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SUMARY

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ORIGINAL ARTICLE

Better Adequacy of Food Intake According to Dietary Recommendations of National Cholesterol Education Program in Vegetarian Compared to Omnivorous Men

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Abstract

Background: The lower frequency of cardiovascular (CV) risk factors observed in vegetarians compared to omnivores may be due to more appropriate nutrient intake according to recommendations for the prevention of cardiovascular diseases.

Objective: To compare the dietary adequacy according to the recommendations of the National Cholesterol Education Program (NCEP) in apparently healthy vegetarian (VEG) and omnivorous (OMN) men.

Methods: This was a cross-sectional study, conducted with apparently healthy men (44 omnivorous and 44 vegetarians, ≥ 35 years), who were assessed for daily food consumption, anthropometric data, physical exercise status, and clinical data. Multiple logistic regression was used to test the association between the type of diet and the dietary adequacy. Significant values were considered for $p<0.05$.

Results: Several clinical CV risk markers were significantly lower in VEG when compared to OMN: body mass index (BMI) (23.1 vs. 27.3 kg/m2), systolic blood pressure (119.5 vs. 129.2 mmHg), and diastolic blood pressure (75.7 vs. 83.9 mmHg). VEG presented significant lower values of blood lipids and glucose. No significant difference was observed in caloric intake; however, VEG consumed significantly more carbohydrates, dietary fibers, and polyunsaturated fats. VEG presented an adequate consumption of dietary cholesterol and saturated and polyunsaturated fatty acids, regardless of caloric intake and age.

Conclusion: VEG were more likely to consume saturated fatty acids, dietary cholesterol, and fibers according to the recommendations of NCEP, factors that may contribute to lower levels of CV risk markers than OMN.

Keywords: Cardiovascular diseases; Life Style; Lipids; Risk factors; Vegetarian Diet.

Introduction

Over the past fifty years, there has been a boom in the production of research about vegetarianism,[1] not only related to its impacts on health, but also on other biological processes[2] and the environment, even suggesting that it may well represent a better alternative in order to preserve natural resources for our planet.[3,4] The number of people consuming a vegetarian (VEG) or a plant-based diet is increasing and this is clearly associated with lower prevalence of risk factors for cardiovascular diseases (CVD).[5-8] VEG subjects consume smaller amounts of total fat, saturated fat, and cholesterol, as well as larger amounts of unsaturated fat and fiber than omnivorous (OMN) individuals.[9,10]

There are dietary recommendations regarding the amounts of energy, macronutrients, and micronutrients that should be taken daily to prevent the development of CVD or prevent the worsening of their risk factors. One of the most well-known recommendations for the prevention of CVD is the National Cholesterol Education Program (NCEP).[11]

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The NCEP recommends that the energy intake should be enough to maintain a desirable weight and suggests that the macronutrients should be consumed according to a specific percentage of the daily energy intake, together with the daily amount of dietary cholesterol and dietary fiber. In addition, recommendations include staying physically active and drinking alcoholic beverages in moderation.[11]

The lower frequency of CV risk factors observed in VEG individuals compared to OMN individuals may be due to more appropriate nutrient intake according to the recommendations for CVD prevention, such as the NCEP. However, no studies documented in the literature have made this comparison.

One recent intervention study showed the higher effectiveness of a VEG diet in promoting a reduction in low density lipoprotein cholesterol (LDL-c) levels, while the Mediterranean diet was more effective in promoting a reduction in triglycerides,[12] increasing the need for investigations to better understand the relationship between different dietary patterns and CV risk factors

Therefore, the present study sought to compare dietary adequacy, according to NCEP recommendations, in apparently healthy VEG and OMN men. It was hypothized that VEG individuals would present a more adequate food intake according CV health recommendations.

Methods

Subjects

The present study's sample consists of healthy men participants from the Carotid Atherosclerosis and Arterial Stiffness in Vegetarians and Omnivorous Subjects (CARVOS) study.[13] Initially 745 adult volunteers were recruited in Sao Paulo through social activities and the Internet. The participants filled out questionnaires regarding past medical history, family history, dietary preferences, and personal data. Exclusion criteria were: 1) being female, 2) history of diabetes, 3) history of dyslipidemia, 4) history of cardiovascular or cerebrovascular diseases, 5) history of hypertension or intake of antihypertensive medication, and 6) smoking. All individuals who declared themselves to be "smokers" or "occasional smokers" in the interview or quit smoking for <1 months prior to the interview were considered smokers. Healthy participants ≥35 years were divided into 2 groups – VEG and OMN – according to their dietary patterns. VEG men were defined as having exclusive consumption of a vegetarian diet devoid of meat, fish, and poultry for at least 4 years, who could be lacto-ovo-vegetarians (consuming egg, milk, and dairy products), lacto-vegetarians (consuming milk and dairy products), or vegans (consuming no eggs or milk and dairy products). OMN men were considered those who consume at least five or more servings of any type of meat per week.

During the period of June 2013 to January 2014, after applying inclusion and exclusion criteria, 88 apparently healthy men were enrolled in the study (44 VEG and 44 OMN). All participants provided informed consent to participate in the study. The study protocol was approved by the research committee and the institutional review board of the Heart Institute (InCor), School of Medicine, University of Sao Paulo (logged under protocol number 35704). The sample of 44 participants from each category was a probabilistic calculation taken from the previously described CARVOS study.[13] The reason to choose the male sex was due to a higher prevalence of CVD development in men as compared to women.[14]

Dietary and clinical assessment

All 88 subjects were screened for health status by means of questionnaires concerning past medical history, dietary preferences and personal data, such as smoking status, alcohol consumption, education level, and physical exercise status. Subjects were interviewed and the average of two 24 h dietary recalls (one on weekdays and one on weekends) were used to estimate daily consumption of different nutrients.

The Multiple-Pass Method (MPM) as applied to structure the collection of 24-hour recall in stages or successive steps. In addition, to standardize data collection, the main advantages in the use of MPM include a detailed description of the food, the method of preparation, and the quantification of consumed items, all of which contribute to increased reliability of dietary measure.[15,16]

A database for Brazilian food composition was used to calculate the daily energy and nutrient intake.[17]

Dietary intake of VEG and OMN was evaluated according to adequacy as regards the recommended percentage of carbohydrates, proteins, lipids, and grams of fibers for the prevention of CVDs.[11] Although the NCEP[11] recommended protein intake is approximately

15% of total calories, allowing individuals to distribute these among the categories of consumption, the percentage of adequate daily intake of protein was considered to be from 12 to 18% in order to enable category analysis.

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured twice in the right arm after 10 min rest in a supine position using a calibrated and averaged digital sphygmomanometer.

Anthropometric evaluation

To measure the weight[18] and height,[19] the previously described method was used. The body mass index (BMI) was calculated by dividing body weight (kg) by the square of height (m).

For waist circumference (WC), the measurement was made at the midpoint between the last rib and the iliac crest, with the abdomen relaxed, at the end of expiration,[20] and the hip circumference (HC) at the gluteal maximum extension.[18]

All measures were performed in triplicate, and the mean value was used for analysis.

Biochemical analysis

After fasting for 10–12 hours overnight, participants had blood samples drawn from the antecubital vein. Serum lipids, including triglycerides (TG), total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-c) were assayed by enzymatic methods, using an automatic multichannel chemical analyzer (Siemens Healthcare, Newark, USA) in the Central Laboratory of the Heart Institute the University of Sao Paulo (USP). LDL-c was calculated by the Friedewald formula.[21]

Glycosylated hemoglobin (HbA1c) was determined by the immunoturbidimetric method, certified by the National Glycohemoglobin Standardization Program (NGSP), using the Flex kit (Siemens Healthcare, Newark, USA). For homocysteine, Apo lipoprotein b (Apo b), and fasting glucose measurements, blood samples were centrifuged at 3000 rpm for 15 minutes within 60 minutes of collection and stored at −70°C until analysis. Fasting serum glucose (FSG) was determined by the glucose oxidase method using a Dimension RXL (Siemens healthcare, Newark, USA) through standard laboratory techniques. Quality control assessment was performed daily for all determinations.

Subclinical carotid vascular disease and arterial stiffness

The arterial stiffening, evaluated as carotid-femoral pulse wave velocity (PWV), functional and structural properties of carotid arteries, measured as carotid intima-media thickness (c-IMT) and carotid relative distensibility were measured as previously described.[13]

Physical Activity

Subjects reported activity levels using the International Physical Activity Questionnaire-Short Form (IPAQ),[22] which measures leisure time, as well as domestic, work-related, and transport-related physical activities. Four domains were measured: sitting, walking, moderate-intensive activities, and vigorous-intensive activity over the last seven days.

For analysis, the follow categorization was considered: physically active (≥ 20 minutes/session of vigorous activities ≥ 3 days/week; and/or ≥ 30 minutes/session of moderate activities or hiking ≥ 5 days/week; and/or ≥ 150 minutes/week of any additional activities – vigorous or moderate or walking), and irregularly active (<150 minutes/week of any of the additional activities – vigorous or moderate or walking).[23]

Statistical Analysis

The normality of data distribution was tested by the Kolmogorov-Smirnov test. Data were presented as means ± standard deviation (SD). The unpaired Student's t-test was used to test differences for numerical variables. The Chi-squared (X^2) was used to compare categorical variables between groups.

The variables presented categorically in this study were the nutrients in the order shown below, within and above that recommended by the NCEP: carbohydrate (< 50%, 50-60% and > 60% of total calories); dietary Fibers (< 20 g, 20-30 g, > 30 g per day); protein (< 12%, 12-18%, and > 18% of total calories); total fat (< 25%, 25-35%, and > 35% of total calories); saturated fatty acids (< 7% and ≥ 7% of total calories); dietary cholesterol (< 200 mg and ≥ 200 mg per day), and plant stanols (< 2 g and ≥ 2 g per day).

The NCEP recommendations were chosen as a reference for this work, as it is a traditional reference that supports several guidelines for cardiovascular prevention in countries on all continents.

To test the association between the type of diet (VEG or OMN) and the dietary adequacy according to NCEP recommendations, multiple logistic regression was used.

The measure of the magnitude of effect was measured by the values of OR (odds ratio) and respective 95% confidence interval (95% CI). The initial procedure followed a univariate analysis, while variables with p<0.20 were included in the multiple regression. The variables of caloric intake and age were maintained for the adjustment of the multiple models, regardless of the level of significance.

Since all individuals consumed ≤ 20% of the total calories from monounsaturated fatty acids and ≤ 10% of the total calories from polyunsaturated fatty acids, it was not possible to carry out the logistical regression for these nutrients.

Significant values were considered for $p < 0.05$, and all analyses were performed using Stata 10.0.

Results

No difference was found between the VEG and OMN ages. VEG presented significantly lower values of BMI, WC, WC/HC ratio, SBP, DBP, TC, TC/HDL-c ratio, LDL-c, non HDL-c, TG, Apo B, FSG, HbA1c, PWV, c-IMT, and carotid distensability (table 1).

Considering the practice of physical activity assessed by IPAQ, the number of VEG classified as physically active (n=36, 81.8%) was significantly greater when compared to 25 OMN (56.8%) (p=0.011).

The table 2 shows the VEG and OMN macronutrient intakes. Although no significant difference was observed between the caloric intakes, VEG consumed significantly more carbohydrates, dietary fibers, polyunsaturated fats,

Table 1 – Anthropometric, clinical, and biochemical characteristics of apparently healthy vegetarians and omnivorous men

	Vegetarians (*n* = 44)	Omnivorous (*n* = 44)	p-value
Age	45.5 ± 7.8	46.8 ± 9.6	0.23
BMI (kg/m^2)	23.1 ± 2.9	27.2 ± 4.8	<0.001
WC	84.9 ± 7.71	95.7 ± 13.8	<0.001
WC/HC ratio	0.87 ± 0.1	0.92 ± 0.1	<0.001
SBP (mmHg)	119.5 ± 10.4	129.2 ± 15.1	<0.001
DBP (mmHg)	75.2 ± 8.6	83.9 ± 10.4	<0.001
TC (mg/dl)	180.1 ± 40.5	202.7 ± 35.3	0.003
HDL-c (mg/dl)	47.6 ± 9.3	45.5 ± 11.6	0.17
TC/HDL-c ratio	4.0 ± 1.3	4.7 ± 1.3	0.005
LDL-c (mg/dl)	110 ± 33.2	128.5 ± 32.4	0.005
Non-HDL-c (mg/dl)	132.5 ± 43.2	157.3 ± 36.6	0.002
TG (mg/dl)	112.2 ± 72.2	143.9 ± 64	0.016
Apo B (mg/L)	0.88 ± 0.28	1.01 ± 0.26	0.009
FSG (mg/dl)	94.8 ± 7.2	102.9 ± 13.1	<0.001
HbA1c (%)	5.3 ± 0.3	5.5 ± 0.5	0.004
PWV (m/s)	7.1 ± 0.8	7.7 ± 0.9	<0.001
c-IMT (μm)	593 ± 94	661 ± 128	0.003
Carotid distensibility (%)	6.39 ± 1.7	5.72 ± 1.8	0.042
Higher physical activity (n, %)	36 (81.8%)	25 (56.8%)	0.011

Data are means ± SD. Significant values for p < 0.05.
Apo B: apolipoprotein B; BMI: body mass index; c-IMT: carotid intima-media thickness; DBP: diastolic blood pressure; FSG: fasting serum glucose; HbA1c: glycosylated hemoglobin; HC: hip circumference; HDL-c: high density lipoprotein cholesterol; LDL-c: low density lipoprotein cholesterol; Non-HDL-c: non high density lipoprotein cholesterol; PWV: pulse wave velocity; SBP: systolic blood pressure; TC: total cholesterol; TG: triglyceride; WC: waist circumference.

Table 2 – Mean intake of macronutrients by apparently healthy vegetarian and omnivore men

	Vegetarian (n=44)	Omnivorous (n=44)	p-value
Energy (Kcal)	2177.2 ± 559.6	2348.9 ± 736.5	0.111
Carbohydrate (g)	341.9 ± 104.4	301.4 ± 99.6	0.033
Carbohydrate (% of energy)	63.2 ± 11.6	51.9 ± 9.7	<0.001
Dietary fiber (g)	28.2 ± 15.9	17.9 ± 13.6	<0.001
Protein (g)	91.3 ± 44.2	112.8 ± 39.9	0.009
Protein (% of energy)	17.1 ± 7.8	19.5 ± 4.5	0.04
Total fat (g)	61.7 ± 29.1	77.4 ± 33.7	0.011
Total fat (% of energy)	24.8 ± 8.3	29.1 ± 7.2	0.006
Saturated fat (g)	10.5 ± 8.8	18.1 ± 10.9	<0.001
Saturated fat (% of energy)	4.4 ± 3.2	6.9 ± 2.9	<0.001
Monounsaturated fat (g)	10.8 ± 7.0	17.6 ± 9.5	<0.001
Mono-unsaturated fat (% of energy)	4.5 ± 2.4	6.8 ± 2.8	<0.001
Polyunsaturated fat (g)	9.5 ± 6.8	6.9 ± 4.1	0.015
Polyunsaturated fat (% of energy)	4.0 ± 2.7	2.7 ± 1.6	0.004
Dietary cholesterol (mg)	69.3 ± 224.8	258.1 ± 169.1	<0.001
Plant stanols (mg)	44.8 ± 40.5	26.6 ± 41.9	0.020

and plant stanols. Moreover, omnivores significantly ingested larger amounts of protein, total fat, saturated fat, monounsaturated fat, and dietary cholesterol.

Most OMN (40.9%) consumed the amount of carbohydrates recommended by the NCEP, while most of the VEG (59.1%) ingested carbohydrates above recommendation (p <0.001). Most of VEG ate the recommended amount of fiber (38.6%) and 36.4% consumed > 30 g of fiber per day, while 65.9% of OMN ingested fibers in a quantity below the recommended amount (p<0.001). Most VEG and OMN ingested protein above the recommended amount, but the percentage of OMN (43.2%) who ingested 12% to 18% of protein is higher when compared to VEG (34.1%) (Table 3).

Most VEG (47.7%) ingested total fat below the recommended level, while most OMN (59.1%) ingested lipids within the recommended percentage, but with no significant difference. Most VEG (77.3%) met the recommendation of the saturated fatty acids rating, while most OMN (52.3%) exceeded this amount. The same thing was found with dietary cholesterol intake, 95.4% of VEG ate < 200 mg per day and 56.8% of OMN ate ≥ 200 mg per day. All VEG and OMN consumed monounsaturated and polyunsaturated fatty acids within the recommendation.

Regarding plant stanols, most VEG and OMN consumed > 2 grams per day, with no difference between groups (Table 3), although the media consumption was statistically higher in the VEG group (Table 2).

To find what type of dietary pattern had a higher chance of meeting the recommendation of each of the macronutrients, it was observed that VEG were more likely to consume < 7% of saturated fatty acids, and < 200 mg of dietary cholesterol (Table 4).

The associations of VEG diet with proper saturated fatty acids (P= 0.030), and dietary cholesterol (P= <0.001) consumption, were maintained after adjustment for caloric intake and age as multiple regression models.

