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SUMARY

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ORIGINAL ARTICLE

Transfusion of Blood Products in the Postoperative of Cardiac Surgery

Antonieta Moraes, Juliana Neves Giordani, Cristiane Tavares Borges, Pauline Eloise Mariani, Laura Maggi da Costa, Leonardo Hennig Bridi, Ari Tadeu Lirio dos Santos, Renato Kalil

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Abstract

Background: The indiscriminate use of blood transfusion in surgery has been associated with increased risk of infection and increased length of hospital stay.

Objective: To identify the average amount of bleeding and rates of transfusion of blood products in the postoperative period of patients undergoing cardiac surgery in a cardiology center.

Methods: Medical records of patients who underwent myocardial revascularization surgery and/or heart valve replacement with use of cardiopulmonary bypass (CPB) were analyzed. Perioperative data such as CPB time, hematocrit and hemoglobin values were collected after surgery. The amount of bleeding (mL), blood transfusion (IU), clinical complications and time of hospitalization were also recorded. The correlation between bleeding in the postoperative period and blood transfusion was performed using the Spearman correlation. A $p < 0.05$ was considered statistically significant.

Results: A total of 423 patients undergoing coronary artery bypass grafting (51.5%) or heart valve replacement (33.6%) were included. During the first 24 hours, the average bleeding volume was 353.3 ± 268.3 mL. Transfusion of blood products was required in 40.1% of cases, most frequently (70.6%) in the immediate postoperative period. Red blood cell concentrate was the most frequently used product (22.9% and 60%).

Conclusion: The occurrence of bleeding in the cases was low, and when transfusion of blood components was indicated, red blood cell concentrates were the most widely used component.

Keywords: Cardiac Surgery; Postoperative Care; Blood Transfusion/methods; Transfusion Reaction/complications.

Introduction

Patients undergoing cardiac surgery are prone to excessive postoperative bleeding. In addition, it is known that the passage of blood through the cardiopulmonary bypass (CPB) circuit triggers the release of inflammatory mediators, resulting in a series of changes in hemostasis. Other situations such as thrombocytopenia, disseminated intravascular coagulation, and liver failure may also influence the occurrence of acute anemia, which should be corrected immediately.[1,2]

However, the indiscriminate use of blood products in cardiac surgery has been associated with increased risk of infection, increased need for mechanical ventilation, increased organ failure, longer length of hospital stay, and higher mortality rates.[3-6]

Although blood transfusion may become imperative for the management of postoperative cardiac surgery patients, several efforts have been made to restrict and standardize transfusion practice and improve outcomes for patients.[7-9]

Much has been discussed about the optimal time for transfusion, although there is no global standardization of hematocrit and hemoglobin values, but only a consensus on clinical criteria. In practice, efforts have focused on maintaining hemoglobin values between 7 and

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9 g/dL.[10] Literature data suggest that hemoglobin levels are not sufficient for the decision to transfuse a patient and individual characteristics such as age, comorbidities and perfusion. associated parameters should be considered to minimize possible complications.[11]

Previous studies have shown that the need for blood transfusion may be reduced by the use of acute normovolemic hemodilution,[12-14] and prophylactic intravenous administration of concentrated fibrinogen or tranexamic acid immediately before and after myocardial revascularization, which reduces the frequency of postoperative bleeding and fibrinolysis in high-risk populations.[15-17] Other methods such as the use of intraoperative autotransfusion in CPB cardiac surgery, hemofiltration, preoperative autologous blood donation and erythropoietin pretreatment, as well as the recognition of normovolemic anemia, have been described to reduce blood transfusion and its potential adverse effects.[18,19]

In this context, this study was designed to assess the amount of bleeding and the number of transfusions in an institution where a high number of cardiac surgeries are performed, located in southern Brazil.

Patients and Methods

Consecutive medical records of patients who underwent cardiovascular surgery from January 2015 to July 2016 were retrospectively analyzed in a cardiology center located in the south of the country. Patients of both sexes, aged ≥18 years, undergoing myocardial revascularization surgery, valve replacement surgery, or both, with use of cardiopulmonary bypass, were included in the study. Exclusion criteria were emergency surgery and incomplete medical records. After the selection of a convenience sample from the surgery list of the institution, the records of health teams (developments and requirements) were reviewed in electronic and/or paper medical records, to collect the information for a specific database.

Demographic and clinical variables, as well as previous comorbidities were collected for sample characterization. The data from pre-, intra- and post-operative periods such as the time of CPB, and hematocrit and hemoglobin values were collected at one, 12 and 24 hours after surgery. The occurrence of bleeding (mL), transfusion of blood products (IU), clinical complications and time of hospitalization were also recorded.

Ethical Considerations and Statistical Analysis

The study was approved by the Research Ethics Committee of the institution, under number 4906/13, and conducted according to the ethical principles related to access and analysis of data of the 466/12 Resolution of the Brazilian National Health Council. A term of commitment and confidentiality for the use of data from medical records was used.

The data were analyzed with the Statistical Package for Social Sciences (SPSS) version 20.0, considering a significance level of $p < 0.05$ for all tests. Categorical variables were described as absolute numbers (n) and relative (%) frequencies and continuous variables were expressed as mean and standard deviation for those with normal distribution or median and interquartile range for those without normal distribution. The correlation between bleeding in the postoperative period and blood transfusion was performed using the *Spearman* correlation. To verify the normality of the data, the Shapiro Wilk test was used. The other associations were performed using the chi-square test.

Results

A total of 423 medical records of patients undergoing elective cardiac surgery with CPB were analyzed. The surgeries performed included coronary artery bypass grafting (51.5%) and valve replacement surgery (33.6%). The study population had a mean age of 60.5 ± 12 years old, and hypertensive or active smoking patients were 77.8% and 28.6%, respectively. These and other baseline characteristics are described in Table 1.

Laboratory Results

The average blood loss through mediastinal and pleural drainage in the perioperative and immediate postoperative periods within the first 24 hours, was 353.3 ± 268.3 mL. The method of measuring perioperative bleeding was by weighing the compresses. The average hematocrit and hemoglobin values in the postoperative period were 31 ± 4.3% and 10.2 ± 1.4g/dL, respectively (Table 2).

Transfusion Parameters

A total of 170 patients (40.1%) required blood transfusion, with 627 bags of blood components, in the pre-, intra- and postoperative periods. Transfusion of red blood cell concentrates was the most used procedure

Table 1 – Demographic and clinical characteristics of the study population (n = 423)

Variable	
Age (years)	60.5 ± 12.4
Male	274 (64.8)
Ischemic heart disease	210 (51.8)
Comorbidities	
Hypertension	329 (77.8)
Active smoking	121 (28.6)
Ex-smoker	96 (22.7)
Dyslipidemia	120 (28.4)
Coronary artery disease	84 (19.9)
Obesity	44 (10.4)
Diabetes Mellitus	94 (22.2)
Ejection fraction (%)	64 (52;70)
Coronary artery bypass grafting	218 (51.5)
Valve replacement surgery	142 (33.6)
Coronary artery bypass grafting and valve replacement surgery	33 (7.8)
CPB time (min)	80 ± 31
Aortic clamping time (min)	58 ± 25
Intensive care unit hospitalization time (days)	4 (3;5)
Time ofhospitalization (days)	14 (10;20)

Categorical variables expressed as n (%); continuous variables expressed as mean ± standard deviation for normal distribution or median and interquartile range for variables without normal distribution

(n=144; 84.7%), and other 26 patients (15.2%) received more than one blood component including fresh plasma, cryoprecipitate, and platelet concentrates. These and other information are described in Table 3.

A greater number of blood bags was used 12 hours after surgery. A weak and reverse correlation was found between bleeding in the postoperative period and blood transfusion r = 0.13 to p = 0.008. (Figure 1).

A total of 146 cases of complications were observed in the immediate postoperative period, of which, 66 (45.2%) needed blood transfusions. There were 11 cases (7.5%) of arrhythmia, 27 (18.5%) of hemodynamic complications, 21 (14.4%) respiratory complications, three (2.1%) renal complications, and four (2.7%) of neurological complications (Table 4).

Discussion

The risks inherent in cardiac surgery are a constant concern due to patients' more advanced age, the greater number of associated comorbidities and the extension of indications for specific groups of patients. The importance of documenting the amount of bleeding in the perioperative period of cardiac surgery has already been established in the literature. This information is important in determining the medical conduct to be taken during the period of hospitalization of the patients.

The massive transfusion of red cell concentrates is strongly associated with reduction of survival and is an independent predictor of early and late mortality outcomes after coronary artery bypass grafting.[20-26]

The average blood loss within the first 24 postoperative hours was 353.3±268.3 mL, and 40% of the patients received blood products. These findings were significantly lower than results reported in the literature. Results of studies conducted with a similar population showed higher transfusion rates, explained by an average volume of 750 ± 250 mL bleeding on the first day after intervention,[21,24] and the need for blood transfusion in approximately half of the patients studied.[23,25] A prospective cohort study conducted with the participation of European surgical services confirmed that severe hemorrhage is uncommon in low-risk patients submitted to cardiac surgery but may be associated with major complications, stressing that even mild bleeding can result in increased risk of adverse events.[22]

The criteria for blood transfusions in general practice and in cardiac surgery vary between institutions and professionals. It has been shown that a conservative strategy (hemoglobin <7.0 g.dL-1) is as effective and possibly more effective than a liberal strategy (hemoglobin <10.0 g.dL-1),[26] reducing blood transfusion complications. However, other studies considered hemoglobin values <8.4 g.dL-1 as a trigger to determine blood transfusion, in order to maintain serum hemoglobin levels >9.0 g.dL-1.[27,28] At the institution where the present study was conducted, blood products are transfused based on patients' clinical conditions, rather than predetermined thresholds or triggers. High doses of vasopressor, signs of severe ventricular dysfunction, weaning failure from mechanical ventilation, assessment of fluid balance, fluid resuscitation and bleeding are among the factors that determine the need for blood transfusions.

In the present study, 40% of the patients were transfused, most frequently with red blood cell concentrates. Transfusion was more frequent in the immediate postoperative period, when hematocrit and hemoglobin levels were lower. Laboratory parameters remained within the normal range in the pre- and intraoperative periods, with less frequent transfusion.

Effective measures for reducing the volume of bleeding should be adopted to reduce the use of blood components. Precautions such as a careful analysis

Table 2 – Laboratory results in the perioperative period of patients undergoing cardiac surgery (n=423)

Variables	Preoperative period	Intraoperative period	Immediate postoperative period
Hematocrit (%)	39.6 ± 4.2	32 ± 6.7	31 ± 4.3
Hemoglobin (g/dL)	13.1 ± 1.7	10 ± 2.1	10.2 ± 1.4
Bleeding (mL)	0.00	413.5* (290;580)	200* (100;300)

*Variables expressed as mean ± standard deviation. * median and interquartile range*

Table 3 – Descriptive analysis of blood transfusion results (n=170)

	Transfusions	Red blood cell concentrates	Red blood cells associated with other blood products
Preoperative	5 (2.9)	3 (1.8)	2 (1.1)
Intraoperative	45 (26.5)	39 (22.9)	6 (3.6)
Postoperative	120 (70.6)	102 (60)	18 (10.4)

Categorical variables expressed as n (%)

of family history of bleeding, appropriate laboratory evaluation, administration of erythropoietin two to three weeks before the surgery, determination of serum iron and oral iron administration, in addition to the use of antifibrinolytics, normovolemic hemodilution, autotransfusion by intraoperative blood reuse in cardiac surgery and hypothermia during CPB, are some of the strategies used in health services.[29]

Among the clinical complications observed in this study, there was a predominance of arrhythmias and hemodynamic and respiratory complications. Although these events are commonly observed in the immediate postoperative period, the transfusion of even smaller amounts of blood can increase adverse clinical outcomes. Infections as mediastinitis, generalized sepsis and acute renal failure have also been documented in similar populations.[29]

Current transfusion practices need to be reevaluated. Despite improvements in the methods of donor selection and careful clinical screening, blood transfusions are still susceptible to complications. Health teams should continue with preventive strategies in complex interventions associated with increased requirement of blood transfusion, such as cardiac surgeries, by intensifying treatment of anemia in the preoperative period, and the use of minimally invasive surgical techniques and of standardized institutional protocols to rationalize the use of blood components. These measures can increase the quality of care and minimize adverse events inherent to major procedures such as cardiovascular surgeries.

Limitation of the study

A retrospective cohort study, with review of medical records, can limit the conclusions, and should be considered as a generator of hypothesis, representative of the clinical practice in a large center for cardiac surgery. It is important to mention that the transfusions were indicated by medical criteria, without a pre-established minimum value of hemoglobin levels.

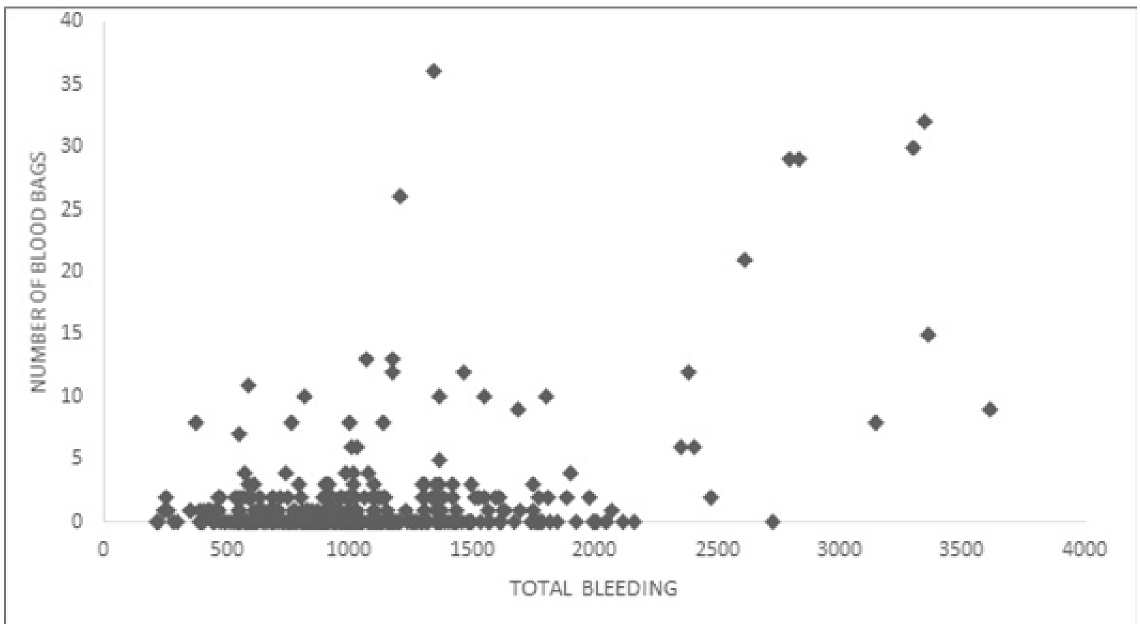

Figure 1 – Relation between the amount of bleeding and number of transfused blood bags.

Table 4 – Postoperative complications of patients undergoing cardiac surgery (n=146)

Complications	Transfusions		
	No	Yes	P
Total	80(54.7)	66(45.2)	< 0.00
Hemodynamic	18(12.3)	27 (18.5)	< 0.00
Respiratory	15 (10.3)	21(14.4)	< 0.00
Arrhythmias	43(29.4)	11 (7.5)	<0.80
Renal	3 (2)	3(2.1)	< 0.46
Neurologic	1 (0.7)	4 (2.7)	<0.15

Categorical variables expressed as n (%). Chi-square test.

Conclusion

In the present study, bleeding rates in patients submitted to cardiac surgery were lower than those reported in the literature. When transfusion of blood components was indicated, red blood cell concentrates were the most widely used component.

Author Contributions

Conception and design of the research: Giordani JN, Borges CT. Acquisition of data: Giordani JN, Borges CT. Analysis and interpretation of the data: Giordani JN, Borges CT, Moraes MA. Writing of the manuscript: Giordani JN, Borges CT, Mariani PE, Costa LM. Critical revision of the manuscript for intellectual content: Bridi LH, Santos ATL, Kalil RAA.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

This article is part of the thesis for the conclusion of a postgraduate course by Juliana Neves Giordani from *Instituto de Cardiologia - Fundação Universitária de Cardiologia* (IC-FUC).

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the IC/FUC under the protocol number 4906/13. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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EDITORIAL

Lower Rate of Blood Transfusion after Heart Surgery in a Tertiary Hospital

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Editorial referring to the article: Transfusion of Blood Products in the Postoperative of Cardiac Surgery

Special interest in surgical bleeding and methods to limit its occurrence is growing after the possibility that transfusion of blood products might be causally related to complications and negative outcomes has been raised.[1] In the same vein, studies have been conducted to evaluate whether limiting blood product transfusions (ie, being more conservative in the indication for it) would increase the safety of transfusion or even reduce some patterns of complications.[2] The current study is a contribution to this larger discussion.

Moraes et al.[3] report the experience of a large tertiary center in bleeding patterns after heart operations. Four hundred and twenty-three patients (51% coronary artery bypass surgery and 33% valve operations) were evaluated for total bleeding and for the use of blood products. Perioperative bleeding was measured by weighing sponges, a validated method for a difficult enterprise. Postoperative bleeding was determined by the total chest tube output in the first 24 h after the end of the operation.

Interestingly, the median bleeding volume during surgery (413 mL) and after surgery (200 mL) were higher than the mean total bleeding volume (353 mL), showing that probably some outlier heavy bleeders skewed the curve to the right. Figure 1 clearly shows us that, although most patients presented with low and controlled total bleeding, a relatively small proportion of the patients suffered severe bleeding with consequential much higher transfusion amounts. The authors indeed show that a weak correlation was found between total bleeding volume and need for transfusion. One should be attentive that single bleeding events can be catastrophic and put pressure on the blood bank system.

Only 40% of patients required any blood product transfusion, a rate lower than that of previous reports. Another interesting aspect of this retrospective cohort is that the majority of blood products being transfused was red blood cell packs. There was indeed a very small number of patients who needed either fresh frozen plasma or platelets (only 26 patients). A possible explanation for both facts could be that total cardiopulmonary bypass time was, on average, short. The operations were probably performed as emergencies. The authors should, however, better describe whether some known specific strategies for blood salvage were present during the operations, such as the use of cell savers or preoperative erythropoietin.

Regarding the complications experienced by the cohort of patients, it is not possible, with this study design, to draw causal correlations between the amount of blood transfusion and the complication rate. It is a real challenge to differentiate previous risk factors that have led both to bleeding and to complications from possible unwanted effects of the transfusions themselves. This line of research reveals itself as a complex endeavor with conflicting results among different studies. In a large British multicenter randomized trial[2] comparing a restrictive threshold for transfusion (postoperative hemoglobin <7.5 g/dL) against a liberal one (postoperative hemoglobin <9.0 g/dL), the conclusions were dubious in terms of complications, quality of life issues, and even costs. Although the restrictive approach was noninferior to the liberal one, the authors themselves reported that "secondary findings create uncertainty about recommending restrictive transfusion," as well as a trend toward higher mortality. A Canadian multicenter randomized trial[4] focusing on patients at moderate-to-high risk for death, on the other hand, demonstrated the safety of a restrictive approach up to 6 months after surgery, with no increase in any complication.

The authors should be congratulated on their enterprise in adequately quantifying the amount of

Keywords

Thoracic Surgery; Coronary Artery Bypass; Blood transfusion.

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bleeding and transfusion requirement in their surgical cohort. Such initiatives might reveal what to expect in terms of blood resource utilization in a tertiary center. Further studies should be performed to test particular interventions to diminish transfusion requirements and their impact on clinical complications.

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ORIGINAL ARTICLE

Continuous Aerobic Training and High Intensity Interval Training Increase Exercise Tolerance in Heart Failure Patients: A Retrospective Study

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Abstract

Background: Conventional aerobic training is the first choice in cardiac rehabilitation for patients with chronic heart failure (CHF). However, high-intensity interval training (HIIT) may be an alternative, although it has little evidence.

Objectives: To evaluate the effect of continuous aerobic training (CAT) or HIIT on exercise tolerance in CHF patients.

Methods: Retrospective study with 30 patients, of both genders, members of a 10-week CAT or HIIT program. The control group (CON) consisted of patients who did not participate voluntarily in the program. Peak oxygen uptake (VO2peak), thresholds (LV1 and LV2), and ventilatory efficiency in the production of dioxide (VE/VCO2 slope), oxygen uptake efficiency (OUES), and VO2 recovery kinetics were analyzed. A two-way or repeated measures ANOVA was used, followed by Fisher's post-hoc test ($p<0.05$).

Results: After 10 weeks of training, the CAT group increased the treadmill speed at LV1 ($p=0.040$), while the HIIT increased both the speed ($p=0.030$) and incline of the treadmill ($p<0.001$) for VO2peak and LV2, as well as the total time of the cardiopulmonary test. The VE/VCO_2 slope was lower than that predicted for CAT ($p=0.003$) and HIIT ($p=0.008$). There was no change in VO_2peak, recovery of heart rate (HR), and VO_2, VE/VCO_2, and OUES in both groups.

Conclusions: After 10 weeks, both CAT and HIIT increased the tolerance to physical exercise. However, HIIT showed improvement in more parameters, differently from CAT.

Keywords: Heart Failure; Exercise. Physical Exertion; Exercise Therapy; Rehabilitation; Exercise Movement Techniques.

Introduction

Chronic heart failure (CHF) is a multifactorial syndrome characterized by cardiovascular and ventilatory abnormalities associated with the increase in the neurohumoral systems.[1,2] The cycle generated between physical decoding and disorders is associated with classic CHF physiopathological mechanisms. Nevertheless, this condition is pinpointed as the main problem of the reduction in tolerance to physical exercise in this population.[1,2]

International guidelines have voiced concern over the theme and have highlighted the heart rehabilitation programs with emphasis on regular physical exercise, and under professional supervision, as being forms of safe, non-pharmacological treatment in adjunct therapy for CHF patients.[3] The benefits of physical exercise are demonstrated in studies that observe improvements in the variable relation to exercise tolerance, functional capacity, and ventilatory efficiency of these patients.[4-6] Improvement in one's cardiorespiratory fitness, illustrated by increases in the VO_2peak and in the total duration of the cardiopulmonary exercise test, present strong prognostic values in CHF, thus confirming the benefits and safety of physical exercise.

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Mild-intensity continuous aerobic training (CAT), maintaining an intensity between 60% and 80% (VO_2peak or reserve heart rate),[7] has been described as the most successful style of training, due to its efficacy and safety.[7-9] Nonetheless, studies have used greater intensities of physical exercise in CHF patients with promising results and, in some cases, even greater than the CAT.[10-12] In this context, interest concerning increasing intensity (75 to 90% VO_2peak) of physical exercise is growing, especially as regards safe training for this population[12]. Some justifications for this type of conduct would be a greater aerobic and cardiovascular adaptation that could be achieved by using this type of strategy,[10] in addition to improvements in exercise capacity, endothelial function, left ventricular function, and ejection fraction.[12] These conclusions, however, seem rather uncertain, since the impacts upon the difference in prognoses, the length of training, and the diversity of protocols, with different durations, recoveries, and intensities used in the studies, make the defense of clinical training standards for CHF patients difficult; thus, a larger body of evidence is needed.

Faced with the continuing key question about which aerobic training method should be ideally prescribed in heart rehabilitation programs, the search for this type of evidence is necessary. Hence, this study sought to evaluate the potential benefits of mild-intensity CAT and high-intensity interval training (HIIT), through the medical records of Class II and III (NYHA) CHF patients who participated in a heart rehabilitation program.

Methods

This study was conducted in accordance with that set forth in the Helsinki Declaration and CNS 466/12. All patients read and signed the Free and Informed Consent Form provided by the Clinical Center where the data were collected upon entrance into the program. The project was approved by the Research Ethics Committee from Universidade Federal de Ciências da Saúde de Porto Alegre (logged under protocol number 3.055.126).

Through a retrospective cohort, this study assessed the records of data referent to the physical training sessions of patients with CHF and who agreed to participate in the heart rehabilitation program of the Sports Medicine Unit of the Clinical Center of Universidade de Caxias do Sul, RS, Brazil, between 2016 and 2017.

Samples and Groups

This study included medical records from 30 CHF patients (64 ± 9 years of age), from both genders, left ventric (CON) consisted of patients who opted not to participate in the heart rehabilitation program at that moment.

The exclusion criteria were: incomplete medical records and patients who did not present reference values during the strength test (R<1.0 to reach the VO_2peak or submaximal heart rate).

Heart Rehabilitation Program

Once the patients had been admitted to the program, a clinical anamnesis was performed by the doctor of the program. After, the patients were referred for initial physical assessments and were distributed randomly (https://www.randomizer.org/) for supervised training in the different methods: CAT (n=10) and HIIT (n=10). Patients that chose not the participate in the rehabilitation program were allocated to the control group (CON, n=10).

Cardiopulmonary Exercise Test

After warming up for 10 minutes, the VO_2peak was evaluated by the gas analyzer (VO2000, Medical Graphics Diagnostics Corporation, USA), using a Super ATL 300 treadmill (Imbramed, Porto Alegre, RS, Brazil). A Ramp protocol was used, beginning at 3 km/h and with no slope. The speed was then increased by 0.3 km/h, and the slope by 1.6%, for each minute of exercise, until patient exhaustion. The exhaled gases were quantified every 20 seconds, obtaining ventilator flows and volumes. The patient's blood pressure (BP), heart rate (HR), minute ventilation (VE), oxygen uptake (VO_2), carbon dioxide production (VCO_2), and respiratory exchange ratio (R), as well as the ventilator equivalents for oxygen (VE/VO_2) and carbon dioxide (VE/VCO_2), were analyzed during the evaluation. Based on this data, the VO_2peak, the first ventilatory threshold (LV1), the second ventilatory threshold (LV2), among other ventilatory and metabolic measures described in the literature, were determined.[13]

Evaluation of Ventilatory Efficiency

The ventilatory equivalent for CO_2 was calculated by means of the ratio between the instantaneous ventilation rate (VE) and the release of CO_2 (VE/VCO2). For this, the present study used the data recorded in the cardiopulmonary exercise test, from the beginning to the LV2. The slope (VE/VCO_2 *slope*) was used to analyze the ventilatory efficiency.[14] The predicted values for this variable were obtained by means of the equation described in the literature.[15]

Evaluation of Oxygen Uptake Efficiency

The *oxygen uptake efficiency slope* (OUES) is represented by the rate of increase of VO_2 in response to VE, and was calculated by measuring the relationship between VO_2 and the VE logarithm.[16] The predicted value for this variable has already been described in the literature.[16]

Recovery Kinetics of Oxygen Uptake and Heart Rate

At the end of the cardiopulmonary exercise test, the patients were instructed to remain seated for three minutes while the metabolic and ventilatory variables continued to be recorded. The data during this period served to analyze and determine the recovery kinetics of VO_2, in the following manner: the magnitude of the recovery through the relationship of VO_2 regarding time (VO_2/t *slope*), calculated by the linear regression model and adjusted to a simple exponential curve.[17] The slope equation was calculated considering the time needed to reach the VO_2peak and recovery in the first three minutes; the established value of the VO_2 recovery was obtained by determining the difference between the value of the VO_2peak and that of VO_2 in the first, second, and third minutes after the end of the VO_2peak test.[18] In addition, the recovery kinetics for HR were calculated by subtracting the HR value at the end of the test from the values of minutes 1, 2, and 3 in the recovery test.[14]

Protocols of the Heart Rehabilitation Training Program

The CAT consisted of a mild-intensity continuous training (70-75% HRreserve) for 47 minutes per session. The time was calculated and duly controlled to guarantee that the training protocols were isocaloric.[12] A fingertip pulse oximeter (NoninOnix 9500, United Kingdom) was used to monitor the patients' HR and peripheral saturation of oxygen (SpO_2). The speed was adjusted continuously to guarantee that each session would be performed in the HR target.

The HIIT consisted of 38 minutes, beginning with the 10-minute warm-up, between 50-60% HRreserve, followed by 4 series of 4 minutes between 90-95% HRreserve. Each series was staggered, with an active pause of 3 minutes (light walk). The training session was finished with a period of 3 minutes of cool down (50% HRreserve).

Data Collection

This study was conducted by consulting the data recorded in the medical records of each patient who trained three times per week, during 10 consecutive weeks. These medical charts were used in the routine of the heart rehabilitation program. After the previous study of the feasibility of the medical records, the data were tabulated within a databank put together in Excel 2013 (*Microsoft Office*).

Statistical Analysis

The normality of the data was evaluated using the Shapiro-Wilk test. The data were expression as average ± standard deviation. The two-way ANOVA was used, together with Fisher's *post-hoc* test. By contrast, the comparison of the data of the VO_2recovery kinetics and HR between the 1, 2, and 3 minute intra-groups was performed using the repeated measures ANOVA, together with Fisher's *post-hoc* test. The *GraphPad Prism* 6 program (*GraphPad Software*, San Diego, California, USA) was used as a computational tool for data analysis, considered significant for a α=0.05.

Results

This study analyzed the medical records of 30 patients with CHF, with LVEF <40%, who voluntarily chose to participate in the heart rehabilitation program between August 2016 and December 2017. One patient was over 80 years of age, nine were between 70 and 80 years of age, eleven were from 60 to 70 years of age, and nine were between 50 and 60 years of age. Of these, five patients were using a pacemaker. All of the patients were hemodynamically stable, with optimized treatment, including β-blockers and antiplatelet aggregation over the past 12 months, even during the period of physical training. No event related to the sessions of physical training occurred in the patients in either group. The presence of participants reached 100% of the scheduled sessions (10 weeks).

Figure 1 presents parameters of intensity (speed and slope) and time to reach the VO_2peak referent to the cardiopulmonary test. After ten weeks of physical training, the CAT group presented improvement in exercise tolerance for LV1 when compared to the initial test. By contrast, the HIIT group presented improvement in the tolerance to the exercise, represented by the higher speed and slope for LV2, as well as in the time to reach the VO_2peak, when compared to the beginning of the physical training. It is possible to observe in Figure 1 that the HIIT group presented a set of greater benefits when compared to the CAT.

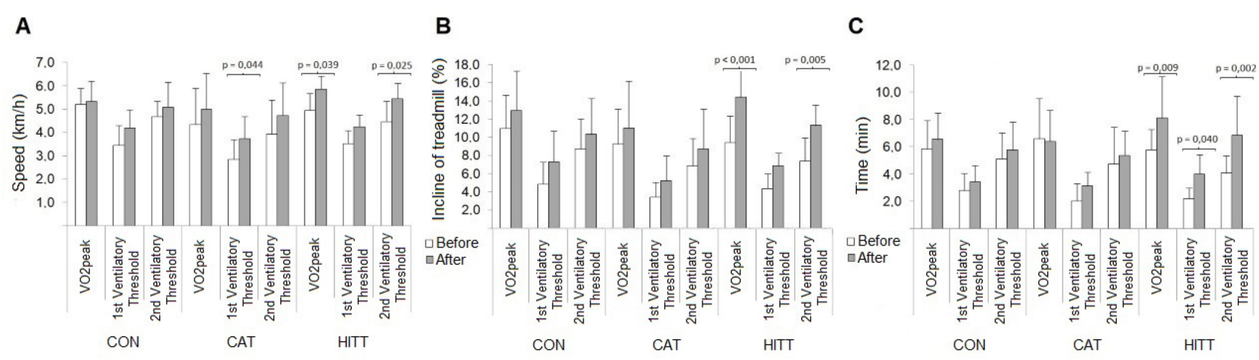

Figure 1 – Cardiovascular exercise test.
Speed (Panel A) and incline of treadmill (Panel B), as well as the time to reach the VO2peak, 1st ventilatory threadshold, and 2nd ventilatory threadshlod, before and after 10 weeks of physical training. CON: control group; CAT: moderate-intensity continunous aerobic training; HIIT: high-intensity interval training. The differences were tested by ANOVA followed by Fisher´s post-hoc test (o<0.050)

Details of the cardiopulmonary test are presented in Table 1. No significant difference was observed in the records of the recovery kinetics of HR and VO_2. The patient presented no difference in the parameters of body composition and physical fitness.

