methods: 47 patients with stable coronary artery disease and at least one moderate coronary artery obstruction were prospectively studied. They were submitted to fractional flow reserve and myocardial perfusion scintigraphy with a median interval of 24.5 days between January 2013 and December 2015. There was no change in clinical status or revascularization procedure between the exams. The population variables were described as medians and interquartile range. Fractional flow reserve was performed in one left main coronary artery; 37 left descending coronary arteries; 12 circumflex arteries and 4 right coronary arteries. Fractional flow reserve < 0.8 was considered positive. The comparative analysis between the results of the tests was performed by two-tailed Fisher's test and a p-value ≤ 0.05 was considered significant.

Results: Fractional flow reserve < 0.8 was found in the left main coronary artery (100%); 13 in the left descending coronary artery (35.14%); 6 in circumflex artery (50%) and 2 in the right coronary artery (50%). Among the patients with positive fractional flow reserve, 83% had myocardial ischemia demonstrated by the myocardial perfusion scintigraphy (p = 0.058). When analyzing specifically the left descending coronary artery, 83% of the patients with negative fractional flow reserve showed no ischemia at the myocardial perfusion scintigraphy, but 69% of the patients with positive fractional flow reserve showed no ischemia at the myocardial perfusion scintigraphy (p = 0.413).

Conclusion: Disagreements can occur between the results of the functional analysis of moderate coronary lesions by invasive and noninvasive tests. (Int J Cardiovasc Sci. 2018;31(4)333-338)

Keywords: Myocardial Ischemia; Praqctional Flow Reserve, Myocardial; Myocardial Perfusion / Diagnostic Imaging; Microvascular Angina.

Introduction

The presence of myocardial ischemia is one of the important prognostic factors in coronary artery disease (CAD) and in the decision-making on the best treatment to be implemented. The combination of coronary anatomy and information on the hemodynamic implication of the obstructive lesion is essential to define the treatment strategy to be carried out in patients with CAD.

The fractional flow reserve (FFR) measurement is a valuable tool to evaluate the functional severity of a coronary stenosis, identifying changes in coronary flow resistance. The FFR can be obtained in the hemodynamic laboratory and can be performed together with the angiography. The FFR is defined as the maximum blood flow to the myocardium in the presence of a certain stenosis, divided by this flow, if there was no such stenosis. The FFR can be determined by dividing the

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mean pressure distal to the coronary lesion by the mean aortic pressure during maximal adenosine-induced vasodilation. The FFR has a normal value of 1, and values less than 0.8 indicate myocardial ischemia. Studies have shown that coronary vessels with FFR ≥ 0.8 can be clinically treated, with cardiovascular event rates similar to those of patients with normal noninvasive tests (< 1% per year). Patients with FFR ≤ 0.8 could benefit from percutaneous or surgical revascularization procedures.[1-3]

Although the FFR has its defined role in moderate lesions and is not very useful in angiographically severe lesions, it helps in the decision-making regarding when to revascularize patients with multivessel disease. In these patients, it helps to define the revascularization strategy, as well as to better evaluate its extent, according to the functional evaluation of stenosis in critical coronary sites.[4]

Myocardial perfusion scintigraphy (MPS) with tomographic images has been validated by several studies in the evaluation of diagnosis and prognosis for patients at risk of cardiovascular events. The functional repercussion of coronary lesions constitutes one of the main purposes of the method, which is based on the perfusion deficit assessment in myocardial segments irrigated by partially occluded arteries. Risk stratification is based on the ability to identify patients according to the test results. SPECT with normal or slightly altered perfusion has an excellent prognosis, with a low mortality risk (< 1%) per year. The risk associated with perfusion alterations varies according to the ischemia extent and severity. The greater the perfusion defects, the higher the likelihood of future events. In those with moderate perfusion defects, the incidence of events is 1 to 3% per year, being > 3% in patients with major perfusion defects.[5]

Most percutaneous coronary interventions are performed based on angiographic criteria alone, with no objective evidence of myocardial ischemia. Coronary angiography has limitations in establishing functional severity, because the stenosis degree of a lesion does not always correlate with functional impairment in the myocardium.6 Thus, it is important to complement anatomical data with functional tests capable of adequately guiding the therapeutic approach regarding a myocardial revascularization procedure. Several studies have been carried out to evaluate the agreement between the FFR with functional methods (MPS, dobutamine stress echocardiogram and exercise testing) to define the presence of myocardial ischemia, with the FFR having the advantage of being specific for each vessel and obstruction.[7] In multi-vessel patients, MPS tends to underestimate or overestimate the functional importance of coronary stenosis when compared to FFR.[8]

The functional tests are performed in a minority of patients referred to coronary angioplasty at *Instituto Nacional de Cardiologia*. In this sense, the FFR can be a useful tool in the hemodynamics room to aid in decision-making regarding whether or not to perform a percutaneous coronary intervention, saving time and costs to the health system. The objective of the present study was to compare the functional analysis between FFR and MPS in patients with moderate lesions at the coronary angiography.

Methods

This is a prospective, observational study of patients of both genders, aged 18 years or older, admitted to the Department of Coronary Disease unit or referred to the Hemodynamic Service of *Instituto Nacional de Cardiologia*, who had an FFR indication after the coronary angiography by the multidisciplinary "Heart team". The sample size of 47 patients was selected by convenience.

Patients with no previous MPS were submitted to the examination. Coronary lesions were classified as moderate (between 50 and 70%) and severe (≥ 70%) according to visual estimation.

Patients with moderate lesions and those for whom there was doubt regarding the indication of myocardial revascularization were included in the study. Patients with chronic occlusion, ST-segment elevation acute myocardial infarction, unstable patients, those with severe valvular disease or cardiomyopathies from other causes, patients with contraindications to the use of adenosine and to scintigraphy (pregnant women, infants and women with suspected pregnancy) were excluded from the study.

The study was approved by the Ethics and Research Committee of *Instituto Nacional de Cardiologia*, and all the participants agreed to sign the Free and Informed Consent Form. The present study has no sources of funding.

Fractional flow reserve measurement

Coronary catheterization was performed with 6 and 7F guide catheters. Prior to the angiography, 10,000 u of intravenous heparin and intracoronary nitroglycerin at a dose of 0.25 to 0.5 mg were administered. Then, pressure measurements were performed in vessels with stenosis ≥ 50% by visual estimation using a guidewire with a

sensor at its tip and was positioned in the distal bed of each coronary to be analyzed. Intravenous adenosine at the dose of 140 mg/kg/minute was administered for 2 to 3 minutes to induce maximal hyperemia.

The FFR was established as the ratio between the mean distal coronary pressure and the mean aortic pressure, measured by the guide catheter during maximal hyperemia. Stenoses with FFR < 0.8 were considered positive for ischemia.

Myocardial perfusion scintigraphy

The MPS was performed using the Single-Photon Emission Computed Tomography (SPECT) technique, using technetium-99m sestamibi (Tc-99m MIBI) with the 2-day protocol at rest and exercise or dipyridamole stress test. The images were semi-quantitatively analyzed using a 17-segment model. The test was considered abnormal when it disclosed evidence of one or more ischemic areas. The percentage of ischemic area was not evaluated in all patients.

Statistical analysis

A descriptive analysis of the selected patients' basal characteristics was performed by calculating medians and interquartile ranges. The assessment of the association between the presence of ischemia in the MPS and FFR was assessed using the two-tailed Fisher's exact test. A p-value < 0.05 was considered statistically significant. The STATA/MP software by StatCorp LP, version 14.2, was used for data analysis.

Results

When characterizing the sample of assessed patients, 47 individuals with stable coronary disease and a median age of 65.4 years (interquartile range between 58.03 and 69.59 years) were selected. Most were women (66%) and had stable angina (82%); and 7% were post-acute myocardial infarction.

Regarding left ventricular function, only 14% had moderate to severe dysfunction. The ejection fraction calculated by the Teichholz method showed a median of 64.5%, with an interquartile range between 45% and 71% (Table 1).

The stress assessment by MPS was performed in 68% with dipyridamole and in 32% through an exercise stress test. The interval between MPS and FFR was 24.5 days between January 2013 and October 2015.

Table 1. Patients' characteristics

Age, years	65.45 (58.03-69.59)
Female, %	65.96
Ethnicity, %	
White	63.83
Mixed-race	25.53
Black	10.64
Diagnosis, %	
Stable angina	82.98
Previous AMI	14.89
Others	2.13
SAH	91.11
Dyslipidemia	91.11
Diabetes Mellitus	42.22
Smoker	40.00
Cerebrovascular disease	8.89
Kidney failure	4.44
Sedentary lifestyle	86.67
Obesity	13.95
Family history	52.27
LVEF < 50%	14.28
EF Teichholz	64.5 (45-71)
Three-vessel anatomy or LMCA	38.80

AMI: acute myocardial infarction; SAH: systemic arterial hypertension; LVEF: left ventricular ejection fraction; EF: ejection fraction; LMCA: left main coronary artery.

In the analyzed sample of patients, 38.8% had a three-vessel lesion or had a left main coronary artery lesion. FFR was performed in the following territories: one left main coronary artery, 37 anterior descending arteries (ADA), 12 circumflex arteries and 4 right coronary arteries.

In the comparative analysis of the MPS and FFR results, 83% of the patients with positive FFR also had positive MPS, but with a non-significant p value (0.058) and 53.57% of the patients with positive MPS had a negative FFR (Figure 1).

When discriminating the assessment of the ADA territory, 83% of patients with negative FFR also had negative MPS, but in those who obtained positive FFR

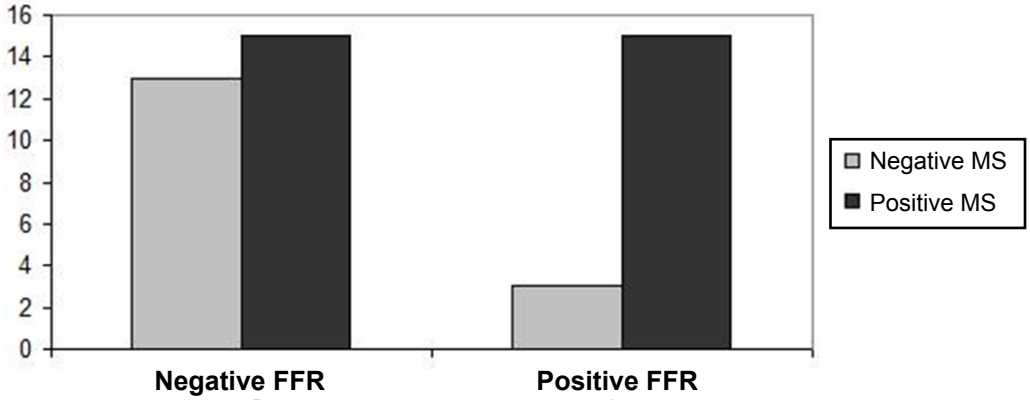

Figure 1 - *Myocardial scintigraphy (MS), according to the fractional flow reserve (FFR).*

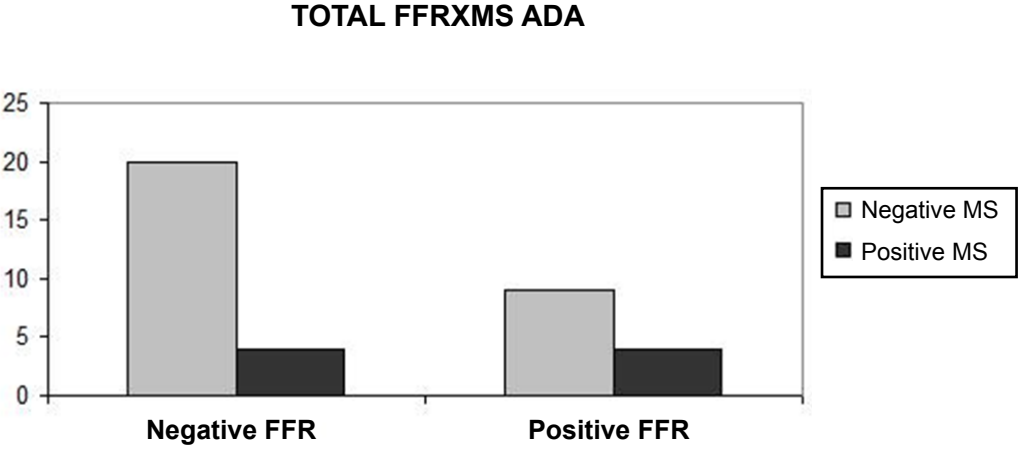

Figure 2 - *Myocardial scintigraphy (MS) in the anterior descending artery (ADA) according to the fractional flow reserve (FFR).*

results, MPS was negative in 69% – both results showed a non-significant p value (0.413) (Figure 2).

Discussion

When assessing ischemia, the agreement between MPS and FFR is a weak one.[8,9] In the present study, we observed the non-agreement between the methods, although 83% of patients with positive FFR had positive MPS; the *p* value was not significant.

Such disagreement becomes more evident in patients with multivessel disease, since MPS tends to underestimate the functional importance of the lesions.[8] The FFR reflects the pressure gradient in a single vessel; on the other hand, the MS makes a comparison of the functional stenosis severity between the vessels. The perfusion defect in MPS is defined by comparison with the region of higher perfusion, considering that this region is normal, but often it is also an altered region – although less affected.[10] In the assessed sample, 38.8 % of the patients had left main coronary artery or three-vessel disease, which may have contributed to a disagreement between the results.

Another factor to be considered regarding the agreement analysis is the presence of microvascular disease, which influences the FFR assessment,[10] although

other invasive evaluations can be performed to better quantify the microvascular disease. The coronary flow reserve (CFR) and index of microcirculatory resistance (IMR) improve risk stratification in patients with negative FFR, being an independent prognostic factor.[11-13] The CFR represents the vasodilation capacity of the coronary vascular bed during hyperemia, being measured by thermodilution indicators. A low CFR value (≤ 2) indicates microvascular dysfunction. Additionally, the microvascular resistance index also provides data on microvascular function, being measured by through the distal coronary pressure multiplied by the mean transit time of 3 mL of saline bolus during adenosine-induced hyperemia, with the normal value being < 20, whereas the altered value is > 30.[11-13] In the total sample, the FFR was negative in 53.57% of the patients who had a positive MPS, a result that can be explained by the presence of microvascular disease, which was confirmed by the abovementioned methods.

No significant agreement was observed in the ADA-specific analysis, but 83% of the patients with negative scintigraphy also had a negative FFR.

There was no significant data on agreement or disagreement in our sample, possibly due to the number of patients studied, requiring that a larger sample be assessed.

Conclusion

Disagreements may occur between the functional analysis results of moderate coronary lesions by invasive and non-invasive tests. This fact can have important consequences in the use of the scintigraphy to establish the optimal revascularization strategy, mainly in multivessel patients. Therefore, fractional flow reserve is good technique to be used together with coronary angiography, especially in patients with multivessel lesions, since anatomic and functional stratifications can be obtained in a single procedure. Regarding patients with microvascular disease, the fractional flow reserve is not defined as an ideal strategy to evaluate ischemia.

Author contributions

Conception and design of the research: Pittella F, Paço P, Leandro SM, Felix R, Issa AFC. Acquisition of data: Paço P, Leandro SM, Tadeu J, Felix R, Issa AFC. Analysis and interpretation of the data: Pittella F, Paço P, Tadeu J, Felix R, Issa AFC. Statistical analysis: Paço P, Issa AFC. Writing of the manuscript: Paço P, Issa AFC. Critical revision of the manuscript for intellectual content: Pittella F, Felix R, Issa AFC. Supervision / as the major investigador: Leandro SM, Felix R, Issa AFC. Conducting examinations: Leandro SM, Felix R.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Instituto Nacional de Cardiologia under the protocol number 5272. 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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International Journal of Cardiovascular Sciences. 2018;31(4)339-358

ORIGINAL ARTICLE

Disparities in Acute Myocardial Infarction Treatment Between Users of the Public and Private Healthcare System in Sergipe

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Abstract

Background: The Brazilian Unified Health System (SUS) was created to ensure universal, integral and equitable access to quality healthcare to Brazilians. However, studies scrutinizing the quality of the healthcare provided by the SUS are scarce. This is especially critical for patients with ST-elevation myocardial infarction (STEMI), who depend on healthcare system responsiveness and timely reperfusion to achieve better outcomes.

Objective: To describe the methodology of the VICTIM Registry aimed at characterizing and comparing the access to effective therapies and the outcomes of patients with STEMI, who use the SUS and the private healthcare system at hospitals capable of performing angioplasty in Sergipe. In addition, that registry aimed at identifying and measuring possible disparities in the quality of the care provided.

Methods and Results: The VICTIM Registry is an observational study, launched in December 2014, being still in the data collection phase, to investigate: the epidemiology of STEMI in Sergipe, the temporal and geographic courses of the patients up to their admission to one of the hospitals capable of performing angioplasty, the reperfusion therapy rates, the quality of the healthcare provided during the event, and the 30-day mortality. It compares the results obtained in the SUS with those of the private healthcare system.

Conclusions: The VICTIM Registry is an interinstitutional effort to identify opportunities for healthcare improvement for SUS and private healthcare system patients with STEMI. It is expected to provide healthcare managers with information to support new, more efficient and equitable healthcare policies. (Int J Cardiovasc Sci. 2018;31(4)339-358)

Keywords: Myocardial Infarction; Healthcare Disparities; Unified Health System; Private Health Care Coverage.

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Introduction

The guarantee that health is a constitutional right and the subsequent creation of the Brazilian Unified Health System (SUS) are fundamental landmarks of the Brazilian public health.[1,2] Based on that, every Brazilian would have universal, integral and equitable access to quality healthcare.[2] Although the SUS is more than three decades old, the quality of the healthcare it provides has been insufficiently scrutinized by the Science of Results.[3] This is particularly critical because 72.1% of the Brazilian population essentially depends on SUS, and only 27.9% of the Brazilians have some other type of healthcare coverage.[4]

Acute myocardial infarction (AMI) continues to be the major cause of cardiovascular morbidity and mortality in Brazil and worldwide.[5-7] In ST-segment elevation myocardial infarction (STEMI), the immediate access to reperfusion therapies increases substantially the chance of survival.[5-8] Although myocardial reperfusion for STEMI has been established since the 1980s,[9] contemporary data from several countries and regions have shown the variability and underuse of that therapy and several other pharmacological or procedural practices, essential to the treatment of patients with STEMI.[10-14] Developing countries, however, lack studies on the quality of the care provided to patients with AMI. In Brazil, studies investigating the quality of the healthcare provided by SUS are scarce.[3]

Therefore, generating representative and comprehensive knowledge on the healthcare quality provided by SUS is justified, in addition to assessing the existence of disparity as compared to the healthcare quality provided by the private system, which, if confirmed, should be quantified. However, assessing the healthcare provided to patients with STEMI in the huge territory of Brazil is a challenge. To fill that gap, limiting the research field to a circumscribed geography and developing pilot projects can be the most realistic strategy.[11,12,15,16]

Thus, Sergipe, by being the smallest state in Brazil, counting on only four referral hospitals specialized in cardiovascular diseases, can serve as a laboratory to measure the presumed disparity in the healthcare provided by the SUS and the private system to treat patients with STEMI.

Context of the VICTIM Registry

The VICTIM (*Via Crucis para o Tratamento do Infarto do Miocárdio*) Registry was designed to investigate and compare patients with STEMI cared for in the public and private health systems considering the following major objectives: 1) celerity in the search for medical care; 2) temporal and geographic course of patients, from symptom onset to search for care and access to referral hospitals specialized in cardiovascular disease; 3) demographic and clinical characteristics of the patients with STEMI referred to the centers specialized in cardiovascular disease in the State of Sergipe; 4) access to the myocardial reperfusion therapies occurring during transportation to those centers and those occurring upon arrival there; 5) to assess whether the healthcare practices of public and private health services are aligned with the metric indicators that represent hospital care quality for the management of STEMI; 6) the rate of cardiovascular events occurring in-hospital and up to 30 days from the index event. In addition, the VICTIM Registry has the following general objectives: 7) to collaborate with the institutions participating in the process of improving the quality of the care provided to patients with STEMI; 8) to identify opportunities of improving the quality of the care provided to patients with STEMI in the entire State of Sergipe; 9) to disseminate knowledge at local and national levels; 10) to serve as a research platform for larger, multicenter and national studies; 11) to influence the public policies regarding the healthcare provided to patients with STEMI at state and national levels, in addition to other countries with similar socioeconomic characteristics.

The present study describes the methodology of the VICTIM Registry and discusses its potential implications.

Domains analyzed

For the outline of the VICTIM Registry, the following domains were considered (Figure 1):

A. Epidemiology of STEMI at referral hospitals

B. Pre-hospital healthcare quality

C. Healthcare quality at the referral center

D. Clinical outcomes

E. Post-discharge healthcare quality

History of the project

Pilot projects for the VICTIM Registry were conducted from May 2013 to November 2014 aimed at training the data collection team and at raising awareness in each referral center about the need for studies on the healthcare quality provided to patients with STEMI.

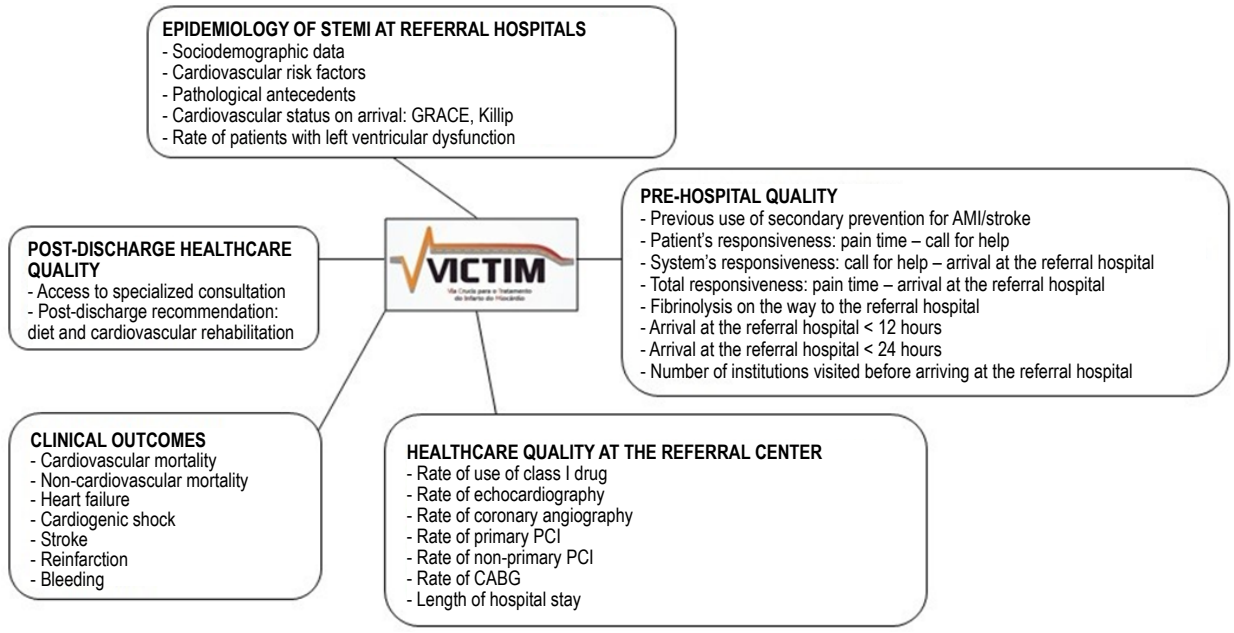

Figure 1 - Domains analyzed in the VICTIM Registry.
STEMI: ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; AMI: acute myocardial infarction.

During that period, 319 patients were included in the study, 274 from the public healthcare and 45 from the private healthcare. During that phase, the variables to be collected were defined, the collection tool was refined (Annex A), and the logistic of data collection was adjusted regarding the number of field researchers, their training in the field and their allocation to the centers.

In December 2014, data collection finally started to feed the VICTIM Registry, an ongoing phase for greater sample representativeness. To participate in the study, the field researcher should undergo training, consisting of a formal presentation of the research's objectives and the data collection methodology, by using the appropriate tool. Then, each investigator underwent a supervised training with the study coordinator at the hospital of allocation to become acquainted with the research site and its functioning routines, in addition to being instructed on data collection. After that basic training, the researchers could undertake their specific tasks. Whenever necessary, the members of the teams underwent updating trainings aimed at refining the technique of data collection. Since the beginning of the post-pilot phase, the coordinators have taken constant and very good care of data collection.

Methods

Hospitals of the state of Sergipe included in the VICTIM Registry

Sergipe is the smallest state of Brazil, occupies an area of 21,918.454 km², has 75 municipalities, the city of Aracaju is the capital, and the Metropolitan region includes the municipalities of Barra dos Coqueiros, Nossa Senhora do Socorro and São Cristóvão.[17] The state has 34 general hospitals, 14 of which are public hospitals, 10 are philanthropic hospitals and 10 are private hospitals.[18]

The VICTIM Registry portrays the care provided to patients with STEMI admitted to the four cardiovascular hospitals of Sergipe that have interventional cardiology services. All of them are located in the city of Aracaju, one provides care to the users of SUS (hospital 1), and three are private hospitals that provide care to users of the supplemental healthcare system (hospitals 2, 3 and 4) (Table 1). All four hospitals can perform primary angioplasty and heart surgery seven days a week.

In the VICTIM Registry, the public hospital is philanthropic, but has no direct entrance to the emergency unit. The users of SUS have access to that public hospital through referral from another health unit.

Table 1 - Characteristics of the hospitals participating in the VICTIM Registry

Characteristics of the hospitals	Public hospital patients N (370*)	Private hospital patients N (82*)		
	Hospital 1 (370*)	Hospital 2 (35*)	Hospital 3 (17*)	Hospital 4 (30*)
Location	Capital	Capital	Capital	Capital
Type	Non-profit-making	Profit-making	Profit-making	Profit-making
Total number of beds	279	208	147	49
COU beds	10	10	0	8
General hospital	YES	YES	YES	NO
Access as user of SUS	YES	NO	NO	NO
Ability to perform PCI	YES	YES	YES	YES
Ability to perform heart surgery	YES	YES	YES	YES
Patients admitted via direct access*	6 (1.5%)	27 (77%)	15 (88%)	12 (40%)
Patients admitted via referral*	364 (98.5%)	8 (23%)	2 (12%)	18 (60%)

N: Number of patients; COU: Coronary Unit; SUS: Brazilian Unified Health System; PCI: Percutaneous Coronary Intervention; (*) Period: December 2014 to April 2016.

The private hospitals, however, provide care to a heterogeneous population, comprising patients with different health insurance plans and those who choose to pay for their own healthcare. Each of the three private hospitals has its specific set of health insurance plans, which makes their population heterogeneous. Such hospitals have direct entrance to their emergency units, thus, the patient can have direct access to those hospitals or can be referred from another health institution.

In the state of Sergipe, 80.7% of the population has no health insurance, relying, therefore, on the SUS, depending consequently on one single hospital as reference for the treatment of STEMI. The other 19.3% of the population has health insurance, counting on three hospitals with catheterization laboratory. Because of the lack of the necessary responsiveness in the SUS, some patients, even with neither health insurance nor a favorable economic condition, opt for the private service care.[19]

Except for those four hospitals, no other hospital of the Sergipe healthcare system has a team of cardiologists on call or a clinical team capable of identifying and treating patients with STEMI, especially regarding the prescription of thrombolytic agents or the infrastructure to perform primary angioplasty.

The basic assumption is that the care provided to patients with STEMI in the four cardiovascular referral hospitals has the best quality in the state (Figure 2). Thus, to compare the quality of the care provided to users of the SUS with that provided at the three private hospitals will reflect the best public and private healthcare provided in the state of Sergipe.

Eligibility of the patients

Patients with the following characteristics are considered eligible for the VICTIM Registry: both sexes; older than 18 years; clinical findings compatible with acute coronary syndrome and electrocardiogram (ECG) showing persistent ST-segment elevation > 1 mm on two contiguous leads;[7,8] and who provide written informed consent.

The diagnosis of AMI is confirmed later, based on the classical changes of the biomarkers CK-MB and/or troponin,[7,8] taking into consideration the final opinion of the medical team.

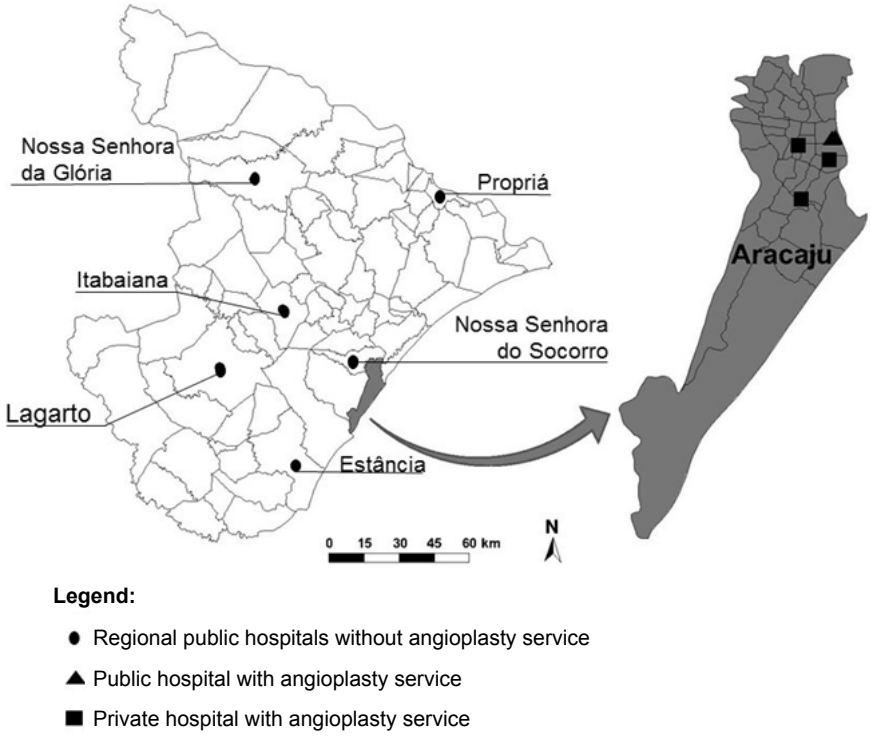

Figure 2 - Location of the regional hospitals that can perform angioplasty in the state of Sergipe.

Patients meeting the eligibility criteria described will be included in this study.

The following patients will be excluded: (1) those who die before the interview; (2) patients who develop STEMI inside the hospital, whose pre-hospital phase cannot be characterized; (3) those who refuse to provide written informed consent; (4) those whose acute event of STEMI is characterized as reinfarction (new AMI within 30 days from the incident infarction); (5) individuals whose diagnosis is changed, that is, their initial diagnostic suspicion of STEMI is not confirmed during hospitalization; (6) patients cared for by use of their health insurance at a philanthropic hospital (Figure 3).

Data collection

The team of field researchers is subdivided so that there is a fixed schedule with a researcher on duty every day of the week at the hospitals participating in the study. This ensures an active search is performed every day for patients with STEMI admitted to the four hospitals of the study.

After the patients provide written informed consent, data are collected as follows: (1) from their medical records with extraction of data pertinent to the study; (2) from an interview with the patients.

The interview collected the following demographic variables: age; socioeconomic level; educational level; marital status; pathological history; and time-related elements, such as the date and hour of symptom onset, the time that help was required, the time the patient arrived at the first institution that could not perform angioplasty, and the time the patient arrived at the specialized institution. From the medical records, the following data are retrieved: characteristics of the diagnostic ECG with ST-segment elevation, physical examination and laboratory tests, drugs used within 24 hours from STEMI detection, tests performed on admission, such as echocardiography and coronary angiography, data regarding the angioplasty or revascularization surgery, in addition to data regarding the in-hospital outcomes.

Fortnightly meetings with the team are systematically held to assess the progress of the investigation and occasional adjudication of doubtful cases, in addition to assessing the quality of data collection.

To obtain the data regarding the outcomes of patients included in the registry, a phone call with structured

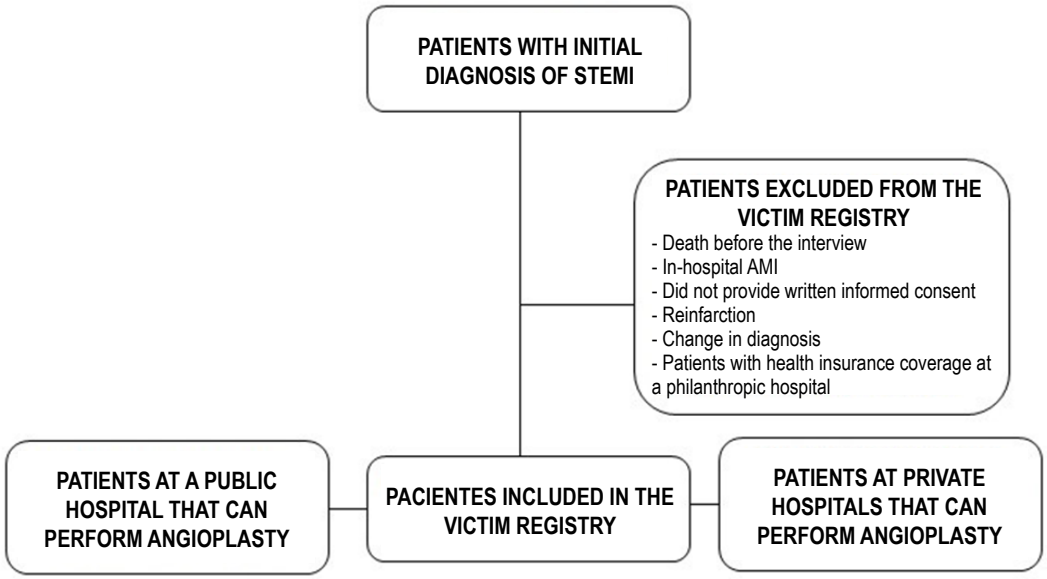

Figure 3 - Flowchart representing the exclusion criteria for patients with ST-segment elevation myocardial infarction (STEMI).
AMI: acute myocardial infarction.

interview is performed 30 days after the detection of STEMI. On the occasion, the coordinator responsible for the calls gets information with the patients and/or their guardians on the occurrence of death, reinfarction, heart failure, cardiogenic shook, angina pectoris, stroke, hemorrhage, cardiac arrest and/or new hospitalization, in addition to assessing whether the patients attended a specialized consultation after discharge, and, if not, whether they have one scheduled.

When the patient cannot be reached via telephone, other resources are used, such as a relative's or neighbor's telephone contact, e-mail or post letter with the major researcher's contacts, to minimize data loss.

If the patient remains hospitalized for 30 days, the final visit is performed during hospitalization, and after that the patient's participation in the study ends.

Case report form and data bank

Case report form (CRF) is the collection tool (Annex A) adopted by the VICTIM Registry and comprises the following: (1) patient's identification; (2) eligibility; (3) time line; (4) clinical presentation; (5) hospitalization; (6) outcomes. In 2015, the CRF passed from the print version to the electronic version, in which data storage is virtually fed, facilitating their maintenance and reducing the form filling out process errors. The data collected in loco are stored in an electronic cloud, ensuring lower risk for data loss.

Data originating from the electronic CRF are transferred to a spreadsheet, facilitating their analysis and interpretation. The system is always fed by a researcher who underwent previous training and is the sole responsible for that activity. Aiming at minimizing errors of data bank input, the procedure is performed systematically right after patient's assessment. Each CRF entered into the system receives an identification number, eliminating, thus, the need for contact with the names of the patients included in the study, and ensuring the right to anonymity.

Statistical analysis

Qualitative variables will be expressed as frequency (percentage), and quantitative variables will undergo Kolmogorov-Smirnov test to determine the distribution type; those meeting the normality assumption will be expressed as mean and standard deviation. The variables without a normal distribution will be described as median and interquartile range or maximum and minimum values. The qualitative variables will be compared by using Pearson's chi-square test or Fisher exact test, when appropriate.[20] Non-paired Student t test will be used to compare between the two major

groups when the continuous or discrete variables have normal distribution. In case of asymmetric distribution, Wilcoxon-Mann-Whitney test will be used.[21]

To assess the effect of demography, clinical data, laboratory data and the time for reperfusion treatment to be performed, a model of multivariate logistic regression will be used with generalized equations that consider the clustering effect[22] and stratified Cox regression.[23]

The Kaplan-Meier method[24] and the log-rank test[25] will be used to compare event-free survival curves in users of the SUS and of the private hospitals, with and without adjustment for the confounding variables. The SPSS Statistics program for Windows version 17 and R Core Team 2014[26] will be used for the statistical analysis. The significance level adopted in future analyses will be 5%.

Ethical considerations

Before entering the study, all volunteers or their guardians provide a written informed consent. Illiterate individuals who choose to participate in the study complete the informed consent process by signing with a fingerprint and two literate witnesses verify the process with a signature. This study was approved by the Ethics Committee in Research of the Federal University of Sergipe (nº 23392313.4.0000.5546).

Commitment of the VICTIM team

In addition to answering specific questions, the leaders of the VICTIM Registry are committed to continuously spreading the study results aiming at contributing to improve the healthcare quality for AMI. The present investigation is expected to provide constantly and systematically the health managers with technical information that can support new health policies or care strategies, contributing to the construction of a more efficient and equitable healthcare system. The central idea is to identify in the presently practiced line of care opportunities to improve the care provided regarding infrastructure, logistics of healthcare processes and especially the healthcare results.

In addition, the VICTIM Registry is expected to constitute a continuous field of training in several research areas, such as cardiovascular biomedicine, outcomes research and health services, for post-graduate and graduate students, to aid in the scientific qualification and formation of researchers in the health sciences area.

Author contributions

Conception and design of the research: Oliveira JC, Oliveira LCS, Oliveira JC, Barreto IDC, Arcelino LAM, Prado LFA, Silveira FS, Nascimento TA, Ferreira EJP, Barreto RV, Moraes EV, Mendonça JT, Sousa ACS, Barreto-Filho JA. Acquisition of data: Oliveira JC, Oliveira LCS, Oliveira JC, Lima TCRM, Arcelino LAM, Barreto-Filho JA. Analysis and interpretation of the data: Oliveira JC, Oliveira LCS, Oliveira JC, Barreto IDC, Almeida-Santos MA, Lima TCRM, Arcelino LAM, Sousa ACS, Barreto-Filho JA. Statistical analysis: Oliveira JC, Oliveira LCS, Barreto IDC, Almeida-Santos MA, Barreto-Filho JA. Obtaining financing: Oliveira JC, Oliveira LCS, Oliveira JC, Barreto-Filho JA. Writing of the manuscript: Oliveira JC, Oliveira LCS, Oliveira JC, Arcelino LAM, Barreto-Filho JA. Critical revision of the manuscript for intellectual content: Oliveira JC, Oliveira LCS, Oliveira JC, Barreto IDC, Almeida-Santos MA, Lima TCRM, Arcelino LAM, Prado LFA, Silveira FS, Nascimento TA, Ferreira EJP, Barreto RV, Moraes EV, Mendonça JT, Sousa ACS, Barreto-Filho JA. Supervision / as the major investigador: Barreto-Filho JA.