Discussion

This study gathered information on the food intake of apparently healthy vegetarian and omnivorous men, and even linked the consumption of these two groups with dietary recommendations for preventing CVD [11]. Although no significant difference was observed

Table 3 – Distribution of the adequacy of the diet of apparently healthy vegetarian and omnivorous men according to dietary recommendations for the prevention of CVDs

Nutrient	NCEP recommendation		Vegetarian (n=44)	Omnivorous (n=44)	p-value
Carbohydrate	50-60% of total calories	< 50 %	11.4	38.6	<0.001
		50-60 %	29.5	40.9	
		> 60 %	59.1	20.5	
Dietary Fibers	20-30 grams per day	< 20 g	25.0	65.9	<0.001
		20-30 g	38.6	25.0	
		> 30 g	36.4	9.1	
Protein	Aproximately 15% of total calories	< 12 %	27.3	2.3	0.004
		12-18 %	34.1	43.2	
		> 18 %	38.6	54.5	
Total fat	25-35% of total calories	< 25 %	47.7	25.0	0.086
		25-35 %	40.9	59.1	
		> 35 %	11.4	15.9	
Saturated fatty acids	< 7% of total calories	< 7 %	77.3	47.7	0.004
		≥ 7 %	22.7	52.3	
Dietary Cholesterol	< 200 mg per day	< 200 mg	95.4	43.2	<0.001
		≥ 200 mg	4.6	56.8	
Plant stanols	2 grams per day	< 2 g	4.6	15.9	0.079
		≥ 2 g	95.4	84.1	

** Unable to parse because all VEG and OMN be in the same category of consumer.*

between the caloric intakes, these groups differed in the consumption of nutrients, which may be responsible for the development of CV risk factors. A greater number of VEG were classified as physically active when compared to OMN, which may have influenced the maintenance of normal clinical and biochemical parameters, as well as the lowest BMI and WC values.

Vegetarians consumed significantly more carbohydrate and dietary fiber, which can mean that, despite the higher consumption of carbohydrate, most of the nutrient may be of a complex type, with a higher fiber content, rather than a simple carbohydrate. Most of VEG men consumed the recommended amount of fiber and 36.4% ate > 30 g of fiber per day [11], while the majority of OMN men had a fiber intake of below the recommended amount. The higher consumption of fiber by VEG men can also be due to their higher consumption of food groups that provide this nutrient, such as fruits and vegetables, which was already demonstrated in a previous study.[24] As the present study did not analyze the food groups consumed, we can only formulate a hypothesis on this issue.

Although VEG men ingested more carbohydrates than the recommended amount, they presented lower BMI and cardiovascular risk factors, which are among the potential benefits of fiber intake.[25] Elorinne et al. (2016) found a higher consumption of carbohydrates and fiber among vegetarians in a sample of Finnish individuals, between 18 and 50 years of age.[26]

This contradicts the recommendations that a diet with less carbohydrate could have a positive influence on one's lipid profile,[27] which was not shown in this sample.

Most VEG and OMN ingest protein above the recommendation, but the percentage of OMN who ingest 12% to 18% of protein is higher when compared to VEG. Schüpbach et al. (2015)[28] also observed a lower intake of protein consumed in vegetarian than in omnivorous

Table 4 – Univariate regression models of association between type of diet and adequacy to dietary recommendations in apparently healthy vegetarian and omnivorous men

	OR	95% CI	p-value
Carbohydrate (50-60%)			
Omnivores	1		
Vegetarians	0.61	0.25-1.47	0.266
Dietary Fiber (20-30 g)			
Omnivores	1		
Vegetarians	1.89	0.76-4.7	0.172
Protein (12-18%)			
Omnivores	1		
Vegetarians	0.68	0.29-1.61	0.382
Total Fat (25-35%)			
Omnivores	1		
Vegetarians	0.48	0.20-1.12	0.090
Saturated fatty acids (<7%)			
Omnivores	1		
Vegetarians	3.72	1.48-9.35	0.005
Dietary Cholesterol (< 200 mg)			
Omnivores	1		
Vegetarians	27.63	5.93-128.74	<0.001
Plant stanols (≥ 2g)			
Omnivores	1		
Vegetarians	3.97	0.78-20.32	0.098

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

Swiss subjects. Furthermore, findings from Gilsing et al. (2013),[29] conducted with 1,150 self-reported vegetarians in the Netherlands Cohort Study, observed increased protein intake among VEG when compared to OMN men, which was due to a higher intake of vegetable protein. Among women, no difference was observed in the intake of total protein, but a significantly higher intake of vegetable protein and a lower intake of animal protein were observed.[29]

Most VEG ingested total fat below the recommended level, while most of the OMN ingested lipids within the recommended percentage, but with no significant difference. What is striking is that most VEG met the recommendation of saturated fatty acids rating and dietary cholesterol intake, while most of the OMN exceeded this level. This finding may well have contributed to the rise in LDL-c and ApoB observed in OMN (Table 1).

Both VEG and OMN consumed monounsaturated fat < 20% of total energy, but when evaluating grams of daily consumption, OMN consumed more monounsaturated fat. There is strong evidence that by replacing saturated fatty acids and carbohydrates with monounsaturated fatty acids, various cardiovascular risk factors will be significantly improved,[30] data that is contradictory to the lipid profile of this sample. The type of carbohydrate, rich in fibers, may well explain this. Many studies explain that an increased intake of fiber is associated with a reduced risk of CVD. One recently published systematic review and meta-analysis provided risk estimates for incident fatal events of CVD regarding total fiber intakes, while fiber sources confirmed the association between low dietary fiber consumption and an increased risk of CVD.[31]

NCEP recommendations do not include trans fatty acid intake, a limit proposed by other references to <1% of the total caloric value, and does not call for a minimum consumption of 5 to 10 grams of soluble fiber per day, as mentioned in the European Guidelines on Cardiovascular Disease Prevention in Clinical Practice,[32] recommending only the intake of 20-30 grams of total fiber per day.

Data similar to the present study were observed by Clarys et al. (2014)[33] in a Belgium sample of VEG and OMN. No differences were observed between total energy intakes, and protein and total fat intakes were significantly lower in VEG, while carbohydrate and fiber intakes were significantly higher in VEG.

In our previous study, the consumption of vegetables, fruits, and other vegetables was correlated with less CV risk factors.[34] Other studies demonstrated a greater variety in the diet of vegetarians, with the consumption of different plant foods, such as fruits and vegetables that have a high amount of antioxidants and compound bioactives, which may result in a beneficial health effect, since its antioxidant potential can help lower oxidation in plasma lipoproteins and lower occurrence of vascular injury.[35]

Tande et al. (2004)[36] observed, in a sample of 9,111 US adults, a positive association between meat and dairy intakes with increased LDL-c, whereas grain and fruit groups were associated with decreased TC and better HDL-c. The dietary pattern found in vegetarian groups is usually associated with an increased consumption of fruits, vegetables, and minimally processed vegetables.[37]

In 2015, Trepanowski and Varady conducted a literature review of available data and observed a greater efficiency of vegetarian diets in controlling glucose metabolism when compared to the application of the dietary recommendations of the American Diabetes Association (ADA) and in regulation of plasma lipoproteins than compared to the implementation of the National Cholesterol Education Program (NCEP) recommendations. The results of this study may suggest that it could be necessary to review the current dietary recommendations to prevent cardiovacular diseases.[38]

Studies seek to compare the food intake of omnivores with traditional dietary recommendations, often showing inadequacies.[39] However, the question that remains in the present study is: Is trying to adapt consumption to nutritional recommendations the best solution or does the adoption of specific dietary patterns, such as vegetarian, despite being outside of specific nutrient quantities, present a better association with cardiovascular health?

The Academy of Nutrition and Dietetics affirm that the low intake of saturated fat and high intake of vegetables, fruits, whole grains, soy products, nuts, and seeds (all rich in fiber and phytochemicals) are characteristics of vegetarian and vegan diets that produce lower total and low-density lipoprotein cholesterol levels and better serum glucose control. These factors contribute to a reduction in chronic diseases.[40]

One limitation of this study was its cross-sectional design, which does not verify causality between the type of diet and the development of cardiovascular risk factors. The was calculated in order to find differences between subclinical atherosclerosis markers, but this did not limit the significant associations observed in the present study. And finally the possible association between dietary intake and cardiovascular risk markers was not directly evaluated in the present study.

Despite this, if there was a representative sample of individuals following each type of vegetarian diet (ovo-lactovegetarian, lacto-vegetarian, and strict vegetarians), we could verify that the adequacy to the dietary recommendations behaves differently for each of these groups. Likewise, this heterogeneity of the vegetarian group may be responsible for the large confidence intervals observed in the analyses for some nutrients, such as dietary cholesterol, since a strict VEG diet is free of dietary cholesterol, and an egg-lactovegetarian can ingest amounts of dietary cholesterol similar to those of OMN individuals, depending on the frequency of consumption of food derived from eggs and dairy products.

This work was innovative in the sense that it compared the adequacy of dietary recommendations for preventing cardiovascular diseases, in the usual diet of apparently healthy VEG and OMN, while characterizing cardiovascular risk factors in both groups.

Conclusion

The present study showed that, despite the higher adequacy of the intake of carbohydrates and proteins by OMN, VEG were more likely to consume saturated fatty acids, dietary cholesterol, and fibers according to NCEP recommendations, regardless of caloric intake and age, factors that may contribute to lower levels of cardiovascular risk factors in VEG than in OMN.

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Author contributions

Conception and design of the research: Antoniazzi L, Acosta-Navarro J. Acquisition of data: Antoniazzi L, Oki AM, Bonfim MC. Analysis and interpretation of the data: Antoniazzi L, Acosta-Navarro J. Statistical analysis: Antoniazzi L. Writing of the manuscript: Antoniazzi L, Gaspar MCA, Oki AM, Bonfim MC. Critical revision of the manuscript for intellectual content: Acosta-Navarro J.

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 CAPPesq under the protocol number 35704. 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

Cardiovascular Benefits of Plant-Based Diets

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Editorial referring to the article: Better Adequacy of Food Intake According to Dietary Recommendations of National Cholesterol Education Program in Vegetarian Compared to Omnivorous Men

Increasing evidence suggests that plant-based dietary patterns, characterized by higher intake of plant foods and lower intake of animal foods, confer benefits to cardiovascular health.[1-4] Vegetarian diets are a subset of plant-based diets that exclude some or all animal products (vegan diets).[5]

A meta-analysis of 86 cross-sectional and 10 cohort prospective studies evaluated the association between vegetarian, vegan diets, risk factors for chronic diseases, risk of all-cause mortality, incidence, and mortality from cardio-cerebrovascular diseases. The overall analysis of cross-sectional studies revealed significantly reduced levels of body mass index, total cholesterol, LDL-cholesterol, and glucose levels in vegetarians and vegans compared with omnivores. In relation to cohort studies, the analysis showed a significantly reduced risk of incidence and/or mortality from ischemic heart disease by 25%.[6]

Yokoyama et al.,[7] conducted a meta-analysis of 30 observational studies and 19 clinical trials to assess the association of plant-based diets and plasma lipids. The authors concluded that plant-based diets are associated with decreased total cholesterol, LDL-cholesterol, and HDL-cholesterol, but not with decreased triglycerides. Eichelmann et al.,[8] observed that plant-based diets are associated with an improvement in obesity-related inflammatory profiles, with reductions in the concentrations of C-reactive protein, interleukin-6, and soluble intercellular adhesion molecule-1.[8]

Keywords

Plant-based diet, vegetarian diet, cardiovascular health.

Recently, the European Society of Cardiology highlighted that a shift from a more animal-based to a plant-based dietary pattern may reduce the risk of atherosclerotic cardiovascular disease.[3] In line with this, the American Heart Association (AHA) published a dietary guidance recommending the consumption of healthy sources of protein, mostly from plants, as soybeans, other beans, lentils, chickpeas, and peas to reduce cardiovascular risk.[9] In addition, there is a growing concern about the impact of the food system on the environment and climate change. A plant-based dietary pattern is more sustainable as it contributes to the reduction of greenhouse gas emissions.[10] The AHA also reinforced that the replacement if animal-source foods by plant-based whole foods has additional benefits to planetary health. Conversely, a sustainable dietary pattern is not necessarily associated with a lower cardiovascular risk, since a plant-based diet, high in refined carbohydrate and added sugar, may increase the risk of type 2 diabetes and cardiovascular disease (CVD).[9]

Baden et al.,[11] investigated the associations between 12-year changes (from 1986 to 1998) in plant-based diet quality assessed by three indices) – an overall plant-based diet index (PDI), a healthful plant-based diet index (hPDI), and an unhealthful plant-based diet index (uPDI) (score range: 18 to 90) – and subsequent total and cause-specific mortality (from 1998 to 2014). The study concluded that improving plant-based diet quality over a 12-year period was associated with a lower risk of total and cardiovascular mortality, whereas increased consumption of an unhealthful plant-based diet was associated with a higher risk of total and CVD mortality.[11] In another cohort, it was observed that

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improving adherence to overall and healthful plant-based diets was associated with a lower risk of type 2 diabetes, whereas decreased adherence to such diets was associated with a higher risk.[12]

In addition to the known benefits of increased fiber intake, the positive effects of healthy vegetarian and plant-based diets also might be attributed by the modulation of gut microbiota composition. Increasing evidence has shown that different dietary patterns affect the gut microbiota, and differences in this ecosystem between vegetarian and omnivores have been documented. Plant-based diets seem to contribute to greater diversity in gut microbiota, which is associated with lower risk of developing metabolic disorders and CVD.[13] This positive impact may be due to the higher amount of fermentable fibers, polyphenols and polyunsaturated fatty acids in the diet, that act as prebiotics and selectively stimulate the increase of beneficial species.[14]

In this issue of the Journal, Antoniazzi et al.,[15] in a cross-sectional study, compare dietary adequacy, according to the recommendations of the National Cholesterol Education Program (NCEP), between apparently healthy vegetarians and omnivorous men. Several cardiovascular risk markers were significantly lower in vegetarians compared to omnivores, including, body mass index, waist circumference, blood pressure, total cholesterol, LDL cholesterol, triglycerides, apolipoprotein B, fasting glucose, glycated hemoglobin, pulse wave velocity, and carotid intima-media thickness. Vegetarians consumed significantly more dietary fibers, polyunsaturated fats and plant stanols, and significantly less protein, total fat, monounsaturated fat, saturated fat and dietary cholesterol. The NCEP recommendations for saturated fat (<7% of total calories), dietary cholesterol (<200mg/day) and fiber (20-30g/day) were met, respectively by 77%, 95% and 39% of vegetarians vs. 48%, 43% and 25% of omnivores ($p<0.01$). All vegetarians and omnivores consumed monounsaturated and polyunsaturated fatty acids within NCEP recommendations. Logistic regression analysis showed that, compared with omnivorous diets, vegetarian dietary patterns were associated ($p<0.05$) with an adequate intake of saturated fat and dietary cholesterol, even after adjustment for energy intake and age. The authors concluded that vegetarians were more likely to consume saturated fat, cholesterol, and fibers according to NCEP recommendations, which may contribute to lower levels of cardiovascular risk markers.

In summary, the findings of the study conducted by Antoniazzi et al.,[15] are in line with recent evidence suggesting beneficial effects of plant-based diets, and highlight that achieving nutritional recommendations for CVD prevention may be easier for vegetarians compared to omnivores.

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ORIGINAL ARTICLE

Cardiovascular Risk Assessment after COVID-19 Infection before Resuming Sports Activities - Practical Flowchart and Meta-Analysis

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Abstract

Background: The risk of sports-related sudden cardiac arrest after COVID-19 infection can be a serious problem. There is an urgent need for evidence-based criteria to ensure patient safety before resuming exercise.

Objective: To estimate the pooled prevalence of acute myocardial injury caused by COVID-19 and to provide an easy-to-use cardiovascular risk assessment toolkit prior to resuming sports activities after COVID-19 infection.

Methods: We searched the Medline and Cochrane databases for articles on the prevalence of acute myocardial injury associated with COVID-19 infection. The pooled prevalence of acute myocardial injury was calculated for hospitalized patients treated in different settings (non-intensive care unit [ICU], ICU, overall hospitalization, and non-survivors). Statistical significance was accepted for p values <0.05. We propose a practical flowchart to assess the cardiovascular risk of individuals who recovered from COVID-19 before resuming sports activities.

Results: A total of 20 studies (6,573 patients) were included. The overall pooled prevalence of acute myocardial injury in hospitalized patients was 21.7% (95% CI 17.3-26.5%). The non-ICU setting had the lowest prevalence (9.5%, 95% CI 1.5-23.4%), followed by the ICU setting (44.9%, 95% CI 27.7-62.8%), and the cohort of non-survivors (57.7% with 95% CI 38.5-75.7%). We provide an approach to assess cardiovascular risk based on the prevalence of acute myocardial injury in each setting.

Conclusions: Acute myocardial injury is frequent and associated with more severe disease and hospital admissions. Cardiac involvement could be a potential trigger for exercise-induced clinical complications after COVID-19 infection. We created a toolkit to assist with clinical decision-making prior to resuming sports activities after COVID-19 infection.

Keywords: Risk Factors; COVID-19; Betacoronavirus; Myocarditis; Inflammation; Sudden Cardiac Death; Sports Medicine; Sports.

Introduction

The recent severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) outbreak has created an unprecedented global challenge and triggered the implementation of interventions to promote social distancing, including cancellation of sports events. Importantly, coronavirus disease (COVID-19) affects relatively young people, with 77.8% of diagnoses in the age range of 30-69 years.[1] Around 80% of patients have mild disease, 15% moderate disease and 5% severe disease, requiring admission to intensive care units (ICU).[1]

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Most of the competitive and recreational athletes infected with COVID-19 fall into the low-risk group and have mild disease. However, many cases of young, healthy subjects who develop severe systemic illness have been reported. Cardiovascular (CV) complications are strongly associated with mortality among infected patients, but the pathophysiological pathway of cardiac involvement is still unclear.[2] Several mechanisms of myocardial injury have been proposed, including systemic inflammation (cytokine storm), microvascular dysfunction, immunological factors, direct cellular damage by viral invasion, stress cardiomyopathy and hypoxia.[3] Cases of acute myocarditis due to COVID-19, confirmed by cardiac magnetic resonance, endomyocardial biopsies and post-mortem analyses, have been reported.[4-6] Myocardial injury is defined as a troponin level above the 99th percentile, with prevalence rates in published data ranging from 7.2 to 27.8% in hospitalized patients. However, a definitive diagnosis and the prevalence of myocarditis is difficult to establish in most settings.[7,8] Furthermore, the pathophysiology of COVID-19-related acute cardiac injury remains unknown and limited data about the long-term sequelae are available.