Discussion

The main finding in this study was that Class II and III (NYHA) CHF patients, who took part in a 10-week program of CAT or HIIT, increased their tolerance to physical exercise, when compared to the pre-training moment. Moreover, the HIIT improved a greater number of evaluated parameters when compared to the CAT, illustrating its superiority to conventional training, thus confirming our hypothesis. The parameters of the cardiopulmonary exercise test proved to be useful in the long-term diagnosis and prognosis of CHF and in the intolerance to physical exercise. The VO_2peak has been used for decades as a universal Market, capable of reflecting the severity of the disease,[17] and has been considered the "gold-standard" measurement to identify patients with a worse prognosis,[19] in addition to being a parameter for the prescription of physical training involving this population.[20,21] In this sense, our study's results present a clinical importance, as they present an improvement in the VO_2peak, which is greater than 1 $ml.kg^{-1}.min^{-1}$, considered relevant for autonomy and performance of many daily life activities (DLAs).[22] Likewise, the VO_2peak data observed in our study are slightly greater than the 0.6 $ml.kg^{-1}.min^{-1}$ found in the *HF–ACTION* trial[8] and corroborate with the meta-analysis findings from Cornelis.[23]

The present study demonstrates a wide range of parameters of gas exchanges verified in the submaximal cardiopulmonary exercise test. Woods et al.,[24] found strong predictors of adverse heart outcomes and survival in CHF patients through submaximal parameters of gas exchange, especially the VE/VCO_2, VE/VCO_2 *slope*, and OUES, found with "R=0.9", formulating prognoses similar to the VO_2peak.[24] Other authors have suggested that changes in these prognostic markers for CHF seem to be more important predictors of the capacity of exercise tolerance than the results from the VO_2peak.[25]

As a result, ventilatory efficiency for the elimination of CO_2 (VE/VCO_2 or VE/VCO_2 *slope*) in response to submaximal exercise was investigated to determine the prognostic values for CHF patients.[25] However, this study found values of lower than 34 and 45, indicating a prognosis of a 50% probability of mortality in two years, regardless of the VO_2peak result. In a study from Chua et al.,[26] it was verified that CHF patients, evaluated by the cardiopulmonary exercise test, with a VE/VCO_2 *slope* >34, presented a greater risk of hospitalization caused by hemodynamic decompensation, as well as death. Ferreira et al.,[27] found the cut-off point for the VE/VCO_2 *slope* ≥43 to be the ideal to determine the recommendation for a heart transplant. The time to obtain the lowest value of VE/VCO_2 (>5:45 minutes) also represents a poor prognosis for this population.[28] In this indicator, our

Table 1 – Responses from the cardiopulmonary test before and after 10 weeks of physical training

	CON		CAT		HIIT	
	Before	After	Before	After	Before	After
VO_2peak (ml.kg^{-1}.min^{-1})	19.3±4,5	19.5±4,8	16.2±5,9	17.3±5,9	18.6±2,7	19.8±3,2
Maximal HR (bpm)	121±18	127±24	116±31	113±24	119±11	129±16
Maximal VE/VCO_2	29.6±5,2	29.1±5,3	28.4±5,4	28.6±5,2	25.4±2,7	25.7±3,7
Minimum VE/VCO_2	27.5±4,6	26.7±4,1	26.7±4,9	27.3±5,3	23.4±3,0	23.6±3,8
Time to reach VE/VCO_2 (min)	04:04±01:36	03:53±02:03	02:57±01:37	03:47±01:37	03:34±01:07	05:22±02:56
VE/VCO_2 *slope*	30.1±10,0	30.5±16,0	26.6±9,0	23.1±4,5	22.0±3,2	21.7±5,3
VE/VCO_2 *slope* % of prediction	113±33	110±52	95±34	82±19*	98±15	79±24*
OUES	2148±1192	1887±841	1559±536	1800±390	2464±807	1926±700
OUES % of prediction	107±105	94±45	83±34	95±21	120±28	90±41
LV1 (ml.kg^{-1}.min^{-1})	12.5±3,8	15.6±4,2	11.2±4,2	11.2±3,9	13.3±2,3	14.2±2,2
HR LV1 (bpm)	99±13	103±20	95±22	98±21	98 ± 16	94 ± 14
LV2 (ml.kg^{-1}.min^{-1})	16.7±4,8	18.0±4,5	14.5±6,1	15.0±5,0	15.9 ± 2,3	17.1 ± 2,5
HR LV2 (bpm)	107±16	113±22	106±20	108±22	108 ± 15	112 ± 16

*VO_2peak: submaximal oxygen uptake; HR: heart rate; CET: Cardiovascular exercise test; LV1: oxygen uptake at the first ventilator threshold; LV2: oxygen uptake in the second ventilator threshold; VE/VCO_2: ratio between the instantaneous respiratory rate and the release of CO_2; OUES: oxygen uptake efficiency slope. Two-way ANOVA followed by Fisher's post-hoc test. * Significant intragroup difference in relation to pre-training; p<0.001.*

patients showed a lesser reach in a shorter period than that which the literature characterized as an indication of poor prognosis.[16] The fact that no changes in the OUES were observed after the physical training may well be related to the characteristics of our sample, which presents an earlier beginning of lactic acidosis during the hyperventilation test, observed by the ventilatory threshold, determined by the central and peripheral incapacity during physical exercise.[28]

Other important records analyzed in this study concern the prognostic implications of the VO_2 and HR recovery values after ending the cardiopulmonary exercise test. No changes in these indicators were observed, which is in accordance with findings from Myers et al.,[29] However, Myers did observe an increase in the VO_2peak in response to eight weeks of aerobic training (walking and cycling) in CHF patients. It is impossible to determine a specific cause for these results. Nevertheless, it can be speculated that the delay in VO_2 recovery is related to the difficulty to recover energy stored in the main muscles used in the cardiopulmonary exercise test.[30]

The HR recovery kinetics, as a prognostic marker, is well-established and is used as an independent factor of mortality, even in CHF patients that take β-blockers.[31,32] Therefore, the results of this study showed that the reduction was greater than12 bpm, in the first minute after ending the exercise. This value was used as a cut-off point to define the mortality in patients with left ventricular dysfunction,[33] whose cut-off point was ≤16 bpm, in an active recovery protocol. Only in the CON group was a reduction of ≤16 bpm observed at the end of the study. The fall in HR immediately after physical exercise occurs in response to the autonomous control, more precisely, the activation of the parasympathetic nerve system due to the sympathetic nerve activity. This adjustment is also an important prognostic marker and is associated with a reduction in the risk of death.[14]

In the evaluation of other variables of the cardiopulmonary exercise test, the time to reach the VO_2peak also reflects the capacity to predict mortality in patients with CHF and a reduced LVEF.[34] This study showed that the time of duration in the HIIT group was greater for the VO_2peak, LV1, and LV2, which is directly related to the positive adaptations of the training. In another study, the authors present results that run in line with those from our study.[35]

Our results demonstrate consistent improvements in the parameters related to one's tolerance to physical exercise, which is a key characteristic in CHF patients. Appropriately, our study presents important clinical implications for the state of health concerning the autonomy and performance of one's DLAs. On the other hand, our study presents a series of limitations that should be observed, one of which refers to the VO_2 evaluation protocol of CHF patients. The reach of VO_2peak does not translate into the maximum capacity of exercise and gas exchanges referent to the evaluation and prescription of adequate intensities for physical training. Thus, the VO_2max would be more accurate, but with greater risk and discomfort for the participants. Another limitation is the relatively small sample. This makes it impossible to stratify the results, such as severity of CHF, time of diagnosis, and inclusion in the rehabilitation program, among others.

Conclusions

This retrospective study showed that both the conventional protocol (CAT) and a high-intensity interval training (HIIT), carried out over a 10-week period, promoted positive adaptations in the capacity of physical exercise, with an increase in time, speed, and treadmill slopes to achieve important CHF prognostic markers. However, the HIIT group showed improvement in a greater number of variables. Based on these results, we support the concept of the need to measure submaximal variables that reflect a better integration between the mechanisms related to changes in the cardiovascular, pulmonary, and musculoskeletal system of these patients, in attempt to reintegrate CHF patients into social life within society.

Author Contributions

Conception and design of the research: Busin D, Lehnen AM, Tairova OS, Lago PD, Nunes RB. Acquisition of data: Busin D, Tairova OS, Comparsi EP, Carneiro D, Potter M. Analysis and interpretation of the data: Busin D, Lehnen AM, Tairova OS, Comparsi EP, Carneiro D, Potter M, Deresz LF, Lago PD, Nunes RB. Statistical analysis: Busin D, Lehnen AM, Tairova OS, Comparsi EP, Carneiro D, Potter M, Deresz LF, Lago PD, Nunes RB. Obtaining financing: Tairova OS. Writing of the manuscript: Busin D, Lehnen AM, Tairova OS, Comparsi EP, Deresz LF, Lago PD, Nunes RB. Critical revision of the manuscript for intellectual content: Busin D, Lehnen AM, Tairova OS, Comparsi EP, Carneiro D, Potter M, Deresz LF, Lago PD, Nunes RB.

Potential Conflict of Interest

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

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Study Association

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Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the *Universidade Federal de Ciências da Saúde de Porto Alegre* under the protocol number 3.055.126. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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EDITORIAL

Exercise-based Cardiovascular Rehabilitation in Chronic Heart Failure: does Exercise Intensity Matter?

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Editorial referring to the article: Continuous Aerobic Training and High Intensity Interval Training Increase Exercise Tolerance in Heart Failure Patients: A Retrospective Study

It is well recognized that chronic heart failure (CHF) is a multifactorial syndrome that reduces physical exercise tolerance.[1] Exercise-based cardiac rehabilitation program is on the frontline of non-pharmacological therapies for CHF patients, counterbalancing the disease-induced issues of physical capacity.[2]

Since a successful exercise rehabilitation program should be efficient and safe,[2] the search for optimal combinations of exercise volume and intensity has sparked interest in the current literature. Although studies have shown feasible combinations of low volume and high intensity, and vice versa, the optimal dose-response of exercise in cardiovascular rehabilitation remains unknown. Classically, aerobic training with moderate intensity (i.e., between 60% and 80% VO_{2peak} or heart rate reserve - HRreserve) is a safe approach to improve physical capacity and provide a cardioprotective effect in CHF disease.[3] As a promising method, short bouts of high-intensity exercise, called high-intensity interval training, seems to be superior than moderate continuous training to reverse left ventricle remodeling and improve aerobic capacity, endothelial function, and quality of life in post-infarction heart failure patients.[4]

Keywords

Exercise; Heart Diseases; High-Intensity Interval Training; Cardiac Rehabilitation.

In the current issue of the International Journal of Cardiovascular Sciences, Busin and colleagues[5] report that both high-intensity interval training and mild-intensity continuous training increase exercise tolerance in CHF patients. However, in their study, a greater number of parameters related to exercise tolerance (e.g., treadmill speed, incline, and time) was improved by high-intensity interval training than conventional training. While continuous aerobic training increased the treadmill speed at the first ventilatory threshold, high-intensity interval training increased both the speed and incline of the treadmill for VO_{2peak} and the second ventilatory threshold. On the other hand, neither high-intensity nor moderate training changed VO_{2peak} or post-exercise heart rate recovery. Although the VO_{2peak} has been used for decades as a universal "gold-standard" of exercise tolerance, reflecting the severity of CHF disease,[6] alternative markers that may indicate an adaptation from exercise-based rehabilitation in CHF seem necessary.

Therefore, novel combinations of high- and low-intensity exercise with different exercise volumes should be investigated in further studies of cardiovascular rehabilitation in CHF patients. Also, additional markers of physical performance in exercises programs should be considered, since exercise tolerance in CHF seems to be multifactorial. Thus, the question remains open: does exercise training intensity matter?

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ORIGINAL ARTICLE

Embolic Stroke of Undetermined Source (ESUS) and Stroke in Atrial Fibrillation Patients: not so Different after all?

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Abstract

Background: Stroke related to atrial fibrillation (AF) is associated with high recurrence and mortality rates. Embolic Stroke of Undetermined Source (ESUS) is associated with fewer vascular risk factors, less disability, and a high recurrence rate.

Objective: To compare risk factors, functional outcomes and the occurrence of primary endpoint (a composite of recurrent stroke, cardiovascular death, and myocardial infarction) between AF stroke and ESUS patients.

Method: A retrospective analysis was conducted including all consecutive patients with first-ever ischemic stroke admitted to the *Hospital de Clinicas* (Clinical Hospital) of the Federal University of Paraná from October 2012 to January 2017 (n=554). There were 61 patients with stroke due to AF and 43 due to ESUS. Both groups were compared for demographic characteristics and vascular risk factors. Logistic regression models were performed to assess the impact of each variable on the primary endpoint in a 12-month follow-up. Statistical significance was considered for p-values < 0.05.

Results: ESUS patients, as compared to AF patients, were younger and more likely to be smokers. ESUS patients presented a mean CHADS2VASc score of 4, while the AF group presented a score of 5 (p <0.001). The primary endpoint was observed in 9 (20.9%) ESUS and 11 (18.0%) AF patients over a 12-month period (p=0.802). Higher glucose levels upon hospital admission (p=0.020) and a higher modified Rankin Scale upon hospital discharge (p=0.020) were predictors of the primary endpoint occurrence.

Conclusion: AF and ESUS stroke patients presented very similar independence rates upon hospital discharge and outcomes after 12 months, despite some baseline differences, including stroke recurrence, vascular death, and myocardial infarction.

Keywords: Cerebrovascular Disorders; Stroke; Brain Infarction; Atrial Fibrillation; Embolism, Intracranial; Brain, Infarction.

Introduction

Embolic Stroke of Undetermined Source (ESUS) is a non-lacunar infarct without proximal occlusive atherosclerosis or major-risk cardioembolic sources. Recent studies have demonstrated a high variability (ranging from 10-39%) in the proportion of ESUS patients, who are subsequently diagnosed with atrial fibrillation (AF) in a long-term follow-up. This result suggests that some groups of ESUS patients can present AF as underlying cause of stroke.[2-5] Approximately one-third of the patients who met the inclusion criteria for ESUS trials presented AF in continuous heart rhythm monitoring for up to three years. A higher AF prevalence was also observed with an increasing number of $CHADS_2$ risk factors. [6]

This definition is important, since AF is the most common embolic source in the cardioembolic stroke

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mechanism. AF presents the worse functional outcome, higher recurrence rates, and greater mortality when compared to strokes resulting from other causes, including a subgroup of ESUS in this profile.[2,7]

The aim of the present study is to compare the occurrence of recurrent stroke, cardiovascular death, and myocardial infarction in a composite endpoint between ESUS and AF stroke patients one year after the first-ever ischemic stroke (IS).

Methods

This study was a retrospective analysis of a prospective data bank including all the consecutive patients with first-ever IS admitted to the *Hospital de Clinicas* (Clinical Hospital) of the Federal University of Paraná from October 2012 to January 2017. This study was approved by the local Ethics Committee.

All the patients with first-ever IS secondary to AF and ESUS were included, based on the TOAST[8] and according to Cryptogenic Stroke/ESUS International-Working-Group criteria,[1] respectively. For the stroke diagnosis, all patients needed to have at least one confirmatory brain image (CT or MR) confirming a brain lesion consistent with the clinical syndrome presented during hospital admission. Patients with AF were submitted to a minimal investigation, including electrocardiography, extracranial and intracranial Doppler ultrasound, and transthoracic echocardiography. For a ESUS diagnosis, besides the screening reported for AF, patients were submitted to 24-hour Holter monitoring and CT angiography, MR angiography, or digital angiography in order to exclude other stroke mechanisms. Although it was not required by the International Criteria, all ESUS patients were also submitted to transesophageal echocardiography (TEE). No patients were submitted to cardiac monitoring for more than 24 hours, as this resource is not available in the Brazilian public healthcare system.

The following variables were analyzed: age, sex, $CHADS_2$, and $CHADS_2VaS_2C$. The last two variables included some of the most significant modifiable risk factors for embolic stroke, such as hypertension and diabetes, and prevalent non-modifiable risk factors, like congestive heart failure and coronary artery disease. The National Institutes of Health Stroke Scale (NIHSS), systolic blood pressure, and diastolic blood pressure upon hospital admission were some of the analyses performed in the hospital. The modified Rankin score (mRS) was analyzed upon hospital discharge, after which patients were evaluated to identify the occurrence of: 1) stroke recurrence (a focal neurological impairment of sudden onset lasting more than 24 hours and confirmed by a brain image during the follow-up period); 2) myocardial infarction (defined as a rise in blood concentrations of cardiac troponins and/or creatine kinase in the context of spontaneous ischemic symptoms or coronary intervention); and 3) cardiovascular death (resulting from an acute myocardial infarction, sudden cardiac death, heart failure, stroke, cardiovascular procedures, hemorrhage, or other cardiovascular causes).

Statistical Analysis

Analyses were performed using the IBM SPSS Statistics v 2.0.0 software. Categorical variables were presented as frequencies and percentage. Quantitative variables with normal distribution were described by mean value and standard deviation (SD). Quantitative variables without normal distribution were described by median and interquartile range.

When comparing etiological groups, Fisher's exact test was used for categorical variables. For quantitative variables, an unpaired Student's t-test was used for those with normal distribution, while a Mann-Whitney test was applied for variables without normal distribution and severity scores. The normality condition of the variables was assessed by the Kolmogorov-Smirnov test. The impact of each variable was analyzed by adjusting the variables for each subgroup (ESUS and AF), using the logistic regression models and the Wald test. Statistical significance was accepted for p-values < 0.05.

Results

During the study, from 544 patients with first-ever IS, 61 (11.2%) presented AF as a stroke mechanism and 43 (7.90%) fulfilled all ESUS criteria. Compared to AF patients (70.9±11.2 years old), ESUS patients (52.5±15.7 years old) were younger (p<0.001) and presented a higher frequency of smoking (34.9% for ESUS and 14.8% for AF patients, p=0.020). When analyzing risk factors through $CHADS_2$ and $CHADS_2VASc$ scores, ESUS patients exhibited a lower score than did the AF patients, as presented in Table 1. Upon hospital discharge, only 7% of ESUS patients were submitted to anticoagulation therapy, as compared to 75.4% of AF patients, p=0.001. All other hospital admission characteristics were presented in Table 1.

In ESUS patients, transesophageal echocardiography demonstrated abnormalities in 22 patients (52.1%), with

Table 1 – Baseline Characteristics

Variable	ESUS (n=43)	Atrial Fibrillation (n=61)	p value
Age (years) mean ±sd	52.5 ± 15.7	70.9 ± 11.2	<0.001
Female sex n(%)	13 (59.1)	30 (49.2)	0.661
Hypertension n(%)	28 (65.1)	43 (70.5)	0.670
Diabetes n(%)	8 (18.6)	13 (21.3)	0.808
Hypercholesterolemia n(%)	10 (23.3)	12 (19.7)	0.808
Current smoking n(%)	15 (34.9)	9 (14.8)	0.020
Alcohol abuse n(%)	5 (11.6)	6 (9.8)	0.759
Previously known AF n(%)	0 (0)	24 (39.3)	<0.001
CHADS2 Score median (Q1 - Q3)	3 (2-5)	4 (2-6)	<0.001
CHA2DS-VASc Score median (Q1 - Q3)	4 (2-7)	5 (2-7)	0.001
NIHSS at admission median (Q1 - Q3)	9 (0-23)	10 (0-26)	0.632
Blood gluose levels (mean) ±sd	115 ± 68,7	122 ±59,2	0.310
IV thrombolysis n(%)	17 (39.5)	30 (49.2)	0.424
Hemorrhagic transformation n(%)	0 (0)	2 (3.3)	1
Anticoagulation at discharge n(%)	3 (7)	46 (75.4)	<0.001
mRS median (Q1 - Q3)	2 (0-5)	2 (0-6)	0.420

Note: ESUS: Embolic Stroke of Undetermined Source, AF: atrial fibrillation, NIHSS: National Institute of Health Stroke Scale; IV: intravenous, mRS: modified Rankin Score.

left atrial enlargement in 14 (32.5%), patent foramen ovale in 12 (27.9%), septal atrium aneurysm in seven (16.2%), and ascending aortic ectasia in three (6.9%). Other minor-risk sources of emboli are listed in Table 2.

At 12 months of follow-up, the primary endpoint occurred at the same rate in both groups: nine patients in the ESUS group (20.9%) and 11 patients in the AF group (18.0%), p=0.408. In the ESUS group, there were seven stroke recurrences (16%), two cardiovascular deaths (4.65%), and no myocardial infarction. Glucose levels upon hospital admission and mRS upon hospital discharge were the only predictors of the outcome in a multivariate analysis model, as presented in Table 3.

Discussion

The current study demonstrated that ESUS patients, despite being younger and with fewer risk factors when compared to AF patients, presented a similar outcome in the first twelve months after the first-ever IS.

In this study, ESUS patients were almost 20 years younger than patients with AF. This difference is consistent with a larger study, in which ESUS patients presented an average age of 68 and cardioembolic stroke patients of 76.[9] When the ESUS group was compared to other cryptogenic stroke patients, they were also significantly younger.[10]

A lower prevalence of vascular risk factors has been previously reported in ESUS patients when compared to AF patients.[11] In our cohort, ESUS and AF patients presented similar risk factors, such as hypertension, diabetesm and hypercholesterolemia. Current smoking was the only isolated risk that proved to be more frequent in ESUS. In a recent study, the authors demonstrated a strong relation between tobacco use and cryptogenic stroke in young adults.[12] A possible explanation for this could be an increased risk of AF for current smokers in a dose dependent manner.[13]

If the isolated vascular risk factors were not so different, except for age and smoking habit, the score values of $CHADS_2$ and CHA_2DS_2VASc revealed a more benign profile of ESUS when compared to AF. Besides being younger, ESUS patients are less likely to present cardiac failure and peripheral vascular disease. There are no current studies comparing these

Table 2 – Possible causes of embolic stroke of undetermined source

Minor-risk embolic sources	N	%
Left atrial enlargement (≥ 40mm)	14	32.55
Patent foramen ovale	12	27.90
Cerebral artery non-stenotic plaques	11	25.58
Non-atrial fibrillation atrial dysrhythmias	8	18.60
Septal atrial aneurysm	7	16.27
Moderate systolic of diastolic dysfunction	6	13.90
Ascending aortic ectasia	3	6.97
Calcific aortic valve disease	2	4.65
Atrial appendage stasis with spontaneous echodensities	2	4.65
Aortic arch atherosclerotic plaques	1	2.32

Table 3 – Predictors of the primary endpoint

Variable	Outcome	Mean (min-max)	p Value	OR (CI 95%)
Glucose levels	No	117.5 (74-319)	0.017	1.11 (1.02-1.22)
	Yes	128 (99-480)		
mRS at discharge	No	2 (0-5)	0.024	1.38 (1.04-1.83)
	Yes	2 (0-6)		

OR: odds ratio, CI: confidence interval, mRS: modified Rankin Score.

scores between ESUS and cardioembolic or AF stroke patients. However, both $CHADS_2$ and CHA_2DS_2VASc scores have been associated with a higher recurrence risk in ESUS.[14]

There was no difference in the primary endpoint in the groups. In a 5-year follow-up, Ntaios et al.[9] found a cumulative probability of 38.1% of composite cardiovascular events in an ESUS cohort, which is almost identical to cardioembolic stroke patients (38.2%). However, in a Finnish population, cardioembolic stroke patients exhibited nearly 4-fold increased risk for composite vascular events when compared to young-onset ESUS patients. The difference in secondary endpoints was mainly due to myocardial infarction rather than to stroke or TIA; moreover, ESUS patients were younger in this study.[15]

During hospital stay, all the ESUS patients were submitted to a 24-hour cardiac rhythm monitoring to be classified as ESUS.[1] None of our 43 ESUS patients presented any episodes of AF in the 24-hour Holter monitoring. However, large RCTs have demonstrated that long-term monitoring increases the chances of detecting brief paroxysmal AF with an unknown clinical significance.[16-18] In a CRYSTAL-AF trial, only 1.3% of arrhythmia events were detected with a 24-hour Holter, compared to a 22.8% detection rate with a 30-day cardiac monitoring,[17] Prolonged monitoring is not available in the Brazilian public healthcare system, which represents a limitation of our analysis.

Ntaios reported a cumulative probability of stroke recurrence similar to cardioembolic strokes, 29% vs 26.8%, respectively.[9] A systematic review reported an annual rate of stroke recurrence ranging from 5% to 14.5%. [5] In our study, 16% of ESUS patients presented recurrence in 12 months, which is slightly higher than that presented in the literature. This probably reflects the poor risk factor control and low adherence to medical therapy by Brazilian patients.[19]

Although AF continues to be a leading candidate for an occult mechanism of ESUS, findings from recent clinical trials suggest that about 70% of patients with ESUS have no AF. However, the same study demonstrated that the incidence of AF is higher among patients with higher $CHADS_2$ scores.[6] In our cohort, the median $CHADS_2$ score for the ESUS group was 3, two points higher than previously demonstrated.[14] We can thus hypothesize that, in a Brazilian population, with poor risk factor control, ESUS patients are more likely to present higher $CHADS_2$ scores and, therefore, are more likely to present paroxysmal AF. Nevertheless, an important proportion of these patients may have other mechanisms for embolic stroke, such as patent foramen ovale or large aortic arch plaques.[20]

Even when no AF is detected, ESUS may be associated with atrial cardiomyopathy. A recent study with late-gadolium-enhancement MRI demonstrated that ESUS and AF patients showed similar rates of atrial fibrosis, supporting the hypothesis that both entities may have different presentations, but a similar physiopathology.[21]

For secondary prophylaxis, anticoagulation therapy was prescribed for 75.4% of the patients in the AF group. This proportion is higher than that observed in non-stroke patients with atrial fibrillation in Latin America.[22] In the clinical base, patients with large stroke size, palliative care, and lower independence outcomes are unlikely to receive OAC. Furthermore, there are safety concerns regarding OAC prescriptions for fragile patients and families with cultural and socioeconomic barriers to adherence. Although a higher number of patients with OAC could reduce the recurrence rate, the current study demonstrated similar recurrence rates when compared to previous studies.[9]

By contrast, ESUS patients were left with single antiplatelet therapy, as recommended by 2015 AHA/ASA Guideline.[23] None of them presented closed patent foramen ovale (PFO). Twelve (27.9%) ESUS patients presented right-to-left shunt, of whcih four (36%) recurred. It is possible that percutaneous closure of PFO could have prevented any of these recurrences; however, a recent meta-analysis comparing percutaneous closure versus medical therapy for stroke with PFO showed a number of 39 was needed to properly treat recurrent stroke.[24] Hence, it is unlikely that PFO closure would change our analysis.

The high outcome rates observed in the ESUS patients of the present study could be reduced with a high anticoagulation therapy rate, although the best treatment choice for ESUS is still controversial. Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients With Recent Embolic Stroke of Undetermined Source (NAVIGATE-ESUS) trial recently proved that rivaroxaban was not superior to aspirin in the prevention of recurrent stroke, with a higher risk of bleeding.[25] In Dabigatran Etexilate for Secondary Stroke Prevention in Patients With Embolic Stroke of Undetermined Source (RE-SPECT ESUS) trial, Dabigatran was no better than aspirin in preventing a second stroke after ESUS, but the rate of major bleeding was similar in both arms.[26] Meanwhile, Apixaban for the Treatment of Embolic Stroke of Undetermined Source (ATTICUS)[27] and Atrial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke (ARCADIA) trials are still ongoing.[28]

The present study presents several limitations. This study was conducted in a single center with a retrospective small sample, which might have underestimated the differences in outcomes between ESUS and AF stroke patients. Nevertheless, ESUS and AF populations were clearly different, considering demographic characteristics and embolic risk factors demonstrated by CHADS and $CHADS_2VASc$ scores. Furthermore, in a 12-month follow-up, the outcome was similar. These results could be different if a non-composite outcome was chosen, in which a larger sample size would be necessary to access stroke recurrence, MI, and cardiovascular death in an isolated analysis.

Conclusion

ESUS and AF stroke patients presented different profiles of embolic risk factors, but similar independence rates and outcomes were observed. Occult paroxysmal AF and atrial cardiomyopathy are the possible links to explain the high recurrence rate in ESUS patients.

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Potential Conflict of Interest

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

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Study Association

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Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the *Universidade Federal do Paraná* under the protocol number 19474013.0.3001.5225. 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.

Author Contributions

Conception and design of the research: Zetola VHF, Lange MC. Acquisition of data: Scavasine VC, Ribasa GC, Costa TR, Ceccato GHW. Analysis and interpretation of the data: Scavasine VC, Lange MC. Statistical analysis: Marcia Olandoski. Writing of the manuscript: Scavasine VC, Lange MC. Critical revision of the manuscript for intellectual content: Zetola VHF, Lange MC.

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ORIGINAL ARTICLE

Echocardiographic and Ultrasonographic Parameters Associated with Protein-losing Enteropathy in Patients with Fontan Physiology: a Systematic Review with Meta-analysis

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Abstract

Background: Fontan circulation can be associated with significant morbidity, especially Protein-Losing Enteropathy (PLE). Echocardiographic parameters can provide valuable diagnostic information about a patient's risk of developing PLE after Fontan surgery.

Objectives: To describe echocardiographic/ultrasonographic parameters associated with PLE in patients after Fontan surgery through a systematic review with meta-analysis.

Methods: A literature search was performed in electronic databases to identify relevant studies about echocardiographic parameters and PLE prediction in children after Fontan surgery. The search terms used were: "echocardiography", "ultrasonography", "Fontan," and "protein-losing enteropathy". A $p < 0.05$ was considered statistically significant.

Results: A total of 653 abstracts were obtained from electronic databases and bibliographic references. From these, six articles met criteria to be included in the qualitative analysis and three in the quantitative (meta-analysis). The resistance index in the superior mesenteric artery was described in three studies, and the quantitative analysis showed statistical significance ($p < 0.001$). Other echocardiographic and ultrasonographic parameters were also described, albeit in single studies not allowing a meta-analysis.

Conclusion: This systematic review with meta-analysis identified echocardiographic and ultrasonographic parameters related to PLE in patients with Fontan physiology. Vascular ultrasonography seems to play a prominent role in this aspect, but additional studies are needed to increase the degree of evidence.

Keywords: Fontan Procedure/methods; Ultrasonics/methods; Echocardiography/methods; Protein – Losing Enteropathies.

Introduction

Fontan circulation was described as the final stage of palliation for congenital heart disease with univentricular physiology.[1] In this circulation, blood from the superior and inferior vena cava is bypassed to the pulmonary circulation, so that the dominant ventricle is responsible for systemic circulation. Since its description, this technique has increased the survival and quality of life of patients with univentricular physiology.[2,3]

However, this type of circulation may be associated with significant morbidity.[4] That is because the patient is predisposed to a chronic low output, with increased central venous pressure and congestive heart failure.[5] These conditions can lead to pleural and pericardial effusion, gastrointestinal dysfunction, and protein-losing enteropathy (PLE).[6]

PLE is a severe condition derived from chronic venous hypertension leading to inflammation, tumor necrosis factor release, and consequent changes in the enterocyte membrane's composition. Related complications from this condition are hypoalbuminemia, hypocalcemia, hypogammaglobulinemia, and hypercoagulable states.[6] PLE affects up to 10% of patients after Fontan

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surgery[7] and can have mortality rates up to 60%.[8] Thus, identifying patients at higher risk of developing PLE after Fontan operation is essential because it can impact on their management.

The use of diagnostic imaging methods is vital for the management of congenital heart diseases. Among them, the echocardiogram gained special prominence for its ability to provide anatomical and hemodynamic information, in addition to being less invasive. As such, identifying echocardiographic or ultrasonographic parameters that can provide information on the risk of a patient presenting PLE or could present PLE at the moment after Fontan surgery can be of paramount importance.

Therefore, this study aims to describe echocardiographic or ultrasonographic parameters associated with PLE in patients after Fontan surgery through a systematic review of the literature with meta-analysis.

Methodology

Literature search

A literature search was performed in electronic databases (Medline/Pubmed, Scopus, Web of Science, Scielo, and LILACS) throughout May 2020 to identify relevant studies on echocardiographic parameters in the prediction of PLE in children after Fontan surgery. The search terms used were: "echocardiography", "ultrasonography", "Fontan" and "protein-losing enteropathy". Details on the search strategy can be seen in the supplementary Table 1. Only articles in English, Portuguese, or Spanish were included in this review. No restrictions were applied regarding the year of publication or sample size. A search for additional studies not presented in the electronic databases was carried out by investigating references and studies that cited the articles found in the initial search.

Studies selection

Studies were included in the analysis when they met the following criteria: 1) studies in patients after the Fontan operation, 2) cohort, cross-sectional or case-control studies, and 3) the study investigated echocardiographic or ultrasonographic parameters associated with PLE. Abstracts of congress or academic research in the gray literature were not included.

Data extraction

Two investigators (Mourato, MF and Mourato, FA) extracted the data independently (Mourato, FA made the search strategy. Both authors analyzed each title/abstract of all articles to select those that would go to a full-text evaluation. Both authors analyzed the full

Table 1 – studies main characteristics

First author	Publication year	Study Design	Main findings from echocardiography/ultrasonographic parameters	Quality Assessment
Du Bois	2018	Cohort	A higher celiac artery resistance index is associated with future PLE after Fontan surgery.	GOOD
Ostrow	2006	Cross-sectional	The superior mesenteric to celiac artery flow ratio is associated with present PLE after Fontan surgery.	GOOD
Rychik	2002	Cross-sectional	The superior mesenteric artery resistance index is associated with present PLE after Fontan surgery.	FAIR
González	2015	Cohort	Patients with higher systolic pressure in the pulmonary artery are at higher risk of developing future PLE after Fontan surgery.	FAIR
Silvilairat	2008	Case-control	Smaller shortening fractions are associated with present PLE after Fontan surgery.	FAIR
Mortezaeian	2020	Cross-sectional	Patients with PLE showed lower left ventricle ejection fraction.	FAIR

Legend: PLE - protein-losing enteropathy.

text to select those that would go to qualitative and quantitative analysis). Discrepancies were resolved by consensus between these authors after discussion of previously determined inclusion criteria. The following data were collected from the selected articles: first author name, year of publication, study design, sample size (divided into with PLE, without PLE, and future PLE), and the average age of the sample when submitted to an echocardiogram/ultrasonography. The echocardiographic/ultrasonographic parameter used in each study was described in the Results section. When two or more studies offered information on the same echocardiographic/ultrasonographic parameter, quantitative analysis (meta-analysis) was performed.

Study quality

The quality of the studies was assessed using the Quality Assessment Tool from the National Institute of Health (NIH).[9] Studies were classified as Good, Fair, or Poor quality by two investigators (Mourato, MF and Mourato FA) and discrepancies were resolved by consensus.

Data standardization

Continuous data were expressed as mean ± standard deviation (SD). For studies that described the interquartile ranges, the mean was estimated by the formula [minimum + maximum + 2 (median)]/4 and the SD was calculated as (maximum-minimum)/4 (in groups with $n \leq 70$) or (maximum-minimum)/6 (in groups with $n > 70$).[10]

Statistical analysis

Non-categorical data included in the quantitative analysis had their combined effect estimated with the difference of means with a 95% confidence interval (CI). When the mean difference assumes a negative value, it means that the group without PLE has higher values in that variable. An $I^2 > 50\%$ was adopted as an indicator of high heterogeneity (in such cases, the random model was used for interpretation). When a parameter was present in more than three articles, meta-regression was performed considering the average age when performing the echocardiogram/ultrasonography as a modulating factor. A $p < 0.05$ was considered significant. OpenMetaAnalyst software was used.[11]

Results

Literature search and included studies

Initially, 653 abstracts were obtained from electronic databases and bibliographic references. The initial review of these articles identified 31 candidates for full-text analysis. Of these, 25 were excluded, totaling six articles for qualitative analysis. From these six articles, it was possible to include three for quantitative analysis (meta-analysis). Figure 1 shows the article selection process. Table 1 shows the main characteristics of the selected studies.

Parameters of present PLE

Three echocardiographic parameters (peak systolic wave velocity of the superior mesenteric artery, peak diastolic wave velocity of the superior mesenteric artery, and resistance index of the superior mesenteric artery) were present in more than one study.

The peak systolic and diastolic wave velocities of the superior mesenteric artery were present in two studies,[12,13] but the joint analysis of the data did not allow for a distinction between the groups. More information on this analysis can be seen in supplementary Figures 1 and 2.