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 Doctoral submitted by Jussiely Cunha Oliveira, from Universidade Federal de Sergipe.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade Federal de Sergipe under the protocol number 483.749. 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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Annex A

Data collection tool

REGISTRATION

Control number: _____ Date of enrollment: ☐☐☐

Researcher's Name: _____

PATIENT IDENTIFICATION

Name: _____

Patient's registration number: _____

ID: _____ **Brazilian Social Security number:** _____

Birth date: ☐☐☐ Sex: ☐ F ☐ M

Age: ☐ Race: ☐ White ☐ Non white

Socioeconomic level* ☐ A ☐ B ☐ C ☐ D ☐ E ☐ NI Total household members: _____

Marital status: ☐ Married ☐ Divorced ☐ Single ☐ Widow ☐ Unmarried couple

Occupation: ☐ Self-employed ☐ Civil servent ☐ Private employee ☐ Retired ☐ Others: _____

Education: ☐ Elementary ☐ High school ☐ Upper level ☐ Post-graduation ☐ Never studied

Healthcare insurance: ☐ SUS ☐ IPES ☐ Private ☐ Health insurance

Which? _____

Address: _____

City: _____ State: _____

E-mail: _____ Telephone: ( ) _____

Zip Code: _____ ( ) _____

( ) _____

( ) _____

Additional Contacts

Name: _____

Degree of kinship: _____

City: _____

State: _____

Telephone: ( ) _____

( ) _____

( ) _____

( ) _____

Additional information:

Additional Contacts

Name: _____

Degree of kinship: _____

City: _____

State: _____

Telephone: ( ) _____

( ) _____

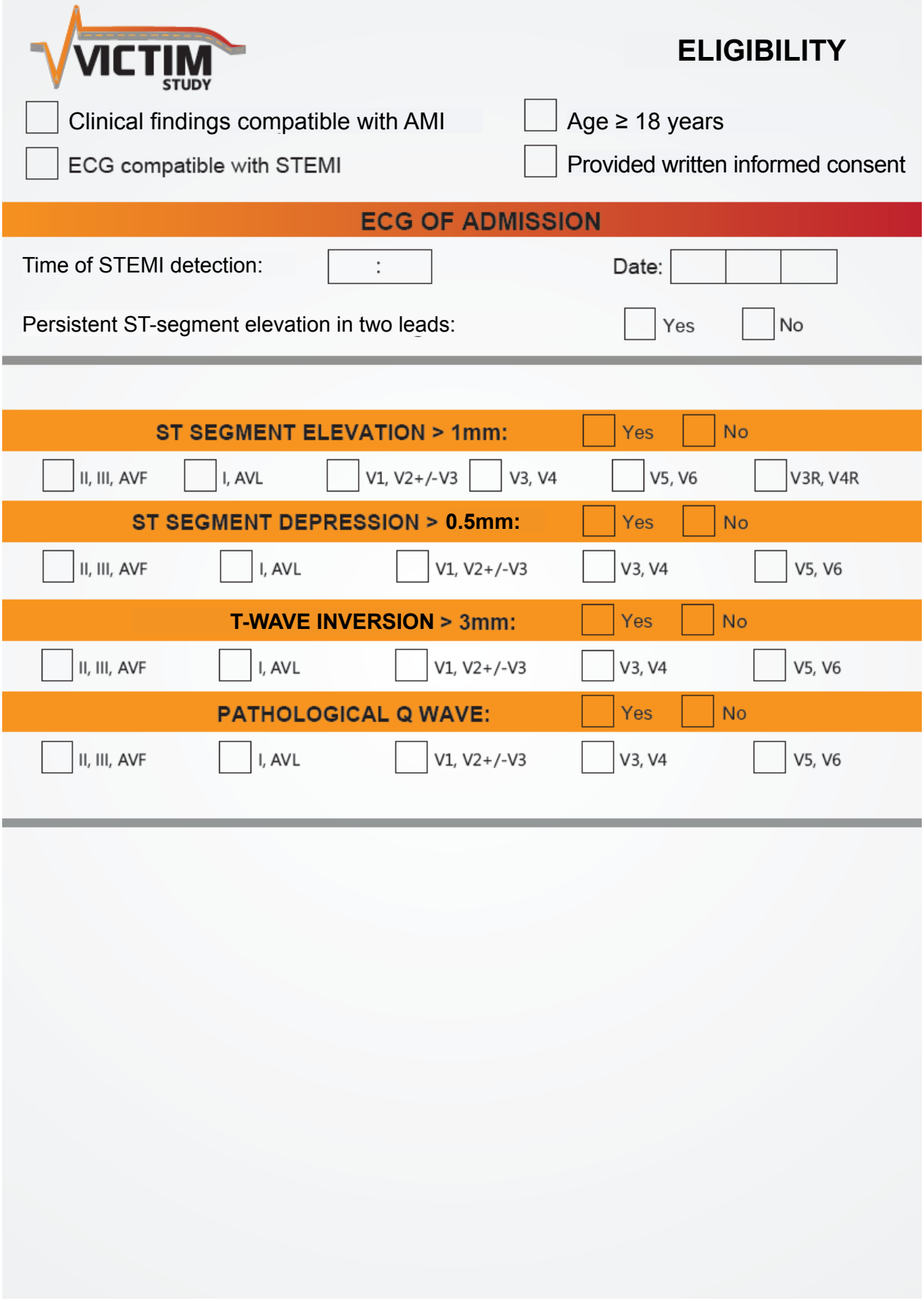
( ) _____

( ) _____

Additional information:

***Socioeconomic level:**

A: income > 20 minimum wages
B: 10-20 minimum wages
C: 4-10 minimum wages
D: 2-4 minimum wages
E: <2 minimum wages
NI: not informed


VICTIM STUDY
ELIGIBILITY
Clinical findings compatible with AMI
ECG compatible with STEMI
Age ≥ 18 years
Provided written informed consent
ECG OF ADMISSION
Time of STEMI detection: :
Date:
Persistent ST-segment elevation in two leads: Yes No
ST SEGMENT ELEVATION > 1mm: Yes No
II, III, AVF I, AVL V1, V2+/-V3 V3, V4 V5, V6 V3R, V4R
ST SEGMENT DEPRESSION > 0.5mm: Yes No
II, III, AVF I, AVL V1, V2+/-V3 V3, V4 V5, V6
T-WAVE INVERSION > 3mm: Yes No
II, III, AVF I, AVL V1, V2+/-V3 V3, V4 V5, V6
PATHOLOGICAL Q WAVE: Yes No
II, III, AVF I, AVL V1, V2+/-V3 V3, V4 V5, V6

VICTIM STUDY

TIMELINES

SYMPTOM ONSET

Date: ___ ___ ___ Address at the time of symptom onset: _____

Hour: ___ : ___ h City: _____ State: _____

DECISION TO CALL TRANSPORTATION

Date: ___ ___ ___ Address at the time transportation was requested: _____

Hour: ___ : ___ h ☐ Mobile emergency medical service ☐ Own transportation ☐ Other

ARRIVAL AT THE 1st HOSPITAL WITHOUT PCI

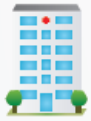
Date: ___ ___ ___

Hour: ___ : ___ h Which? _____

ARRIVAL AT THE 2nd HOSPITAL WITHOUT PCI

Date: ___ ___ ___

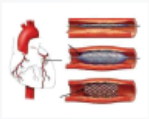
Hour: ___ : ___ h Which? _____



ARRIVAL AT THE 3rd HOSPITAL WITHOUT PCI

Date ___ ___ ___

Hour: ___ : ___ h Which? _____



ARRIVAL AT THE HOSPITAL WITH PCI

Date: ___ ___ ___

Hour: ___ : ___ h Which? _____

STEMI DETECTION: Date: ___ ___ ___ Hour: ___ : ___ h Where? _____

DOOR-BALLOON Date ___ ___ ___ Hour: ___ : ___ h Hospital: _____ ΔDoor-balloon: _____

FIBRINOLYSIS: ☐ Yes ☐ No Which? ☐ SK ☐ t-PA ☐ TNK

Date: ___ ___ ___ ΔT:

Hour: ___ : ___ h Place: _____

Cardiopulmonary arrest during transfer? ☐ Yes ☐ No Local: _____

***Hospitals:**

Hospital São Lucas - HSL
Hospital Primavera - HP
Hospital do Coração - H.Cor
Hospital de Cirurgia - HC
Hospital de Urgências de Sergipe - HUSE
Hospital Zona Norte - HZN
Hospital Zona Sul - HZS
Hospital Regional de Itabaiana - HRI

VICTIM STUDY

CLINICAL PRESENTATION

PRODROMAL SYMPTOMS FOR MORE THAN 24H FROM THE MAJOR FINDING

☐ No ☐ Yes ☐ 24-72 h ☐ >72h - 1 week ☐ >1 week - 30 days

☐ Chest Pain ☐ GI/Indigestion ☐ Dyspnea ☐ Others

PRESENTATION SYMPTOMS ☐ Yes ☐ No

☐ Typical anginal chest pain/epigastric pain
☐ Atypical chest pain
☐ Sweating
☐ Pre-syncope/ syncope
☐ Dyspnea
☐ Nausea/vomiting
☐ Fatigue/ Asthenia
☐ Palpitations
☐ Others: _____

INFARCTION TRIGGERS ☐ Yes ☐ No

☐ Strenuous physical exertion 2h before symptom onset
☐ Sexual intercourse 2 hours before symptom onset
☐ Cocaine or other illicit drug use within the previous 24h _____
☐ Infection in the past 10 days: _____
☐ Severe emotional stress within the previous 24h
☐ Alcohol use within the previous 24h
☐ Copious meal (last meal)

PREVIOUS PATHOLOGICAL HISTORY AND CARDIOVASCULAR RISK FACTORS

Current smoker: ☐ Yes ☐ No

Ex-smoker: ☐ Yes ☐ No ☐ Stopped how long ago? : _____

Systemic arterial hypertension: ☐ Yes ☐ No

Diabetes Mellitus: ☐ Yes ☐ No Treatment ☐ Diet ☐ Medicament ☐ Insulin

Dyslipidemia: ☐ Yes ☐ No

Family history of early CAD / male<55 and female<65: : ☐ Yes ☐ No

Congestive heart failure: ☐ Yes ☐ No

Angina pectoris: ☐ Yes ☐ No

Previous CAD (>50%): ☐ Yes ☐ No

Previous AMI: ☐ Yes ☐ No How long ago?_____

Previous PCI: ☐ Yes ☐ No

Previous CABG: ☐ Yes ☐ No

Previous stroke or TIA: ☐ Yes ☐ No

Peripheral vascular disease: ☐ Yes ☐ No

Chronic kidney disease: ☐ Yes ☐ No

Renal replacement theraphy (dialysis): ☐ Yes ☐ No ☐ Hemodialysis ☐ Peritoneal dialysis

PREVIOUS DRUG THERAPY ☐ Yes ☐ No

Aspirin:	☐ Yes	☐ No	*DOSAGE: _____
Clopidogrel:	☐ Yes	☐ No	DOSAGE: _____
Prasugrel:	☐ Yes	☐ No	DOSAGE: _____
Ticagrelor:	☐ Yes	☐ No	DOSAGE: _____
Beta-blocker	☐ Yes	☐ No	DOSAGE: _____
ACE inhibitor:	☐ Yes	☐ No	DOSAGE _____
ARB:	☐ Yes	☐ No	DOSAGE: _____
Statin:	☐ Yes	☐ No	DOSAGE: _____
Calcium-channel blocker	☐ Yes	☐ No	DOSAGE: _____
Nitrates:	☐ Yes	☐ No	DOSAGE _____
Diuretics:	☐ Yes	☐ No	DOSAGE _____
Aldosterone Antagonist:	☐ Yes	☐ No	DOSAGE: _____
Insulin:	☐ Yes	☐ No	DOSAGE: _____
Others:	☐ Yes	☐ No	

*DOSAGE: Amount of prescription drug in 24 hours

If yes, which? _____

PHYSICAL EXAMINATION OF ADMISSION

BP: _____ X _____ mm Hg | **HR.:** _____ bpm | **WEIGHT** kg _____ | **HEIGHT:** _____ cm

HEMOGLOBIN: _____ g/dl | **HEMATOCRIT:** _____ % | **LEUKOCYTES:** _____

CREATININE: _____ | **GLYCEMIA:** _____ mg/dl | **KILLIP:** ☐ I ☐ II ☐ III ☐ IV

GRACE SCORE: _____ In-hospital (Age, HR, systolic blood pressure, creatinine, KILLIP)

BIOMARKERS OF ADMISSION

High CK-MB: ☐ Yes ☐ No Highest value: _____

High TpN +: ☐ Yes ☐ No Highest value: _____

VICTIM STUDY

HOSPITALIZATION

DRUG THERAPY IN THE FIRST 24 HOURS ☐ Yes ☐ No

Aspirin:	☐ Yes	☐ No	*DOSAGE: _____	Eligible:	☐ Yes	☐ No
Clopidogrel:	☐ Yes	☐ No	DOSAGE: _____	Eligible:	☐ Yes	☐ No
Prasugrel:	☐ Yes	☐ No	DOSAGE: _____	Eligible:	☐ Yes	☐ No
Ticagrelor:	☐ Yes	☐ No	DOSAGE: _____	Eligible:	☐ Yes	☐ No
Beta-blocker:	☐ Yes	☐ No	DOSAGE: _____	Eligible:	☐ Yes	☐ No
ACE inhibitor:	☐ Yes	☐ No	DOSAGE: _____	Eligible:	☐ Yes	☐ No
ARB:	☐ Yes	☐ No	DOSAGE: _____	Eligible:	☐ Yes	☐ No
Statin:	☐ Yes	☐ No	DOSAGE: _____	Eligible:	☐ Yes	☐ No
Calcium-channel blocker:	☐ Yes	☐ No	DOSAGE: _____	Eligible:	☐ Yes	☐ No
Nitrates:	☐ Yes	☐ No	DOSAGE: _____	Eligible:	☐ Yes	☐ No
Diuretics:	☐ Yes	☐ No	DOSAGE: _____	Eligible:	☐ Yes	☐ No
Aldosterone antagonist:	☐ Yes	☐ No	DOSAGE: _____	Eligible:	☐ Yes	☐ No
Insulin:	☐ Yes	☐ No	DOSAGE: _____			
Low-molecular-weight heparin:	☐ Yes	☐ No	DOSAGE: _____			
Conventional heparin:	☐ Yes	☐ No	DOSAGE: _____			
Others:	☐ Yes	☐ No				

*DOSAGE: Amount of prescription drug in 24 hours

If yes, which? _____

IN-HOSPITAL TESTS ☐ Yes ☐ No

ECHOCARDIOGRAPHY Date: ☐☐☐

EF:_____ %

Simpson: ☐ Yes ☐ No

LA:_____ cm

LA volume: _____

Segment deficit: ☐ Yes ☐ No

Anterior ☐ Inferior ☐

Lateral ☐ Septal ☐

Posterior ☐

FIRST CORONARY ANGIOGRAPHY ☐ Yes ☐ No

Date: ☐☐/☐☐/☐☐ Hour: ☐☐:☐☐ h Hospital: _____ Cath number: _____

Access: ☐ Femoral ☐ Radial ☐ Other: _____

RESULT OF CORONARY ANGIOGRAPHY

	LCA	AD	Dg	Cx	Mg	PD-Cx	RC	PD-RC
Lesion severity								
Culprit artery								

*Normal angioplasty = 0%; LCA: Left main coronary artery; AD: Anterior descending artery; Dg: Diagonal artery; Cx: Circumflex artery; Mg: Marginal artery; PD-Cx: Posterior descending-Circumflex artery; RC: Right coronary artery; PD-RC: Posterior descending-Right coronary artery.

PATHOLOGICAL SEARCH OF GUILTY ARTERY ☐ Yes ☐ No

Finding ☐ Thrombus ☐ Spasm ☐ Embolism ☐ Myocardial bridging ☐ Dissection

PRIMARY PCI: ☐ Yes ☐ No

Less than 12 hours: ☐ Yes ☐ No Date: ☐☐/☐☐/☐☐ Hour: ☐☐:☐☐ h Hospital: _____

Access: ☐ Femoral ☐ Radial ☐ Other: _____

Artery	Obstruction %	Number of stents	Conventional stent	Drug-eluting stent
LCA				
AD				
Dg				
Cx				
Mg				
PD-Cx				
RC				
PD-RC				
Other				

Angiographic success ☐ Yes ☐ No

ADJUVANT PHARMACOTHERAPY

Bivalirudin: ☐ Yes ☐ No DOSAGE: _____

GPIIb/IIIa inhibitors ☐ Yes ☐ No DOSAGE: _____

NON-PRIMARY PCI ☐ Yes ☐ No

Date: ☐☐☐ Hour: : h Hospital:_____ _____

Access: ☐ Femoral ☐ Radial ☐ Other: _____

Artery	Obstruction %	Number of stents	Conventional stent	Drug-eluting stent
LCA				
AD				
Dg				
Cx				
Mg				
PD-Cx				
RC				
PD-RC				
Other				

Angiographic success ☐ yes ☐ No

CORONARY ARTERY BYPASS GRAFTING ☐ Yes ☐ No

Date: ☐☐☐ Hospital: _____

Left internal mammary artery: ☐ Yes ☐ No

Right internal mammary artery: ☐ Yes ☐ No

Radial: ☐ Yes ☐ No

Number of saphenous vein grafts: _____

Complete CABG: ☐ Yes ☐ No

Cardiopulmonary bypass: ☐ Yes ☐ No

VICTIM STUDY

OUTCOMES

IN-HOSPITAL OUTCOMES

☐ Yes ☐ No

CARDIOVASCULAR DEATH: ☐ Yes ☐ No Date: ☐☐/☐☐/☐☐

NON-CARDIOVASCULAR DEATH: ☐ Yes ☐ No Date: ☐☐/☐☐/☐☐

CARDIOGENIC SHOCK: ☐ Yes ☐ No Date: ☐☐/☐☐/☐☐

REINFARCTION: ☐ Yes ☐ No Date: ☐☐/☐☐/☐☐

POST-AMI ANGINA: ☐ Yes ☐ No Date: ☐☐/☐☐/☐☐

HEART FAILURE: ☐ Yes ☐ No Date: ☐☐/☐☐/☐☐

STROKE: ☐ Yes ☐ No Date: ☐☐/☐☐/☐☐

CARDIAC ARREST: ☐ Yes ☐ No Date: ☐☐/☐☐/☐☐

HEMORRHAGE: ☐ Yes ☐ No

- Lowest hemoglobin recorded _____ Date ☐☐/☐☐/☐☐
- Lowest hematocrit recorded _____ Date: ☐☐/☐☐/☐☐
- Eye hemorrhage: ☐ Yes ☐ No Date ☐☐/☐☐/☐☐
- Puncture site-related hemorrhage ☐ Yes ☐ No Data: ☐☐/☐☐/☐☐
- Brain hemorrhage: ☐ Yes ☐ No Date: ☐☐/☐☐/☐☐
- Fatal hemorrhage: ☐ Yes ☐ No Date: ☐☐/☐☐/☐☐
- Blood transfusion: ☐ Yes ☐ No Date: ☐☐/☐☐/☐☐

If yes, how many blood bags? _____

DIAGNOSTIC OUTCOME

In the medical record, the diagnosis of STEMI was maintained: ☐ Yes ☐ No

If not, what was the final diagnosis? _____

Does the medical record have any post-infarction dietary/nutritional instruction? ☐ Yes ☐ No

If yes, who recorded the instruction? ☐ Nutricionist ☐ Doctor ☐ Nurse ☐ Others: _____

Does the medical record have any instruction on post-infarction cardiac rehabilitation?

☐ Yes ☐ No

If yes, who recorded the instruction? ☐ Doctor ☐ Physiotherapist ☐ Physical trainer ☐ Others: _____

HOSPITAL DISCHARGE

Date: ☐☐/☐☐/☐☐ Hour: ☐☐:☐☐ h

DISCHARGE MEDICATION

Aspirin:	☐ Yes	☐ No	DOSAGE: _____	Eligible:	☐ Yes	☐ No
Clopidogrel:	☐ Yes	☐ No	DOSAGE: _____	Eligible:	☐ Yes	☐ No
Prasugrel:	☐ Yes	☐ No	DOSAGE: _____	Eligible:	☐ Yes	☐ No
Ticagrelor:	☐ Yes	☐ No	DOSAGE: _____	Eligible:	☐ Yes	☐ No
Beta-blocker:	☐ Yes	☐ No	DOSAGE: _____	Eligible:	☐ Yes	☐ No
ACE inhibitor:	☐ Yes	☐ No	DOSAGE: _____	Eligible:	☐ Yes	☐ No
ARB:	☐ Yes	☐ No	DOSAGE: _____	Eligible:	☐ Yes	☐ No
Statin:	☐ Yes	☐ No	DOSAGE: _____	Eligible:	☐ Yes	☐ No
Aldosterone antagonist:	☐ Yes	☐ No	DOSAGE: _____	Eligible:	☐ Yes	☐ No
Calcium-channel blocker:	☐ Yes	☐ No	DOSAGE: _____			
Nitrates:	☐ Yes	☐ No	DOSAGE: _____			
Diuretics:	☐ Yes	☐ No	DOSAGE: _____			
Insulin:	☐ Yes	☐ No	DOSAGE: _____			
Others:	☐ Yes	☐ No				

*DOSAGE: Amount of prescription drug in 24 hours

If yes, which? _____

OUTCOMES 30 DAYS AFTER STEMI

Contact after 30 days?	☐ Yes	☐ No	If not, what reason? _____	
CARDIOVASCULAR DEATH:	☐ Yes	☐ No	Date: ☐☐☐	
NON-CARDIOVASCULAR DEATH:	☐ Yes	☐ No	Date: ☐☐☐	
REINFARCTION:	☐ Yes	☐ No	Date: ☐☐☐	
POST-AMI ANGINA:	☐ Yes	☐ No	Date: ☐☐☐	
HEART FAILURE/SHOCK:	☐ Yes	☐ No	Date: ☐☐☐	
STROKE:	☐ Yes	☐ No	Date: ☐☐☐	
CARDIAC ARREST:	☐ Yes	☐ No	Date: ☐☐☐	
NEW CORONARY ANGIOGRAPHY:	☐ Yes	☐ No	Date: ☐☐☐	
HEMORRHAGE:	☐ Yes	☐ No	Date: ☐☐☐	Where? _____
REHOSPITALIZATION:	☐ Yes	☐ No	Date: ☐☐☐	Reason? _____ Hospital? _____
Post-discharge consultation?	☐ Yes	☐ No	Date: ☐☐☐	Where? _____
If not, is it scheduled?	☐ Yes	☐ No	Date: ☐☐☐	

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ORIGINAL ARTICLE

Carotid Atherosclerosis in Pre- and Post-Menopausal Women with a History of Pregnancy-Induced Hypertension: Case-Control Study

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Abstract

Background: Cardiovascular disease mortality among women remains high. Observational studies are controversial about the participation of a history of gestational hypertensive disorder in cardiovascular risk.

Objective: To verify the association between carotid atherosclerosis in menopausal women who had pregnancy-induced hypertension.

Methods: Case-control study, with cases consisting of women with carotid atherosclerosis, defined as carotid intima-media thickness > 1 mm and/or presence of carotid plaques; the controls did not have these alterations. The significance level was set at 95%.

Results: A total of 504 women without previous cardiovascular disease were assessed, 126 cases and 378 controls. Of the total, 67% were hypertensive; 76% were dyslipidemic; and 16% were diabetic. Approximately 10% reported a history of hypertension during pregnancy. Women with carotid atherosclerosis had higher values of systolic blood pressure (134.18 mmHg vs. 128.59 mmHg, p = 0.008) and LDL-cholesterol (156.52 mg% vs. 139.97 mg%; p = 0.0005). No statistical difference was found regarding the presence of carotid atherosclerosis and history of hypertension during pregnancy (OR 1.672, 95% CI: 0.883-3.131).

Conclusion: The history of hypertension during pregnancy was not associated with subclinical carotid atherosclerosis in menopausal women. However, an association was observed between carotid atherosclerosis and classic risk factors, such as elevated systolic blood pressure and LDL-cholesterol levels. (Int J Cardiovasc Sci. 2018;31(4)359-366)

Keywords: Carotid Artery Diseases/physiopathology; Hypertension, Pregnancy-Induced; Women, Premenopause; Postmenopause; Case-Control Studies.

Introduction

Cardiovascular diseases (CVD) are the leading cause of death among women worldwide.[1,2] In the United States, they account for almost a third of all causes of death in the female gender,[3,4] and similar data are observed in Europe[5] and in Brazil.[6] Advances in CVD treatment in the last three decades have allowed a sustained decrease in mortality. However, socioeconomic and behavioral aspects have interrupted this process in recent years.[7] In 2014, there were 340,284 CVD deaths among Brazilian women, representing an increase of almost 20% in relation to those occurring 10 years earlier.[6] The cardiovascular risk stratification in the female population has failed to detect and prevent the disease. The exploration of new risk factors thus becomes essential to reduce such indices.

Pregnancy is an important moment to evaluate women's cardiovascular health, since the development of complications during this period may indicate an increase in future cardiovascular risk.[8] Several observational studies have shown a higher prevalence of atherosclerosis in women with a history of gestation-induced hypertension,[9-11] and some have observed an association between the number of cardiac events and

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the number of complicated pregnancies,[12] even after the normalization of blood pressure levels after childbirth.

Nonetheless, Romundstad et al.[13] questioned whether such an association would be a factor of ambiguity, because pre-gestational characteristics – especially obesity, hypertension and dyslipidemia – would attenuate the effect that the gestational hypertensive disorder has on the late cardiovascular outcome. Unfortunately, most studies have insufficient evidence, such as limited sample size and clinical follow-up.

Considering that atherosclerosis is a gradual process that starts in childhood, the aim of this study was to verify the association between carotid atherosclerosis in menopausal women who had pregnancy-induced hypertension.

Methods

A case-control study was carried out, with a population of women aged between 45 and 65 years, who had had menstrual irregularities or interruption in the last year. Women receiving hormone replacement therapy, those with chronic inflammatory conditions or any previously diagnosed conditions with high cardiovascular risk or heart disease were excluded from the analysis.

The sample was calculated based on the systematic review performed by Brown et al.,[14] using as reference a hypertension exposure during pregnancy of around 8% and Odds Ratio (OR) to increase the risk of atherosclerosis of 2.28. For a paired study with a one-tailed hypothesis test, we calculated at least 116 cases and 348 controls in order to obtain a 95% level of significance and 80% of test power with a ratio of one case for three controls. Controls were obtained from the same database, and were paired by age group.

All women underwent carotid ultrasound with the same examiner; the carotid intima-media thickness (CIMT) was quantified and the presence of carotid plaques was assessed. For image acquisition, a high-resolution device (EnVisor, Philips) was used with a 12.3 MHz linear transducer. The data were recorded for subsequent analysis using the QLAB-Intima Media Thickness (QLAB-IMT, Philips) software.

The presence of carotid atherosclerosis was defined when the CIMT was greater than 1 mm (mean values obtained in the analyzed segments of the right and left carotid arteries) and / or the presence of atheroma plaque. Atheroma plaque was defined as: (1) localized parietal structure with a thickness greater than 1.5 mm; (2) protrusion into vessel lumen > 0.5 mm or; (3) thickness > 1.5-fold the adjacent CIMT, according to the Mannheim Carotid Intima-Media Thickness and Plaque Consensus.[15]

The cases consisted of women who had carotid atherosclerosis and the controls, of women who did not have this alteration at the ultrasonographic assessment.

The independent variable was pregnancy-induced hypertension, considered as the self-reported information of blood pressure increase during pregnancy. According to Diehl et al.,[16] this information shows good accuracy (specificity of 96% and sensitivity of 79.6%) for the antecedents of pregnancy-induced hypertension, even 24.5 years after the pregnancy. Other variables were considered, namely: blood pressure, income, smoking, type 2 diabetes mellitus, family history of coronary artery disease (CAD), body mass index (BMI), number of pregnancies, preterm birth, low birth-weight offspring, fasting glycemia, total cholesterol (CT), high-density lipoprotein cholesterol (HDL-cholesterol), low-density lipoprotein cholesterol (LDL-cholesterol), triglycerides and ultrasensitive C-reactive protein (us-CRP).

The study was approved by the Research Ethics Committee of *Complexo Hospitalar Hospital Universitário Oswaldo Cruz/ Pronto-Socorro Cardiológico de Pernambuco* under CAAE number 55361416.0.0000.5192 and Opinion number 1,593,189 of June 16, 2016.

Statistical analysis

The results were expressed as percentages for categorical variables and as statistical measures such as means, standard deviation and medians, when indicated, for numerical variables. The association between the occurrence of carotid atherosclerosis and the categorical variables was performed using Pearson's chi-square test, whereas the non-paired Student's *t* test was used to compare carotid atherosclerosis in relation to numerical variables. Cox regression analysis was performed to evaluate the influence of covariates on carotid atherosclerosis development in the menopausal period. The strength of the association between the categorical variables was evaluated using the odds ratio (OR) with the respective confidence interval. The normality hypothesis verification was performed using the Kolmogorov-Smirnov test. The level of significance used in the statistical test decisions was 5% and the intervals had 95% of confidence. The Statistical Package for the Social Sciences (SPSS) version 21 was the statistical program used for the statistical calculations.

Results

A total of 504 women were studied, of which 126 had carotid atherosclerosis and 378 did not. The groups did not differ regarding age, ethnicity, marital status and literacy (Table 1). There was also no difference regarding the number of pregnancies, preterm birth and low birth-weight offspring (Table 2).

Carotid atherosclerosis showed a higher association with systemic arterial hypertension (OR 1.837, 95% CI 1.154-2.925, p = 0.01) and dyslipidemia (OR 1.971, 95% CI, 1.149-3.380, p = 0.01). There was a tendency to a higher prevalence of carotid atherosclerosis in women with metabolic syndrome (OR 1.442, 95% CI, 0.957-2.172, p = 0.08). Carotid atherosclerosis was also directly associated with higher systolic blood pressure (134.18 mmHg vs. 128.59 mmHg, p < 0.01), LDL-cholesterol (156.52 mg% vs. 139.97 mg%, p < 0.01) and TC levels (229.68 mg% vs. 214.31 mg%, p < 0.01). There was no difference in relation to diastolic blood pressure, BMI, waist circumference, hip circumference, glycemia, HDL-cholesterol, triglycerides or CRP levels (Tables 3 and 4).

Approximately 10% of the sample had a history of pregnancy-induced hypertension. No statistically significant difference was observed between carotid atherosclerosis in the menopausal period and history of pregnancy-induced hypertension (OR 1.631, 95% CI: 0.874-3.042, p = 0.12). When analyzing only the women with a history of pregnancy-induced hypertension and those with systemic arterial hypertension in the menopausal period, no statistical difference was observed either (OR 1.862, 95% CI: 0.955-3.628, p = 0.07).

When the mean CIMT was evaluated, no statistical association was observed with the history of pregnancy-induced hypertension (0.8516 ± 0.1491 vs. 0.8101 ± 0.1441,

Table 1 - Comparison of sociodemographic characteristics with carotid atherosclerosis in menopausal women

Characteristics	Total (504) n (%)	Carotid atherosclerosis		p value*
		No (378) n (%)	Yes (126) n (%)	
Age, years				
45-50	86 (17.1)	67 (17.7)	19 (15.1)	0.585
51-55	122 (24.2)	89 (23.5)	33 (26.2)	0.550
56-60	169 (33.5)	132 (34.9)	37 (29.4)	0.277
61-65	127 (25.2)	90 (23.8)	37 (29.4)	0.236
Ethnicity				
White	149 (29.6)	115 (30.4)	34 (27)	0.500
Black	83 (16.5)	65 (17.2)	18 (14.3)	0.491
Asian	8 (1.6)	6 (1.6)	2 (1.6)	1.000
Mixed-race	252 (50)	182 (48.1)	70 (55.6)	0.181
Native Brazilian	4 (0.8)	3 (0.8)	1 (0.8)	1.000
Marital status				
Single	216 (42.9)	158 (41.8)	58 (46)	0.408
Married	288 (57.1)	220 (58.2)	68 (54)	0.408
Literate				
No	76 (15.1)	56 (14.8)	20 (15.9)	0.775
Yes	428 (84.9)	322 (85.2)	106 (84.1)	0.775

** Chi-square test.*

Table 2 - Comparison of pregnancy-related characteristics with carotid atherosclerosis in menopausal women

Characteristics	Total (504) n (%)	Carotid atherosclerosis		p value*
		No (378) n (%)	Yes (126) n (%)	
Number of pregnancies				
None	38 (7.5)	27 (7.1)	11 (8.7)	0.561
One	42 (9)	36 (10.2)	6 (5.2)	0.132
Two	112 (24)	82 (23.3)	30 (26.1)	0.530
Three	114 (24.4)	86 (24.4)	28 (24.3)	1.000
Four	67 (14.3)	50 (14.2)	17 (14.8)	0.879
Five	41 (8.8)	29 (8.2)	12 (10.4)	0.453
Six	32 (6.9)	22 (6.3)	10 (8.7)	0.396
Pregnancy-induced hypertension				
No	454 (90.1)	345 (91.3)	109 (86.5)	0.124
Yes	50 (9.9)	33 (8.7)	17 (13.5)	0.124
Low birth-weight newborn				
No	475 (94.2)	358 (94.7)	117 (92.9)	0.507
Yes	29 (5.8)	20 (5.3)	9 (7.1)	0.507
Preterm birth				
No	454 (90.1)	340 (89.9)	114 (90.5)	1.000
Yes	50 (9.9)	38 (10.1)	12 (9.5)	1.000

** Teste do qui quadrado.*

p = 0.06). Also, no statistical difference was observed when only the presence of carotid plaques was compared with a history of pregnancy-induced hypertension (OR 1,332, 95% CI: 0.668-2.655, p = 0.41).

In the logistic regression model, only systemic arterial hypertension (B = 0.108, p = 0.01) and dyslipidemia (B = 0.122, p = 0.01) showed statistical significance with carotid atherosclerosis in the menopausal period (Table 5).

Discussion

In our study, carotid atherosclerosis was associated with systemic arterial hypertension and dyslipidemia, but not with a history of pregnancy-induced hypertension, although the CIMT and the presence of carotid plaques were analyzed separately. These results indicate that pregnancy-induced hypertension is not associated with subclinical atherosclerosis.

Increased CIMT and the presence of carotid plaques have been described as independent cardiovascular risk predictors.[17-20] However, most studies attempting to associate a history of pregnancy-induced hypertension and carotid atherosclerosis are conflicting, since they did not use standardized CIMT and carotid plaque measurements.

Our data add information to the literature due to the large number of assessed patients. All ultrasonographic assessments were performed by the same examiner, blinded for the variable history of pregnancy-induced hypertension, eliminating measurement bias. The latest recommendations for CIMT and carotid plaque measurements were followed.[15]

The physiological behavior of CIMT was described by Akhter et al.,[21] who, after analyzing 57 healthy women, showed that CIMT remains practically stable during pregnancy, but decreases one year after delivery. Blaauw

Table 3 - Comparison of clinical characteristics, life habits and family history with carotid atherosclerosis in menopausal women

Classic risk factors	Total (504) n (%)	Carotid atherosclerosis		p value*
		No (378) n (%)	Yes (126) n (%)	
Systemic arterial hypertension	341 (67.7)	244 (64.6)	97 (77)	0.011
Diabetes mellitus	84 (16.7)	61 (16.1)	23 (18.3)	0.583
Dyslipidemia	387 (76.8)	280 (74.1)	107 (84.9)	0.014
BMI – obesity	166 (32.9)	122 (32.3)	44 (34.9)	0.586
Central obesity	481 (95.4)	366 (96.8)	115 (91.3)	0.014
Metabolic syndrome	270 (53.6)	194 (51.3)	76 (60.3)	0.081
Sedentary life style	146 (29)	105 (27.8)	41 (32.5)	0.310
Consumption of ≥ 5 servings of fruit/day	133 (26.4)	99 (26.2)	34 (27)	0.907
Passive smoking < 6 months	398 (79)	300 (79.4)	98 (77.8)	0.706
Family history of CAD	85 (16.9)	60 (15.9)	25 (19.8)	0.336

** Test of the chi square. BMI: body mass index; CAD: coronary artery disease.*

Table 4 - Comparison of classic cardiovascular risk factors with carotid atherosclerosis in menopausal women

Dependent variables	Total	Carotid atherosclerosis		p value*
		No	Yes	
Age	56.23 (± 5.40)	56.25 (± 5.334)	56.63 (± 5.089)	0.477
SBP	130.40 (± 20.29)	128.59 (± 19.87)	134.18 (± 21.54)	0.008
DBP	84.03 (± 11.51)	83.30 (± 11.30)	84.50 (± 13.07)	0.322
BMI	28.45 (± 5.05)	28.29 (± 4.94)	28.79 (± 5.07)	0.328
Abdominal circumference	92.11 (± 11.51)	91.73 (± 11.29)	91.82 (± 11.34)	0.945
Brachial circumference	28.72 (± 4.47)	28.73 (± 4.58)	28.56 (± 4.57)	0.714
Hip circumference	103.11 (± 12.06)	103.09 (11.86)	102.39 (± 12.18)	0.571
Glycemia	102.41 (± 42.16)	100.00 (± 36.03)	107.72 (± 48.67)	0.060
Total cholesterol	219.43 (± 43.42)	214.31 (± 42.48)	229.68 (± 47.44)	0.001
HDL-cholesterol	51.80 (± 11.11)	52.36 (± 11.02)	51.91 (± 12.39)	0.709
LDL-cholesterol	143.85 (± 40.84)	139.97 (± 40.38)	156.52 (± 42.59)	0.0005
Triglycerides	141.46 (± 81.19)	134.26 (± 74.68)	149.41 (± 85.32)	0.058
us-CRP	0.34 (± 0.54)	0.32 (± 0.52)	0.34 (± 0.47)	0.773

** Unpaired Student's t test. SBP: systemic blood pressure; DBP: diastolic blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein; us-CRP: ultra-sensitive C-reactive protein.*

Table 5 - Logistic regression of variables with p < 0.20 in the univariate analysis with carotid atherosclerosis

Variables	B	p value*
LDL	0.002	0.0005
Glycemia	0.001	0.0005
Diastolic blood pressure	- 0.006	0.003
Systolic blood pressure	0.005	0.002

LDL: low-density lipoprotein-cholesterol.

et al.[22] believe that the effects of pregnancy, mediated by metabolic and immunological responses, could take up to more than one year to return to basal levels.

When comparing the CIMT of women who developed hypertension during pregnancy and those who had uneventful pregnancies, the literature data show to be similar to those found in our study. Akhter et al.[23] did not detect a statistically significant difference during pregnancy and up to one year postpartum when evaluating 55 women. Blaauw et al.[22] also found no differences 5 years after the pregnancy. Moreover, when women between 40 and 50 years of age were assessed, there was no statistical difference regarding CIMT between those who had hypertension during pregnancy and those with uneventful pregnancies.[24]

Nevertheless, several observational studies have shown an association between gestational hypertensive disorder and cardiovascular clinical outcomes. Haukkama et al.,[25] when assessing 141 women, identified an almost three-fold higher cardiovascular risk in those with a history of gestational hypertension disorder. In the study by Kessous et al.,[26] the previous history of gestational hypertensive disorder was associated with a greater number of hospitalizations secondary to atherosclerosis 11 years after the pregnancy complicated by hypertensive disorder, even after statistical adjustment for maternal age, parity, diabetes and obesity. Canoy et al.[27] identified in a large cohort that pregnancy-induced hypertension increased the risk of CVD in women in the menopausal period.

Similarly, studies with longer follow-up periods also showed an increase in severe cardiac complications in women with a history of pregnancy-induced hypertension. As verified by Arnadottir et al., women who had hypertensive complications during pregnancy had a higher risk of death due to ischemic heart disease and cerebrovascular diseases after 30 years, in addition to a shorter time of survival.[28]

One of the explanations for not finding an association between carotid atherosclerosis and a history of pregnancy-induced hypertension would be the method used to measure CIMT. That would be caused by the fact that CIMT measured in the common carotid artery would not be a good parameter for the determination of cardiovascular outcomes, as it estimates the total thickness of the intima and media layers. Some authors have shown that only the increase in the intima layer in association with the reduction in the media layer would be important to increase cardiovascular risk.[21,23,24] In our study, we did not analyze the measurements of the intima and media layers separately.

In agreement with the literature,[19,29] we have identified an association between carotid atherosclerosis and traditional cardiovascular risk factors, such as systemic arterial hypertension and hypercholesterolemia. A possible explanation is that both atherosclerosis and gestational hypertension share several common metabolic abnormalities, such as obesity, insulin resistance, dyslipidemia and hypertension itself, as well as the favoring of endothelial dysfunction.[30]

According to Brandão et al.,[31] endothelial dysfunction precedes the clinical manifestations of a gestation complicated by hypertension and, therefore, it would accelerate the atherogenic process.[32]

According to McDonald et al.,[33] the persistence of classic risk factors is the foundation of carotid atherosclerosis development, since even after two decades, women with a history of pregnancy-induced hypertension still had more cardiovascular risk factors than those with uncomplicated pregnancies. In our study, women with a history of pregnancy-induced hypertension had a higher prevalence of obesity and chronic hypertension (data not shown in the tables).

Although our population consists of outpatients from the public health care system, the sociodemographic characteristics did not differ from those of the general population. Moreover, it was not possible to evaluate information prior to the pregnancy, due to the proposal of the original study.

Conclusion

Carotid atherosclerosis was positively associated with some classic cardiovascular risk factors, such as increased systolic blood pressure and higher levels of LDL-cholesterol. A history of pregnancy-induced hypertension was not associated with carotid atherosclerosis in a group

of menopausal and asymptomatic women, from the cardiovascular point of view. More studies are needed to understand the atherosclerosis process in women with a history of pregnancy-induced hypertension.

Author contributions

Conception and design of the research: Gomes RAF, Barros IML. Acquisition of data: Gomes RAF, Barros IML. Analysis and interpretation of the data: Gomes RAF, Barros IML. Statistical analysis: Gomes RAF, Barros IML. Writing of the manuscript: Gomes RAF. Critical revision of the manuscript for intellectual content: Barros IML, Ferreira MNL, Costa LOBF.

Potential Conflict of Interest

This manuscript is part of the master of the Graduate Program in Health Sciences of the University of Pernambuco by Rafael Alessandro Ferreira.

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Study Association

This article is part of the thesis of master submitted by Rafael Alessandro Ferreira Gomes, from Universidade de Pernambuco.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Complexo Hospitalar Hospital Universitário Oswaldo Cruz/Pronto-Socorro Cardiológico de Pernambuco* under the protocol number 55361416.0.0000.5192 (CAAE) and number 1.593.189 of June 16, 2016. 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

Evaluation of Lipid Profile in Adolescents

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Abstract

Background: Atherosclerosis is a chronic, multifactorial and insidious disease that can begin in childhood and adolescence, and whose major consequences appear during adulthood. Serum levels of lipoproteins, such as LDL-c, total cholesterol (TC), HDL-c, and non-HDL-c can be used as a screening method for disease diagnosis. In Brazil, few studies have correlated the serum levels of those lipoproteins with age.

Objective: To evaluate the serum concentrations of TC, LDL-c, HDL-c, VLDL-c, non-HDL-c and triglycerides (TG) of adolescents aged 10 to 19 years in the municipality of Araucária, Paraná state.

Methods: Cross-sectional retrospective study, collecting the following data from 600 adolescents: age, sex and serum levels of TC, LDL-c, HDL-c and TG from June to December 2016. Data were analyzed using the SPSS software 2.0, with Mann-Whitney U test and Spearman coefficient of correlation to identify statistical significance ($p < 0.05$).

Results: The female sex showed higher serum levels of TC, TG and LDL-c than the male sex. The HDL-c levels were identical in both sexes, with 48% of desirable values and 52% of low values. This study identified a strong correlation between the lipids and association with the age group of 10 to 14 years.

Conclusion: Non-HDL-c showed stronger correlation with the other lipids (TG, LDL-c and TC) as compared to LDL-c, suggesting that non-HDL-c can be used as an effective complementary diagnostic method to assess the risks for atherosclerosis in adolescents. (Int J Cardiovasc Sci. 2018;31(4)367-373)

Keywords: Dyslipidemias/epidemiology; Adolescent; Lipoproteins; Hypercholesterolemia/epidemiology.

Introduction

Cardiovascular diseases (CVD) are the major cause of death of men and women worldwide.[1] In Brazil, according to the last 2013 Ministry of Health survey, of a total of 201,062,789 inhabitants, 678,556 of the deaths were related to the circulatory system.[2]

The risk factors for CVD are classified as modifiable and nonmodifiable. Some of the modifiable risk factors are sedentary lifestyle, smoking, obesity and dyslipidemia.[2] Some nonmodifiable risk factors are family history of CVD, age, sex and ethnicity.[3] Dyslipidemia has a great influence on the development of CVD, since an inadequate diet increases the concentration of low-density lipoprotein cholesterol (LDL-c) in blood vessels.[4,5] Such lipoproteins can adhere to the intimal layer of arteries, causing the formation of atheromatous plaques that lead to atherosclerosis.[6] This atherosclerotic process begins in childhood, before clinical symptoms can be perceived.[7] In the aorta, fatty streaks begin at the age of 3 years, while in the coronary arteries, 5 to 10 years later.[8] Over time, such fatty streaks form fatty plaques that can rupture, leading to different ischemic processes, such as acute myocardial infarction and stroke.[9]

The lipid profile is a panel of blood tests to assess the serum concentrations of lipoproteins, such as total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), LDL-c, very-low-density lipoprotein cholesterol (VLDL-c), non-HDL-c, and triglycerides (TG).[10]

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Knowing that dyslipidemia is associated with CVD, its diagnosis in adolescence can reduce the chances of future complications, because a change in lifestyle to healthier habits can be the best prevention.[11,12]

This study was aimed at assessing the lipid profile of adolescents of the municipality of Araucária, Paraná state. It collected data of 600 adolescents aged 10 to 19 years and compared them to those of studies conducted in other regions of Brazil.

Methods

This study was approved by the Ethics Committee in Research of the *Instituto Paranaense de Otorrinolaringologia* and is registered under the number 65932917.0.0000.5529, according to the Resolution 466/12 of the National Board of Health of the Ministry of Health, which regulates research with human beings. The results of 600 lipid profiles were collected from the Araucária Municipal Laboratory, which had been approved by the local coordinator, so that the study could begin even before approval by the Ethics Committee in Research.

This is a cross-sectional, retrospective study with convenience sampling of the lipid profile of 600 adolescents aged 10 to 19 years, through systematic random sampling, from July to December 2016. Tests with TG levels greater than 400 mg/dL were excluded. The samples were collected 5-mL tubes containing serum separating gel and particles to activate clotting, and were tested by enzymatic photometric assay (Abbott Architect c8000), using the direct precipitation method for HDL-c quantitation (Ultra HDL). To calculate VLDL-c, the TG level was divided by 5, and to calculate LDL-c, the Friedewald formula was used. The collected data were organized in Excel 2007 sheets and stratified as TC, LDL-c, HDL-c, non-HDL-c (sum of the lipoproteins without HDL), VLDL-c and TG, in addition to age and sex of the adolescents, being identified by codes and organized in tables and graphs.