Exercise is a known trigger for sudden cardiac arrest after myocarditis. Usually, a 3 to 6 months of exercise restriction is recommended.[9] As society returns to "normal" after COVID-19, a considerable number of recovered individuals will face the challenge to resume regular exercise, which is associated with health benefits. Although some experts have issued statements, no evidence-based recommendations are yet available. Therefore, we identified an urgent need to collate existing evidence of recommendations on resuming physical activity after COVID-19, which could be used as basis for policy-making to sports authorities.

The aim of the current review and meta-analysis was to estimate the pooled prevalence of acute myocardial injury caused by COVID-19 infection and to provide a CV risk assessment toolkit for patients recovered from COVID-19 to resume sports activities.

Methods

Study identification and selection

We performed a literature search of Medline and Cochrane Library (Cochrane Central Register of Controlled Trials) databases using the search terms "COVID-19" and "myocardial injury" on 11 June 2020. We also searched the references of the articles using the same keywords. Articles that reported the prevalence of acute myocardial injury due to confirmed COVID-19 infection were included. Acute myocardial injury was defined as elevation of cardiac troponin above the 99th percentile upper reference limit with or without new abnormalities in electrocardiography (ECG) or transthoracic echocardiography (TTE). Exclusion criteria were non-English language, duplicate publications, and publications only available as abstract or oral presentation.

A total of 107 studies were retrieved from the Medline database, six studies were identified in the Cochrane database, and seven studies were identified by reference cross-checking. From all these studies, 67 were excluded based on title and abstract evaluation, as they did not meet the inclusion criteria. A full-text analysis of 52 studies was conducted by two independent reviewers (LP and PD). Of these studies, 32 did not meet the inclusion criteria and were excluded. Finally, a total of 20 studies were included in the meta-analysis. Figure 1 shows the details of the study identification and selection process.

Study endpoints and data collection

The primary endpoint of the study was prevalence of acute myocardial injury. The following data were also collected: date of publication, study setting (ICU or non-ICU, survivors vs non-survivors), study location, and participants' gender, age and history of previous CV disease.

Data analysis and statistical methods

The prevalence of acute myocardial injury was calculated as a proportion (number of affected subjects per total number of participants). Statistical analyses were performed using the R Statistical Software (R Core Team 2020) with the package for meta-analysis.[10] Since the heterogeneity between the cohorts of the studies analyzed did not allow a single metanalysis, a four-group analysis was performed according to the setting – "non-ICU": cohort of hospitalized patients out of ICU; "ICU": cohort of hospitalized patients in ICU; "non-survivors": cohort of hospitalized patients with an outcome of death; and "overall hospitalized patients": cohort that included studies with hospitalized patients regardless of the setting in which they were treated.

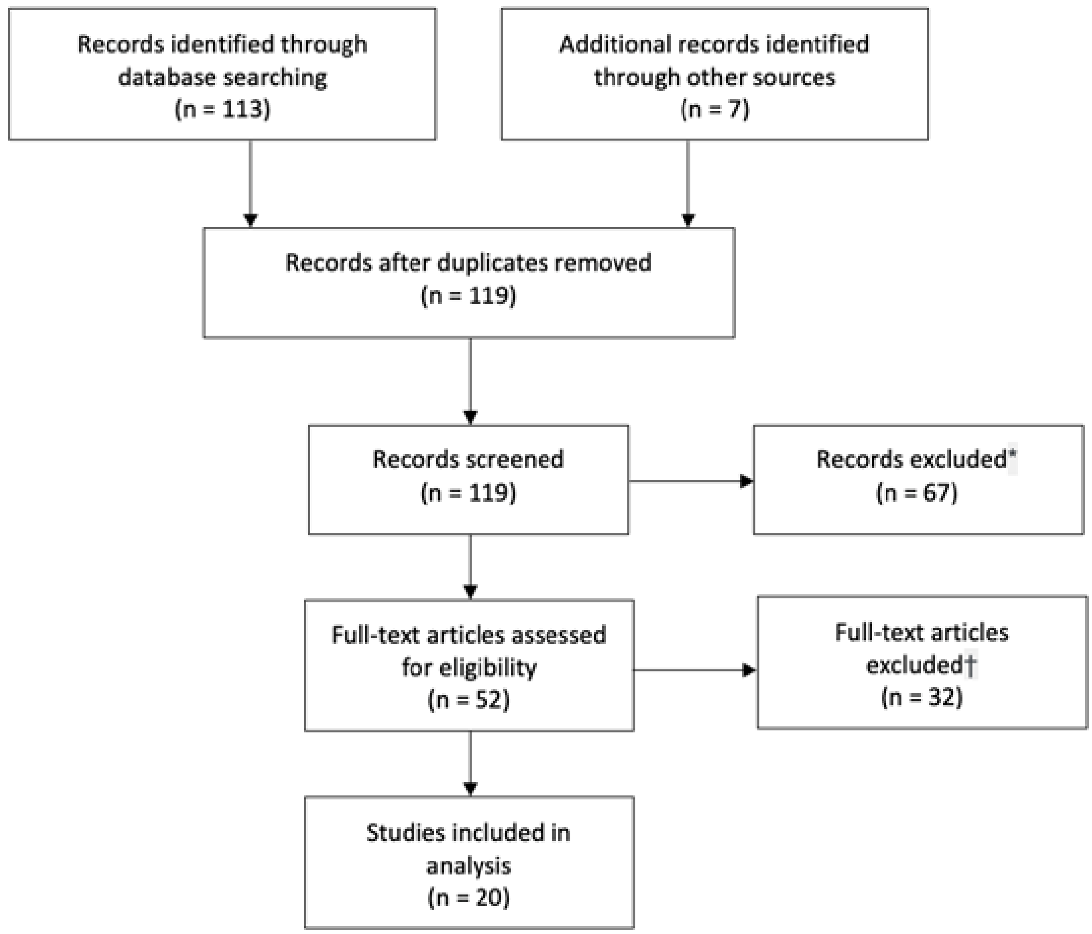

Figure 1 – Flow diagram of the study selection process
**Reasons for exclusion: 40 review studies not relevant to this meta-analysis, 11 studies were written in non-English language, 8 studies were case reports, 7 studies were on children and 1 study was an editorial comment.*
†24 were study reviews that did not provide any new data, 6 studies were drug trials, one study was a trial protocol, and one study was on oncological patients and could not be included in the analysis.

Some studies were included in more than one group analysis if they provided information that matched more than one setting. A random effects model was used for each setting to calculate the pooled prevalence. Pooled prevalence and 95% confidence intervals (CI) were expressed as percentages. The I^2 statistic was used to assess heterogeneity across studies; moderate heterogeneity was defined as values between 30-60%. Statistical significance was accepted for p values <0.05.

A clinical management flowchart for individuals recovered from COVID-19 was built as a cardiovascular risk assessment tool. The flowchart was based on the different treatment settings, which were surrogate markers for disease severity according to the metanalysis.

Results

Prevalence of acute myocardial injury

A total of twenty studies were included. The total number of participants included in the non-ICU, ICU, non-survivors and overall hospitalized settings were 518, 1042, 368 and 6573, respectively. Table 1 shows the key characteristics of the included studies and the numbers of participants in each setting. Forest plots of pooled data are depicted in Figure 2. The overall pooled prevalence of acute myocardial injury considering all hospitalized patients was 21.7%, (95% CI 17.3-26.5%, $p < 0.01$, $I^2 = 93\%$), and increased with increasing disease severity. The pooled

Table 1 – Summary of studies included in the meta-analysis

						Number of participants included (n)			
Author	Cohort (setting)	Location	Age	Males	Previous CVD	Non-ICU	ICU	Non-Survivors	Overall Hospitalized
Huang, C[17]	Hospitalized (ICU vs Non-ICU)	Wuhan, China Jinyintan Hospital	49 (41–58)	73	15	28	13		41
Zhou, F[18]	Hospitalized (Survivors vs Non-survivors)	Wuhan, China Jinyintan Hospital and Pulmonary Hospital	56 (46–67)	62	30 HTN 19 DM 8 CAD			54	191
Wang, D[7]	Hospitalized (ICU vs Non-ICU)	Wuhan, China Zhongnan Hospital	56 (42-68)	75	20	102	36		138
Shi, S[19]	Hospitalized (Cardiac injury vs without cardiac injury)	Wuhan, China Renmin Hospital	64 (range 21-95)	49.3	30.5 HTN 14.4 DM 10.6 CAD				416
Guo, T [8]	Hospitalized (Cardiac injury vs without cardiac injury)	Wuhan, China Seventh Hospital	58.5 (14.7)	48.7	32.6 HTN 15.0 DM 11.2 CAD				187
Yang, X[20]	ICU (survivors vs non-survivors)	Wuhan, China Jinyintan Hospital	59.7 (13.3)	67	10		52	32	
Ruan, Q[21]	Hospitalized (survivors vs non-survivors)	Wuhan, China Jinyintan Hospital	50 (44-81) 67 (15-81)	68	8.7			68	
Zhou, B[22]	Hospitalized (Severe vs Very Severe)	Wuhan, China Tongji Medical College	63 (58-69) 67 (66-75)	50	0†	26 SEVERE*	8 VERY SEVERE*		
Yang, F[23]	Non-survivors	Wuhan, China Renmin Hospital	69.8 (15)	53.3	17.4			92	
Deng, Q[24]	Hospitalized (Severe vs Very Severe)	Wuhan, China Renmin Hospital	65 (49-71)	50.9	32.1 HTN 17.0 DM 13.4 CAD	45 NON-SEVERE‡	67 SEVERE‡		112
Aggarwal, S[25]	Hospitalized (Severe vs non-severe)	Iowa, USA UnityPoint, Des Moines Hospital	67 (range 38-95)	75	57 HTN 19 DM 19 CAD				16
Wei, J[26]	Hospitalized (Cardiac injury vs without cardiac injury)	Sichuan, China Chengdu and West China Hospital	49 (34-62)	54	21 HTN 14 DM 5 CAD				101
Li, D[27]	Hospitalized (Cardiac injury vs without cardiac injury)	China ERS-COVID-19 study (2 hospitals)[28]	CI 71 (66-83), No CI 60 (48-68)	CI 24 (61.5), No CI 75 (52.4)	0†				182
Shi, S[29]	Severe and critical hospitalized patients (survivors vs non-survivors)	Wuhan, China Renmin Hospital	63 (50– 72)	48	29.7 HTN 14.5 DM 8.9 CAD		671	62	
Ni, W[30]	Hospitalized (survivors vs non-survivors)	Wuhan, China Central Hospital	67 (57–73)	57.4	49.3 HTN 26.7 DM 14.2 CAD			60	176

Yang, Q[31]	Hospitalized (moderate vs severe or critical)	Wuhan, China Third Hospital	56 (44-64)	48.5	27.1 HTN 14.7 DM	103 MODERATE§	33 SEVERE/ CRITICAL§		136
Zhao, M[32]	Hospitalized	Wuhan, China Renmin Hospital	61 (46-70)	46.6	28.2 HTN 11.8 DM 6 CAD				1000
Arentz, M[33]	Hospitalized in ICU	Washington state, USA Evergreen Hospital	70 (range, 43-92)	52	33.3 DM		21		
Richardson, S[34]	Hospitalized	12 hospitals in New York, USA	63 (52-75)	60.3	56.6 HTN 33.8 DM 11.1 CAD				3522
Suleyman, G[16]	Admitted to Emergency department	Hospitals in Henry Ford Health System in Detroit, Michigan, USA	57.5 (16.8)	44.1	63.7 HTN 38.4 DM 12.7 CAD	214	141		355
		Total number of participants				518	1042	368	6573

CAD: coronary artery disease; CI: Cardiac injury; DM: diabetes mellitus; ECG: electrocardiography; HTN: hypertension; ICU: intensive care unit; IQR: interquartile range; SD: standard deviation
Age data is presented as median (IQR) or Mean (SD); Male gender and Previous CVD expressed as %
Ruan, Q[35]; Zhou, B[36]; Ni, W[30] did not provided level of accepted significance. Arentz, M[33] and Richardson, S[34] did not performed analysis of significance. All other studies accepted p values < 0.05 for statistically significant differences.
**Severe disease considered as one of the following: 1) Respiratory distress with respiratory rate more than 30 times/min; 2) Oxygen saturation ≤93% in resting state; 3) PaO2/FiO2≤300mmHg; Very severe disease considered as one of the following: 1) Respiratory failure in need of mechanical ventilation; 2) Shock; 3) Other organ dysfunction.*
†Excluded patients with previous cardiovascular disease
‡Severe defined as having one of the following: respiratory distress and respiratory rate higher than 30 times per minute; fingertip blood oxygen saturation less than 93% at rest; partial arterial oxygen pressure (PaO2) / fraction of inspiration oxygen (FiO2) less than 300mmHg, respiratory failure requiring mechanical ventilation; shock; multiple organ failure, requiring intensive care management
§Moderate considered as having one of the following: fever and respiratory symptoms, pneumonia manifestations in the imaging; Severe and critical defined as having one of the following: shortness of breath with respiratory rate (RR) ≥30 bpm or finger SpO2 ≤93% at rest, respiratory failure (requiring mechanical ventilation), shock or other organ failure (requiring ICU monitoring and treatment)

prevalence of acute myocardial injury was the lowest for the non-ICU setting, 9.5% (95% CI 1.5–23.4%, $p < 0.01$, $I^2 = 94$). Patients admitted to ICU had a pooled prevalence of acute myocardial injury of 44.9% (95% CI 27.7-62.8%, $p < 0.01$, $I^2 = 95\%$), whereas non-survivors had the highest pooled prevalence of acute myocardial injury, 57.7% (95% CI 38.5-75.7%, $p < 0.01$, $I^2 = 93\%$). The pooled prevalences showed high heterogeneity among the settings, with $I^2 > 90\%$.

Cardiovascular risk assessment before resuming sports activities

We propose a CV risk assessment tool, constructed based on the estimated disease severity, for patients who recovered from COVID-19 infection and wish to resume sports activities. A flowchart summarising our approach is presented in Figure 3. The treatment settings were used as surrogate markers for disease severity (outpatient, mild disease; 'inpatient non-ICU setting', moderate disease and 'inpatient ICU setting', severe disease). For the purpose of our study, a simplified approach to disease classification was defined as follows: 1) Mild disease – patients treated at home, who responded well to symptomatic medication and did not show signs of respiratory insufficiency; 2) Moderate disease – patients with some degree of respiratory insufficiency or need for hospitalization for supplemental oxygen or symptomatic control; 3) Severe disease – patients with respiratory or other end-organ failure requiring mechanical ventilation, ICU admission, or any other vital organ support.

Discussion

Our study results showed that the overall prevalence of COVID-19-related acute myocardial injury is high, and increases with disease severity, as observed by the increased prevalence in the inpatient non-ICU setting, inpatient ICU setting and non-survivors.