The analysis of the superior mesenteric artery resistance index (SMAR), calculated according to Pourcelot, was present in three studies.[12–14] The quantitative analysis demonstrates statistical significance with $p < 0.001$ (Figure 2). Therefore, when meta-regression was performed using the patient's age at the time of the echocardiogram as a modulating factor, the difference in means between the groups still was not significant ($p = 0.253$), as shown in Figure 3. Additionally, one of the studies[13] included patients with PLE or plastic bronchitis in the same group and the separation between them was not possible with the available data.

One echocardiographic/ultrasonographic parameter (the ratio between flow in the superior mesenteric artery and celiac artery) was present in only one study.[14]

Ostrow et al.,[14] described the ratio between the flow of the superior mesenteric artery and the celiac artery. In this study, patients with PLE had a lower ratio (0.23 ± 0.1) as compared to patients without PLE (0.34 ± 0.18) with $p = 0.03$.[12]

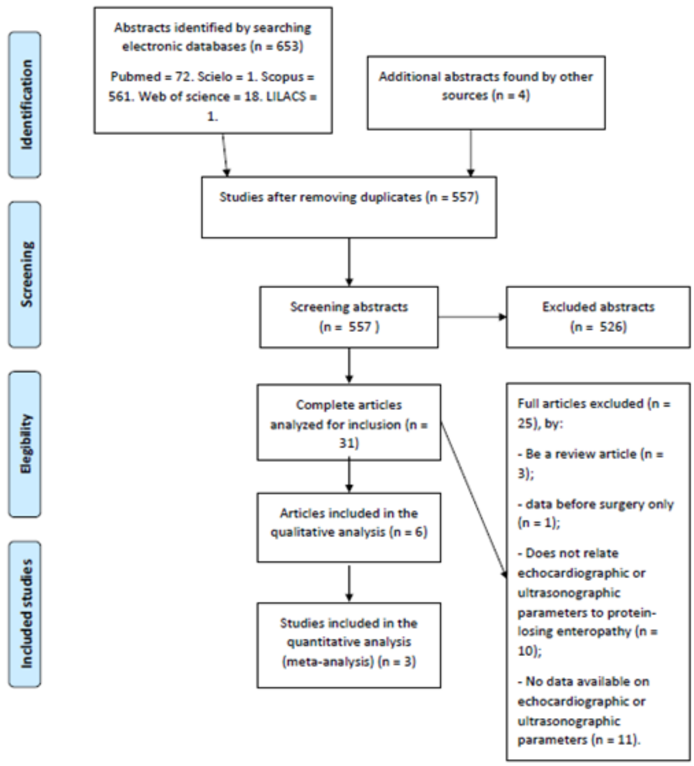

Figure 1 – Articles selection process.

Additionally, a study conducted by Mortezaeian et al.,[15] showed that patients with PLE had a lower left ventricular ejection fraction (35.00 ±15.18) than patients without PLE (49.04±5.48).[15] Another one showed that the fractional area change in different echocardiographic sections was significantly lower in patients with PLE after Fontan in a case-control study. In this study, the biplane variation was 50% vs. 56% (p <0.001), on the short axis it was 50% vs. 57% (p <0.001), and apical was 49% vs. 59% (p = 0.01) in patients with PLE and without PLE, respectively.[16]

More details on these studies can be seen in Table 2.

Predictors parameters of future PLE

Two echocardiographic/ultrasonographic parameters (celiac artery resistance index and estimated systolic pressure in the pulmonary artery) were described in only one study each.

The resistance of the celiac artery index (RCA) was described by Du Bois et al.,[13] comparing patients who would develop PLE or plastic bronchitis after Fontan and patients who would not have either one. The median of this index in patients who would develop PLE was 0.9 (with a maximum and minimum value of 0.8 and 0.9, respectively), while in patients who would not develop PLE it was 0.8 (maximum and minimum value of 0.6 and 0.9, respectively) with p = 0.01.[13]

The estimated pulmonary artery systolic pressure between 12 and 15 mmHg has been described as a risk factor for the development of PLE after Fontan surgery in a sample of Mexican patients, even after assessment with confounding factors, with p <0.01.[17]

Discussion

The increasing survival of patients with Fontan circulation brings an increase in their risks of developing adverse events, such as PLE. These patients are usually submitted to several echocardiographic exams throughout their lives; accordingly, the use of parameters derived from this exam for diagnosis or prediction of adverse events may have a substantial impact on guiding their therapeutic approach. In this systematic review, the

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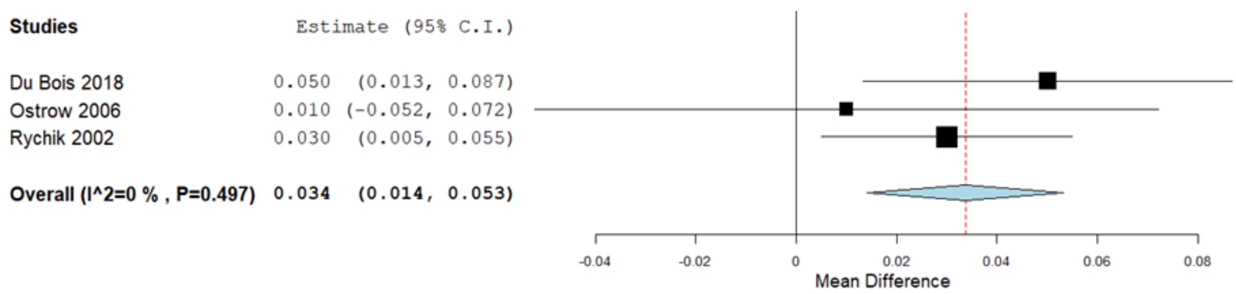

Figure 2 – Superior mesenteric artery resistance index (SMAR) quantitative analysis.

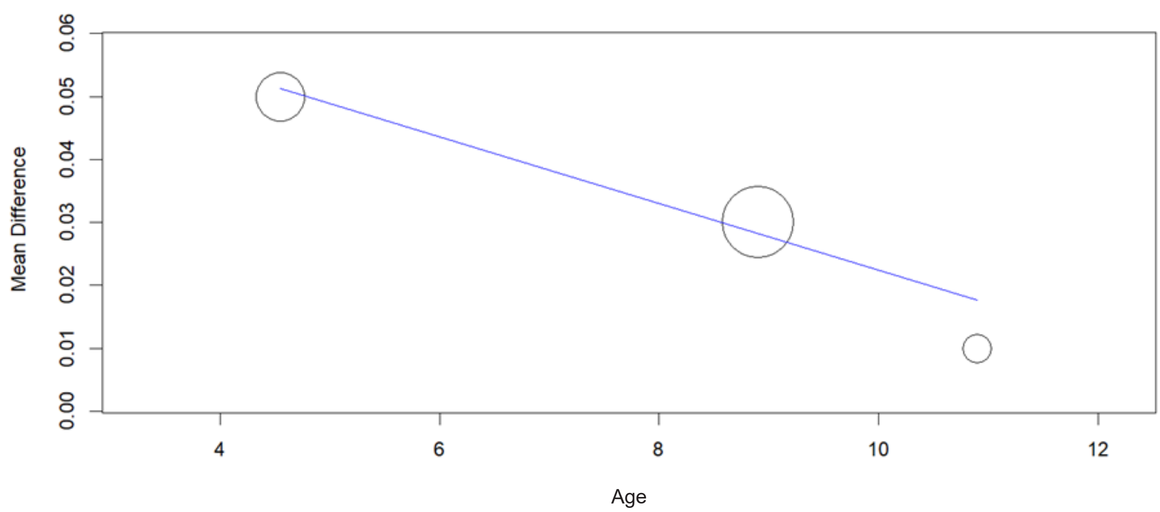

Figure 3 – meta-regression analysis of the SMAR index mean difference between patients with and without PLE and their age

Table 2: Main data from the selected studies

First author	Publication year	Fontan patients with future ple	Fontan patients with present ple	Fontan patients without ple	Mean age at echocardiogram / ultrasonography	Female patients (%)
Du Bois	2018	6*	8*	91	4.26	40
Ostrow	2006	-	7	54	10.9	-
Rychic	2002	-	13	27	8.9	-
González	2015	11	-	31	15 (median)	48
Silvilairat	2008	-	44	472	18 (median)	43
Mortezaeian	2020	-	4	73	-	42

*Legend: PLE - protein-losing enteropathy. *- This group also included patients with plastic bronchitis.*

main echocardiographic findings associated with PLE in patients after the Fontan operation were described. In this analysis, we divided these parameters into two: parameters in the presence of PLE and parameters of future PLE.

Among the parameters in the presence of PLE, SMAR has been more often described in the literature and tended to be higher in patients who presented PLE. Patients after Fontan surgery have a lower cardiac output, on average 2.4 L/min/m^2.[18] Of these, those who evolve with PLE have even lower rates of 1.5 - 2.0 L/min/m^2.[18] The state of low cardiac output leads to higher peripheral vascular resistance and, consequently, to vasoconstriction of the mesenteric circulation.[18] The low mesenteric flow promotes the release of inflammatory cytokines that alter the enterocyte cell membrane, increasing intestinal permeability and promoting protein loss.[18,19] Thus, an increased mesenteric vascular resistance may be found in PLE.

In this context, Ryckik et al.,[18] calculated the SMAR index in patients without Fontan circulation, with Fontan circulation but no PLE, and with Fontan circulation and PLE.[12] In their study, the control group had the lowest index value (0.74 ± 0.08). Patients with Fontan physiology had higher indices, being (0.88 ± 0.05) in those without PLE, and the highest (0.91 ± 0.03) in those with PLE ($p < 0.001$). Subsequently, two studies also show a tendency for a higher index in patients with Fontan and PLE circulation, but without statistical significance.[11,12] The combined analysis of data from these articles (Figure 2) shows statistical relevance ($p < 0.001$). Thus, there is evidence that leads to crediting the SMAR index as a potential parameter. Nonetheless, we must view this finding with caution, because in one study[13], it was not possible to distinguish patients with PLE from plastic bronchitis. For instance, one problem with the use of the SMAR index is its proximity between the two Fontan groups, besides the fact that the majority of patients with Fontan circulation have indices greater than usual (defined as a SMAR index between 0.75 and 0.917). This fact may make it hard to find specific cutoff points for PLE in these patients.

The ratio between the flow of the superior mesenteric artery and the celiac artery was lower in patients with PLE.[14] Thus, the analysis of the mesenteric vascularization can be individualized, as the resistance in the celiac artery is generally low in normal circulatory physiology, but may vary in patients with Fontan circulation. This analysis might lead to a better assessment of the distribution of the mesenteric flow and, consequently, the determination of a higher risk of PLE.[14] It is worth noting that this study also evaluated the SMAR, but no significant difference was observed between the groups.

Additionally, PLE after the Fontan operation usually occurs in two peaks, one earlier (in childhood) - which usually responds to therapy - and another later in life, which tends not to.[6] It should be noted that the studies reviewed here included data from different age groups, with echocardiographic parameters based on SMAR being derived from younger patients (Table 1). These different parameters may reflect different mechanisms leading to PLE, with one more linked to poor mesenteric perfusion and the other involving additional hemodynamic changes that contribute to subsequent failure of the Fontan circulation. The prevalence of one or the other could be influenced by age. With this in mind, we performed a meta-regression analysis of the SMAR index mean difference between patients with and without PLE and their age; however, it showed no statistical significance (Figure 3).

Parameters of future PLE were found only in single studies. They are the celiac artery resistance index, estimated systolic pressure in the pulmonary artery, and change in the fractional area.

Low cardiac output leads to peripheral vasoconstriction. It may explain the fact that the RCA index, measured at the site of origin of three arteries responsible for the vascularization of a large part of the abdominal organs, was higher in patients with PLE.[13] However, despite the statistical significance, such finding has limitations. The difference between the groups described by Du Bois et al.,[13] was exceedingly small, like SMAR, and the analysis also included patients with plastic bronchitis (that is, the group was not homogeneous for PLE only).

Fontan physiology is characterized by high pressures and congestion of the venous system, which is ultimately influenced by the impedance of the pulmonary vessels.[5,20] Therefore, flow is directed by the pressure difference between the systemic and pulmonary systems, and small hemodynamic changes (such as an increase in pulmonary pressure) can impair the blood flow.[6,21] Furthermore, myocardial dysfunction, which leads to a reduction in cardiac output, is associated with a higher chance of Fontan circulation failure and the development of PLE.[6]

In this context, in a retrospective Mexican evaluation, it was shown that patients with Fontan circulation and PLE tend to have higher values of pulmonary systolic pressure (between 12-15 mmHg), with a risk ratio of 2.6 ($p = 0.01$).[17] In another case-control study, it was shown that minor changes in the fractional area were associated with PLE since this measure is related to systolic function.[16]

Also, a lower left ejection fraction was correlated with the presence of PLE in patients after Fontan surgery.[15] Therefore, echocardiographic changes in pulmonary pressure and systolic function may be associated with PLE as well.

It is worth noting that the parameters obtained in other procedures can also predict the risk of PLE. An example is an increase in central venous pressure (CVP) in the postoperative period of Fontan surgery.[22] This is likely to occur because CVP leads to more significant venous congestion, altering the intestinal lymphatic drainage, thus leading to PLE. Another hemodynamic aspect that can predict the development of PLE is low pulmonary compliance, even when corrected by other hemodynamic variables.[23] Likewise, low pulmonary compliance is related to more extended pleural effusion periods, yet another risk factor for the onset of PLE.[24]

Finally, this study has some limitations. The majority of the described parameters were present in only one study, not allowing a meta-analysis and reducing the quality of evidence presented (although the majority of the selected studies presented a Fair to Good qualification in the Quality Assessment Tool). Some clinical and surgical aspects of PLE in Fontan patients were not explored due to the lack of information about them in the selected studies (correlation of the parameters with fenestrated tunnel, for example). However, such limitations are a consequence of scarce literature on the topic .

Conclusion

This systematic review with meta-analysis demonstrated the echocardiographic/ultrasound parameters related to the presence and predictors of future PLE in patients with Fontan physiology. The SMAR index was the most frequently described in the literature and showed statistical significance after quantitative assessment. Other indexes, such as the ratio of the flow between the superior mesenteric artery and the celiac artery, may, at least in theory, present better results. Other echocardiographic findings, such as increased pulmonary systolic pressure and measures related to systolic function, are correlated with PLE, but only in single studies.

Author contributions

Conception and design of the research: Mourato MF. Acquisition of data: Mourato MF, Mourato FA. Analysis and interpretation of the data: Mourato FA. Statistical analysis: Mourato FA. Writing of the manuscript: Mourato MF. Critical revision of the manuscript for intellectual content: Neves JR, Mattos SS.

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

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ORIGINAL ARTICLE

Effects of Low-to-Moderate Doses of Anabolic Steroids on Lipid Profile and Muscle Hypertrophy in Resistance Training Practitioners: A Systematic Review with Meta-Analysis

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Abstract

Background: The use of androgenic anabolic steroids (AAS) is prevalent among young bodybuilders, motivated by aesthetic results. Although the medical community condemns this practice for its potential deleterious effect, we must recognize the need for more scientific research on the likelihood and magnitude of the adverse events.

Objective: To evaluate whether high-quality, scientific evidence supports that AAS negatively affect lipid profile and promote muscle hypertrophy in resistance training practitioners.

Methods: A systematic review of the literature of randomized clinical trials was conducted in the PubMed / Medline, Scielo and Science direct databases. The searches were conducted by two independent researchers by June 2018. A significance level of 5% was considered in the analysis.

Results: Six clinical trials involving 170 resistance training practitioners were included. A significant heterogeneity was found in studies evaluating the effects of AAS on lipid profile and muscle hypertrophy (I^2 = 97, 95 and 91%, respectively), with no significant effects on HDL-cholesterol (-5.62mg/dL, 95%CI -12.10, 0.86, p= 0.09), LDL-cholesterol (7.76 mg/dL, 95%CI -9.70, 25.23, p= 0.57) and muscle hypertrophy (2.44kg 95%CI 0.02, 4.86, p=0.05).

Conclusion: Current evidence does not support that low-to-moderate doses of AAS cause serious negative effects on lipid profile or promote muscle hypertrophy in resistance training practitioners.

Keywords: Receptors Androgen; Young Adult; Esthetics; testosterone Congeners; Resistance Training.

Introduction

After the discovery of the effects of testosterone on muscle strength and hypertrophy, a synthetic formula of this hormone was developed in the late 1930s and came to be called androgenic-anabolic steroids (AAS).[1] These drugs have been used legally by particular individuals, such as the elderly, patients with acquired immunodeficiency syndrome, hypogonadism, anemia that accompanies renal failure, bone marrow failure, endometriosis, cancer and osteoporosis.[2]

The use of AAS by young sports practitioners has increased due to the need to obtain results in the short term, such as breaking records in competitions, and for muscle hypertrophy, either for aesthetic or bodybuilding purposes.[3,4] However, these substances are known to be associated with adverse effects, including acne, testicular atrophy, mood changes, water retention and gynecomastia. The prevalence of use of AAS varies across geographic regions, ranging from 0.2% in Asia, 4.8% in South America, reaching 21.7% in the Middle East.[5]

In addition, biochemical changes induced by AAS can promote changes in the lipid profile, characterized by a

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decrease in high-density lipoprotein cholesterol (HDL-c) levels and increase in low-density lipoprotein cholesterol (LDL-c) levels by changes in apolipoproteins AI, synthesis of apolipoprotein B, and activation of hepatic lipase. Changes in lipid and lipoprotein metabolism are risk factors for atherosclerotic disease and risk predictors of coronary artery disease and cerebrovascular disease,[6] and therefore, AAS-induced changes in lipid metabolism can increase the risk of acute myocardial infarction and sudden death.[7]

Despite these cardiovascular[8] and metabolic[1] problems associated with the use of ASS, some authors have questioned this association due to the reduced number of randomized clinical trials on this subject,[9] mainly for ethical reasons involved in studies with young athletes or practitioners of physical exercises.[10]

In parallel, we observed that there is a conflict in the literature regarding which AAS and doses would cause greater changes in lipid profile, and which ones would be safer from the risk-benefit point of view.[11-13] Other factors known to affect influence lipid levels must also be considered, such as genetic rearrangements and users' diet.[14,15]

Therefore, the purpose of this review was to assess whether high-quality scientific evidence supports that AAS negatively affects the lipid profile and promotes muscle hypertrophy in resistance trainers.

Methods

A systematic review of the literature was carried out following the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) statement.[16] The review protocol was registered in PROSPERO (CRD 42018086525).

Literature Search Strategy

The databases used were PubMed / Medline, Scielo, and Science direct, and the following Mesh terms and names of the main AAS used in the search: "anabolic androgenic steroids"; "testosterone congeners"; "testosterone"; "resistance training"; "strength training"; "resistance exercise"; "strength exercise"; "HDL"; "LDL"; "lipoprotein"; "triglycerides", using the Boolean operator "and". In addition, all terms were translated into Portuguese and used for searches in Portuguese language databases. The searches ended in June 2018.

Inclusion and Exclusion Criteria

The inclusion criteria for the articles were: randomized clinical trials that evaluated the effects of AAS in healthy adults who did resistance training and were evaluated for the following outcomes: HDL, LDL, TG and muscle hypertrophy. Articles that did not use control groups, that did not present a detailed description of the resistance training program, and studies including patients that used any medication that could influence the lipid profile were excluded.

The Kappa coefficient was calculated to identify the level of agreement between researchers.

Data Collection

Two independent researchers (M.C.C.T and C.L.S.L.P) selected the articles by titles, excluding those that did not address the proposed theme. Then, the abstracts were analyzed to identify the articles that met the inclusion criteria.

Subsequently, studies that met the inclusion criteria were selected for systematic review and subsequent meta-analysis. In case of divergence, a third researcher (C.K.C.S) was consulted. The relevant data were extracted from the included studies by two independent reviewers (CLSLP and MCCT) – mean ± standard deviation (SD) of pre- and post-intervention period, and changes from baseline (post-test - pre-test) and pooled SD. Data presented in mmoL/L were converted to mg/dL.

The studies that did not present grouped SD of one of the interventions had their values estimated through p-value, confidence interval, or correlation coefficient, and a correlation of $R = 0.80$ was adopted in the calculations.[17]

Risk of Bias

The risk of bias was assessed by the Cochrane Collaboration's Risk of Bias Tool 1.0. The tool was used in its full version, with no insertions or changes in any of its seven domains,[18] which were assessed independently by two reviewers (M.C.C.T and C.L.S.L.P).

The following domains were considered for bias assessment: (a) selection bias due to the generation of random sequence, (b) selection bias due to allocation concealment, (c) performance bias, (d) detection bias, (e) attrition bias, (f) reporting bias and (g) other bias. The supporting material of the RoB 1.0 tool (no internal assumptions were made) was used as support for the evaluation of the domains. Discrepancies were resolved by consensus between the reviewers. The data are shown in Figure 6.

Meta-analysis

The meta-analyses were conducted using the Review Manager software (RevMan 5.3. Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014). Random effect models with inverse variance method for continuous data were adopted, and data were expressed as difference of means and confidence intervals (95%CI). The heterogeneity between the studies was calculated using Cochrane's Q analysis with a statistical significance level of 0.10 for heterogeneity, and the I^2 for inconsistencies in treatment effect sizes ($I^2 > 50\%$ accepted for substantial heterogeneity).[19] For exploration of heterogeneity among studies, each study was removed one at a time to verify whether it was a potential cause of heterogeneity. Kappa statistics were performed using SPSS software version 21 to identify the agreement in the selection of studies, and analysis of the methodological quality evaluated by the Risk of Bias Tool 1.0 tool from the Cochrane Collaboration. Accuracy of searches was analyzed by dividing the number of articles included by the number of articles selected was divided after duplicates were removed. Subsequently, the NNR (Number needed to read) = 1 / precision was calculated, according to Lee et al.[20].

Results

After the search was complete, 9,767 articles were retrieved from the databases. Then, 6,257 duplicate articles were excluded. After reading the titles, 3,244 articles were excluded and 228 were excluded after reading the abstracts. Thus, 38 articles were selected for full reading. Then, 32 articles were excluded – 11 for not being randomized, 9 for not having evaluated the lipid profile, 7 for not having described the use of RT, 3 for the population included in the study (elderly individuals on hormone replacement therapy), 1 for not having a control group and 1 for including substances that were not AAS in the experimental group. Therefore, 6 studies were included in the qualitative and quantitative analyses (Figure 1). A Kappa index of 0.67 was found between the two evaluators. The search precision was 0.0014 and the NNR was 714.

Risk of bias

Based on the Cochrane collaboration tool for assessment of controlled clinical trials, no study was judged as low risk of bias (Figure 6).

As for the selection bias (randomization and allocation concealment), all studies were classified as "risk of uncertain bias". For performance (accreditation of participants and professionals), approximately 33.3% of the studies[11,21] were classified as "low risk".

In the assessment of detection bias (blinding of evaluators), only one study was classified as low risk.[11]

Approximately 50% of the studies were classified as "high risk" for "attrition bias" (incomplete outcomes).[11,21,22] Four studies (66.7%) were classified as low risk for reporting bias (selective outcome report)[12,21,23,24] and two were classified as risk of uncertain bias.[11,22] Only two studies were classified as low risk for other biases;[21,23] the others were classified as risk of uncertain bias.

It should be noted that the studies included had a small sample size and did not describe the evaluation of statistical power, allowing random errors due to low power.

In domain assessment, the Kappa coefficient for agreement between the two reviewers was 0.70.

Characteristics of Studies and Participants

General description of the included studies is summarized in Table 1. In total, 170 individuals completed the studies with RT, mean sample size 22.3 ± 12.5, and age range between 18 and 65 years. The highest mean age reported was 47 years.[22] Four studies evaluated trained individuals,[11,21,23,24] only one study included sedentary individuals,[12] and one study did not describe the physical activity status of participants, whether experienced practitioners or beginners.[22] In the meta-analysis, the number of subjects evaluated was 134, 54, 67 and 133 for the outcomes HDL, LDL, triglycerides and muscle hypertrophy, respectively. Of the included studies, one study evaluated lipid profile as the primary objective,[23] one study did not describe dietary control/guidance,[24] two studies reported adverse effects related to acne, nipple tenderness,[11] headaches, muscle cramps, dehydration and mood swings.[21] One study presented the calculation of sampling power a posteriori for its main outcome,[22] but no study presented a sample calculation for the analyzed outcomes; all studies showed multiple comparisons. The study by Bhasin et al.[11] used

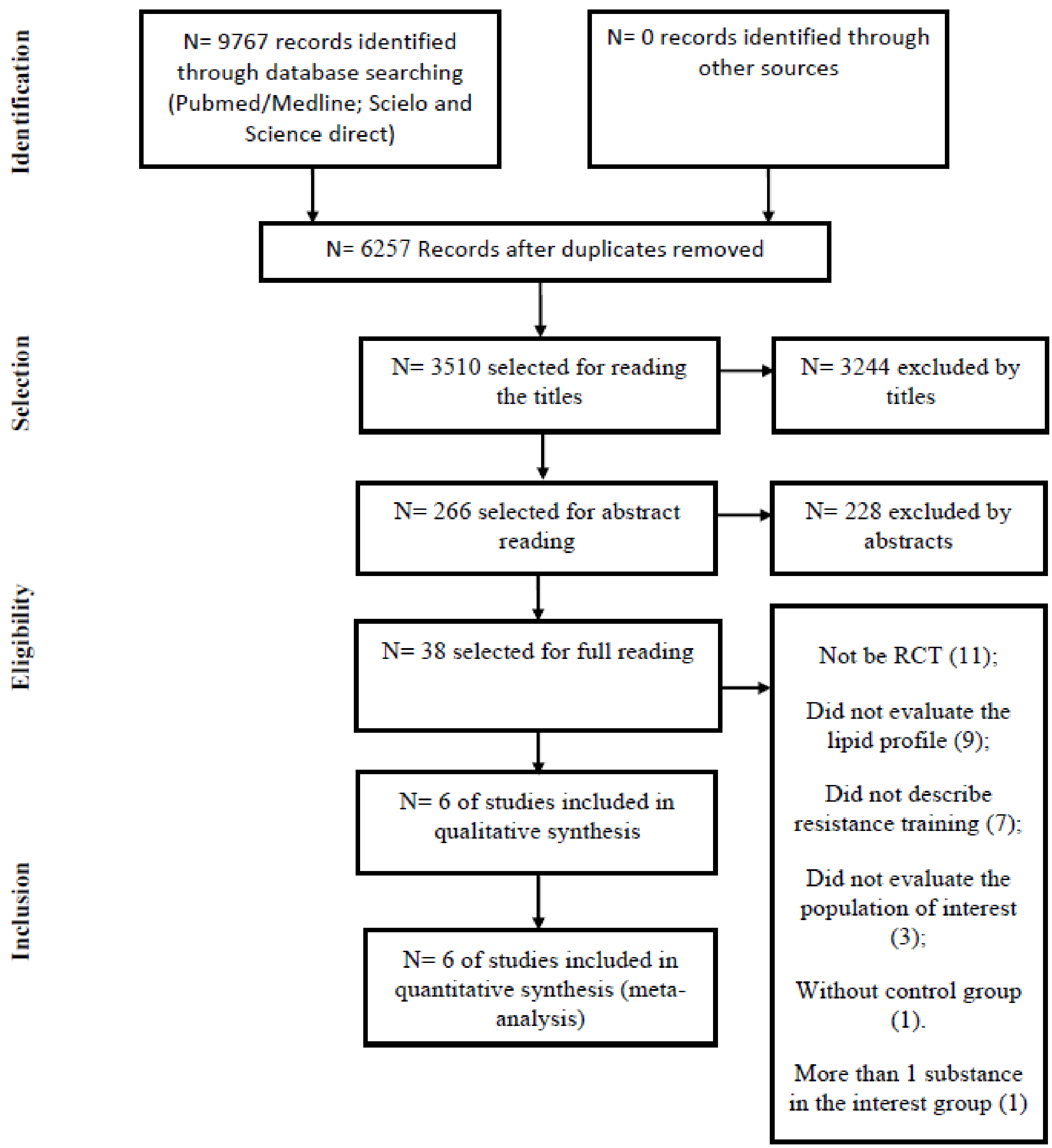

Figure 1 – Flowchart of study selection.

different samples for the analysis of lipid profile and anthropometric outcomes.

Characteristics of the Interventions

Interventions lasted from 4 to 12 weeks, with a weekly frequency of 3-4 sessions per week. Regarding the dose-response of strength training, the volume varied from 3 to 5 sets per exercise of 3-15 repetitions at an intensity of 65 to 95% of a maximum repetition. Only Broeder et al.[22] used a non-linear (wave) periodization.

AAS doses were applied intramuscularly weekly[11,23,24] or as capsules consumed two to three times a day, every day.[12,21,22] The doses of injectable steroids ranged from 200mg/week of testosterone decanoate[23,24] to 600mg/week of testosterone enanthate.[11] Only the study by

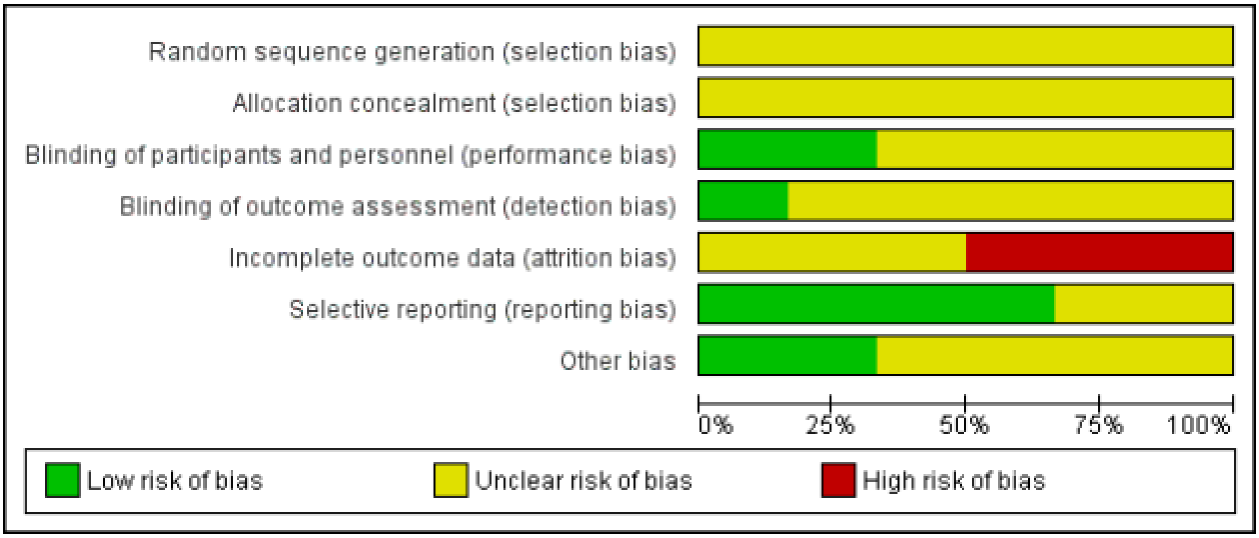

Figure 2 – Bias risk assessment.

Bashin et al.[11] used supraphysiological doses. Control groups received weekly intramuscular administration of sesame oil[11] or peanut oil,[23] or consumed rice flour-,[12] maize starch-[22] or maltodextrin- derived placebos.[21] The study by Kuipers et al.[24] did not report the substance used as a placebo.

AAS and HDL

Six studies were included in the statistical analysis, which revealed substantial heterogeneity (I^2 = 97%) among the studies. Three of the six studies showed no effects on HDL,[11,23,24] and three [12,21,22] showed changes in HDL levels, with only one reporting a great reduction.[21] All these studies that showed changes in HDL levels used oral prohormone drugs, whereas studies that used injectable drugs did not show changes in HDL. In the subgroup analysis, no heterogeneity was found between the studies that used injection drugs (I^2 = 0%, p = 0.46); however, considerable heterogeneity was found in the analysis of the studies that used oral drugs (I^2 = 97%, p <0.001).

No changes in HDL were identified with the use of oral or injectable substances (-9.33 mg/dL, 95%CI -18.30, -0.36, p<0.00001; I^2=97% and 0.75 mg/dL, 95%CI -0.93, 2.42, p=0.46; I^2 = 0 %, respectively).

As shown in Figure 2, in the total analysis, no significant difference was found in HDL-c reduction for AAS groups (-5.62mg/dL, 95%CI -12.10, 0.86, p=0.09; I^2 =97%). In general, an average decrease of 6.2±6.1mg/dL was observed in the AAS group after the intervention, while a decrease by 0.8±3.0mg/dL was observed in the control group. No great methodological heterogeneity was identified in the studies.

AAS and LDL

Three studies that evaluated LDL-c levels were included in the statistical analysis. The meta-analysis revealed considerable heterogeneity among the studies (I^2=95%). Only one study reported a reduction in LDL-c levels,[11] and only the study by Granados et al.[21] showed a significant increase. Due to the limited number of studies evaluating changes in this outcome, it was not possible to perform a sensitivity analysis of the substances used.

As shown in Figure 3, no significant difference was found in LDL values between AAS and control groups (7.76mg/dL, 95%CI -9.70, 25.23, p=0.57; I^2 =95%). In general, an average change of 9.1±18.2mg and 0.9±4.2mg in LDL was found in the AAS group and control groups, respectively, after the interventions.