Statistical analysis

The descriptive statistical analysis included percentage and median with respective interquartile range (IQR). Continuous variables were expressed as median and IQR, because they had no normal distribution, while categorical variables were expressed as percentages. Normality was assessed by use of the Kolmogorov-Smirnov test. The statistical analysis comprised Mann-Whitney U test and Spearman coefficient of correlation (S), using the SPSS software 2.0. The adopted significance level was 5% of probability and 95% confidence interval, and all tests were two-tailed.

Results

The lipid profiles of 600 adolescents aged 10 to 19 years from the Araucária Municipal Laboratory were assessed. Of the 600 adolescents, 322 (54%) were of the female sex and 278 (46%) were of the male sex. Table 1 shows the analyzed data, which, in 1.83% (n = 11) of the adolescents, it is suggested familial hypercholesterolemia.[10] Tables 2, 3 and 4 show the correlations between the lipids, where 1 means perfect positive correlation, that is, when one variable increases, the other increases at the same intensity, and -1 means perfect negative correlation, that is, when one variable increases, the other decreases at the same intensity.

When comparing between sexes, the female sex had a higher TC than that of the male sex (Figure 1A). Regarding non-HDL-c, the female sex had a median of 109 and IQR of 40.25, while the male sex had a median of 101 and IQR of 32.25, with no significant difference between them. In addition, in the non-stratified sample, positive correlations of non-HDL-c were found with TG, TC and VLDL-c as compared to LDL-c, and fewer negative correlations with HDL-c (Table 2).

In adolescents aged 10 to 14 years, more positive correlations of non-HDL-c with TG, TC and VLDL-c were found as compared to LDL-c, and some negative correlations of LDL-c, TC and non-HDL-c with age (Table 3). When comparing between sexes, only TG showed a difference (Figure 1B). Regarding sexes, in adolescents aged 15 to 19 years, the correlations showed the same trend of the other age group (Table 4), and the comparisons between sexes achieving significance for the LDL-c (Figure 1C) and TC (Figure 1D), while the other lipids showed no statistically significant variation.

Discussion

The study by Silva et al.[11] has reported desirable values of TC of 50%, similar to those found in the present study (49%), but different from the 37% reported by Araki et al.[13] This difference was observed in a study conducted in the city of Aracaju, Sergipe state, which has found a higher TC value in the female sex as compared to that in the male sex, a result that corroborates that found

Table 1 - Lipid profile of adolescents aged 10 to 19 years

GENERAL TABLE (n = 600; male = 278; female = 322)				
Values	**(%) n**	**(%) n**	**(%) n**	**(%) n**
Lipids	TC	HDL-c	LDL-c	TG
Desired	(72) 432	(48) 288	(77) 465	(70) 421
Increased	(28) 168	----------	(23)135	(30) 179
Low	----------	(52) 312	----------	----------
STRATIFICATION BETWEEN SEXES				
Values	**(%) n**	**(%) n**	**(%) n**	**(%) n**
FEMALE 54% n = 322				
Lipids	TC	HDL-c	LDL-c	TG
Desired	(69) 221	(48) 155	(75) 243	(67) 216
Increased	(31) 101	----------	(25) 79	(33) 106
Low	----------	(52) 167	----------	----------
MALE 46% n = 278				
Lipids	TC	HDL-c	LDL-c	TG
Desired	(76) 211	(48) 133	(80) 222	(74) 205
Increased	(24) 67	----------	(20) 56	(26) 73
Low	----------	(52) 145	----------	----------

Values according to the 2017 Brazilian Guideline on Dyslipidemia and Atherosclerosis Prevention.[10] TC: total cholesterol; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; TG: triglycerides; n: absolute number of individuals.

in this study and in the specialized literature. Similar results have also been reported by Silva et al.[14] in a study conducted in the city of Janeiro, and by Araki et al.[15] in a study conducted in the city of Aracaju, Sergipe state, and by Kruger et al.[16] in a study conducted in the municipality of Mamboré, Paraná state.[16]

The serum levels of TG in adolescents aged 10 to 14 years were higher in the female sex, which has been also reported by Silva et al.[14] and Kruger et al.[16]

Regarding LDL-c, the findings are similar to those reported by Araki et al.[13] and by Seki et al.,[17] who have shown a strong positive correlation between LDL-c and non-HDL-c, between LDL-c and TC, and between non-HDL-c and TC. Some negative correlations have been reported involving non-HDL-c and HDL-c, coinciding with the same studies. In addition, our study showed that as the adolescents from the 10-to-14-year-old group aged, their serum levels of LDL-c, TC and non-HDL-c decreased.

Several studies have shown that non-HDL-c is one of the best indicators of the atherosclerotic risk in children and adolescents,[18-20] because it is more strongly associated with lesions in the abdominal aorta and coronary arteries than the other lipids are,[20-22] in addition to being associated with metabolic diseases.[23] The stronger correlations of non-HDL-c with the other lipids (TG, LDL-c and TC) found in this study as compared to those of LDL-c are in accordance with the literature, and the National Heart, Lung and Blood Institute (NHLBI) has already included reference values for non-HDL-c, recommending it for screening during childhood.[24] In adults, non-HDL-c is a better predictor of CVD than LDL-c is.[25,26]

In this study, among the adolescents aged 10 to 19 years, changes in HDL-c levels were observed in 52% of the sample, similarly to the study by Silva et al.[11] conducted in the municipality of Barras, Piauí state, which reported changes in HDL-c levels in 70% of the sample, and the

Table 2 - Correlations of the lipid variables in adolescents aged 10 to 19 years (n = 600)

		Age	TG	LDL-c	HDL-c	TC	VLDL-c	Non-HDL-c
Age	S	1	0.004	-0.079	-0.010	-0.071	0.004	-0.080
TG	S	0.004	1	0.292**	-0.232**	0.396**	0.999**	0.493**
LDL-c	S	-0.079	0.292**	1	0.024	0.896**	0.289**	0.935**
HDL-c	S	-0.010	-0.232**	0.024	1	0.282**	-0.230**	-0.032
TC	S	-0.071	0.396**	0.896**	0.282**	1	0.394**	0.934**
VLDL-c	S	0.004	0.999**	0.289**	-0.230**	0.394**	1	0.490**
Non-HDL-c	S	-0.080	0.493**	0.935**	-0.032	0.934**	0.490**	1

*TC: total cholesterol; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; TG: triglycerides; Non-HDL-c: sum of the lipoproteins without HDL-c; S: Spearman correlation. * p < 0.05; ** p < 0.001.*

Table 3 - Correlations of the lipid variables in adolescents aged 10 to 14 years (n = 339)

		Age	TG	LDL-c	HDL-c	TC	VLDL-c	Non-HDL-c
Age	S	1	-0.056	-0.140**	-0.079	-0.138*	-0.056	-0.136*
TG	S	-0.056	1	0.262**	-0.300**	0.337**	0.999**	0.457**
LDL-c	S	-0.140**	0.262**	1	0.039	0.912**	0.257**	0.949**
HDL-c	S	-0.079	-0.300**	0.039	1	0.282**	-0.298**	-0.053
TC	S	-0.138*	0.337**	0.912**	0.282**	1	0.333**	0.926**
VLDL-c	S	-0.056	0.999**	0.257**	-0.298**	0.333**	1	0.452**
Non-HDL-c	S	-0.136*	0.457**	0.949**	-0.053	0.926**	0.452**	1

*TC: total cholesterol; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; TG: triglycerides; Non-HDL-c: sum of the lipoproteins without HDL-c; S: Spearman correlation. * p < 0.05; ** p < 0.001.*

Table 4 - Correlations of the lipid variables in adolescents aged 15 to 19 years (n = 261)

		Age	TG	LDL-c	HDL-c	TC	VLDL-c	Non-HDL-c
Age	S	1	0.063	0.064	0.071	0.086	0.065	0.054
TG	S	0.063	1	0.328**	-0.143*	0.468**	0.999**	0.537**
LDL-c	S	0.064	0.328**	1	0.006	0.878**	0.329**	0.919**
HDL-c	S	0.071	-0.143*	0.006	1	0.281**	-0.142*	-0.007
TC	S	0.086	0.468**	0.878**	0.281**	1	0.468**	0.944**
VLDL-c	S	0.065	0.999**	0.329**	-0.142*	0.468**	1	0.538**
Non-HDL-c	S	0.054	0.537**	0.919**	-0.007	0.944**	0.538**	1

*TC: total cholesterol; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; TG: triglycerides; Non-HDL-c: sum of the lipoproteins without HDL-c; S: Spearman correlation. * p < 0.05; ** p < 0.001.*

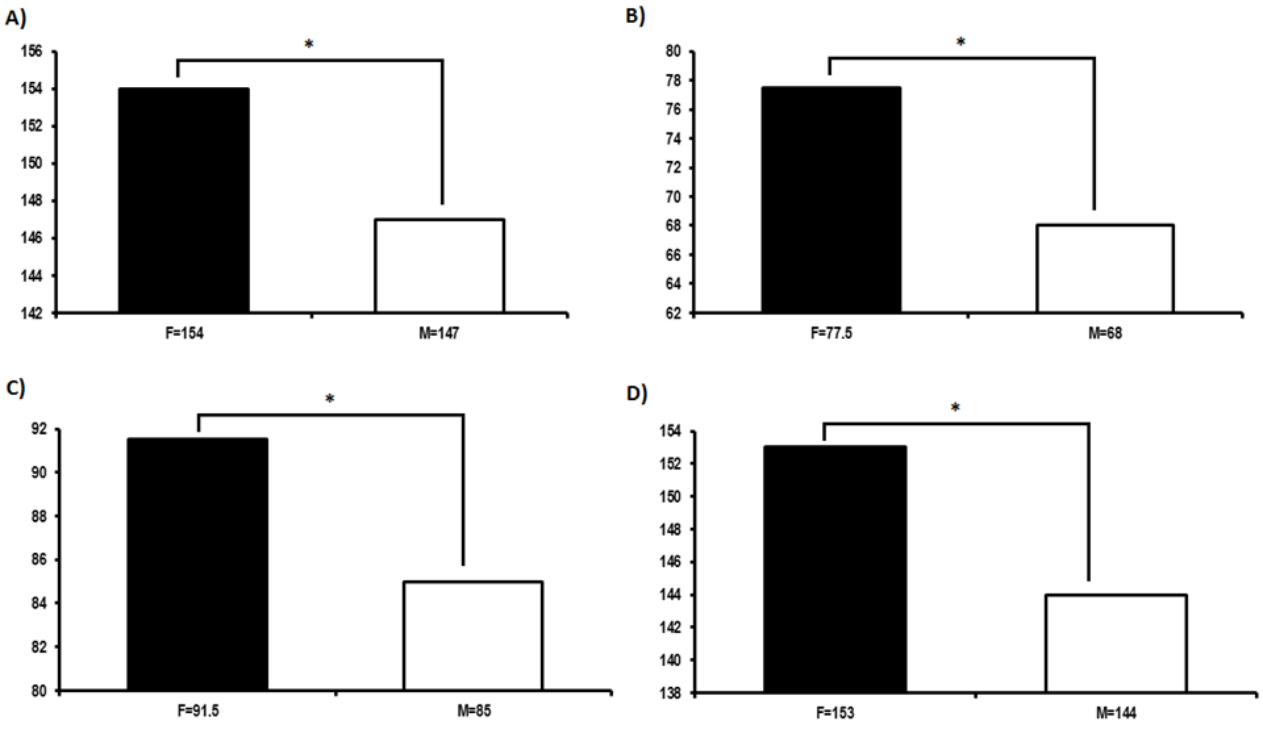

Figure 1 - Assessment of the lipid profile of adolescents for the serum levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c) and triglycerides (TG). F: female; M: male. A) TC; difference between F (IQR = 44) and M (IQR = 36.25), p: 0.043* (Mann-Whitney U test); B) TG; difference between F (IQR = 37.5) and M (IQR = 42), p: 0.017* (Mann-Whitney U test); C) LDL; difference between F (IQR = 31.75) and M (IQR = 29.5), p: 0.049* (Mann-Whitney U test); D) TC; difference between F (IQR = 43.5) and M (IQR = 32), p: 0.026* (Mann-Whitney U test).

study by Ramos et al.[25] conducted in the municipality of Campina Grande, Paraíba state, which reported changes in HDL-c levels in 80.6% of the sample. Some different results have also been reported. Silva et al.[14] have reported 22% of changed HDL-c values in a study conducted in the city of Rio de Janeiro, while Seki et al.,[28] in a study conducted in Londrina, Paraná state, have reported 14.3% of changed HDL-c values. Such differences reported in the literature might be related to genetic, environmental and local factors, because the studies are from distinct geographic, ethnical and cultural regions. It is worth noting that this study has limitations, because it is a retrospective study with convenience sampling of a specific population, whose samples had already been collected.

Conclusion

This study's results showed that, of the 600 adolescents, 30% had some type of hypercholesterolemia and more than 50% had some type of dyslipidemia. Regarding the adolescents with dyslipidemia, the female sex had the highest prevalence, suggesting that preventive measures should be taken considering sex.

In conclusion, the serum level of non-HDL-c showed stronger correlation with the other lipids (TG, LDL-c and TC) as compared to LDL-c. This suggests that non-HDL-c can be used as an effective complementary diagnostic method to assess the risks for atherosclerosis in adolescents of this study's age group. Non-HDL-c can be an important biomarker, and should be included in the lipid profile, as already used for adults.

Author contributions

Conception and design of the research: Cunha EDBB, Fagundes RP; Acquisition of data: Fagundes RP; Analysis and interpretation of the data: Cunha EDBB; Statistical analysis: Cunha EDBB, Scalabrin EE; Writing of the manuscript: Cunha EDBB; Critical revision of the manuscript for intellectual content: Herai RH.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Instituto Paranaense de Otorrinolaringologia* under the protocol number 65932917.0.0000.5529. 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

Waiting for Cardiac Procedure in Congenital Heart Disease: Portrait of an a Hospital in the Amazonian Region

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Abstract

Background: Congenital heart disease is an important cause of morbidity and mortality in childhood, and in 50% of cases, surgery is required in the first year of life. A high deficit of surgical procedures is estimated in Northern Brazil.

Objective: To analyze the waiting time for elective surgical treatment and/ or intervention in children with congenital heart disease in a Cardiology referral center, and to make considerations about heart diseases and forms of treatment in that institution.

Methods: A cross-sectional study of all patients aged less than 14 years, with a diagnosis of congenital heart disease that were waiting for elective surgical or percutaneous cardiac treatment.

Results: Among the 407 children with congenital heart defects, the most prevalent age group was > 2 to 6 years (34.0%). The average waiting time was 23.1 ± 18.3 months, with a median of 19. The most frequent heart disease was ventricular septal defect (28.98%), patent ductus arteriosus (18.42%) and atrial septal defect (11.05%). Most children (63.4%) were not from the metropolitan area. The percutaneous interventions represented only 27.84% of the catheterization procedures and 14,85% of all heart treatments. Approximately 60% of the pediatric surgeries occurred in children who were not previously registered due to urgency cases.

Conclusion: Most of the children waiting for a cardiac procedure were not from the metropolitan area and had malformations potentially treatable by catheterization. It is necessary to increase the capacity of the single referral center in the state of Pará, as well as decentralize the high-complexity cardiological care in the metropolitan region. (Int J Cardiovasc Sci. 2018;31(4)374-382)

Keywords: Heart Defects, Congenital / therapy; Waiting Lists; Heart Defects, Congenital / surgery; Epidemiology.

Introduction

Congenital heart defects, defined as structural abnormalities of the heart or the intrathoracic vessels, in different anatomical forms, are one of the most frequent congenital anomalies identified at birth.[1-3] These malformations are the ones with the greatest impact on children's morbidity and mortality and on the cost of health services[4] and they represent the main cause of death among all congenital malformations.[5]

The prevalence of congenital heart diseases is between four and nine per thousand live births, with an estimated 1.5 million new cases per year worldwide.[2,6,7]

Hoffman estimated that between 1940 and 2002, 1.5 million people were born in the United States affected by heart disease.[2] In Brazil, 28,846 new cases of congenital heart disease are estimated per year. Spontaneous cure occurs in approximately 20% of the cases, related to less complex defects with a mild hemodynamic effect.[8]

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The estimated need for surgical procedures to repair congenital heart defects is 7.2 per thousand births, with reports of more significant deficits for treatment in the North and Northeast Regions, with rates close to 90%, and less significant in the Southern and Midwest regions, with rates of 46.4% and 57.4%, respectively.[8,9]

Congenital heart diseases are important causes of hospital admissions in the pediatric population, and the earlier the diagnosis and the therapeutic intervention of these conditions, the lower the mortality and hospital readmission rates, and the better the quality of life of these children.[10]

Considering the severe or potentially severe nature of these cardiopathies, which may have significant effects for morbidity and mortality, it is essential to know the reality of heart diseases in the only public referral hospital for these conditions in the State of Pará, Brazil.

The aim of this study was to analyze the waiting time for elective surgical and/or interventional treatment in children with congenital heart defects in a cardiology referral center, as well as to evaluate the patients' origin and make considerations about heart diseases and their types of treatment in that institution.

Methods

Cross-sectional study of patients aged 14 years or less, diagnosed with congenital cardiac malformations, who were waiting for surgical or percutaneous cardiac treatments, including reoperation cases.

The data were obtained from the medical and statistical archive service (SAME) of *Fundação Hospital de Clínicas Gaspar Vianna*. The study variables were: gender, age, place of residence, diagnosis and time waiting for the procedure. Additionally, data from patients submitted to surgical and/or catheterization treatment were collected from January 2012 to October 2014.

The descriptive analysis of data was performed using the BioStat program, and the variables were shown as measures of central tendency and dispersion or frequencies.

The present study was submitted to and approved by the Research Ethics Committee Involving Human Beings of Fundação Hospital de Clínicas Gaspar Vianna, under CAAE number 39903014.2.0000.0016.

Results

Of the 417 children waiting for cardiac surgery or hemodynamic procedure, 407 had a diagnosis of congenital heart disease; of these, 55.1% were females, and the most prevalent age groups were preschoolers (> 2 to 6 years), with 34.0%, and schoolchildren (> 6 to 12 years), with 33.3% (Table 1). The mean age was 5.7 (± 3.9), with a median of 5.0 years, ranging from 1 month to 14 years. There were no neonates waiting for treatment.

The mean waiting time, in months, was 23.1 ± 18.3, with a median of 19, a minimum of 1 month and a maximum of 94 months. The two patients who had been waiting for 91 and 94 months (longer waiting periods) were incommunicable by the social service of the institution, which may justify the delay.

Regarding their origin, 36.6% came from the municipality of Belém Metropolitan Mesoregion, followed by 27.2% from the Northeast of Pará, 17.6% from the Southeast of Pará and the remaining 18.1% from the Lower Amazon region, Southwest of Pará and Marajó together; one patient was from Amapá state (Figure 1).

The most commonly diagnosed type of congenital heart disease was ventricular septal defect (VSD), isolated or associated with other cardiac malformations, totaling 28.98%, followed by persistent ductus arteriosus (PDA) with 18.42%, atrial septal defect (ASD) with 11.05%, with or without associations, and Tetralogy of Fallot, with 8.59% (Table 2).

Regarding the performed surgeries, in 2012, 172 children underwent 201 pediatric cardiac surgeries; in 2013, 176 patients underwent 207 surgeries; and in 2014, until October 146 children underwent 158 cardiac surgeries. In 85.3% of the cases, it was possible to determine whether the child was previously enrolled for elective treatment or not: in 2012, 62.2% were not enrolled, being submitted to emergency procedures, and only 37.7% belonged to the elective enrollment group. In 2013, the same thing occurred, with 59.0% and 40.9% of cases, respectively (Table 3).

In 2012, an average of 16.7 pediatric heart surgeries were performed per month. In 2013, this average was 17.2 and in 2014, until the end of October, of 15.8. Among pediatric hemodynamic procedures, there was a greater increase: in 2012, the average number of monthly procedures was 9.5, in 2013, 9.8 and until October 2014, 13.6 (Table 4).

Regarding the type of hemodynamic procedure, the rate of cardiac diagnostic catheterization was 73.9%, while the rate of therapeutic interventions corresponded to 26.1% of the total procedures performed since 2012 (Table 5, Figure 2).

Table 1 - Patients enrolled for elective pediatric cardiac procedures

Characteristic	n total (%)
Gender	
Male	183 (44.94)
Female	224 (55.06)
Age group, years	
< 1	45 (11.06)
1-2	66 (16.22)
> 2-6	142 (34.89)
> 6-12	133 (32.68)
> 12	21 (5.16)
Waiting time	
< 1 month	0
1-6 months	80 (19.66)
7 months-1 year	50 (12.29)
> 1-3 years	197 (48.4)
> 3-5 years	57 (14)
> 5 years	23 (5.65)
Pará Mesoregion*	
Belém Metropolitan Area: Ananindeua, Barcarena, Castanhal, Santa Izabel do Pará, Belém, Santo Antonio do Tauá, Benevides and Marituba	149 (36.60)
Northeast of Pará: Abaetetuba, Santa Luzia do Pará, Acará, Irituia, Santa Maria do Pará, Augusto Corrêa, Aurora do Pará, Mãe do Rio, São Caetano de Odivelas, Baião, São Domingos do Capim, Maracanã, Bragança, Marapanim, Mocajuba, São João de Pirabas, Cametá, Moju, São Miguel do Guamá, Capanema, Nova Esperança do Piriá, Tailândia, Capitão Poço, Colares, Oeiras do Pará, Tomé-Açu, Ourém, Tracuateua, Curuçá, Peixe-Boi, Primavera, Viseu, Igarapé-Açu, Igarapé-Miri and Salinópolis	111 (27.27)
Southeast of Pará: Rio Maria, Itupiranga, Rondon do Pará, Jacundá, Bom Jesus do Tocantins, Marabá, Santana do Araguaia, Nova Ipixuna, Breu Branco, Novo Repartimento, São Félix do Xingu, Canaã dos Carajás, Conceição do Araguaia, Paragominas, Curionópolis, Parauapebas, Tucumã, Dom Eliseu, Pau D'arco, Tucuruí, Eldorado do Carajás, Ulianópolis, Redenção and Xinguara	72 (17.69)
Lower Amazon: Alenquer, Juruti, Almeirim, Monte Alegre, Prainha, Óbidos, Santarém, Curuá, Oriximiná and Placas	33 (8.10)
Marajó: Curralinho, Salvaterra, Anajás, Gurupá, Melgaço Breves, Soure, Cachoeira do Arari, Ponta de Pedras, Chaves and Portel	22 (5.40)
Southwest of Pará: Altamira, Medicilândia, Pacajá, Itaituba and Rurópolis	19 (4.66)

** For all characteristics, n = 407, for mesoregions, n = 406; † except for one patient from Santana (AP).*

Of the total of 662 therapeutic cardiac procedures performed between 2012 and October 2014, 86.1% corresponded to cardiac surgeries and only 13.8% to percutaneous interventions. This proportion remained stable over the years (Table 6).

Discussion

In Brazil, it is estimated that the average need for cardiovascular surgery in congenital cases is approximately 23,000 procedures/year, considering in

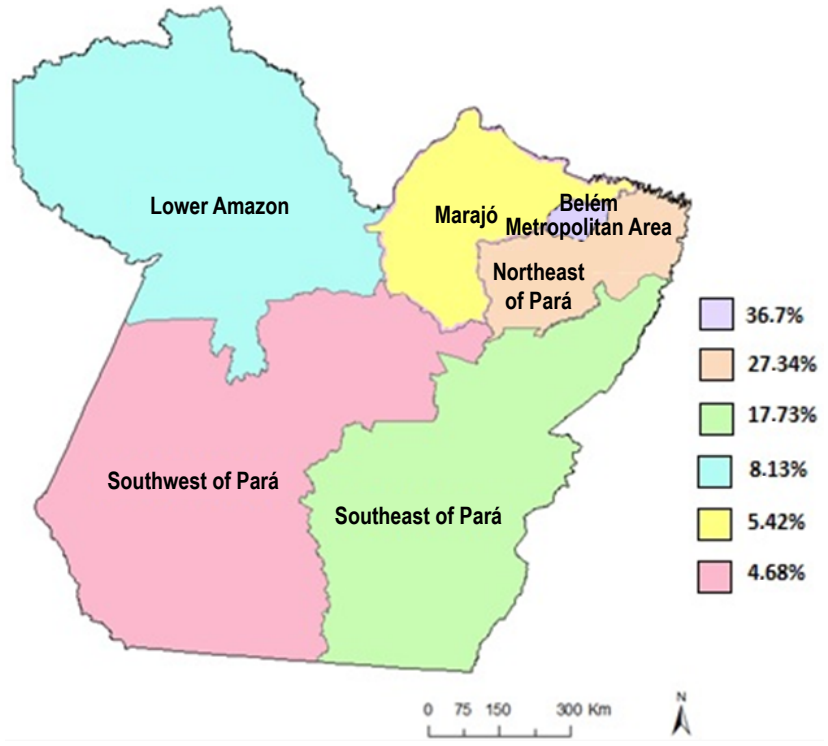

Figure 1 - Distribution of patients waiting for elective pediatric cardiac procedures according to the place of residence in mesoregions.

this estimate, in addition to new births with congenital heart disease, the reintervention cases. In 2002, a total of 8,092 patients underwent surgery, which shows a 65% gap – with higher rates in the Northern Region (93.5%).[9]

In the present study, it was observed that of the 407 children diagnosed with congenital heart disease, the most prevalent age groups were preschoolers (> 2 to 6 years) and schoolchildren (> 6 to 12 years), with no neonates waiting for treatment. These results differ from those observed in the analysis of the prevalence of congenital heart diseases at the time of the first consultation in a pediatric hospital in the city of Curitiba, state of Paraná, where there was a predominance of children with congenital heart disease in the infancy period, followed by the neonatal period, with 52.1%, and 19.4%, respectively.[11] Considering that the sample of the present study refers to the patients waiting for elective procedures, this may reflect the differences regarding the time of referral for these patients and the delay during the waiting period.

Regarding the type of congenital heart disease, the most frequent one was VSD, followed by PDA and ASD. These results are consistent with those found in the study by Aragão et al.,[12] who demonstrated the following frequencies: VSD (21%), PDA (18%), Tetralogy of Fallot (14%) and ASD (7.7%). As for Huber et al.,[13] they were as follows: VSD with or without associations (13.9%), Tetralogy of Fallot (12.9%), obstructive lesions of the right ventricular outflow tract (9.8%), and isolated ASD (9.6%). It can be said that the assessed institution had similar characteristics to those observed in other regions of Brazil.

The most frequent origin of the children who comprised the waiting list for cardiologic procedures was the Belém Metropolitan Mesoregion, a result consistent with those of a referral hospital in the Northeast region of Brazil, where most of the children came from the metropolitan region of the state.[12]

However, 63.4% of the children did not live in the Metropolitan Region of Belém; thus, a point to be discussed is the need to qualify new high cardiovascular complexity referral units in the State of Pará. For the geographical distribution of the High Complexity Care Services in Pediatric Cardiovascular Surgery, according to Ordinance 210,[14] which is based on the proportion of 1:800 thousand inhabitants, the State of Pará needs nine centers capable of performing pediatric cardiovascular surgery, but the regionalization of services has not yet occurred, generating

Table 2 - Type of congenital heart disease of patients enrolled for elective procedure

Cardiopathies	n (%)
Ventricular septal defect	110 (27.02)
Patent ductus arteriosus	75 (18.42)
Atrial septal defect	41 (10.07)
Tetralogy of Fallot	35 (8.59)
Congenital pulmonary stenosis	24 (5.89)
Coarctation of the aorta	15 (3.68)
Pulmonary atresia	12 (2.94)
Ventricular septal defect + associations*	8 (1.96)
Congenital aortic stenosis	8 (1.96)
Atrioventricular defect	7 (1.71)
Double-outlet right ventricle	5 (1.22)
Congenital tricuspid stenosis	5 (1.22)
Congenital mitral regurgitation	5 (1.22)
Hypoplastic right heart syndrome	4 (0.98)
Common arterial trunk	3 (0.73)
Double inlet left ventricle	3 (0.73)
Atrial septal defects + pulmonary stenosis	3 (0.73)
Congenital subaortic stenosis	2 (0.49
Cor triatriatum	1 (0.24)
Ebstein's anomaly	1 (0.24)
Hypoplastic left heart syndrome	1 (0.24)
Anomalous pulmonary venous return	1 (0.24)
Cardiac aneurysm	1 (0.24)
Discordant atrioventricular connection	1 (0.24)
Discordant ventriculoatrial connection	1 (0.24)
Double outlet left ventricle	1 (0.24)
Aortic regurgitation	1 (0.24)
Double mitral valve lesion	1 (0.24)
Congenital pulmonary insufficiency	1 (0.24)
Others†	34 (8.35)

** Patent ductus arteriosus, atrial septal defect, pulmonary stenosis and coarctation of the aorta; † other congenital malformations of the tricuspid valve, other congenital malformations of the cardiac chambers and connections, congenital malformations of the cardiac septa, non-specific congenital malformation of the tricuspid valve, malformations of the coronary vessels, primary and secondary pulmonary hypertension, and unregistered ones.*

a deficit of 78.49%.[15] This reality can be explained by several causes, such as the lack of qualified professionals and hospital institutions with infrastructure to perform the required complex procedures.

In our reality, there is also the hypothesis that the low rate of patients coming from the Lower Amazon region, Marajó island and southwest of Pará regions is due to the difficulties of access to basic care for this population, thus resulting in the underdiagnosis of congenital heart diseases and, therefore, fewer referrals to the assessed center.

A highly complex service requires multiprofessional attention, with cardiac surgeons, hemodynamicists, pediatric cardiologists, anesthesiologists, pediatric intensivists, in-hospital and outpatient clinic pediatricians, perfusionists, nurses and physical therapists. The treatment outcomes should be part of a lifelong care cycle, and not only the immediate surgical outcome. The large number of patients with cardiac malformations requires multi-institutional cooperation to achieve these goals.[16]

Fundação Hospital de Clínicas Gaspar Vianna is the only referral public hospital in Pará that performs hemodynamic and surgical treatment of pediatric congenital heart disease. The mean monthly number of cardiac surgeries was similar in the study period (16.6 surgeries/month). Regarding pediatric hemodynamic procedures (diagnostic and/or therapeutic cardiac catheterization), there was an increase: in 2012, the average number of monthly procedures was 9.5; in 2013, of 9.8; and in 2014, until October, of 13.6 – it is noteworthy that this increase was accompanied by an increase in the number of diagnostic cardiac catheterizations to the detriment of therapeutic ones. The latter, in turn, accounted for only 14.85% of all therapeutic procedures.

The low number of therapeutic cardiac catheterizations when compared to diagnostic procedures is a consequence of the absence of other diagnostic methods, such as computed tomography and cardiac magnetic resonance, due to the possible lack of devices for therapeutic percutaneous procedures.

Considering that VSD, ASD, PDA, congenital pulmonary stenosis and coarctation of the aorta account for 65.2% of all diagnoses, which are malformations potentially treatable by cardiac catheterization, it can be observed that there is a low rate of these interventions in our country. Thus, investing in hemodynamic treatment is a strategy to reduce the waiting time, since the interventional treatment does not require prolonged

Table 3 - Patients submitted to pediatric cardiac surgery according to the enrollment status in the waiting list for cardiac procedures

Month	2012 (n = 201)			2013 (n = 207)		
	Enrolled	Not enrolled	Not informed	Enrolled	Not enrolled	Not informed
January	8 (3.98)	8 (3.98)	1 (0.50)	5 (2.42)	11 (5.31)	6 (2.90)
February	6 (2.99)	5 (2.49)	3 (0.49)	6 (2.90)	14 (6.76)	5 (2.42)
March	4 (1.99)	10 (4.98)	4 (1.99)	8 (3.86)	17 (8.21)	2 (0.97)
April	0	3 (1.49)	2 (1.00)	6 (2.90)	3 (1.45)	2 (0.97)
May	0	12 (5.97)	0	6 (2.90)	4 (1.93)	0
June	4 (1.99)	14 (6.97)	2 (1.00)	4 (1.93)	7 (3.38)	2 (0.97)
July	6 (2.99)	6 (2.99)	3 (1.49)	5 (2.42)	12 (5.80)	6 (2.90)
August	4 (1.99)	12 (5.97)	5 (2.49)	6 (2.90)	11 (5.31)	1 (0.48)
September	9 (4.48)	5 (2.49)	2 (1.00)	6 (2.90)	6 (2.90)	4 (1.93)
October	12 (5.97)	8 (3.98)	1 (0.50)	8 (3.86)	7 (3.38)	0
November	5 (2.49)	13 (6.47)	3 (1.49)	4 (1.93)	8 (3.86)	1 (0.48)
December	7 (3.48)	11 (5.47)	3 (1.49)	8 (3.86)	4 (1.93)	2 (0.97)

Table 4 - Surgical and hemodynamic procedures (diagnostic and therapeutic) performed per year

Month	Surgical procedures			Hemodynamic procedures		
	2012	2013	2014	2012	2013	2014
January	17	22	21	10	9	18
February	14	25	17	8	7	4
March	18	27	16	7	11	11
April	5	11	18	3	3	13
May	12	10	13	13	9	15
June	20	13	15	11	11	14
July	15	23	17	14	14	15
August	21	18	15	12	9	12
September	16	16	12	20	12	20
October	21	15	14	6	18	13
November	21	13	-	4	8	-
December	21	14	-	7	7	-

hospital length of stay,[17] and therefore favors a greater turnover of recovery beds, consisting of pediatric intensive care units and pediatric ward beds.

At the same time, it can be observed that at *Instituto do Coração* of *Hospital das Clínicas* of *Faculdade de Medicina* of *Universidade de São Paulo*, the number of percutaneous

Table 5 - Hemodynamic procedures performed according to the type of intervention per year

Procedure	2012	2013	2014
Diagnostic cardiac catheterization	77	87	108
Diagnostic cardiac catheterization + percutaneous intervention	24	27	27
Cardiac catheterization + angioplasty	23	17	13
Cardiac catheterization + embolization	0	3	0
Cardiac catheterization + PDA/ ASD/ VSD closure	0	3	5
Cardiac catheterization + atrial septostomy	0	1	0
Cardiac catheterization + valvuloplasty	1	3	9
Percutaneous intervention	14	4	0
Pulmonary Embolization	1	1	0
Valvuloplasty	5	1	0
Angioplasty	8	1	0
PDA closure	0	1	0

PDA: patent ductus arteriosus; ASD: atrial septal defect; VSD: ventricular septal defect.

interventions remained stable, with only one record of case that was not treated due to structural limitations, considering the limited number of beds in the institution.[18]

Making investments aiming to reducing the waiting time for congenital cardiovascular procedures also improves morbimortality outcomes. However, this generates high short-term costs to the Brazilian Unified Health System (SUS). The devices used for closure of ASD, VSD and PDA are not covered by SUS, which creates more difficulties in their acquisition. There is also the challenge of financial transfer, sometimes insufficient for cardiac surgeries, limiting their increase. The fact that there is almost no differentiation regarding the payment of the procedure related to its degree of complexity punishes the referral center dedicated to the more complex cases and discourages the increase in the number of procedures in neonates and infants, especially in the higher complexity cases. Some international studies

Table 6 - Cardiac surgery and therapeutic hemodynamic procedures

Treatment	2012	2013	2014
Surgical	201 (84.10)	207 (86.97)	158 (85.40)
Percutaneous	38 (15.89)	31 (13.02)	27 (14.59)

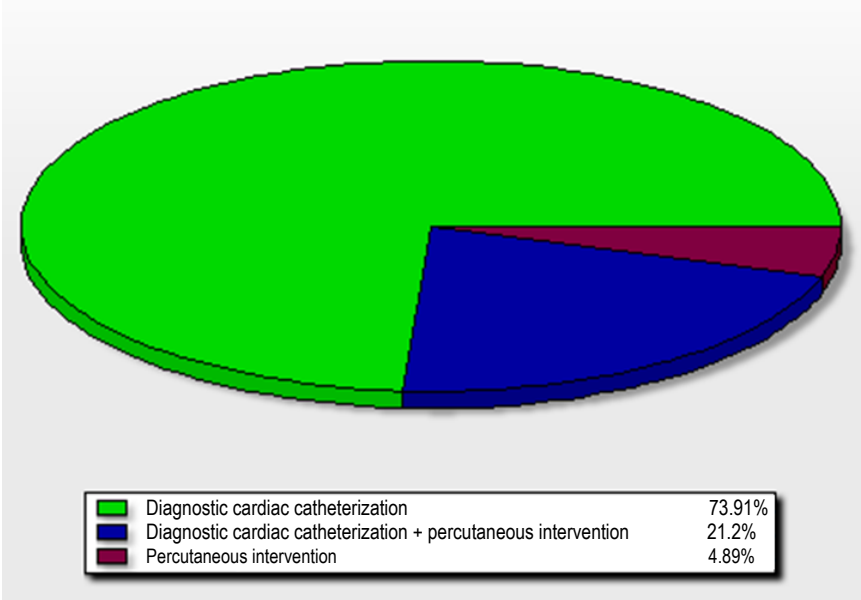

Figure 2 - Type of hemodynamic procedure performed.

have shown that there is a linear association between the complexity and cost of the procedure.[19]

Another great difficulty that the service faces in reducing the waiting list for elective cardiac surgery is the high demand for urgent surgeries in patients without previous enrollment, as these cases are prioritized to the detriment of elective ones. A strategy to mitigate the problem in the short term would be the performance of congenital heart surgeries in patients already enrolled for it, aiming to reduce the repressed demand of SUS users.[19]

In this sense, it is proposed: the creation of outpatient care and specialized centers for the diagnosis and early treatment of the population, reducing underdiagnosing and improving pre- and postoperative clinical follow-up, with a possible reduction of costs for out-of-home treatment and, consequently, less social impact for the affected families; investment in diagnosis performed through computed tomography and cardiac magnetic resonance imaging, which would reduce diagnostic cardiac catheterizations and increase the availability of hospital support for therapeutic procedures; the promotion of hemodynamic procedures, including a funding policy for Orthoses, Devices and Special Materials (*Órteses, Próteses e Materiais Especiais* – OPME) not covered by SUS, due to the proven effectiveness and shorter hospital length of stay, with a consequent decrease in hospital expenses and an increase in the volume of treated cases per unit of time; increased functional capacity at the referral hospital; decentralization of surgical and cardiac hemodynamic care, with the internalization of this type of service in medium-sized municipalities, such as Marabá and Santarém, both in the state of Pará; and reliable, detailed and updated data registry regarding the surgical and hemodynamic procedures, for permanent control and evaluation of the outcomes. The promotion of improvements in the care for children with heart disease is a priority and involves the participation of all – public services, professionals and several sectors of society.

Conclusion

Most of the children awaiting cardiac procedures come from outside the metropolitan area and have malformations potentially treatable through cardiac catheterization. However, even with changes in the treatment profile, with the increase in percutaneous procedures in the last years, it still requires further increase.

The limitations of the public hospital system in meeting the great demand of the region for elective therapeutic cardiovascular procedures generate an important care deficit, with the need to increase the functional capacity of the only public referral center for these diseases in the region, as well as decentralization of cardiological, clinical, surgical and hemodynamic care, to better treat the population that depends on SUS.

Author contributions

Conception and design of the research: Jesus VS, Nascimento AM, Miranda RA, Veríssimo AOL. Acquisition of data: Jesus VS, Nascimento AM, Lima JS. Analysis and interpretation of the data: Jesus VS, Nascimento AM, Veríssimo AOL. Statistical analysis: Jesus VS, Nascimento AM. Writing of the manuscript: Jesus VS, Nascimento AM, Lima JS, Tyll MAG. Critical revision of the manuscript for intellectual content: Miranda RA, Tyll MAG, Veríssimo AOL.

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 *Fundação Pública Estadual Hospital das Clínicas Gaspar Vianna* under the protocol number 39903014.2.0000.0016. 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

Adherence Score for Users of Oral Anticoagulants

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Abstract

Background: The score is an effective instrument for the assessment of treatment adherence in users of oral anticoagulants and maintenance of INR (international normalized ratio) within the therapeutic range.

Objective: To develop an adherence score for oral anticoagulant users for the maintenance of INR within the therapeutic range.

Methods: This was an analytical, observational, cross-sectional study, with a quantitative approach, conducted in a public cardiology hospital. A total of 607 patients who met the inclusion criteria were evaluated. Variables with a significance level of 5% in the exploratory analysis and considered clinically relevant were included and subjected to a multiple logistic regression model. Predictive accuracy of the model was determined using the C statistic.

Results: The variables with a significance level of 5% in the multivariate analysis were: education, family income, inadequate use of medications, drug-drug interactions, invasive procedures, food-drug interactions, physical activity, medical conditions, other factors, and complications related to oral anticoagulant therapy. The following prognostic variables were identified: family income, inadequate use of medications, invasive procedures, drug-drug interactions, dietary habits, medical conditions, other factors (stress, thinness, weight loss). C-statistic for adherence score was 0.94.

Conclusion: The Simonetti adherence score proved to be easily applicable and feasible, with high predictive value for influencing factors, promoting the improvement of adherence and maintenance of INR in the ideal range. (Int J Cardiovasc Sci. 2018;31(4)383-392)

Keywords: Cardiovascular Diseases; Anticoagulants / therapy; Probability; Medication Adherence; Health Education.

Introduction

Health promotion is a key strategy for prevention of thromboembolic events in patients on oral anticoagulant therapy (OAC-T) in addition to other aspects related to the assistance of this population. In this context, health professionals, nurses and physicians play the role of educators, particularly in providing clear guidance on risk factors and possible signs and symptoms and related complications associated with a OAC-T.[1]

Stability of OAC-T is associated with treatment adherence, in addition to other factors including age, concomitant use of other drugs, comorbidities, irregular use of vitamin K, inadequate use of the drug, and hereditary polymorphism.[2] Educational programs for outpatient management of patients on OAC-T have been crucial for the approach of drug and dietary interactions with coumarin derivatives, which may affect treatment adherence.[2,3]

A study[4] pointed out important considerations about adherence to OAC-T. First, knowledge about adherence to OAC-T is still a challenge among health professionals in national and international contexts. Second, the study provides data on instruments proposed by health professionals aimed at improving patients' adherence and knowledge about the treatment, and on patients' sociodemographic status. The authors also reported the scarcity of studies on factors that may influence therapy

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adherence. Studies have so far highlighted the importance of health education as an efficient strategic intervention to improve the use of oral anticoagulants (OACs) but have not provided enough evidence on instruments to measure adherence and non-adherence. Finally, the study support the emerging need for a medication adherence scale for this population.[4]

In light of this context and current recommendations, a need for the development of a score to assess adherence and non-adherence in users of OACs has emerged.

Methods

This was an analytical, observational, cross-sectional study, with a quantitative approach, conducted at the Oral Anticoagulation Center of a public, cardiology hospital associated to the São Paulo State Secretary of Health.