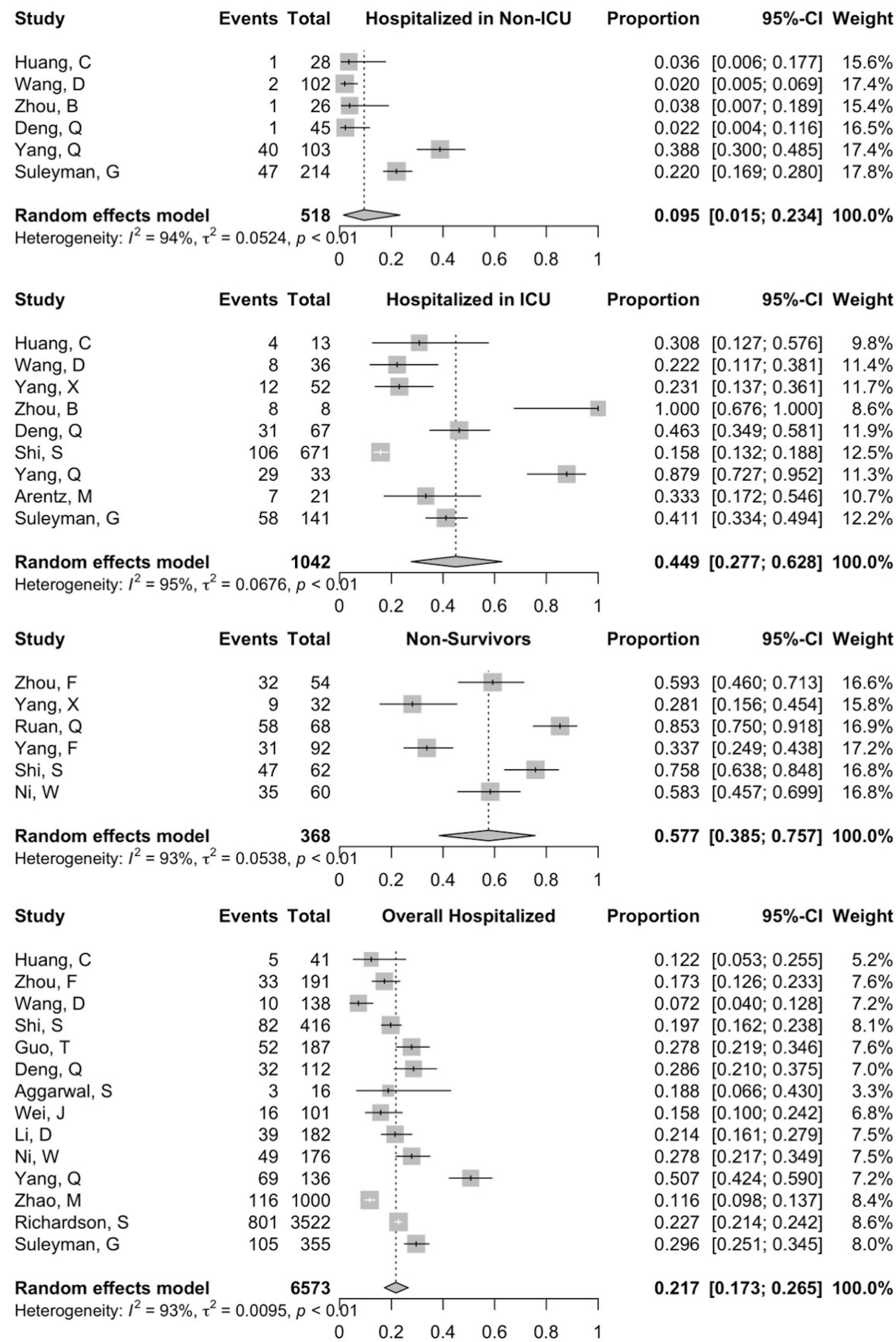

Figure 2 – Forest plot of the pooled prevalence of acute myocardial injury

CI: confidence interval; ICU: intensive care unit; IV: individual value

Prevalence and 95% confidence intervals expressed as proportions

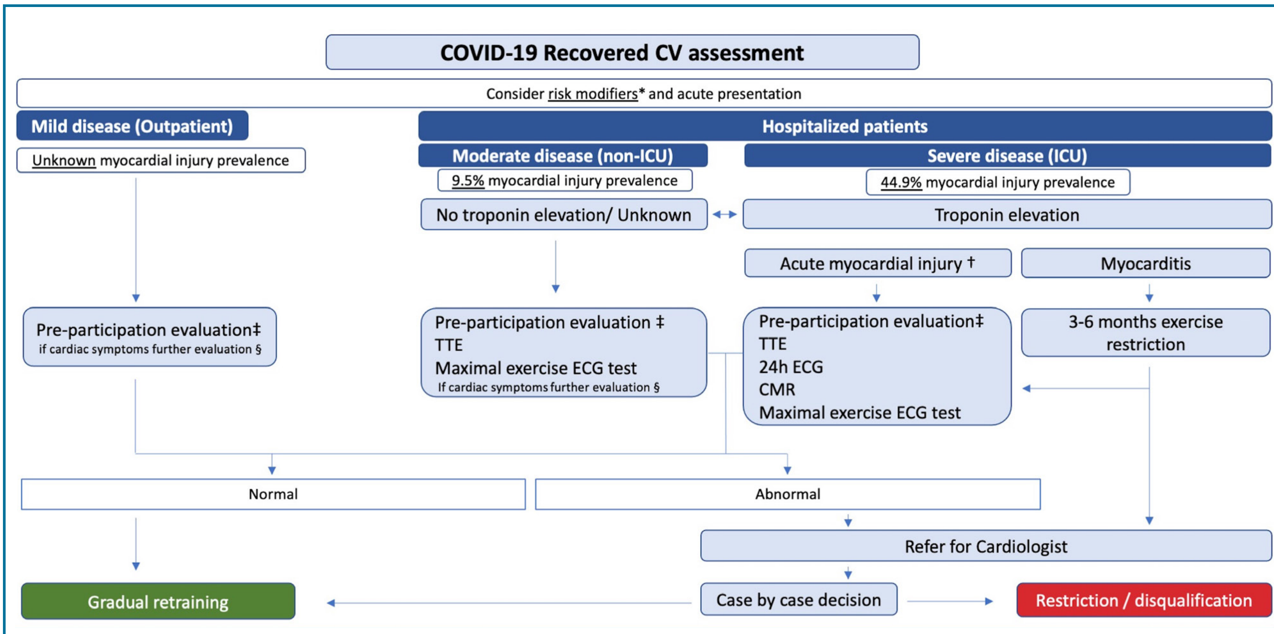

Figure 3 – Cardiovascular assessment flowchart for patients recovered from COVID-19 to resume sports activities
CV: Cardiovascular; ECG: Electrocardiography; ICU: intensive care unit; CMR: cardiac magnetic resonance; TTE: transthoracic echocardiography
** Risk modifiers (Pre-existing CV disease; Exercise type (intensity and competitive level)*
† Acute myocardial injury: evidence of myocardial injury at hospital admission - Elevated serum biomarkers of myocardial injury (troponin)
‡ 12-lead ECG included
§ Systematically search for symptoms of myocardial injury (chest pain, syncope, palpitations, dyspnea, fatigue); consider additional testing accordingly

Risk stratification and flowchart implementation

The pooled prevalence of acute myocardial injury showed that patient care setting reflected disease severity. Estimation of disease severity is the first step to determine the treatment approach and ensure patient safety. Although it is not known if COVID-19-related myocarditis is associated with sudden cardiac death, the prevalence of myocardial injury may be the best approximation for risk stratification based on available data. We present a proposed flowchart (Figure 3) that aids clinical decision-making for cardiovascular workup. We acknowledge that the decision to admit patients to the ICU varies widely based on local policies and other non-clinical factors such as availability of resources (e.g., beds, ventilators, healthcare insurance, etc.). However, we believe that this was the simplest and most practical way to standardise data from different cohorts. In addition, this approach based on patient care setting is fast and easy-to-use for physicians evaluating individuals wishing to engage in exercise training after COVID-19 infection.

The objective of the flowchart is to serve as an aid to clinical decision-making. This flowchart should only be applied to individuals who had completely recovered. Although the management of infected individuals falls out of the scope of our work, it has been proposed an interval of at least seven days free from symptoms before resuming exercise.[11-13] Full recovery must be confirmed (as recommended by local authorities) before conducting additional diagnostic tests. In particular, a treadmill test or other exercise tests, and pulmonary function tests (PFT) have an associated risk of aerosolization and should preferably be avoided in SARS-Cov-2 positive patients. However, if these tests are essential, adequate personal protective equipment must be used. For sports activities, local authorities' recommendations for the use of personal protective equipment and social distancing should be followed.

We also recommend that this cardiovascular risk assessment tool be used regarding potential risk factor modifiers. Age, male gender and previous CV disease have been associated with adverse outcomes.[14] The impact of exercise type, exercise intensity, and a state of deconditioning on immune system, oxidative stress and inflammation has been extensively debated in the literature. For competitive athletes, team physicians, exercise physiologists and coaches should all be involved to prescribe an appropriate training plan with progressive increases in exercise intensity. In clinical practice, we suggest that patients with pre-existing CV diseases, such as coronary artery disease (CAD), heart failure, cardiomyopathies, and arrhythmias warrant further CV investigations before resuming sports activities, preferably with a cardiology specialist. The type of sport, intensity and competitive level should also be taken into account. High-intensity sports athletes, elite and professional athletes often undergo routine cardiovascular screening that may include TTE and maximal exercise test as a pre-participation evaluation. We recommend that the physician repeat the screening after recovery from COVID-19.

Based on our findings, we recommend that a full pre-participation clinical evaluation (including a resting 12-lead ECG) be performed in all recovered individuals willing to return to sports activities. The ECG is a key component of the pre-participation screening as recommended by most European societies.[15] Special attention should be placed on QT interval measurements in patients treated with chloroquine or hydroxychloroquine.

Outpatient setting

Suleyman et al.[16] reported a prevalence of myocardial injury of 1,9% (2 of 108) in symptomatic patients treated in an outpatient setting, however, cardiovascular outcomes of these patients were not evaluated. To the best of our knowledge, there is no other work addressing the prevalence or the outcomes of myocardial injury in outpatients with COVID-19 infection. Moreover, management of asymptomatic patients wishing to engage in sports is also an important issue, with no data supporting safety. Clinical experience suggests that the majority of athletes will probably experience mild or asymptomatic disease, and be treated in an outpatient setting. Therefore, the prevalence of myocardial injury is expected to be even lower in athletes compared with the non-ICU hospitalized setting. In addition, it is reasonable to assume that young, healthy individuals will most likely be able to recover from a more severe form of the disease without seeking medical attention. In our opinion, a pre-participation clinical evaluation (including resting ECG) is mandatory and we strongly recommend a systematic approach to identify signs and symptoms of cardiac disease (e.g. chest pain, syncope, palpitations, dyspnoea or abnormal fatigue). The presence of these signs and symptoms should warrant further investigations with TTE, maximal exercise ECG test or 24-hour ambulatory ECG monitoring test based on the symptoms exhibited. Referral to a cardiologist is recommended if any of these tests are abnormal.

Inpatient setting

Although non-CV assessments are outside the scope of our review, it is important to note that most of hospital admission criteria are based on pulmonary disease. For that reason, PFTs, lung CT scans (if not performed during admission) and routine laboratory tests may provide further information to assess exercise fitness.

Elevation of serum biomarkers of cardiac injury has shown to be an important prognostic factor among hospitalized patients for COVID-19.[8] For recovered individuals treated in an inpatient setting who wish to resume exercise, the physician should carefully assess patients for evidence of myocardial injury (i.e. serum troponin above the 99th percentile of upper reference limit during hospitalisation). If a patient is discharged from hospital with a definitive diagnosis of myocarditis, specific treatment recommendations must be followed,[9] with exercise restrictions for 3 to 6 months and regular follow-up with a cardiologist. As recommended by the European Association of Preventive Cardiology, these patients may resume training and competition if left ventricle systolic function has returned to the normal range, serum biomarkers of myocardial injury have normalized and clinically relevant arrhythmias, such as frequent or complex repetitive forms of ventricular or supraventricular arrhythmias are absent on 24-h ECG monitoring and exercise test. Regular surveillance should be kept for two years and annually if late gadolinium enhancement persists on cardiac magnetic resonance (CMR)[9]

Patients without a definitive diagnosis of myocarditis, but with evidence of acute myocardial injury, fall into a "grey area". It is reasonable to consider that this group of patients may have recovered but with cardiac sequelae. Whether or not this will impact on clinical events is still unknown. However, we suggest that these patients undergo an assessment of cardiac anatomy and function, with specific focus on arrhythmias in a resting state and during exercise. Moreover, CMR imaging may play a fundamental role in the assessment of the risk for adverse outcomes during follow-up and should be performed when available.

With respect to hospitalized patients in a non-ICU setting without elevation of troponin, or in cases where cardiac biomarkers were not assessed, the authors recommend performing a TTE and maximal exercise ECG test as part of the clinical evaluation, including a 12-lead ECG. Signs and symptoms of cardiac disease must also be assessed.

Based on published data, young, healthy individuals who require ICU admission are rare. A minority group will most likely have a severe form of disease that will impact on physiological functions, including respiratory, cardiovascular, renal, and musculoskeletal. A multidisciplinary approach and a complete cardiac assessment (12-lead ECG, TTE, 24h ECG ambulatory monitoring and maximal exercise ECG test) is therefore recommended. If cardiac abnormalities are detected in these patients a CMR to assess myocardial sequelae should also be completed.

Limitations

Most data on the prevalence of myocardial injury derived from one country (China), especially from the city of Wuhan. Additionally, there isn't any information regarding the level of physical activity from participants of the studies. Also, the possibility that duplicate patients were included in the meta-analysis cannot be excluded. Therefore, it is difficult to extrapolate these results to a worldwide scenario and particularly to competitive athletes. Still, the authors point out that exercise-associated sudden cardiac death after a viral myocarditis is a significant issue in the context of SARS-COV-2 pandemic and for any individual wishing to engage in physical activity after SARS-COV-2 infection.

Our meta-analysis included different cohorts that may have different policies for COVID-19 testing. Also, the criteria for hospital and ICU admission may vary significantly from one place to another, as may the availability of resources. This may influence such decisions, and hence the prevalence and severity of COVID-19-associated cardiac injury. These limitations may affect the proportion of patients with COVID-19-related myocardial injury. Therefore, our approach may be unpredictable in different contexts and must never replace a thorough clinical judgement.

Statistical analysis suggests significant heterogeneity in the prevalence of acute myocardial injury among the patient care settings. However, the clinical meaning of such heterogeneity for the purpose of a prevalence study may be irrelevant given that the prevalence of myocardial injury is used as a parameter of disease severity rather than for clinical decision-making.

The absence of clinical trials including individuals who resumed sports activities after COVID-19 infection makes it difficult to establish the link between myocardial injury and sports-related adverse outcomes.

It is also likely that this meta-analysis overestimates the prevalence of myocardial injury due to selection bias, since some of the studies excluded patients without clinical records of cardiac biomarkers.

Our approach is focused on the clinical safety of patients, however, no cost-effectiveness data are available. Furthermore, the sports community involves different financial capacities that may make this strategy difficult to implement in some settings and may carry a heavy burden of costs.

Conclusions

Our data showed that the prevalence of myocardial injury in patients with COVID-19 is high and may be associated with disease severity. As myocardial involvement can be a trigger for severe clinical complications induced by exercise, we provide a practical flowchart to assist clinical decisions that may be the basis for evidence-based recommendations.

Our study proposes a CV risk stratification strategy for patients recovered from COVID-19 infection to resume any type of physical activity. Further studies are required to test the sensitivity and specificity of this approach in a real clinical scenario and its economic impact on a global scale.

Author contributions

Conception and design of the research: Puga L, Dinis P, Teixeira R, Dores H, Goncalves L. Acquisition of data: Puga L, Dinis P. Analysis and interpretation of the data: Puga L, Dinis P, Ribeiro J, Teixeira R. Statistical analysis: Puga L, Ribeiro J, Teixeira R. Writing of the manuscript: Puga L, Dinis P Critical revision of the manuscript for intellectual content: Goncalves L, Dores H, Teixeira R, Dinis P.

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EDITORIAL

Exercise Is Medicine! How to Safely Return to Sports after COVID-19? A Meta-Analysis and a Practical Flowchart for Cardiovascular Risk Assessment may Help you

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Editorial referring to the article: Cardiovascular risk assessment after COVID 019 infection before resuming sports activities-practical flowchart and meta-analysis

"There are truly two different things: knowing and believing one knows. Science consists in knowing; in believing one knows lies ignorance."

Hippocrates

Exercise is medicine! Although this premise is well established, how to maintain this "treatment" for various diseases during the COVID-19 pandemic? This has been a concern of all doctors in the world since exercise contributes to the control of cardiovascular diseases and other comorbidities recognized as risk factors for a worse outcome in COVID-19. Moreover, it has already been shown that higher cardiorespiratory fitness is inversely associated with the likelihood of hospitalization due to COVID-19.[1]

In addition to the hygiene and social distancing measures necessary to prevent coronavirus infection, cardiovascular sequelae in individuals recovering from COVID-19 may contribute to the delay in resuming exercise. Cardiovascular complications, including myocarditis, are relatively common in patients affected by SARS-CoV-2. Although the occurrence of myocarditis as a consequence of COVID-19 was initially described in hospitalized patients with severe presentation of the disease, subsequent studies have reported its occurrence in individuals with mild COVID-19 and even in asymptomatic patients.[2]

Thus, an alert was raised regarding the return to sports after COVID-19, since myocarditis is an important cause of sudden death in young individuals, especially in athletes. Since then, experts around the world have studied the occurrence of COVID-19-related myocarditis and discussed what would be the best way to return to exercise safely after recovering from the disease.[3]

The meta-analysis by Puga et al.,[4] makes a review of studies published until June 2020, to evaluate the prevalence of myocardial injury and propose a flowchart to assess cardiovascular risk in patients affected by COVID-19, to ultimately guide a safe return to exercise. Data from more than 6,000 hospitalized patients from China and the USA were divided according to the severity of the disease, based on requirement of intensive care unit (ICU) admission including non-survival. This interesting article, published in this issue, shows that there is a correlation between elevated troponin levels and the presence of myocardial injury. Also, the prevalence of myocarditis in hospitalized COVID-19 patients (21,7%) increased with disease severity – 9.5% among patients who did not require intensive care unit (ICU) admission, and 57.7% among those who did not survive. These findings are similar to another recent review[4] that reported a prevalence of myocarditis of 24.4% in hospitalized patients with COVID-19 and troponin elevation in 90% of them.

Puga et al.,[4] highlighted the lack of information in asymptomatic patients, including athletes, and reported a frequency of 1.9% of myocarditis in symptomatic non-hospitalized individuals (considered to have mild COVID-19), and many cases of severe COVID-19 in previously healthy individuals. Based on these, the authors discussed the urgent need for recommendations for resuming exercise after COVID-19 and proposed an evaluation based on the severity of the disease. The recommendations suggested by the Portuguese group are very interesting, and have similarities to the

Keywords

Exercise; Athletes; cardiovascular Diseases; Comorbidities; COVID-19; SARS-CoV-2, Sport; Sudden Death; Pandemic.

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ones suggested by the Department of Ergometry, Exercise, Nuclear Cardiology, and Cardiovascular Rehabilitation (DERC) of the Brazilian Society of Cardiology (SBC) and the Brazilian Society of Exercise and Sports Medicine (SBMEE) in the "Position Statement on Post-COVID-19 Cardiovascular Preparticipation Screening: Guidance for Returning to Physical Exercise and Sports – 2020" recently published.[5] Both recommend a preparticipation cardiovascular screening of all individuals recovered from COVID-19, according to the clinical presentation of the disease (mild, moderate or severe) and the intensity of exercise practice.