AAS and Triglycerides

Four studies were included in the statistical analysis. It was not possible to perform a sensitivity analysis of the substances used. In the total analysis, as shown in Figure 4, there was a statistically significant difference in the

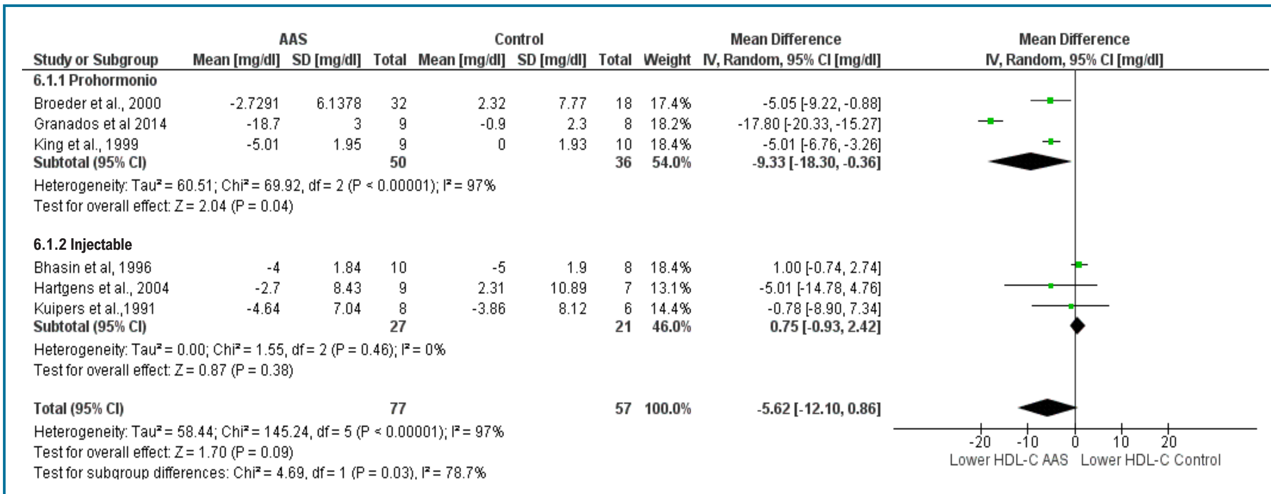

Figure 3 – Effect of the use of androgenic anabolic steroids (AAS) on high-density lipoprotein cholesterol (HDL-c) levels.

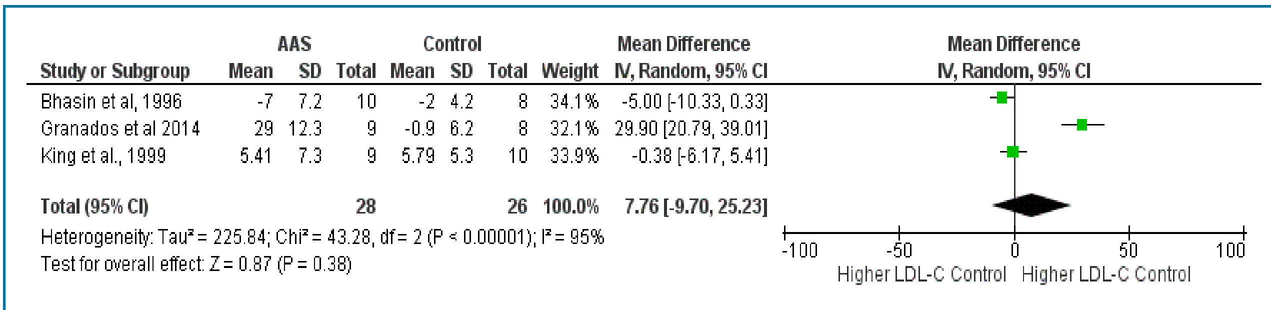

Figure 4 – Effect of using androgenic anabolic steroids (AAS) on low-density lipoprotein cholesterol (LDL-c) levels.

reduction of triglycerides for the steroid group (-11.68mg/dL, 95%CI -23.07,-0.26, p=0.04; I^2 = 42%). In general an average decrease of 5.6±24.2mg/dL and 0.8±14.4mg/dL in triglyceride levels was observed in AAS group and control group, respectively, after the interventions.

AAS and Hypertrophy

Considering the effects of AAS on muscle hypertrophy, considerable heterogeneity was demonstrated (I^2=91%, p<0.00001) among the studies analyzed. Of the studies that evaluated the effects of AAS on lipid profile, four evaluated muscle hypertrophy, of which, two did not demonstrate hypertrophic changes.[12,22] As shown in Figure 5, there was no statistical difference in muscle hypertrophy between AAS and placebo groups (±2.44kg; 95CI% 0.02; 4.86, p=0.05). The experimental group obtained an average hypertrophic increase of 3.7 ± 2.0 kg after the intervention, while the control group obtained an increase of 1.4±1.1kg.

Discussion

The aim of this review was to perform a qualitative and quantitative assessment of literature data on the effects AAS use on lipid profile and muscle hypertrophy in resistance training practitioners. The qualitative analysis showed that the studies included in this review did not have a low risk of bias. In the meta-analysis, the results were conflicting for the evaluated outcomes.

In the analysis of the six articles that evaluated HDL levels, we found that while three studies showed a decrease;[12,21,22] the other three did not show significant changes[11,23,24] and Bhasin et al.[11] reported a reduction in HDL in the control group. These data are in agreement with a study with individuals in andropause,[25] which showed that the use of steroids may not be able to promote significant changes in HDL.[25] Thus, results of this review demonstrate that the existing studies on the effect of AAS on HDL levels indicate conflicting results.

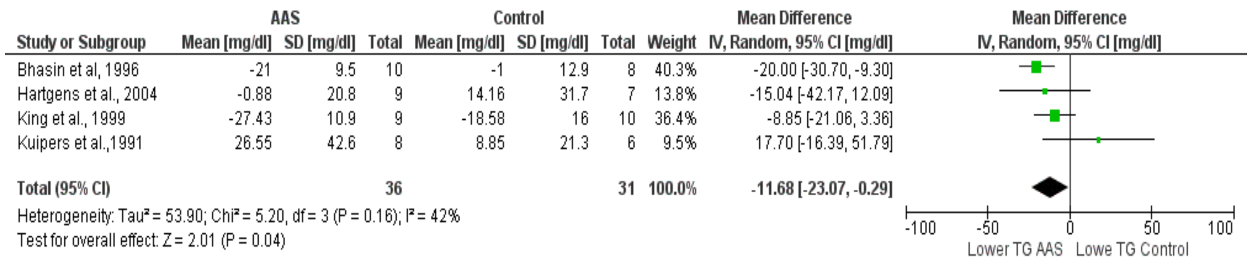

Figure 5 – Effect of androgenic anabolic steroids (AAS) on triglyceride values.

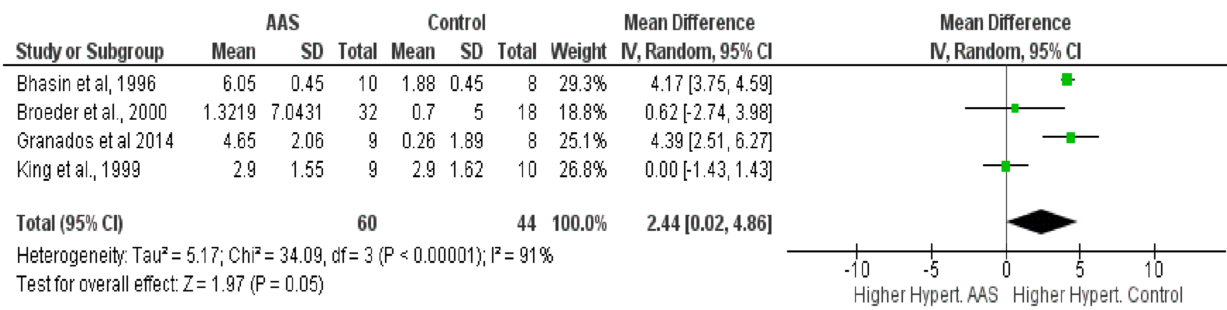

Figure 6 – Effect of androgenic anabolic steroids (AAS) on muscle hypertrophy.

Two studies, by Bhasin et al.[11] and Granados et al.[21] reported adverse effects of AAS, such as acne, sensitive nipples, headaches, muscle cramps, dehydration and mood swings. However, Granados et al.[21] reported non-significant difference in adverse effects reported between groups.

Conflicting results were also observed for the LDL outcome. Among the four studies included, only one showed an increase in LDL levels,[21] while the others suggested that the use of steroids, in the dosages used, does not promote significant changes in LDL. On the other hand, regarding triglycerides, the meta-analysis of studies that used oral AAS drugs demonstrated a significant decrease in triglyceride levels with the intervention.

Garevik et al.[26] demonstrated that the use of low doses (125mg) of AAS did not alter the lipid profile, and that changes in this outcome may be directly related to the dose used, even when only one dose was evaluated. This dose-response relationship was also mentioned by Hartgens et al.[23] In this study,[23] the authors evaluated two experiments – the use of self-prescribed drugs and dosages versus the use of pre-established dosages that were randomly and blindly distributed. In the first experiment, where volunteers used drugs *ad libitum (high doses)*, changes in HDL were identified, however, triglyceride and total cholesterol did not change. In the randomized double-blind study, no significant changes in HDL and triglycerides values were observed after eight weeks of nandrolone decanoate (200 mg/week). Thus, the dose-response relationship was reported at the end of the study.

However, many studies that reported this dose-response relationship were case studies and cross-sectional studies, that is, the evidence may still be contradictory.[27-29] While changes in the lipid profile have been demonstrated with the use of oral AAS in randomized clinical trials, such as reduced HDL-c[12,21,22] and increased LDL-c,[21] other randomized controlled trials, which used predominantly injectable substances, had negative results.[11,23,24]

Possible metabolic changes may be related to the dosage and the type of substance used. It has been shown that the dose used without medical advice is greater than the therapeutic doses used in most clinical trials and

Table 1 – Characteristics of the included studies

Author	Objective / Sample (n, sex and age)	Duration and intervention	Drug/dosage	Hypertrophy	Result
Bhasin et al.(9)	To determine whether supraphysiological doses of testosterone, taken alone or in conjunction with a standardized strength training exercise program, increase strength, fat-free mass and muscle mass in normal men	RCT: 10 Weeks; 35 male practitioners (19-40 years) / 4 groups (9 PGWE, 8 SGWE, 8 PPEG, 10 SPEG); 4 control weeks, 10 weeks treatment and 16 weeks recovery	SG: Testosterone enanthate 600mg/week PG: Sesame oil	SPEG: ↑ FFM#	PPEG: ↓ HDL; ↔ TG, LDL e HB SPEG: ↔ HDL
King et al. (10)	To determine the acute and chronic effect of oral Androstenedione on testosterone levels, skeletal muscle fiber size, strength and examine its effect on blood lipids and liver function markers.	RCT. 19 sedentary men (19-29 years); 2 groups PG:10, SG:9, RT: 8 weeks, 3x/week;	Androstenedione SG: 300mg/day PG: 250mg (rice flour)	↔ FFM# between groups	SG: ↓ HDL (12%)
Hartgens et al.(20)	To investigate the effects of two different EAA regimens on serum lipids and lipoproteins and recovery of these variables after drug withdrawal.	Study 1 (open). 35 men, 2 groups (CG+SG), SG:n=10 Use/14week, n=9. Use/14week; CG: n=16. BG performed RT. Self-administered AAS. Study 2 (RCT). 16 men (20-45 years). SG: n=9, PG: n=7. RT: 8 weeks, 7-9h/week Dosages during and 6 weeks after stopping use	Study 1. Uncontrolled doses. Stanozolol, Drostanolone, Testosterone, Clenbuterol, Testosterone cypionate, Nandrolone decanoate, etc. Study 2. SG: Nandrolone decanoate (200mg), PG: Peanut oil.	NE	Study 1. SG: ↓ HDL, ↓ HDL2, ↓ HDL3, ↔TG, ↔ TC CG: ↔ Study 2. ↔ HDL, HDL2, HDL3 ↔ TG, ↔ TC
Broeder et al. (19)	To elucidate the physiological and hormonal effects of androstenediol and oral androtenedione in men	RCT. 50 men § (35-65 years) PG: 18 GDiol: 17 GDione:15 RT: 12weeks, 3x/week	PG: Maize starch GDione: 200mg/day GDiol: 200mg/day	↔ FFM$ between groups	↔ HDL, ↔TG
Granados et al. (18)	To evaluate the effects of the use of prohormone on metabolic aspects in men	RCT. 17 men (18-35 years) GP: 8 GU: 9 RT: 4 weeks, 4x/week	PG: Maltodextrin SG: 110 mg Androstenedione, 50mg of bergamotine	SG: ↑ FFM#	SG: ↓ HDL, ↑ LDL
Kuipers et al (21)	To examine the effects of anabolic steroids on body composition, muscle fiber dimensions, liver function and risk factors for cardiovascular disease in experienced and healthy bodybuilders.	ECR. 14 men (18-45 years) SG: 6 PG: 8 RT: 8 weeks, 3-4x/week	PG: Placebo UN SG: 200mg/week Nandrolone Decanoate	↑ FFM	↔ HDL, ↔ LDL, ↔ TG

RCT: randomized clinical trial; SG: steroid group; PG: placebo group; PGWE: placebo group without exercise; SGWE: steroid group without exercise; PPEG: placebo plus exercise group; SPEG: steroid plus exercise group; GDiol: androstenediol; GDione: androstenedione; CG: control group; BG: both groups; TG: Triglycerides; TC: Total cholesterol; HB: hemoglobin; RT: resistance training; NE: Did not evaluate LDL; FFM: fat free mass; #: hydrostatic weighing; $: DEXA; ↑: increase; ↔ : no difference; ↓: UN: unreported; §: Did not report physical activity status of participants; [a]: muscle biopsy; The level of significance adopted in the studies was 5%

that high doses can promote metabolic changes, unlike the usual therapeutic doses.[23,26,30] Although therapeutic doses can vary from 50mg to 144mg per day,[31] the usual doses for aesthetic purposes exceed 1000mg per week.[23] In addition, the oral use of AAS, especially 17-alpha-alkylated AAS, can affect liver metabolism, as they undergo first-pass metabolism,[32,33] thereby promoting more marked changes.

Lipoproteins are influenced by the activity of hepatic lipase, with formation of smaller and denser particles.[34] An overexpression of hepatic lipase has a negative impact on plasma values of HDL-c and LDL-c, and increases the hepatic cholesterol concentrations without altering bile cholesterol secretion.[35,36] Therefore, hepatic lipase plays an essential role in the negative regulation of HDL-c levels.

Changes in lipid profile are known to increase cardiovascular risk, which can be aggravated by other factors such as obesity and physical inactivity.[37-40] Usually, these risk factors are not present in individuals who use steroids for aesthetic or competitive purposes. However, some cardiovascular changes could be identified among users, such as increased blood pressure,[1] ventricular hypertrophy,[41] and endocrine changes, such as hypogonadism,[42,43] which can cause chronic infertility.[44,45] However, as in lipid variables, there are controversies about echocardiographic results, as demonstrated by Hartgens et al.[46]

When assessing hypertrophic gain, no significant change was identified in the overall analysis. Although this was not the main objective of this review, the analysis of hypertrophic gains was important to demonstrate that, although the use of AAS did not significantly alter the lipid profile, the doses used were also unable to promote the changes expected by the users. Considering that one of the main factors for the non-therapeutic use of AAS is the concern with physical appearance,[47] hypertrophic gain is the main objective of recreational users. This may justify the high doses used in non-therapeutic situations.

It should be noted that the studies did not present the sample size calculation and did not report the sample power. The study by Broeder et al.[22] presents sample calculation, however, it did not describe for which outcome it was calculated. In addition, the study showed a loss of follow-up of 29%, which did not affect the sample power due to the high number of individuals included initially.[22] All studies were susceptible to the bias of multiple comparisons, since they did not clearly present the main outcome assessed.

The gray literature and clinical trial records were not accessed for this review. In addition, there was a risk of bias in the included studies, which limits the extrapolation of the results.

Pratical Applications

We conclude that current evidence does not support an effect of low-to-moderate doses of AAS on HDL-c and LDL-c levels. In addition, the use of AAS, in the doses used in clinical trials, had no beneficial effect on muscle hypertrophy.

Author Contributions

Conception and design of the research: Tenório MCC, Correia L, Paz C. Acquisition of data: Tenório MCC, Paz C, Guimarães Junior M, Valladares F. Analysis and interpretation of the data: Tenório MCC, Correia L, Paz C. Statistical analysis: Tenório MCC, Correia L, Paz C. Writing of the manuscript: Tenório MCC, Correia L, Paz C. Critical revision of the manuscript for intellectual content: Tenório MCC, Correia L, Valladares F, de Sá C.

Potential Conflict of Interest

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

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Study Association

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Ethics Approval and Consent to Participate

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

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ORIGINAL ARTICLE

Does Hypertension Knowledge Influence Levels of Physical Activity in Hypertensive Patients From a Southern Brazilian Community?

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Abstract

Background: Increased level of physical activity (PA) and health education are known as non-pharmacological treatments of hypertension (HP). There is a lack of studies investigating the influence of HP knowledge on the level of PA among hypertensive patients.

Objective: To examine the influence of patient's knowledge about HP on PA level and the relationship between these variables.

Methods: A cross-sectional study was conducted in in a primary care center located in a city in the southern Brazil. A total of 199 hypertensive patients (median 61.2 [13] years; body mass index (BMI) 21.9 (7.5) kg/m2; 72.4% women) were included. The level of PA was assessed by measuring the number of steps taken daily. The knowledge about HP was assessed by a standardized questionnaire (HIPER-Q). The Kruskall-Wallis test was used to compare age, BMI and PA level between HP knowledge categories, and the Spearman test was used to assess correlations ($p < 0.05$).

Results: The median score of knowledge about HP for patients categorized as insufficient (n=6, 3%), poor (n=24; 12.1%), acceptable (n=101; 50.8%) and good (n=68; 34.2%) was 11.0 (8.0), 20.0 (4.0), 26.0 (5.0) and 38.0 (2.0), respectively. No patient has achieved an "excellent" level of knowledge. There was no significant difference in PA level ($p = 0.341$), BMI ($p = 0.510$) or age ($p = 0.073$) between these categories. Age was negatively correlated with knowledge about HP ($p < 0.05$ and rho = 0.02).

Conclusions: Patient's knowledge about HP did not influence the level of PA in hypertensive patients. Age, number of steps per day and BMI were not significantly different between the categories of knowledge. Public policies and organizational strategy should be addressed to improve health education and avoid sedentary behavior in this population.

Keywords: Hypertension; Health Programs and Plans; Health Education; Exercise; Physical Activity; Epidemiology; Quality of Life; Blood Pressure.

Introduction

Hypertension (HP) contributes significantly to the high prevalence of cardiovascular diseases (CVD), which are the main causes of mortality in the world.[1] It is believed that HP accounts for up to 7.6 million (12.8%) of total number of deaths each year.[2]

Despite recent advances in the prevention and treatment of HP, the economic and health impacts of this condition have increased, with significant repercussions on public health worldwide.[3,4] In this regard, strategies for the mitigation and control of hypertension, such as moderate to high levels of physical activity (PA), are recommended as important

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non-pharmacological approaches in the management of the disease.[4–6]

A systematic review evaluated 96,073 hypertensive patients and showed that all-causes of mortality were inversely related to PA, and that walking was the most common mode of exercise.[8] The practice of this exercise modality, complemented with the use of measurement tools, such as pedometers, has increased, as these are easy-to-handle and cheap devices.[8,9]

Some studies have shown that walking between 10,000 and 13,000 steps/day contributes to blood pressure lowering.[10–13] Thus, increases in PA are an important strategy in the prevention and treatment of HP, [7,13-15] although there is still a lack of studies investigating the effect of the use of pedometer-assessed PA in hypertensive patients.

Understanding lifestyle behaviors among individuals with HP is important to achieve hypertension control and to determine contributing factors to knowledge and treatment.[6,7] Although significant progress has been made in HP detection and control, up to 70% of diagnosed hypertensive patients do not have adequate blood pressure control.[5]

Knowledge of hypertension is associated with and considered co-responsible for treatment success. Patients participating in educational procedures can take better care of their own health.[16]

Maruf et al.[17] demonstrated that hypertensive patients had good knowledge about PA behavior, positive attitude in terms of benefits, importance and involved risk, in addition to a high level of participation. There were significant correlations between knowledge about PA, attitude towards PA and participation in PA.[17] However, to the best of our knowledge no study investigated whether hypertension knowledge influences the level of PA. Thus, the aim of this study was to examine the influence of hypertension knowledge on PA level and the relationship between these variables in hypertensive patients in a primary care center in southern Brazil.

Methods

In this cross-sectional study, 199 hypertensive individuals attending a primary care center in a city of southern Brazil were included in the study. In 2015, 921 hypertensive patients, representing 16.5% of the city's total population, were enrolled in this primary care unit. The sample size estimation was performed by proportion approximation, based on the work of Lwanga and Lemeshow.[18]

Estimates of proportions were made as follows: n= (1-α)2 (p) (1-p)/(d)X(d), where "p" indicates the prevalence of the disease in the population (16.5%); 1-p is the proportion of individuals without the disease (83.5%); 1- α is the level of confidence (95%; z=1.96), and "d" is the required accuracy (0.05). Therefore, the calculated sample was 211 hypertensive patients. A total of 302 individuals were invited to participate in the study, but 105 were excluded because of missing data (n=82) or because they did not meet the inclusion criteria (n=23). Therefore, the number of volunteers was lower than the calculated value, also because the researchers had a limited time to assess these patients.

The inclusion criteria were a) diagnosis of hypertension; b) age older than 18 years; and c) clinical follow-up lower than three months in the primary care center. The diagnosis was defined according to the VII Brazilian Guidelines on Hypertension (systolic and diastolic blood pressure levels, respectively): (1) office blood pressure ≥ 140 and/or 90 mmHg; ambulatory blood pressure ≥ 130 and/or 80 mmHg; (3) home blood pressure ≥ 135 and/or ≥ 85 mmHg.[7] Individuals with cognitive impairment to answer the questionnaire, or musculoskeletal and neurological impairments to walk were excluded.

The study was conducted for six months, and all the study procedures and patient inclusion being performed weekly. The study design followed 466/12 resolution of the Brazilian National Health Council and was approved by the Ethics Committee on research involving human beings of Santa Catarina State University, under the protocol n. 689798/2014. All patients signed an informed consent form.

Sociodemographic and personal data were collected using a specific form. Anthropometric evaluations were also performed; body mass was measured using a digital scale (Filizola PL 180) with a resolution of 0.1kg, and height was measured using a wall-mounted stadiometer (ate the nearest 1.0 cm). These measurements were performed as described by Alvarez and Pavan.[19] Body Mass index (BMI) was classified based on the World Health Organization (WHO) recommendations: normal weight (BMI < 25 kg/m^2), overweight (25 kg/m^2 ≤ BMI < 30 kg/m^2) and obesity (BMI ≥ 30 kg/m^2).[20]

To assess the level of knowledge about hypertensive disease, the HIPER-Q instrument was applied. It consists of 17 questions that encompass seven areas regarding patient education: self-care, treatment, diagnosis, PA, concept and pathophysiology, signs and symptoms and risk factors. For each item, one answer is considered the "most correct" and receives a score of 3, and another answer is considered "partially correct" and receives a score of 1. The other two options - the incorrect and the "I don't know" option – are assigned a score of 0. After completion of all questions, the sum of the scores obtained represent the average total knowledge, and the maximum score of 51 points represents the "perfect" knowledge.[21]

Finally, the level of PA was assessed using a pedometer (Power Walker TM® Model PW-610/611). The equipment was programmed to store the number of steps taken for 24 hours. The number of steps were registered for four days, and the mean was used for analysis. A number <5,000 steps per day indicated a "sedentary" lifestyle; between 5,000 and 9,999 steps per day indicated "low-active"; ≥10,000 steps per day "active", and >12,500 steps per day "very active".[22]

Statistical Analysis

Data were analyzed descriptively using Statistical Package for the Social Sciences (SPSS), version 20.0. The Kolmogorov-Smirnov test was used, which showed that the data did not follow a normal distribution. Absolute and relative frequencies were used for categorical variables and median and interquartile range for continuous variables. The Spearman's correlation was used to test the correlation of knowledge about HP with age, BMI and PA level. To compare PA level, age and BMI between different categories of HP knowledge, the Kruskall-Wallis test was used. All statistical tests adopted a significance level of 5% ($p<0.05$)."

Results

Sociodemographic data, BMI, PA level, and patient's knowledge about HP are described in Table 1. Of the 199 patients included, 144 (72.4%) were women and 55 were

Table 1 – Sociodemographic data, body mass index, physical activity level, and patient's knowledge about hypertension (n=199)

Variable	Category	f	%
Schooling	Up to 8 years	163	81.9
	More than 8 years	36	18.1
Income*	Up to 5 salaries	183	92
	More than 5 salaries	16	8
Body mass index	Normal weight	55	27.6
	Overweight	75	37.7
	Obesity	69	34.7
Level of physical activity	Sedentary	27	13.6
	Not very active	85	42.7
	Moderately active	36	18.1
	Very Active	51	25.6
Knowledge about hypertension	Excellent	-	-
	Good	68	34.2
	Acceptable	101	508
	Poor	24	12.1
	Insufficient	6	3

*f: absolute frequency; %: relative frequency; *family income based on a current minimum wage of R$ 998.00.*
The correlation tests of knowledge about HP with age, BMI and level of PA are illustrated in Table 2. Age was negatively related to HP knowledge, but the correlation found was very weak and the correlation coefficient between the variables was rho=0.02.

men (27.6%). Median knowledge about HP was 32 (10) points, which means acceptable knowledge according to HIPER-Q.[21]

The correlation tests of knowledge about HP with age, BMI and level of PA are illustrated in Table 2. Age was negatively related to HP knowledge, but the correlation found was very weak and the correlation coefficient between the variables was rho=0.02.

Comparison of PA level, BMI and age between different HP knowledge categories are presented in Table 3. No significant difference was found between KHP groups.

Discussion

The present study examined the influence of HP knowledge on PA level and the relationship between these variables in hypertensive patients. The results showed that there was no significant difference between different levels of HP knowledge and the number of steps taken per day, which means that the knowledge about the disease does not seem to be determinant to increase PA level in these individuals.

Despite the well-established literature on the importance of knowledge about the disease as a strategy to promote better blood pressure control and cardiovascular prognosis, there is still a lack of studies correlating this knowledge with other variables, such as PA. Some authors found that only 13.6% of hypertensive patients evaluated in cardiology outpatient clinics identified physical inactivity as a risk factor for HP. This could result from the perception of these patients that changes in lifestyle have no impact on high blood pressure management.[23]

Iyalomhe and Iyalomhe [24] demonstrated a low level of knowledge on HP, ineffective attitudes towards treatment and adoption of inappropriate lifestyles in a study with 108 patients undergoing antihypertensive treatment. In addition, only 10 patients (9.3%) reported practicing physical exercises regularly.[24] On the other

Table 2 – Correlation of knowledge about hypertension with age, body mass index and physical activity level (n=199)

Variables	Total n=199		Men f=55		Women f=144		Correlation	
	Md	IQ	Md	IQ	Md	IQ	rho	p
Age (years)	61.2	13	62.6	12	63	14	-0.150	0.035*
BMI (kg/m²)	27.9	7.5	27.7	7.3	28.3	7.2	-0.075	0.290
LPA (Steps/day)	9183	6186.5	11266.7	8813	8702.5	5259.7	0.070	0.336

*n: total sample number; f: absolute frequency; Md: median; IQ: interquartile range; BMI: Body Mass Index; LPA: level of physical activity; rho: Spearman correlation coefficient; * p<0.05.*

Table 3 – Levels of patient's knowledge about hypertension by age, body mass index, and level of physical activity

	Excellent		Acceptable		Poor		Insufficient		Sig.
	MD	IQ	MD	IQ	MD	IQ	MD	IQ	p
KHP score	38.0	2.0	26.0	5.0	20.0	4.0	11.0	8.0	0.001*
BMI (kg/m²)	27.7	8.1	28.6	5.8	27.9	10.6	25.3	7.9	0.510
Age (years)	59	14	63.5	12	64.5	14.0	65.5	10.0	0.073
LPA (Steps/day)	9287	4689.5	9014.12	7085.1	7193.2	5371.5	10864.2	7050.9	0.341

*Md: median; IQ: interquartile range; KHP: knowledge about hypertension; BMI: Body Mass Index; LPA: level of physical activity; Sig.: Statistical significance; *p<0.05.*

hand, qualitative research exploring the knowledge of hypertensive patients about cardiovascular risk factors showed that even though patients were aware of the importance of PA for their health, the majority declared to be insufficiently active.[25] A possible reason for this is a gap in the knowledge about effective strategies for modifying cardiovascular risk factors. Furthermore, resistance to the adoption of healthy lifestyles, even by patients with good knowledge on the disease, may indicate that the expectations about the results are relatively low, that is, these patients are not confident that PA actually improves health.[26]

An educational program intervention had a significant impact on both mean levels of knowledge and adherence to healthier habits by patients with coronary artery disease (CAD) .[27]

In the same manner, significant associations were found between some aspects of health literacy and increased levels of PA in patients diagnosed with acute myocardial infarction, stroke or angina pectoris.[28] Significant positive correlations were also found between the level of knowledge about risk factors for coronary disease and PA level in patients who underwent cardiovascular procedure or event.[29] On the other hand, a recent research conducted in China showed that patients with a higher level of knowledge about cardiovascular disease were more likely to not adhere to a healthy lifestyle, including the practice of PA.[30] The authors attributed these findings to the possibility that patients with a lower level of knowledge may have followed physicians' advice without questioning, which may also have been influenced by socioeconomic factors.

In our study, the median of steps/day was 9,138, without difference between men and women. Although these patients were classified as low-active,[22] these findings exceed those found in another study where, after four weeks of dietary changes and increase in PA levels, the hypertensive and diabetic patients had a median of 4,043 steps,[13] the half of the daily steps registered in the present study. Another study, in which 75% of the respondents were women, reported that diabetics and hypertensive patients submitted to a health literacy program walked 11,686 daily steps,[31] a similar quantity to that found in males in our study. Other researchers demonstrated that women performed a mean of 7,453 steps per day.[32]

Another study conducted in Hong Kong showed that physically inactive people used to walk 8,147 steps daily, and the number of steps taken was negatively associated with health complications, such as HP.[14] These results became relevant since the number of daily steps seems to be inversely correlated with the incidence of HP and, possibly, other cardiovascular outcomes.[14,15]

Hypertensive patients with low level PA are a concern, since insufficient PA represents the fourth risk factor for mortality worldwide, with more than 3.2 million deaths per year and 32.1 million quality-adjusted life years (QALYs).[33] Therefore, the benefits of regular PA are significant for individuals with cardiovascular risk factors, such as HP, as it can reduce mortality by up to 16%.[34]

Although our results indicated a weak correlation between the level of knowledge about HP and age of patients, there was no significant difference in age between different categories of knowledge. This result could be explained by the high percentage of patients in the same age group (70% were between 50 and 70 years old). Conversely, a study based on WHO data regarding global aging and adult health, examined patterns of prevalence of HP in low and middle-income countries and found that awareness of the disease was associated with older age.[35] Another study demonstrated that knowledge and awareness about HP are different between the elderly and high school students, suggesting that there might exist a generational difference in knowledge about the disease.[36] Besides, the fact that HP increases with age may contribute to the relationship between age and HP knowledge.

It is well established that obesity and a sedentary lifestyle are associated with cardiovascular risk factors, including HP.[6,37] This was confirmed by characteristics of our study population, with a high percentage of inactive individuals (42.7%) and even higher percentage of overweight or obese hypertensive patients (72.4%).

However, no significant differences were found in BMI between the categories of knowledge about HP. Corroborating our findings, Knuth et al.,[38] demonstrated an association between knowledge about the effects of PA on hypertension prevention and BMI; however, BMI was not associated with knowledge of the effects of PA on the treatment of HP and type 2 diabetes. This may have been due to the prevalence of these diseases be higher in individuals with a higher BMI.[38]

With respect to knowledge about HP, most patients (50.8%) were classified in the category of "acceptable knowledge". These results are similar to those of other studies[21,39] and reflect the importance of assessing knowledge about health and formulating hypotheses that may elucidate the determining factors for information gaps. It is also noteworthy that no patient presented an optimal level of knowledge about the disease, according to the classification of the instrument.[21]

Therefore, patient knowledge is a central component in the treatment of HP and is associated with successful self-management of the disease and behavioral changes.[16,40] Health education interventions can result in significant reductions in risk factors associated with lifestyle diseases, such as HP.[41] Thus, the WHO[33] recommends that health promotion strategies should be designed to improve knowledge about health and self-management of the disease, beyond the adoption of healthy lifestyles. Therefore, understanding the barriers to obtaining adequate knowledge on HP can contribute to the overall improvement of prevention and management of this condition, with implications for clinical practice.[41]

We did not find longitudinal studies in the literature demonstrating the effects of the higher level of knowledge about HP on outcomes, such as worse prognosis or mortality. In this context, studies on other chronic diseases have shown promising results, suggesting that disease-related education may be determinant in the control of risk factors, such as sedentary lifestyle, smoking and continuity of treatment, which can lead to reductions in comorbidities, health costs and even mortality [42,43] Thus, we expect that our findings can be used as a basis for future studies.

Caution is needed with the interpretation of the results, since this work has some limitations. First, it is notable that our research presents a cross-sectional design, thus hindering the relationships of causalities and effects between the variables. Second, in our population, there were some patients that performed physical exercises on a regular basis, which was not controlled in this research. Third, the instrument used to assess the level of PA, the pedometer, does not allow detecting activities performed with upper limbs or sedentary time and does not measure the intensity and duration of PA. Although this equipment has been widely used to evaluate PA levels, these points limit the extrapolation of the results.

Conclusion

In summary, our results showed that level of knowledge about HP did not influence the level of PA in hypertensive patients from a primary care unit in the south of Brazil. Age, number of steps per day and BMI was not significantly different between four HP knowledge categories. Health education should be emphasized as a strategy to improve knowledge and promote behavior change among hypertensive patients. Public policies and organizational strategy should be addressed to improve health education and avoid sedentary behavior among hypertensive patients.

Author Contributions

Conception and design of the research: Zulianello RS, Martins ETC, Benetti M. Acquisition of data: Zulianello RS, Martins ETC, De Lucca M. Analysis and interpretation of the data: Zulianello RS, Korbes AS. Statistical analysis: Zulianello RS, Korbes AS. Obtaining financing: Zulianello RS, Martins ETC. Writing of the manuscript: Zulianello RS, Korbes AS, De Lucca L. Critical revision of the manuscript for intellectual content: Zulianello RS, Karsten M, Benetti M.

Potential Conflict of Interest

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

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Study Association

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

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the *Universidade do Estado de Santa Catarina* under the protocol number 689789/2014. 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

Relationship between Discordance of Low-Density Lipoprotein and Non-High-Density Lipoprotein Cholesterol and Risk Stratification in Acute Myocardial Infarction

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Abstract

Background: Sizeable proportion of patients have discordant low-density lipoprotein cholesterol (LDL-C) and non-high density lipoprotein cholesterol (NHDL-C). It has been shown that discordance of LDL-C and NHDL-C either underestimates or overestimates coronary risk.