For sample calculation, we considered the prevalence of altered INR (international normalized ratio), i.e., 5% among patients without other conditions that may affect this parameter; 15% among patients with conditions that may affect this parameter, additionally to an alpha of 5% and power of 95%. Therefore, inclusion of 5 and 2 patients with and without factors known to affect INR, respectively, was considered, resulting in a sample size of 574. An additional 5% was considered for possible dropouts, yielding a sample of 607 patients on OAC-T that met eligibility criteria. Altered INR was used as outcome measure and the following predicting variables were assessed: drug handling, drug-drug and drug-food interactions, surgeries and other procedures, clinical condition, health problems, among other factors – stress, weight loss / gain, use of (generic or similar) warfarin, alcohol abuse and physical activity.

Data collection was performed in two stages – in phase I, general features of the sample were collected, and in phase II, clinical characteristics were collected. All patients signed an informed consent form before being included in the study. The study was approved by local ethics committee (approval number 4420; CAAE: 24118513.7.0000.5392).

Statistical analysis

Qualitative variables were expressed as absolute and relative frequency, and quantitative variables as mean and standard deviation. The chi-square test and Fisher's exact test were used to assess associations between qualitative variables. Variables with $p < 0.10$ and / or with clinical significance for adherence and INR within recommended therapeutic range were analyzed by a multiple logistic regression model, followed by a stepwise backward analysis for the final model. C-statistic was calculated by the ROC (receiver operating characteristic) curve to evaluate the final model and final score. Significance level was set at 5%. Analysis was performed using the Statistical Package for Social Sciences (SPSS) version 19 (Armonk, NY: IBM Corp.) and the R Core Team 2016 software.

Results

Clinical profile of users of OACs

A total of 607 patients on OAC-T participated in the study. Fifty-two percent of patients were women, 57% married, 56% older than 60 years, 42% had some elementary school, in 55% the family income was between 1 and 3 minimum wage, and almost all of them (93%) came from Sao Paulo. Sociodemographic characteristics are described in Table 1.

Normal INR levels used as reference were: < 2 and > 3 for patients with thromboembolic events, and < 2.5 and > 3.5 for patients with mechanical prosthesis. Forty percent of patients (n = 247) had altered INR, whereas 60% (n = 360) had normal INR.

Most INR results were within the range from 2 to 3, whereas 119 participants (36%) with mechanical prosthesis had an INR < 2.5 and > 3.5. In addition, the presence of atrial fibrillation and / or atrial flutter was considered for patients with mechanical prosthesis. Most

Table 1 - Sociodemographic characteristics of patients on oral anticoagulation therapy (n = 607)

Variables	Nº	%
Female sex	315	52
Age > 60 years	341	56
Married	348	57
Some elementary school	280	42
Family income (1 - 3 minimum wages)	332	55
Patients with MP and altered INR	119	36
Evidence of thromboembolism with altered INR	105	54

MP: mechanical prosthesis; INR: international normalized ratio.

patients on OAC-T with INR < 2.0 were those with atrial fibrillation (n = 105, 54%) (Table 1).

For patients with INR > 2 (conditions with risk for thromboembolic events) and/or > 2.5 (mechanical prosthesis), atrial fibrillation was the most frequent disease and mechanical prosthesis was the main valvular prosthesis – mitral valve (n = 58; 26%) and aortic valve (n = 41; 18%).

With respect to participants' diseases and indication for OAC, 30 types of heart diseases were identified, 51% (783) clinical conditions and 24% (360) of surgical type, as well as related comorbidities (364; 25%).

Multiple logistic regression model

The following variables were selected for the multiple logistic regression model: family income, educational attainment, inadequate doses, invasive procedures, drug interactions, eating habits, physical activity, health problems, OAC-related complications, among other factors (Table 2).

Since all predictive variables showed a significative response, seven logistic regression models were considered for analysis at first. However, the model adopted in the study included the variables described in Table 2, considering also the interactions between them.

Simonetti medication adherence score

The variables used in the scores are shown in Table 3. First, the percentage of adherence was determined by Simonneti SH by multiplying the number of positive variables for adherence by the total number of predictive variables. A score was also developed to determine whether INR was within the normal range (Figure 1). The score was calculated by odds ratio.

Then, each condition known to affect INR was categorized into high (≤ 10 points), intermediate (11 – 30 points) and high (≥ 31 points) for normal INR (Figure 2).

The area under the ROC curve was determined based on the results of the variables proposed in the present study (Figure 3). For the logistic model, C-statistic was 0.940 (95% CI = 0.920 – 0.960; p < 0.001), indicating a satisfactory performance in detecting the occurrence of an event.

Discussion

The optimal dose of OAC is variable between individuals and should be adjusted to ensure that INR is maintained within the therapeutic range. In addition, it is known that the patient may reduce, discontinue (e.g. bleeding) or increase (e.g. double dose to make up for a missed dose) the dose of OAC.[5]

OAC-T-related complications may also be associated with the use of Marevan®, due to underdosing (risk of thrombus formation) or overdosing (bleeding), and the seek for medical care due to gum bleeding, hematuria, and other complications.[6]

Therefore, the lack of appropriate instructions and recommendations for patients on OAC-T in the perioperative period of any clinical or surgical procedure may cause variability in routine practice and affect the maintenance of INR within therapeutic range. Nevertheless, evidence shows that changes in OAC-T are not required prior to tooth extraction for example, providing that INR is maintained between 2 and 4, and bleeding control measures are implemented in the perioperative period to prevent embolic events.[7]

Studies have suggested that patients on OAC-T may require parenteral anticoagulation in the perioperative period. The decision to discontinue anticoagulation and start an antithrombotic therapy is determined by the risk of bleeding, surgical treatment to which patients were submitted and the risk for thrombosis due to underlying diseases.[8] However, for patients at low risk of bleeding (skin biopsies, cataract or dental procedures), the use of OAC may be continued, providing that INR is maintained at lower values and control of local bleeding is successfully achieved.[8]

Due to the risk of bleeding, when management of patients on OAC-T includes major surgery, it is recommended[8] that these individuals are classified into patients at minimal risk (atrial fibrillation without history of venous thromboembolism), intermediate risk or high risk of thromboembolism.

In addition, one of the main factors that affect INR and treatment adherence is drug-drug interactions. Antonio et al.[7] described the main drugs that interact with and potentiate the effect of OACs – allopurinol, amiodarone, cimetidine, cisapride, clofibrate and other fibrates, chloramphenicol, cotrimoxazole, erythromycin, fluconazole, isoniazid, metronidazole, miconazole, omeprazole, phenylbutazone, piroxicam, propafenone, propranolol, salicylate, phenylbutazone. These drugs may increase INR and cause bleeding. However, some drugs may inhibit the effects of OAC, including barbiturates, carbamazepine, chlordiazepoxide, cholestyramine,

Table 2 - Predictive variables by International Normalized Ratio (INR) values (normal/altered)

Variables	Categories	Normal INR		Altered INR		p-value
			%	Nº	%	
Educational attainment	Elementary	160	64.8	217	60.3	0.03
	High-school	59	23.9	94	26.1	
	College	28	11.3	49	13.6	
Family income	< MWs	128	51.8	217	60.3	0.08
	3 - 7 MWs	87	35.2	110	30.6	
	> 7 MWs	32	13	33	9.2	
Use of medication	Correct use	237	96	188	52.2	< 0.001
	Higher dose	2	0.8	43	11.9	
	Lower dose	8	3.2	129	35.8	
Drug-drug interaction	Yes	5	2.0	132	36.7	< 0.001
	No	242	98.0	228	63.3	
Invasive procedures	Minimum risk	1	0.4	32	8.9	< 0.001
	Maximum risk	1	0.4	33	9.2	
Drug-food interaction	No change	245	99.2	295	81.9	< 0.001
	Increased the intake	2	0.8	44	12.2	
	Decreased the intake	3	1.2	40	11.1	
Physical activity	No change	242	98	276	76.7	0.02
	Active	3	1.2	17	4.7	
	Non-active	2	0.8	14	3.9	
	Not reported	242	98	329	91.4	
Clinical conditions	Influenza and similar conditions	5	2	29	8.1	< 0.001
	Diarrhea, vomiting	4	1.6	17	4.7	
	Clinical and invasive infections	4	1.6	34	9.4	
	Not reported	234	94.7	280	77.8	
Other factors	Yes	15	6.1	132	36.7	< 0.001
	No	232	93.9	228	63.3	
Drug-related complications	Yes	2	0.8	24	6.7	< 0.001
	No	245	99.2	336	93.3	

griseofulvin, nafcillin, rifampicin, sucralfate and trazodone. These drugs may decrease INR results, and hence, increase the risk for thromboembolic events.[7]

Drug interactions related to OAC-T are of more or less importance, and are associated with processes that involve many pharmacodynamic and pharmacokinetic mechanisms – altered platelet function (clopidogrel, salicylic acid), gastrointestinal lesion (nonsteroidal anti-inflammatory drugs), impaired vitamin K synthesis in the gastrointestinal tract (antibiotics - amoxicillin, ampicillin, cephalosporin, metronidazole, clarithromycin, norfloxacin and trimethoprim/sulfamethoxazole),

Table 3 - Logistic regression model reduced by stepwise selection

Variables	Category	B-Coefficient	OR [95%CI]	p-value
Age/years	A	-0.006	0.994 [0.975 - 1.014]	0.569
Sex	A	-0.243	0.784 [0.456 - 1.347]	0.378
Family income	A	0.855	2.352 [1.161 - 4.765]	0.018
Inadequate use of medication	A	3.765	43.183 [19.575 - 95.262]	< 0.001
Invasive procedure	A	1.619	5.047 [1.015 - 25.107]	0.048
Drug-drug interaction	A	4.221	68.095 [25.306 - 183.234]	< 0.001
Eating habits	A	2.822	16.805 [3.291 - 85.810]	0.001
Clinical conditions	A	1.649	5.202 [2.265 - 11.943]	< 0.001
Other factors	A	2.502	12.206 [6.016 - 24.763]	< 0.001
Constant	-------	-14.328	-------	-------

OR: odds ratio; 95%CI: 95% confidence interval.

SIMONETTI ADHERENCE SCORE FOR PATIENTS ON ORAL ANTICOAGULANT THERAPY

INFLUENCING FACTORS	YES	NO	SCORE
• Drug-drug interaction	0	30	---
• Inadequate use of medications	0	18	---
• Eating habits	0	07	---
• Invasive procedures	0	02	---
• Clinical conditions/ Health problems	0	02	---
• Others	0	05	---
TOTAL	*(0 a 64)*		---

□ Low (≤ 10 points)

□ Intermediate (11 - 30 points)

□ High (≥ 31 points)

Figure 1 - Simonetti medication adherence score.

impaired warfarin metabolism (amiodarone, rifampicin, simvastatin, gemfibrozil), and impaired vitamin K metabolism (acetaminophen).[9] In general, drug interactions reduce the therapeutic effects of OACs and increase the risk for clotting or potentiate such effects and increase the risk of bleeding.

Some factors, however, should be considered[9] when the effects of OACs are decreased, such as inhibition

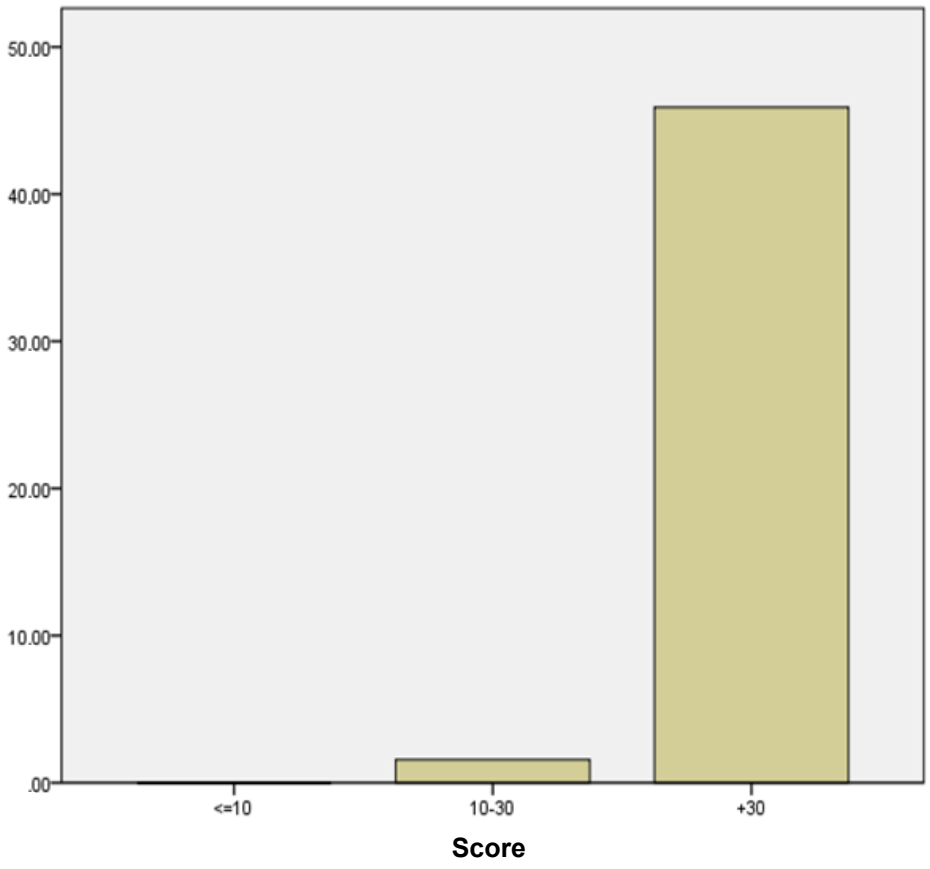

Figure 2 - Internal validation of Simonetti adherence score.

of warfarin absorption by cholestyramine or by foods in the gastrointestinal tract; increased distribution volume and half-life reduction due to hypoproteinemia; increased metabolism caused by stimulation of CYP2C9 by other drugs (barbiturates); excess intake of vitamin K-rich foods. On the other hand, CYP2C9 inhibition by other drugs (fluoxetine, amiodarone, clopidogrel), protein binding displacement caused by diuretics and sodium valproate, as well as vitamin K deficiency may reduce vitamin K metabolism, and consequently increase its effect.[10]

Amiodarone and simvastatin were the main drugs that significantly affected the required dose of OACs. Amiodarone is an antiarrhythmic that inhibits warfarin, due to its role as a potent cytochrome P450 inhibitor including CYP2C9, which is involved in S-warfarin metabolism.[10] Amiodarone inhibits warfarin metabolism and increases its effect, and the concomitant use of both drugs also affects prothrombin time. Simvastatin potentiates the effect of warfarin by binding to plasma proteins, reduces platelet aggregation and promotes thrombus formation.[11]

Besides, it is essential that patients on OAC-T are aware of the consumption of vitamin K-rich foods. Variations in the amount or in the frequency of consumption of these foods may change INR to values outside the therapeutic range.[10]

In case of acute alcohol consumption, dehydrogenase pathway plays a key role in ethanol metabolism in the liver. Nevertheless, in case of chronic consumption, the microsomal ethanol oxidizing system, which requires the CYP2E1 enzyme, is used and increases ethanol metabolism by ten-fold.[10] Therefore, in the pharmacokinetics of warfarin, there is an interaction between ethanol and the drug – in case of acute ethanol consumption, warfarin metabolism is decreased by enzymatic inhibition, resulting in increased OAC effect and increased risk of bleeding.[10] In chronic alcohol consumption, enzymatic activity decreases, with consequent increase of warfarin metabolism, reduction

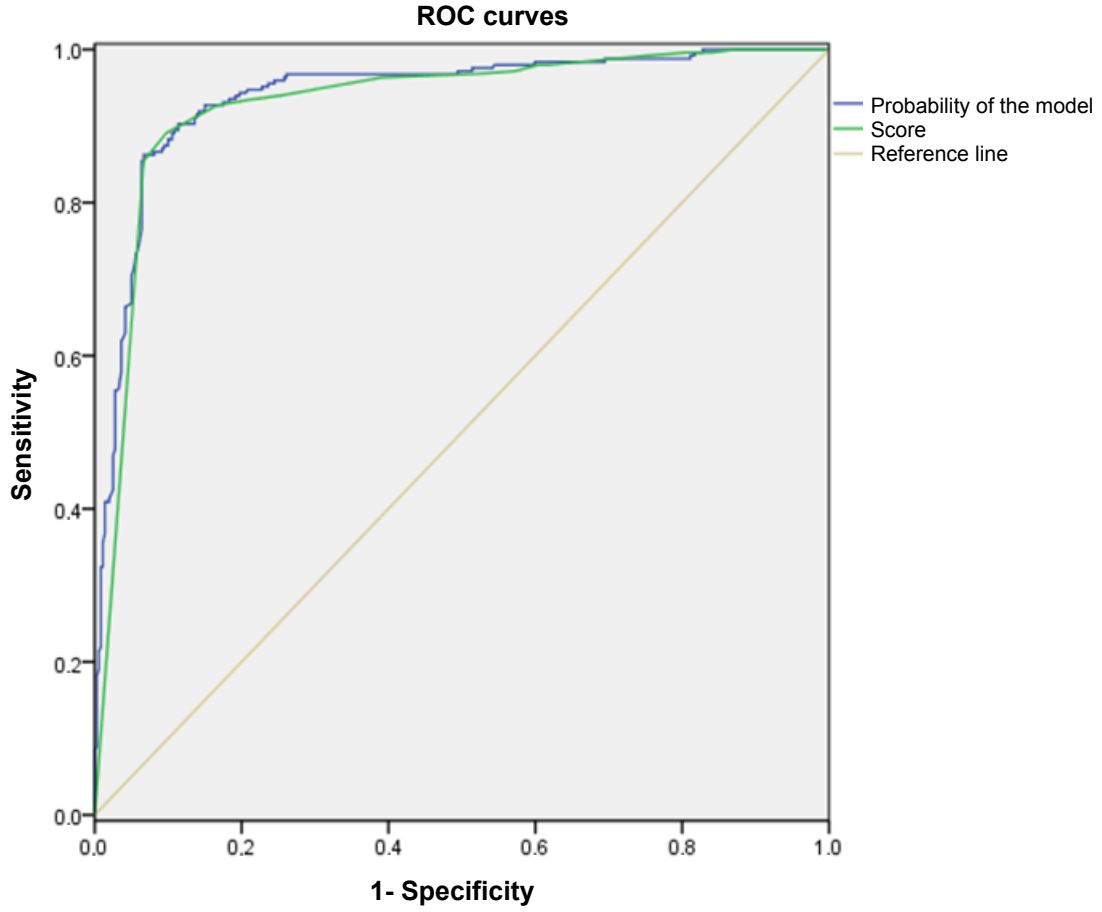

Figure 3 - Areas under the ROC (Receiver Operating Characteristic) curves for medication adherence by the Simonetti score.

of its half-life and pharmacological effect. In this case, a higher dose of warfarin is recommended to reach the therapeutic range.[10]

In addition, psychological distress has been associated with a prothrombotic state. In patients with diagnosis of thromboembolism, decreased INR was associated with psychological distress, anger, depression and anxiety.[11,12]

To minimize the risk of OAC-related complications, such as bleeding and thromboembolic events, the emergence of specialized clinics for the management of patients on OAC-T has become a common scenario worldwide. Besides, health professionals including pharmacists, nurses and physicians are responsible for implementing educational programs with oral and written instructions, videos, home visits, telephone follow-up and quality control indicators.[6]

In this perspective, predisposing factors related to oral anticoagulant therapy as continuous use in treatment of thromboembolic diseases and cardiac valvar prosthesis have to be studied. Mundial recommendations are relevant and published by of the American Heart Association[13] and European Society of Cardiology.[14]

Considering this assumption and the necessity to develop a medication adherence score for users of OACs, we adopted a complex, well-articulated and decisive methodological approach. This included the selection of predictive variables based on the clinical practice and also on researcher's opinion, determined by practice-based evidence and current science.

Variables with statistical significance lower than 5% were selected for multiple logistic regression analysis, with adjustment for determinant factors and covariables of adherence. Variables related to adherence were then independently determined.

For adherence score development, variables known to affect INR were considered, including inadequate

use of medication (higher or lower doses, missing doses), history of invasive or surgical procedures, drug-drug interaction, nutrient-drug interaction (particularly vitamin K), health problems or clinical conditions, other related factors such as considerable psychological distress, weight gain or loss and OAC-related complications. Thus, the score was developed using the variables of several models, classified and compared based on descriptive analysis of the independent variables, as well as interaction tests.

Then, a score model for a Brazilian population of patients in OAC-T was developed (Table 3); this was a simple instrument, easily applicable in the clinical setting of OAC-T. Results of the score were presented as odds ratio and respective 95% confidence interval and descriptive analysis.

The tests revealed the independent nature of the variables and the impartiality of the event occurrence. Therefore, a score that attributed the same weight for the variables was developed.

The proportion of the occurrence of an event will then be calculated by the number of positive variables for adherence and the number of predictive variables established in the model.

Simonetti adherence score had a c-statistic of 0.94, indicating satisfactory performance and applicability. Therefore, the score proposed in the present study will contribute to a more accurate evaluation and decision-making process. However, a long-term evaluation of the instrument should be performed in the clinical setting, like any stratification model, in order to evaluate the occurrence of new variables that may affect adherence.

Some limitations of the study should be considered. First, since the study was conducted in only one center, the model may not be reproducible in other settings. Second, since the score was not applied in an independent population for external validation, the performance of the instrument may not be satisfactory. It is worth pointing out, however, that our next step is to validate the instrument in another group of patients on OAC-T.

Despite these limitations, we successfully developed a medication adherence score using a model with good statistical performance. We believe that the score is of public interest and can contribute to the improvement of oral anticoagulation centers.

This study aimed to ensure and improve the provision of nursing services to patients on OAC-T in a specialized center, using a specific protocol. Although this characterized a limitation of the study, this would encourage different centers to revise their own protocols and to be informed of how treatment is being performed in other centers.

The proposed model of medication adherence score is in conformity with the significant and independent variables identified in the study. This ensures its accessibility and applicability. Using adequate statistical methods, we developed the Simonetti adherence score, and confirmed the hypothesis of this study.

Conclusion

The medication adherence score here proposed for patients on OAC-T was shown to be an easy-to-use instrument, with high predictive value and good performance. We successfully developed an instrument aimed at measuring and improving adherence of patients to OAC-T by means of the proposed methods and results obtained, confirming the hypothesis of the study.

This instrument will help professionals in accurately dealing with and hence improving adherence of patients to OAC-T and consequently improve the quality of life of this population.

Author contributions

Conception and design of the research: Simonetti SH, Bianchi ERF, Faro ACM. Acquisition of data: Simonetti SH. Analysis and interpretation of the data: Simonetti SH, Bianchi ERF, Faro ACM. Statistical analysis: Simonetti SH. Writing of the manuscript: Simonetti SH, Bianchi ERF, Faro ACM. Critical revision of the manuscript for intellectual content: Simonetti SH, Faro ACM. Supervision / as the major investigador: Simonetti SH.

Potential Conflict of Interest

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

Sources of Funding

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Study Association

This article is part of the thesis of Doctoral submitted by Sérgio Henrique Simonetti, from USP Nursing School.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Instituto Dante Pazzanese de Cardiologia do Estado de São Paulo under the protocol number 4420 e CAAE: 24118513.7.0000.5392. 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

Superior Cardiovascular Effect of the Periodized Model for Prescribed Exercises as Compared to the Conventional one in Coronary Diseases

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Abstract

Background: Physical exercise improves the survival and quality of life of coronary patients, but the ideal way of prescribing these exercises is still controversial.

Objective: To create a new periodized model for the prescription of exercises for coronary patients and compare it with a conventional model.

Methods: 62 coronary patients under pharmacological treatment were randomized into two groups: conventional (NPG, n = 33) and periodized (PG, n = 29) training. The two groups were submitted to the same exercises during the 36 sessions making up the program, but prescribed in different ways. All patients underwent an evaluation consisting of: medical admission consultancy, cardiopulmonary endurance testing, 1 maximum repetition test (1MR) and body composition evaluation.

Results: The VO_2 peak improved in both groups, although more effectively in the PG (4% against 1.7%, $p < 0.001$). In addition, the functional capacity of this group improved by 13%, and there was a significant reduction in the percent body fat (2.1%, $p < 0.005$) and body weight (1.9 kg, $p < 0.005$). The muscle strength of both groups improved as diagnosed by the 1RM test for six different muscle groups (quadriceps, hamstrings, brachial biceps, brachial triceps, pectoral and large dorsal), and showed no significant difference between the groups, evidencing that the two models had the same efficiency.

Conclusions: The present study showed that periodization of the training of cardiac patients can improve their cardiorespiratory capacity and reduce the percent body fat more effectively than the conventional one. (Int J Cardiovasc Sci. 2018;31(4)393-404)

Keywords: Coronary Artery Disease / physiopathology; Exercise; Exercise Therapy; Exercise Movement Techniques; Percutaneous Coronary Intervention.

Introduction

According to the World Health Organization, cardiovascular disease is responsible for 33% of all deaths occurring in the world per year.[1] In Brazil, more than 900,000 deaths of individuals over the age of 30 years were registered in 2011.[2] Despite this, the number of patients over the age of 60 years who survive a cardiovascular event and require secondary care is increasing every year.[2] Therefore, the regular practice of physical exercise and/or of cardiac rehabilitation has become fundamental for the reduction in mortality and comorbidities associated with cardiovascular disease.[3,4] Exercise training in coronary artery disease (CAD) patients include improvements in cardiovascular and skeletal muscle functions, endurance, inflammation,

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quality of life, and cognitive functions, and relieved clinical symptoms (dyspnea, sleep disorders, stress and depressive symptoms).[5,6]

Guidelines which involve physical exercise as a form of treatment for CAD respect a relationship of equilibrium between safety and effect of training,[7,8] and recommend that resistance training (RT) be performed in combination with aerobic exercise training (AT).[5,6] For RT, they provide recommendations concerning the maximum load limits during training, such as 50% of intensity in the one repetition maximum (1RM) test.[7-9] For AT, the ventilatory threshold measured during maximum cardiopulmonary exercise test (CPT) is often used in CAD patients. For beginners with low physical function/greater cardiac risk, the guidelines recommend 40% to 50% of maximum oxygen consumption (VO_2 peak), and for CAD patients with higher fitness level or less cardiac risk, 50% to 75% of VO_2 peak.[5,6] However, none of those documents describe the way in which the prescription of the exercises should be organized by time. The maximum load limits for training allow for the elaboration of an exercise session but not for a progressive training program. Such organization, which should involve the type of stimulus according to the training phase (continuous and/or with intervals), the form of load progression (volume and/or intensity),[10] the frequency (session/week) and the evaluation and reevaluation dates, is known as periodization.[11]

Periodization has been used in sport training since the 1990s,[12] and its inclusion in rehabilitation has been recently debated.[13-15] The training can be described in more detail using periodization, emphasizing its basic principles as: specificity, overload and reversibility. Periodization is the process of manipulating training variables to prevent overtraining, maximize training adaptations, and attain overcompensation or a training effect.[9] The classical approach to periodization is linear periodized training which appears in exercise guidelines for cardiac patients.[8] This type consists of initial high-volume and low-intensity. For this reason, the clinical and physical results obtained from periodized physical training in cardiopulmonary and metabolic rehabilitation programs could be improved, improving the quality of life of the patients involved.

Therefore, the objective of this study was to create a periodization model for the prescription of exercises aimed at patients with CAD in phase II of the cardiac rehabilitation program, and compare the results with those of patients submitted to a non-periodized program.

Method

Subjects

After approval of the project by the Ethics in Research of the Parana Pontific Catholic University (434/2010), 534 patients referred to the rehabilitation service of the Hospital Cardiológico Costantini (HCC) were evaluated.

The inclusion criterion was: men undergoing a percutaneous coronary intervention (angioplasty) or post-acute myocardial infarction with a left ventricular ejection fraction ≥ 50% (evaluated by transthoracic echocardiography) and stratified as of low or moderate risk for the practice of exercise according to the American Association of Cardiopulmonary Rehabilitation and Prevention.[16] The exclusion criteria were: musculoskeletal injuries induced by exercise, failure to complete the 36 sessions and/or cardiovascular complications that lead to stop the exercise program. Patients stratified as at low or moderated risk according to the American College of Sports Medicine (ACSM)[10] were submitted to a medical admission consultancy (MAC).

After evaluation, 62 patients who met the inclusion criterion were selected.

Outcomes of the measures

Cardiopulmonary exercise test

Cardiopulmonary exercise test was carried out by a doctor from the HCC using a gas analyzer (Cortex, model Metalyzer3B), an electric treadmill (Inbramed, model Inbrasport Super ATL) and a computer program (Ergo PC Elite). The CPT chosen was an individualized ramp protocol for each patient, measuring blood pressure every 3 minutes with an analogical sphygmomanometer (Missouri) and a stethoscope (BD). In addition, the electrocardiographic tracing was monitored using electrodes (3M) throughout the entire endurance phase and recovery period. The volumes and gases (O_2 and CO_2) were calibrated before the tests. The V-slope method was used to determine the first ventilatory threshold (VT1). The second ventilatory threshold (VT2) was determined by respiratory point compensation, that is, transition between aerobic and anaerobic system in CPT. At this moment, the production of CO_2 loses linearity, exponentially increases and exceeds oxygen consumption (VO_2). This point was considered the VT2. Maximum oxygen consumption was established from the mean measured during the last 30 seconds of exercise.

One repetition maximum test

The 1RM test was carried out by one of the instructors from the HCC rehabilitation service. It was defined as the heaviest weight that can be moved in an exercise with no more than one repetition. Before starting the test, all subjects performed a 5-minute general warm-up of cycling and, after that, they carried out 10 repetitions with no additional load to adjust the speed and angle of movement. First, the instructor explained how to carry out each movement. The 1RM test was done encompassing the large muscle groups (quadriceps, hamstrings, pectoral, biceps, triceps and large dorsal), and the weight was increased by 5 kg at every repetition, with 3-5 minutes of rest between lifts after three to four subsequent attempts. The test was interrupted when the patient was unable to complete the one repetition with the proposed load, and, in this case, the previous load was considered the ideal one. The MEGAMOVEMENT station was used for the test in the following positions: extensor chair, leg curl, hip adduction and abduction, bench press, biceps and triceps curl, and high pulley rear.

Body composition evaluation

The body composition (Bc) was evaluated by a rehabilitation instructor. The Faulkner protocol was composed of six circumference measures (calf, thigh, arm, forearm, hip, and abdomen) and four skinfold measures (abdomen, suprailiac, subscapular and triceps).[15]

A tape measure (Wiso model R88) was used combined with an adipometer (Cescorf). Fat percentages, ideal body mass, lean and fat masses were calculated using the Faulkner equation.[17]

The volunteers were reevaluated after 36 sessions (MAC + CPT + 1MR + Bc).

Experimental design

This study was a randomized controlled trial, in which 62 male patients were included and randomly assigned to two groups: a non-periodized training group (NPG, n = 33) and a periodized exercise training group (PG, n = 29). Blinded scaled envelopes were prepared with papers named PG and NPG and kept secure by an independent person (Figure 1).

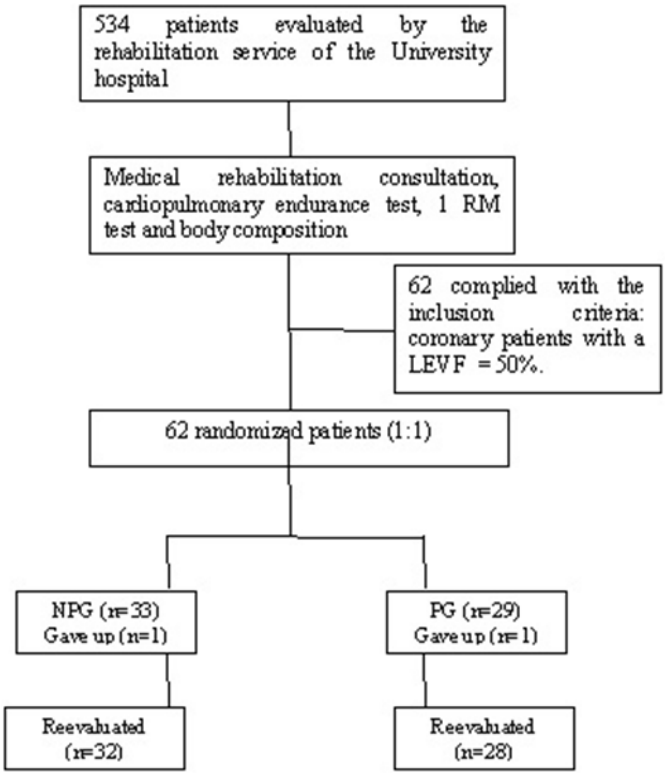

Figure 1 - Study design.
PG: periodized exercise training group; NPG: non-periodized exercise training group; LEVF: left ventricular ejection fraction; RM: maximum resistance.

Training protocols

All subjects of both groups carried out AT and RT for 12 weeks, 3 sessions per week (36 sessions) on non-consecutive days.

The AT was carried out on a treadmill (Movement models RT250, LX160 and LX150), while, in the RT, ankle weights, dumbbells, and a muscle toning machine (MEGAMOVEMENT II station) were used.

Resistance protocol

The RT was made in upper and lower limbs, being two sessions for lower limbs and one session for upper limbs. Hence, 24 sessions of AT were carried out on a treadmill and with lower resistance exercise (LRE), whereas, in the other 12 sessions, the treadmill and upper resistance exercise (URE) were used. Thus, every two consecutive sessions of treadmill + LRE were followed by one of treadmill + URE.

The exercise selection for RT was similar in the two groups and included: leg extension, leg curl, hip flexion, knee flexion, hip abduction and adduction, ankles planti-flexion and hip flexion associated with knee flexion, elbow flexion and extension, shoulder abduction, scapular adduction, shoulders anterior flexion, pendulum exercise for the decoaptation of the shoulder joint, bench press, lat pulldown, biceps and triceps curl and pulley. The two groups carried out three sets of 15 repetitions of each exercise and the intensity of the RT varied from 30% to 50% of the loads obtained in the 1RM test. The difference between the two groups was that, in the PG, the intensity was increased progressively in each microcycle (four weeks) and, in the NPG, the intensity was increased according to patient's resilience (Table 1). According to the ACSM,[10] the rest intervals between sets were of 1 to 2 minutes.

Table 1 - Resistance and aerobic training programs for NPG and PG

Training periods	Sets	Repetitions	Load (%1RM)
Resistance training			
NPG			
Weeks 1 - 12	3	15	30-50%
GP			
Weeks 1 - 4	3	15	30%
Weeks 5 - 8	3	15	40%
Weeks 9 - 12	3	15	50%
Endurance training		**Intensity**	
NPG			
Weeks 1 - 12		HRVT1 to HRVT2	
GP			
Weeks 1 - 6		HRVT1	
Weeks 7 - 12		Interval training (2 min HVT1+AHR, 1 min HRVT2)	

PG: periodized exercise training group; NPG: non-periodized exercise training group; HRVT1: heart rate ventilatory threshold 1; HRVT2: heart rate ventilatory threshold 2; AHR: average heart rate.

Aerobic protocol

The intensity of the AT on the electric treadmill for the two groups was defined from the result obtained in the CPT. The heart rate (HR) corresponding to the VT1 was defined as the lower limit training (HRVT1), whereas the HR corresponding to the VT2 was defined as the upper limit training (HRVT2). The interval between HRVT1 and HRVT2 corresponded to the ideal training intensity for each patient, known as the target zone (TZ).[3]

The two groups began the AT program with 25 minutes of activity divided into 5 minutes of warm-up, 15 minutes of training in the TZ and the 5 final minutes of cool down. After every three sessions, 5 extra minutes of training within the TZ were added. From the 10th to the 36th session, the total work time was of 40 minutes, 30 of which were within the TZ. The 5 minutes of warm up and cool down each were maintained throughout the 36 sessions.

The NPG trained along the 36 sessions within the TZ range proposed prescribed by HR (corresponding to the VT1 and VT2 of the CPT) without a predict load progression. The patient chose the training intensity, provided it was within the TZ (Figure 2A).

The AT of PG was divided in two microcycles of 18 sessions. First the average of HR (AHR) was determined between HRVT1 and HRVT2, obtained from the formula: AHR = (HRVT2-HRVT1)/2. The training intensity until the 18th session was determined by HRVT1 + AHR. This was designated as target zone 1 (TZ1). The second target zone (TZ2) was determined by the interval between HRVT1 + AHR and HRVT2. For instance, if the patient displayed HR in VT1 of 100 bpm and 130 bpm in VT2,

the TZ1 was the interval between 100 and 115 bpm, and the TZ2 between 115 to 130 bmp. After the 18th session, the interval training commenced, corresponding to 2 minutes of intensity in AHR and 1 minute in HRVT2.

Thus, the difference between the models of the AT proposed was based on the progression of load, that is, pre-determined in PG (18th session), regulated by the increase of HR of training and change within the TZ (TZ1 for TZ2), whereas in NPG, the intensity was regulated only by patient, always between TZ1 and TZ2 (Table 1). The patients of NPG and PG trained with a conventional HR monitor (Oregon model HR102). Additionally, the instructors check regularly the HR with finger oximeters (Nonin). It is important to emphasize that coronary patients at low risk for the practice of exercises were reminded to train between the ventilatory thresholds, following the recommendation of the Brazilian Society of Cardiology.[3]

Throughout the 36 training sessions of the NPG, the safety criteria for training and the intensity limits were respected, the loads for RT varied from 30% to 50% of the 1RM test, and the TZ limits for AT were also respected. Moreover, the volume of training was maintained, carrying out three sets of 15 repetitions for each localized exercise and a maximum time of 40 minutes of AT after the 10th session. These limits were presented to the patients, who defined their ideal training loads themselves according to their comfort zone and received orientation from the instructor regarding the implementation of the movements.

In the PG the prescription of their exercises was periodized. This group performed the same volume of training with the same intensity intervals prescribed for the NPG, but with the prescription organized by time. Thus, three training macrocycles were created, the first known as adaptation (MAD), the second as fundamental (MFU) and the third as specific (MSP). Each macrocycle, which presented a different objective, was composed of 12 microcycles and each microcycle was defined as a group of three classes or training sessions. The objective of MAD was to improve neuromuscular coordination and cardiopulmonary adaptation. The objective of MFU was to improve the ventilatory threshold and muscle fiber recruitment. And the objective of MSP was to improve VO_2 peak (Figure 2) and resistance strength.

Data analysis

The results obtained in this study were expressed as means, medians, minimum and maximum and standard deviations (quantitative variables) or frequencies and percentages (qualitative variables). The data were tested through normal distribution using the Kolmogorov-Smirnov test. The groups were compared regarding the quantitative variables using Student t test for dependent samples or Mann-Whitney nonparametric test. Regarding the qualitative variables, the comparisons were made considering Fisher exact test or chi-square test. Student t test was used to compare the moments of evaluation in the case of paired samples or nonparametric Wilcoxon test. In order to compare the groups and the evaluation moments (initial x final), a variance analysis model with a repeated measurements factor (split-plot) was considered. All variables which presented significant interaction between group and evaluation moment were analyzed by comparing the groups at each moment, and the evaluation moments within each group, where values for $p < 0.05$ indicated statistical significance. The data were analyzed using the Statistica V 8.0 program.

Results

Baseline characteristics

One NPG patient and another from the PG did not complete the 36 exercise sessions. As a consequence, a total of 60 patients (NPG n = 32 and PG n = 28) were reevaluated.

Table 2 provides the baseline characteristics of the 60 patients who met the inclusion criteria. All variables evaluated had a normal distribution (Kolmogorov-Smirnov test, $p > 0.05$) (Table 2).

Adverse events during treatment period

No significant adverse events were registered during the training period.

Body composition parameters

No significant differences were observed between groups. However, there was a significant difference within the groups in all variables in PG and only in %fat above ideal in NPG (Table 3).

Cardiopulmonary testing

There was no significant difference between baseline values for all cardiopulmonary variables between the two groups. However, significant post-training changes were observed in functional capacity (FCR) reached, VO_2 peak and VO_2 for the VT1 and VT2, with superior training

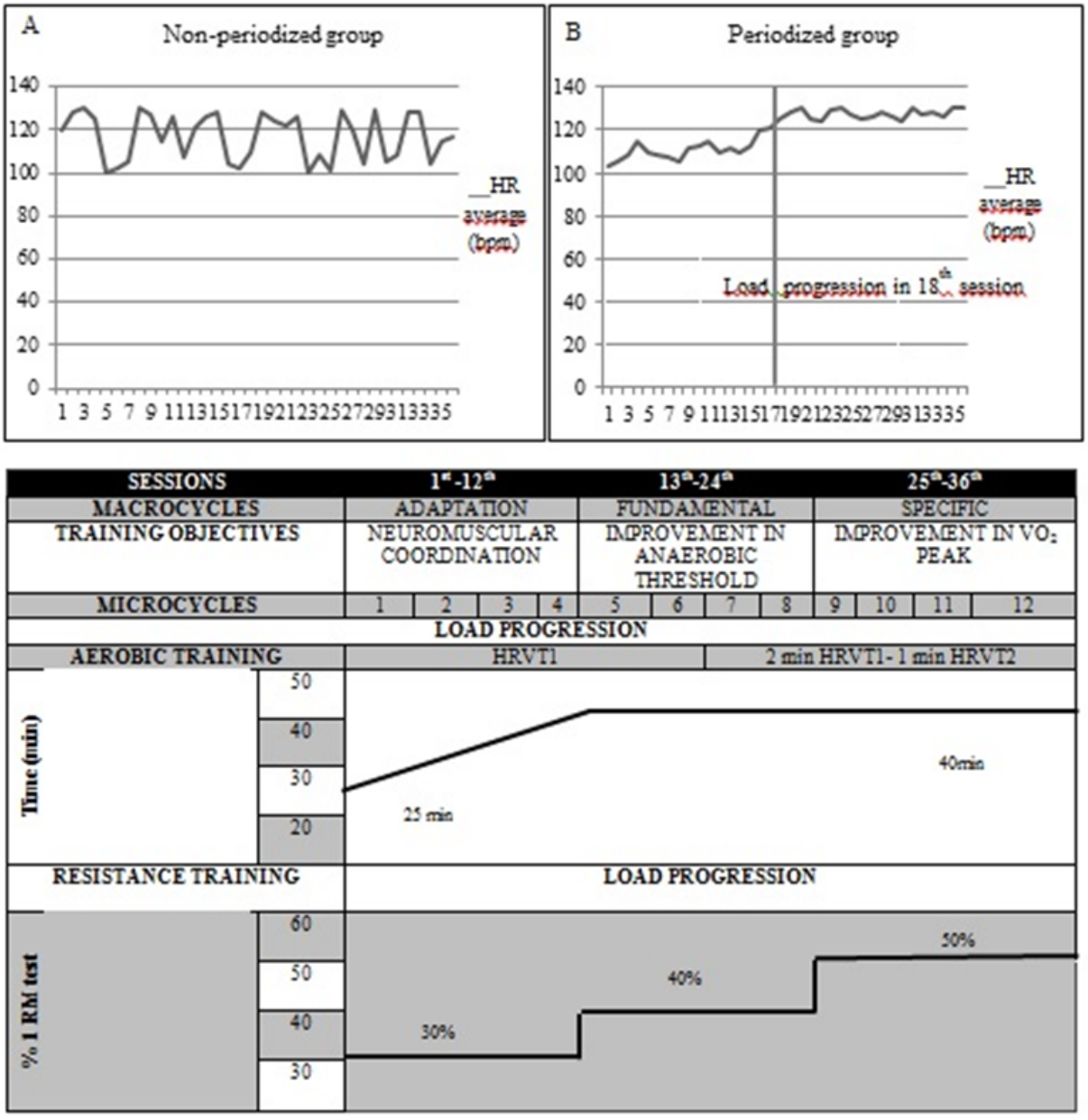

Figure 2 - Periodized exercise prescription model. A, B- Heart rate variation in aerobic training. C- Exercise prescription model.
RM: maximal resistance; HRVT1: heart rate ventilatory 1; HRVT2: heart rate ventilatory 2.

effect for PG. In addition, there was a significant difference within groups in FCR, VO_2 peak, VO_2VT1, VO_2VT2, VT2 speed in both groups compared pre- and post-training. A significant difference was noted in maximum speed reached in PG and VT1 and VT2 inclination in NPG in the comparison between groups (Table 4).