Measurement of serum troponin T has been considered important in the screening of patients with moderate and severe clinical conditions, as it can be a marker of myocardial injury.[6] However, its use in athletes has been much discussed due to its variations during physical training and consequent lack of standard normal values. However, considering it is a low-cost and easy-to-perform test, I believe that determination of cardiac troponin T is useful in the evaluation of these individuals, if analyzed in both clinical and training context.

Resting 12-lead electrocardiography (ECG) is another low-cost method that can be very useful in cardiac evaluation of COVID-19 patients, as 90% of patients with COVID-19 myocarditis have some electrocardiographic changes.[6] However, like troponin, ECG must be carefully evaluated in athletes, because some findings may be confused with common physiological adaptations to training.

Exercise testing and transthoracic echocardiography (ECHO) are also recommended in the preparticipation screening (PPS) of individuals with moderate or severe clinical presentation of COVID-19, as they reveal important information on functional capacity, exercise-related arrhythmias and changes in ventricular function and anatomy. The addition of cardiac magnetic resonance (CMR) is recommended for those who had a severe clinical presentation of the disease or who had abnormal results in other tests.

Cardiovascular assessment of athletes is always a challenge due to the peculiarities of the athlete's heart. The decision about including tests in the PPS is frequently controversial since misinterpretations can lead to unnecessary costs. This is not different in the PPS after COVID-19, as some of the changes considered as complications of the disease may also overlap with common findings of the athlete's heart. Therefore, the indications for tests, particularly CMR, have been debated.

Until the completion of the present review, data about myocarditis secondary to COVID-19 in athletes were lacking. Lately, studies including CMR in the evaluation of young athletes with COVID-19 have been published and reported a prevalence of diagnosed myocarditis ranging from 2.3% to 15% of athletes. This large variation is probably due to the difference in the sample studied, and mainly to the interpretation of the tests' findings.[7-9] In CMR, myocardial injury or inflammation is detected by increased extracellular volume, T1 and T2 mapping, and presence of late gadolinium enhancement (LGE), which were the most used findings for the diagnosis of myocarditis in these studies. Although CMR is considered the gold standard for diagnosing myocarditis, these findings (2018 Lake Louise criteria) have been validated only in symptomatic individuals, and in these studies, a large proportion of the athletes were asymptomatic. Many of these findings, considered alone, do not have known long-term significance or prognosis, particularly in athletes.

Myocardial fibrosis, especially fibrosis of the right ventricular (RV) insertion point, has been described as a relatively common finding in some athletes, mainly endurance and master athletes. However, although some of the studies did not exclude this type of pattern from CMR findings and did not have a control group for comparison, most of them included predominantly young athletes and from different sports modalities. A large study involving 13 universities in the USA (The Big Ten COVID-19 Cardiac Registry),[8,9] evaluated 1,597 young athletes with a positive COVID-19 test who underwent CMR. The authors excluded fibrosis of the RV insertion point as an abnormality and reported the presence of myocarditis in about 2.3% of the athletes, with only 0.31% of them symptomatic. Changes in ECG, echocardiogram and troponin were also not significant among these cases, with an increase of 7.4 fold in the detection of myocarditis with the addition of CMR.

Thus, if on the one hand there is a recommendation of including CMR in the PPS for its capacity to detect myocarditis after COVID-19 and prevent sudden death in sports, on the other hand we must keep in mind that the interpretation of its findings may be controversial and should be done with caution. The physician's expertise with athletes and the performance of the tests in experienced centers are essential for a good result.

The main concern mentioned by the authors of the review is genuine and the theme is relevant.[10] The Brazilian Society of Cardiology and Brazilian Society of Exercise and Sports Medicine Updated Guidelines for Sports and Exercise Cardiology – 2019[10] and the European Society of Cardiology Position paper[11] recommend PPS for sudden death prevention in sports. Based on this, after the pandemic, during which most people reduced or stopped exercising, the PPS should be performed before returning to sports practice. In the context of individuals recovering from COVID-19, medical assessment becomes essential, since there are reports not only of cardiac injury but also of different clinical sequelae. Moreover, we are still in the learning curve of the disease. PPS may be also useful in the readaptation to training, because the drop in performance is frequent and may be related from a simple deconditioning, peripheral dysfunction due to mitochondrial damage, to cardiac and pulmonary sequelae. A good evaluation minimizes the risks to the athlete's health, contributes to a gradual reintegration and adequate guidance for returning to the routine training.

The authors' idea of suggesting an assessment flowchart is very welcome, as it aims to help physicians in risk stratification and decision making. Experts play an important role to propose guidelines, using their knowledge and experience, aiming at the preservation of ethics and health. The authors also point out that the focus is on patient safety and that there is no data on the cost-effectiveness of the proposal. Less experienced physicians may follow the recommendations, but clinical decision should be individualized and consider local difficulties and regional differences. The use of additional tests in PPS was based on the clinical history of patients, and magnetic resonance imaging was recommended only for hospitalized patients and those with abnormalities detected in the initial PPS. The presence of symptoms in fully recovered individuals should always be considered as a red flag, but we must keep in mind that the occurrence of sequelae in asymptomatic patients is possible as well. Despite its variable and probably rare occurrence, post-COVID myocarditis does exist, and should not be underestimated by physicians.

In conclusion, PPS is recommended for a safe return to sports after COVID-19. However, complementary tests should be individualized, preferably performed in specialized centers and by physicians experienced with athletes, and their results carefully interpreted. Some clinical and test findings in the post-COVID-19 period must still be observed with caution and their significance evaluated in the long term, so that more robust guidelines can be defined. Only with much study and as time goes by, perhaps we can unite what we believe we know with what science will actually present to us.

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ORIGINAL ARTICLE

Comparison between Bruce and Ramp Protocols for Exercise Testing in the Diagnosis of Myocardial Ischemia

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Abstract

Background: Exercise tests are an important tool in the investigation of myocardial ischemia. The ramp protocol has gained increasing importance in clinical practice because of the possibility of individualizing its exercise intensity.

Objective: To assess and compare the sensitivity, specificity, and accuracy of Bruce and ramp protocols for exercise testing in the diagnosis of myocardial ischemia considering myocardial perfusion scintigraphy as the reference standard. Secondary objectives included the assessment of hemodynamic profiles, functional capacity, and the incidence of arrhythmias in each of the protocols.

Methods: Participants underwent exercise testing using the ramp and Bruce protocols, and the tests' diagnostic power was assessed. For testing the difference between data provided by both protocols, we used a paired Student's t-test or Wilcoxon test, depending on the assumption of data normality. The level of significance adopted for all tests was 5%.

Results: The ramp protocol showed sensitivity, specificity, and accuracy values of 55.6%, 82.4%, and 76.7%, respectively, whereas the Bruce protocol had results of 77.8%, 64.7%, and 67.4%, respectively. The maximum heart rate and double product at peak exercise were significantly higher in the Bruce protocol ($p = 0.043$ and $p = 0.040$, respectively). No differences were observed between the incidence of arrhythmias in both protocols.

Conclusion: The Bruce protocol presented higher sensitivity for detecting ischemia on the exercise test, while the ramp protocol presented higher specificity and accuracy.

Keywords: Myocardial Ischemia/diagnosis; Exercise; Jogging; Exercise Test; Myocardial Perfusion Imaging; Coronary Artery Disease; Sensitivity and Specificity.

Introduction

The stress test consists in a procedure where an individual undergoes programmed physical exercise in order for the physician to assess clinical, hemodynamic, and electrocardiographic responses.[1] The exercise can be performed using a treadmill or a stationary cycle ergometer, and many protocols are available according to the test objective, being adaptable to patient conditions.

Even though it was created more than 5 decades ago, the Bruce protocol is still the most widely used in the world's main laboratories.[2] Its increments are performed every 3 minutes, but an increase of around 3 metabolic equivalents of task (MET) at each stage may hinder the adaptation of sedentary individuals and those who have heart diseases and physical limitations, leading to the early interruption of the test.

Technological advances allowed the creation of new protocols with smoother speed and incline increments, the so-called ramp tests.[3] The first report of the ramp protocol is from the 1980s using a stationary cycle ergometer and, in the following decade, with a treadmill.[4,5]

The main advantage of the ramp protocol, with smoother and more linear increments when

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compared to protocols that use abrupt work increments, would be a better physiological response when considering hemodynamic and ventilatory variables.[3,5,6] Moreover, speed and incline can be individually adapted to each patient.[3–5]

However, literature is lacking when it comes to robust evidence of the accuracy of this protocol for myocardial ischemia, since most diagnostic studies of stress tests were performed using stage protocols.[7]

Objectives

Our primary objective was to assess and compare the sensitivity, specificity, and accuracy of the Bruce protocol, owing to its wide application on clinical practice, with the treadmill ramp protocol. The reference standard used in this study was exercise myocardial perfusion scintigraphy.

As for secondary objectives, we aimed to assess and compare the hemodynamic behavior, presence of arrhythmias, and functional capacity between both protocols.

Methods

This study was performed at a cardiology referral center in the city of São Paulo. Our sample included male and female participants aged 18 or older, who underwent treadmill exercise myocardial perfusion scintigraphy as recommended by their respective physicians. Patient selection was performed consecutively between October 2018 and February 2020.

Patents who had a resting electrocardiogram with an ST segment depression > 1 mm, left bundle branch block, atrial fibrillation, pacemaker rhythm, or ventricular pre-excitation were not included. Exclusion criteria were (i) therapeutic interventions (angioplasty or myocardial revascularization) between any of the study phases; (ii) patient dropouts at any phase; and (iii) contraindications to the exercise test, according to the literature.[8]

After myocardial scintigraphy examination and the invitation to participate in the study, individuals were randomized for exercise testing using the Bruce and ramp protocols. The randomization was performed through codes generated by the Sealed Envelope software.[9] The interval between each phase of the study was 14 days. Study phases are illustrated on Figure 1.

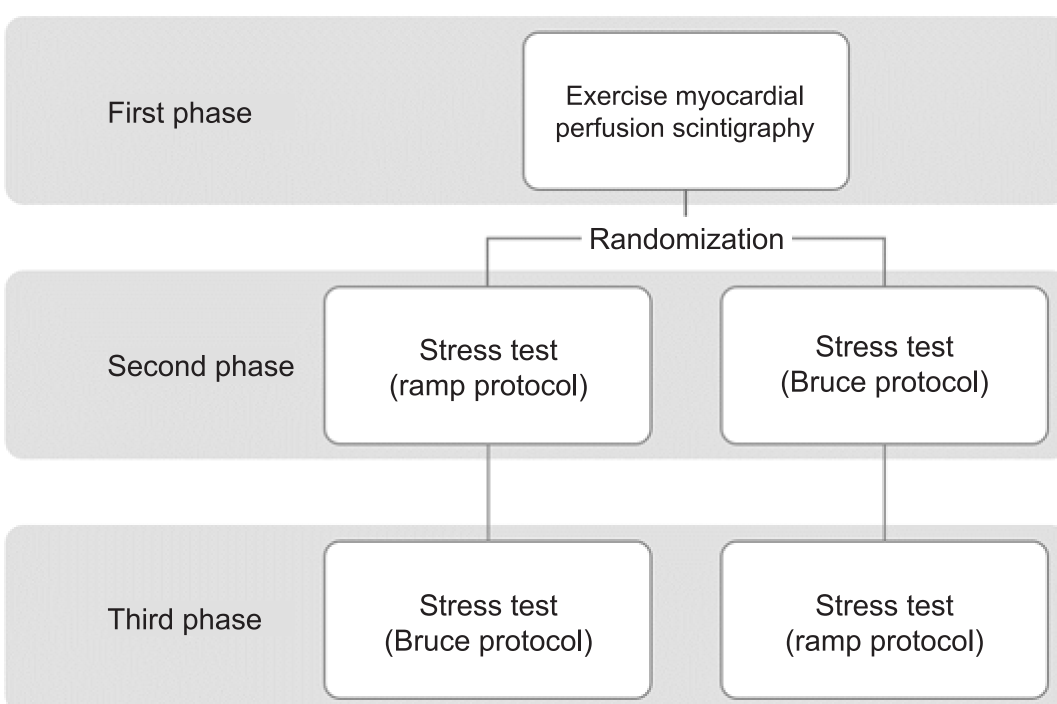


Figure 1 – Selection and randomization
Source: this study

All participants received a free and informed consent form (FICF) that was previously approved by the Research Ethics Committee (CEP) and were also informed of the risks and benefits of performing the study. Participants were instructed to wear appropriate clothes and shoes during the test. Moreover, they were instructed not to drink or smoke and to have a light meal up to 3 hours before the test.

According to the last myocardial scintigraphy guideline and to the nuclear medicine unit of the center where this study was conducted, participants were instructed to interrupt the use of medications with negative chronotropic effects (betablockers and dihydropyridine calcium channel blockers) 72 hours before each test.[10] This instruction was adopted in all study phases to avoid differences in the sensitivity of ischemia detection between myocardial scintigraphy and the subsequent exercise tests.[8,11,12] Other medications were maintained in all study phases.

For the ramp protocol, functional capacity was estimated through an interview with the participant using the Portuguese version of the Veterans Specific Activity Questionnaire (VSAQ).[1,13] Increments were automatically calculated by the software based on the functional activity programming and a target duration of 10 minutes.

During the test, both in the Bruce and ramp protocols, we allowed patients to use front or side bars for maintaining balance, with minimal support. Participants were stimulated to reach exhaustion, as long as there were no criteria recommending the interruption of the test. Functional capacity was calculated using the equation derived from the Fitness Registry and the Importance of Exercise (FRIEND) registry.[14]

The interpretation of exercise tests was performed by an experienced physician who was blinded to the participant data, test protocol, and myocardial scintigraphy results. Physicians overseeing the tests were also unaware of the results of the previously performed scintigraphy.

ST segment measurement was performed in 3 consecutive complexes, considering the last PR segment as baseline. Tests were considered positive for myocardial ischemia when they presented, at peak exercise or recovery phases, one of the following alterations:

a) A horizontal or downsloping ST segment depression ≥ 1.0 mm measured at the J point.
b) An upsloping ST segment depression ≥ 1.5 mm measured 80 ms after the J point.
c) An ST segment elevation ≥ 1.0 mm in the absence of a pathological Q wave.

In patients with right bundle branch block, we did not analyze the V1, V2, and V3 leads since they presented alterations in ventricular repolarization when at rest, which could be intensified during exercise and hinder the electrocardiographic analysis of ischemia.[15]

Arrhythmias were recorded during and after exercise and classified as complex ventricular arrhythmias: frequent ventricular extrasystoles (over 10% of QRS complexes in a 30-second period); bigeminy; or ventricular tachycardia.

Myocardial scintigraphy results were independently analyzed by blinded physicians at the nuclear medicine unit. Images at rest and after exercise were evaluated, aiming to compare alterations in myocardial perfusion between phases. Scintigraphy results were considered positive for myocardial ischemia when a transient low uptake was observed, that is, a difference in perfusion between resting and stress states. In this study, analyses were conducted categorically, that is, results were considered positive or negative for ischemia and were classified according to the extent of left ventricular myocardial impairment[16], according to the following description:

a) mild – stress-induced perfusion defect encumbering less than 5% of the myocardium;
b) moderate – stress-induced perfusion defect encumbering 5% to 9.9% of the myocardium;
c) important – stress-induced perfusion defect encumbering 10% or more of the myocardium.

Statistical analysis

Participant data and test results were registered using Microsoft Excel 365 software. The analysis of collected data was performed using R 4.0.2 software. The DTComPair package was also used for calculating confidence intervals (CIs).

For testing the difference between data derived from each of the studied protocols, we used the paired Student’s t-test or the Wilcoxon test when our data normality assumption was not satisfied via a Kolmogorov-Smirnov test. Continuous variables with normal distribution were presented through means and standard deviations, and those that did not have a normal distribution were presented as medians and interquartile ranges. For comparing the incidence of arrhythmias between protocols, we used the McNemar test, since participants underwent the same test using different protocols. The significance level adopted for all tests was 5%.

Sensitivity, specificity, and accuracy calculations, in addition to likelihood ratios and predictive values, were calculated for all protocols so that each classification could be compared to that of the reference standard (myocardial perfusion scintigraphy). CIs were constructed considering a 95% confidence level.

For comparing ST segment analyses for each protocol and estimating the odds ratio, we adjusted a statistical model considering the predominant morphology as the response variable and the protocol (ramp or Bruce) as the explanatory variable. We adjusted an ordinal logistic regression model with proportional odds considering a mixed model, since assessments by both protocols were performed with the same participants.

Results

After patient selection, our sample contemplated 43 participants who went through all 3 study phases: myocardial scintigraphy and exercise testing with the Bruce and ramp protocols, according to randomization. Our first results refer to sample characterization and are described on Table 1.

Out of 86 tests, the criteria for interrupting the study were exhaustion (94.1%), impairing thoracic pain (3.5%), nonsustained ventricular tachycardia (1.2%), and a drop in systolic arterial pressure (SAP) along with cardiovascular symptoms (1.2%). Data referring to the

Table 1 – Clinical characteristics of the selected sample

(n = 43 participants)	
Sex - male	32 (74.4 %)
Weight (kg)	79.65 (± 12.51)
Height (cm)	166 (± 76.46)
Age	61.72 (± 8.64)
Medical history	
Systemic arterial hypertension	37 (86.0%)
Diabetes mellitus	20 (46.5%)
Dyslipidemia	37 (86.0%)
Smoking	18 (41.9%)
Coronary artery disease	28 (65.1%)
Previous acute myocardial infarction	13 (30.2%)
Previous angioplasty	9 (20.9%)
Myocardial revascularization	12 (27.9%)
Continuous medications	
Platelet antiaggregants	37 (86.0%)
Statin	38 (88.4%)
ACEI/ARB	34 (79.1%)
Diuretics	19 (44.2%)
Nitrate	7 (16.3%)
Beta blockers	33 (76.7%)

Source: this study
Kg: kilogram; cm: centimeters; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker.

tests and comparing the ramp and Bruce protocols are described on Table 2 .