Objectıve: We assessed whether this discordance has an impact on GRACE and TIMI risk scores in patients with acute myocardial infarction (AMI).

Methods: We retrospectively evaluated the data of 198 consecutive patients with AMI. Fasting serum lipid profiles were recorded, GRACE and TIMI scores were calculated. Patients were divided into 3 groups according to LDL-C and NHDL-C percentiles: Discordant group: LDL-C<NHDL-C (n=38), concordant group: LDL-C=NHDL-C (n=112) and discordant group LDL-C>NHDL-C (n=48). GRACE and TIMI scores, mortality and cardiovascular events (heart failure, non-fatal myocardial infarction and angina) at sixth month were compared between these three groups. Differences between these groups were analyzed with One-way ANOVA or Kruskal-Wallis rank test, and with chi-square for percentages. Also, post hoc LSD or Conover-Iman's non-parametric multiple comparison test were used. A p value <0.05 was accepted as statistically significant.

Results: TIMI risk score didn't differ between discordant or concordant groups. Mean GRACE (death) and GRACE (death and MI) scores were higher in group with LDL-C<NHDL-C than with LDL-C=NHDL-C and LDL-C>NHDL-C (p=0.029 and 0.008, respectively). Cardiovascular events and mortality at sixth month were not different among groups (p=0.473 and p=0.176, respectively).

Conclusion: GRACE score was higher in discordant group with LDL-C<NHDL-C, but there is no difference regarding TIMI scores between discordant and concordant groups in AMI patients.

Keywords: Atherosclerosis; Low Density Lipoprotein Receptor –Related Protein; Cholesteroç-HDL; Triglycerides; Cardiovascular Diseases/complications.

Introduction

Low-density lipoprotein-cholesterol (LDL-C) is the primary target of lipid lowering therapy to prevent atherosclerotic events.[1] However, despite the LDL-lowering therapy, some acute myocardial infarction (AMI) patients continue to have residual risk.[2]

Non-high-density lipoprotein-cholesterol (NHDL-C) is recommended as a secondary target for lipid management.[1] There is a growing body of evidence that NHDL-C is a better predictor of major cardiovascular events after AMI.[3] However, not all patients have concordant LDL-C and NHDL-C levels. It has been shown that discordance of LDL-C and NHDL-C either underestimates or overestimates coronary risk.[4]

The GRACE and TIMI risk scores are widely used models to assess patients prognosis after acute coronary

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syndromes.[5,6] They incorporate patient's characteristics, clinical and laboratory findings for risk stratification. In this study, we aimed to evaluate the relationship between discordance of LDL-C and NHDL-C and risk scores to find out whether the discordance of lipid parameters have impact on mortality after AMI.

Methods

This study assessed the data of 209 consecutive patients admitted to cardiology department with a diagnosis of acute myocardial infarction between January 2009 and June 2009. Among these, 11 patients were excluded because of incomplete data. Finally, we evaluated the data of 198 patients in our analysis. Exclusion criteria were as follows: age above 85 years old, clinical active infection, active malignancy, hematological or autoimmune disorders, receiving chemotherapy or steroids, cardiogenic shock, decompensated heart failure, arrhythmia with hemodynamic instability, and percutaneous coronary intervention or surgery within 30 days before admission. The assessed clinical parameters were age, gender and coronary risk factors. Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or current medication with antihypertensive drugs. Patients were defined as diabetic if they had been informed of this diagnosis before and had been using oral antidiabetic drugs or insulin treatment on admission. Body mass index was calculated as body weight in kilograms divided by the squared value of body height in meters (kg/m^2).

Type of acute coronary syndrome, admission blood pressure and heart rate, ST- segment changes in ECG, Killip classification or presence of cardiac arrest at admission, and ejection fraction were evaluated. GRACE and TIMI scores were calculated from the clinical history, electrocardiogram, and laboratory values collected on admission. TIMI risk score represents the sum of seven variables including age, >65 years, >3 risk factors for coronary artery disease, use of aspirin in the past 7 days, known coronary artery stenosis >50%, ≥ 2 episodes of angina within 24 hours, ST-segment deviation and elevated cardiac markers. One point is given to each of the variables present at the time of assessment. Higher risk score is correlated with increased incidence of death, myocardial infarction and revascularization. Grace score was calculated using GRACE 2.0 calculator at the time of admission by using the following variables: age, heart rate, systolic blood pressure, creatinine, cardiac arrest at admission, ST-segment deviation, elevated cardiac markers and Killip class. GRACE (death) represents in-hospital and 6-month mortality after a myocardial infarction and GRACE (death and MI) represents death or myocardial infarction from admission to six months after discharge. Also, in-hospital mortality and cardiovascular events at sixth month including angina, non-fatal myocardial infarction and heart failure were recorded. Data were obtained from patient files and hospital computer registry system. Also, 6-month mortality was assessed by contacting patients and their family with a telephone call.

The study was approved by the local Ethics Committee. Data from subjects were analyzed retrospectively.

Laboratory Measurements

Lipid measurements were performed on fasting blood samples that were taken before the angiography. Plasma concentrations of total cholesterol, LDL-C, HDL-C and triglyceride (TG) were measured with biochemistry analyzer (Abbott Architect c8000). The enzymatic colorimetric method was used for the quantitative determination of total cholesterol. Endpoint colorimetric method was used for the quantitative determination of HDL-C. Glycerol phosphate oxidase method was used for the quantitative determination of triglyceride. The Friedewald equation was used to calculate LDL-C.[7] NHDL-C was calculated as total cholesterol minus HDL-C.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD) for normal distributions and median (interquartile range) for skewed distributions. Categorical variables were defined as numbers and percentages. Whether the distribution of continuous variables was normal or not was determined by Kolmogorov-Smirnov test. Levene test was used for the evaluation of homogeneity of variances. Correlation between continuous variables including LDL-C and NHDL-C was examined with Spearman correlation analysis. Percentile distributions of LDL-C and NHDL-C were calculated. Discordance was determined based on the difference in the percentile of NHDL-C and percentile of LDL-C. Six percentile points was used as a cutoff so that the numbers of patients that would be classified as concordant or discordant were as close as possible. Patients were divided into 3 groups according to percentiles: Discordant group: LDL-C<NHDL-C

(n=38), concordant group: LDL-C=NHDL-C (n=112) and discordant group LDL-C>NHDL-C (n=48). Differences between baseline characteristics of patients across these groups were analyzed with One-way ANOVA for normally distributed variables, with Kruskal-Wallis rank test for not normally distributed variables, and with chi-square for percentages. When the p-value from One-Way ANOVA or Kruskal Wallis test statistics were statistically significant, post hoc LSD or Conover-Iman's non-parametric multiple comparison test were used to know which group differ from which others. A p value <0.05 was accepted as statistically significant. Data analyses were performed by using SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL, United States).

Results

The mean age of study population was 62.7±10.7 years and of the 198 patients 73.7% were males. More than half of the patients had hypertension, 30% had diabetes mellitus, 61% had any smoking history and 38% had dyslipidemia. Baseline characteristics are presented in Table 1. Fifty-one and a half percent of the patients had NSTEMI and 48.5% had STEMI. Mean difference between NHDL-C and LDL was 31.9±20.5 mg/dl. LDL-C levels were strongly and positively correlated with NHDL-C levels (r=0.858, p<0.001). In-hospital mortality rate was 2%. In 10 patients, death occurred during six months follow-up.

To further evaluate the characteristics of patients with discordance and concordance of LDL-C and NHDL-C, we classified patients into 3 subgroups according to percentiles: Discordant group: LDL-C<NHDL-C (n=38), concordant group: LDL-C=NHDL-C (n=112) and discordant group LDL-C>NHDL-C (n=48) (Figure 1). Gender, age, smoking history, percentage of patients with hypertension or percentage of patients with dyslipidemia were not different among the groups. Patients in the discordant group LDL-C<NHDL-C, had the highest prevalence of diabetes mellitus (p=0.013). Median TIMI score was not different among groups. Mean GRACE (death) score and GRACE (death and MI) score were highest in the discordant group LDL-C<NHDL-C than in the concordant group LDL-C=NHDL-C and the discordant group LDL-C>NHDL-C (p=0.029 and p=0.008, respectively) (Table 2). Cardiovascular events and mortality at sixth month were not different among groups (p=0.473 and p=0.176, respectively). Because of the small number of in-hospital deaths in each group, analysis of these subgroups regarding in-hospital mortality was not possible.

Discussion

In the present study, we assessed the cross-sectional association between LDL-C and NHDL-C discordance and Grace and TIMI scores. Median TIMI score was not different between discordant and concordant groups. Mean GRACE score was highest in the discordant group with LDL- C<NHDL-C.

Table 1 – Baseline characteristics of study population

Characteristics	
Clinical characteristics	
Gender (% male)	73.7
Age (years) (mean±standart deviation)	62.7±10.7
Smoking (%)	61.6
Hypertension (%)	60.6
Diabetes (%)	30.3
Dyslipidemia (%)	37.9
Body mass index (kg/m²) (mean±standart deviation)	26.8±4.1
Biochemical analysis (mean±standart deviation)	
Total cholesterol (mg/dl)	185.8±41.4
LDL-C (mg/dl)	116.7±33.3
HDL-C (mg/dl)	37.1±9.8
Triglyceride (mg/dl)	162.7±112.9
NHDL-C (mg/dl)	148.6±40.1
Fasting glucose (mg/dl) glucose(mg/dl)	116.6±42.1
Creatinine (mg/dl)	1.1±0.55
Risk scores (mean±standart deviation)	
Mean GRACE (death) score	110.2±29.2
Mean GRACE (death and MI) score	124.3±44.0
Median TIMI score (interquartile range)	3.0(2.0)

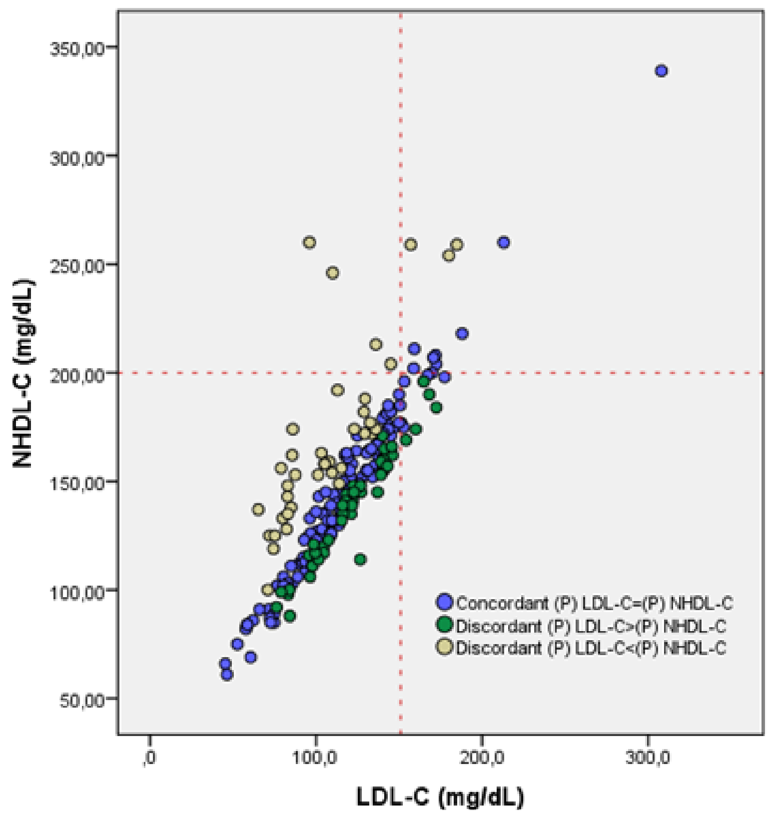

Figure 1 – Scatterplots and prevalence of discordance and concordance defined according to percentiles of LDL-C and NHDL-C.

It has been demonstrated that NHDL-C is a predictor of cardiovascular disease mortality in individuals free of cardiovascular disease.[8-10] Also, it is associated with mortality in patients with coronary heart disease.[11] However, the studies specifically evaluated its role on cardiovascular mortality after an index myocardial infarction were limited. In one study, it has been reported that NHDL-C >130 mg/dl during follow-up after a myocardial infarction was associated with higher risk of long-term major cardiovascular events (MACE).[3] Besides all-cause death, myocardial infarction, stroke and cardiovascular hospitalization were other components of MACE in that study.

LDL-C is the main target for lipid lowering therapy after myocardial infarction in daily clinical practice.[1] In a recent study, LDL-C was found to be independently associated with increased cardiovascular disease mortality in individuals free of cardiovascular disease in 27-year follow-up period.[12] It has also been demonstrated that LDL-C levels predict coronary heart disease mortality in men with preexisting cardiovascular disease.[13,14] However, studies evaluating LDL-C on prognosis after myocardial infarction have mixed results. In 2476 patients hospitalized for MI, small dense LDL was associated with low cardiovascular mortality.[15] In a study by Reddy et al. the lowest LDL-C levels were associated with highest risk of in-hospital mortality after myocardial infarction.[16]

Sizeable proportion of patients have discordant LDL-C and NHDL-C (high LDL-C and low NHDL-C, and vice versa). Discordance rate changes from 11% to 29% in previous studies.[4,17,18] It has been shown that discordance of LDL-C and NHDL-C either underestimates or overestimates coronary risk defined as non-fatal MI, percutaneous coronary intervention, coronary artery bypass grafting or coronary death.[4] It was suggested that the LDL-C alone may give a false sense of security with one fifth of the subjects still having high cardiovascular risk, despite having normal LDL-C levels.[19] Studies evaluating the impact of discordance of LDL-C and NHDL-C on coronary heart disease prognosis are limited and to the best of our knowledge, this is the first study to investigate the association between discordance of

Table 2 – Characteristics of patients with concordant and discordant LDL-C and NHDL-C

	LDL-C<NHDL-C n=38 (group 1)	LDL-C=NHDL-C n=112 (group 2)	LDL-C>NHDL-C n=48 (group 3)	p
Age (years) *	58.9±9.3	63.5±11.1	63.7±10.4	0.054
Gender (% male)^{β}	73.7	70.5	81.3	0.369
Smoking (%)^{β}	68.4	57.1	66.7	0.331
Hypertension (%)^{β}	60.5	64.3	52.1	0.351
Diabetes (%)^{β}	50.0	25.9	25.0	0.013 ^{a,b}
Dyslipidemia (%)^{β}	50.0	35.7	33.3	0.221
Body mass index (kg/m^2) *	27.9±6.2	26.2±4.5	25.1±4.1	0.376
Total cholesterol (mg/dl) *	200.8±40.5	182.8±44.7	180.9±30.8	0.044 ^{a,b}
LDL-C (mg/dl) ^{δ}	105.2(46.0)	115.7(46.8)	121.8(40.2)	0.053
HDL-C (mg/dl) ^{δ}	30.0(6.0)	35.0(9.0)	42.0(17.0)	<0,001^{a,b,c}
Triglyceride *	321.2±164.9	140.1±43.8	90.0±24.6	<0.001^{a,b,c}
NHDL-C (mg/dl) ^{δ}	158.5(37.0)	147.0(53.5)	141.0(42.5)	0.002 ^{a,b}
Mean GRACE (death) *** score *	114.5±29.5	98.7±22.1	112.0±30.3	0.029 ^{a,b}
Mean GRACE (death and MI) **score ^{δ}	133.4±41.5	104.3±31.1	127.0±46.9	0.008 ^{a,b}
TIMI risk score ^{δ}	3.0(2.0)	3.0(2.0)	3.0(2.0)	0.925
In-hospital mortality (%)	1(2.6)	2(1.8)	1(2.1)	-----
Mortality at sixth month(%)^{β}	5.7	5,7	4.4	0.176
Cardiovascular events at sixth month (%)^{β}	11.2	18.4	19.6	0.473

*Data are expressed as mean±standard deviation or median(interquartile range) for continuous variables and number (percentage) for categorical variables; *: One Way Anova,* **δ**: *Kruskal Wallis, β:Chi-square. LSD or Conover-Iman test was performed for the binary comparisons among the groups and the p value was set at 0.05. Significant differences were found between a: group 1 vs group 2, b: group 1 vs group 3, c: group 2 vs group 3. Statistically significant p-values are in bold.*

LDL-C and NHDL-C and widely used prognostic risk scores in MI patients.

Patients with AMI are heterogeneous in terms of clinical presentation, risk factors and prognosis. Identifying patients at higher risk for recurrent cardiovascular events and death after AMI is important to manage cardiovascular care. GRACE and TIMI risk scores are the most widely used risk scores for prediction of prognosis in AMI. In a study by Guler et al.,[20] lipoprotein(a) levels were higher in the group of patients with high GRACE score than in the group with intermediate or low GRACE score, and lipoprotein(a) was found to have an additional prognostic value over GRACE score in predicting one-year adverse outcomes in NSTEMI patients.[20] In the present study, we found that GRACE score is highest in the group with LDL-C<NHDL-C compared to groups with LDL-C=NHDL-C and LDL-C>NHDL-C. One of the reasons for low LDL-C and high NHDL-C is the amount of remnant cholesterol and lipoprotein(a) in plasma. Increased remnant cholesterol is associated with increased incident coronary heart disease and all cause mortality in general population.[21,22] It is also associated with increased all-cause mortality in patients with ischemic heart disease.[23] On the contrary, in a study with AMI patients, remnant cholesterol was found to be associated with low mortality.[24] In our study, we didn't have data on patients' lipoprotein(a) levels and directly measured remnant cholesterol. However, TG was highest in the group with LDL-C<NHDL-C and TG is marker of remnant cholesterol.[25] Remnant cholesterol such as VLDL and IDL, as well as lipoprotein(a), is also atherogenic and associated with inflammation.[26,27] Increased atherogenicity and increased inflammation may be related to high GRACE score in discordant group with increased remnant cholesterol. In a recent trial, lowering TG provides additional mortality benefit in patients with cardiovascular disease and using statin.[28]

Study Limitations

This study has several limitations. It is a retrospective study and there is the possibility of bias from unmeasured cofounders. There is no absolute definition and standard cut-off values for the discordance of LDL-C and NHDL-C. Other limitations include small sample size and short duration follow up. Further large-scale prospective studies will be required to validate our results.

Conclusion

GRACE score was higher in discordant group with LDL-C<NHDL-C, but there is no difference regarding TIMI scores between discordant and concordant groups. Risk stratification in AMI is mandatory to guide its management and patients with discordant LDL-C and NHDL-C may represent a group with poor prognosis. Individuals with AMI and discordance may be the target of the most aggressive pharmaceutical interventions.

Author Contributions

Conception and design of the research: Eren M, Kurmus O. Acquisition of data: Eren M, Aslan T, Akbuga K, Tolunay H. Analysis and interpretation of the data: Eren M, Kurmus O, Aslan T, Akbuga K, Tolunay H. Statistical analysis: Eren M, Kurmus O. Writing of the manuscript: Eren M, Kurmus O. Critical revision of the manuscript for intellectual content: Kurmus O, Aslan T, Akbuga K, Tolunay H.

Potential Conflict of Interest

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

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Study Association

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

Ethics Approval and Consent to Participate

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

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ORIGINAL ARTICLE

How much do the Patients with Acute Myocardial Infarction Know about Chest Pain, Thrombolytic Therapy, and Other Factors Affecting the Treatment Time in the Emergency Room?

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Abstract

Background: Treatment time in the emergency room for acute myocardial infarction is very important and can be life-saving if one understands the importance of a patient's chest pain.

Objetice: The aim of this study is to evaluate how much patients entering the emergency room due to acute myocardial infection (AMI) know about chest pain and thrombolytic therapy .

Materials and Methods: One hundred fifty patients (126 males,14 females) from three different institutes with complaints of chest pain were randomly chosen to participate in this study. The mean age of the patients was 55.4 ± 11.2 years (71+33). Patients were asked to fill out a questionnaire consisting of 70 questions within the first seven days. All differences in categorical variables were computed using the $\chi 2$-test and Fisher Exact test. A two-tailed hypothesis was used in all statistical evaluations, and $p<0.05$ was considered significant.

Results: It was observed that 17% of the patients came to the hospital within the first 30 minutes; 18.3% of them came to the hospital between 30 minutes and 1 hour; 27.5% of them came to the hospital between 1 hour and 3 hours; and 21.4% of them came to the hospital more than 6 hours after symptoms began. It was also observed that 68% of the patients were not aware of the AMI, and 96% of them had no prior knowledge of antithrombolytic therapy.

Conclusion: Because the majority of the patients did not have enough information about AMI, a training program should be implemented to ensure that people to come to the hospital earlier.

Keywords: Coronary Artery Disease; Myocardial Infarction; Chest Pain; Emergency Medical Services; Thrombolytic Therapy.

Introduction

Coronary artery disease is the leading cause of death for men and women in Turkey and worldwide. In our country, acute coronary syndrome and acute myocardial infarction (AMI) cause approximately 32% of all yearly mortality .[1] Coronary Artery Disease can manifest itself in the form of cardiac arrest, angina pectoris, or AMI.[2]

Recent research has shown that 25-50% of the patients with AMI come to the hospital more than six hours after symptoms begin.[3] Some reasons that patients may delay coming to the hospital are a lower level of education and awareness, concern about causing other people to panic, not recognizing the symptoms, not accepting the disease, an attempt to avoid hospital costs, fear of the hospital, or

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the patient's own self-treatment.[4,5] If it is recognized that the symptoms are related to AMI, the time it takes to be admitted to the hospital is diminished .[6,7]

Thrombolytic therapy for AMI is one of the most important developments in cardiology. When thrombolytic therapy is used as early as possible, the efficiency of the therapy is maximized, the infarct area is reduced, and the left ventricular function will be optimally protected.[8] The thrombolytic therapy administered in response to AMI results in a 25-50% decrease in mortality when administered in conjunction with conventional therapy.[9-15] Weaver et al.,[16] have reported that the time to arrival at the hospital for patients in developed countries is four hours. Nevertheless, the public should be aware of the importance of coming to the hospital as soon as possible after the appearance of symptoms. However, these days, this can be achieved for 1/3 patients with a recommendation for thrombolytic therapy, even in developed countries with good health organizations. Public health efforts are needed to increase the recognition of the major heart attack symptoms in both the general public and groups at high risk for an acute cardiac event, especially in socioeconomically disadvantaged subgroups, including people with low levels of education, low household incomes, and no health insurance coverage.[17]

The objective of this study is to investigate how much the patients coming to the hospital with a diagnosis of AMI know about Coronary Artery Disease, Coronary Artery Disease therapy, AMI, thrombolytic therapy, and the importance of coming to the hospital upon recognizing the first sign of symptoms.

Materials and Methods

One hundred and fifty patients, including 70 patients from the İstanbul University Cardiology Institute, 42 patients from Istanbul University Cerrahpasa Medical Faculty, and 38 patients from Şişli Etfal Hospital, were randomly chosen to be included in this study. Randomization is performed by the free web based system at: http://www.tufts.edu/~gdallal/PLAN.HTM. All patients complained of chest pain and were diagnosed with AMI. The mean age of the patients was 55.4 ± 11.2 years. This study used a convenience sampling size, and patients were chosen at random.

Patients were interviewed within the first seven days of hospitalization and asked to fill out a questionnaire consisting of 70 questions. The questions contained within the questionnaire were chosen to evaluate the patients' level of education, the symptoms that led the patients to come to the hospital, the time of onset of these symptoms, the patients' reactions to the symptoms, and the time that the patients took to arrive at the hospital. The patients who reported having no complaints within 48 hours after filling out the questionnaire were considered to be patients with no symptoms. The location of the AMI, presentation, and clinical outcomes of the patients were also evaluated.

Statistical Analysis

Statistical analysis was performed using SPSS (SPSS for Windows, SPSS Inc, Chicago, IL) 15.0 program package. The Shapiro-Wilk test was used for the analysis of compliance with the normal distribution. Continuous variables are presented as mean ± standard deviation. Categorical variables are presented as frequencies and percentage. All differences in categorical variables were computed with the x^2 test and Fisher Exact test. A two-tailed hypothesis was used in all statistical evaluations, and $p<0.05$ was considered significant.

Results

Seventy-five of the patients (49.9%) included in this study presented prior AMI; 43 of the patients (28.7%) reported inferior AMI; 13 of the patients (8.7%) had non-Q wave MI; and 19 of the patients (12.7%) presented AMI in other regions. Nineteen of this study's patients (12.6%) had experienced at least two AMIs, 17 of whom (89.5%) were male.

One hundred and forty-four of the patients complained of chest pain (retrosternal, spreading to the chest or to the precordial region, not responsive to nitrate, and continuing for more than 30 minutes); two of the patients complained of pain in the arms; three of the patients complained of abdominal pain; and one of the patients came to the hospital with other complaints. Fifty-six percent of the patients described their pain as a pressing type; 28% of the patients described their pain as a stinging type; and 16% of the patients described their pain as a burning type (Table-1).

Ninety-three percent of the patients had experienced prior chest pain. No significant differences were observed between the patients who reported prior chest pain and those who did not in terms of gender, education, and income level.

Table 1 – The Features of Chest Pain in Patients

Type of Chest Pain			
	Pressing type		84 (56%)
	Burning Type		24 (16%)
	Drilling Type		42 (28%)
Localization of Chest Pain:	Retrosternal		84 (56%)
	Precordial		24 (16%)
	Diffuse		36 (24%)
	Other		6 (4%)
		Pain in arms	2
		Abdominal Pain	3
		Other	1
	Office (Job)		14 (9.3%)
	Home		114 (76%)
Place where the symptoms begun:	Medical Institution		3 (2%)
	Car		1 (0.7%)
	Other		18 (12%)
Activity while symptoms were occurring:	Effort		96 (64%)
	Rest		54 (36%)

A majority of patients, 76.7%, had no information about chest pain and its causes, while 22% of the patients received information from their physicians and 1.3% of the patients received information from other people. The percentage of patients who were aware of the relationship between chest pain and the heart was 51.3% (mean age= 57.3±9.2 years), while the percentage of patients who were unaware of this relationship was 48.7% (mean age= 53.3±3.6 years). A significant difference in age was observed between the two groups (*p=0.021*). No significant difference was found in terms of gender, level of education, and economic situation. Nevertheless, the first degree relatives of the patients who were aware of the relationship between chest pain and the heart had more ischemic heart disease. It was determined that 68% of the patients had no information about AMI. The level of education and economic situation of the patients who had information about heart attacks was significantly higher than those patients who had no information about heart attacks (*p=0.001* vs. *p<0.01*, respectively). Of the patients who had information about heart attacks, 41.6% received the information from other people, while 29.12% received the information from their physician (Table-2). Of the patients who had had AMI twice, 84.2% claimed that they were informed in the hospital or by the physician, and 15.8% claimed that they were not informed again.

When evaluating the initial behavior of the patients at the onset of chest pain, 70.9% of the patients who had not had chest pain before preferred to rest, while only 34.4% of the patients who had had chest pain before preferred to rest (p<0.01). It should be noted that the patients who had not had chest pain before were not taking aspirin, while 6.45% of the patients who had chest pain before were taking aspirin (p=0.05). Of the patients who had not had chest pain before, 1.81% first took Isordil 5 mg SL, whereas 21.5% of the patients who had had chest pain before first took Isordil 5 mg SL (*p<0.001)* (Table-3).

It was found that 58.1% of the patients who had chest pain after taking precautions came to the hospital, while only 9% of the patients who had no chest pain after taking precautions came to the hospital (*p<0.0001).* Twenty percent of those who had had chest pain before came to the hospital if the chest pain did not subside after

Table 2 – The knowledge level of the patients and their sources of information

No information	102 (68%)
Media	9 (18.75%)
Books	2 (4.16%)
Physicians	14 (29.16%)
Other people	20 (41.66%)
Media + Other people	3 (6.25%)

Table 3 – The initial behaviors exhibited by the patients at the onset of chest pain

Type of Chest Pain	No Chest Pain Experienced before (n=55)	Chest Pain Experienced before (n=95)	p-value
Rest	39 (70.90%)	32 (34.40%)	< 0.01†
Come to hospital	10 (18.80%)	12 (12.90%)	0.6†
Taking aspirin	0	6 (6.45%)	N/A
Taking Isordil SL (5 mg)	1 (1.81%)	20 (21.50%)	< 0.001†
Taking antihypertensives	0	3 (3.22%)	N/A
Taking analgesics/anti-inflammatory drugs	4 (7.27%)	8 (8.60%)	0.4*
Call his/her MD	1 (1.81%)	8 (8.60%)	0.7†
Return home	2 (3.63%)	4 (4.30%)	0.8†

(χ^2-test and †Fisher Exact Test)*

taking Isordil 5 mg SL, while 3.6% of those who had not experienced chest pain before came to the hospital if the chest pain did not subside after taking Isordil 5 mg SL (*p=0.006*). There was no significant difference in gender, job, level of education, and economic situation between those patients who used SL nitrate and those that did not. The mean age of those who used nitrate was higher (Table-4).

It was determined that 17% of the patients who were experiencing a first time AMI came to the hospital within the first 30 minutes after the onset of symptoms; 18.3% of them came between 30 minutes and 1 hour after the onset of symptoms; 27.5% of them came between 1 hour and 3 hours after the onset of symptoms; 15.3% of them came between 3 hours and 6 hours after the onset of symptoms; and 21.4% of them came more than 6 hours after the onset of symptoms. For the patients experiencing AMI for the second time, 21% came to the hospital in the first 30 minutes, 15.8% came to the hospital between 30 minutes and 1 hour after the onset of symptoms; 26.3% came to the hospital between 1 hour and 3 hours after the onset of symptoms; 15.8% came to the hospital between 3 hours and 6 hours after the onset of symptoms; and 11% came to the hospital more than 6 hours after the onset of symptoms (Table-5) (Graph 1). No significant differences were observed in the time it took to arrive at the hospital in terms of age, gender, level of education, hospital admittance, and whether the patient had experienced chest pain previously. The length of time it took to arrive at the hospital from home was determined to be 30 minutes. Most of the patients (86%) did not come to the hospital by ambulance. The percentage of patients who arrived at the hospital by ambulance was 5.3%.

Table 4 – The knowledge level of patients who have experienced chest pain and those who have not experienced chest pain regarding coming to the hospital, using SL Nitrate, and thrombolytic therapy

Type of Chest Pain	No Chest Pain Experienced before (n=55)	Chest Pain Experienced before (n=95)	p-value
Come to the hospital	54 (58.10%)	54 (58.10%)	< 0.0001*
Come to the hospital if the pain does not disappear	2 (3.60%)	19 (20.00%)	0.006†
Informed about thrombolytic therapy	0	6 (6.45%)	N/A

Table 5 – The amount of time it took patients to arrive at the hospital after the start of chest pain

	First AMI (n=131)	Second AMI (n=19)
First 30 minutes	23 (17.6%)	4 (21.0%)
30 min- 1 hour	24 (18.3%)	3 (15.8%)
1-3 hours	36 (27.5%)	5 (26.3%)
3-6 hours	20 (15.3%)	3 (15.8%)
6-10 hours	8 (6.1%)	2 (10.5%)
10-12 hours	20 (15.3%)	2 (10.5%)

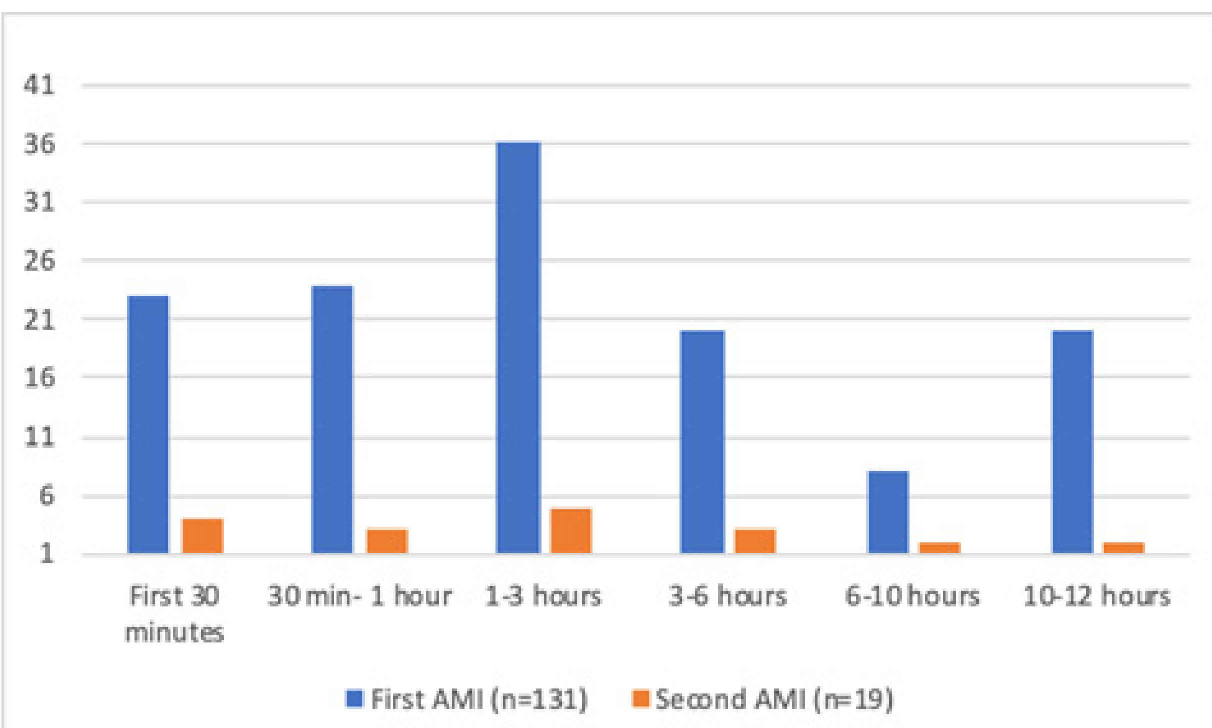

Figure 1 – The amount of time it took patients to arrive at the hospital after the start of chest pain

It was observed that all of the patients thought that it was necessary to come to the hospital if they experienced pain reminiscent of a heart attack. However, 96% of the patients had no information about antithrombolytic therapy. It was found that antithrombolytic therapy was administered to only 52 of the 150 patients in this study (34.6%). Of the patients hospitalized due to AMI, 78.7% were not informed about their status and the therapy that was applied during hospitalization.