Skeletal muscle function

The evaluation of the muscle strength parameters within groups, compared pre- and post-training, showed a significant improvement. In a comparison made between the groups, no significant difference could be found (Table 5).

Table 2 - Baseline characteristics of the study population

Sample characteristic	PG	NPG
n (men)	28 (100%)	32 (100%)
Age ± SD, years	55.89 ± 8.2	62.4 ± 11.8
Left ventricular ejection fraction, ** %	65.57 ± 5.5	66.09 ± 5.7
Body mass index	28.2 ± 3.5	28.9 ± 4.4
Abdominal circumference	100.7 ± 9.0	101.0 ± 10.6
Positive family history / cardiovascular disease	20 (71.5%)	24 (80%)
Dyslipidemia	27 (96.7%)	32 (100%)
Obesity	12 (42.8%)	22 (68.75%)
Sedentary life style	22 (78.5%)	25 (78.1%)
Stress	25 (89.2.8%)	22 (68.75%)
Smoking habit	4 (14.2%)	8 (25%)
Diabetes mellitus	5 (17.8%)	3 (9.3%)
High blood pressure	12 (42.8%)	15 (46.8%)
Stratification of risk for exercises		
Low risk	21 (75%)	25 (78.1%)
Moderate risk	8 (21.6%)	3 (8.1%)
Anatomic location of injuries		
Right coronary	5 (14.2%)	
Posterior descending	0	
Left main coronary	2 (7.1%)	
Anterior descending	18 (64.2%)	
Diagonal	5 (17.8%)	
Circumflex	6 (21.4%)	
Marginal	0	
Arteries with stent implants		
Right coronary		
1 stent	4 (14.2%)	
2 stents	1 (3.5%)	
3 stents	0	
Posterior descending		
1 stent	1 (3.5%)	
Left main coronary		
1 stent	2 (7.1%)	
Anterior descending		
1 stent	16 (57.1%)	
Diagonal		
1 stent	1 (2.7%)	
Circumflex		
1 stent	6 (21.4%)	
2 stents	6 (21.4%)	
Marginal		
1 stent	0	
Incomplete revascularization of myocardium	1 (3.5%)	
Prior surgery for revascularization of myocardium	2 (7.1%)	
Prior angioplasties	5 (14.2%)	
Medications,†%		
Antiplatelet agents	28 (100%)	
Anticoagulant	28 (100%)	
Antihypertensive	13 (46.4%)	
Beta-blockers	26 (92.8%)	

*PG: periodized exercise training group. NPG: non-periodized exercise training group; ** Obtained by transthoracic echocardiography; † Standard dose of medication.*

Discussion

This study ascertained the following outcomes: superior improvement of body fat, fat above ideal and body mass, VO_2 peak and VO_2 at VT1-2 in the PG; muscle strength improvement in both groups. Periodization training is suggested in most recent guidelines.[5-8] However, the superiority of periodized training (RT and AT) has been poorly studied in CAD patients.

The main finding of this study was that the periodized exercise prescription program was superior to the conventional one with respect to the increase in VO_2 peak for coronary patients taking part in a rehabilitation program. VO_2 peak is closely associated with morbidity and mortality in cardiac patients.[18] This information is very important since periodization is still not in the rehabilitation programs of CAD patients.[19] In addition, VO_2 peak is recognized as being the best indicator of survival for this population.[20-22] Therefore, the inclusion

Table 3 - Body composition parameters

Group	PG (n = 28)		p	NPG (n = 32)		p
	Pre	Post		Pre	Post	
Body fat (%)	24.0 ± 3.5	21.9 ± 3.6	0.03*	23.9 ± 4.4	22.9 ± 4.1	0.34
Fat above ideal (%)	6.7 ± 3.2	4.8 ± 2.9	0.02*	5.6 ± 5.7	4.5 ± 5	0.42
Body mass (kg)	85.9 ± 11.7	77.4 ± 9.7	0.02*	83.9 ± 15.1	83.2 ± 14.9	0.84

*PG: periodized exercise training group; NPG: non-periodized exercise training group. *p < 0.05 (Student t test) within-group differences.*

Table 4 - Cardiopulmonary testing

Group	PG (n = 28)		p	NPG (n = 32)		p
	Pre	Post		Pre	Post	
FCR (% of predicted value)	88.7 ± 12.4	101.9 ± 13.8†	0.00*	80.2 ± 15.3	86.5 ± 12.2†	0.00*
VO_2 peak (mL/kg/min^{-1})	27.2 ± 6.3	31.5 ± 7.3†	0.00*	22.9 ± 5.7	24 ± 6†	0.00*
VO_2 VT2	23.64 ± 4.8	27.7 ± 3†	0.00*	19.9 ± 5.4	21.6 ± 5.4†	0.04*
VO_2 VT1	17.0 ± 2.3	20.7 ± 2.3†	0.00*	15.8 ± 3.5	16.4 ± 3.4†	0.23
HR maximum reached	159.7 ± 22	162.6 ± 18.5	0.30	138.3 ± 18.3	136.1 ± 18.6	0.33
HR VT2	169.9 ± 21	141.9 ± 20.5	0.39	119.2 ± 16.2	118.8 ± 15.8	0.86
HR VT1	110 ± 14.5	114.3 ± 15.7	0.10	100 ± 15.6	96.1 ± 20.6	0.29
Maximum speed reached (km/h)	8.2 ± 2.4	8.8 ± 2.4	0.05*	6.8 ± 1.9	7.2 ± 1.9	0.19
Speed VT2 (km/h)	7.1 ± 1.8	7.9 ± 1.8	0.05*	5.7 ± 1.5	6.3 ± 1.3	0.02*
Speed VT1 (km/h)	5.4 ± 1.4	6 ± 1.9	0.06	4.5 ± 1.3	4.8 ± 1	0.12
% max inclination (degrees)	13 ± 6.1	14.3 ± 6.1	0.12	12.3 ± 4.4	13.8 ± 4.3	0.12
% inclination VT2 (degrees)	12 ± 5.4	12.5 ± 6.6	0.45	10.3 ± 4	12.2 ± 3.3	0.01*
% inclination VT1 (degrees)	8.4 ± 4.2	9.6 ± 5.2	0.14	7.4 ± 3.2	8.7 ± 3	0.05*

*PG: periodized exercise training group; NPG: non-periodized exercise training group; FCR: functional capacity reached; HR: heart rate; * Intra-group difference (Student t test for dependent samples, p ≤ 0.05); † Difference between groups (Student t test, p < 0.05).*

of periodization as a fundamental basis for exercise prescription in cardiac rehabilitation programs could improve the results in VO_2 peak.

Cardiopulmonary testing

The two training groups showed improvements in VO_2 peak and in the VO_2 of the VT2, but only the PG showed a significant increase in the VO_2 of the VT1. VO_2 peak is an independent predictor of mortality and morbidity in CAD patients.[6] In the comparison between groups, the PG showed a significant effect compared to the NPG. Also, both groups improved their functional capacity (% of the predicted value), with most significant differences in favor of PG, which were attributed to the better structuring of the load progression in this group. The classical approach to periodization is the linear periodized training that appears in exercise training

Table 5 - Intra & intergroup comparison of muscle strength

Group	PG		p	NPG		p
	Pre	Post		Pre	Post	
Extensor chair (kg)	13.5 ± 5.5	24.0 ± 8.3	0.00*	10.4 ± 5	20.6 ± 8.4	0.00*
Leg curl (kg)	7.9 ± 3.3	14.1 ± 4.3	0.00*	6.5 ± 3	11 ± 6.5	0.00*
Bench press	12.6 ± 4.5	21.2 ± 6.5	0.00*	9.7 ± 5	18.2 ± 6.9	0.00*
Triceps	8.9 ± 3.6	15.5 ± 4.4	0.00*	7.2 ± 3.5	12.3 ± 3.5	0.00*
Biceps	8.4 ± 2.5	13.3 ± 3.4	0.00*	7.2 ± 3.1	11.4 ± 3.6	0.00*
High pulley rear	15.5 ± 5.7	28.5 ± 7.9	0.00*	11.8 ± 7.2	23.9 ± 11.4	0.00*

** Intra-group difference (Student t test for dependent samples, $p < 0.05$)*

guidelines for cardiac patients,[6,8] but has never been compared to non-periodized training in this population. Linear periodized training has superior cardiac and musculoskeletal function as compared to non-periodized training for athletes and healthy subjects[10,23] and with respect to cardiometabolic risk in obese adolescents.[24] Ribeiro et al.[25] have described that, for beginners, walking programs remain the most prescribed modality for CAD patients because they are safe, controlled, and can be performed anywhere.

The intensity of the AT of the NPG was moderate, between VT1 and VT2, that is, between the minimum and maximum stable phases of lactate production.[19] Therefore, they trained during almost the whole period (36 sessions) predominantly using the aerobic system as their energy source, without generating acidosis, and metabolic recovery was not necessary during the session, allowing for the maintenance of continuous training. Jolliffe et al.[1] have carried out a meta-analysis involving 8,440 patients with 32 randomized and controlled studies. They concluded that AT was safe, improved the aerobic capacity and reduced mortality, confirming the findings of the present study for PG.

The volunteers in the PG trained in the same interval of intensity as the NPG (between the HRVT1 and HRVT2). A training TZ was created for both groups corresponding to the HR interval for VT1 and VT2, but a load progression was organized for the PG. The intensity of AT was limited to the AHR up to the 18th session and this interval training was defined as the ideal to improve aerobic performance.[22] The improvement of the VO_2 of the VT2 in the PG was attributed to this specificity of the training, which did not occur in NPG. As from the 19th session (half of the fundamental macrocycle), the volunteers started training above the AHR up to the HR corresponding to the VT2. Due to the increased intensity of training, interval training started in PG. From the 5th minute of walking on the treadmill, the patient trained 2 minutes close to the HRVT1 followed by 1 minute close to the HRVT2, and maintained this alternating scheme until completing 30 minutes of workout. Due to its specificity, this training intensity promoted a greater increase in the VO_2 of the VT2, a fact confirmed by the findings of the present study. It is important to highlight that this AT with intervals, limited by the maximum stable lactate phase, has already been proven. Cornish et al.[26] have published a meta-analysis involving 213 patients with seven randomized studies, which demonstrated the need for more studies in order to determine the risks and benefits of interval training above the VT2. In addition, the authors have noted different prescription methodologies, with the patients starting the exercise program with sets of high intensity training with intervals in the majority of cases.[27] We believe that periodization allows for a greater chance of standardizing the prescriptions.

Body composition

The volunteers in the PG showed reductions in their fat mass, weight of fat above the ideal value and in their body weight. Increments in body mass and body fat are associated with several chronic diseases, such as diabetes and cardiovascular disease.[28]

Studies have shown that moderate AT promotes an improvement in body composition.[29,30] This was important because obesity is considered to be an important modifiable cardiovascular risk factor.[31] A simple improvement in food habits is not sufficient for a rapid and appropriate decrease in fat mass. Therefore, the physical exercise association was fundamental for body weight decrease and long-term maintenance of these changes.[31] Studies[28,32,33] have recognized aerobic exercise as the most suitable form of training by providing positive effects on glucose and lipids and decrease on body fat and the strength exercises. Inoue et al.[24] have shown that the association of strength and AT was more effective than only AT to improve lipid profile and insulin resistance sensitivity on obese adolescents.

The improvement in aerobic capacity or exercise tolerance results in a greater consumption of calories to maintain the activity and, consequently, burning more fat.[24] Lira et al.[34] have studied the effects of intensity and type of exercise on lipoprotein profiles and highlighted the higher energy expenditure achieved by associating volume and intensity. This fact justifies the finding that the PG, with its greater cardiopulmonary evolution and tolerance to exercise, presented greater body fat decrease. This is because improving the aerobic capacity increases the caloric expenditure per session, since the patient is walking more within a same time interval.

Skeletal muscle function

Both training groups presented a significant improvement in strength after the training period. In this case, the PG showed no advantage.

During MAD the patients worked with loads equivalent to 30% of the maximum determined in the 1RM test, in the MFU, with 40%, and in the MSP, with 50%. This organized progression of the load was not more effective than the random progression used for the NPG. This could be attributed to the fact that these low training loads did not recruit different energy sources and/or types of muscle fibers. In addition, in the first 12 weeks of training, the increase in strength occurs due to neural adaptation and not to hypertrophy, which is independent of the load.[8,11] The increase in strength noted in both groups could have contributed to the improvement in the VO_2 peak, in the walking speed and in the inclination reached during the treadmill test.[27]

Therefore, the training study is extremely important to both athletes, to reach high performance, and patients, such as those with heart disease, to reduce the risk of mortality, which has great social relevance.

Conclusion

The present study showed that, within the cardiac rehabilitation programs for coronary disease patients, periodization of the training can improve the results as compared to the conventional model, when considering the following variables: VO_2 peak, VO_2 for the VT2, VO_2 for the VT1, %fat and body weight. These findings are very important for future studies involving physical training and cardiac rehabilitation.

We believe that, at the present moment, before evolving into comparative studies between continuous exercises of moderate intensity versus high intensity exercises with intervals, periodization should be included as a prescription tool aimed at improving the results of the intervention or treatment of those with coronary disease with physical exercise.

Study limitations

Some of the study limitations were the small size of the sample and not using the Faulkner protocol to evaluate body composition. In addition, inflammatory biomarkers, oxidative stress analysis and drug reduction for hypertension were not performed.

Author contributions

Conception and design of the research and analysis and interpretation of the data: Macedo RM; Acquisition of data: Macedo RM, Sebastião Neto F; Statistical analysis: Macedo RM, Macedo ACB, Olandoski M; Obtaining financing:Macedo RM, Guarita-Souza LC, Silveira RP; Writing of the manuscript: Macedo RM, Macedo ACB, Faria-Neto JR, Costantini CR, Costantini CO, Guarita-Souza LC, Carvalho KAT; Critical revision of the manuscript for intellectual content: Macedo RM, Macedo ACB, Faria-Neto JR, Guarita-Souza LC.

Potential Conflict of Interest

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

Sources of Funding

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Pontifícia Universidade Católica do Paraná* under the protocol number 434/2010. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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ORIGINAL ARTICLE

Prevalence of Peripheral Artery Disease and Associated Risk Factors in a Brazilian Rural Population: The Baependi Heart Study

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Abstract

Background: The identification of peripheral artery disease (PAD) can help prevent further progression of the disease and additional complications, considering that this condition is a risk factor for all-cause mortality and cardiovascular death.

Objective: To assess the prevalence of PAD in the Baependi Heart Study and investigate associated risk factors in different age groups.

Methods: A total of 1,627 individuals (of both genders and aged 18 - 102 years) residing in the municipality of Baependi (Minas Gerais, Brazil) were selected for this study. Anthropometric and biochemical parameters were evaluated by standard techniques. Physical activity level was determined by the International Physical Activity Questionnaire - Short Form (IPAQ-SF). The screening of PAD was performed by determination of the ankle-brachial index (ABI). The level of statistical significance was set at 5%.

Results: In the overall sample, the prevalence of PAD was 1.05%, and reached 5.2% after the age of 70 years. The frequency and intensity of smoking were higher in individuals with PAD. A prior history of myocardial infarction and a higher prevalence of hypertension, diabetes, obesity, and sedentary lifestyle were also associated with PAD. In addition, PAD was more frequent in blacks than whites. In multivariable analysis, age, diabetes, smoking, and physical inactivity remained independently associated with PAD.

Conclusion: The prevalence of PAD was low and increased clearly with age in our sample from a Brazilian rural population. Furthermore, the main risk factors for PAD in the investigated sample were smoking, sedentary lifestyle, diabetes mellitus, and age. (Int J Cardiovasc Sci. 2018;31(4)405-413)

Keywords: Peripheral Arterial Disease / prevalence; Risk Factors; Rural Population; Tobacco Use Disorder; Ankle-Brachial Index.

Introduction

Peripheral artery disease (PAD) is classically defined as a condition affecting noncardiac, nonintracranial arteries, majorly due to atherosclerosis, that leads to partial obstruction of the peripheral arteries, reducing perfusion to the tissues irrigated by these arteries.[1,2] Even though PAD is asymptomatic in most patients, the disease may progress with clinical symptoms (like claudication) and eventually lead to tissue necrosis. The identification of PAD can help prevent further progression of the disease itself and additional complications, considering that this condition is a risk factor for all-cause mortality[3-8] and cardiovascular death,[3,4,7,9] including coronary artery disease[3,7] and stroke.[5,7] PAD is also a major cause of quality of life impairment, which in turn, worsen even more with the progression of the disease.[10,11] Therefore, information

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on the prevalence of PAD is important to allow proper planning in public health care. Recommendations on the identification and management of this condition have been published by international medical societies.[12-14]

Epidemiological studies have determined that the prevalence of PAD in the general population range from 4-10%;[15-23] however, there is a clear increase in prevalence with increasing age,[13,17,19,24] with rates as high as 20% over the age of 70 years.[19,20] Data on the prevalence of PAD in the general Brazilian population are scarce. Only one large multicenter study assessed the prevalence of PAD and found a high rate (10.5%) in 1,159 individuals in the general population.[18] Other studies have investigated the prevalence of PAD specifically in Japanese-Brazilians[25,26] and in a small sample of patients with diabetes.[27] Therefore, other large studies are needed to better access the prevalence of PAD and understand the risk factors associated with this condition in the general Brazilian population.

The Baependi Heart Study is an ongoing Brazilian cohort study established in 2005 to investigate cardiovascular risk factors and heritability.[28] The study has now expanded to include other investigations such as nocturnal polygraph, heart rate variability, pulse-wave velocity, 24-hour ambulatory blood pressure monitoring, 24-hour electrocardiography (Holter), and assessment of vascular age by plethysmography. Using data collected from 2010 to 2013 from the above-mentioned research project, the present study aimed to assess the prevalence of PAD and investigate associated risk factors in different age groups.

Methods

Study sample

The Baependi Heart Study is a genetic epidemiological study of cardiovascular disease risk factors with a longitudinal design, whose methodology has been previously described.[28] For the present analysis, we carried out a cross-sectional evaluation of data collected in the second visit of the protocol (between 2010 and 2013). This study invited 2,072 individuals (of both genders and aged 18 - 102 years), distributed across 109 families residing in the municipality of Baependi, a city in a rural area (752 km^2, 18,072 inhabitants) located in Minas Gerais State, Southeast of Brazil. Of these, 1,634 participants underwent screening for PAD. The study protocol was approved by the ethics committee of the *Hospital das Clínicas* (SDC: 3485/10/074), University of São Paulo, Brazil. All procedures involved in this study are in accordance with the Declaration of Helsinki from 1975, updated in 2013. Informed consent was obtained from all participants included in the study.

Anthropometric evaluations

Anthropometric parameters were measured according to a standard protocol.[28] Height was measured in centimeters and weight in kilograms using a calibrated digital balance. Body mass index (BMI) was calculated as body weight (kg) divided by squared height (m^2). Waist circumference was measured at the mean point between the lowest rib margin and the iliac crest with the subject standing and at the maximum point of normal expiration. Obesity was defined as a BMI ≥ 30 kg/m^2.

Blood pressure measurements

Blood pressure was measured with a standard digital sphygmomanometer (OMRON, OMRON Eletrônica do Brasil Ltda., SP, Brazil) on the left arm after 5 minutes of rest, with the subject in the sitting position. Systolic (SBP) and diastolic blood pressures (DBP) were calculated from three readings (mean value of all measurements), with a minimal interval of 3 minutes.[28] Hypertension was defined as a mean SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg and/or use of antihypertensive drug.[29]

Biochemical measurements

Blood levels of triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and fasting glucose were measured by standard techniques in 12-h fasting blood samples.[30] Glycated hemoglobin (HbA1c) levels were determined by high-performance liquid chromatography (National Glycohemoglobin Standardization Program, USA). Diabetes mellitus was diagnosed in the presence of a fasting glucose ≥ 126 mg/dL, HbA1c ≥ 6.5%, or use of antidiabetic drugs. *Hypercholesterolemia was defined* as a total cholesterol level ≥ 240 mg/dL.

Assessment of risk factors and depression

Physical activity level was determined by the International Physical Activity Questionnaire - Short Form (IPAQ-SF). Sedentary lifestyle was identified based on a duration of physical activity lower than 10 minutes/day on the previous week.

Information regarding medical history (angina pectoris, myocardial infarction, stroke, kidney failure, and depression) and environmental risk factors such as smoking and alcohol use were evaluated through a questionnaire completed by each participant. The questionnaire was based on the World Health Organization's Multinational Monitoring Trends and Determinants in Cardiovascular Disease (MONICA)[31] project epidemiological instrument, and was applied and filled out by research assistants specifically trained for this task.

Screening of peripheral artery disease

The screening of PAD was performed with the ankle-brachial index (ABI), which was measured by a single trained examiner using a sphygmomanometer (Heidji, Brazil) with a cuff suitable for the circumference of the limbs and a 10 MHz portable Doppler device (DV 610B, MEDMEGA, SP, Brazil).

The ABI was determined for each leg by the ratio between the highest SBP obtained at the ankle (posterior tibial and dorsalis pedis arteries) and highest SBP obtained in the arms (brachial artery).[12-14] The methodology of the test and the ABI classification were based on recommendations of the American College of Cardiology / American Heart Association (ACC/AHA).[12,13] ABI values between 0.91 and 1.39 were considered normal. Values ≤ 0.90 were considered compatible with PAD and values ≥ 1.40 were considered inconclusive for PAD and were excluded from the analysis.

Statistical analysis

Categorical variables were compared using the chi-square test and are presented as percentage, while continuous variables are presented as mean ± standard deviation. The normality of the data was confirmed with the Kolmogorov-Smirnov test. Unpaired Student *t* test was performed to analyze demographic, hemodynamic, and biochemical data according to PAD status. Since the cutoff value for PAD diagnosis based on ABI is well-established in the literature, we carried out univariate and multivariate logistic regression analyses to determine the association between PAD (ABI < 0.9) as the dependent variable and age, hypertension, diabetes, myocardial infarction, smoking, and sedentary lifestyle as predictor variables. Statistical analyses were carried out using SPSS (version 19) software (Chicago, IL, USA), with the level of significance set at 5%.

Results

A total of 1,634 individuals were screened for PAD. Seven individuals presented an ABI above 1.4 and were excluded from the analysis. Therefore, 1,627 volunteers were included in the study. The age of the participants ranged from 18 to 102 years (mean 44.9 ± 16.4 years). Table 1 shows the demographic, anthropometric, biochemical, and hemodynamic characteristics of the individuals with and without PAD, defined as an ABI equal to or lower than 0.9. Age, BMI, HbA1c, and SBP were higher in volunteers with PAD. The presence of PAD was also more frequent in elderly compared with younger individuals, and in blacks compared with whites.

Figure 1 presents the data related to the prevalence of PAD using the ABI in different age groups. Overall, the prevalence was very low (1.05%). Only one case of PAD was observed below the age of 30 years, and the prevalence of PAD increased after the fifth decade, peaking at the age of 70 years, when it reached 5.2%. The frequency of PAD by decade is presented in the Table 2.

Table 3 presents the data related to the lifestyle characteristics of the volunteers. The frequency and amount of smoking were higher in individuals with PAD. There was also a higher frequency of physically inactive volunteers in the PAD group.

Table 4 presents a comparison of clinical characteristics in individuals with and without PAD. A higher prevalence of hypertension, diabetes, and obesity was observed in individuals with a diagnosis of PAD. The presence of hypercholesterolemia was not different between groups. Also, a prior history of myocardial infarction was more frequent in the PAD group.

Table 5 presents univariate and multivariate logistic regression models for PAD. In multivariate analysis, age, diabetes, smoking, and physical inactivity were significantly and independently associated with PAD.

Discussion

In terms of the number of individuals included, the present study is the largest investigation of the prevalence of PAD in a Brazilian population. The Baependi Heart Study is a Brazilian cohort study investigating cardiovascular risk factors and heritability in residents of

Table 1 - Demographic, anthropometric, biochemical, and hemodynamic characteristics of individuals with and without peripheral artery disease

Variables	Total	PAD present	PAD absent	P value
n	1,627	17	1,610	***
Age (years)	44.9 ± 16.4	66 ± 15	45 ± 16	< 0.001
Gender				
Men (%)	41.5	41.2	41.5	0.59
Women (%)	58.5	58.8	58.5	
Ethnicity				
White (%)	76.7	70.6	76.8	0.001
Black (%)	5.5	29.4	5.2	
Mulatto (%)	17.5	0	17.7	
Others (%)	0.3	0	0.4	
ABI (ratio)	1.11 ± 0.1	0.78 ± 0.11	1.12 ± 0.7	< 0.001
BMI (kg/m²)	25.8 ± 5.1	28.7 ± 5.3	25.7 ± 5.1	0.02
WC (cm)	91 ±12	100 ± 10	91 ± 12	0.003
TC (mg/dL)	197.8 ± 40.7	195.6 ± 59.9	197.9 ± 40.5	0.83
LDL-c (mg/dL)	124.5 ± 35.4	122.2 ± 56.3	124.6 ± 35.2	0.79
HDL-c (mg/dL)	47.2 ± 11.7	45.2 ± 13.1	47.2 ± 11.8	0.49
Triglycerides (mg/dL)	130.3 ± 68.1	141.1 ± 60.0	130.2 ± 68.2	0.52
Fasting glucose (mg/dL)	92.6 ± 19.0	114.6 ± 43.2	92.3 ± 18.5	0.06
HbA1c (%)	5.7 ± 0.7	6.5 ± 1.2	5.7 ± 0.8	0.02
SBP (mmHg)	125.4 ± 16.3	133.5 ± 19.2	125.4 ± 16.2	0.04
DBP (mmHg)	76.2 ± 10.3	75.3 ± 9.2	76.2 ± 10.4	0.72

Categorical variables were compared using the chi-square test, and continuous variables were compared using Student t test. PAD: peripheral artery disease; n: sample size; ABI: ankle-brachial index; BMI: body mass index; WC: waist circumference; TC: total cholesterol; HDL-C: high-density lipoprotein; LDL-C: low-density lipoprotein; HbA1c: glycated hemoglobin; SBP: systolic blood pressure; DBP: diastolic blood pressure.

the rural city of Baependi, located in Southeastern Brazil. In the study sample, which included 1,627 volunteers, the overall prevalence of PAD was 1.05%. The prevalence clearly increased with age, peaking at 5.2% above the age of 70 years. Individuals with PAD were older, heavier, more often smokers, and less physically active. Identified risk factors for PAD in the study sample were age (odds ratio [OR] = 1.08), smoking (OR = 4.01), sedentary lifestyle (OR = 3.75), and diabetes mellitus (OR = 3.07).

The occurrence of PAD in the general population has been assessed in different countries.[15-17,19,20,22,23,32] In Brazil, Makdisse et al.[18] reported in 2008 a high prevalence of PAD (10.5%) in a population with a mean age of 43.8 ± 14.7 years. The study involved volunteers in large cities (over 100 thousand inhabitants) from different Brazilian regions. Another study specifically assessed the Japanese-Brazilian population and determined a prevalence of PAD of 21.1%;[26] however, the mean age of the participants in this study was higher (about 56.5 years). The present study assessed volunteers from a city with an estimated population of 18,072 inhabitants at the time of the study. The prevalence found (around 1%) is considerably low.

Most studies assessing the prevalence of PAD have included samples of individuals older than 40 years (sometimes above the ages of 55 or 65 years). If we consider only the prevalence of PAD in individuals

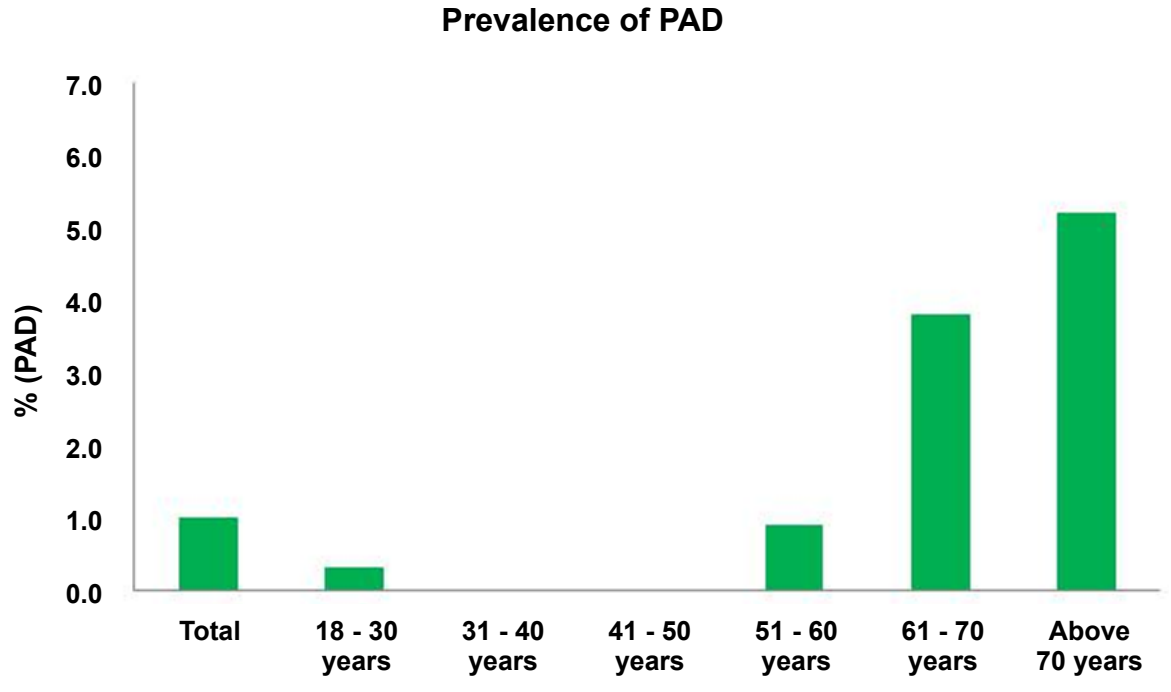

Figure 1 - Prevalence of peripheral artery disease (PAD) in the overall population and stratified by age group.

Table 2 - PAD prevalence by decade in men and women

Age (n)	PAD overall prevalence n cases (%)	PAD prevalence men n cases (%)	PAD prevalence women n cases (%)
Below 30 (397)	1 (0.3)	1 (0.6)	0 (0)
31 - 40 (279)	0 (0)	0 (0)	0 (0)
41 - 50 (335)	0 (0)	0 (0)	0 (0)
51 - 60 (316)	3 (0.9)	1 (0.8)	2 (1.1)
61 - 70 (184)	7 (3.8)	2 (2.5)	5 (4.8)
Above 70 (116)	6 (5.2)	3 (5.4)	3 (5.0)

PAD: peripheral artery disease.

older than 40 years in the present study (1.7%), the data are lower but in agreement to those of other studies such as the ones performed in Sri Lanka by Weragoda et al.[32] in 2015 (3.6%, n = 2,912) and in the US by Razzouk et al.[22] in 2015 (the Life Line Screening®, 4.1%, n = 3.67 million), and Eraso et al.[16] in 2015 (4.6%, n = 7,058), which identified prevalence rates below 5% in the general population. In a study published in 2016, Alzamora et al.[15] described a prevalence of new PDA of 4.3% (n = 2,256) in a study with a follow-up of 5 years conducted in a Spanish population aged more than 55 years and described as having low-risk factors for cardiovascular disease.

In the present study, the prevalence of PAD above the age of 50 years was 2.6%. As expected, age was independently associated with a diagnosis of PAD, as identified by the present and previous studies. Therefore, the low prevalence of PAD in the present study is partially due to the low mean age of the participants, the inclusion of volunteers with age starting at 18 years, and the fact that most volunteers (62.1%) were below the age of 50 years. Additionally, our sample had only about 7% (n = 116) of the volunteers above the age of 70 years, a group in which a higher prevalence of PAD is expected.[15-17,19,20,32]

Volunteers with PAD in the present study were older and had higher BMI, HbA1c, and SBP levels compared

Table 3 - Lifestyle characteristics of individuals with and without peripheral artery disease

Lifestyle characteristics	Total (1,627)	PAD present (n = 17)	PAD absent (n = 1,610)	p value
Smoking				
Have you ever smoked cigarettes?				
Yes, and still smoke	11.0%	5.9%	11.1%	
Yes, in the past	23.3%	58.8%	22.9%	0.02
No	65.7%	35.3%	66.0%	
Nº of cigarettes/day	13.3 ± 12.3	23.2 ± 14.3	13.1 ± 12.2	0.007
Alcohol consumption				
Daily	0.9%	0%	0.9%	
1-3 days/week	10.0%	0%	10.1%	
4-6 days/week	0.9%	0%	0.9%	
1-3 days/month	11.0%	5.9%	11.1%	0.70
Less than 1 day/month	6.0%	11.8%	6.0%	
Gets drunk at least once a month	0.7%	0%	0.7%	
None	70.4%	82.3%	70.3%	
Physical activity				
Very active	3.4%	0%	3.5%	
Active	30.1%	5.9%	30.4%	0.05
Irregularly active	25.2 %	17.6%	25.3%	
Sedentary	41.2%	76.5%	40.8%	

Alcohol consumption (mean frequency of alcohol intake in the last 12 months); physical activity (activities carried out in the last week - International Physical Activity Questionnaire - Short Form [IPAQ-SF]). All variables are categorical and were compared using chi-square test. PAD: peripheral artery disease.

with volunteers with normal ABI. Furthermore, a higher prevalence of physical inactivity, obesity and smoking frequency and intensity (cigarettes/day) was found in volunteers with PAD. These variables are frequently associated with PAD in other studies.[15-17,19,20,22,23,32] The present study also identified a higher frequency of PAD in blacks compared with whites. This finding is aligned with recent data published by Eraso et al.,[16] who assessed data from the National Health and Nutrition Examination Survey (NHANES), including 7,058 subjects above the age of 40 years. Another potential explanation for the low prevalence of PAD in the assessed population is the fact that the study was conducted in a small town where overall habits (e.g., nutritional) and exposure to risk factor (e.g., mental stress), other than the investigated here, are different from those observed in large cities. Comparing our population with the one included in the study by Makdisse et al.[18] (conducted in large Brazilian cities), our results showed a lower percentage of smokers (34.3% versus 46.7%) and physically inactive individuals (41.18% versus 64.8%). Also, the study by Makdisse et al.[18] had a larger number of individuals with chronic kidney disease (2.46% versus 6.12%), which is a well-known risk factor for PAD.[16,33]

Upon applying a multivariable logistic regression model, we determined the independent predictors associated with PAD. Only age, diabetes mellitus, smoking, and sedentary lifestyle emerged as significant

Table 4 - Comparison of clinical characteristics among individuals with and without peripheral artery disease

Clinical characteristics	Total (1,627)	PAD present (n = 17)	PAD absent (n = 1,610)	p value
Hypertension (%)				
Yes	40.0	82.4	39.6	< 0.001
No	60.0	17.6	60.4	
Diabetes (%)				
Yes	7.7	41.2	7.4	< 0.001
No	92.3	58.8	92.6	
Obesity (%)				
Yes	19.1	41.2	18.9	0.03
No	80.9	58.8	81.1	
Hypercholesterolemia (%)				
Yes	15.9	12.5	15.9	0.52
No	84.1	87.5	84.1	
Angina pectoris (%)				
Yes	3.0	5.9	2.9	0.40
No	97.0	94.1	97.1	
Myocardial infarction (%)				
Yes	2.2	11.8	2.1	0.05
No	97.8	88.2	97.9	
Stroke (%)				
Yes	0.6	5.9	0.5	0.09
No	99.4	94.1	99.5	
Kidney failure (%)				
Yes	2.5	5.9	2.4	0.35
No	97.5	94.1	97.6	
Depression (%)				
Yes	19.2	29.4	19.1	0.21
No	80.8	70.6	80.9	

All variables are categorical and were compared using the chi-square test. PAD: peripheral artery disease.

Table 5 - Univariate and multivariate logistic regression analysis of peripheral artery disease (defined as an ankle-brachial index < 0.90) in a Brazilian population

Variables	PAD	
	OR (95%CI), p value	
	Univariate	Multivariate
Age	1.08 (1.05 to 1.13), < 0.001	1.08 (1.03 to 1.13), 0.001
Hypertension	7.12 (2.04 to 24.90), < 0.001	1.53 (0.39 to 5.98), 0.54
Diabetes	8.77 (3.28 to 23.46), < 0.001	3.07 (1.07 to 8.85), 0.04
Obesity	3.01 (1.14 to 7.96), 0.03	2.89 (0.97 to 8.66), 0.06
Myocardial infarction	6.18 (1.36 to 28.07), 0.02	2.19 (0.44 to 11.02), 0.34
Smoking	3.56 (1.31 to 9.68), 0.01	4.01 (1.34 to 11.97), 0.01
Sedentary lifestyle	4.70 (1.53 to 14.48), 0.007	3.75 (1.16 to 12.03), 0.03

Multivariate model: age, hypertension, diabetes, obesity, myocardial infarction, smoking, and sedentary lifestyle. PAD: peripheral artery disease; OR: odds ratio; 95%CI: 95% confidence interval.

risk factors in the study sample. This finding is aligned with that of several other studies.[16,17,19,32,34] Even though PAD is majorly caused by atherosclerotic disease, hypercholesterolemia was not found as a significant risk factor. Other studies have also found a weak association between PAD and hypercholesterolemia when comparing risk factors[16] or no association whatsoever.[35]

Our study has some limitations. First, as a cross-sectional analysis, a causal relationship between several cardiovascular risk factors and PAD could not be established. Second, the diagnosis of PAD in the present study was established only by ABI. Despite being a simple and inexpensive method, studies have shown that ABI has a high sensitivity (90 - 97%) and specificity (98 - 100%) for detection of arterial stenosis greater than 50%.[36]

Conclusion

In summary, in a sample from the Brazilian population, aged 18 years and above and residing in a small rural town, PAD had a low prevalence, clearly increased with age, and was more frequent in blacks than whites. Additionally, risk factors for PAD in the investigated population were smoking, sedentary lifestyle, diabetes mellitus, and age,

which are similar to those in other epidemiological studies including different ethnic groups.

Author contributions

Conception and design of the research and writing of the manuscript: Alvim RO, Dias FAL, Krieger JE, Pereira AC; Acquisition of data abd analysis and interpretation of the data: Alvim RO, Dias FAL, Oliveira CM, Horimoto ARVR, Ulbrich AZ; Statistical analysis: Alvim RO; Obtaining financing: Krieger JE; Critical revision of the manuscript for intellectual content: Oliveira CM, Horimoto ARVR, Ulbrich AZ, Pereira AC.

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 das Clínicas da Faculdade de Medicina da Universidade de São Paulo under the protocol number SDC: 3485/10/074. 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

Methods of Screening for Depression in Outpatients with Heart Failure

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Abstract

Background: Depression is a syndromic clinical condition underdiagnosed in patients with heart failure. Several instruments are currently applied to screen for depression.

Objective: To determine the prevalence of depression and the agreement among screening methods for depression in patients with heart failure.

Methods: Cross-sectional study conducted between March 2015 and January 2017 including 76 outpatients following up at a clinic specialized in heart failure. Depression was screened with the Hamilton Depression Rating Scale (HAM-D), Beck Depression Inventory-II (BDI-II), and Patient Health Questionnaire-9 (PHQ-9). The agreement among the three instruments was analyzed with Fleiss' kappa coefficient (k_F), Krippendorff's alpha coefficient (C_k) and Cronbach's alpha coefficient. The accuracy, sensitivity, and specificity, as well as false-positive and false-negative results of the HAM-D and PHQ-9 were calculated considering the BDI-II as the gold-standard instrument in the diagnosis of depression.

Results: The prevalence rates of depression were 72.4% (n = 55) with the HAM-D, 67.1% (n = 51) with the BDI-II, and 40.8% (n = 31) with the PHQ-9 scales. The prevalence of depression simultaneously identified by all three instruments was 28.9% (n = 22) and the diagnostic agreement (presence or absence of depression) was 47.4% (n = 36). The analysis revealed a superficial agreement ($k_F = C_k = 0.27$) and moderate consistency (($\downarrow C = 0.602$, significantly not null, $p = 0.000$). Sociodemographic and clinical variables were not risk factors for depression in the evaluated sample.

Conclusion: The screening methods analyzed showed agreement and were useful in detecting depression among outpatients with heart failure. (Int J Cardiovasc Sci. 2018;31(4)414-421)

Keywords: Heart Failure; Depression / diagnosis; Depression / prevalence; Medical Records; Surveys and Questionnaires; Cross-Sectional Studies.

Introduction

Depression is a disorder of multifactorial nature.[1] When associated with heart failure (HF), depression compromises the functional capacity, quality of life, and survival of the patient.[2-7] It is necessary to explore the screening methods used to diagnose depression because despite the variety of applied instruments, no studies have been conducted to evaluate the agreement of these methods in patients with HF.[1,8]

The diagnosis of depression is established through the patient's clinical history and duration of signs and symptoms, as well as the application of specific scales.[1,8-9] There are approximately 49 scales used in the multidimensional assessment of depression,10 including the Hamilton Depression Rating Scale (HAM-D),[11] Beck Depression Inventory-II,[12] and Patient Health Questionnaire-9 (PHQ-9),[13] among others.

A study conducted by Matias et al.[1] comparing the screening of depression with the PHQ-9 and the

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Geriatric Depression Scale of Yesavage concluded that both instruments are useful in identifying depression in elderly individuals, with a rho correlation of 0.387 ($p < 0.000$), kappa reliability 0.41 ($p < 0.001$), sensitivity 80%, specificity 44%, and moderate agreement.

A randomized study conducted by Freedland et al.[14] evaluated the efficacy of an integrative cognitive behavior therapy intervention for depression (measured by the scales BDI-II [46%] and HAM-D [51%]) and self-care in outpatients with HF (n = 158); the results of the study showed that the intervention was effective for depression, but not for self-care.