Participants presented at least one episode of arrhythmia in 60.5% of the ramp protocol tests, of which only 7% were complex ventricular arrhythmias. On the other hand, the incidence of arrhythmias was 69.8% in Bruce protocol tests, with 9.3% of complex ventricular arrhythmias. No statistically significant difference was observed between both protocols considering episodes of arrhythmia (p = 0.453) and complex ventricular arrhythmia (p = 1.000). We also analyzed the incidence of arrhythmias between test phases (exercise and recovery) and did not find significant differences (p = 0.211 and p = 0.453, respectively).

Out of the performed tests, the ramp protocol presented criteria for myocardial ischemia in 11 participants (25.5%) while the Bruce protocol was positive in 19 cases (44.2%), considering the study criteria. The Bruce protocol resulted in 12 participants with false positive results and 2 participants with false negative results, whereas the ramp protocol had more false negative results (4 participants) and only 6 false positive results. These data can be seen on Figure 2.

The difference between protocols as to the morphological classification of the ST segment depression was significant (p = 0.008), and participants who underwent the Bruce protocol had a higher chance of developing morphologies related to a worse prognosis when compared to the ramp protocol (odds ratio 5.83, 95% CI 1.58–21.45), as demonstrated on Figure 3.

Nine participants had a transient low uptake at myocardial scintigraphy, indicating that 21% of the study sample presented myocardial ischemia diagnosed by the standard reference test. Five participants presented discrete alterations at myocardial scintigraphy, 2 had moderate alterations, and 2 had important impairment.

The sensitivity, specificity, and accuracy of each of the protocols and their respective CIs, as well as the likelihood ratio and predictive values for each protocol, are presented on Table 3.

Discussion

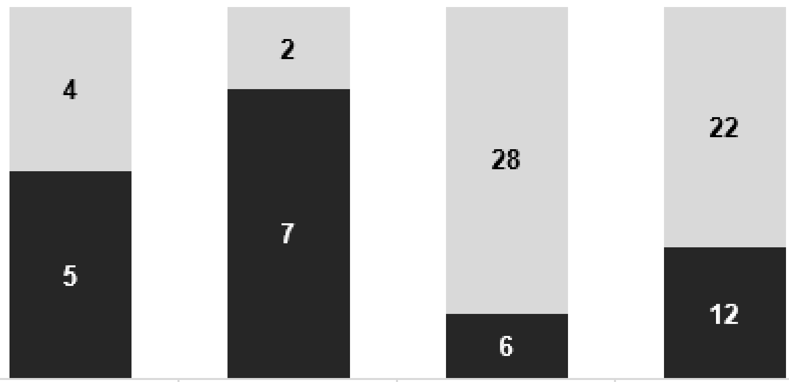
In this study, both protocols had their mean duration within the recommended 8–12-minute interval, which allows the optimization of VO2 max in this period of time.[1,17–19] When undergoing the ramp protocol, participants had a longer exercise duration, which was justified by the adaptation of patients to smoother work increments, corroborating other studies.[5,20,21]

Estimating functional capacity through objective tools such as the VSAQ can help in elaborating the ramp protocol. The questionnaire, initially developed for male individuals, was further validated in other populations including women and other nationalities; it was thus revealed to be a useful instrument for programming ramp protocol data, since this protocol can be influenced by the physician's experience.[13,22–24]

Table 2 – Clinical data of exercise tests

	Ramp	Bruce	p-value
Duration of exercise (seconds)	706 (± 166)	600 (± 165)	<0.001
Resting HR (bpm)	75.86 (± 14.66)	72.51 (± 12.80)	0.066
Maximum HR (bpm)	146 (± 21.37)	150 (± 18.10)	0.043
% maximum HR	92.22% (± 11.96)	94.85% (± 9.43)	0.042
HR at the first minute of recovery (bpm)	121.84 (± 21.22)	123.47 (± 18.81)	0.708
Resting SAP (mmHg)*	130.0 [120.0; 140.0]	130.0 [120.0; 140.0]	0.441
Maximum SAP (mmHg)*	190.0 [170.0; 207.5]	190.0 [180.0; 220.0]	0.075
Maximum DP (bpm.mmHg x 10^3)*	27.7 [24.0; 32.3]	29.88 [26.15; 32.63]	0.040
Workload (MET)	9.46 (± 2.18)	9.57 (± 2.27)	0.109

Source: this study
** values represented by median and interquartile range*
HR: heart rate; bpm: beats per minute, SAP: systolic arterial pressure; mmHg: millimeters of mercury; DP: double product; MET: metabolic equivalent of task.



	Positive MPS		Negative MPS	
	Ramp	Bruce	Ramp	Bruce
Negative ET	4	2	28	22
Positive ET	5	7	6	12

Figure 2 – Test results divided by protocol and compared to myocardial scintigraphy results
Source: this study
MPS: myocardial perfusion scintigraphy; ET: exercise test.

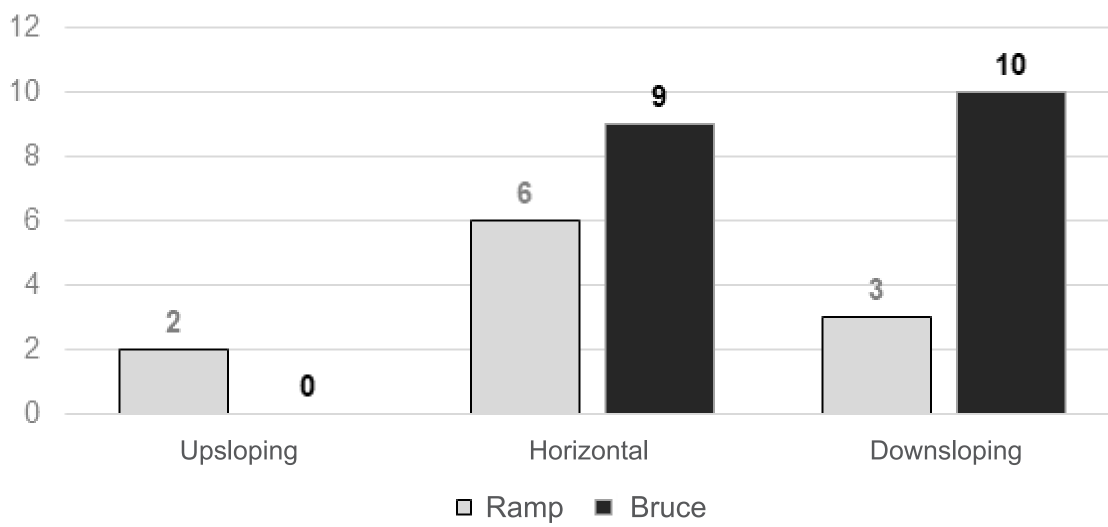


Figure 3 – Comparison between predominant ST segment morphologies in both protocols
Source: this study

Functional capacity was calculated using the equation derived from the FRIEND registry, which has been applied to different protocols (including the Bruce and ramp protocols) in healthy populations and in those with coronary artery disease (CAD).[14,25,26] Its results are closer to the VO2 max measured through ergospirometry than to those obtained by the American College of Sports Medicine (ACSM) equation, which is still widely used.[14,25,26]

Stress-induced arrhythmias are associated with a higher incidence of cardiovascular events and higher long-term mortality.[27–31] Jouven et al.,[27] demonstrated that asymptomatic individuals who presented complex ventricular arrhythmias during the exercise period had

Table 3 – Diagnostic power of protocols evaluated in this study

	Ramp			Bruce		
	Value	95% CI		Value	95% CI	
		Inferior limit	Superior limit		Inferior limit	Superior limit
Sensitivity	55.6%	23.1%	88.0%	77.8%	50.6%	100.0%
Specificity	82.4%	69.5%	95.2%	64.7%	48.6%	80.8%
Accuracy	76.7%	64.1%	89.4%	67.4%	53.4%	81.4%
PLR	3.1	1.2	8.0	2.2	1.2	3.9
NLR	0.5	0.3	1.1	0.3	0.1	1.2
PPV	45.5%	16.0%	74.9%	36.8%	15.2%	58.5%
NPV	87.5%	76.0%	99.0%	91.7%	80.6%	100.0%

Source: this study
CI: confidence interval; PLR: positive likelihood ratio; NLR: negative likelihood ratio; PPV: positive predictive value; NPV: negative predictive value.

a higher risk of cardiovascular death. Dewey et al.,[30] however, observed that the presence of ventricular arrhythmias at the recovery phase was associated with a worse prognosis when compared to the exercise phase, which is similar to what was found in a recent meta-analysis.[31]

The incidence of stress-induced arrhythmias was superior in our study when compared to the literature, which can be justified by the severity of the studied population, referred by a high-complexity cardiology center. Despite a high incidence of arrhythmias, no statistical difference was observed in this aspect when comparing both protocols, even when considering the exercise and recovery phases.

When evaluating the morphological patterns of ST segment depression, we observed that the Bruce protocol had a higher chance of detecting morphologies related to a worse prognosis. It is known that downsloping and horizontal morphologies are related to a higher ischemic load and a probability of multi-arterial impairment.[32,33] Guidelines diverge when associating the upsloping morphology with an ischemic response, but it has been shown that this morphology may be associated with CAD, even if associated with better prognosis and a lower ischemia extent when compared to the downsloping and horizontal morphologies.[11,33–35]

Studies performed for evaluating the diagnostic power of exercise tests present heterogeneous methodologies and most of them used staged protocols, particularly the Bruce protocol. Therefore, sensitivity and specificity values present a wide variation in the literature.[7] Data for the Bruce protocol obtained in this work are within value intervals from previously published studies.[7,36,37] Moreover, data referring to the sensitivity, specificity, and accuracy of the exercise test using the ramp protocol were similar to results obtained by Macedo Júnior and Silva (2015).[38]

Aspects that may explain a higher number of tests suggesting myocardial ischemia at the Bruce protocol include a higher heart rate and double product at peak exercise, secondary to more abrupt increments. It is known that an increase in heart rate generates higher oxygen consumption by the myocardium, while an elevation of the double product is associated with a reduction in myocardial perfusion.[12,20] In our study, we observed that the ramp protocol presented a lower sensitivity for detecting myocardial ischemia. This finding could be related to lower increments at each stage, which would result in an attenuation of the ischemic response, as demonstrated by other studies.[20,39,40]

For assessing only the test's diagnostic power, without the influence of disease prevalence, we used likelihood ratios. The positive likelihood ratio for the ramp protocol was slightly higher, that is, a positive test had a stronger influence in confirming the probability of myocardial ischemia. On the other hand, the negative likelihood ratio was lower in the Bruce protocol, indicating that a negative test represented a lower probability of ischemia. Our likelihood ratio values are compatible with those of Thiers et al.,[37] who evaluated diagnostic thresholds of non-invasive tests for CAD.

Finally, the interpretation of the exercise test should not be limited to the electrocardiographic pattern. Clinical and hemodynamic variables are fundamentally important for result interpretation, providing relevant information to the diagnosis, prognosis, and clinical conduct. Therefore, the choice of the test and best protocol for investigating ischemia should always consider the patient's clinical characteristics and the objective to which the test is being requested. In case the exercise test has the main objective of screening for CAD, protocols with higher sensitivity are recommended. That is, based on the data presented by this study, the Bruce protocol is a better alternative when compared to the ramp protocol.

Among possible limitations of this study, we highlight the smaller sample size when compared with the initial calculation. This information reflects a lower statistical power that was achieved with the evaluated sample. We also note the availability bias, that is, patients with less cardiovascular limitations are more prone to accepting to participate in studies, also indicating a small number of participants with systemic perfusion alterations observed through myocardial scintigraphy.

Conclusion

The ramp protocol, when compared to the Bruce protocol, had higher specificity and accuracy. However, a higher sensitivity achieved by the Bruce protocol favors its use in exercise testing when screening patients for myocardial ischemia is the main goal.

We had more participants with positive criteria for ischemia at the exercise test using the Bruce protocol and a higher chance of developing horizontal and downsloping ST segment depression, which are associated with a worse prognosis. The main variables found in this study that justified this finding were higher heart rate and double product at peak exercise at the Bruce protocol.

The achieved workload and maximum systolic arterial pressure were similar in both protocols. No significant difference was observed on the incidence of arrhythmias.

Author contributions

Conception and design of the research: Fagundes, TTS; Mizzaci, CC; Wohnrath, FC; Meneghelo, RS. Acquisition of data: Fagundes, TTS; Mizzaci, CC; Wohnrath, FC; Medina, FRC; Buglia, S. Analysis and interpretation of the data: Fagundes, TTS; Mizzaci, CC; Buglia, S; Meneghelo, RS. Statistical analysis: Fagundes, TTS; Mizzaci, CC; Meneghelo, RS; França, JID. Writing of the manuscript: Fagundes, TTS; Mizzaci, CC; Meneghelo, RS. Critical revision of the manuscript for intellectual content: Fagundes, TTS; Mizzaci, CC; Meneghelo, RS; Buchler, RDD; Mastrocolla, LE.

Potential Conflict of Interest

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

Sources of Funding

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Study Association

This article is part of the thesis of master submitted by Thiago Fagundes, from *Instituto Dante Pazzanese de Cardiologia*, São Paulo.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Instituto Dante Pazzanese de Cardiologia* under the protocol number 2928697. 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 Testing Protocols to Detect the Presence of Coronary Artery Disease: Bruce or Ramp?

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Editorial referring to the article: Comparison between Bruce and Ramp Protocols for Exercise Testing in the Diagnosis of Myocardial Ischemia.

The investigation of ischemic response through clinical, metabolic, hemodynamic, and electrocardiographic parameters displayed in the exercise stress test (ET) in multifactorial analysis increases the ET's diagnostic and prognostic accuracy indication of ischemic response.[1]

Coronary artery disease (CAD) is a pathology that requires quick and safe decisions for the patient, and it is always a challenge. The protocols for performing the ET, whether on a cycle ergometer or a treadmill, must be adapted to the patient's biomechanical conditions so that they are comfortable and can reach the criteria that define a maximum or close to the maximum effort level. The protocol must seek a satisfactory mobilization of myocardial reserves so that the sensitivity to the presence of an ischemic response can be increased.[2]

Myers et al.[3] compared ramp protocols versus standardized protocols. They inferred that protocols with progressive increments of loads and an average duration of ten minutes, such as the ramp tests, establish a better relationship between oxygen consumption and the applied load and minor variation in the "slope" between the two variables in a regressive way, considering that this test appears to be better when applying equations to estimate oxygen consumption. They conclude that the individualized ramp protocol on a treadmill exhibits the best linear relationship between oxygen consumption and applied load, preferable when there is no equipment for direct gas measurement.

Keywords

Exercise; Testings; Protocols; Detect; Presence.

Noël et al.[4] compared exercise-induced myocardial ischemia in coronary patients submitted to exercise tests performed with the Bruce protocol, treadmill ramp, and cycle ergometer ramp. They evaluated the onset of ST depression (-1.0mm or more), characterizing the ischemic threshold (IT), relating it to the double product, equivalent to myocardial oxygen consumption and maximum oxygen consumption ($V'O_2$). The IL was higher during the cycle ergometer ramp protocol (DP:24009±5769) when compared to the Bruce protocol (DP:20429±3508) and treadmill ramp (DP:19451±3392), regardless of $V'O_2$, which did not exhibit significant differences between the tests. Thus, they concluded that the type of exercise applied in a test, which is more important than the type of protocol, is associated with a variation in electrocardiographic parameter indications of myocardial ischemia, regardless of the intensity of effort and myocardial oxygen demand.

Many studies contributed to legitimizing exercise-induced myocardial ischemia. We highlight the "ischemic cascade" in which metabolic and biochemical changes are observed at the beginning of myocardial ischemia, soon after perfusion reduction, which is then followed by the contractile changes electrocardiogram and, finally, precordial pain.[5] Various methods can identify these. We believe that the Cardiopulmonary Exercise Test, using hemodynamic variables, such as the oxygen pulse curve, related to systolic volume, often at a plateau or descending with the progression of exercise,[6] can better display left ventricular dysfunction at the onset of ischemia.

In the study, "Comparison between the Bruce and Ramp protocols in the Treadmill Test for the Diagnosis of Myocardial Ischemia,"[7] the authors conclude

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that the Bruce protocol had a greater sensitivity for detecting ischemia in the exercise test, while the ramp protocol had better specificity and accuracy. Despite highlighting the greater sensitivity of the Bruce Protocol for the diagnosis of exertion-induced myocardial ischemia, they mention the advantage of the ramp protocol in better adapting to the biomechanical conditions of patients with protocols that use steeply staggered load increments. The results obtained in myocardial perfusion scintigraphy with physical stress were used as a reference standard, without reference to the applied protocol. Although the authors evaluated changes in the ST segment during exercise and recovery, there was no relationship with the electrocardiographic lead where the change in ventricular repolarization occurred. The authors comment that the interpretation of the exercise test should not be limited only to the electrocardiographic pattern. They considered the clinical and hemodynamic variables of fundamental importance in interpreting the results, allowing for diagnostic and prognostic inference. A well-designed study with a larger sample size will contribute to other research in this crucial area of Exercise Medicine.

When performing an exercise test, we can conclude that poor adaptation to exercise or excessive loads can generate undefined changes, compromising the test result. Therefore, the test, either performed on a treadmill or a cycle ergometer, must always be adapted to the clinical and biomechanical conditions of the patients for an accurate interpretation of clinical, metabolic, hemodynamic, and electrocardiographic variables.