Discussion

Chest pain is a major symptom of AMI. Chest pain is most commonly experienced as retrosternal pain which spreads to the chest wall, neck, and the right and left arms. The pain is usually of a pressing type and may be accompanied by nausea and dyspnea.

In this study, 96% of the patients had chest pain. The localization of the pain was retrosternal for 58% of the patients and precordial for 32% of the patients. Pain was described as a pressing type for 56% of the patients, a pricking type for 28% of the patients, and a burning type for 16% of the patients. In a study by Zerwic et al., the authors reported that the percent of patients experiencing chest pain was 99.8%, that the localization of the chest pain was retrosternal for 97.5% of patients, and that 93% of the patients described the pain as a pressing type.[18]

In 76% of our patients, it was observed that the symptoms began at home. It was also observed that 64% of the patients were doing exercise when the symptoms began. These results are similar to the findings of Dracup et al.,[5] and Ashton.[19]

In 62% of the patients, chest pain was reported. It was observed that 51.3% of the patients were aware of the relationship between the experience of chest pain and the occurrence of Coronary Artery Disease. The mean age of the patients who were aware of this relationship was significantly higher than those who were not aware of this relationship. The increase in ischemic heart disease with age could explain this observation. Additionally, in the REACT study .[20], the knowledge level of elderly patients was higher than that of middle-aged patients. In our study, no differences were found between the knowledge level, economic situation, jobs, or gender of the patients with ischemic heart disease. In the REACT study, no differences were found between the knowledge level and gender of the patients, whereas a strong correlation was found between the level of education, and the economic situation of the patients. In the present study, it was observed that people who had first degree relatives with ischemic heart disease were well informed about chest pain. This evidence suggests that the patient's experiences in the first and second degree are effective in educating people. Similar results were found in the REACT study.[20] It was found that more than half of the patients did not know that chest pain may originate from the heart. Those who were aware of the relationship between chest pain and the heart were patients who had previously visited a medical doctor (MD) for the same complaint (22%). They were informed by the MD directly, while other medical staff did not inform them. This illustrates that the medical staff does not properly educate at-risk patients. Moreover, visual and printed media did not contribute to informing the patient.

The present study found that only 40% of the patients with complaints of chest pain – including those experiencing AMI for the second time – had visited any health institution. For an efficient therapy, the awareness of the patient as to the symptoms of a heart attack and informing the patient about the importance of coming to the hospital as soon as possible are very important. Our study also determined that the majority of patients prefer to rest initially when the chest pain first begins. Other behaviors preferred by the patients at varying frequencies were as follows: coming to the hospital, sublingual administration of Isordil 5 mg, administration of analgesics and/or anti-inflammatory drugs, contacting the patient's physician, returning home if the patient had been away from home, taking aspirin, or taking antihypertensives. Patients who had experienced chest pain before preferred to take Isordil 5 mg SL initially and then take aspirin. Patients who had not experienced chest pain before preferred to rest. Of the patients who came to the hospital first, 58.1% reported prior chest pain. The percentage of patients who had not experienced prior chest pain and decided to come to the hospital was 9%. A significant difference was found between these two groups.

The present study determined that 20% of the patients who had chest pain and 36% of the patients who had no chest pain came to the hospital if the chest pain did not subside with the sublingual administration of Isordil 5 mg. Of the patients experiencing AMI for the second time, 57.9% came to the hospital without taking sublingual Isordil 5 mg, while 26.3% came to the hospital if the chest pain had not subsided after taking one dose of Isordil 5 mg. The mean age of the patients who were using Isordil 5 mg was significantly higher than that of the patients who were not using Isordil 5 mg. No differences were found between the groups in terms of gender, level of education, and economic situation. Because ischemic heart disease is predominantly found in elderly people, they are generally well informed about this disease. The delay in the time it takes patients get to the hospital generally stems from a wrongful evaluation the heart, failure to take the symptoms into account, the cost of visiting the hospital, anxiety experienced by the patients, and attempts of self-treatment by the patients themselves. To improve this situation, efforts should be focused on educating the patients directly. Patients are more informed about heart attacks as compared to what they know about the relationship between chest pain and the heart. It was determined that first degree relatives, other people living around the patients, medical staff, and the media play important roles in informing the patients. People who were well informed about heart attacks were well educated and had higher economic situations.

In many studies, most of the patients stated that chest pain was their major symptom; however, they interpreted this incorrectly, Dracup et al.,[5] [21,22] found that patients evaluated heart attack symptoms and chest pain as being related to GIS pain, muscle pain, fatigue, and respiratory infection. Despite the fact that most patients are aware of the classic symptoms, they do not know how to distinguish the appearance of these symptoms from other ailments, they think that heart attacks should appear with violent pain, and they have a severe lack of awareness. It should be explained to the patients that heart attack symptoms can develop slowly, that symptoms may not be continuous, and that symptoms may vary among individuals. The patient's family should be informed at the same time.

The amount of time between the onset of symptoms and the arrival at the hospital wasn on average, 1-3 hours for both patients who were experiencing AMI for the first time and for patients who were experiencing AMI for the second time. The average time spent in route to the hospital was 30 minutes, and 86% of the patients came to the hospital in privately owned vehicles. Meischke et al. ,[23] found that the average duration of time from the onset of symptoms until the arrival at the hospital was 2 hours, and the percentage of people coming to the hospital by means other than an ambulance was 45%. Mumford et al.,[4] determined that the average time spent before coming to the hospital was 172 minutes (approximately 3 hours). Even though the average time spent before coming to the hospital was similar to that of other studies, patients in our study exhibited a preference for the use of their own private vehicles. This result is because the patients do not realize the significance of their symptoms, and they think that it will be easier and quicker to reach the hospital in their own vehicles. No significant correlation was observed between the time it took to arrive at the hospital and age, level of education, or economic situation. In other studies, the length of time to arrival at the hospital was lower in females when compared to males, in elderly people when compared to younger people, and in people of higher socioeconomic status when compared to people of lower socioeconomic status. Moreover, patients who know the relationship of chest pain with the heart, who are informed about thrombolytic therapy, who have a higher level of education, and who smoke arrived at the hospital more quickly (5,19,20,24,25). Mumford et al.,[4] determined that there was no association between the time it took to arrive at the hospital with age, gender, socioeconomic status, marriage, level of education, being informed about chest pain and ischemic heart disease, family history, where the patient was when symptoms developed, when the symptoms developed, distance to the hospital, where the hospital was located, or the severity of the symptoms.[4]

Thrombolytic therapy is the one of the most important developments that has occurred in the last 20 years in the field of cardiology. As a result of this therapy, not only has the mortality due to AMI encountered in hospitals decreased by 20-25%, but this therapy also prevents impairment of myocardial perfusion and remodeling by ensuring the continuity of blood vessels.[6-15] In the GISSI study, it was shown that mortality was decreased by 47% when streptokinase was administered within the first hour following the onset of symptoms, 23% when administered within 1-3 hours, and 17% when administered within 3-6 hours. Weaver et al. determined that the average time until arrival at the hospital was 4 hours even in developed countries.[16] The reasons that reperfusion therapy in AMI patients is not begun earlier was determined to be the patients' failure to realize the significance of the symptoms, the length of time until the patient arrived at the hospital, and the time spent from the evaluation of the patient until the beginning of the reperfusion therapy.[16]

It was observed that 96% of the patients included in our study had no prior knowledge of thrombolytic therapy. Thrombolytic therapy was administered to 34.6% of these patients. The patients' understanding of the vital importance of thrombolytic therapy plays an important role in ensuring that patients come to the hospital more quickly. Therefore, patients need to be informed about thrombolytic therapy.

As a result, it is important that the patients have information about heart attacks, chest pain, and thrombolytic therapy. Arrival at the hospital as soon as possible after the onset of symptoms is crucial, especially for both anti-ischemic therapy and efficient thrombolytic therapy, which should be administered as quickly as possible. The present study observed that, because the majority of our patients were unfamiliar with thrombolytic therapy, they spent precious time attempting self-treatment. A small subset of patients showed a preference for using an ambulance to arrive at the hospital. Since ambulances are likely to be the quickest way to reach the hospital, patients must be encouraged to use them.

Limitations

In this study our sample included only 3 hospitals in Turkey, and therefore may not be representative of the entire population that came to hospital with chest pain. On the other hand, this study does include patients that came to hospital with chest pain. Nevertheless, further study on healthy subjects in this population is warranted.

Conclusion

Arranging training programs to educate patients will be useful. Considering the effects of the media, it may be useful to request that the media contribute to campaigns and to ensure that the media properly informs patients.[24] Considering the effects of the people in direct contact with the patients, it will be helpful to include the families of the patients and the people around them in any implemented training programs.[25] This will aid patients in making informed decisions and will be more likely for patients to come to the hospital as soon as possible when it is necessary to do so.

Author Contributions

Conception and design: Ozmen B, Okcun B, Yigit Z. Acquisition of data: Ozmen B, Conkbayir C, Hural R, Okcun B, Yiğit Z. Analysis and interpretation of the data: Ozmen B, Conkbayir C, Hural R, Oztas DM, Ugurlucan M, Okcun B, Yiğit Z. Writing of the manuscript: Ozmen B, Conkbayir C, Hural R, Okcun B, Yiğit Z. Critical revision of the manuscript for intellectual content: Ozmen B, Conkbayir C, Hural R, Oztas DM, Ugurlucan M, Okcun B, Yiğit Z.

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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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REVIEW ARTICLE

Kawasaki-Like Disease, a New Phenotype in Sars-CoV-2?

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Abstract

The coronavirus disease (COVID-19), that assumed pandemic proportions in March 2020, mainly affects the respiratory tract, causing severe interstitial pneumonia in adults. Worldwide data indicate that COVID-19 tends to be more benign in children, which is evidenced by a high incidence of asymptomatic or mild upper airways' infection cases in this population. However, recent studies have been associating Kawasaki-like symptoms as a nonclassical presentation of coronavirus disease in pediatrics. It is suggested that the intense cytokine cascade, promoted by the SARS-CoV-2 infection, can trigger a multisystem inflammatory response as an atypical Kawasaki form in genetically predisposed individuals. In this context, patients may develop more severe clinical features with a greater predisposition to myocardial involvement, Macrophage Activation Syndrome, and Kawasaki Disease Shock Syndrome. Despite critical conditions, patients usually respond to conventional treatment of Kawasaki Disease with intravenous immunoglobulin. This article intends to provide an approach to the association between Kawasaki-Like Syndrome and COVID-19.

Background

The Sars-CoV-2 virus was initially isolated in the city of Wuhan, China, during a pneumonia outbreak of unknown cause in December 2019, a disease then named COVID-19. Due to its progressive worldwide spread, the World Health Organization decreed, three months later, the state of pandemic.[1] Sars-CoV-2 usually affects the respiratory tract, causing severe interstitial pneumonia in adults. In children, however, it tends to be more benign, manifesting asymptomatically or as a mild infection of upper airways. A systematic review that assessed a 12-case series of children from China found that 39%–82% of the patients with COVID-19 developed a moderate course of the disease.[2] A minority of pediatric cases presented severity, with respiratory failure, shock, coagulation dysfunction, and renal injury.[3,4] Data from many countries indicate that the rate of Sars-CoV-2 infection in the population under 18 is low, ranging from 1%–2%. Among the cases, the occurrence of unfavorable outcomes is even rarer. A cohort study by DeBiasi et al.,[5] with 177 young patients diagnosed with coronavirus disease found that 44 (24.8%) patients needed hospitalization, among these, only 9 (2.8%) were critically ill.[5] Interestingly, one of them developed hypotension and myocardial depression associated with signs of hyperinflammatory state, a Kawasaki-like presentation. Despite being an unusual manifestation, the increase in the number of reported associations between Kawasaki Disease (KD) and COVID-19 in children raises new concerns about its consequences.[5, 6]

Keywords

COVID-19; Betacoronavirus; Pandemics; Mucocutaneous Lymph Node Syndrome; Respiratory System/complications; Phenotype.

Search Methods: In order to develop a nonsystematic narrative review, we executed literature searches in multiple databases (Google Scholar, PubMed, SciELO, and Medscape) with no time restriction for articles published in English. Search terms included the keywords: "Sars-CoV-2", "COVID-19", "Kawasaki-like", "MIS-C", "PIMS-TS" and "Autoimmune disease". We emphasized in case reports, clinical trials, systematic and nonsystematic reviews, and guidelines aiming to

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provide an overview of the main aspects of Kawasaki-like syndrome following Sars-CoV-2 infection.

Discussion

Definition

KD is a rare systemic medium-vessel acute vasculitis of the childhood of undefined etiology. It usually has a predilection for coronary arteries and its main complication is the formation of aneurysms. The disease typically occurs in children between 5 months and 5 years of age and is more incident in Asian descendants. According to the American Heart Association (AHA), its diagnosis involves persistent fever associated with five other criteria: oral mucosal changes, bilateral nonexudative conjunctivitis, exanthematous rash, flaking of hands and feet, and cervical lymphadenopathy. [7] Among its laboratory findings, anemia, leukocytosis, and thrombocytosis can be detected from the 7th day of fever, in addition to hypoalbuminemia and increased transaminases. Other complementary exams, such as echocardiography, can demonstrate coronary aneurysms or cardiac dysfunction (left ventricular function depression, mitral valve regurgitation or pericardial effusion). [3] New studies suggest a potential correlation between infectious agents, like Sars-CoV-2, and the inflammatory cascade that results in KD.[3] The first report of KD in a patient with COVID-19 was a 6-month-old female child who manifested fever, tachycardia, signs of respiratory distress, persistent polymorphic maculopapular rash and sparing conjunctivitis, with no echocardiogram alterations. She was treated with intravenous immunoglobulin (IVIG) and high-dose aspirin, achieving clinical resolution.[4] Since then, numerous cases associating both diseases have been related. A publication by the Royal College of Paediatrics (2020) proposed that this presentation be called "Pediatric Inflammatory Multisystem Syndrome Temporally Associated with Sars-CoV-2" (PIMS-TS).[8] The US Center for Disease Control [9] has assigned the name “Multisystem Inflammatory Syndrome in Children” (MIS-C) for the same condition.[9] According to them, clinical aspects of PIMS-TS/MIS-C may be similar to an atypical KD, including prolonged fever, skin rash, high levels of inflammatory biomarkers, lymphadenopathy, gastrointestinal symptoms, and multiple organ dysfunction.[8,9]

Epidemiology

A retrospective cohort study conducted by Verdoni et al.[3] in Bergamo, Italy, between 2015 and April 2020, found a 30 times higher monthly incidence of KD symptoms during the coronavirus disease outbreak when compared to previous years. In terms of epidemiology, Asian children are more likely to have the typical form of KD. However, the Kawasaki-like syndrome associated with SARS-COV-2 infection seems to affect Afro-Caribbean descent more often than expected. In a cohort study by Riphagen et al.[10], carried out in a pediatric population diagnosed with coronavirus disease in the United Kingdom, six children (75%) had Afro-Caribbean origin, which may suggest a genetic susceptibility or a higher rate of COVID-19 in this offspring.[10]

Pathogenesis

Concerning tissue damage in COVID-19, PIMS-TS/MIS-C appears to be mostly mediated by the host innate immunity. The “cytokine storm” provided by Sars-CoV-2 infection, that is similar to macrophage activation in viral-induced hemophagocytic lymphohistiocytosis and resembles Macrophage Activation Syndrome (MAS) in KD, might be a trigger to Kawasaki-like response, regarding the hypothesis of KD deriving from an aberrant immune response to a pathogen in genetically predisposed individuals.[3] It is suggested that its mechanism is based on a post-inflammatory antibody-mediated reaction, therefore, the identification of viral replication has not proved to be truly relevant in these cases.[6]

Clinical Aspects

Compared to classic KD, PIMS-TS/MIS-C presents a later onset, with an average of 9 versus 3 years of age. Moreover, fever and asthenia are prevalent related features in this context.[9,11] Kawasaki-like syndrome associated with Sars-CoV-2 also comprises increased incidence of gastrointestinal manifestations, including abdominal pain, mesenteric lymphadenopathy, vomiting, diarrhea or even acute abdomen, demanding surgery.[9,12] In the study of Bergamo, by Verdoni et al.,[3] patients who had Kawasaki disease presentations during the COVID-19 pandemic had more leucopenia with marked lymphopenia, thrombocytopenia, increased ferritin, and abnormalities in the echocardiogram, than KD cases from previous years.[3]

Along with a higher occurrence of MAS and Kawasaki Disease Shock Syndrome (KDSS), myocardial injury has also been more frequent in PIMS-TS/MIS-C.[9,13] Another divergence from typical KD is that patients with MIS-C often have low blood pressure due to reduced left ventricular systolic function.[9] An analysis of 35 children with MIS-C by Belhadjer and colleagues (2020), detected an important reduction in ventricular ejection in 1/3, and the presence of coronary artery dilation in 17%. In addition, 80% of these patients needed inotropic support. In the same study, the presence of the "cytokine storm" was evidenced in all children by the high levels of C-reactive protein, Interleukin-6, and D-dimer, indicating macrophage activation.[9] Although aneurysms have been less observed than in previous cases of KD, it is worth mentioning that this is a possible late complication and must be investigated in follow-up evaluations.[9]

Diagnosis

Sars-CoV-2 infection can be detected by nasopharyngeal and oropharyngeal PCR swab in the first 5-7 days of disease, and from the 10th to 15th day of symptoms, qualitative antibody tests (IgM and IgG) can be performed.[3] According to the pathophysiology of PIMS-TS/MIS-C, based on an exacerbated inflammatory reaction mediated by immunoglobulins, diagnosis is best established by serology, rather than RT-PCR, which was also demonstrated by 8 out of 10 patients with Kawasaki-like Syndrome studied by Verdoni et al. (2020), who had positive antibodies against Sars-CoV-2, IgG, IgM or both.[3] It is important to note that not all antibody tests for coronavirus are highly accurate. False negative results are frequently obtained in low sensitivity tests, and false positives for Sars-CoV-2 IgG can occur due to a cross reactivity of other preexisting immunoglobulins, especially in patients with disorders of hyperinflammatory state, such as KD.[12]

Treatment

In order to control the exacerbated immune response, and based on the standard treatment for KD, IVIG has been used as the main therapy for PIMS-TS/MIS-C. Its exact mechanism is still not well understood, but it presumably works by reducing the action of monocytes, macrophages and other inflammatory cells, preventing the progression of myocardial damage. Positive outcomes have been established in several studies. Belhadjer et al.[9] , for example, detected restored ventricular function in 25 of the 35 MIS-C patients treated with immunoglobulins.[9] Other supportive treatments include antibiotics, anticoagulants, corticosteroids, like methylprednisolone, and anti-inflammatories, such as aspirin, which can be used concomitantly with IVIG to reduce the risk of immunoglobulin resistance, especially in MAS and KDSS.[3,9,13] For cases unresponsive to IVIG, anti-interleukin 1 and anti-interleukin 6 immunomodulators, like Anakinra and Tocilizumab, are therapeutic options.[14] Most of the children achieve clinical improvement quickly, on average in 4 days, but more critical cases may require longer hospitalization with mechanical ventilation, administration of vasopressors, or extracorporeal circulation.[10,13]

Conclusion

The clinical spectrum of COVID-19 in pediatrics is not clearly defined. However, new studies indicate that children may experience an acute cardiac decompensation related to the inflammatory response that follows Sars-CoV-2 infection. Its potential Kawasaki-like presentation evidences the heterogeneity of clinical manifestations and the need to test patients with non-classic symptoms.[4] Reports of complete recovery of cardiac function due to immunoglobulin therapy support the importance of early diagnosis and treatment.[7,9] The adjunctive use of steroids and anti-inflammatories has also been shown relevant in more critical features, such as MAS and KDSS, ensuring a better prognosis. Although multisystem inflammation syndrome is still rare, affecting about 0.1% of children exposed to Sars-CoV-2, it is important for the medical community to be aware of this new phenotype and its immunological mechanisms to anticipate the identification of the most severe cases.[3,6]

Author contributions

Conception and design of the research: Ronsoni RM, Magno Gonçalves MV. Acquisition of data: Chara BS, Rickli JM, da Silva CF, Pomaleski G. Analysis and interpretation of the data: Chara BS, Rickli JM, da Silva CF, Pomaleski G. Statistical analysis: Chara BS, Rickli JM, da Silva CF, Pomaleski G. Writing of the manuscript: Chara BS, Rickli JM, da Silva CF, Pomaleski G. Critical revision of the manuscript for intellectual content: Ronsoni RM, Magno Gonçalves MV.

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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EDITORIAL

What have we Learned about the Different COVID-19 Phenotypes in the Pediatric Population so Far?

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Editorial referring to the article: Kawasaki-like disease, a new phenotype in SARS–CoV-2?

The understanding of SARS-CoV-2 related syndromes in the pediatric population needs to grow worldwide. In its severe presentation, COVID-19 is a systemic disease characterized by hyperinflammation, cytokine storm and increased myocardial injury markers. Cardiac involvement in seen in 20-30% of hospitalized adult patients and accounts for about 40% of deaths.[1]

An intriguing aspect of the COVID-19 is the fact that most children and adolescents have mild or asymptomatic forms of the disease, perhaps related to a lower expression of virus receptors, recent exposure to other coronaviruses generating cross-protection, more developed innate immunity, among others. [2] In fact, it is known that 40% of individuals under the age of 18 exposed to the virus get infected and that only 20-30% of children and adolescents infected with SARS-Cov-2 have symptoms.

However, in some cases, a late immune response (up to 6 weeks after the insult) has been observed, with involvement of one or more organs (cardiac, renal, respiratory, gastrointestinal or neurological organ), due to a massive inflammatory response that was called Multisystem Inflammatory Syndrome in Children (MIS-C). The World Health Organization (WHO) defined very clear criteria for MIS-C, including clinical, laboratory and echocardiographic aspects that have helped in the diagnosis and management of children and adolescents.[3] Henderson et al.,[4] described different phenotypes of COVID-19 in the pediatric population, and proposed a guidance document on the management of MIS-C associated with COVID-19. According to the authors, clinical manifestations of this combination are: 1- febrile syndrome: characterized by persistent fever, mild change in inflammatory markers and indirect signs of organ dysfunction; 2- Classic MIS-C: important change in inflammatory markers, multisystem involvement and severe cardiac involvement with shock and cardiovascular dysfunction; 3- Kawasaki-like disease: cutaneous-mucosal involvement with milder cardiac involvement (American Heart Association criteria for complete or incomplete Kawasaki disease); 4- COVID-19 simile: major respiratory involvement (acute respiratory distress syndrome). [4]

Despite the lower number of deaths in the pediatric age group than adults, higher mortality rates due to COVID-19 in children have been recorded in Brazil compared with other countries (852 deaths in children under nine years and 518 deaths in infants younger than one year of age), although a reduction in mortality from 8.2% in 2020 to 5.8% in 2021 has already been observed in the population aged 0 to 19 years.[5]

The first case of Kawasaki-like disease in Covid-19 was reported in a 6-month-old infant with fever, tachycardia, signs of respiratory distress, maculopapular rash, conjunctival hyperemia, who was treated with intravenous immunoglobulin (IVIG) and high-dose aspirin, with clinical improvement. Since this report, numerous cases have been reported during the pandemic.[6] DeBiasi et al.[7] reported 177 young patients diagnosed with COVID-19. Of these, 44 (24.8%) required hospitalization, nine (2.8%) were critically ill and one developed signs and symptoms of Kawasaki-like disease, mainly

Keywords

COVID-19; Coronavirus; Cardiomyopathies; Child; Heart Failure; Severe Acute Respiratory Syndrome; Myocardial Stunning; Kawasaki Disease.

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cardiovascular ones, including ventricular dysfunction and arterial hypotension.[7] Verdoni et al.,[8] observed a 30-fold increased incidence of Kawasaki-like disease in a month during the pandemic compared to previous years.[8] The mechanisms of Kawasaki-like disease seem to be based on the exacerbated inflammatory reaction mediated by antibodies, which occurs mainly in genetically predisposed individuals. Therefore, in most cases, the identification of viral replication is not relevant (RT-PCR may already be negative at this stage), and the disease is better diagnosed by serology (IgM, IGG or both), emphasizing that SARS-CoV-2 infection is not mandatory, and the patient may only have a history of exposure.

Some studies have drawn attention to the absence of Kawasaki-like and MIS-C cases in Asian countries where the Covid-19 pandemic started, probably due to ethnic, genetic, and immunological factors, with higher incidence of cases in populations of African ancestry.

The scientific paper "Kawasaki-like disease, a new phenotype in Sars-CoV-2?"[9] brings interesting information about SARS-CoV-2 in childhood and adolescence and its association with the Kawasaki-like disease and MIS-C,[9] and highlights different clinical and laboratory aspects that stand out in cases of Kawasaki-like disease. For example, a higher frequency of gastrointestinal manifestations (abdominal pain, mesenteric lymphadenopathy, vomiting, diarrhea, and in some cases an acute abdomen requiring exploratory surgery), lymphopenia, elevation of inflammatory markers and myocardial injury (C-reactive protein, interleukins, procalcitonin, D-dimer, N-terminal prohormone of brain natriuretic peptide [NT-proBNP], troponin, lactate, transaminases, etc.), cardiovascular manifestations such as myocarditis, valvulitis, left and/or right ventricular dysfunction, changes in the coronary artery and pericardium, hemodynamic instability, shock and greater need for intensive care support compared to classic Kawasaki. Table 1 lists aspects of cardiovascular involvement in MIS-C with Kawasaki–like disease and aspects of classic Kawasaki disease (Figures 1 and 2).

Fedstein et al.,[10] published the manifestation of MIS-C in 186 children and adolescents (mean age 8.3 years) in 26 American states;[10] 148 patients (80%) had cardiovascular manifestations, 74 had Kawasaki-like disease (40%), 15 patients (8% with z-score > 2.5) had coronary-artery aneurysms, and four patients died (2%). Elevation of NT-proBNP occurred in 73% and left ventricular dysfunction with LVEF < 55% in 33%.

Table 1 - Most common differences found in cardiovascular manifestations on echocardiography and ECG in Kawasaki-like and Kawasaki disease and in markers of inflammatory evidence and myocardial injury.

Kawasaki-like disease		Kawasaki disease
ECG (100%): tachycardia - negative T wave, QRS with decreased amplitude		**ECG** (30%): tachycardia - negative T wave, QRS with decreased amplitude
Echocardiogram - Moderate to severe LV dysfunction - Right ventricular dysfunction - Valvulitis - Coronary changes (increase in brightness) - Pericardial effusion (mild/moderate/important)		**Echocardiogram** - Mild LV dysfunction - Mild pericardial effusion - Valvulitis - Coronary changes (with dilations and aneurysms - z-scores ↑)
CRP ↑↑↑↑	Cytokine storm	↑↑
Platelets ↓	Cytokine storm	↑
Ferritin ↑	Cytokine storm	↑
D- dimer ↑↑↑	Cytokine storm	↑
NT-proBNP ↑↑↑↑	Myocardial injury	↑
Troponin ↑↑	Myocardial injury	↑
Hypoalbuminemia	No	Yes

ECG: electrocardiography; LV: left ventricular; NT-proBNP: N-terminal prohormone of brain natriuretic peptide

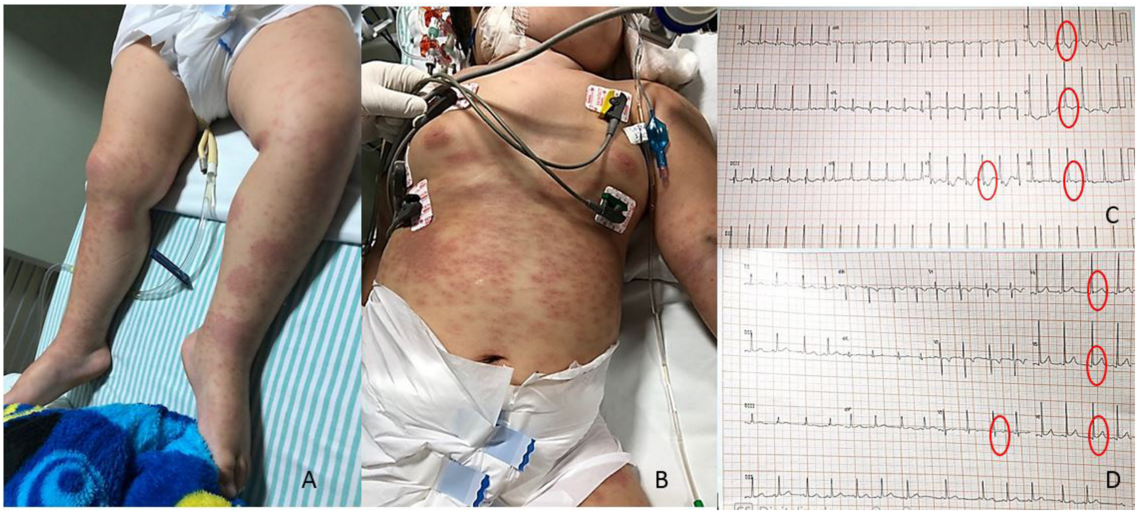

Figure 1 – Boy, 3 years old, weight: 30 kg, with Kawasaki-like, fever, skin rash (A,B), vomiting, respiratory distress and severe hemodynamic instability and myocarditis. ECG with negative T waves in the left precordials before IVIG infusion and corticosteroid (C) and already normal T waves after therapy (D).

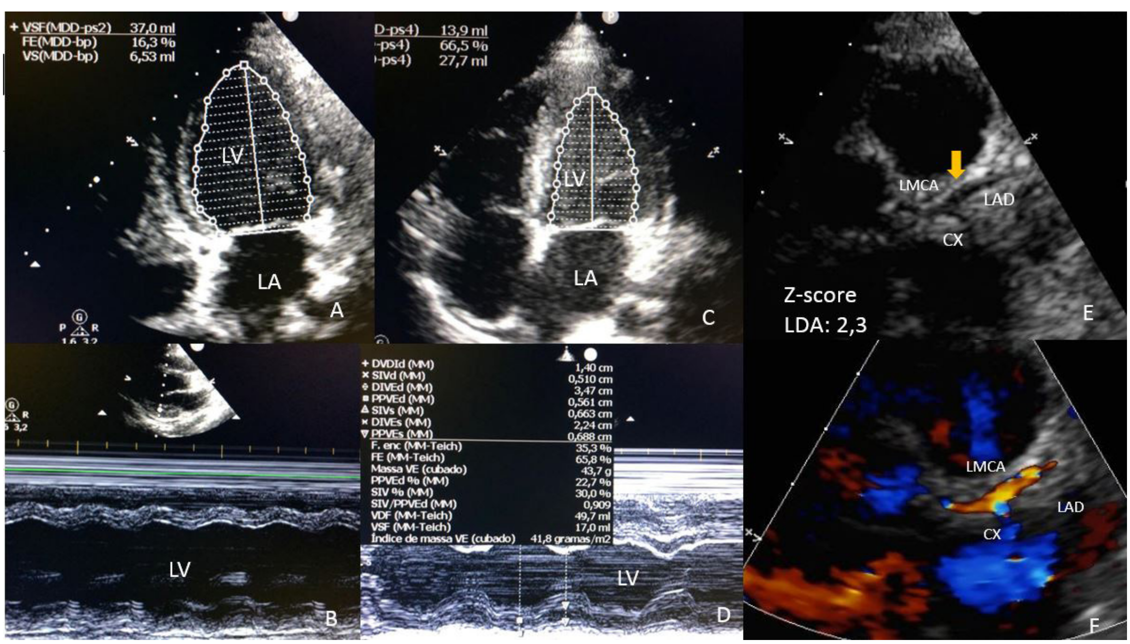

Figure 2 – Transthoracic echocardiogram of the boy with Kawasaki-like showing severe left ventricular dysfunction by Simpson (A) and Teichholz (B) and significant improvement after treatment (C,D). LDA dilation (z-score : 2,3) with increased brightness and refringence of the left coronary wall on the twodimensional (E) and on the color Doppler (F) . LV: left ventricle; LA: left atrium; LMCA: left main coronary artery; LAD : left anterior descending coronary artery, CX: circumflex coronary artery.

In Kawasaki-like disease patients, changes in coronary artery are characterized by increased brightness and parietal thickening of the coronary arteries in echocardiography , and an increase in the z-score, although giant aneurysms are rarely observed. In several series published during the pandemic, coronary involvement in MIS-C occurred from 8 to 36%, probably due to endothelial dysfunction associated with cytokine storm caused by SARS-CoV- 2.

Pignatelli et al.,[11] in a multicenter study in Latin American countries observed that patients with MIS-C and cardiac involvement had more laboratory abnormalities, respiratory involvement, and more intensive care unit admissions.[11]

In addition, classic Kawasaki disease usually affects children up to five years of age (average age of three years), while Kawasaki-like disease occurs in older children (average age of nine years). This was well demonstrated by Belay et al.,[12] in a study with 1,733 patients with MIS-C and median age of nine years (5-13 years); 66.5% of these patients had abdominal pain, 53.7% diarrhea, 55.6% skin rash, 53.6% conjunctival hyperemia, 50.8% arterial hypotension, 36.8% shock, 31% myocardial dysfunction, 17.3% myocarditis and 16.5% coronary dilation. It is worth remembering that myocarditis, ventricular dysfunction, shock and the need for intensive care in classic Kawasaki disease are very rare.[12]

Diniz et al.,[13] evaluated an interesting correlation between echocardiographic abnormalities, biomarkers of inflammation and myocardial injury in 48 patients with MIS-C.[13] There was a statistically significant correlation between left ventricular dysfunction and increased D-dimer, C-reactive protein, ferritin and troponin; there was also a significant correlation between right ventricular dysfunction and increased D-dimer and C-reactive protein. Coronary abnormalities correlated only with D-dimer elevation.

The Clinical Guidance for Pediatric Patients with MIS-C recommends, for patients with MIS-C, SARS-CoV-2 infection and hyperinflammation, measurement of BNP/troponin at diagnosis, and serial controls until discharge, and ECG during and after hospitalization. Also, performance of echocardiography to aid in the diagnosis (with evaluation of ventricular function, valvular alterations, pericardial effusion and the coronary arteries), as well as in adequate treatment and subsequent follow-up.