Another study,[15] conducted to determine the best sensitivity and specificity values of the BDI-II and HAM-D in patients (n = 73) seen at a reference center in neuropsychiatric showed that the BDI-II had higher sensitivity and specificity (94.4% and 90.6%, respectively) than the HAM-D (95% and 75.5%, respectively).

The BDI-II has been described as a gold-standard instrument to screen for depression in HF.[3,16] However, as a self-rating scale, the BDI-II has limited application in patients with cognitive impairment or low education level. In these cases, interviewer-rated scales may be applied by professionals experienced in interviewing depressed patients.[15,17]

The objective of this study was to determine the prevalence of depression and the agreement among methods of screening for depression in patients with HF.

Methods

Type of study

Cross-sectional study with a consecutive sample, carried out between March 2015 and January 2017 in a clinic specialized in HF in *Universidade Federal Fluminense* (UFF), Niterói, RJ, Brazil.

Participants

The participants were enrolled in a multidisciplinary program of a clinic specialized in HF (UFF).

The participants included in the study were patients enrolled in the clinic's program, diagnosed with HF according to the criteria by McMurray et al.[18], of both genders, and with the ability to answer the questionnaires. We excluded patients with cognitive impairment, as identified in their medical records, difficulty or inability of understanding the instruments, and with a prior history of cognitive therapy or use of antidepressants.

In all, 76 patients comprised the final study sample and were assessed with three questionnaires for the screening of depressive symptoms: HAM-D, BDI-II, and PHQ-9.

The interview was conducted by a single interviewer, who followed the guiding protocol of the interviewer-rated questionnaire (HAM-D).[17]

The questionnaires BDI-II and PHQ-9 were applied as recommended in the literature.

The questionnaires were applied during the same interview, conducted by a single examiner. In the case of the self-rating questionnaires (BDI-II and PHQ-9), the patients were informed that these questionnaires were meant to evaluate their mental health status. They were then instructed to read the questionnaires attentively and mark the answers according to the intensity of their symptoms, with all following the same direction (i.e., the greater the severity of the symptom, the higher the score to be checked). There was no time constraint for the participants to complete the questionnaires and the examiner did not interfere with the reading of the questions to avoid a biased interpretation by the patient.

In regards to the HAM-D questionnaire, whose interview follows a protocol, the examiner conducted structured interviews and assigned a score to each response according to the intensity of the patient's signs and symptoms.

Instruments

Hamilton Depression Rating Scale

The HAM-D was the first interviewer-rated scale, i.e., applied by an interviewer. This scale was designed and developed by Hamilton at the end of the 1950s decade.[19] In 1994, the HAM-D was adapted to the Brazilian population as a valid instrument for an early diagnosis of a depressive episode. The HAM-D scale initially had 21 items but was subsequently reduced to a 17-item version after some items were removed (paranoid symptoms, obsessional symptoms, derealization, and diurnal variation), due to the low incidence or reliability of these items in relation to the measure of depression.[11,19]

In 1988, a structured manual was prepared for the HAM-D scale interview[20] to standardize the questions by the interviewer. Hamilton did not establish a cutoff value to discriminate normality from morbidity. Currently, it is accepted that scores with more than 25 points characterize

severely depressed patients, scores between 18 and 24 points characterize patients moderately depressed, and scores between 7 and 17 points characterize patients with mild depression.[17,19]

The items of the HAM-D scale focus on somatic symptoms (28%), cognitive symptoms (28%), motor symptoms (12%), anxiety (16%), mood (8%), and social symptoms (8%).[19]

This scale has been validated by several studies comparing the scores in groups of patients with diseases of different severity, including HF.[10]

Beck Depression Inventory-II

The BDI-II[12] has been validated in psychiatric inpatients and outpatients by comparison with the HAM-D, in which the BDI-II has been shown to be more effective.[12] The BDI-II is a self-rating instrument that screens for the presence of depressive symptoms using a scoring scale comprising 21 questions with four answer choices ranging from zero to three, ordered according to severity. To fill out the inventory, the individual selects the option that best fits the way he feels at the moment, with the scores ranging from zero (absence of symptoms) to three (highest intensity of the symptom).[21]

The overall BDI-II assessment is done by adding the numbers marked beside each question. A sum of 0-9 is considered normal, while 10-15 indicates mild depression, 16-23 indicates moderate depression, and 24 or more points indicate severe depression.

The screening properties of the BDI-II have been validated in Brazil. This scale is considered the gold-standard method for depression screening and has demonstrated good psychometric and operational characteristics.[3,10,12,16,21]

Patient Health Questionnaire-9 (PHQ-9)

The PHQ-9 evaluates the presence of depressive symptoms using a Likert-like scale comprising nine questions categorized into four response options ranging from "not at all" (zero points) to "nearly every day" (3 points) and a total score ranging from zero to 27 points. Thus, the higher the score, the worse the severity of the depressive signs. The PHQ-9 is a quick self-rating instrument that screens individuals at higher risk of presenting a major depressive episode.

The screening properties of this questionnaire were validated in the general Brazilian population in 2013,[22] and the questionnaire has demonstrated good psychometric and operational characteristics, with a sensitivity of 77% to 98% and specificity of 75% to 80%, having also been validated for the population of adults and elderly individuals.[1,23,24]

Procedures for data analysis

The descriptive analysis characterized the studied population according to frequencies and proportions. For quantitative variables, we used the statistics of minimum, maximum, mean, median, values, standard deviation, and coefficient of variation (CV). The variability of the distribution of a quantitative variable was considered low if $CV < 0.20$, moderate if $0.20 \leq CV < 0.40$, and high if $CV \geq 0.40$. In order to investigate the significance of the association between two qualitative variables, we used the chi-square test, and when this proved inconclusive, we applied Fisher's exact test for 2 x 2 tables.[25]

In the inferential analysis, complementary proportions were compared using the binomial test. The hypothesis of normality of a quantitative variable distribution was verified by the Kolmogorov-Smirnov (KS) and Shapiro-Wilk (SW) tests. The distribution was considered normal if both tests did not reject the null hypothesis of normality. In order to compare two independent groups when the variable had a normal distribution, we used unpaired Student's t test; otherwise, the comparison between the groups was performed with the Mann-Whitney non-parametric test.[25]

The agreement of the three instruments in diagnosing depression in the HF population was analyzed by Fleiss' kappa (k_F) and Krippendorff's alpha coefficients (C_k). The consistency of the three instruments in diagnosing depression in the HF population was assessed by Cronbach's alpha coefficient (C_c). Agreement and consistent were evaluated according to the Landis & Koch classification (1977).

We calculated the accuracy, sensitivity, specificity, and rates of false-positive and false-negative results of the HAM-D and PHQ-9 instruments considering the BDI-II as the gold-standard instrument in the diagnosis of depression (the definition of these concepts can be found in Medronho et al., 2009).

The statistical analysis was performed using the program Statistical Package for the Social Sciences (SPSS), version 20.0, and all analyses were carried out considering a maximum significance level of 5.0%.

Ethical procedures

The study was approved by the Research Ethics Committee of *Hospital Universitário Antônio Pedro/ Universidade Federal Fluminense* with the number 630.078. The patients were informed about the objectives of the research, signed a free and informed consent form, and were assured about their right to data confidentiality and care in regards to the use of their information in written work. The patients presenting symptoms related to any mental disorder during the clinical interview of the main study were referred to a mental health service integrated into the clinic specialized in HF.

Results

A total of 76 patients participated in this study, of whom 40 (52.6%) were female and 36 (47.4%) were male. The binomial test showed no significant difference between these proportions (p = 0.731), i.e., the sample was balanced in relation to the distribution of men and women, and the observed prevalence of women was not significant. The age of the patients followed a normal distribution (p = 0.094 by the KS test and p = 0.467 by the SW test), with an interval of 35 to 91 years, a mean of 63.0 years, standard deviation of 11.6 years, and a median of 65 years. The CV of age (0.18) showed that the distribution of age had low variability in the sample.

The monthly income of the patients did not follow a normal distribution (p = 0.000) and ranged from R$ 500.00 to 3,000,00, with a mean of R$ 1,118.74 (standard deviation R$ 576.32 and median R$ 1,000.00). The CV of the income (0.51) showed that the distribution of income had high variability in the sample. The frequency distribution of the observed variables characterizing the patients are shown in Table 1.

Typically, all patients had a white self-declared color (67.1%), education level of Elementary School I (56.6%), NYHA functional class II (51.3%), hypertension (100%), dyslipidemia (81.6%), diabetes (56.4%), and obesity (44.8%). There was no significant difference between the age of men and women (p = 0.056) or between the incomes of men and women (p = 0.644).

The male and female groups did not differ in relation to the distribution of self-declared color (p = 0.641), education level (p = 0.352), and incidence of diabetes (p = 0.223), dyslipidemia (p = 0.827), chronic renal failure (CRF; p = 0.426), chronic obstructive pulmonary disease (COPD; p = 0.601), and stroke (p = 1.000).

Table 1 - Sociodemographic and clinical characteristics of outpatients with heart failure

Sociodemographic variables	n (76)
Gender	
Female	52.6% (n = 40)
Male	47.4% (n = 36)
Age (mean ± SD)	63.03 ± 13.5 years
Self-declared color	
White	67.1% (n = 51)
Black	28.9% (n = 22)
Indeterminate	3.9% (n = 3)
Education level*	
Literacy	2.6% (n = 2)
Elementary School I	56.6% (n = 43)
Elementary School II	36.8% (n = 28)
Middle School	3.9% (n = 3)
Family income in reais (mean ± SD)	1,118.74 ± 576.32
Functional class (NYHA)	
I	30.3% (n = 23)
II	51.3% (n = 39)
III	18.4% (n = 14)
Hypertension	100% (n = 76)
Dyslipidemia	81.6% (n = 62)
Diabetes	56.6% (n = 43)
BMI (kg/m^2)	
Low weight	1.3% (n = 1)
Normal weight	23.7% (n = 18)
Overweight	14.5% (n = 11)
Pre-obesity	15.8% (n = 12)
Obesity I	30.3% (n = 23)
Obesity II	9.2% (n = 7)
Obesity III	5.3% (n = 4)
Anemia	19.7% (n = 15)
CRF	23.7% (n = 18)
COPD	3.9% (n = 3)
Stroke	5.3% (n = 4)

n: number of patients; SD: standard deviation; NYHA: New York Heart Association; BMI: body mass index; CRF: chronic renal failure; COPD: chronic obstructive pulmonary disease.

The prevalence rates of depression diagnosed by the instruments were: 72.4% (n = 55) by the HAM-D, 67.1% (n = 51) by the BDI-II, and 40.8% (n = 31) by the PHQ-9, as shown in Table 2. Considering a simultaneous diagnosis by all three instruments, the prevalence of depression was 28.9% (n = 22). The three instruments showed a diagnostic agreement (presence or absence of depression) in only 47.4% of the sample (n = 36).

Comparing the three instruments in terms of diagnosing depression in the HF population, there was superficial agreement ($k_F = C_k = 0,27$, as evaluated by Fleiss' kappa (k_F) and Krippendorff's alpha coefficients (C_k), and moderate consistency (significantly not null, p = 0.000), as assessed by Cronbach's alpha coefficient (C_C).

Table 3 shows the quality measures of the HAM-D and PHQ-9 instruments as diagnostic tests for depression in outpatients with HF, using the BDI-II as the gold-standard instrument. The HAM-D scale proved to be the best instrument to diagnose depression, as it showed higher accuracy and sensitivity and a lower percentage of false-negative results. The PHQ-9 instrument was conservative in diagnosing depression, with a high percentage of false-negative results and a low sensitivity in identifying patients who in fact had depression.

Table 2 - Prevalence (P) of depression in outpatients with heart failure

Instrument	Results
HAM-D	72.4% (n = 55)
BDI-II	67.1% (n = 51)
PHQ-9	40.8% (n = 31)
Agreement among all three instruments	k↓F = C↓k = 0.27
Consistency of the three instruments	(↓C 0.602; p < 0.000

n: number of patients; HAM-D: Hamilton Depression Rating Scale; BDI-II: Beck Depression Inventory-II; PHQ-9: Patient Health Questionnaire-9.

Considering the BDI-II as the gold-standard instrument in diagnosing depression, we investigated the association of depression with the patients' characteristics. There was no significant association between depression and the following factors: gender (p = 0.291), self-declared color (p = 0.976), education level (p = 0.918), obesity (p = 0.324), diabetes (p = 0.316), dyslipidemia (p = 0.056), COPD (p = 0.250), stroke (p = 0.296), and CRF (p = 0.536).

The age and income of the patients with and without depression were also not associated with depression (p = 0.862 [unpaired Student's t test] and p = 0.776 [Mann-Whitney test], respectively).

Therefore, none of the variables included in this study was associated with depression or was a risk factor for depression in outpatients with HF.

Discussion

This is the first study comparing screening methods for depression in outpatients in a multidisciplinary clinic specialized in HF. Depression has not been systematically analyzed in patients with HF, but when specifically researched, has been observed to be frequent in this population.[28-36] This condition affects between 14.0% and 26.0% of the patients without HF, but the incidence increases to 24.0% to 85.0% in patients with HF.[33,34]

The main findings of this study indicate a relevant prevalence of depression in HF patients when screened by the HAM-D, BDI-II, and PHQ-9 instruments. BDI-II has been considered the gold-standard instrument for depression screening in patients with HF, but in individuals with cognitive impairment or illiterate, this instrument is not recommended.[10,12,21] Therefore, the results of our investigation in relation to the internal

Table 3 - Quality measures of the HAM-D and PHQ-9 instruments as diagnostic tests for depression in outpatients with heart failure

Instrument	Accuracy	Sensitivity	Specificity	% of false-positives	% of false-negatives
HAM-D	76.3	86.3	56.0	14.5	9.2
PHQ-9	55.3	47.1	72.0	9.2	35.5

HAM-D: Hamilton Depression Rating Scale; PHQ-9: Patient Health Questionnaire-9.

consistency of the scales show that the BDI-II, HAM-D, and PHQ-9 proved to be useful tools for application in patients with HF.

We observed in this study a possible agreement advantage of the HAM-D with the BDI-II, the gold-standard instrument. This is probably due to the number of items in both questionnaires. The significant agreement among the scales indicates an evaluation of the intensity of the symptoms in the same direction, i.e., the greater the score, the greater the severity.[37,40]

A possible explanation for the difference in prevalence identified in the PHQ-9 scale may be due to its self-rating features since they portray an individual's subjective response (as how he perceives his health and symptom). Although the instrument has already been tested in various levels of health care attention and different cultural contexts,[1] still limited research has been carried out in Brazil using the PHQ-9 to screen for depression in outpatients with HF. A study carried out in Minnesota applied the PHQ-9 scale to evaluate the occurrence of depression in a sample of 425 outpatients with HF and identified a prevalence of 42.1% (n = 179),[38] which is in line with our findings.

Self- and interviewer-rating scales should take into account several aspects, including the individual's educational level and time availability for the assessment, as well as the objective of the evaluation.

The BDI-II and HAM-D scales are instruments used in more than 50% of the studies;[10] the sensitivity and specificity of these instruments is approximately 0.84 and 0.72, respectively,[37,39] which is also in line with our results.

A review[9] has assessed the scales HAM-D, BDI-II, Zung Self-Rating Depression Scale, Geriatric Depression Scale of Yesavage, and Montgomery-Åsberg Depression Rating Scale (MADRS). The results showed relevance in the identification of signs and symptoms of depressive disorders, directing the attention to mental health interventions in the elderly.

We observed that the patients in the present study had important clinical comorbidities (diabetes, dyslipidemia, obesity, CRF, and hypertension), which were not associated with depression. In a study conducted by Aguiar et al. (2010) in hospitalized patients with HF (n = 43), patients with depression (55.8%, n = 24) according to the HAM-D scale did not differ from non-depressed ones in regards to gender, age, anemia, and renal function, factors that are known to influence the occurrence of clinical manifestations.

Depression is an important risk factor associated with HF,[2] a syndromic clinical condition. When depression is not specified, it is mistaken and underdiagnosed in these individuals,[35] probably due to the superposition of symptoms of HF (dyspnea, weight change, sleep, fatigue) and the neurovegetative symptoms of depression (insomnia, psychomotor slowing, and decreased energy, concentration, and appetite).[36]

A study conducted by Freedland et al.[32] in a sample of 682 patients with HF showed that 245 (36%) patients had clinically significant depression (according to the Diagnostic and Statistical Manual of Mental Disorders [DSM-IV] criteria), while 436 (64%) were classified as non-depressed. Patients with depression also were not significantly affected by the presence of other important comorbidities, such as diabetes or kidney disease, or by the presence of only one of these conditions. These results are aligned with those of our study and differ in some aspects from the observations described in the literature. However, considering that depression emphasizes the clinical manifestations and worsens the progression of patients with HF, more attention should be dedicated to this condition, including to its screening. The importance of this initiative has been increasing in clinics specialized in HF, since studies have documented that the treatment of depression promotes improvement of the symptoms and quality of life of the patients.[2]

Limitations

This study presents limitations due to its experimental, observational, and cross-sectional design, which did not allow us to establish the variables predicting depression in HF. However, through the data presented, it becomes evident the importance of this discussion, because different depression scales are applied in this population.

This research demonstrates a need for further work on the screening of depression in outpatients in practices specialized on HF, due to the relevant prevalence of and damage from this association. It is important to highlight the need to deepen the knowledge of the association of depression with the sociodemographic and clinical characteristics present in this population for the development of preventive work in outpatients with HF.

Conclusions

Based on the results of this study on the prevalence of depression associated with HF, we found the following:

1) depression has a relevant prevalence in outpatients with HF; 2) the diagnosis and detection of depression are obtained through the use of questionnaires in outpatients with HF; 3) the three questionnaires evaluated have a superficial agreement and moderate consistency in the diagnosis of depression in the population with HF; 4) the HAM-D scale proved to be the best instrument in diagnosing depression, since it showed greater accuracy and sensitivity, and a lower percentage of false-negative results; 5) the PHQ-9 instrument was conservative in diagnosing depression, with a high percentage of false-negative results and low sensitivity to identify patients who are in fact depressed.

In the present study, the HAM-D questionnaire showed greater accuracy in the diagnosis of depression, due to its convenience in grading this condition and for demonstrating (in several studies) the ability to evaluate the severity of the depression.

These conclusions identify areas with gaps requiring further research, in addition to new questions in the screening of depression, and adds more information on the prevalence of depression in HF, guiding researchers and clinicians in terms of screening for depression and issues relevant to the association of these two pathologies, depression and HF.

Author contributions

Conception and design of the research: Guerra TRB, Mendlowicz MV, Mesquita ET, Cavalcanti ACD; Acquisition of data: Guerra TRB, Venancio ICD, Pinheiro DMM; Analysis and interpretation of the data: Guerra TRB, Mesquita ET, Cavalcanti ACD; Statistical analysis: Guerra TRB; Obtaining financing: Mesquita ET, Cavalcanti ACD; Writing of the manuscript: Guerra TRB, Pinheiro DMM; Critical revision of the manuscript for intellectual content: Mendlowicz MV, Mesquita ET, Cavalcanti ACD.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital Universitário Antônio Pedro under the protocol number 630.078. 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

Vitamin D Deficiency and Cardiovascular Diseases

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Abstract

Vitamin D is considered a steroid hormone with a broad spectrum of action in the human body. Its action arises from the binding of its active metabolite (1α,25-dihydroxyvitamin D) to its receptor (VDR), which is present throughout the body, including vascular smooth muscle cells and cardiomyocytes. Initially, vitamin D deficiency was related only to changes in the musculoskeletal system, but in recent years, researchers have demonstrated its relationship with several pathologies related to other systems, such as cardiovascular diseases. The objective of this study is to review vitamin D's pathophysiology, describe its relationship with cardiovascular diseases based on the most recent publications, and highlight the results of vitamin supplementation in the prevention of such pathologies.

Introduction

Vitamin D, the fourth vitamin to be described, was initially characterized as a factor capable of curing rickets, a disease characterized by bone demineralization and skeletal deformities.[1]

Currently, vitamin D comprises a group of secosteroid molecules derived from 7-dehydrocholesterol (7-DHC) that includes the active metabolite (1α,25-dihydroxyvitamin D or calcitriol), its precursors (cholecalciferol or vitamin D3, ergocalciferol or vitamin D2 , and 25-hydroxyvitamin D or calcidiol), as well as its degradation products.[2] These molecules, along with their carrier proteins and receptors, comprise an important metabolic axis: the endocrine vitamin D system.[3]

Keywords

Vitamin D Deficiency / physiopathology; Cardiovascular Diseases; Solar Radiation; Calcium; Phosphorus.

The active vitamin D has a fundamental role in regulating bone and mineral physiology, in particular, calcium and phosphorus metabolism. It is also involved in the homeostasis of several other cellular processes, such as the modulation of autoimmunity and synthesis of inflammatory interleukins,[4] blood pressure control,[5] and participation in the process of cell multiplication and differentiation.[6] The spectrum of action of vitamin D is so broad that microarray studies show that 1α,25-dihydroxyvitamin has more than 900 potential gene targets, corresponding to approximately 3% of the human genome.[7]

Epidemiological studies have found that a significant portion of the world population, regardless of age, ethnicity, and geographical location, has low serum levels of vitamin D,[8] as illustrated in Figure 1. Some countries even present rates of vitamin D deficiency above 50%, as observed in Brazil, Denmark, and Germany.

Recent studies have associated inadequate serum vitamin D levels with several diseases unrelated to the musculoskeletal system, such as cancer (colon, prostate, and breast), autoimmune and inflammatory diseases (multiple sclerosis, Crohn's disease), depression, and cardiovascular diseases (CVDs) such as hypertension, coronary artery disease (CAD), and heart failure (HF).[9]

The objective of this study was to review vitamin D's pathophysiology, describe its relationship with CVD based on the most recent publications, and highlight the results of vitamin supplementation in the prevention of such diseases.

Physiology and mechanism of action

In humans, only 10 to 20% of the vitamin D derives from the diet, and the remaining 80% is synthesized endogenously.[10] Few foods have significant amounts of this vitamin, of which the main ones are listed in Table 1.

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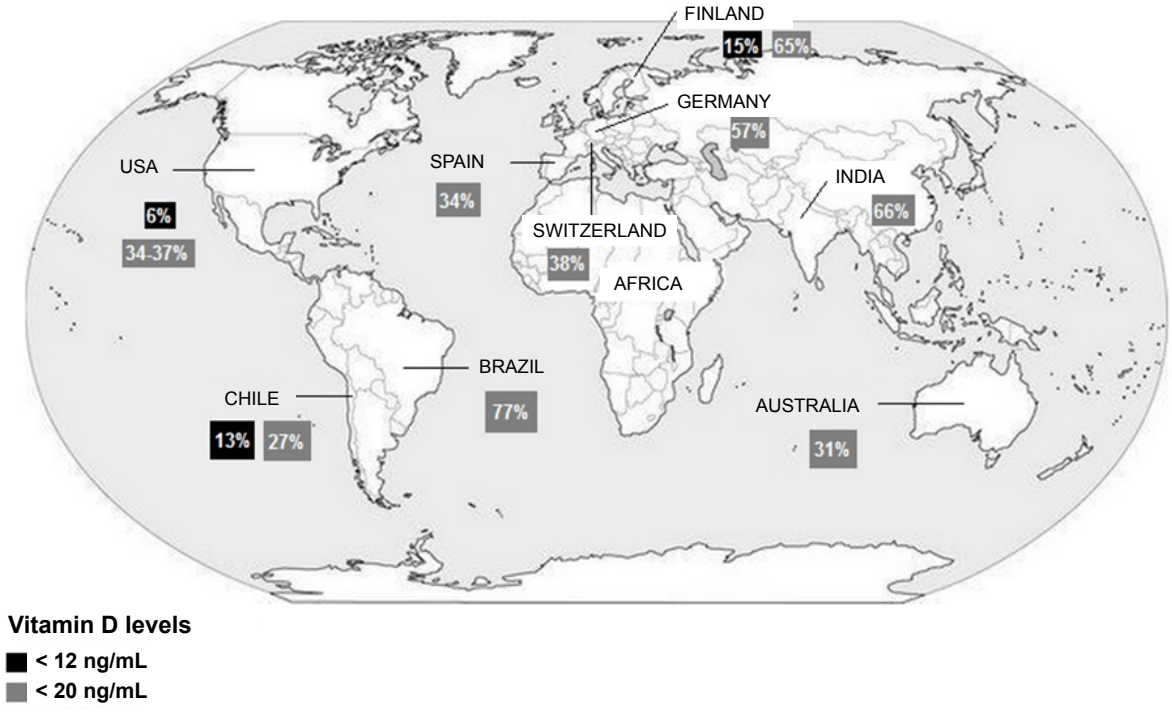

Figure 1 - Global prevalence of vitamin D deficiency in adults.
Adapted from: Palacios C, Gonzalez L. Is vitamin D deficiency a major global public health problem? J Steroid Biochem Mol Biol. 2014 October; 144PA: 138–145. doi:10.1016/j.jsbmb.2013.11.003.

Table 1 - Some food sources of vitamin D. Adapted from the Brazilian Society of Endocrinology and Metabolism[11]

Food	Portion	Amount of vitamin D per portion
Wild salmon	100 g	600 – 1,000 IU of vitamin D_3
Farmed-raised salmon	100 g	100 – 250 IU of vitamin D_3
Canned sardines	100 g	300 IU of vitamin D_3
Canned mackerel	100 g	250 IU of vitamin D_3
Canned tuna	100 g	230 IU of vitamin D_3
Cod liver oil	5 mL	400 – 1,000 IU of vitamin D_3
Egg yolk	1 unit	20 IU of vitamin D_3
Fresh mushrooms	100 g	100 IU of vitamin D_2
Sun-dried mushrooms	100 g	1,600 IU of vitamin D_2

The molecular structure of vitamins D2 and D3 is very similar. Ergocalciferol differs from cholecalciferol by a double bond between carbons 22 and 23 and a methyl group on carbon 24, as shown in Figure 2. Both vitamins are synthesized from energy derived by photolysis (solar radiation) on their precursors: ergosterol (vitamin D2) and 7-DHC (vitamin D3). Following ingestion by humans, both vitamins follow the same metabolization pathway in the liver and are converted into 25-hydroxyvitamin D.[11]

Synthesis of endogenous vitamin D starts in the deep layers of the epidermis, where the precursor 7-DHC is stored in the double lipid layer of the cell membrane. Ultraviolet B (UVB) radiation promotes 7-DHC photolysis, leading to the formation of a secosteroid molecule: previtamin D3. This molecule is thermally unstable and undergoes an isomerization reaction induced by heat, converting it into vitamin D3. Skin melanin competes for the radiation photon, decreasing the availability of photons for 7-DHC photolysis, hence the observation of lower vitamin D levels in blacks.[11]

When reaching the liver, vitamins D2 and D3 undergo hydroxylation by cytochrome P450 and originate 25-hydroxyvitamin D, which is the form of the vitamin that predominates in the circulation. In the blood, about 85 to 90% of the 25-hydroxyvitamin D is bound to vitamin

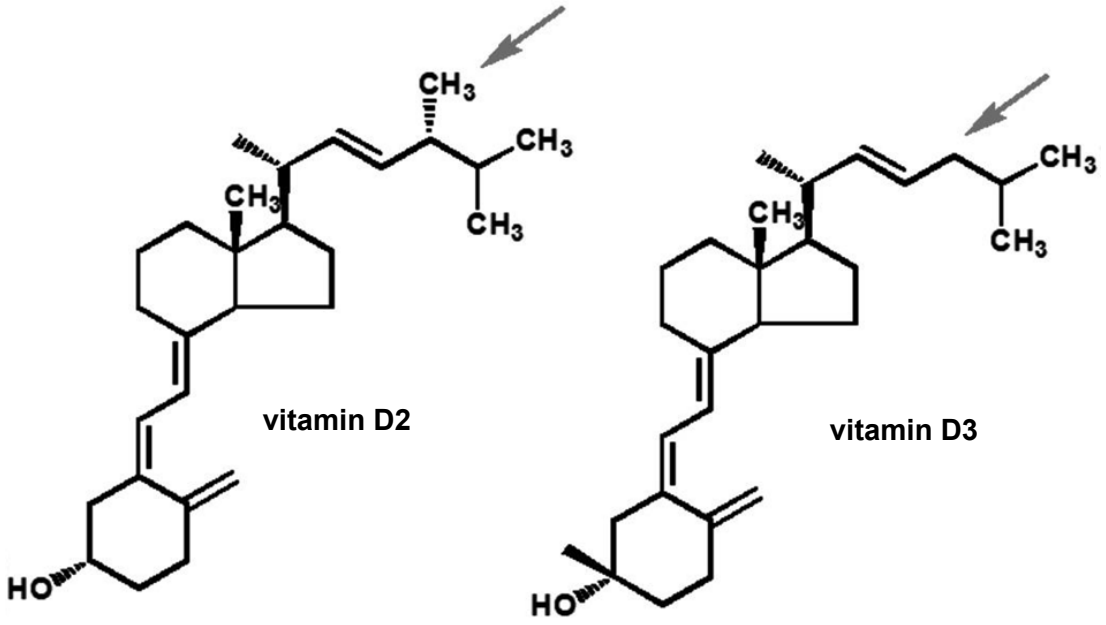

Figure 2 - Vitamin D2 and D3 molecules, showing the difference in methyl group (CH3), which is present in the former and absent in the later (arrows).
Extracted from: Peixoto PV et al. Hypervitaminosis D in animals [Hipervitaminose D em animais]. Pesq. Vet. Bras. 32(7):573-594, julho 2012.

D-binding protein (VDBP), 10 to 15% to albumin, and the remaining (less than 1%) circulate in a free form. There are few data in the literature on the bioavailability of vitamin D bound to albumin; therefore, the expression "vitamin D bioavailability" is used for the 25- hydroxyvitamin D form not bound to VDBP.[12]

When reaching target tissues, 25-hydroxyvitamin D is converted by the enzyme 1α-hydroxylase into 1α,25-dihydroxyvitamin D, which is the metabolically active form of the vitamin.

The effects of 1α,25-dihydroxyvitamin D are mediated by its receptor, VDR, which belongs to the family of nuclear receptors 1. Both the enzyme 1α-hydroxylase and the VDR receptor are found in almost all human cells, including cardiomyocytes[13] and vascular smooth muscle cells.[14] Experimental models with absence of VDR allow the understanding of the tissue-specific activity of the receptor. As an example, the absence of VDR results in increased ventricular mass, increased brain natriuretic peptide (BNP) levels and deregulation of cardiac metalloproteinases and fibroblasts, promoting a fibrotic extracellular matrix and leading to ventricular dilation and electromechanical uncoupling.[15] After the binding of vitamin D to the VDR, the complex promotes gene activation or suppression, with the help of coregulator proteins. On the other hand, the VDR also presents prompt nongenomic responses by inducing voltage-dependent calcium channels, leading to increased cell inflow of calcium and activation of other messengers, such as cyclic AMP, protein kinase A, and phospholipase C.[16]

Vitamin D deficiency

The American guideline for evaluation, prevention, and treatment of vitamin D deficiency[17] establishes that the body pool of the vitamin should be determined by measurement of serum 25-hydroxyvitamin D with the following cutoff points: (i) deficiency, when below or equal to 20 ng/mL, (ii) insufficiency, when between 20 and 30 ng/mL, and (iii) sufficiency when greater than 30 ng/mL.

Some risk factors for vitamin D deficiency have been observed and relate to sun exposure, dietary habits, and intestinal absorption. These include an indoor lifestyle (sun deprivation), use of sunscreens, advanced age, distance from the Equator, black skin, air pollution, smoking, poor food absorption (malabsorption syndromes), drugs (anticonvulsants, glucocorticoids), and kidney and liver disease.[10,17]

Despite the increased prevalence of vitamin D deficiency in the adult population and the growing evidence of its association with CVD, both American and Brazilian guidelines recommend that serum 25-hydroxyvitamin D levels should not be measured routinely in the general population and should only be measured in patients of populations considered at risk for deficiency of this vitamin.[10,17]

Association of vitamin d deficiency and cardiovascular diseases

Although numerous studies have confirmed an association between vitamin D and CVD, a cause-effect relationship between both remains unclear.

In this review, we discuss the association of vitamin D deficiency with the main cardiovascular pathologies and, subsequently, we analyze some outcomes with vitamin replacement.

Hypertension

The association of vitamin D deficiency and hypertension has its basis on the renin-angiotensin-aldosterone system (RAAS). Renin is synthesized by renal juxtaglomerular cells and stimulates the production of angiotensin II (from angiotensin I) and aldosterone, which increase blood pressure (BP) directly by vasoconstriction and indirectly by fluid and salt retention.[18] Inappropriately increased RAAS activation has been reported in studies with VDR and 1α-hydroxylase knockout mice.[19] Vitamin D acts by inhibiting renin gene expression, decreasing the synthesis of renin and, thus, preventing hyperstimulation by this system.[20]

The Third National Health and Nutrition Examination Survey (NHANES III),[21] a large population study that analyzed a sample of 12,644 North-Americans, has shown that systolic BP and pulse pressure correlate inversely with levels of 25-hydroxyvitamin D. These results have been confirmed by subgroup analyses in which increases in BP associated with age were significantly lower in vitamin D sufficient individuals.[22] The prevalence of hypertension was also associated with vitamin D deficiency in other large studies such as the German National Interview and Examination Survey[23] and the British Birth Cohort.[24] A study carried out in Brazil with 91 hypertensive elderly patients has shown that the serum concentrations of 25-hydroxyvitamin D is inversely associated with BP and positively associated with the weekly frequency of fish consumption.[25]

Few prospective studies have evaluated the association between vitamin D and changes in BP or emergence of hypertension. In 2015, van Ballegooijen et al.[26] followed up 5,066 individuals without hypertension at the Dutch city of Groningen; the individuals had their serum vitamin D level measured and were followed up for 6.4 years. At the end of follow-up, 1,036 (20.5%) developed hypertension and, as expected, low levels of vitamin D were associated with a greater risk of development of the disease.[26]

Diabetes mellitus

Type 1 diabetes occurs due to an autoimmune destruction of pancreatic beta cells leading to complete deficiency of insulin production. As for the development of type 2 diabetes, the major mechanisms involved are beta cell dysfunction, peripheral insulin resistance, and systemic inflammation. According to evidence, vitamin D deficiency is associated with all these processes.[27]

Vitamin D may exert effects on beta cell function through a direct connection to VDR receptors and by local expression of the enzyme 1α-hydroxylase. Vitamin D may also increase insulin sensitivity by stimulating VDR expression in peripheral tissues and activating peroxisome proliferator-activated receptor-gamma (PPAR) receptors, a factor that is involved in regulating the metabolism of fatty acids in skeletal muscles and adipose tissue. On the other hand, vitamin D may also act through indirect pathways in insulin secretion and sensitivity by regulating calcium concentration and flux in beta cell membranes and peripheral tissues.[27]

Observational studies have shown that the incidence and prevalence of type 1 diabetes are higher in countries with higher latitude and that the disease is most often diagnosed in the winter months.[28] Some studies have related vitamin D deficiency in pregnant women with the incidence of type 1 diabetes in children after birth.[29] Other studies have evaluated the protective role of vitamin D supplementation in early childhood against the development of type 1 diabetes, showing a lower incidence of the disease in children who received vitamin supplementation.[30]

With respect to insulin resistance and type 2 diabetes, the results have been conflicting. Some studies have associated low concentrations of 25-hydroxyvitamin D with insulin resistance and dysfunction of pancreatic

beta cells in western populations.[31] While studying 1,807 healthy Korean individuals, Ock et al.[32] have recently reported that vitamin D has an inverse association with insulin resistance.[32] While analyzing the relationship between vitamin D deficiency, diabetes, and CAD, Nardin et al.[33] evaluated 1,859 patients undergoing elective angiography for evaluation of CAD and concluded that diabetes is not an independent predictor of vitamin D deficiency, but diabetic patients with vitamin D deficiency presented increase CAD prevalence and severity.[33] In a recent study, Schafer et al.[34] followed up more than 5,000 elderly women for 8.6 ± 4.4 years to investigate a possible relationship between vitamin D levels and the emergence of type 2 diabetes; the authors concluded that the serum levels of vitamin D were not independent predictors of the incidence of type 2 diabetes in this population.[34]

Obesity

Recent evidence suggests that vitamin D deficiency is associated with obesity and other components of the metabolic syndrome.[35]

Low levels of 25-hydroxyvitamin D are common in obese individuals, and many studies have demonstrated an inverse relationship between serum vitamin D levels and body mass index (BMI).[36] Vitamin D has also been associated with regional fat distribution, and high levels of the vitamin have been associated with a lower amount of visceral and subcutaneous fat.[37] Some of the explanations proposed for this association are: differences in dietary intake between obese and nonobese individuals, decreased sun exposure among obese individuals, lower vitamin D bioavailability in obesity, and altered vitamin D metabolism in obese individuals.[38]

Wortsman et al.[39] proposed the hypothesis of sequestration of vitamin D by fat tissue to explain the prevalence of low levels of this vitamin in obese individuals.[39] They demonstrated that obese individuals presented a lower increase in serum 25-hydroxyvitamin D when compared with nonobese individuals under the same conditions of exposure to sunlight and vitamin intake. Since vitamin D is liposoluble, they proposed that the vitamin must accumulate in fatty tissue and not be readily available in the circulation, which would lead to low serum levels of this vitamin.

On the other hand, Drincic et al.[40] suggested that the difference in serum levels of vitamin D between obese and nonobese individuals is related to the distribution volume of this vitamin, which is greater in obese individuals and would justify its lower serum levels in these individuals.[40]

Smoking and lifestyle habits

Smoking is a risk factor for CVD and systemic inflammation, and vitamin D has been associated with both these conditions. Lee et al.[41] studied 560 Korean individuals aged 60 years or older to investigate the association between vitamin D and inflammatory markers and evaluate whether this association would change with the smoking profile of the patients.[41] The authors observed a significant association between vitamin D deficiency and high-sensitivity C-reactive protein (hsCRP) and a modifying effect of smoking on this association, in which smokers show a stronger association between vitamin D deficiency and hsCRP than nonsmokers.[41]

With the aim of relating lifestyle characteristics with vitamin D deficiency, Skaaby et al.[42] conducted a longitudinal study with 4,185 individuals with a follow-up time of 5 years. In this study, multivariate analyses of repeated serum measurements 25-hydroxyvitamin D were used to evaluate the association of this vitamin deficiency with BMI, practice of physical activity, type of diet (more healthy *versus* less healthy), alcohol consumption, and smoking. As a result, lower serum levels of vitamin D were associated with higher BMI, lower levels of physical activity, consumption of a less healthy diet, increased alcohol consumption, and smoking.[42]

Coronary artery disease

The occurrence of CAD has been associated with vitamin D deficiency, but the pathophysiological mechanisms of this association have not been well understood yet. The main evidence to suggest such an association is the VDR presence in both the myocardium and vascular cells, and the demonstration by epidemiological studies that the incidence of both CAD and vitamin D deficiency increase in winter months and in countries furthest from the Equator.[43]

Vitamin D deficiency appears to be common in acute myocardial infarction (AMI), and preliminary studies indicate a possible association of vitamin deficiency with AMI prognosis in the short and long term.[43] Moreover, vitamin D deficiency seems to predispose to recurrent adverse cardiac events, due to its association with the number of affected coronary arteries, AMI complications, and cardiac remodeling.[44]

The Health Professionals Follow-up Study followed up 18,225 men during 10 years and observed an association between low vitamin D levels and increased AMI risk, even after adjustment for other risk factors.[45] Prospective studies have also found a high prevalence of vitamin D deficiency in patients hospitalized with AMI. A multicenter study carried out with 239 patients with acute coronary syndrome (ACS) showed that 96% of the individuals had low vitamin D levels at hospital admission.[46]

Some studies show a potential independent association between severe vitamin D deficiency and intrahospital mortality in patients with ACS. Correia et al.[47] studied 206 patients with ACS and found that individuals with serum vitamin D levels lower than 10 ng/mL had a 24% rate of intrahospital cardiovascular mortality, which was significantly higher than that observed in the remaining patients (4.9%).[47]

Heart failure

HF has been associated with vitamin D deficiency. Shane et al. demonstrated a high prevalence of vitamin D deficiency in patients with HF, as well as an inverse correlation between serum levels of vitamin D with left ventricular function and disease severity.[48]

Vitamin D deficiency has been associated with severe adverse events, such as hospitalization due to HF and mortality. Liu et al.[49] reported in a study with 548 patients that low levels of 25-hydroxyvitamin D were associated with higher BNP levels, as well as a higher rate of hospitalization due to HF and increased mortality rate from all causes.[49] In the LURIC study, a prospective cohort study with 3,299 patients undergoing coronary angiography, the levels of N-terminal (NT)-proBNP related inversely to the levels of vitamin D.[50]

In regards to HF with normal ejection fraction (HFNEF), studies have shown conflicting results in terms of its association with vitamin D deficiency. In 2013, Lagoeiro et al. studied 85 outpatients with suspected HFNEF, of whom 32 had confirmed HFNEF, and observed a negative correlation between vitamin D deficiency and E/E' ratio.[51] On the other hand, Pandit et al.[52], in 2014, conducted a retrospective study with 1,011 patients and found no significant association between vitamin D levels and left ventricular diastolic performance.[52]

Despite evidence demonstrating an association between vitamin D and HF, the exact mechanism by which this vitamin's deficiency leads to worse clinical outcomes in patients with HF has not been clearly established yet. A potential mechanism could be through the occurrence of cardiorenal syndrome or worsening of renal function.[53] It is well known that the cardiovascular and renal systems are interrelated and that a decline in one of them could influence the other. Progression of cardiorenal syndrome involves hyperactivation of RAAS and sympathetic nervous system, as well as systemic inflammation, which may lead to electrolyte disturbances and disorders in fluid regulation, causing endothelial dysfunction, potentially leading to left ventricular remodeling and myocardial fibrosis. These changes generate a vicious cycle in which a decline in a system's function contributes to its further deterioration.[54]

Evidence supports vitamin D as an important regulator in the progression of cardiorenal syndrome. Deregulations in vitamin D metabolism due to reduced activity of the enzyme 1α-hydroxylase and depletion of VDBPs due to proteinuria are responsible for vitamin D deficiency in chronic renal patients; given the high prevalence of chronic renal insufficiency in patients with HF, such changes can be prevalent in these patients.[55]

Other evidence supporting the role of vitamin D deficiency in the pathogenesis of cardiorenal syndrome relates to the involvement of RAAS and inflammatory cytokines. Vitamin D deficiency leads to RAAS hyperactivation, contributing to left ventricular remodeling and emergence or worsening of HF.[56] Vitamin D deficiency can lead to increased production and release of inflammatory cytokines, which may have a direct or indirect negative effect in the myocardium, contributing to cell apoptosis, hypertrophy, fibrosis, ventricular remodeling, and negative inotropic effects, in addition to increased renal fibrosis and renal insufficiency.[57]

Vitamin D deficiency and myalgia induced by statins

Statins are very effective agents in primary and secondary cardiovascular prevention in high-risk patients.[58] However, the side effects most frequently observed in the musculoskeletal system, such as myalgia, have been commonly observed in patients treated with statins, and these effects directly affect the adherence to treatment using these medications.