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ORIGINAL ARTICLE

Association between Deep Subcutaneous Adipose Tissue Estimated by DAAT Index and Dietary Intake in Patients with Acute Coronary Syndrome

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Abstract

Background: Abdominal obesity has been associated with cardiovascular disease and may be modulated by dietary intake. The deep abdominal subcutaneous adipose tissue (dSAT) is a body fat compartment that can be estimated by using mathematical formulas.

Objectives: To evaluate the association between dSAT estimated by the Deep-Abdominal-Adipose-Tissue (DAAT) index and dietary intake in patients with acute coronary syndrome (ACS).

Methods: This is a cross-sectional study conducted with patients ≥ 18 years of age admitted to a tertiary hospital. Sociodemographic, clinical, and anthropometric (body weight [kg], height [m], waist, hip and neck circumferences [cm]) data were evaluated. A food frequency questionnaire was applied to identify each patient's nutrient intake. The DAAT index was calculated according to specific formulas for men and women. Possible association between food intake and the DAAT index was evaluated by multiple linear regression. The level of significance adopted was 0.05.

Results: This study evaluated 138 patients, with a mean age of 61.2±10.8 years. Prevalence of obesity was 29.4% in men and 37.7% in women. Regarding waist circumference, 83% of the women showed values considered to be very high. The DAAT index was significantly higher in men when compared to woman ($P < 0.0001$) and proved to be positively correlated with proteins ($r= 0.22$, $P= 0.01$) and monounsaturated fatty acid ($r= 0.18$, $P= 0.04$) intake in the entire sample. After adjustment for sex, alcohol consumption, and levels of physical activity, the DAAT index was associated with the female sex ($B= -129.84$, $P <0.001$) and a sedentary lifestyle ($B= 57.99$, $P <0.001$).

Conclusion: dSAT estimated by the DAAT index was not associated with dietary intake in patients with ACS.

Keywords: Cardiovascular Diseases; Myocardial infarction; Subcutaneous Fat; Abdominal obesity; Diet.

Introduction

According to the World Health Organization (WHO), in recent decades, cardiovascular diseases (CVD) accounted for 30% of the world's deaths.[1] Among CVDs, acute coronary syndrome (ACS) – represented by acute myocardial infarction, unstable angina, and sudden death,[2] is the most prevalent. ACS is influenced by non-modifiable and modifiable risk factors,[3] the most important of which are inadequate diet[4,5] and sedentary lifestyle,[5,6] which also interfere in body adiposity.

Central adiposity is associated with the development of CVD.[4] The abdominal region has two compartments of adipose tissue: visceral adipose tissue (VAT), already known for its association with CVD,[7] and subcutaneous adipose tissue (SAT), subdivided into two functionally different compartments:[8] superficial SAT (sSAT) and deep SAT (dSAT). dSAT has similar characteristics to VAT and is associated with cardiometabolic complications.[7,9] In addition, it is suggested that men have a greater area of dSAT when compared to women,[10-12] considering tissue-

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specific effects of sex hormones on the proliferation/ differentiation of adipocytes and the expansion of specific adipose tissue depots (visceral in males and gluteal in females).[12,13]

The golden standard for estimating dSAT is computed tomography. However, this method presents technical and cost difficulties that limit its use in clinical practice.[10] Hence, predictive equations were created for the estimation of dSAT in men and women. The applicability of the Deep-Abdominal-Adipose-Tissue (DAAT) index was tested in the Brazilian population among subjects aged 30 to 80 years without CVDs, and the DAAT index proved to be positively related to type 2 diabetes mellitus (T2DM),[7] while in individuals with obesity, it was correlated to body mass index (BMI), waist circumference, percentage of body fat, and free fat mass.[14]

It is known that dietary intake and physical activity levels modulate abdominal SAT concentrations. Modifications in lifestyle, based on changes in eating habits and practice of physical activity, are associated with a decrease in abdominal fat concentrations.[15,16] Regarding the quality and quantity of the diet, abdominal obesity and SAT seems to be more strongly influenced by total dietary fat and a daily excess of energy consumed, as compared to the quality of the diet itself.[17-20]

To the best of our knowledge, the use of the DAAT index was not appropriately tested in a population with ACS, nor as regards its relationship with nutrients and energy intake. Therefore, the present study sought to evaluate the association between dSAT, estimated by the DAAT index, and the dietary intake of patients with ACS.

Methods

This was a cross-sectional study conducted in a tertiary hospital in Porto Alegre, Rio Grande do Sul, Brazil. This study evaluated patients with a medical diagnosis of ACS who received medial care in the Brazilian Unified Health System (SUS, in Portuguese) between July 2015 and September 2016. Inclusion criteria were individuals of both sexes, aged between 18 and 80 years, and who consented to participate in the study, signing the Informed Consent Form according to Resolution 466/2012. Individuals with cognitive impairment and without proper conditions of weight, height, and anthropometric measurements were excluded.

Demographic data (age, sex, and ethnicity), education (years of schooling), source of income, lifestyle characteristics (smoking, abusive alcohol consumption), previous medical diagnoses, and family history of heart attack or stroke were collected by means of a standardized questionnaire. The level of physical activity was assessed using a short version of the International Physical Activity Questionnaire (IPAQ).

Dietary data were obtained through a quantitative food frequency questionnaire (FFQ), containing 135 foods/ preparations and validated for the population of Porto Alegre, Rio Grande do Sul, Brazil.[21] Food consumption during the 30 days before the hospital admission was investigated. Total energy intake (TEI, in kcal/day) consumed daily was calculated. The macronutrients of interest [carbohydrates, proteins, total fats, and saturated fatty acids (SFA), monounsaturated fatty acids (MUFA), and polyunsaturated fatty acids (PUFA)] were calculated in % of TEI. Dietary calcium, zinc, sodium, potassium (in mg/day), dietary cholesterol (in mg/day), and dietary fiber (in g/day) were evaluated as well. Monthly intake was estimated and divided proportionally between the respective days. Analyses of all nutrients were carried out with the Avanutri Revolution® software (Rio de Janeiro, Brazil). The energy density (in kcal/kg) was obtained by dividing the TEI by the body mass.

The anthropometric evaluation was performed after the interview ended. Body mass (in kg) was measured with the participant using light clothing, and body height (in m) was obtained using a stadiometer. Waist circumference (WC), hip circumference (HC), and neck circumference (NC) were measured with an inelastic tape measure of 0 to 143 cm, with an accuracy of 1 mm. BMI and waist-to-hip ratio (WHR) were calculated. General obesity was defined by a cut-off point of BMI>30kg/m²; for WC, cutoff points were >94 cm and >80 cm for men and women, respectively (higher risk for CVD), and WC≥102 cm for men and ≥88 cm for women (very high risk for CVD). For WHR, the cut-off point for men and women was >1.00 and >0.85, respectively. For the DAAT index calculation, the following mathematical formulas were used: DAAT (cm^2) = -382.9 + [1.09 x body mass (kg)] + [6.04 x WC (cm)] + 29 x BMI for men and DAAT (cm^2) = -278 + [-0.86 x body mass (kg)] + [5.19 x WC (cm)] for women.[10]

Sample size calculation was performed through the WinPepi® program for Windows. Assuming a correlation coefficient (r) of 0.38 for the correlation between total fat consumption and central adiposity,[22] a significance level of 5%, and a power of 90%, a sample of at least 69 patients would be required.

Statistical analysis

Data were analyzed using the Statistical Package for Social Science program (SPSS version 17.0, Il, U.S.A.) for Windows. The normality of the data was evaluated according to the Kolmogorov-Smirnov test. Continuous variables were described in means and standard deviation (normal distribution) or in medians and interquartile range (non-normal distribution); categorical variables were described as absolute and percentage numbers. Unpaired Student's t-tests and the Wilcoxon-Mann-Whitney test were used for comparison between continuous variables, while Fisher's exact, or Pearson's Chi-square, test was used for comparisons between categorical variables. The Pearson correlation coefficient and partial correlation (adjusted for TEI) were used for correlations. A multiple linear regression analysis was used to evaluate possible associations after having checked all the necessary assumptions. The level of significance adopted was 0.05.

The present study is part of a larger project entitled "Nutritional and anthropometric profile of patients with acute coronary syndrome (ACS)", which was approved by the Research Ethics Committee of *Instituto de Cardiologia do RS / Fundação Universitária de Cardiologia* (CAAE nº 26591214.3.0000.5333) in 01/24/2014.

Results

The total sample consisted of 138 individuals, with a mean age of 61.2 ± 10.8 years, in which 61.6% were males (n = 83), 80.4% (n = 111) of the sample were white, and 45% (n = 62) were retired. Regarding the medical diagnoses of previous disease, 38.4% (n = 53) had T2DM, 69.6% (n = 96) had hypertension, 63.8% (n = 88) had dyslipidemias, 7.2% (n = 10) had a history of previous stroke, and 63% (n = 87) had a family history of heart attack. The mean BMI of the total sample was 28.2 ± 5.3 kg/m².

Table 1 shows the characterization of the sample according to sex. Men presented a higher prevalence of smokers/ex-smokers and daily alcohol consumption. By contrast, women presented a higher prevalence of very high WC, higher values of WHR, and lower values of the DAAT index when compared to men.

The dietary intake in men and women is shown in Table 2. In comparison to women, men ingested larger daily amounts of energy, dietary cholesterol, sodium, potassium, and dietary fiber. No difference was found in relation to the consumption of other nutrients.

When correlating the DAAT index with nutrient intake, a positive and significant correlation was observed among protein intake (r = 0.28, p <0.001), total fat (r = 0.25, p = 0.01), and MUFA (r = 0.25, p = 0.003). No correlation was found between the DAAT index and the total energy intake, nor with other macronutrients, micronutrients, and dietary fiber intake. However, after adjusting for TEI, the DAAT index was positively correlated only with protein intake (partial correlation [r] = 0.22, p = 0.01) and MUFA (partial correlation [r] = 0.18, p = 0.04).

Table 3 shows the association between the DAAT index and the intake of proteins and MUFA. After adjusting for age, sex, TEI, alcohol consumption, and physical activity, only the female sex was negatively associated with the DAAT index (P <0.001), and physical inactivity (sedentary lifestyle) was positively associated with the DAAT index (P <0.001). Macronutrients were not associated with DAAT index.

Discussion

The present study detected no associations among dSAT estimated by the DAAT index, daily energy, and nutrient intake in patients with, which only pointed to a sedentary lifestyle and the female sex .

In contrast to other studies,[23-25] the female population evaluated in this protocol showed higher WHR values when compared to men. However, the age of the enrolled women indicates that they were in the postmenopausal period, and at this stage of life, women tend to accumulate more total abdominal adipose tissue[26,27] and VAT,[28,29] which would contribute to an increase in WC and, consequently, in WHR. Another hypothesis is related to the loss of muscle mass, which depends on age. One study carried out in Japan showed that women aged 50-79 years lost about 7.1% of their lower limb muscle mass with a concomitant increase of 65.3% in visceral fat, thus increasing the ratio between the circumferences. The study also showed that the loss of body muscle mass was negatively associated with visceral obesity in both sexes.[30]

The DAAT index was statistically different between men and women. This data corroborates with studies conducted in Asian, American, and Indian populations, which demonstrated a greater area of dSAT (obtained through computed tomography, ultrasonography, or DAAT) in men.[11, 12, 25] The lower values of the DAAT index, plus higher WHR and WC in women, could be explained by the fact that women seem to have larger compartments of dSAT when compared to males.[31]

Table 1 – Characteristics of the sample according to sex (n = 138; mean ± SD or n (%) or median [IQR])

	Men (n=85)	Women (n=53)	p-value
Age (years)	60.1±10.7	62.4±10.8	0.32*
Education (years of schooling)	8 [5-11]	5 [4.75-11]	0.28¶
Smoking			0.14‡
Smoker	17 (20)	12 (22.6)	
Former smoker	46 (54)	20 (37.7)	
Never smoked	22 (26)	21 (39.6)	
Alcohol consumption			0.01†
Daily	17 (20)	2 (3.8)	
Never/Almost never	68 (80)	51 (96)	
Physical Activity			0.93†
Active	41 (48)	26 (49)	
Irregularly Active/Sedentary	44 (52)	27 (51)	
Body Mass Index (kg/m²)	27.9±5.0	28.5±5.6	0.59*
Obesity (BMI ≥30 kg/m²)	25 (29.5)	20 (37.7)	0.35†
Waist Circumference (cm)	100.8±13.0	98.4±13.0	0.29*
WC classification			<0.0001‡
Normal	22 (26)	2 (3.8)	
High	25 (29.4)	7 (13)	
Very high	38 (45)	44 (83)	
Waist-to-Hip ratio	0.97±0.12	1.05±0.10	<0.0001*
Neck Circumference (cm)	39.9±3.6	36.9±3.3	<0.0001*
DAAT (cm³)	304.1±95.0	171.9±59.0	<0.0001*

BMI: body mass index; WC: waist circumference; DAAT: Deep-Abdominal-Adipose-Tissue index.
** Unpaired Student´s T test; ¶ Wilcoxon-Mann-Whitney test; † Fisher´s exact test; ‡ Pearson´s Chi-square test.*

Women showed a higher prevalence (83%) when compared to men (44.7%) of a very high risk for CVD according to their WC. This result corroborates with studies conducted in other countries, where values of WC considered to be very high were more prevalent in women.[25,32,33] In a sample of individuals after a heart attack, no such difference was observed in WC values according to sex; however, it was found that WC values increased with age in both men and women.[34]

Regarding nutrient intake, our participants showed a daily energy consumption considered high in relation to their body mass, which could be related to obesity rates (general and abdominal).[35] Similar to other studies conducted in individuals with heart disease, there was a high intake of SFA and dietary cholesterol, as well as a reduced intake of PUFA, MUFA, potassium, calcium, and dietary fiber.[22,36]

The DAAT index correlated positively with proteins, total fats, SFA, and MUFA, but no association was observed after controlling for other variables. Among Israelis, there was also no association between dSAT assessed by computed tomography and dietary intake in general; however, there was a weak correlation between dSAT with the consumption of trans fatty acids.[31] It is known that excessive energy intake is related to increased fat depots;[35] however, excessive intake of SFA may contribute substantially to adipose cell hyperplasia in the abdominal region; conversely, PUFA tends to contribute to a reduction in the number of adipose cells.[37]

Table 2 – Energy, macronutrient and micronutrient intake in the total sample and according to sex (n = 138, mean ± SD or median [IQR])

Nutrients	Entire sample (n=138)	Men (n=85)	Women (n=53)	p-value
Total energy intake (kcal)	2330.9 ±834.9	2470.1 ±861.3	2107.6 ±745.5	0.01*
Energy density (kcal/kg)	31.3 ±12.6	31.5 ±13.1	31.1 ±12.0	0.86*
Carbohydrate (% of TEI)	54.8 ±7.1	54.5 ±6.8	55.3 ±7.5	0.55*
Protein (% of TEI)	16.3 ±3.1	16.5 ±2.8	15.9 ±3.5	0.29*
Total fats (% of TEI)	28.8 ±5.2	28.7 ±5.0	28.82 ±5.6	0.92*
SFA (% of TEI)	8.5 ±2.7	8.8 ±2.6	8.1 ±2.7	0.15*
PUFA (% of TEI)	2.9 ±1.0	3.0 ±1.0	2.9±1.0	0.54*
MUFA (% of TEI)	6.9±2.0	7.1±2.2	6.5 ±1.8	0.12*
Dietary cholesterol (mg)	263 [185.15-374.6]	270.4 [204.1-392.4]	233.6 [156.7-348]	0.04†
Sodium (mg)	1981.5 [1597.9-2667.1]	2201.4 [1742.7-2782.5]	1655.5 [1401.9-2278.3]	<0.001†
Potassium (mg)	2128.3 [1884.1-2768.2]	2183.4 [1966-2843.2]	2000.7 [1781-2576.9]	0.04†
Calcium (mg)	691.8 [380.3-940.7]	627.8 [374.3-927.6]	730.8 [417.7-947.6]	0.67†
Zinc (mg)	10.0 ±3.8	10.3 ±3.7	9.4 ±3.8	0.14*
Dietary fibers (g)	17.4 [14.2-23.2]	17.9 [15-24.6]	16.5 [14.1-21.5]	0.09†

TEI: total energy intake; SFA: saturated fatty acids; PUFA: polyunsaturated fatty acids; MUFA: monounsaturated fatty acids.
** Student´s T Test; †Wilcoxon-Mann-Whitney test.*

Table 3 – Association between the DAAT index and macronutrients [multiple linear regression adjusted for sex, total energy intake (TEI) alcohol consumption, and physical activity level]

	Beta; SE (95% CI)	p-value
Age, in years	-0.044; 0.662 (-1.35 - 1.27)	0.95
Female sex	-129.84; 14.23 (-158.12 - -101.56)	< 0.001
Daily consumption of alcohol	23.02; 20.48 (-17.49 - 63.52)	0.26
Sedentary lifestyle	57.99; 13.34 (31.60 - 84.39)	< 0.001
Total energy intake (kcal)	-0.01; 0.02 (-0.29 – 1.40)	0.20
Proteins (% of TEI)	0.33; 0.23 (-0.12 - 0.78)	0.20
MUFA (% of TEI)	4.63; 3.30 (-1.89 - 11.15)	0.16

SE: standard error; CI: confidence interval; MUFA: monounsaturated fatty acids; TEI: total energy intake.