IVIG has been widely used for a variety of conditions including Kawasaki disease and toxic shock syndrome, as an effective and safe therapy. Although the use of IVIG has been extended to MIS-C and Kawasaki-like disease, its effectiveness still needs to be determined in these cases. Also, the exact mechanism of this therapy is not yet clear, but presumably, IVIG reduces the action of monocytes, macrophages and other cells, preventing the progression of myocardial injury. Belhadjer et al.,[14] detected an improvement in ventricular function in 25 of 35 MIS-C patients treated with IVIG. Corticosteroid therapy (methylprednisolone) also appears to be beneficial in preventing or attenuating the effects of inflammatory responses induced by SARS-CoV-2.[14] The combination of IVIG and corticosteroid treatment seems to avoid major complications such as ventricular dysfunction and the need for more vasoactive drugs for hemodynamic support. The use of anticoagulants and antiplatelet agents should be considered in patients with MIS-C admitted to the intensive care unit, with risk of thromboembolism and significant elevations in D-dimer.[15] Patients with Kawasaki-like disease and coronary aneurysms should use antiplatelet agents such as aspirin, and in some cases, the association with clopidogrel may be necessary.

With the increase in vaccination coverage of the general population, there has been a substantial reduction in deaths and hospitalizations. Vaccination of adolescents aged 12 and over is already becoming a reality in our country. This strategy will serve not only to protect children and adolescents from serious disease, but also to help control the transmission of the virus throughout the community. In addition, with the increase in vaccination rates, it is totally feasible to return to school, which is so fundamental for the physical, mental, intellectual and psychological well-being of our children and adolescents, who have been seriously harmed in many aspects in this pandemic.

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VIEWPOINT

The Athlete's Return in the Post-COVID-19

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The disease caused by Coronavirus 2019 (COVID-19) is associated with significant mortality and morbidity, including pulmonary and cardiac adverse sequelae.[1-3] It began in December 2019 in the city of Wuhan, and quickly became a pandemic, declared by the World Health Organization (WHO) on March 11 of 2019.[4] By early September 2020, more than 28 million patients have been confirmed infected by COVID-19 in more than 200 countries.[3]

Infection by COVID-19 can develop with severe acute respiratory syndrome (SARS-CoV-2), acute respiratory distress syndrome (ARDS), neurological, cardiac and vascular manifestations being not unusual, and are associated with increased mortality.[1,4-6] The pattern of COVID-19 infection and its late sequelae has its pathogenesis only partially elucidated.[1,5]

Most individuals infected with COVID-19 will be either asymptomatic or will have mild to moderate symptoms[1,5]. The highest mortality rates are observed in patients over 60 years old and with comorbidities, especially cardiovascular diseases, obesity, and diabetes. Patients with worst outcomes also had high serum levels of ultra-sensitive troponin (Tus) and other inflammatory markers, such as interleukin 6 and ferritin.[1-5,7]

Notably, the lungs are the main organs involved by COVID-19, and angiotensin-converting enzyme 2 (ACE2) is part of the virus pathway into the lung cell. ACE2 is not only found in the lungs, but also in several other organs, including the heart, the endothelium of the cardiovascular system, the small intestine and the nervous system.[1,3,4,7] The inflammatory response described as "cytokine storm" seems to be responsible for ARDS, vascular/endothelial inflammation, myocarditis, and related events such as arrhythmias, ventricular dysfunction, and sudden death.

Based on Chinese data, cardiac injury appears to be a relevant feature of the disease, occurring in 20 to 30% of hospitalized patients and contributing to 40% of deaths. Cardiovascular complications have been described, such as: myocardial injury (20%), arrhythmias (16%), myocarditis (10%), acute heart failure (HF) and shock (up to 5% of cases), sometimes with a dysfunction similar to Takotsubo's disease. These data may vary depending on the authors.[1-5,7]

Specific Complications in the Organs and Influences in Athletes

Lungs

Lungs are the organs most frequently involved by COVID-19. Pneumonia affects about 20% of those tested positive in China, 14% with severe or critical forms of pneumonia, characterized by pulmonary infiltration affecting more than 50% of the lungs with important hypoxia.[1,5]

During SARS outbreak in 2002-2003, affected patients showed pulmonary restriction, with reduced pulmonary diffusion capacity and functional capacity for at least 2 years of follow-up.[1,5] Recently, in a case report from the University of Innsbruck, six divers also developed severe pulmonary changes after being affected by COVID-19.[5]

It is noteworthy that, in athletes, even small reductions in ventilatory capacity and pulmonary diffusion might affect performance.[5] Exercise capacity would be limited due to changes in pulmonary diffusion, which may

Keywords

COVID-19; Betacoronavirus; Pandemic; Athletes; Sport; Exercise; Return to Sport/psychology; Patient Discharge.

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trigger pulmonary arterial hypertension, right heart overload and, in the long-term, cor pulmonale.[1,5]

Nieß et al.,[5] recommend that spirometry should be performed on those athletes with a history of pulmonary involvement due to COVID-19 infection, as it may allow, and better elucidate functional changes.[5] When available, preliminary findings in spirometry, performed during annual assessments, could be comparatively used to help analyze these sequelae.

Some authors recommend non-invasive capillary observation of arterial oxygen saturation, by pulse oximetry along with exercise test (ET) or cardiopulmonary exercise test (CPET).[5] CPET associate's variables allow a better demonstration of a possible pulmonary limitation to exercise: respiratory equivalents, the slope of the VE/VCO_2 ratio, in addition to the drop in $SatO_2$. In the case of identified alterations compatible with a pulmonary limitation, we should deepen this functional assessment by testing the diffusing capacity of the lungs for carbon monoxide (DLCO) and possible imaging exams.[5]

Cardiovascular System

Recognizing a possible myocardial involvement during COVID-19 infection is of cardinal importance for athletes. Myocarditis is one of the main causes of sudden death in athletes under 35 years old,[8,9] with viral myocarditis emerging after viruses with respiratory and/or gastrointestinal involvement.[6,8,9]

Of patients with the severe form of COVID-19, 15% to 31%, had an increase in Tus during hospitalization, which could indicate cardiac involvement and myocardial injury,[1-4,7] and might be related to their prognosis.[3,4]

Cardiac involvement is demonstrated by increased Tus levels, electrocardiographic (ECG) and echocardiographic (ECO) changes, mentioned in more than 22% of hospitalized patients with COVID-19, compared to 1% of patients with other viruses.[10]

Different Factors are Related to Myocardial Damage and Can be Dummarized in Chart 1.[7]

Cardiac involvement is best demonstrated by cardiac nuclear magnetic resonance (MRI), which allows the identification of edema, fibrosis and contractile dysfunction.[1,3,4,7] The question that remains open is whether there is a risk of myocardial involvement in mild and moderate forms or even in asymptomatic.[5,11] Nieß et al. mention the occurrence of severe myocarditis in the convalescence phase as well as cases of sudden death in patients infected by COVID-19 with home treatment.[5]

The Athlete Facing the Pandemic

Engaging in some type of physical activity is an important component of a health promotion program and is recommended to be done by all those who are isolated at home.[11,13]

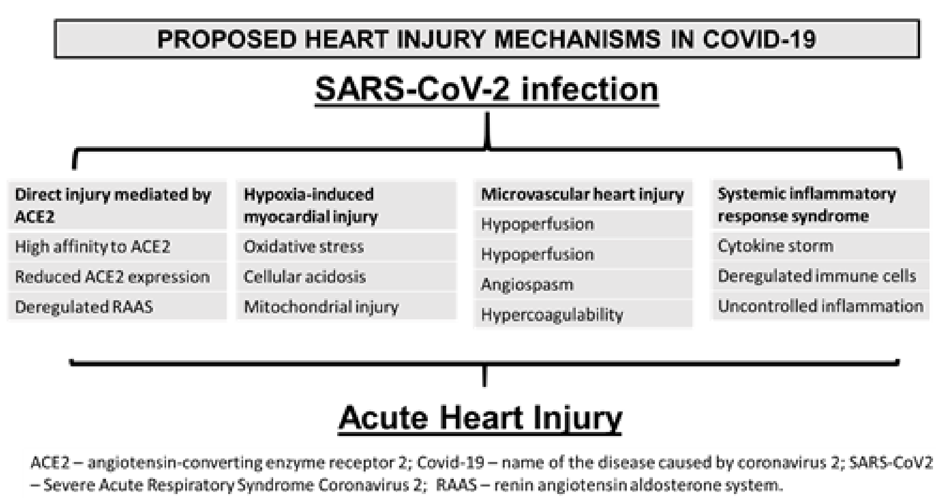

Figure 1 – Proposed factors related to myocardial damage in SARS-CoV-2 infection. Source: Brandão et al.[7] COVID-19 and heart. Practical pipeline manual. 1st edition. April 20, 2020.

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Viewpoint

There is no specific data available on prevalence, nature and behavior of the disease associated with COVID-19 in the athlete.[5,6,11] The increasing reports about pulmonary and cardiac involvement, in mild to moderate clinical forms[2], points out the need for a new health policy in relation to athletes, for both recreational and professionals sports. A new challenge arises in determining when and how the athletes infected with COVID-19, especially those who had the disease and recovered, will have medical clearance to return to training and competing.[2,5,6,10,11]

Existing epidemiological and clinical data are scarce to safely guide this process. Notably, the numbers of asymptomatic cases in the community, the prevalence of cardiac injury in non-hospitalized individuals and the long-term evolution of those who have had proven cardiac involvement, all of these questions are still unanswered.[10]

In this pandemic, the athlete theme, with its specific particularities, is pertinent. It includes concerns about continuing training, risk of transmission between team members, and the potential deleterious effect of vigorous exercise increasing susceptibility to COVID-19 infection.[10,11,13]

Intense training, with or without a sudden increase in intensity, are associated with transient immune changes, elevation of systemic inflammatory markers, oxidative stress and muscle damage.[11] A potential increase in the risk of falling ill during periods of high training load is a reality[5,6,11,13]. The transmission of COVID-19 is facilitated in several training scenarios, such as: in group sports, contact sports, not obeying the distancing rule, sharing equipment, not following universal rules of personal hygiene, in addition to the use of collective changing rooms.

Athletes often present with non-specific symptoms, like fatigue, asthenia, reduced performance, myalgia and disproportionate tachycardia at rest. The last might be blurred by a mix of differential diagnosis in this population such as overtraining syndrome, anxiety and depression. In such way, the diagnosis of an infection, or even cardiac involvement due to COVID-19, will not be suspected. Thus, additional diagnostic and therapeutic measures might be delayed and neglected.[6]

COVID-19 cardiac injury can have long-term repercussions, and we can underestimate it if we only define it by the increase in Tus. In those athletes with mild symptoms, cardiac injury should always be ruled out, and even in those with abnormal baseline exams, the diagnosis cannot be given with certainty. Some of the changes in the ECG, for example, may be the consequences of adaptations to prolonged training, as well as transient elevations of creatine phosphokinase and Tus, which may occur due to the acute effect of a high-volume session or training intensity.[6]

Another observation is that the typical presentation of a suspected myocarditis differs from the scenario observed in a COVID-19 hospitalized patient compare to an athlete with mild symptoms of the disease. Athletes are extremely sensitive to changes in their health status with reduced performance. Attention must be given to prolonged recovery time to training stimuli, dyspnea and/or fatigue disproportionate to the effort performed, as well as greater myalgia triggered by training, all may represent unspecific symptoms of COVID-19 infection.[6]

Possible pulmonary sequelae, even if without clinical significance for everyday life, can be highly relevant for those who participate in competitive sports, which imposes high training loads, and cannot rule out damaging effects that may occur in their performance. The prolonged convalescence process itself with persistent symptoms of fatigue, asthenia, myalgia certainly decreases physical performance after an infection by COVID-19.[5,10,11]

Recommendations to Return to Training

The recommendations to return to training after an airway infection were that those with signs and symptoms of infection restricted to the upper airways (nasal congestion, runny nose), should not be removed from training[11]. The scientific evidence for this recommendation was weak, and the potential risk of developing complications as myocardial damage due to vigorous training was known.

Currently, for COVID-19 viruses, recommendation for the return to training, even with only upper airway symptoms, is to prolong the period of absence and use more conservative return strategies (10 to 14 days after symptom onset plus 7 to 14 days of symptom absence).[5,10,11]

Due to the great variability in the severity of Covif-19 infection, variation in the scope of evaluation also seems logical in the evaluation to return to play a competitive sport with the intensity of training that it usually requires.[2,5,6,10,11]

Some societies and institutions (American College of Cardiology's Sports & Exercise Cardiology Council, International Olympic Committee) started to provide guidance, based on expert opinions, regarding the return of athletes to competitive practice.[5,6,10,11]

Recommendations for Screening Athletes in Post-COVID-19

The categorizations are based on the clinical signs and symptoms obtained initially through an anamnesis and physical exam, associated with the clinical findings on pulmonary, cardiovascular and neuromuscular system involvement, in addition to the results of the screening tests. Recommendations based on algorithms must be individualized and adapted with respect to the individual course of the disease, the use or not of therapies, such as hydroxychloroquine that prolongs QTc interval, and additional diagnostic measures required.[2,5,6,10,11]

The definition of the onset of typical symptoms of the disease must be performed to estimate the time of medical clearance to return training, in addition to basic and specific laboratory tests, these depending on the involvement of each case.

Nieß et al.[5] proposed a categorization of patients shown in Table 1. These recommendations may be valid for today and only for a short period in the light of the development of new knowledge, and may need to be reviewed.[5,6,10,11]

Our Recommendation

After considering the recommendations for evaluating athletes from different authors,[2,5,6,10,11] we make the following suggestions.

All athletes returning to training and presenting to the medical department, must undergo a clinical history and a physical examination, highlighting the search for compatible signs and symptoms of COVID-19 infection. In case of a positive history, characterize the onset of symptoms, its evolution, tests performed, hospitalization and when asymptomatic. This way, we can see ourselves in different situations (Chart 2).

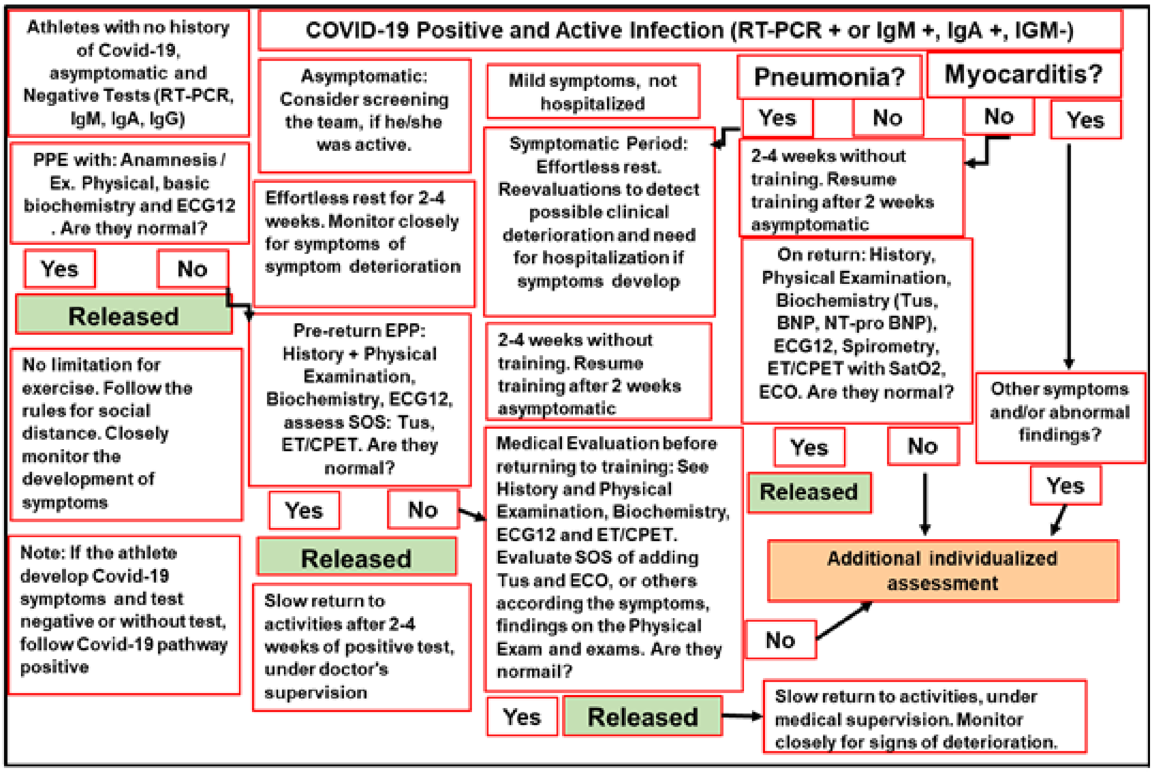
I - Asymptomatic and negative tests

Asymptomatic athletes, with no reported disease. In addition to anamnesis and physical examination, routine biochemical tests, and baseline ECG. All athletes should be tested for antigen and antibodies for COVID-19. If all negative for COVID-19 (RT-

Table 1 – Proposed categorization for COVID-19 patients.

Categorization
A - Positive tests for COVID-19, but no signs and symptoms of infection
B - Positive tests and patient with signs and symptoms of the disease, such as: fever with temperature above 37.8, dry cough, myalgia, headache, loss of smell and/or taste etc., but without confirmed pneumonia
C – COVID-19 infection with confirmed pneumonia
D – COVID-19 infection with suspected or confirmed myocarditis with or without pulmonary involvement and with or without other symptoms
History and Physical Examination
Assess the severity of the evolution of the disease, symptoms related to exercise, such as: chest pain, cough and/or dyspnea (in each case especially if induced by exercise), fever and its duration, dizziness, myalgia, fatigue, headache, loss of taste and smell, mood changes, medications used and your sports background
Highlight in the evaluation of the affected lymph nodes and chains, baseline heart rate, blood pressure in different positions, pulmonary examination (see wheezing and crackles), peripheral and cardiac cardiovascular examination (see arrhythmias, accessory sounds, murmurs and attritions), abdomen (with emphasis on visceromegaly), body temperature and basic neurological examination (assessing neuropathies).
Laboratory analysis
Complete blood count, US C-Reactive Protein (PCR), transaminases, creatine phosphokinase (CPK), urea, creatinine, blood glucose, urinalysis.
Depending on the clinical history data, physical examination and the above results: ferritin, troponin, D-dimer, interleukin 6, procalcitonin, nasal swab and oropharynx RT-PCR, antibody search for COVID-19 (IgM, IgA, IgG)

Nieß et al[5].



Legends: Covid-19 - name of the disease caused by coronavirus 2; PPE – pre participation evaluation; RT-PCR - reverse-transcriptase polymerase chain reaction; ECG - electrocardiogram; Ex. - exam; ET - exercise test; CPET - cardiopulmonary stress test; Tus - ultra sensitive troponin; SOS - if necessary; ECO - echocardiogram; Ig - immunoglobulin; BNP - type B natriuretic peptide; NT-pro BNP - Inactive N-terminal of the pro-BNP.

Figure 2 – Recommended evaluation flowchart for post - COVID-19 in athletes.
Adapted from Schellhorn et al.[6]

PCR-, IgM-, IgA-, IgG-), the athlete will be allowed to return to training, without additional specific evaluation.[10]

II - Asymptomatic with positive tests

II a) Asymptomatic with positive tests for active infection

Asymptomatic patients, but with positive tests showing active infection (RT-PCR+, IgM+, IgA+, IgG-), must stay at home following the strict rules of home isolation and without training, for at least two weeks. The duration of the disease is shown to be critical to the patient's clinical outcome, with an increased risk of deterioration after the first week of symptom onset. Therefore, it is recommended to follow closely after the onset of the first symptoms and to establish marks in this evolution and recommendations.

After two weeks of observation, if they remain asymptomatic, they should be reassessed by the medical department for prior evaluation, in addition to have their clinical evolution monitored for another two weeks, plus another evaluation before slowly returning to training.[10]

This group of athletes represents, by the current data, a great unknown. Due to reports of cardiac and pulmonary involvement, even in asymptomatic patients, our opinion, and agreeing with some reviewed authors,[5,10] is that, in addition to the anamnesis, physical examination, blood routine, resting ECG, Tus and an ET/CPET should be added, with additional investigation if in the presence of altered exams.

II b) Asymptomatic athletes, but positive tests for previous infection

In asymptomatic athletes who detect previous infection, only with IgG + and the other negative tests (RT-PCR-, IgM-, IgA-, IgG +), an assessment like those in group II a who are returning after the isolation period is recommended. In these two populations, the clinical examination, ECG, and additional stress tests (ET/CPET), should be performed, especially if they demonstrate clinical signs of cardiopulmonary symptoms and/or changes in the resting ECG and stress tests.[10]

III - Athletes who had symptomatic disease and positive test for previous disease

In those symptomatic athletes and tested positive for previous disease (RT-PCR-, IgM-, IgA-, IgG+), with or without pulmonary involvement, but without the severe form of the disease, in the pre-return assessment, in addition to clinical history, physical examination and ECG, routine biochemical and an ET or, preferably, a CPET associated with $SatO_2$. Depending on the clinical findings and the results of these tests, associate biochemical markers of injury and cardiac dysfunction (Tus, natriuretic peptide type B (BNP), inactive N-terminal proBNP (NT-proBNP)) and an echocardiogram (ECO). We also recommend a baseline control spirometry and a 24h Holter.[5,10]

Athletes with a history of illness in the most severe forms portray a high-risk population. Although we know that myocarditis is not present in the majority of patients hospitalized by COVID-19, it is recommended to evaluate these patients thinking as if they had had it, and to follow the recommendations for complete evaluation for myocarditis in the pre-participation evaluation.[10]

If the biochemical markers of injury and dysfunction (Tus, BNP, NT-proBNP), ECG and ECO are normal, it is recommended at least 2 to 4 weeks after the symptoms cease of relative rest. They will then undergo a careful cardiac clinical reassessment, prior examinations and a CPET should be repeated before resuming gradual training.[8-10]

If evidence of myocardial involvement is found, along with high levels of Tus, BNP, NT-proBNP and complemented by the findings on physical examination, an MRI should be performed.[3,5]

IV) Suspected and/or confirmed cases of myocarditis

In a suspected and/or confirmed case of myocarditis, we must follow the existing guidelines in relation to this entity while providing full medical clearance to return to sport.[5,8,9]

Myocarditis due to viral aggression can lead to dysfunction, arrhythmias, and death. During the acute phase, the practice of exercise can result in accelerating viral replication, increasing the inflammatory component and cellular necrosis, and providing a pro arrhythmic substrate.[10]

Returning to sports after myocarditis is based on the normalization of inflammation and dysfunction biomarkers, myocardial function, and absence of resting and/or stress-induced arrhythmias.[8-10] A new risk stratification will take place from 3 to 6 months of withdrawal from their sports activities according to the clinical follow-up and complementary exams (biochemical markers of injury and myocardial dysfunction, ECO, ET/CPET, 24h Holter and MRI).[5,6,8-10]

The prognosis, for myocarditis for other viruses, is generally favorable in those with acute myocarditis, with normalization of ventricular function, and absence of fibrosis areas on MRI, however, we still do not know the long-term prognosis of COVID-19 myocarditis. We must keep in mind that athletes who developed cardiovascular complications due to COVID-19 infection may have late manifestations, e.g., arrhythmias, and deserve to have a long-term follow-up.

Data on athletes who have recovered from COVID-19 infection will be of the utmost importance. To optimize the counseling and treatment of future cases, prospective data should be collected in this current pandemic.

Author Contributions

Conception and design of the research: Teixeira JAC. Acquisition of data: Teixeira JAC, Teixeira MF, Teixeira PS, Jorge JG. Analysis and interpretation of the data: Teixeira JAC. Writing of the manuscript: Teixeira JAC, Teixeira MF, Teixeira PS, Jorge JG.

Potential Conflict of Interest

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Study Association

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VIEWPOINT

Home Physical Activity Programs for Children and Adolescents as a Healthy Strategy During Social Isolation Caused by COVID-19: viewpoint

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Background

The recent outbreak of coronavirus disease (COVID-19) is considered a global health emergency. The global impact of this viral infection is of great concern to everyone.[1] As the COVID-19 outbreak continues to appear unstoppable, preventive and hygiene measures have been implemented to safeguard against infection. Among these precautions, social isolation is considered to have the greatest potential for reducing contagion, at least until a vaccine becomes available. This isolation measure works as a kind of "necessary evil" for preventing a wide-reaching disaster. Thus, social distancing and staying home remain the most effective restrictive measures to prevent the exponential increase in contagion.[2]

One of the crucial focal points of this strategy was oriented toward the closure of schools, thus affecting thousands of children and adolescents, who comprise approximately half of the global student population. The closure of educational institutions could have a significant impact on their lives, requiring them to adapt to new routines. Considering that they are now being confined to their homes due to the new situation generated by the pandemic, this cohort may experience moments of stress.[3]

Studies reveal that the lack of social interaction can lead to the development of various symptoms of anxiety and depression, and consequently, to the development of mental illnesses and an inevitable increase in stress.[4] Additionally, a study suggests that the proportion of patients with obesity will increase during the COVID-19 pandemic. This raises additional medical concerns because obesity is linked to decreased immune function, which could in turn increase viral pathogenicity.[5] In this context, there is a continued need for developing improved communication strategies to provide the general population with actionable information for self-protection, including the identification of symptoms, and clear guidelines for seeking supporting treatments.[6] Evidently, such programs must adopt behavioral elements, and they should be feasible to implement for individuals who face changes in schedules, work, and school requirements. This is especially true for those who experience anxiety owing to being confined to their home. Additionally, sedentary behaviors of children and adolescents, who tend to resort to screen-based leisure activities (using tablets/smartphones, TV games/videos/DVDs, and computers/laptops), should be addressed.[7]

Given these factors, intervention programs that include physical activity could minimize anxiety and stress, and they could play an important role in preventing weight gain, dyslipidemia, and cardiovascular events.[8,9] The importance of physical exercise is well evidenced in the literature; however, under conditions of social isolation, children and adolescents cannot exercise in other spaces with face-to-face guidance from a qualified professional (e.g., at the school, club, or gym). However, it is relevant to mention that home-based training programs and exercise routines could also be effective for children and

Keywords

COVID-19; Betacoronavirus, Pandemics; Child; Adolescent; Students; Sports; Exercises; Schools Closure; Social Isolation; Physical Activity.

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adolescents,[9] as it increases levels of physical activity, and consequently, improves the quality of life of those involved.

In recent years, the literature has increasingly addressed the effectiveness of physical exercise as a therapeutic and preventive measure against mental and physical disorders.[5,10] It is a great way of maintaining and caring for the physical body. At a chemical level, it increases serotonin synthesis and activates the endogenous opioid system (endorphin synthesis), which, along with other benefits, results in a decrease in sensitivity to anxiety and amplifies positive emotions.[11]

In the context of the COVID-19 pandemic and in the absence of studies on possible strategies to increase physical activity in children and adolescents, these discussions are imperative.[12,13] Until new discoveries emerge, we must emphasize that modifiable lifestyle factors, such as diet and physical activity, should not be marginalized because decades of evidence corroborate the role of physical activity in promoting health and well-being. In times of crisis, whether real or perceived, the benefits of enabling people to actively preserve their own health, for example by performing exercises at home, cannot be discounted.[14]

Thus, to address the relationship between children's and adolescents' general health and physical exercise at home, this study sought to answer the following question: Which evidence-based exercise programs can be implemented at home for children and adolescents during this period of social isolation related to the COVID-19 pandemic?

General Guidelines on Physical Activities for Children and Adolescents

The guidelines of the World Health Organization (WHO) on physical activities for children and adolescents (5–17 years) recommend at least 60 minutes of daily physical activity of moderate to vigorous intensity (e.g., which lead to an increase in heart rate). Some recommended activities include games, sports, task-based online games, recreation, physical education, or planned exercise, which are conducted in the context of the family, school, and community activities.[15]

With the spread of COVID-19, some recommendations have been modified to facilitate the implementation of protective measures against the infection and to help individuals during social isolation. These modifications mainly pertain to spaces where these recommendations are implemented. For instance, it is recommended that children and adolescents remain active or begin to engage in physical activities at home, together with their families.[16] Some of these activities, such as a resistance-based exercise program, games, dance, sports activities, and task-based online games, should be encouraged for children and adolescents (Figure 1).

Games and play offer children with opportunities to receive diverse experiences and achieve new stages in their learning. Playing, a typical childhood activity, paves the way for children to be more assertive and provides constant opportunities to interact with other individuals and cultures. This, in turn, facilitates the collective construction of knowledge. Thus, games and play are relevant, educational, and ludic activities that can be performed at home.[17] Aerobic exercises that can be performed to improve cardiorespiratory fitness include jumping rope, going up and down stairs, walking, stationary or treadmill running, cycling, performing cyclical or repetitive movements, and dancing. Resistance exercises, which improve strength, power, and muscular

Figure 1 – Different physical activities to be performed at home by children and adolescents

endurance, can be performed by children and adolescents by using their own body weight for creating resistance. Plyometric or jump exercises, such as burpees, jump squats, and jumping jacks, are recommended for bone strengthening. These exercises can be performed alone or in combination with other exercises at home.[5,18,19]

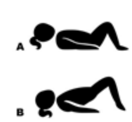
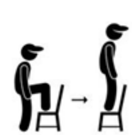
Additionally, recommended physical activities include active games associated with video games, applications, or software. Such activities were developed in response to the increase in the number of hours children and adolescents spend on sedentary activities such as watching television, using their cell phones, and playing video games. To counter this sedentary behavior trend, studies have started testing the use of technology to remedy this sedentary lifestyle while encouraging children to continue to play. Active video games (AVGs) emerged with the need to encourage movement through interaction with technology. Such games encourage physical activity of mild to moderate intensity while motivating children and adolescents to increase their energy expenditure.[19] Evidently, AVGs could be an essential tool during this period of social isolation.

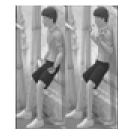
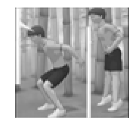
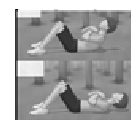
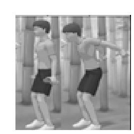
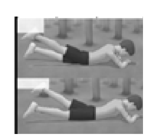
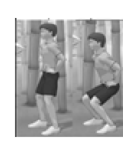
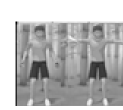
A study that sought to test the effectiveness of a home-based physical activity intervention led by parents of young individuals (age < 18 years old) found that the intervention led to improvements in motor skills such as upper-limb coordination, bilateral coordination, balance, running speed, agility, and muscle strength. Thus, it is indicated that such tools could facilitate the implementation of physical activity routines that improve motor proficiency in young individuals.[20] Table 1 shows some activities that can be conducted at home, with suggestions that incorporate readily available household materials and simple movements that can be practiced by children and adolescents during this period of social isolation.

Conclusion

Home-based exercise programs for children and adolescents include resistance-based exercises or muscle-

Table 1 – Examples of programs of physical activity at home.

Authors	Programs	Exercise	Properties	Material	Ways to explain to children/ adolescents	Example
Schranz et al., [11]	High intensity circuit (HICT), with exercises performed at home with 10 to 12 repetitions during 3 rounds (circuit)	Sit to stand (adapted=using the chairs)	10-12 repetitions 3 sets (repeat)	Chair or Bunch	With your feet parallel, with the tips slightly turned out, do not let your knee go too far in front of the toes. The movement is done by throwing the hips back, as if to sit on a chair.	
		Heel rises (stand on end)	10-12 repetitions 3 sets (repeat)	Body weight	Place your feet shoulder-width apart, lift and then lower your heels.	
		Reverse Lunges (knee on the floor)	10-12 repetitions 3 sets (repeat)	Body weight	Bend your knee and hip with one leg forward and, with it sunk, propel the back and move it forward. The feet must always be parallel to the knees. Keep the posture straight, with the torso aligned, avoiding forward bending.	
		Bridging (bridge with the body)	10-12 repetitions 3 sets (repeat)	Carpet or towel	Lie on the floor or on a towel or rug on your back with your arms extended at your sides. The knees must be bent and the feet fixed on the ground. Then push your hips upwards, extending them as far as you can.	
		Lateral step ups (up and down)	10-12 repetitions 3 sets (repeat)	Chair or Bunch	Support your foot on the seat, inhale and climb into the chair. Release the air to descend, controlling the movement, and using only one leg at a time. Do not let the knee go too far from the tip of the foot, so as not to hurt the knee.	

Bruno et al., [12]	Training circuit with increasing intensity, including aerobic activity (brisk walking) Interspersed with ten muscle strength exercises that recruit major muscle groups, to be performed at low intensity with a high number of repetitions; five weekly sessions lasting 60 min.	Skipping in place	10 sec 20 sec 30 sec Brisk walgink (1 min)	Body weight	Practice the movement of the run with knee elevation stopped or displaced.	
		Biceps curl	10 rep. 15 rep 20 rep Brisk walgink (2 min)	Body weight	Position your feet shoulder-width apart. Place your back against the wall, bend your knees and lean your hips back. Stick your elbows to your body, leaving them fixed. Raise your arms at chest level and then at face level. Slowly lower your arms. As you bend your arms, inhale and, as you stretch, exhale.	
		Vertical jumps	5 rep 7 rep 10 rep Brisk walgink (1 min)	Body weight	Make the act of jumping up in the air.	
		Abdominal curl-ups	15 rep 20 rep 25 rep Brisk walgink (1 min)	Body weight	You should lie on your back on the floor and bend your knees, then place your hands crossed in front of the chest. Then just lift the torso with your eyes towards the knees and return to the original position.	
		Wall Push-ups	20 rep 25 rep 30 rep Brisk walgink (2 min)	Body weight	Stand with your feet at least one meter away from the wall (the farther you are, the greater the challenge). Lean forward and place your hands on the wall, again slightly wider than shoulder width. Fold your arms and bring your chest towards the wall and then go back.	
		Running in place Buttock- kicks	10 sec 20 sec 30 sec Brisk walgink (1 min)	Body weight	Practice the movement of the race trying to touch the foot on the gluteus, which can be stopped or displaced.	
		Kick Back	15 rep 20 rep 25 rep Brisk walgink (1 min)	Body weight	Lean slightly forward from your waist. Lift your elbow back and keep it flexed. It should remain fixed at the same height as the shoulder during the movement. The movement consists of flexing and extending the elbow.	
		Prone hip extensions	15 rep 20 rep 25 rep Brisk walgink (1 min)	Carpet or towel	Lie face down on a rug or towel with your arms resting in front of your face / head. Lift your right leg off the floor for a set time. Then relax. Repeat with the opposite leg.	
		Squats	10 rep 15 rep 20 rep Brisk walgink (1 min)	Body weight	With your feet parallel, with the tips slightly turned out, do not let your knee go too far in front of the toes. The movement is done by throwing the hips back, as if to sit on a chair.	
		Shoulder horizontal Abductions	10 rep 15 rep 20 rep Brisk walgink (1 min)		Standing two pet bottles (to replace halters) with your palms facing inwards and your feet shoulder-width apart. Position the weights very close to your hips with your elbows slightly bent. The torso should be straight or slightly tilted forward. The movement consists of raising and lowering.	

strengthening activities, games, dance (aerobic exercises), sports activities, and task-based online games (for bone strengthening). These exercises will enable them to remain active.