Observational studies show that myalgia may occur in approximately 15 to 20% of the individuals treated with statins.[59] However, evidence from daily clinical practice shows that this prevalence is even greater. VDRs are present in muscle cells, and low vitamin D levels are

associated with hypotonia, proximal muscle weakness, and nonspecific musculoskeletal pain.[60] Recent studies have reported that vitamin D deficiency is associated with a higher prevalence of myalgia induced by statins.[61]

In 2014, Shantha et al.[62] performed a retrospective study with 5,526 patients followed by a prospective analysis in which the patients were followed up for 7 years. The patients with measured serum vitamin D levels who started treatment with statins were considered as the exposure group. The aim was to analyze the association between statin-induced myalgia and vitamin D levels, as well as to establish a cutoff level for vitamin D that would demonstrate a high accuracy for the emergence of myalgia. The authors concluded that low levels of vitamin D were associated with myalgia and that a cutoff level of 15 ng/mL for vitamin D showed a high accuracy in predicting the emergence of myalgia induced by statins.[62]

In 2015, Morioka et al.[63] performed a study with 5,907 patients to analyze if the level of vitamin D would modify the association between the use of statin and the emergence of musculoskeletal pain. The authors concluded that the group with vitamin D level below 15 ng/mL and using statins presented an approximately two-fold greater chance of developing musculoskeletal pain than patients who also had vitamin D levels below 15 ng/mL but were not treated with statins.[63]

Prospective and randomized studies are needed to confirm the actual association between vitamin D deficiency and the emergence of myalgia induced by statins. In addition, the pathophysiological mechanism that could explain this association still needs to be elucidated.

Genetic factors of vitamin D and its implications in cardiovascular disease

The increased worldwide prevalence of vitamin D deficiency, or at least of its measurable circulating form, 25-hydroxyvitamin D, can be explained in part by genetic determinants. In 2010, an important multicenter study carried out by Wang et al. pointed out that serum vitamin D levels may be influenced by genetic variations involving its synthesis (7-DHC), hydroxylation (CYP2R1, CYP24A1), and transport protein (VDBP).[64]

Most studies analyzing the association between vitamin D deficiency and CVD are epidemiological, which prevents discrimination between association and causality. In this context, Mendelian randomization (MR) is an alternative approach to estimate the causal relationship between modifiable biological exposures and clinical outcomes of interest using genetic variants (single nucleotide polymorphisms, SNPs) as instrumental variables. Thus, MR using summarized data allows the combination of results already published in previous studies, becoming a relevant alternative to investigating causality.[65]

Some studies have used MR to investigate a possible causal relationship between vitamin D deficiency and CVD. With respect to hypertension, Vimaleswaran et al.[66] found that increased vitamin D levels could reduce the risk of development of CVD, showing a causal relationship.[66] On the other hand, the results of MR studies have not demonstrated a causal relationship for diabetes mellitus[67] and CAD,[68] in which vitamin D deficiency appears to be a confounding factor.

Vitamin D replacement

Based on growing evidence of an association between vitamin D deficiency and CVD, many authors have investigated the role of vitamin D supplementation in the prevention and treatment of these pathologies.

A randomized study conducted by Hsia et al.[69] with 36,282 postmenopausal women evaluated the supplementation of vitamin D 200 IU plus calcium carbonate twice a day or placebo during a follow-up of 7 years and found that supplementation of vitamin D was unable to reduce cardiovascular risk.[69] This was one of the few randomized studies that evaluated the impact of vitamin D in reducing hard outcomes, namely, incidence of AMI, stroke, and CAD-related death.

With regard to hypertension, studies with vitamin D replacement have shown conflicting results. An important systematic review and meta-analysis published by Wu et al.[70] comprising 36,806 patients showed no significant effect of calcium plus vitamin D supplementation in variations in systolic and diastolic BP when compared with lack of supplementation of both.[70]

In diabetes mellitus, studies involving vitamin D supplementation have proved disappointing. A study involving 70 children with type 1 diabetes of recent onset, supplementation with calcitriol had a modest effect on the residual function of pancreatic beta cells, but the reduction of glycated hemoglobin after 1 year of treatment was not statistically significant.[71] With respect to type 2 diabetes, study results are conflicting, perhaps due to lack of standardization of the supplemented vitamin D dose or the use of small samples in these studies. A meta-analysis involving 35 controlled studies evaluated the impact of vitamin D supplementation

in healthy patients and individuals with vitamin D deficiency, obesity, prediabetes, and diabetes. Compared with placebo, vitamin D had no effect on insulin resistance, insulin secretion, or glycated hemoglobin.[72]

In regards to obesity, several studies have evaluated the effect of vitamin D supplementation with and without the addition of calcium on weight and body composition. Most of these studies showed no significant effect of vitamin D on BMI or body composition.[73]

Additionally, CAD does not seem to be significantly influenced by vitamin D supplementation. An important study named RECORD[74] involving 5,292 individuals compared the effects of vitamin D, calcium, vitamin D *plus* calcium, or placebo on cardiovascular events. The results showed that although vitamin D can exert a protective role on HF, it does not seem to protect against AMI and stroke. A meta-analysis of 51 controlled studies found that supplementation of vitamin D has no significant impact on AMI.[75]

Vitamin D supplementation seems to have some benefits on HF, although the mechanisms of action have not been well established. Recent studies have reported that in individuals with established HF and vitamin D deficiency, vitamin supplementation is associated with improved survival.[76]

Conclusions

CVDs remain the main cause of mortality in several countries worldwide. An understanding of the pathophysiological mechanisms involved, as well as their risk factors, is essential for planning of prevention and treatment strategies.

In recent years, many studies have shown a relationship between vitamin D deficiency and CVDs, with a direct influence on prognosis. Based on the understanding of this association, the focus of researchers has been in the correction of vitamin deficiency with the aim of preventing diseases and improving the prognosis of established diseases. However, there are still no consistent data to recommend vitamin D replacement in the context of cardiac diseases.

One point that deserves attention is the broad worldwide variation in the prevalence of vitamin D deficiency. Since endogenous vitamin D synthesis is dependent on solar exposure, which in turn varies according to latitude, perhaps the reference level for serum vitamin D also differs among countries depending on sunlight exposure.

It is unclear whether the disappointment of the results of studies with vitamin D supplementation is due to an inability of the vitamin in exerting effects on established disease, or use of inappropriate supplementation doses. It is important to understand the doses required to maintain the serum levels of vitamin D above the desired level, as well as serial measurements of 25-hydroxyvitamin D with the aim of maintaining adequate levels of this vitamin during the entire follow-up duration.

Author contributions

Conception and design of the research: Jorge AJL, Cordeiro JR. Acquisition of data: Cordeiro JR. Writing of the manuscript: Jorge AJL, Cordeiro JR, Bianchi DBC. Critical revision of the manuscript for intellectual content: Jorge AJL, Rosa MLG.Supervision / as the major investigador: Jorge AJL.

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REVIEW ARTICLE

Fatigue: A Complex Symptom and its Impact on Cancer and Heart Failure

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Abstract

In chronic diseases like cancer and heart failure (HF), fatigue is a common and complex symptom from an etiological and pathophysiological point of view, thus, a relevant issue in the recent area of oncocardiology. Fatigue is prevalent in 80-90% of the oncological patients treated with chemotherapy and/or radiotherapy and affects approximately 50-96% of the individuals with IC. The toxicity attributed to chemotherapeutic agents can determine the patients' degree of fatigue and may even predict their survival. In recent decades, the advancement of antineoplastic therapies has substantially impacted the survival of patients with cancer, and the risks of harmful effects from these therapies to the cardiovascular system have been increasingly described. Therefore, the cooperation between oncologists and cardiologists has led to the emergence of oncocardiology and the new concept of cardiac surveillance. Cardiotoxicity is one of the clinical complications in the treatment of cancer, and its typical manifestation is left ventricular systolic dysfunction. New diagnostic and therapeutic strategies have been employed in the cardiac surveillance of patients with cancer. Fatigue in these patients has been carefully studied with a multidisciplinary approach and with the development of visual scales to quantify and correlate better its real impact on these individuals' quality of life and survival. The Fatigue Pictogram and Piper Fatigue Scale are tools increasingly used in research and clinical practice. The mechanisms involved in fatigue, from a conceptual point of view, may be of central (central nervous system) or peripheral (muscular skeletal) origin, both of which may be present in patients with cancer. The present review aims to discuss the new concepts in the assessment of fatigue in oncological patients. These concepts are fundamental to professionals who work in the emerging area of oncocardiology.

Keywords

Heart Failure / physiopathology; Neoplasms / physiopathology; Cardiotoxicity / complications; Ventricular Dysfunction, Left; Neoplasias / drug therapy.

Introduction

The survival rate of patients with cancer has improved substantially in recent decades with the emergence of new chemotherapeutic agents and advancement of radiotherapy. However, oncological patients are more susceptible to cardiotoxic effects developed during treatment, which can increase the morbidity and mortality of this population.[1] Within this new scenario, oncocardiology emerged as a new area of specialization based on a multidisciplinary integrative approach. Oncocardiology seeks to improve the quality of cardiologic care offered to patients with cancer, and to study the different dimensions of cardiotoxicity.

Among cardiovascular symptoms, fatigue is a common and very prevalent clinical manifestation in patients with cancer, and its characterization and mechanisms still defy healthcare professionals. Fatigue associated with cancer is a subjective experience characterized by fatigue not relieved by sleep or rest, and is considered a predictor of decreased personal satisfaction and quality of life.[2] The symptom fatigue varies in duration and intensity, reduces in varying degrees the patient's ability to develop daily activities, and decreases the functional capacity of patients with cancer.[3] Fatigue can affect 80-99% of the patients with cancer treated with chemotherapy and/or radiotherapy[4] and may persist for months to years. Cella et al.[5] reported that one-third of the patients cured of cancer showed fatigue for 5 years after the end of chemotherapy.

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The multifactorial nature of fatigue associated with cancer is a crucial point to be considered by professionals dealing with oncological patients. The main causes of fatigue are associated with the cancer effects and treatment on the central nervous system. Other causes include depression and anxiety, anemia, endocrine abnormalities (such as hypothyroidism and diabetes), activation of the immune system, inflammatory mediators, emotional stress, electrolytic disorders, myopathies, pulmonary fibrosis, and heart failure (HF).[6]

HF is a complex and multisystemic syndrome found in elderly patients presenting with the clinical triad fatigue, dyspnea, and edema. The mechanisms associated with fatigue in HF are triggered by inadequate blood perfusion affecting the respiratory and peripheral muscles, leading to decreased oxidative capacity.[7,8] Fatigue affects 50-96% of the patients with HF and is associated with a reduction in quality of life, restriction of physical activity, and worse prognosis.[8]

A successful HF treatment depends on a comprehensive assessment of the symptoms and knowledge of the available approaches to alleviating not only the physical aspects of the patient but also his emotional and spiritual suffering. The "person-centered care" strategy, including a partnership between healthcare professionals and patients with HF, decreases the duration of hospitalization.[9] The prescriptions are specific to those patients with HF who present with dyspnea at the end of life, with the objective of symptom relief, in addition to full support of the team specialized in palliative care.[10,11]

In clinical practice, healthcare professionals dedicated to oncology and cardiovascular diseases encounter patients, especially elderly ones, presenting with both conditions. Therefore, the identification and evaluation of fatigue by these professionals is fundamental and must include scientifically validated instruments, as well as a clinical assessment and complementary tests to perform an adequate therapeutic plan.

The objective of this review is to discuss the new aspects of fatigue present in oncological patients and emphasize the importance of early detection of HF and monitoring of cardiac function for more appropriate management of patients undergoing chemotherapy and radiotherapy.

Defining fatigue in clinical practice

There is no consensus in regards to the concept of fatigue. Describing fatigue is a difficult task due to a large number of synonyms associated with this term. Healthcare professionals attribute different terms to fatigue, such as asthenia, lethargy, exhaustion, feeling of weakness, extreme tiredness, and lack of motivation. Patients with cancer refer to fatigue using different terms, such as weakness, exhaustion, fatigue, depletion, slowness, or weight.[11]

The scientific literature, in turn, defines fatigue as "a subjective feeling of physical tiredness or exhaustion disproportionate to the level of activity." Additionally, "fatigue may manifest as difficulty or inability in initiating an activity (perception of general weakness); reduced capacity of maintaining an activity (easy tiredness); and difficult concentration, memory problems, and emotional stability (mental fatigue)."[12]

Muscle fatigue, in turn, is regarded by many authors as "an inability to maintain a level of potency or strength during repeated muscle contractions,"[13] "decreased strength in sustained maximal contraction,"[14] and "reduced availability of energy substrate for the skeletal muscle during exercise."[15]

Mechanisms of fatigue

Fatigue originates in the cerebral cortex and may extend up to the cross-bridges of the muscle, induced by a reduction in the number of functional motor units involved in the activity or in the frequency of triggering. The mechanisms responsible for fatigue may be central or peripheral and are investigated through kinesthetic sensations (effort and strength) and by electromyography.[15]

Electromyographic signs allow the identification of the manifestation of fatigue of a given muscle through a reduction in the amplitude of the electrical impulse registered, indicative of loss of recruitment or synergic activation of multiple muscles. Another method of study of the physiology of fatigue is the addition of a force by supramaximal electrical stimulation during a maximal voluntary contraction, which translates into impaired muscle activation (at a level proximal to the neuromuscular junction).[16]

The central mechanism of fatigue occurs due to changes in the neural input arriving at the muscles, *i.e.*, the recruitment of motor units remains below the ideal one for generation of adequate muscle strength during exercise.[16]

Peripheral fatigue stems from homeostatic changes in the skeletal muscle itself and from decreased contractile force. One of the mechanisms inducing muscle fatigue

during exercises influencing the production of force is the depletion of energy substrate required for ATP synthesis and the variation in intracellular concentration of Ca++, H+, lactate, phosphate, and ADP. A failure of the muscle in maintaining homeostasis (depending on variations in Ca++ and H+ levels, for example) compromises force production at the cross-bridge level, resulting in the development of fatigue. Another mechanism that contributes to muscle fatigue is the production of free radicals. Current evidence suggests that free radicals can damage the contractile proteins myosin and troponin and decrease the number of cross-bridges, compromising muscle strength. The increased production of free radicals can also compromise the function of the sodium/potassium pump in the skeletal muscle and cause muscle fatigue.[17]

Skeletal muscle contraction is a complex process that involves a certain number of cellular proteins and the energy production system, with the interaction of the contractile proteins actin and myosin in the presence of intracellular ATP and Ca++. The process of muscle contraction begins with the arrival of a nerve impulse in the neuromuscular junction. The action potential of the motor neuron causes the release of acetylcholine in the synaptic cleft, which in turn leads to depolarization of the muscle cell. When it reaches the sarcoplasmic reticulum, the action potential promotes the release of Ca++, which binds to troponin and causes a change in the position of tropomyosin. The active sites in actin are then exposed, allowing an "energized" myosin cross-bridge to bind to the actin molecule. When the neural activity ceases at the level of the neuromuscular junction, Ca++ is removed from the sarcoplasm and actively pumped into the sarcoplasmic reticulum by the Ca++ pump, breaking the cycle of muscle contraction. The term "excitation-contraction coupling" is defined as the sequence of events in which the nerve impulse reaches the muscle membrane and causes shortening of the muscle via cross-bridge activity.[18]

Fatigue in chronic diseases

Clinical fatigue is often found in chronic diseases like HF and cancer. Several metabolic, neurological, and myofibrillar adaptations are involved in these conditions and implicated in the onset of fatigue.[19] Ewans & Lambert[4] have pointed out that cachexia and deconditioning are probably involved in the persistence of fatigue at the end of treatment and after resolution of the disease.

Fatigue in heart failure

Fatigue and dyspnea are cardinal symptoms of HF. Fatigue is triggered by inadequate blood perfusion affecting the respiratory and peripheral muscles and leads to reduced oxidative capacity. Dyspnea, in turn, is caused by an excessive ventilatory demand or a ventilatory disorder arising from sensory systems involved in breathing. The symptom fatigue can be caused by cardiac cachexia and malnutrition that accompany the severe metabolic stage of the disease.[8] Patients with advanced HF may develop sarcopenia associated with aging and physical inactivity, resulting in worsening of fatigue. The symptom fatigue connected to HF is also related to anemia, sleep apnea, electrolyte disturbance, use of beta-blockers and diuretics, in addition to depression.[20]

The exercise intolerance present in HF may be associated with central (chronotropic response and reduced ejection fraction) or peripheral (endothelial dysfunction with decreased release of nitric oxide, increased total peripheral resistance and lower vasodilatory response) limitations. The ventilatory muscle weakness present in HF, in turn, is also a limitation that may reflect a greater increase in the work of the diaphragm, triggering a sensation of dyspnea.[21]

Another adaptation found in HF that can contribute to aggravate fatigue is the decrease in contractile function. The myopathy observed in HF clearly reflects the reduction in oxidative phosphorylation with increased type IIb fibers and decreased type I fibers, which are regarded as determinants in the reduction of functional capacity. The administration of drugs used in HF, such as losartan and enalapril, improves exercise tolerance with normalization of the composition of the muscle fibers (i.e., reduction in glycolytic fibers [type IIb] and increase in aerobic fibers [type 1]), in addition to improving the maximum energy expenditure (VO_2).[22] Similar results have been obtained with exercise training in patients with HF, which resulted in improved endurance, physical activity, and oxidative phosphorylation of the skeletal muscle.[23]

The muscle weakness eventually observed in patients with HF can be attributed to changes in function and amount of proteins in the myofilaments and not only to muscle atrophy. These changes are probably secondary and apparent in relation to the deconditioning and/or disuse resulting from the disease and allow the definition of the muscle phenotype in patients with HF.[24,25]

Assessment of fatigue in heart failure

Several validated scales are available to measure symptoms during care of patients with HF, which allows for individualized treatment to each patient based on his scores. For a better understanding of the symptoms, numerical scales are used with the purpose of evaluating physical, emotional, and cognitive aspects of the patient in relation to the aspects observed by other professionals, for example, the Edmonton Symptom Assessment System (ESAS). The information collected with ESAS helps to measure HF symptoms not traditionally evaluated.[26]

ESAS is a simple instrument, of easy application, which may be filled out by the patient himself (self-assessment) or by a family member or professional. This scale comprises 10 common symptoms found in patients with cancer receiving palliative care, including lack of appetite, fatigue, nausea, depression, sleepiness, anxiety, pain, dyspnea, malaise, and other symptoms. The scale is graded from 0 to 10, where 0 represents the absence of the evaluated symptom and 10 represents the presence of the evaluated symptom in its strongest intensity.[26]

A prospective study conducted in Canada assessed the applicability of different questionnaires of palliative care in patients with HF. The study correlated the New York Heart Association (NYHA) functional class and the Kansas City Cardiomyopathy Questionnaire (KCCQ) with the palliative care scales ESAS and Palliative Performance Scale (PPS). The study found a positive correlation of NYHA with PPS and ESAS ($R2 = 0.57$, $p = 0.001$); however, the KCCQ questionnaire correlated negatively with ESAS ($R2 = -0.72$, $p = 0.001$). Depending on the difficulty of the identification of patients with HF eligible for palliative care, these tools may be useful in clinical practice.[27]

Fatigue related to cancer

The symptom fatigue is directly associated with cancer itself and the side effects of its treatment, including toxicity from chemotherapy. Patients with cancer who present severe fatigue during treatment remain fatigued after the end of the therapy or the resolution of the disease. The chronicity of fatigue is implicated in possible metabolic and physiological adaptations, such as deconditioning and cachexia. Increased physical activity is a strategy adopted to reduce the loss of skeletal muscle during chemotherapy.[28]

Cachexia in cancer is characterized by a continuous loss of skeletal muscle mass and may cause generalized weakness and fatigue. Roberts et al.[29] investigated the weakness of the diaphragm muscle due to cachexia associated with cancer in animal models and observed that muscle weakness was attributed to muscle atrophy and contractile dysfunction.

Lee et al.[30] evaluated the difference in physical performance between women and men with and without lymphoma, with the application of the 6-minute walk test (6MWT) and the Brief Fatigue Inventory. The results obtained showed a higher fatigue score in patients who presented worse functional physical capacity.

The multifactorial nature of fatigue associated with cancer hinders the identification of underlying mechanisms involved in the disease. Bower et al.[31] have confirmed the relationship between increased inflammatory cytokines with worse fatigue in patients with breast and prostate cancer during treatment. Dower et al.[32] demonstrated that women with breast cancer and fatigue had reduced levels of cortisol in the morning, suggesting possible abnormalities in the hypothalamic-pituitary-adrenal axis. Fink et al.[33] found that low levels of hemoglobin, depression, and physical limitation may be considered predisposing factors of fatigue.

The diagnosis of fatigue related to cancer is established with the exclusion of reversible causes that can be treated and investigated. Among cited reversible causes are the types of fatigue, hypothyroidism, anemia, sleep disorder, pain, emotional stress, menopause, electrolyte abnormalities, adverse effects of medications, cardiac dysfunction, renal and hepatic failure, myopathy, and pulmonary fibrosis.[34] The diagnosis of fatigue can be complemented with information from the patient's clinical history, physical exam, and laboratory tests, with the application by a multidisciplinary team of instruments for the assessment of fatigue.

The classification of cancer-related fatigue follows the Common Terminology Criteria for Adverse Events (CTCAE, version 4.0) of the National Cancer Institute of the United States and is widely used by Brazilian oncologists (figure 1).[35]

Dimeo et al.[36] concluded that exercises are the only factors with strong evidence in the control of fatigue during and after treatment of tumors of the breast, prostate, and several other solid tumors. Schwartz et al.[37] pointed out the effectiveness of therapeutic exercises in improving the patients' fatigue and quality of life, with a reduction of the adverse effects of therapies against cancer. Aerobic training performed during 4 months by women with hypertension, cardiovascular disease,

and breast cancer undergoing treatment resulted in a reduction of systolic and diastolic blood pressure and resting heart rate. A systematic review involving 4,826 participants with cancer, in turn, showed improved quality of life and functional capacity during and after a training program with exercises (tables 1 and 2).[38]

Risks of cardiotoxicity

The signs and symptoms of HF may be similar to those observed in oncological patients. Fatigue is a common clinical manifestation in both pathologies. In cancer, it can deteriorate due to oncological treatment, which increases the risk of injury to the myocardium, which in turn triggers cardiovascular complications.[39]

The substantial decline in cardiopulmonary capacity is a consequence of immobility, chronic fatigue, loss

Table 1 - Potential benefits of exercises before and after cancer treatment[38]

Before treatment	After treatment
Improved cardiorespiratory and cardiovascular function	Improved self-esteem, mood, and self-image
Effects on body composition (preservation or increase in muscle mass, loss of fat mass)	Reduced duration of hospitalization
Improved muscle strength and flexibility	Reduced stress, depression, and anxiety
Improved immune system	Reduced of serious adverse effectsk including nausea, fatigue and pain

Source: Adapted from Mishra SI et al, 2012[38]

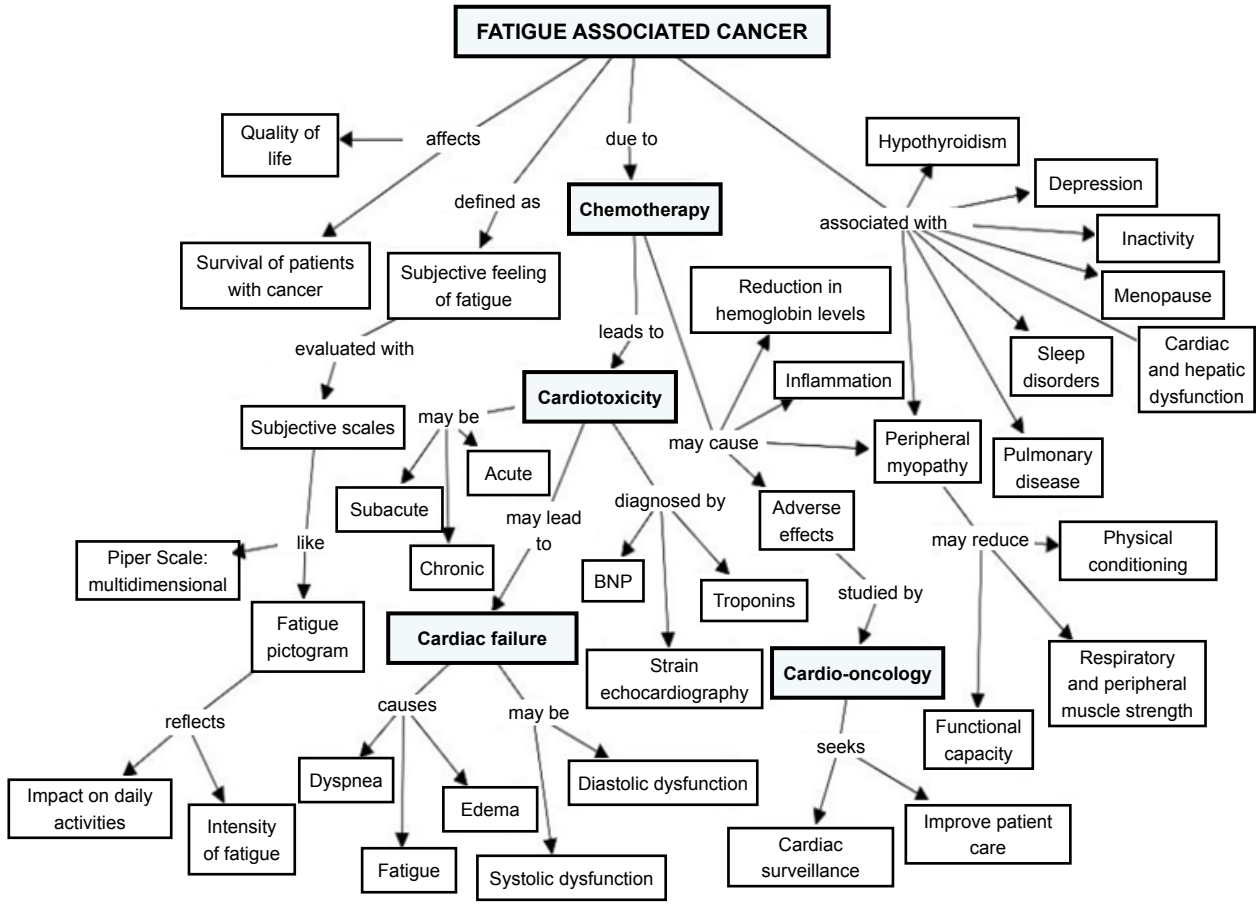

Figure 1 - Conceptual map of fatigue related to cancer

Table 2 - Differences between oncologic fatigue and fatigue related to heart failure

Fatigue associated with cancer	Fatigue related to heart failure
Generalized muscle weakness	Weakness of the peripheral and respiratory muscles
No improvement with rest or sleep	Improves with rest and sleep
Worsens with chemotherapy and radiotherapy	Worsens with corticosteroids and anti-inflammatory drugs
There is no association direct with dyspnea	Associated with dyspnea on exertion
Dysfunction of the central and peripheral nervous system	Dysfunction of the peripheral nervous system
Disuse of muscle fibers and contractile alteration	Atrophy of Type I aerobic muscle fibers
Triggered by low levels of hemoglobin, cortisol, TSH, and free T4	Triggered by an increase in inflammatory mediators
Related with worsening nutritional status	Associated with cardiac cachexia with disease progression
Associated with mild, moderate, or severe pain	

Source: Author, 2017

of muscle mass, anemia, increased inflammatory activity, changes in coagulation, and adverse events from chemotherapy and/or radiotherapy. All these changes consequently lead to worse quality of life among cancer patients.[39]

Cardiotoxicity induced by chemotherapy has been a major concern among oncologists and cardiologists in search of early identification of cardiac dysfunction and monitoring of cardiovascular function during treatment. Cardiac toxicity is one of the most important complications of cancer therapy and is responsible for considerable morbidity and mortality.[40]

Several drugs used in cancer treatment have been associated with left ventricular dysfunction, in particular, drugs in the anthracyclines group, like doxorubicin. Anthracycline-induced cardiotoxicity manifests early (< 3 months after treatment) or late (3 to 12 months after treatment), but can also occur 1 year after treatment. According to Suter & Ewer,[41] medications can be classified according to the injury that they cause to the myocardium as leading to reversible (type 1) and irreversible (type 2) injury. One of the effects of cardiac toxicity by anthracyclines involves oxidative stress and lipid peroxidation of the cardiomyocytes. Swain et al.[42] identified 149 cardiac events and reduced left ventricular ejection fraction (LVEF) in 50% of 630 cancer patients treated with doxorubicin.[43] A noninvasive hemodynamic evaluation of patients with HF showed an increase of the following variables: cardiac output, stroke volume, heart rate, and blood pressure.[43]

The harmful events of chemotherapeutic agents/drugs on the cardiovascular system include HF, hypertension, thromboembolic disease, and myocardial diseases (table 3). The main risk factors for cardiotoxicity associated with chemotherapeutic agents are hypertension, age above 60 years, prior left ventricular dysfunction, and prior thoracic irradiation. According to its clinical presentation, cardiotoxicity may have an acute, subacute, or late presentation.[1]

The diagnosis of cardiotoxicity is established using biomarkers (including brain natriuretic peptide [BNP] and troponins) and echocardiographic resources. Approximately one-third of the patients have elevated levels of troponins, which are sensitive and specific markers of myocardial injury with the ability to signal the development of ventricular dysfunction in patients receiving elevated doses of chemotherapeutics.[44]

The European Society of Cardiology currently proposes a discussion about the relevance of the biomarkers and serial evaluations of LVEF in clinical practice and research. The simultaneous use of blood samples for measurement of biomarkers levels and characterization of genetic and epigenetic factors may be useful in identifying patients with cancer susceptible or resistant to cardiotoxicity. With this approach, it is possible to compare the clinically relevant results before and during cancer treatment, allowing the planning of strategies based on evidence through oncocardiology.[44]

Evaluation of oncological fatigue

Standardized questionnaires have been incorporated into the assessment of fatigue. Several instruments for assessment of fatigue are available, seven of which have been validated in Brazil for the evaluation of the impact of fatigue on quality of life of oncological patients.[52]

Table 3 - Pathophysiological triggers of coronary artery disease in cancer treatment

Agent	Pathophysiological mechanism	Potential coronary events
5- fluorouracil, capecitabine, gemcitabine	Endothelial lesion and vasospasm	Up to 18% of myocardial ischemia and 10% of silent ischemia
Platinum components - cisplatin	Arterial thrombosis and procoagulant	20 years of absolute risk above 8% after testicular cancer
Vascular endothelial growth factor (VEGF) inhibitors: bevacizumab, sorafenib, sunitinib	Procoagulant, arterial thrombosis Endothelial injury	Risk of arterial thrombosis: bevacizumab 3.8%, sorafenib 1.7%, and sunitinib 1.4%
Radiotherapy	Endothelial lesion, platelet rupture, and thrombosis	A 2- to 7-fold increase in the relative risk of myocardial infarction 10% of coronary events in survivors of Hodgkin lymphoma The risk is proportional to the radiation dose

Source: Adapted from the Guideline of the European Society of Cardiology[64]

The Fatigue Pictogram, prepared for the evaluation of the intensity and impact of fatigue in patients with cancer, is a useful tool in clinical practice and research (Figure 2). It is described as a method that is fast, simple, valid, reliable, and applicable to patients with cancer and low educational level, although it requires adjustments for application to healthy individuals. This instrument was developed and validated in 2007 in four oncology outpatient clinics in the city of São Paulo, with the participation of 584 patients with

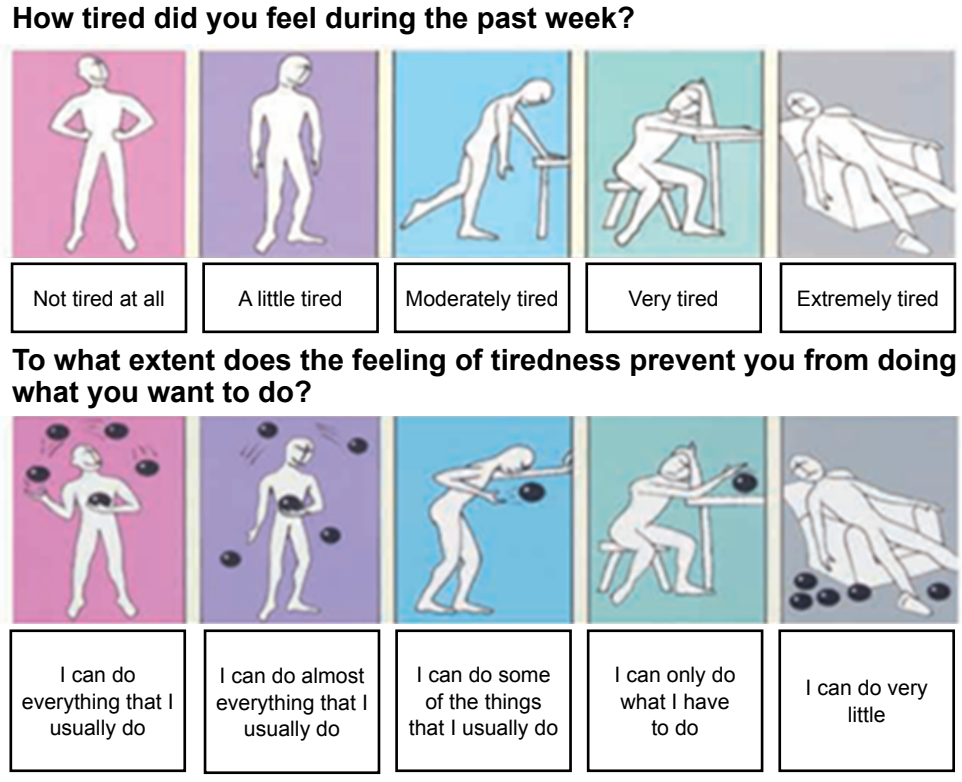

Figure 2 - The Fatigue Pictogram (Mota, Pimenta, Fitch. 2009)[53]

different types and stages of cancer receiving or not treatment with radiotherapy.[53]

Fatigue may also be assessed with the Piper Fatigue Scale. Revised and validated in Brazil in 2009, this scale covers all dimensions of fatigue and can be applied to cancer patients at all stages of the disease. This scale establishes a cutoff point from which the individual should be regarded as fatigued.[54] Another widely used questionnaire is the Functional Assessment of Cancer Therapy-Fatigue (FACT-F), which was validated and applied in a study carried out at the Instituto Nacional de Câncer José Alencar Gomes da Silva (INCA) in 2008 and showed a negative impact of fatigue on the quality of life of patients with breast cancer undergoing chemotherapy.[55]

Conclusion

Although fatigue is a common symptom in patients with cancer, it receives little attention in daily clinical practice. In recent decades, fatigue has been progressively recognized by its impact on the patients' quality of life and survival. Fatigue is also one of the cardinal symptoms of HF. Cardiac surveillance and oncocardiology are concepts that are being incorporated by multidisciplinary teams caring for patients with cancer. Therefore, the identification of fatigue and its pathophysiological mechanisms, as well as its correct stratification and therapeutic approach, are fundamental steps to be met by healthcare professionals involved in the care of patients with cancer.

Author contributions

Conception and design of the research: Borges JA, Quintão MMP, Chermont SSMC, Mendonça Filho HTF, Mesquita ET. Acquisition of data: Borges JA, Quintão MMP, Chermont SSMC, Mendonça Filho HTF, Mesquita ET. Analysis and interpretation of the data: : Borges JA, Quintão MMP, Chermont SSMC, Mendonça Filho HTF, Mesquita ET. Statistical analysis: Borges JA. Writing of the manuscript: Borges JA, Quintão MMP, Chermont SSMC, Mendonça Filho HTF, Mesquita ET. Critical revision of the manuscript for intellectual content: Borges JA, Quintão MMP, Chermont SSMC, Mendonça Filho HTF, Mesquita ET.

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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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REVIEW ARTICLE

Telerehabilitation for Cardiac Patients: Systematic Review

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Abstract

Cardiovascular rehabilitation is one nonpharmacological intervention used to treat cardiovascular diseases. Despite the proven benefits of cardiovascular rehabilitation, the adherence of patients with heart disease is low. Thus, the alternative of telerehabilitation has gained importance, and many studies are being carried out to verify its efficacy.

To review the literature and assess the efficacy of telerehabilitation for the cardiac population.

This is a systematic review of the literature. The search was conducted in the electronic databases MEDLINE/PubMed (Medical Literature Analysis and Retrieval System Online), PubMed Central® (PMC), Cochrane Library, and Physiotherapy Evidence Database (PEDro), using the combination of descriptors, including terms of the Medical Subject Headings (MeSH) and its entry terms. The MeSH terms used in combination were: "telerehabilitation" AND "cardiac rehabilitation" (Table 1). Then, a manual search by use of the articles selected, as well as a search in the gray literature, was conducted.

The search strategy collected 154 studies, of which 109 were excluded because of duplication in the databases and 29 for not being clinical studies. Sixteen clinical studies were included for full analysis, of which 2 were excluded for being prospective, 2 for being duplicate and 5 for not including any outcome. Thus, 7 studies were included.

Cardiac rehabilitation using telerehabilitation is a feasible and safe alternative to conventional rehabilitation, and has high adherence of patients with heart disease. It can be added to conventional cardiovascular rehabilitation programs or used in isolation.

Keywords

Cardiovascular Diseases; Cardiac Rehabilitation; Telerehabilitation; Physical Therapy Specialty; Review.

Introduction

Cardiovascular diseases (CVD) are increasingly frequent. Their epidemiology has been compared to that of the great epidemics of the past centuries.[1] According to the World Health Organization (WHO), in recent decades, approximately 30% of a total of 50 million deaths were caused by CVD, 17 million people worldwide.[2,3]

Similarly, Brazil has equally alarming indices, with CVD as the major cause of death, representing 30% of all causes of death recorded, and being the third major cause of hospitalization in the country.[2,3] In addition, WHO states that those diseases are a threat to the socioeconomic development, mainly due to the large number of premature deaths that could be prevented by reducing the risk factors.[4]

Some nonpharmacological interventions are used to treat CVD, such as cardiovascular rehabilitation (CVR), consisting in the set of interventions aimed at improving the patients' physical, psychological and social conditions.[5] Over the past 40 years, the role of the CVR services in the secondary prevention of cardiovascular events has been recognized and accepted by health organizations, and the interventions used in the care provided to patients with CVD have proved fundamental to treat those individuals.[6]

Despite the confirmed CVR benefits, low adherence of the patients with CVD has been observed. Some studies have attributed it to the lack of transportation for the patients, lack of time, return to work or

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financial problems, those being the major hindrances to participation in CVR programs. Some authors have reported that only 27% of the patients adhere to CVR.[7]

Therefore, different strategies to encourage physical exercise and changes in behavior and lifestyle are necessary and should be implemented to modify the patients' risk factors, preventing new cardiovascular events and enabling the patients' return to their usual daily activities.[7]

Considering all that and the recent technological advance, an alternative to conventional CVR has been the use of the technology of telemedicine,[8] which proposes the delivery of healthcare services by use of information and communication technologies in situations where a health professional and a patient (or two health professionals), each in a different place, can communicate in real time, or even enables data storage for further analysis, consultation and opinion. In addition, it provides the safe transmission of medical data via texts, sounds and images required for prevention, diagnosis, treatment and patients' follow-up.[9]

Rehabilitation using telemedicine resources is known as telerehabilitation and has gained importance. Several ongoing studies are assessing its efficacy, but they are heterogeneous and use different tools to conduct telerehabilitation. Thus, this study was aimed at reviewing the literature and assessing the efficacy of telerehabilitation for cardiac patients.

Methodology

Study design and search strategy

This is a systematic review of the literature, which does not require Ethics Committee in Research approval, but is being analyzed by the International Prospective Register of Systematic Reviews (PROSPERO). In addition, this systematic review has met the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The search was conducted in the electronic databases MEDLINE/PubMed (Medical Literature Analysis and Retrieval System Online), PubMed Central® (PMC), Cochrane Library, and Physiotherapy Evidence Database (PEDro), using the combination of descriptors, including terms of the Medical Subject Headings (MeSH) and its entry terms. The MeSH terms used in combination were: "telerehabilitation" AND "cardiac rehabilitation" (Table 1). Then, a manual search by use of the articles selected, as well as a search in the gray literature, was conducted.

Table 1 - Search strategy used in PubMed

#1	("Telerehabilitation"[mesh] OR "Telerehabilitations" OR "Tele-rehabilitation" OR "Tele rehabilitation" OR "Tele-rehabilitations" OR "Remote Rehabilitation" OR "Rehabilitation, Remote" OR "Rehabilitations, Remote" OR "Remote Rehabilitations" OR "Virtual Rehabilitation" OR "Rehabilitation, Virtual" OR "Rehabilitations, Virtual" OR "Virtual Rehabilitations")
#2	("Cardiac rehabilitation" [mesh] OR "Cardiac Rehabilitations" OR "Rehabilitation, Cardiac" OR "Rehabilitations, Cardiac" OR "Cardiovascular Rehabilitation" OR "Cardiovascular Rehabilitations" OR "Rehabilitation, Cardiovascular" OR "Rehabilitations, Cardiovascular")
#3	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR ("latin square"[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animal[mh] NOT human[mh])
#4	(#1 AND #2 AND #3)

Inclusion and exclusion criteria

This study included all randomized or nonrandomized clinical trials found in the databases, published in Portuguese, English or Spanish, with the full text available and no date restriction, conducted in human beings aged at least 18 years, in which patients with CVD participated in CVR programs, using telerehabilitation or telemedicine resources.

Studies with the following characteristics were excluded: duplicate studies; not performed in human beings; not published in full text; whose population had been studied in more than one study and whose outcomes were similar, situations in which the first study was considered for inclusion in this review.

Two reviewers evaluated independently the abstracts. The studies selected had their full text assessed for inclusion according to the criteria established.

Identification and selection of studies

Two reviewers independently read the titles and abstracts of each pre-selected study, identifying

separately the articles that met the inclusion and exclusion criteria. In the next phase, each reviewer read the full articles that met the criteria presented in the abstract, and selected only those compatible with the criteria proposed for this systematic review. In case of doubt, a third reviewer would be consulted; however, in this study, there was no disagreement between the first two reviewers.

Data extraction

Two researchers were responsible for data extraction. The following characteristics were extracted from the studies: title, authors, publication year, name of the scientific journal of publication, publication form, keywords, geographical origin, study design, sample size, methods, study period, instrument used for telerehabilitation, other results and conclusions. In addition, the following data about the participants of each study were recorded: number, sex, age, interventions performed, rehabilitation time, outcomes. The risk of bias of the randomized clinical trials was assessed by using the Cochrane Collaboration's tool (Table 2).

Data analysis

Data analysis was performed in a descriptive and qualitative form, being presented as figure and tables.