Children and adolescents should be encouraged to change their routines during this period of social isolation. A reasonable goal could be to engage in 60 minutes or more of moderate and/or vigorous intensity activities each day.

Further, it is important to engage in such activities under the supervision of parents or guardians since they play an important role in providing age-appropriate activities for children and adolescents. It is also noteworthy that adolescents usually tend to reduce their levels of physical activity. Accordingly, it is important for parents to motivate them to initiate and maintain good physical exercise habits that contribute to an increase in energy expenditure during the COVID-19-related quarantine period.

This review points out that children and adolescents could engage in moderate-intensity physical activity with AVGs and task-based online games. Such home-based activities could improve their self-esteem, facilitate positive family interactions, and maintain physical activity during social isolation.

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Author Contributions

Conception and design of the research: Medeiros RCSC, Santos IK, Medeiros JA, Cobucci RN, Silva TAL, Araujo JS, Varela PWA, Cabral BGAT, Dantas PMS. Acquisition of data: Medeiros RCSC, Santos IK, Medeiros JA, Cobucci RN, Silva TAL, Araujo JS, Varela PWA, Cabral BGAT, Dantas PMS. Analysis and interpretation of the data: Medeiros RCSC, Santos IK, Medeiros JA, Cobucci RN, Silva TAL, Araujo JS, Varela PWA, Cabral BGAT, Dantas PMS. Writing of the manuscript: Medeiros RCSC, Santos IK, Medeiros JA, Cobucci RN, Silva TAL, Araujo JS. Critical revision of the manuscript for intellectual content: Medeiros RCSC, Santos IK, Medeiros JA, Cobucci RN, Silva TAL, Araujo JS, Varela PWA, Cabral BGAT, Dantas PMS.

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

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CASE REPORT

Exercise Training Improved Pulmonary Gas Exchange Abnormalities in Pulmonary Hypertension due to Heart Failure: A Case Report

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Abstract

Heart failure (HF) is the most common cause of pulmonary hypertension (PH), and reduced exercise capacity and exertional dyspnea are the most frequent concerns in patients with PH-HF. Indeed, carbon dioxide end-tidal partial pressure ($PETCO_2$) during exercise is a well-established noninvasive marker of ventilation/perfusion ratio in PH. We aimed to evaluate the effect of aerobic exercise training on $PETCO_2$ response during exercise in a 59-year-old woman with PH secondary to idiopathic dilated cardiomyopathy. The patient with chronic fatigue and dyspnea at mild-to-moderate efforts was admitted to a cardiorespiratory rehabilitation program and had her cardiorespiratory response to exercise assessed during a cardiopulmonary exercise testing performed before and after three months of a thrice-weekly aerobic exercise training program. Improvements in aerobic capacity (23.9%) and endurance time (37.5%) and reduction in ventilatory inefficiency (-20.2%) was found after intervention. Post-intervention improvements in $PETCO_2$ at ventilatory anaerobic threshold (23.3%) and change in $PETCO_2$ kinetics pattern, with progressive increases from rest to peak of exercise, were also found. Patient also improved breathing pattern and timing of ventilation. This case report demonstrated for the first time that aerobic exercise training might be able to improve $PETCO_2$ response during exercise in a patient with PH-HF.

Keywords

Aerobic Capacity; Exercise Test; Cardiovascular Diseases; Pulmonary Gas Exchange; High Frequency Ventilation.

Introduction

Heart failure (HF) is the most common cause of pulmonary hypertension (PH)[1] and is associated with increased morbidity and mortality.[1,2] Exertional dyspnea and reduced exercise capacity are the most frequent concerns in patients with PH due to HF (PH-HF),[2] The key physiological mechanism in PH-related exertional dyspnea is a lung vasculature abnormality due to excessive pulmonary vascular resistance, which attenuates cardiac output response to exercise.[3] Noteworthy, patients with PH show a sharp increase in physiologic dead space and hence reduced gas exchange efficiency.[3] Indeed, patients with HF often display ventilatory abnormalities likely related to dysregulation in peripheral control (i.e., impaired skeletal muscle ergoreflex and increased peripheral chemoreceptor sensitivity).[4-6]

Cardiopulmonary exercise testing (CPX) is an useful tool for assessing severity and prognosis in cardiorespiratory disease.[7] Carbon dioxide end-tidal partial pressure ($PETCO_2$) during CPX is a well-established noninvasive marker of ventilation/perfusion ratio in patients with lung and heart diseases.[8] Indeed, the $PETCO_2$ decrease from rest to ventilatory anaerobic threshold (VAT) during CPX is associated with pulmonary gas exchange abnormalities in patients with PH.[9]

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Therapeutic strategies are available for treating primary PH; however, the same does not occur for PH-HF, whereas target therapy agents have failed to demonstrate benefit or have even been harmful.[1,2] Although exercise training is a well-established non-pharmacological therapy for HF,[10] its effect on patients with PH-HF, particularly on $PETCO_2$ response during exercise, is unknown. Therefore, our aim was to report the effect of aerobic exercise training on $PETCO_2$ response during exercise in a patient with PH-HF.

Case Report

Patient´s characteristic and evaluation

A 59-year-old sedentary female (weight: 86 kg, height: 162 cm) with PH secondary to idiopathic dilated cardiomyopathy was admitted for cardiorespiratory rehabilitation in the TotalCare clinic, São Paulo, Brazil. Her comorbidities included systemic hypertension, diabetes, and dyslipidemia. No lower limb edema or increased jugular venous pressure, and resting blood pressure and heart rate of 140/100 mmHg and 60 bpm, respectively, were found during physical examination. Patient had regular heart rhythm with mitral regurgitation and clear breath sounds during auscultation. Her symptoms were chronic fatigue and dyspnea at mild-to-moderate efforts. She had never participated in any exercise program and had no history of hospitalization associated with HF.

Normal sinus rhythm and left branch bundle block were showed during resting electrocardiography. Global left ventricular (LV) hypokinesia with mildly impaired overall systolic function (ejection fraction: 37%), LV dilatation, and moderate PH (PASP: 55 mmHg) were showed during echocardiogram. Echocardiography diagnosis of PH was obtained through right ventricular systolic pressure (RVSP). The echocardiographic assessment was evaluated by the maximal tricuspid regurgitation velocity and the systolic gradient between the right ventricle and the right atrium was calculated.[11]

Baseline medications included carvedilol, hydrochlorothiazide, spironolactone, amlodipine, losartan, acetylsalicylic acid, and synvastatin, and no changes occurred during the previous three month before and throughout the study. The study was approved by the local Ethics Committee (CAEE :26442619.9.0005533) and patient signed an informed consent form.

A symptom-limited maximal CPX was carried out on treadmill (Centurion model 300; Micromed, Brazil) using a Balke modified protocol,[12] at controlled room temperature (20-23°C), 2 and 3 days before beginning and after ending the exercise program, respectively. Gas exchange and ventilatory variables were measured breath-by-breath throughout the test by a computerized system (Cortex model III B; Leipzig, Germany) and expressed as 30 sec averages, as previously described.[12] Heart rate was continuously recorded by 12-lead ECG (Elite Ergo PC; Micromed, Brazil) during resting, exercise, and recovery phases of CPX. VAT, peak oxygen consumption (VO_2peak), oxygen uptake efficiency slope (OUES), ventilatory equivalent of CO_2 production (V_E/VCO_2) slope, noninvasive estimate for physiologic dead space to tidal volume ratio (V_D/V_T), $PETCO_2$ pattern, and ventilatory pattern analysis (i.e., breathing frequency (BF), tidal volume (V_T), expiratory time (T_E), inspiratory time (T_I), total respiratory time (TOT), mean inspiratory flow (V_T/T_I), and mean expiratory flow (V_T/T_E)) were assessed during CPX.[12] As previously described, VAT was considered the point at which ventilatory equivalent of O_2 (VE/VO_2) reached the minimum value and began to rise without a concomitant rise in VE/VCO_2.[14] VO_2peak was defined as the maximum VO_2 attained at the end of the exercise period, at which time the patient had reached his/her maximum level of exhaustion (Borg's rating of perceived exertion scale).[13]

Exercise Training Program

A thrice-weekly supervised exercise training program were performed for three months at the TotalCare clinic's cardiorespiratory rehabilitation center. Exercise sessions included warm-up (5 min), aerobic (50 min), and cool-down (5 min) exercises. Aerobic exercise was a treadmill walking at the heart rate corresponding to the VAT during CPX (± 5 bpm). Heart rate was monitored throughout the session to ensure that patient exercised within the limits of intensity. The participant attended 90% of the programmed exercise sessions (33 sessions) and did not perform any exercise at home or any other exercise modality.

Outcomes

Severe impairment in cardiorespiratory fitness (< 50% of age predicted peak VO_2), reduced gas exchange efficiency, and abnormal $PETCO_2$ pattern with progressive decreases were observed at baseline (Table 1 and Figure 1A).

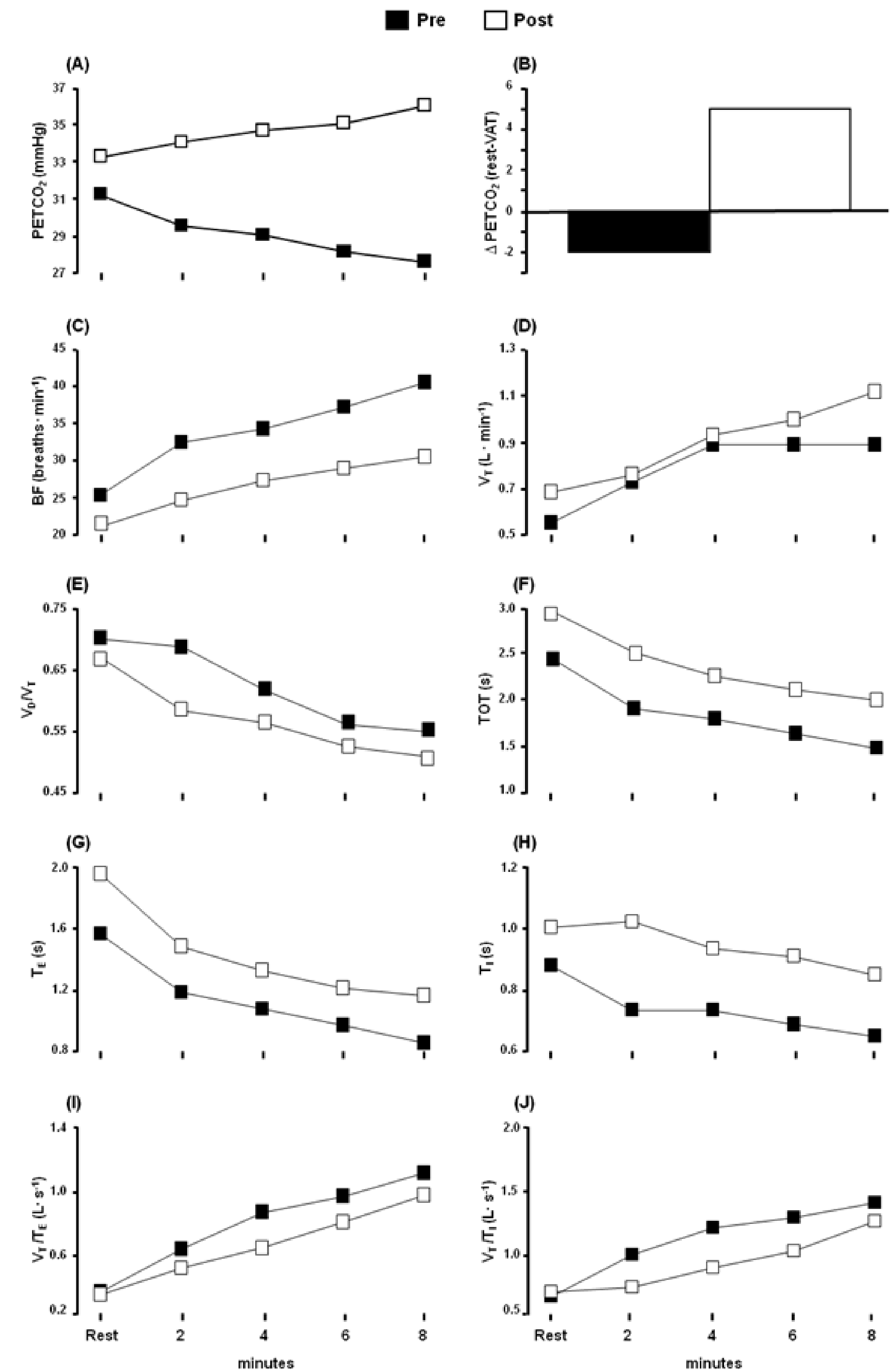

Figure 1 – Ventilatory response to cardiopulmonary exercise testing before (pre) and after (post) 3 months of aerobic exercise training. *A: Carbon dioxide end-tidal partial pressure (PETCO2), B: Carbon dioxide end-tidal partial pressure change (ΔPETCO2) from rest to ventilatory anaerobic threshold (VAT), C: breath frequency (BF), D: tidal volume (VT), E: physiologic dead space to tidal volume ratio (VD/VT), F: total respiratory time (TOT), G: expiratory time (TE), H: inspiratory time (TI), I: mean inspiratory flow (VT/TI), J: mean expiratory flow (VT/TE).*

After three month of aerobic exercise training, patient showed an increase in body mass (1 kg), peak VO_2 (23.9%), peak O_2 pulse (24.1%), and endurance time (33.3%), as well as in VO_2 at VAT (38.1%) and OUES (14.5%) (Table 1). Patient also showed lower V_EVCO_2 slope levels (Table 1). $PETCO_2$ analysis during CPX showed increased $PETCO_2$ at VAT (23.3%) and a change in $PETCO_2$ kinetics pattern with progressive increases from rest to peak of exercise when compared to pre-intervention (Figure 1A and 1B). Patient also improved breathing pattern (Figure 1C and 1D) and timing of ventilation (Figure 1G, 1H, 1I, and 1J).

Discussion

Progressive increase in $PETCO_2$ from resting to VAT (nearly 5-8 mmHg), followed by its maintenance or slight increase up to the onset of respiratory compensation point and its progressive decrease from respiratory compensation point to maximal effort, is expected in healthy subjects during CPX.[12] In contrast, our data showed progressive decreases in $PETCO_2$ from resting to VAT and maximal effort at baseline (Figures 1A and 1B), which is in accordance with a previous study assessing the $PETCO_2$ response in patients with primary PH.[9] Indeed, the abnormal $PETCO_2$ response was directly associated with disease severity.[9]

Physiological mechanisms involved in the altered $PETCO_2$ pattern found at baseline may include: (1) ventilation-perfusion inequalities due to ventilated alveoli hypoperfusion, resulting in increased physiologic dead space (V_D/V_T) and (2) increased acidosis at lower work rates, resulting in augmentation of ventilation drive induced by higher levels of hydrogen ion (H^+).[9] For instance, the increased pulmonary vascular resistance in patients with PH may blunt cardiac output response during exercise, which results in reduced O_2 transport to working muscle, thereby increasing the contribution of anaerobic glycolysis to exercise. Indeed, patients with HF demonstrate impaired skeletal muscle metabolism, which reduces mitochondrial oxidative capacity.[13] Thus, it is possible that both pulmonary gas exchange and muscle metabolism abnormalities may be involved in the impaired baseline $PETCO_2$ response during exercise in the patient with PH-HF.

In contrast, to the best of our knowledge, the present report showed for the first time that three months of aerobic exercise training might improve $PETCO_2$ response to exercise in a patient with PH-HF, as shown by the sharp increase in $PETCO_2$ from rest to VAT (Figure 1B), as well as by the increased $PETCO_2$ levels at both VAT and peak of exercise (Table 1). This result is in line with a previous study demonstrating the effectiveness of aerobic exercise training for improving $PETCO_2$ response in coronary artery disease patients.[13]

It is known that exercise training improves muscle oxidative metabolism during exercise in individuals with HF (e.g., increased O_2 uptake and arteriovenous O_2 difference, lower phosphocreatine depletion, lower increase in adenosine diphosphate, and decreased lactate accumulation).[14] In addition, training-induced improvements in ventilation efficiency during exercise are, at least in part, due to improvements in muscle receptor reflexes and skeletal muscle metabolism in individuals with HF.[15,16] In this context, it can be suggested that a training-induced improvement in muscle aerobic metabolism may be reduced acidosis-related ventilatory stimulus during CPX, and thus may be associated with the improved $PETCO_2$ response after training in the present study. The improvements in both VO_2 at VAT and OUES suggest an increase in muscle aerobic capacity and thus support this hypothesis.

Improvements in gas exchange efficiency and breathing pattern may be induced by the reduction of physiologic dead space ventilation and may also be involved in the improved $PETCO_2$ response after training.[12] In this context, the reduced V_EVCO_2 slope, V_D/V_T, and tachypneic (BF) and shallow pattern of breathing (T_E and T_I) after training support this hypothesis. In fact, the reduced V_T/T_I and V_T/T_E after training indicate a decrease in neuromuscular inspiratory and expiratory drive, respectively. It is important to note that breathing pattern has a significant influence in the V_D/V_T ratio during exercise. Specifically, a tachypneic breathing pattern during exercise increases V_D/V_T ratio and decreases $PETCO_2$ levels.[17] Moreoever, higher levels of breathing frequency are closely related to decreases in expiratory time and, as a consequence, in premature cessation and greater $PETCO_2$ increase during progressive exercise.[17] Thus, the decrease in breathing frequency and the increase in expiratory time found after exercise training may also be associated with the improved $PETCO_2$ response during follow-up in the present study. Interestingly, peripheral chemoreflex control was normalized after exercise training in a rabbit model of heart failure,[18] suggesting that it may be associated with the improvement in ventilation efficiency.

It is noteworthy that the patient also reported an improvement in exertional dyspnea sense after training, which is in line with the improved exercise capacity, as shown by the training-induced increase in exercise time during CPX. In conjunction, these improvements may result in an increased quality of life.

The echocardiography used for assessing PH is a limitation of the present study. However, we used sequential assessments to confirm the diagnosis. The assessment of only one patient during the follow-up is also a limitation that should be acknowledged.

In summary, this case report showed for the first time that the impaired $PETCO_2$ response to exercise in PH-HF might be improved by three months of a thrice-weekly aerobic exercise training program. Given that $PETCO_2$ is a noninvasive marker of ventilation/perfusion ratio[8] and that its abnormal response during CPX is associated with pulmonary gas exchange abnormalities in patients with PH,[9] the present results suggest that aerobic exercise training may be an important tool for improving pulmonary gas exchange abnormalities in patients with PH-HF.

Author Contributions

Conception and design of the research: do Prado DM, Fonseca de Campos JP, Miranda TP. Teixeira AB, Staroste M. Acquisition of data: do Prado DM, Fonseca de Campos JP, Miranda TP. Teixeira AB, Staroste M. Analysis and interpretation of the data: do Prado DM, Rocco EA, Ciolac EG. Writing of the manuscript: do Prado DM, Ciolac EG. Critical revision of the manuscript for intellectual content: do Prado DM, Rocco EA, Ciolac EG.

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 Samaritano* under the protocol number 26442619.9.0005533. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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CASE REPORT

Cardiac Arrest and Exercise-Induced Polymorphic Ventricular Tachycardia: An Elusive Diagnosis

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Introduction

Polymorphic ventricular tachycardia (VT) is defined as a rapid rhythm with continuously changing ventricular activation.[1] In the absence of QT interval prolongation, its evaluation is a challenging activity with a series of differential diagnoses. The present study reports on a case of a young man who had an out-of-hospital cardiac arrest and and who later presented an episode of exercise-induced polymorphic VT. A rational investigation is discussed based on the patient's clinical findings and baseline ECG.

Case Report

A 30-year-old Brazilian man received medical care at our ambulatory services to evaluate an aborted sudden death two months earlier while running at an airport. Return of spontaneous circulation was achieved using an automated external defibrillator (AED), and he has remained asymptomatic ever since. He had no past medical record, aside from using testosterone esters for competitive sports during one year at the age of 18. He denied smoking tobacco or using other drugs. He always lived in Natal, RN, Brazil, and reported no contact with triatomine bugs. Physical examination was unremarkable, with a BMI of 24.2 kg/m^2 and BP of 110/80 mm Hg.

A routine laboratory panel showed a hemoglobin of 11.4 g/dL, a leukocyte count of 6490/mm^3, a platelet count of 188.000/mm^3, a creatinine of 0.6 mg/dL, a blood urea nitrogen of 8.8 mmol/L, a sodium level of 144 mEq/L, and a potassium level of 4.5 mEq/L. His Chagas disease serologies were negative. His fasting blood glucose, thyroid function, and lipid profile were within the reference range. His baseline ECG (Figure 1) showed a sinus rhythm (HR of 60 bpm) and a discreet ST-segment elevation in leads V3-V5, with no other alterations. A transthoracic echocardiogram revealed ventricular apical hypokinesis and was otherwise normal, depicting a left ventricular ejection fraction (LVEF) of 69%. Afterwards, an exercise stress test elicited an episode of asymptomatic polymorphic VT upon the first minute of the recovery phase (Figure 2A). The patient reached 89% of his predicted maximum HR, and the rest of the stress test was normal. A 24-hr ambulatory ECG monitoring recorded eight monomorphic ventricular premature beats (VPBs).

A coronary CT scan (Figure 2B) revealed a hypodense plaque in the left anterior descending (LAD) coronary artery resulting in a stenosis of 70%. In fact, cardiac catheterization (Figure 2C) showed that the LAD harbored an unstable plaque with 90% stenosis, and catheter angioplasty with the placement of a drug-eluting stent was undertaken uneventfully. At follow-up, the patient was screened for causes of premature coronary artery disease (CAD). Tests for antinuclear antibodies, rheumatoid factor, syphilis, hyperhomocysteinemia, and antiphospholipid syndrome were unrevealing. Therefore, therapy with aspirin, clopidogrel, atorvastatin, enalapril, and propranolol was instituted. Six months later the patient presented no symptoms, and a new exercise test showed normal results.

Discussion

Polymorphic VT evaluation in individuals with normal QT interval depends on underlying structural heart disease, inherited arrhythmia syndromes, early

Keywords

Death Sudden Cardiac; Tachycardia,Ventricular; Exercise Induced; Diagnosis.

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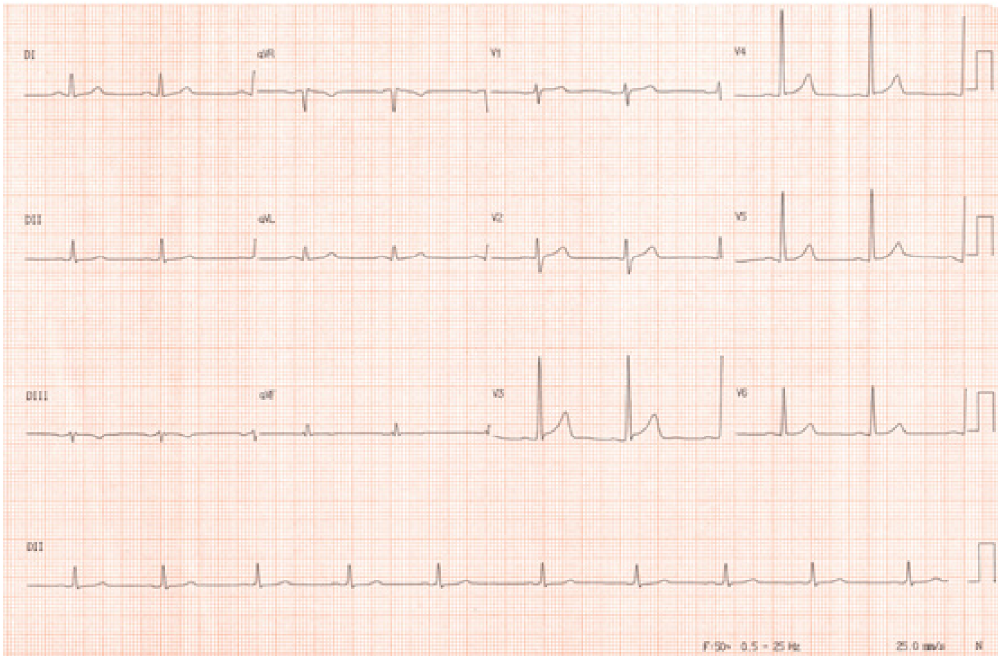

Figure 1 – The baseline tracing showed sinus rhythm (HR of 60 bpm) and ST-segment elevation in leads V3 to V5 with maximum amplitude of 0.15 mV. Lead III presents isolated T wave inversion.

repolarization (ER), and ischemia.[1,2] Our patient is an otherwise asymptomatic 30-year-old man with a previous cardiac arrest who developed an episode of polymorphic VT during exercise. His baseline ECG showed a discreet ST-segment elevation in leads V3-V5, but it was otherwise unrevealing, while his echocardiogram depicted a ventricular apical hypokinesis. Due to his episode of exercise-induced polymorphic VT, catecholaminergic polymorphic ventricular tachycardia (CPVT) was among the initial hypotheses. CPVT is an inheritable adrenergic-dependent disorder in which VPBs and polymorphic VT may be induced during exertion, emotional stress, and isoproterenol or epinephrine infusion.[1-3] Arrhythmias become more complex as the HR rises and resolve upon discontinuation of the inciting factor.[3] Our patient's VT, nevertheless, occurred during exercise recovery and was not preceded by progressive rhythm deterioration. On the other hand, as the use of beta-blockers has been found to suppress exercise-induced polymorphic ventricular arrhythmias in up to 65% of the patients,[3] his normal testing six months later could be explained by a lack of arrhythmia reproducibility. The diagnosis of CPVT would be supported by a family history of syncope or sudden death and by appropriate genetic testing.[1-3]

The presence of ST-segment elevation in leads V3-V5 may also resemble ER,[1,2,4] a typically benign condition characterized by J-point elevation of at least 1 mm in 2 contiguous leads. Some individuals, however, may harbor an increased risk of idiopathic ventricular fibrillation (VF). The strongest association is seen in patients with horizontal or downsloping ST-segment elevation and an end-QRS notch or slur, as well as involvement of inferior leads.[4] This has led to a 2015 consensus document[4] that suggests that patients without end-QRS notch or slur should not be characterized as presenting ER. Hence, it is uncertain whether our patient's ascending ST-segment elevation in precordial leads portends an increased risk of arrhythmias.

Importantly, both CPVT and ER syndrome occur in structurally normal hearts.[1-4] Our patient's echocardiogram, however, revealed a ventricular apical hypokinesis. This finding is typical of Chagas disease,[2-5] which is a protozoal infection endemic to most of South America, including the region where the patient lives. Transmission may be unnoticed and can also be taken by nonvectorial means,[5] such as the ingestion of contaminated food or drinks. Up to 45% of patients present late cardiac findings[5] characterized by myocardial inflammation and fibrosis with a preference for LV apex involvement, often leading

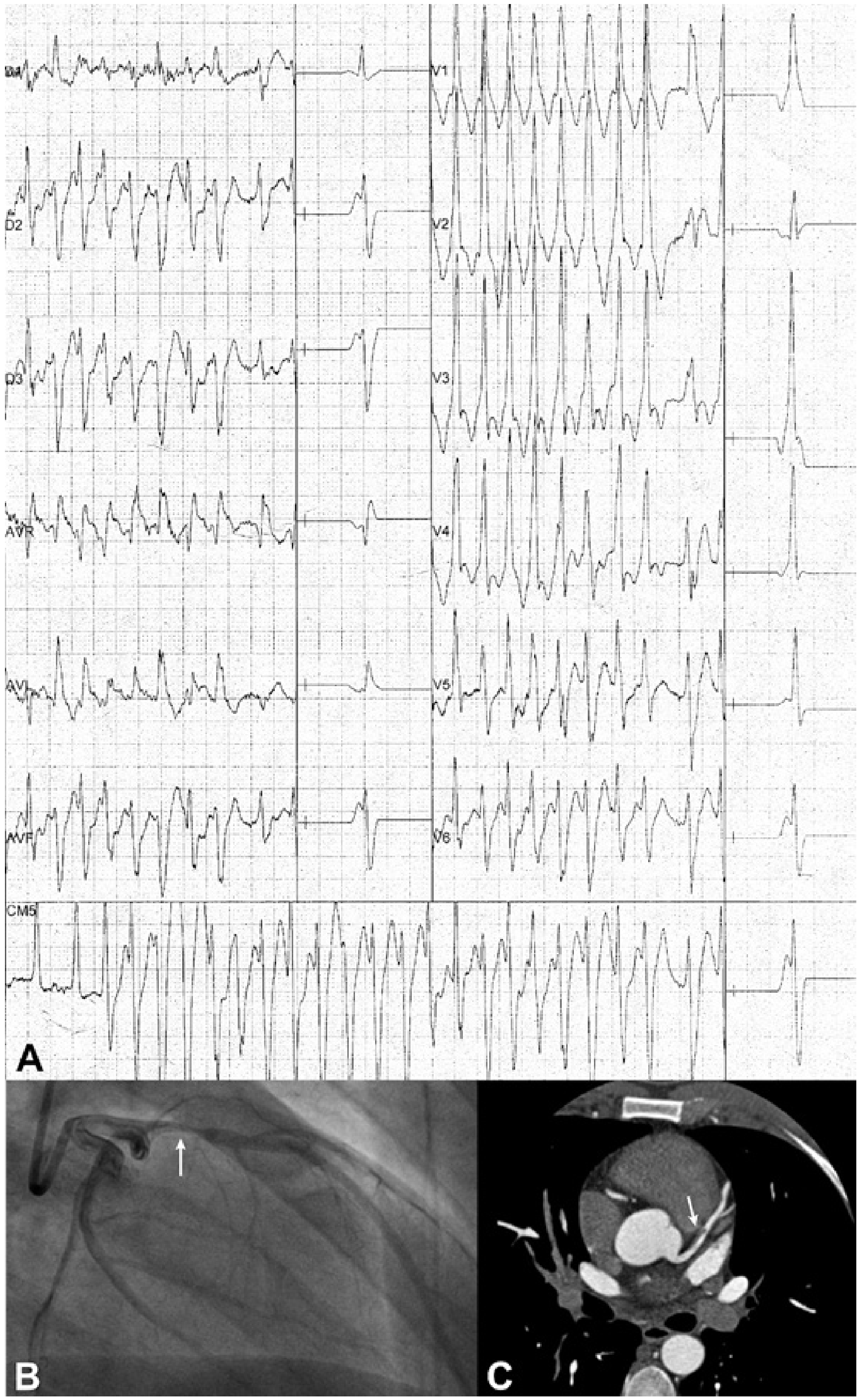

Figure 2 – (A) A polymorphic ventricular tachycardia with HR of 220 bpm is elicited during the recovery phase of an exercise stress test. (B) Coronary CT scan shows a hypodense plaque in the left anterior descending coronary artery with a stenosis of 70% (arrow). (C) Coronary angiography shows the lesion to cause a stenosis of 90% (arrow).

to aneurismal changes.[5] Nevertheless, the diagnosis during the chronic phase is done with serologic assays, for which our patient had negative results. His hypokinesis could also be explained by left ventricular arrhythmogenic cardiomyopathy (LVAC).[6] This exceedingly rare disease crosses with fatty infiltration of the LV and may overlap with the more common right ventricular arrhythmogenic cardiomyopathy. The LV shows reduced LVEF and significant dilation, with a median end-diastolic diameter of 65.2±5.6 mm in a Chinese series.[6] The diagnosis, despite the lack of standardization, is supported by cardiovascular magnetic resonance imaging, genetic testing, and, in select cases, heart biopsy. However, in face of our patient's otherwise normal echocardiogram, his apical hypokinesis was considered as most likely a manifestation of regional ischemia. Accordingly, as about 50% of unexplained sudden cardiac arrests are caused by ischemia,[1] coronary CT or angiography is recommended for assessing the presence of CAD or coronary anomalies in such cases.[1,2] Arrhythmias may occur in the setting of acute coronary syndromes, due to transient ischemia during exertion, or in patients with stable CAD.[2] Our patient's CT suggested the presence of a 70% LAD stenosis. Though we deemed angiography as a preferable next step in view of current recomendations,[1,2] a functional imaging test could have also been performed due to the borderline value of stenosis at CT. Ultimately, his angiography revealed an even more serious lesion with a stenosis of 90%.

Due to the setting of premature CAD in the absence of major cardiovascular risk factors, prothrombotic conditions were investigated with normal results. However, androgenic-anabolic steroid abuse was associated with coronary plaque formation and LV dysfunction in a large prospective study,[7] which might have contributed to our patient's disease.

Conclusions

Polymorphic VT may be the only manifestation of CAD, sometimes leading to cardiac arrest. In young subjects, this arrhythmia presents a challenging etiologic investigation, in which a comprehensible approach to patient history and baseline ECG is invaluable in order to guide further workup.

Author contributions

Conception and design of the research: Oliveira Neto NR, de Oliveira, WS. Acquisition of data: Porto AA, Oliveira Neto NR, Mendonça RM. Analysis and interpretation of the data: Oliveira Neto NR, Mastrocola F. Writing of the manuscript: Oliveira WS, Novaes AEM. Critical revision of the manuscript for intellectual content: Oliveira Neto NR, de Sousa JCV, Mastrocola F.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

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

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