Table 2 - Risk of bias of the randomized clinical trials - Cochrane Collaboration's tool

Domain	Studies						
	Vieira, 2017	Brouwers, 2017	Piotrowicz, 2015	Bernocchi, 2017	Szalewska, 2015	Korzeniowska-kubacka, 2015	Piotrowicz, 2014
Selection bias							
1. Sequence generation	Low risk	Low risk	High risk	Low risk	High risk	High risk	High risk
2. Allocation concealment	Low risk	Low risk	High risk	Low risk	High risk	High risk	High risk
Performance bias							
3. Blinding of study participants and personnel	Uncertain risk	High risk	Uncertain risk	High risk	High risk	High risk	High risk
Detection bias							
4. Blinding of outcome assessors	Uncertain risk	High risk	Uncertain risk	Low risk	High risk	High risk	High risk
Attrition bias							
5. Incomplete outcome data	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Reporting bias							
6. Selective outcome reporting	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Other biases							
7. Other sources of bias	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Results

This systematic review gathered 154 studies identified through the determined search strategy in electronic databases. Of those 154 studies, 109 were excluded due to duplication in databases, 29 were excluded because of being abstracts, systematic reviews or other studies. Thus, 16 clinical trials were included for complete analysis, of which 2 were excluded because of their prospective character, 2 were excluded due to cohort duplication, and 5 were excluded for not contemplating an outcome. Thus, 7 studies were included for complete analysis in this review (Figure 1).

Data regarding the methodology and results of the studies included in this review are shown in Table 3. They assessed the effectiveness of telerehabilitation as compared to conventional CVR, in addition to comparing the effectiveness of conventional CVR to that of hybrid cardiac rehabilitation (HCR), in which the patient practices the exercises at home using sensors that transmit information to the rehabilitation center. Some studies' outcomes were as follows: influence of rehabilitation on oxygen consumption (VO_2), physical capacity, acceptance and efficacy of the technique in different patients. Of the underlying pathologies that led the patients to look for rehabilitation, the following stand out: coronary artery disease (CAD), chronic heart failure (CHF) and diabetes mellitus (DM).

Discussion

The present systematic review of the literature analyzed seven clinical trials involving telerehabilitation for patients with CVD, adding up to a sample of 1,133 patients. The studies were heterogeneous regarding both their populations and interventions; thus, a meta-analysis could not be performed.

Catalina et al.[10] have suggested that CAD is still one of the major causes of premature death in Europe and worldwide, being considered a public health problem. Considering that, some studies have assessed the effects of CVR and telerehabilitation on patients with CAD. According to Vieira et al.,[11] the group undergoing telerehabilitation performed better in executive functions, conflict resolution and attention as compared to the group undergoing conventional CVR. According to Brouwers et al.,[12] telerehabilitation has provided better physical activity levels in the long run as compared to conventional CVR. Likewise, other authors have evidenced that patients with CAD

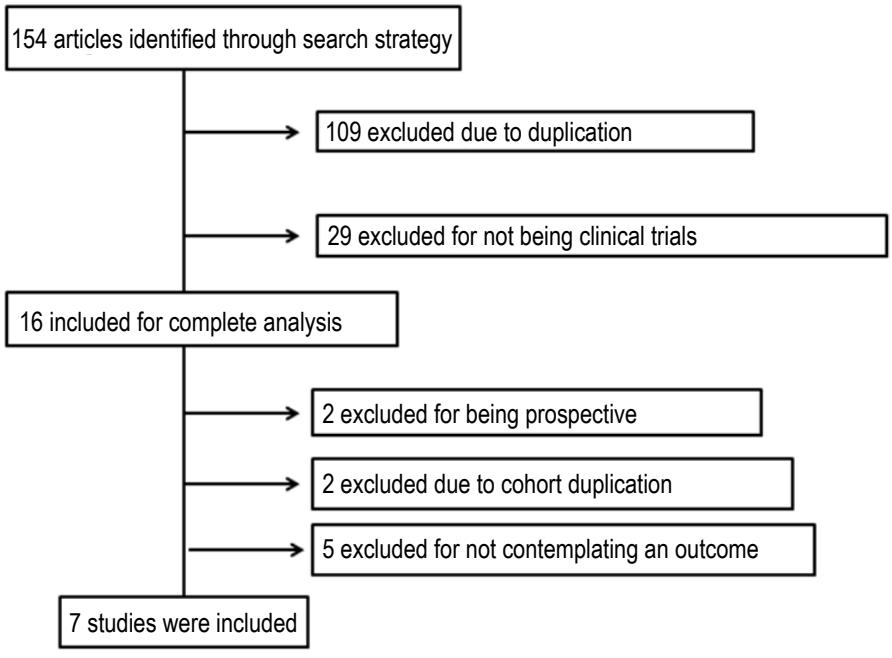

Figure 1 - Flowchart of the selection of the studies.

Table 3 - Methodology and results of the studies included

Author/Year	Groups	N	Objective	Technique / Instruments	Conclusion
Vieira et al.,[11] 2017	G1 = home CVR + Kinect G2 = home CVR + booklet G3 = usual care	N = 33 G1 = 11 G2 = 11 G3 = 11	To assess the effect of a home-based phase III CVR specific exercise program, for 6 months, on changes in executive function, quality of life and depression, anxiety and stress of individuals with CAD.	Compared G1 x G2 x G3 G1 = Specific Kinect software G2 = Booklet with exercises G3 = Guidance on risk factors and encouragement of walking	G1 showed better performance regarding executive function, mainly in conflict resolution and attention.
Brouwers et al.,[12] 2017	CG = CVR at a center IG = home-based telerehabilitation	N = 300 GC = 150 GI = 150	To compare cardiac telerehabilitation with conventional CVR, regarding behavior change and physical activity level in patients with CAD.	IG: Web App for patients to adjust their rehabilitation goals, inspect their trainings and physical activity data; such data are shared, and video consultation is available; heart rate monitor; accelerometer.	Telerehabilitation using modern technology and behavior change strategies results in better long-term physical activity levels as compared to conventional CVR for patients with CAD.
Piotrowicz et al.,[15] 2015	CG = control TG = home-based telerehabilitation	N = 111 GC = 77 GT = 34	To assess the influence of reversion of depression (Beck score) and physical capacity improvement (VO_2 peak) in patients with CAD.	TG: 5-10-minute warm-up, Nordic training (walking) for 15-45min, and 5-minute cool-down. Patients trained 5 times per week, for 8 weeks, and received an instrument for data transmission through the cellular phone. CG: No exercise prescription. All participants were instructed on healthy lifestyle.	Home-based rehabilitation using telerehabilitation resulted in reversion of depression and improvement in physical capacity of patients with CHF.
Bernocchi et al.,[16] 2017	IG = intervention/ telerehabilitation group CG = control group	N = 112 GI = 56 GC = 56	To assess the feasibility and efficacy of an integrated home-based telerehabilitation program in patients with COPD + CHF.	IG: weekly phone calls, instructions/lifestyle, supervised exercise with oximeter; CG: medications, O_2 and visits, instructions on how to practice the exercise of their choice, without supervision.	The IG increased the walked distance, while the CG showed no significant improvement. MRC dyspnea scale and Barthel index improved in IG as compared to CG in 4 months. IG kept the benefits acquired for 6 months. This 4-month telerehabilitation program was feasible and effective for patients with COPD and CHF.

Szalewska et al.,[13] 2015	CRD = cardiac rehabilitation with DM CCR = cardiac rehabilitation without DM	N = 125 RCD = 37 RCC = 88	To compare the effects of HCR in patients with CAD with and without DM.	Both groups trained for 10 days at the rehabilitation center, received instructions, and then passed to home-based rehabilitation, during which they were monitored with tele-ECG and trained with supervised exercises. The device enabled recording ECG data from 3 precordial leads and their transmission through a cellular phone network to the monitoring center. A cellular phone was also used for daily voice communication between the patient and the doctor who asked about the patient's health status.	HCR was effective for patients with DM. Adherence to HCR was high. Patients with DM had higher rates of obesity and significantly lower tolerance to exercise than those without DM. Patients of both groups had similar benefits regarding physical capacity, heart rate at rest and heart rate recovery.
Korzeniowska-Kubacka et al.,[17] 2015	Men after AMI: 57 Women after AMI: 30	N = 87	To compare the influence of HCR on the physical capacity, safety, adherence and return to work of post-AMI male and female patients.	Ten rehabilitation sessions were performed at the center, and the others at home with tele-ECG monitoring. Before and after the trainings, all patients underwent a symptom-limited exercise stress test. The evaluation included the results of exercise tests.	HCR resulted in a comparable improvement in physical capacity in post-AMI low-risk male and female patients. Although HCR facilitated patients' adherence to the training program, their return to work was significantly greater only in post-AMI men.
Piotrowicz et al.,[18] 2014	Telerehabilitation Group: all participants practiced 3 days at a center and 4 months at home.	N = 365	To assess the implementation and feasibility of a wide home-based cardiac telerehabilitation program for patients with CVD, as well as its safety, and the patients' acceptance and adherence to the program.	Participants underwent a 4-week HCR based on walking, Nordic walking or cycle ergometer training. They were monitored via telephone with a device to record ECG and to transmit data via cellular phone to the monitoring center. Automatic ECG recording was pre-defined and coordinated. The influence on physical capacity was assessed by comparing the changes in: time of the exercise test, functional capacity, distance in 6-minute walk test at the beginning and end of the program. All participants used an APP for ECG and BP transmission.	HCR resulted in a significant improvement in all parameters. It is a feasible and safe form of rehabilitation, well accepted by patients. The adherence to HCR was high and promising.

Kinect: movement sensor; Booklet: with information and guidance about the practice of the exercises; CAD: coronary artery disease; CHF: chronic heart failure; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; AMI: acute myocardial infarction; CVD: cardiovascular disease; Tele-ECG: electrocardiogram transmission system; HCR: hybrid cardiac rehabilitation; APP: application for data transmission; MRC: Medical Research Council; BP: blood pressure.

submitted to telerehabilitation showed a significant increase in their daily activity level and VO_2 peak after 6 weeks.

Hybrid cardiac rehabilitation has been used for patients with CAD. Szalewska et al.[13] have compared the use of that technique in patients with CAD and DM and patients with DAC but without DM. Those authors have reported that adherence to HCR was high, and that HCR was effective in patients with and without DM.

According to Bocchi et al.,[14] heart failure (HF) is the common end of most heart diseases, being classified as an epidemic and representing one of the most important current clinical challenges in health care. Telemedicine has been increasingly used for that population. In a clinical study with 111 patients with HF, Piotrowicz et al.[15] have shown that home-based rehabilitation using telerehabilitation caused reversion of depression and improved physical capacity in those patients.

Corroborating the results demonstrated, Bernocchi et al.[16] have suggested, in a study with 112 patients diagnosed with HF and chronic obstructive pulmonary disease (COPD), that a home-based telerehabilitation program increased the walked distance, reduced the dyspnea and improved the functionality of those individuals as compared to those of the group undergoing conventional CVR, confirming the feasibility and effectiveness of telerehabilitation programs for patients with HF and COPD.

Hybrid cardiac rehabilitation has also been used for post-acute myocardial infarction (AMI) patients. In a study with 87 post-AMI patients, the authors have evidenced that HCR facilitated patients' adherence to the training program, but the return-to-work indices were higher in men than in women, although the physical capacity improvement was similar for both sexes.[17]

Similarly to the studies assessed, Piotrowicz et al.[18] have confirmed in a sample of 365 patients that HCR using telerehabilitation resulted in a significant improvement in functional capacity, being a feasible, safe and well accepted rehabilitation form, with a high index of patients' adherence.

Conclusion

After analyzing the studies, we concluded that HCR and home-based rehabilitation using telerehabilitation are feasible and safe alternatives, with high adherence by patients with CVD. They can be added to conventional CVR programs or be used in isolation. In addition, they help to improve depression, functional capacity and the physical activity level.

Author contributions

Conception and design of the research: Cristo D, Dias AS, Sachetti A. Acquisition of data: Cristo D, Nascimento NP, Sachetti A. Analysis and interpretation of the data: Cristo D, Nascimento NP, Sachetti A. Statistical analysis: Cristo D. Writing of the manuscript: Cristo D, Sachetti A. Critical revision of the manuscript for intellectual content: Cristo D, Dias AS, Sachetti A.

Potential Conflict of Interest

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

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VIEWPOINT

Cardiology and Films: An Important Teaching Tool

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The use of films and literary texts as didactic material in medical school has increased based on the perception that it might benefit the discussion of certain technical aspects of clinical conditions and enable students to experience the illness process.

An article on literature and cardiology[1] has shown that the description of the death process in Tolstoy's novel "The death of Ivan Ilyich" could be more powerful to provide medical students and physicians with the perception of the finitude process than reading theoretical texts about the end of life. Similarly, Marguerite Yourcenar's "Memoirs of Hadrian" could help to understand the suffering of a patient with heart failure.

Similarly to literature, films have been used for medical education to discuss questions related mainly to ethics and medical practice. Some films, such as "Patch Adams", "Cry Danger", "The Sea Inside", "Black Swan", "As Good as it Gets", "Wit", are classically presented to medical students for medical education.

If on the one hand, by telling a story and showing an image, films can reduce our ability to imagine how the story's characters and places would be, on the other, they provide us with a different aesthetic experience, usually shorter than book reading, by offering images and sounds that affect our sensitivity in a different way than book reading does. Both literature and films allow us access to a level of internalization difficult to achieve when reading a medical book or text about a certain disease. Medical books provide the description of cells, organs and diseases, how to establish a diagnosis, in addition to the drugs and other treatments to be used, while literature and films provide us with the experience of patients with their illnesses.

Regarding cardiology, the year 2016 was particularly interesting, because two awarded films, "Manchester by the Sea" and "I, Daniel Blake", approached under different aspects one of the most prevalent heart conditions worldwide: heart failure.

Kenneth Lonergan's "Manchester by the Sea" was awarded with the 2017 Oscar for best actor in a leading role (Casey Affleck) and best original screenplay. Its central plot is the return of a man to his hometown after the death of his brother to take care of his 16-year-old nephew, re-opening an unspeakable tragedy. The film scene that interests us, due to its potential to foster a cardiology class discussion, lasts less than three minutes and approaches the disclosure of his brother's heart failure diagnosis to the patient and his family (wife, brother and father) by a female doctor during one of his hospitalizations. The doctor talks with the patient about his diagnosis and prognosis, explaining that the data presented were statistics and not definitive numbers about a particular patient. The scene raises ethical and technical questions, such as possible heart failure etiologies, its treatment, its mechanisms of death, its prognosis. In addition, that scene provides us with the different ways to react to such talk, always difficult, especially the patient's and his wife's reactions.

Talks involving the disclosure of the diagnosis and prognosis of life-threatening diseases, also known as bad news, are one of the most difficult attributions of a doctor. Bad news in the healthcare field are any information that will drastically affect the future perspective of patients and families. Difficulties in communicating bad news usually postpone discussions with the patients and families about terminal diseases,

Keywords

Communication; Humans; Cardiovascular Diseases; Neoplasms; Physician Patient Relations; Prognosis; Truth Disclosure.

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proximity of death and indication for exclusive palliative care.[2-4]

But we might have to face even tougher situations when managing patients with heart failure, such as answering the following questions: "How many years do I still have?", "Will I live to attend my child's graduation?", "Will I live to see my grandchildren grow up?", and other questions that might cross their mind. Perhaps one of the defenses we put up is to restrict all room for that sort of questioning. In addition to not being the proper solution, this attitude somehow postpones coping with those issues, which ends up avoiding that discussion, because, not rarely, the outcome soon becomes clear to both patients and families. However, that attitude hinders the communication with patients and families, delaying their understanding of the situation.

In addition, the discussion about that scene can go beyond medicine as we realize that the diagnosis is established by a female doctor of Asian origin. This can lead us to debate our reality in the Brazilian medicine, in whose graduation programs female students predominate. How will this affect medical practice? Will this change the doctor-patient relationship? Moreover, the Asian origin of the doctor can open the discussion about "the other", "the foreigner" in a country that seems to move away from its cosmopolitan tradition. Perhaps we could draw a parallel to the issue that "the other", through the quota system, affirmative actions, ProUni and FIES, has become an increasing presence at medical schools in Brazil, one of the most elitist courses in the country.

The other film from 2016, Ken Loach's "I, Daniel Blake", was awarded with the *Palm d'Or* in the Cannes Film Festival and also approaches the heart failure issue, but from a social perspective. In that film, set in England, Daniel Blake, interpreted by Dave Johns, after having a heart attack, is advised by his doctor not to return to his work at a carpentry, and, thus, must fight the bureaucratic forces of the system to receive Employment and Support Allowance. He faces the bureaucratic system, the coldness of the institutions, which supposedly exist to make the patients' lives easier, the difficulties enlarged by his digital illiteracy, and a whole process that reminds us of the Franz Kafka's novel "The Trial", which tells about the distressing, meaningless and cruel bureaucratic trial to which citizens are submitted.

Watching this film can bring to the classroom discussions about situations rarely approached in lectures on myocardial infarction and heart failure, but which are extremely frequent when managing patients with such conditions. Who has not been asked: "Doctor, when can I go back to work?", "Doctor, am I entitled to retirement benefits?", "How do I receive my support allowance?", "Doctor, they have cut my benefits. What should I do?". These situations are so frequent for those following patients up after myocardial infarction and with heart failure that we have to know something about the legislation to instruct our patients in a responsible way regarding their rights, providing them with reports to allow them to have their rights ensured. Usually such reports need to be systematically renewed, which not rarely makes the patient feel shy, fearing to be bothering the doctor.

An additional theme for discussion in that film is the question of "the other". In one of his several visits to the government offices, Daniel Blake befriends a white woman who had just moved to the city and also seeks for social support. She has two children, one of them is a black girl, who also suffers with the social security insensitivity. Although our patients might face much bigger difficulties than English citizens do, this film shows that bureaucracy and insensitivity are not exclusive characteristics of our society.

Conclusion

The use of films or film scenes is an important tool to discuss heart conditions, not only regarding the disease's technical aspects, but also the social, ethical and existential aspects involved in the diagnosis of a severe heart disease. To quote Arthur Kleinman, the laureate films "Manchester by the Sea" and "I, Daniel Blake" are examples that can help us practice medicine in a more sensitive and reflexive, alert and morally responsible way in face of the emotional and experiential challenges presented by the profession.[5]

Author contributions

Conception and design of the research: Mallet ALR, Geovanini F, Andrade L, Kestenberg D. Analysis and interpretation of the data: Mallet ALR. Writing of the manuscript: Mallet ALR, Geovanini F, Andrade L, Kestenberg D. Critical revision of the manuscript for intellectual content: Mallet ALR, Geovanini F, Andrade L, Kestenberg D.

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CASE REPORT

Sirolimus-Eluting Balloon Treatment of Distal Internal Mammary Artery Anastomosis: Optical Coherence Tomography Findings

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Drug-eluting balloons (DEB) represent an interesting alternative to current generation drug-eluting stents (DES) in selected anatomic scenarios, such as in-stent restenosis, small-vessel disease and bifurcation lesions, where the systematic implantation of DES may result less appealing.[1,2] In particular, lesions located at the distal anastomosis of a bypass graft (an artificially created bifurcation) constitute a unique anatomic setting, where DEB may overcome some inherent limitations of DES resulting from the implantation of a metallic platform throughout the bypass graft into and across the native distal vessel.

Herein we present, to the best of our knowledge, the first report of the treatment of a lesion located at the distal anastomosis of a left internal mammary artery (LIMA) to the left anterior descending coronary artery (LAD) with a novel sirolimus-DEB. Interestingly, optical coherence tomography (OCT) findings proved to be of major value to guide the procedure.

An 83-year-old man with previous history of hypertension, hyperlipidemia and ex-smoker was admitted with acute coronary syndrome. Coronary angiography revealed 3-vessel coronary artery disease, with a total occlusion at the mid-segment of the LAD and additional significant lesions at the obtuse marginal branch (OM) and mid-segment of the right coronary artery (RCA). After discussion in a Heart-Team meeting, a decision for a hybrid revascularization strategy was made. Off-pump coronary artery bypass grafting (CABG) was performed with a LIMA anastomosed to the distal LAD and a saphenous vein graft from LIMA to OM. The postoperative period was uneventful. A week later, the scheduled percutaneous coronary intervention was successfully performed with a DES implanted at the mid RCA. However, during the procedure a revision of the bypass grafts revealed the presence of a significant lesion at the distal anastomosis of LIMA to LAD (Figure 1A). Due to a suspicious of pseudo-stenosis secondary to edema or spasm related to the recent surgery, it was decided to reevaluate this lesion later on. The scheduled control angiogram at 1 month revealed the persistence of the same image of a severe lesion at the distal anastomosis of the LIMA. The lesion appearance remained unaltered after repeated boluses of nitroglycerin. To gain further diagnostic insights, OCT imaging was performed. This imaging technique confirmed the presence of a critical stenosis with a severely reduced lumen (minimal lumen area 1.0 mm^2) (Figure 2A). After lesion predilation with a 2.0 mm semi-compliant balloon, a 2.5/15 mm sirolimus-DEB (MagicTouch, Concept Medical Inc, Surat, India) was used to treat the distal anastomosis (Figure 1B). A good immediate result was confirmed both by angiography (Figure 1C) and OCT (Figures 2B and 2C). The patient was discharged the day after and remains completely asymptomatic at the 9-month follow-up.

The diagnosis of lesions located in the distal LIMA anastomosis may be very challenging. When these lesions are detected in the early postoperative period technical problems should be differentiated from reversible causes, such as edema or spasm. Notably, however, the value of OCT to get further diagnostic insights on these elusive lesions has not been previously reported. Our findings underscore the usefulness of this technique to disclose the underlying substrate and to assess lesion severity before intervention and to guide and optimize the results of interventions. Lesions

Keywords

Angioplasty, Balloon, Coronary / methods; Coronary Artery Disease / diagnosis; Drug-Eluting Stents; Treatment Outcome; Sirolimus.

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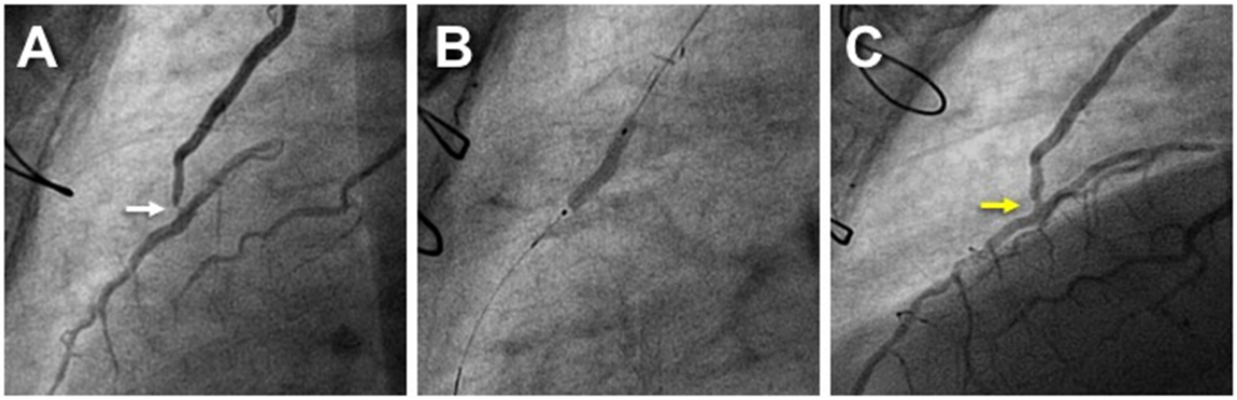

Figure 1 - A) Coronary angiogram depicting a significant stenosis at the distal anastomosis of LIMA to distal LAD (white arrow). B) sirolimus-DEB inflated at the lesion after predilation. C) Final angiogram reveals excellent result (yellow arrow).

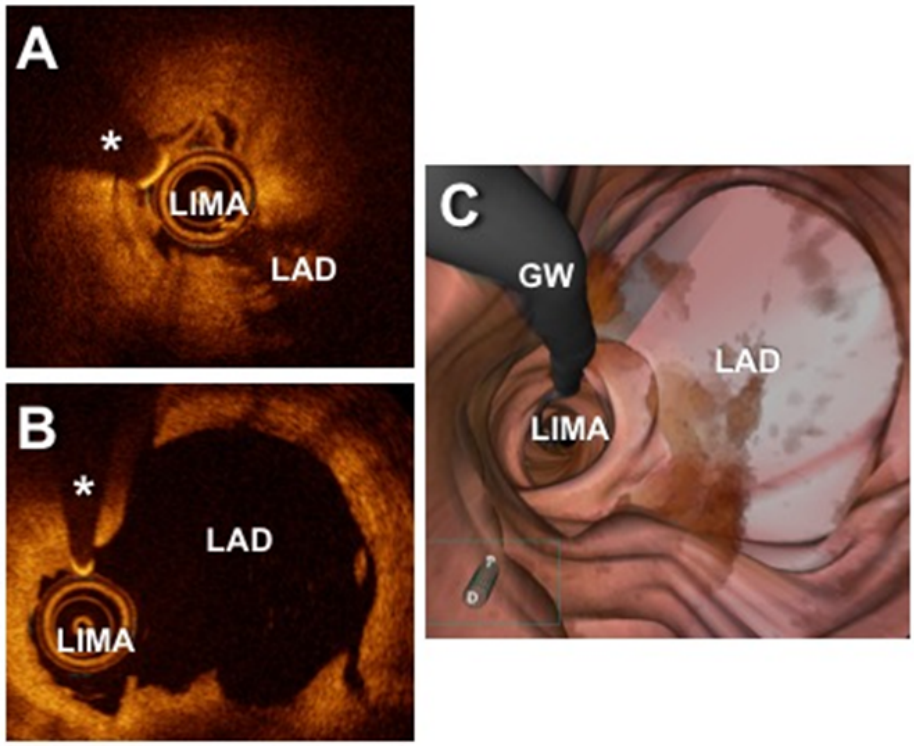

Figure 2 - A) Pre-intervention OCT at the zone of the LIMA to LAD anastomosis showing a reduced lumen area about 1.0 mm². B) OCT after predilation and sirolimus-DEB inflation confirming good final result at the zone of anastomosis with an excellent lumen area (6.4 mm²). C) 3D reconstruction of final OCT run, showing from distal to proximal an "en face view" of the distal anastomosis of LIMA to LAD, confirming good result after Sirolimus-DEB. * denotes wire artefact. GW: guidewire.

located on LIMA distal anastomosis are frequently treated with plain balloon angioplasty, but more recently DES has been widely used. The value of DEB in this setting has not been well established.

Most of the evidence on the efficacy of DEB in both in-stent restenosis and de novo lesions has been generated with first generation paclitaxel-DEB.[1,2] However, this technology is continuously evolving and, currently, novel

devices with limus-type drugs and more modern carrying systems, are available.[3] We selected a novel sirolimus-DEB with a carrying system based on nanoparticles that enable an efficient drug transfer. Preclinical studies have shown that these nanocarriers have better bio-availability and in-tissue uptake, therefore, allowing a reduction in the drug dosage, therefore, potentially diminishing vessel toxicity.[3] Preliminary experience with these novel devices appears highly promising.[4] Our findings suggest the value of sirolimus-DEB in the treatment of de novo lesions at the distal anastomosis of LIMA bypass grafts. This therapy may represent a safe and valid alternative to current-generation DES in this setting. However, further studies with long-term clinical and angiographic follow-up are required to fully elucidate the relative value of this novel strategy in this unique anatomic scenario.

Novel sirolimus-DEB technology seems to be an alternative to current DES at curious scenarios such as distal LIMA bypass anastomosis. OCT may be helpful to assess the results after DEB treatment.

Author contributions

Conception and design of the research: Garcia-Guimarães M. Acquisition of data: Garcia-Guimarães M. Writing of the manuscript: Garcia-Guimarães M, Alfonso F. Critical revision of the manuscript for intellectual content: Maruri-Sanchez R, Cuesta J, Rivero F, Bastante T, Alfonso F.

Potential Conflict of Interest

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CASE REPORT

Cardiac Amyloidosis with Heart Failure and Middle Range Ejection Fraction

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Introduction

Cardiac amyloidosis (CA) is a disease with a difficult diagnosis, limited management and a reserved prognosis.[1,2] A high level of suspicion is necessary for its identification. There are some clinical clues, such as elderly individuals with unexplained left ventricular hypertrophy (LVH), heart failure with preserved ejection fraction (HFpEF) and restrictive pattern, dissociation between LVH on echocardiography and low voltage on the electrocardiogram, among others.[1,2]

CA can occur with several hemodynamic forms and patterns of remodeling, according to the disease evolution stage. It may occur as the restrictive form, with left ventricular ejection fraction > 50%; and dilated form, with reduced ejection fraction.[1,2] Recently, the European Society of Cardiology has established a new classification with the creation of "Heart Failure with Mid-Range Ejection Fraction" (HFmrEF).[3] We report a case of CA with HFmrEF.

Case report

A female patient, aged 80 years old, was treated at the emergency unit at the first evaluation showing fatigue with medium exertion, orthopnea, nocturnal paroxysmal dyspnea and lower limb edema. She also had frequent complaints of muscle weakness and asthenia. She was admitted with a diagnosis of acute heart failure (HF). She reported macrocytic anemia 3 years before, with no defined etiological diagnosis. She was submitted to an echocardiogram, which showed LVH and ejection fraction of 64%. She was discharged without an etiological definition of HF.

Fifteen days after discharge, she came to the outpatient clinic with pallor (2+/4+) and jugular swelling at 45°; *ictus cordis* in the sixth intercostal space in the anterior axillary line; presence of third heart sound; pulmonary component of the second heart sound greater than the aortic component, without murmurs. Pulmonary auscultation showed vesicular murmur abolished at both bases; crepitant rales up to the middle third of both hemithoraces. The liver was palpable at 2 cm from the right costal border. She had symmetrical lower-limb swelling, with pitting edema up to the thigh root, cold and painless. The patient was hospitalized for HF compensation and etiological investigation.

Laboratory tests showed macrocytic and hypochromic anemia; vitamin B12 deficiency; erythrocyte sedimentation rate of 134 mm; electrophoresis; and proteins with monoclonal lambda chain peak.

The electrocardiogram showed junctional rhythm, with low voltage. Chest x-ray showed signs of pulmonary congestion and moderate bilateral pleural effusion. The transthoracic echocardiogram showed dilation of the left and right atria, left ventricular ejection fraction (LVEF) of 42% and alterations suggestive of infiltrative heart disease. Global strain with apical sparing pattern (Figure 1A to 1D) was observed. Myocardial resonance (MRI) was suggestive of the presence of subendocardial amyloid deposits and late enhancement of 35%. LVEF was 45% (Figures 1E to 1H).

The bone marrow aspirate showed a predominance of plasma cells in > 90% of the slide. Immunohistochemistry confirmed the diagnosis of multiple myeloma. Biopsy of facial lesion and abdominal fat with histopathological analysis showed amyloid deposits (Figure 2).

Keywords

Heart Failure / physiopathology; Amyloidosis; Stroke Volume; Hypertrophy, Left Ventricular; Aged.

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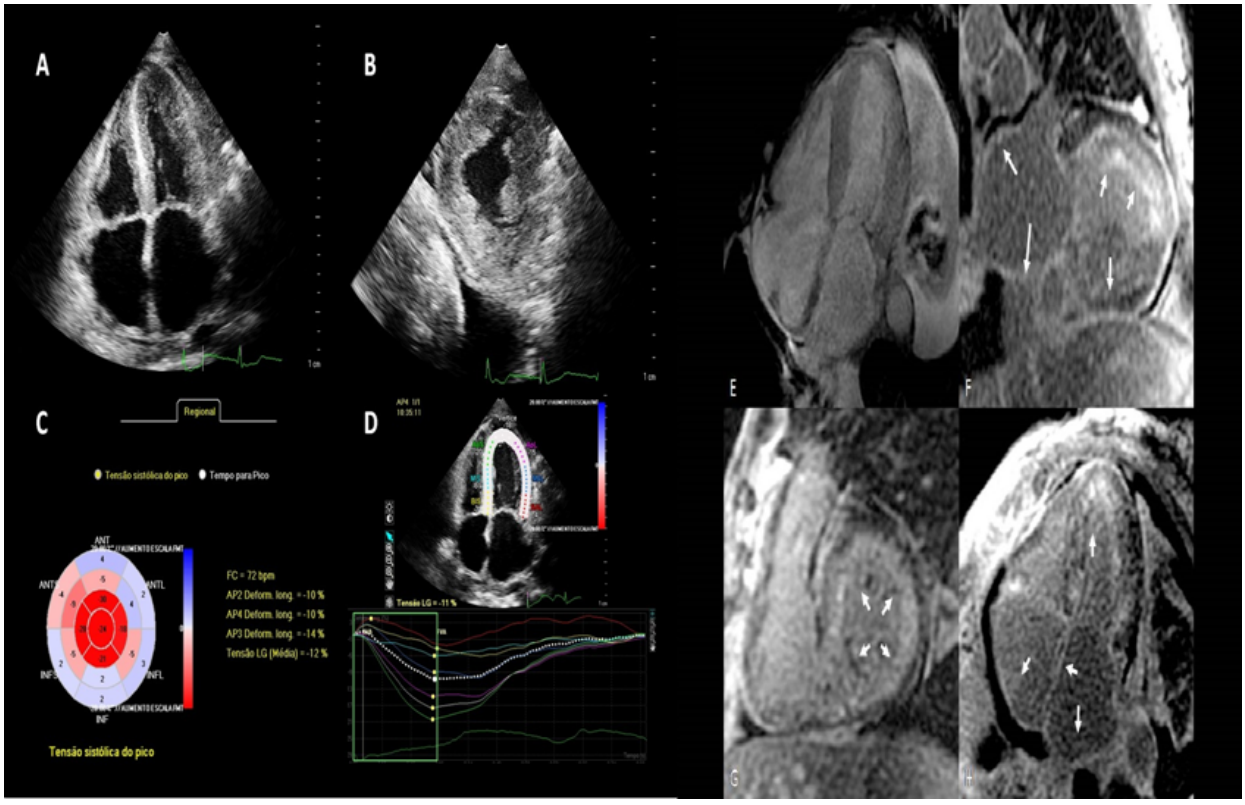

Figure 1 - (A) Apical four-chamber view showing biatrial enlargement, thickened interatrial septum, left ventricular wall hypertrophy, with hyperechoic texture of the myocardium. (B) Parasternal short axis view. Concentric left ventricular hypertrophy. (C) Bullseyes. Global longitudinal systolic strain (mean value of (-)12%), with prominent basal and medium impairment, and preserved apical mechanical function. (D) Apical four-chamber strain showing that the ratio between the apical inferior septal strain and the lower basal septal strain is greater than 3. (E) Cine-mode of the stationary state free precession showing diffuse left ventricular myocardial thickening. (F) Long axis post-gadolinium image showing diffuse late improvements (arrows) in the left atrium, as well as subendocardial enlargement of the left ventricle, more prominent in the anterior wall. (G) Short axis post-gadolinium image showing diffuse subendocardial enhancement (arrows) in the left ventricle. (H) Four-chamber post-gadolinium image showing late enhancement (arrows) not only in the left chambers, but also of the right atrium.

The diagnosis was systemic amyloidosis and multiple myeloma associated with cardiac involvement. Pulse therapy with prednisone was initiated. The HF became refractory to treatment, and the patient died 3 months after the disease onset.

Discussion

Amyloidosis is a rare and multisystemic disease. Patients with amyloidosis usually have few specific symptoms, which makes the diagnosis difficult in the initial phase, as the case presented herein. Cardiac impairment due to amyloidosis can lead to HF, as well as conduction system involvement, with low voltage at the ECG, which increases clinical suspicion.[4] In addition to myocardial infiltration, amyloid infiltrates can be found in the conduction system, valve tissues, coronary arteries, large vessels and autonomic or peripheral nerves, leading to many clinical manifestations.[2]

More than 25 proteins have been described as possible amyloid-forming agents; however, two of them predominate in cardiovascular impairment: transthyretin (TTR) and immunoglobulin light chains – amyloid light chains or AL.[2] The TTR protein is synthesized and secreted by the liver and choroid plexus, and functions as a carrier of thyroxine and retinol binding protein. This protein is typically found in soluble tetramers in their native form. TTR has become the most prevalent form of CA found in clinical practice, with greater identification being made by noninvasive imaging tools.[5] Cardiac involvement by TTR occurs most commonly in the sixth and seventh decades of life as HFpEF,[6] with the wild-type or senile

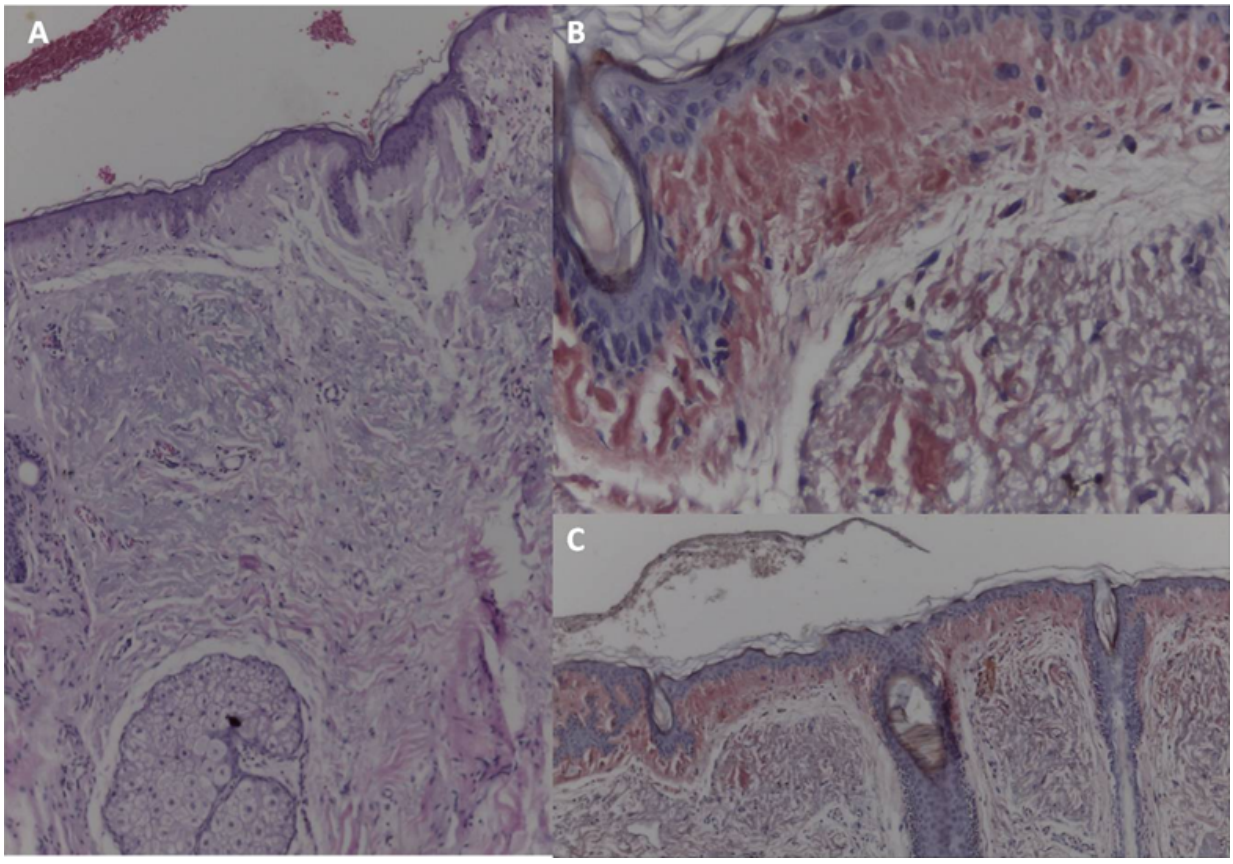

Figure 2 - (A) Skin biopsy showing deposits of amorphous and eosinophilic material on the papillary dermis (hematoxylin-eosin - original 40x magnification). (B) Congo red staining showing amyloid material in the dermal papillae (original magnification 100x and 400x). (C) Amyloid deposit around the sebaceous gland (Congo red - original magnification 400x). (D) Amyloid deposit around adipocytes (Congo red - original magnification 400x).

systemic amyloidosis. The AL form of amyloidosis is caused by the deposition of immunoglobulin light chains segregated from monoclonal proliferation of plasma cells. Currently, the AL amyloidosis is considered less frequent than TTR. The cardiac diagnosis in patients with AL amyloidosis is often earlier, at a mean age of 65 years and more commonly associated with the female gender, with lower left ventricular mass and lower voltage at the ECG than those with TTR.[2] The AL form of amyloidosis (immunoglobulin light chain deposition disease) may coexist in patients with myeloma in 10 to 15% of cases, such as the patient in this case report. That does not mean the presence of multiple myeloma with secondary amyloidosis, but the coexistence of two separate and concomitant plasma cell diseases.[7]

HF in amyloidosis is classically described as either HFpEF or HFrEF (heart failure with reduced ejection fraction) in their more advanced forms.[8] HF guidelines have recognized that there is a gray area between HFrEF and HFpEF, which shows mild systolic dysfunction and has some characteristics of diastolic dysfunction, defined as HF with mid-range ejection fraction (HFmrEF).[3] The patient in this case had LVEF between 40 and 49% both in the second echocardiogram and the cardiac MRI and, therefore, was characterized as having HFmrEF.

The disease can be suspected noninvasively through a characteristic low-voltage ECG. Recently, cardiac imaging techniques have allowed the diagnosis to be attained through the echo-doppler-cardiogram with an apical sparing of the longitudinal strain, MRI with transmural global subendocardial late enhancement, and technetium-99m-pyrophosphate myocardial scintigraphy.[1] The definitive diagnosis of amyloid

cardiomyopathy is obtained from an endomyocardial biopsy using Congo red or thioflavin staining[2,9] technique and identifying the type of amyloid infiltrate by molecular genetic techniques.

The gold standard for the diagnosis of amyloidosis is the myocardial biopsy. The guidelines of the American Heart Association/American College of Cardiology Foundation show a II-A recommendation for endomyocardial biopsy in the presence of HF associated with unexplained restrictive cardiomyopathy.[10] The abdominal fat biopsy can confirm the diagnosis in 70% of cases and, in this reported case, amyloidosis was confirmed by the abdominal biopsy.

The prognosis of patients with amyloidosis is reserved. The mean untreated survival is 13 months and may be extended to 17 months with melphalan and prednisone, which in this case were not used due to the patient's clinical worsening. The cardiac impairment makes the prognosis even worse, with a life expectancy of approximately 6 months.

Author contributions

Conception and design of the research: Jorge AJL, Avila D, Ribeiro ML, Bruno KEH, Pires C; Acquisition of data: Jorge AJL, Avila D, Vilar EG, Ribeiro ML, Bruno KEH, Pires C; Analysis and interpretation of the data: Jorge AJL, Avila D, Bruno KEH; Writing of the manuscript: Jorge AJL, Avila D, Pires C; Critical revision of the manuscript for intellectual content: Jorge AJL.

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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