In the present study, a positive association was observed between dSAT and a sedentary lifestyle. The practice of regular physical activity exerts positive effects on the decrease of SAT and VAT, in addition to preventing the increase in these compartments over time.[18,19] The effects of a one-year lifestyle modification program on body fat distribution were assessed among Canadians, and the results showed that physical exercise significantly reduced VAT, dSAT, and sSAT.[38]

Among the limitations of this study, it is important to mention its cross-sectional design (patients were evaluated in a single moment). Regarding the FFQ, the limitations are related to memory bias and flat slope syndrome, and this may not represent the patient's general eating habits, since only the 30 days preceding the cardiac event were evaluated. In this sense, the estimate of habitual intake may not be reliable when applying a single FFQ.[39,40] There are also limitations on the IPAQ, which considers only the prior seven days to assess the level of physical activity. Some patients, however, had already presented limitations in physical performance more than seven days before the coronary event, and light activities may be considered by them as intense and vigorous activities considering a greater effort and fatigue due to illness.

Conclusions

We concluded that dSAT, estimated by the DAAT index, was not associated with total energy intake, macronutrients, and micronutrients, but rather with the female sex (negatively) and with a sedentary lifestyle (positively), suggesting that women and active people have a smaller area of dSAT. Further studies are needed to confirm our findings.

Data Sharing: Data can be provided by Prof. Aline Marcadenti, who can be reached by e-mail: marcadenti.aline@gmail.com.

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 *Instituto de Cardiologia do RS / Fundação Universitária de Cardiologia* under the protocol number CAAE: 26591214.3.0000.5333. 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

Analysis and interpretation of the data: Marcadenti A. Writing of the manuscript: Stein E. Critical revision of the manuscript for intellectual content: Stein E, Barbiero S, Portal VL, Luz V, Marcadenti A.

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EDITORIAL

Abdominal Subcutaneous Adipose Tissue, Diet, and Risk of Cardiovascular Disease: What do we Know?

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Editorial referring to the article: Association between Deep Subcutaneous Adipose Tissue Estimated by DAAT Index and Dietary Intake in Patients with Acute Coronary Syndrome

Excess adiposity increases the risk of cardiovascular disease (CVD) due to dyslipidemia, systemic inflammation and other risk factors.[1] The distribution of body fat depots, and central adiposity in particular, is related to cardiometabolic diseases.[2] The different adipose tissue depots in the body, ie, epicardial adipose tissue, visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT), have different biochemical characteristics and produce unique biologically active molecules that affect normal and pathological processes related to CVD risk.[2,3] Abdominal SAT is classified as superficial or deep. Deep subcutaneous adipose tissue (DSAT) has a higher ratio of saturated to monounsaturated fatty acids, and, consequently, is more saturated than superficial subcutaneous adipose tissue (SSAT).[4] Despite being in the subcutaneous compartment, DSAT differs from VAT because of differences in gene transcription, having different metabolic functions than SSAT.[5]

In Acute Coronary Syndrome (ACS) patients, coronary plaque instability is related to abnormal abdominal fat distribution. Analyses of the abdominal fat distribution of ACS patients have demonstrated that both VAT and SAT are positively correlated with vessel and plaque volumes, but not with plaque tissue components, the fibrous and lipid content of plaque.[6] However, considering coronary plaque characteristics, a higher VAT/SAT ratio was independently associated with a higher percentage of plaque lipid content, with a lower percentage of fibrous volumes and a thinner fibrous cap thickness,[6] characteristics that define greater plaque rupture vulnerability and a high risk for coronary events.

Keywords

Abdominal Subcutaneous Fat; Acute Coronary Syndrome; Diet; Obesity, Abdominal; Inflammation; Metabolic Syndrome; Risk Factors/prevention and control.

Subcutaneous adipocytes express higher adiponectin and lower pro-inflammatory adipokines, as well as increased adipogenesis.[3] However, most studies have not evaluated abdominal fat depots, ie, DSAT and SSAT. In patients recently diagnosed with type 2 diabetes mellitus, muscle insulin sensitivity and metabolic flexibility (the ability of insulin-sensitive individuals to switch from lipid to carbohydrate oxidation in response to insulin) were negatively associated with DSAT thickness, which was also related to impaired suppression of lipolysis and liver fat.[7] These results suggest that DSAT may play a deleterious role in mechanisms related to cardiometabolic health.

Diet plays a crucial role in abdominal fat accumulation. In a longitudinal analysis of the Framingham Heart Study, the lowest diet quality, evaluated by adherence to a Mediterranean-style diet score, was associated with the greatest abdominal SAT.[8] In addition, in a systematic review of observational and controlled intervention studies,[9] the quantity and quality of carbohydrates, protein, fat, and dietary fiber, as well as the intake of calcium, alcohol, phytochemicals, probiotics, cereal-based foods, sweets, sugar-sweetened beverages, between-meal snacks, and dietary patterns, were related to VAT and/or SAT. Thus, while it is clear that dietary exposure is related to abdominal fat depots, the relationship among diet, abdominal adiposity, and CVD outcomes is poorly understood.

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In the current issue, Stein et al.,[10] investigated the relationship between the dietary intake of ACS patients and DSAT estimated by the Deep-Abdominal-Adipose-Tissue (DAAT) index. In a cross-sectional analysis of data from 138 Brazilians, no association was found between dietary intake, as assessed through a quantitative food frequency questionnaire validated for the population, and DSAT. The results of the multivariate analysis demonstrated a positive relationship between DSAT and sedentary lifestyle and a negative relationship between DSAT and female sex. In addition, women had a higher waist circumference and waist-to-hip ratio, and lower DSAT levels than men. Although the DAAT index is not the gold standard for estimating DSAT, it can be easily calculated in clinical settings, and might encourage more clinicians to assess their patients' body fat distribution during office visits so that appropriate interventions, especially healthy lifestyle practices, can be prescribed. Based on Stein et al., increased physical activity would benefit ACS patients, but following a healthy diet would also be expected to promote weight loss and decrease adiposity and DSAT.

Finally, more research is needed to answer some remaining questions. First, what roles do adipose tissue and the different fat depots play as an endocrine organ by releasing inflammatory and/or anti-inflammatory molecules that may influence a coronary patient's metabolic response? Second, how does diet affect this relationship? Third, the way that diet can affect abdominal SAT, especially SSAT and DSAT, and their relationship with CVD outcomes are poorly understood. In summary, future studies should focus on clarifying the relationship between dietary intake, abdominal fat depots, including SSAT and DSAT, and cardiovascular health.

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Int J Cardiovasc Sci. 2022; 35(1):48-55

ORIGINAL ARTICLE

Ischemic Heart Disease in German Immigrants and Their Descendants in a Region of Southern Brazil: A Comparison of Initial Symptoms Reported between two Generations

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Abstract

Background: Nothing is known about ischemic heart disease (IHD) in the Germans who emigrated to Brazil during the last century.

Objective: We sought to compare age at diagnosis and IHD manifestations between German immigrants and their first-generation descendants in the region of Blumenau, Brazil.

Methods: We reviewed medical records of hospitals in Blumenau. Comparison of the groups in the evaluation times was made by analysis of variance (ANOVA) with repeated measures, and comparison of two factors was made by two-way ANOVA. The level of significance was set at $p < 0.05$.

Results: Study population comprised 68 patients who were born in Germany (group G) and 99 descendants (group D). Twenty-nine patients of group D had two German parents and 70 had one. Mean age at diagnosis was 66.8 ± 10.6 years, with a significant difference between the groups, four years higher in Group G than group D (69.0 ± 8.8 vs 65.4 ± 11.5 years old) ($p = 0.025$). There was no significant difference in risk factors or coronary angiography data between the groups. HDL cholesterol levels were significantly higher in group G than in group D (48.4 ± 11.1 mg/dL vs 43.3 ± 11.2 mg/dL, $p = 0.005$).

Conclusion: At the time of first IHD diagnosis, mean age of the group G was significantly higher than group D, with no differences between groups in sex, risk factors, LDL levels, or clinical and angiographic manifestations. An earlier manifestation of the disease could be part of lifestyle changes in descendants, in this population that mantained eating habits characterized by high saturated fat consumption.

Keywords: Ischemic Heart Disease, Coronary Artery Disease, Germans, Emigration and Immigration, Epidemiology.

Introduction

International migration has been an important factor in the economic, social, and cultural aspects of several countries. In Brazil, immigration has played an important role in building and modeling a variety of communities, some of which are in confined areas, with their own socioeconomic and cultural behaviors.[1]

Waves of migration from Germany to Brazil occurred primarily during the nineteenth and twentieth centuries and had an impact in the southern region of the country. These German immigrants formed nuclei first and then cities and have maintained the strong cultural and culinary habits characteristic of their homeland.[2] One of these communities, and perhaps the most representative one, is the city of Blumenau, located in Itajai valley. Blumenau is a predominantly industrial but also touristic city in the state of Santa Catarina, with a population of 357,199 inhabitants, corresponding to 45.6% of the population of this region (Itajai valley).[2,3] The city was founded by Dr. Hermann Otto von Blumenau, a former philosopher and administrator with a doctoral degree in chemistry.

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Studies around the world have explored the incidence and characteristics of ischemic heart disease (IHD) caused by coronary artery disease (CAD) in immigrants. For example, Japanese immigrants living in the USA or in Brazil,[4-12] Italians who migrated to Australia,[13] Norwegians, Finns, Germans and Hungarians who migrated to Sweden,[14] and Turkish immigrants living in Germany.[15]

However, no previous study has assessed the German population and their first-generation descendants in Brazil to determine their risk factors for IHD. This would allow the implementation of health actions that would specifically promote good health to these populations. Additionally, such studies could identify changes from traditional habits that may have contributed to increased incidence of specific diseases. The aim of the study was to address relevant consequences of German migration to confined and specific areas in Brazil.

Methods

We performed a retrospective study of patients with IHD who reside in the Blumenau region. Data were collected from the medical records of hospitals and cardiology clinics in the region. Then we separated patients into two groups, G- Germans and D- descendants.

The diagnosis of IHD was made based on: a) a coronary angiography or a computed tomographic angiography for coronary anatomy showing at least one artery with a lumen obstruction of ≥ 50% or b) the patient had experienced an acute myocardial infarction (AMI) that was confirmed by electrocardiographic criteria and/or biochemical markers of myocardial necrosis.

Regarding the clinical data, the time of onset of CAD was defined as the date of the first presentation of IHD recorded in the medical record and/or presence of AMI or angina pectoris. Angina was classified according to the criteria of the Canadian Cardiovascular Society (CCS);[16] sex and age on the date of the first symptoms were recorded. Diabetes was defined as the use of oral antidiabetic drugs or insulin, and hypertension was defined according to the ESH/ESC Guidelines for managing arterial hypertension.[17] We determined whether the patient was a smoker at the time they were diagnosed and identified former smokers those who quit smoking at least five years before, and nonsmokers as those who had never smoked.[18] Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula. In cases in which triglyceride levels were above 400 mg/dL, calculation was performed using the standard lipid profile method.[19] LDL cholesterol levels were obtained at two time points (baseline and during treatment). Blood samples obtained during acute coronary events, regardless of whether the patient was already using lipid lowering agents, were not considered for analysis. HDL cholesterol levels were directly measured.

Statistical analysis

All variables were analyzed descriptively. Quantitative variables were expressed as mean and standard deviation. For qualitative variables, absolute and relative frequencies were calculated. The normality of the data was tested using the Kolmogorov-Smirnov test.[20] For comparison of means between two groups, the unpaired Student's t-test was used.[20]

To test the homogeneity between proportions, the chi-square test[20] or Fisher exact test[20] was used. Comparison of the groups in the evaluation moments was made by analysis of variance (ANOVA) with repeated measures,[21] comparison of two factors was made by two-way ANOVA.[20] The statistical software used for the calculations was SPSS 21.0. The level of significance was set as 5%.

Sample size was not calculated because this retrospective study aimed to explore an existing and limited population in which all patients who were registered and attended cardiology services in the region were surveyed. They used the same strategy in a previous study comparing Japanese subjects and descendants (nisei) in Brazil[22] where we found a 10-fold greater probability of an early coronary event in Japanese descendants than in the Japanese group.

Results

A total of 299 records were obtained; 167 patients were included in the study and separated into two groups: group G, 68 patients (40.7%) who had emigrated from Germany, and group D, 99 patients (59.28%) born to German mothers and/or fathers. The other 132 subjects were excluded for the following reasons: a) not enough data were available in 80 records, b) no data related to IHD were available in 44 records, c) seven patients did not undergo coronary angiography and had no documented AMI, and d) one patient had only temporarily lived in the area (Figure 1)

The 299 medical records were reviewed from January 2008 to January 2016. Among German immigrants, the earliest diagnosis of IHD was made immigrant in 1981, and the latest record was in 2014. In the German descendants' group, the earliest diagnosis of IHD was made in 1986 and the latest in 2014.

There was no significant difference in sex, smoking status, hypertension, or diabetes between the groups. However, when we divided the populations using age cutoff values for CAD risk[23] of 55 years for men and 65 years for women, we found significantly older people in group G than in group D (Table 1). No data regarding smoking were found in seven subjects and no data regarding arterial hypertension were found in two subjects.

There was no significant difference between groups in the occurrence of AMI with or without ST segment elevation, Canadian Cardiovascular Society class of angina, or presence of angina. The first manifestation of IHD was AMI in 72 (43.4%) of all patients: 39 (39.8%) in group D and 33 (48.5%) in group G. Of those with AMI, 67 (93.1%) displayed ST elevation, 35 (89.7%) in group D and 32 (97%) in group G. No data were obtained regarding AMI in one subject and regarding angina in three subjects (Table 2).

Baseline LDL values were 159.0 ± 48.9 mg/dL in group D and 157.4 ±42.9 mg/dL in group G, and this difference was not statistically significant (p = 0.355). When we compared baseline and post-treatment cholesterol measurements between the groups, no statistically differences were found (Table 3). HDL levels, however, were significantly higher in Germans than in descendants (48.4 ± 11.1 mg/dL vs. 43.3 ± 11.2mg/dL; p= 0.005). No data regarding HDL levels were available in 13 patients.

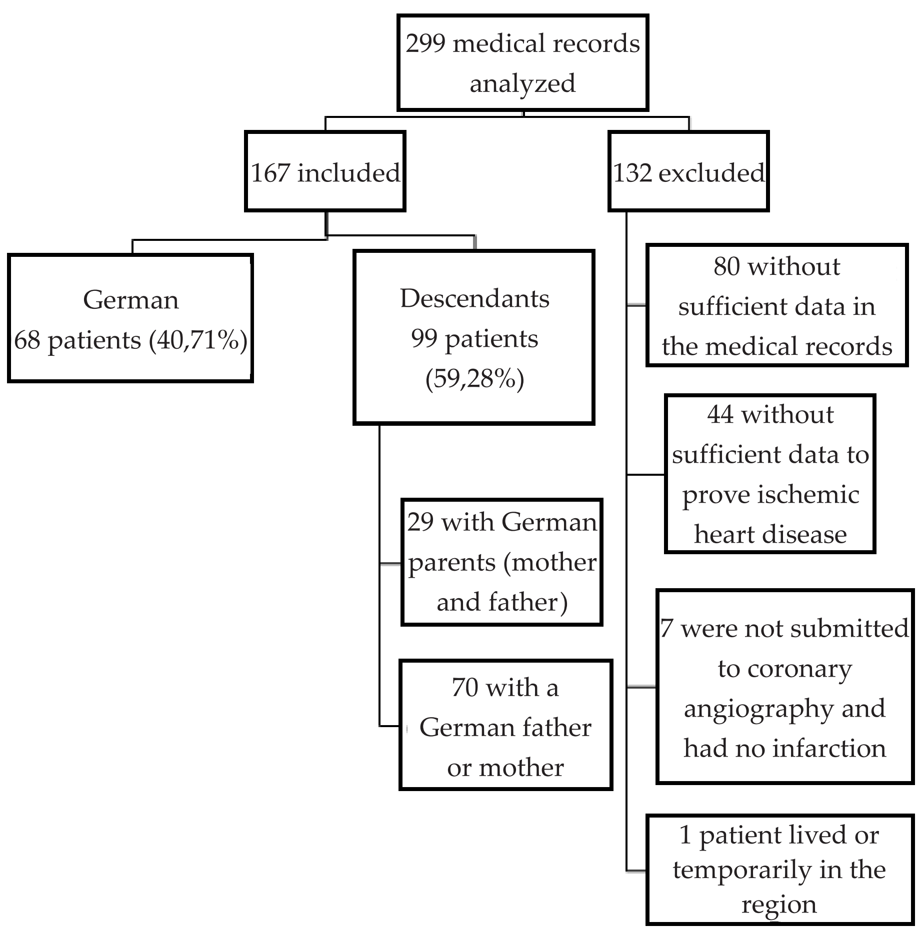

Figure 1 – Flowchart of data acquisition Last box bellow.

Table 1 – Sex, age, and risk factors in Germans (n=68) and descendants (n=99)

Variable		Cohort n=167 (%)		Group Descendants n=99 (%)		Germans 68 (%)		p
Sex								0.137
	Female	42	(25.2)	29	(29.3)	13	(19.1)	
	Male	125	(74.8)	70	(70.7)	55	(80.9)	
Smoking †								0.371
	No	127	(78.9)	78	(81.2)	49	(75.4)	
	Yes	34	(21.1)	18	(18.8)	16	(24.6)	
Hypertension	‡							0.218
	No	55	(33.3)	29	(29.6)	26	(38.8)	
	Yes	110	(66.7)	69	(70.4)	41	(61.2)	
Diabetes								0.431
	No	135	(80.8)	82	(82.8)	53	(77.9)	
	Yes	32	(19.2)	17	(17.2)	15	(22.1)	
Sex/Age	Male < 55 and Female < 65 yo	36	(21.6)	29	(29.3)	7	(10.3)	0.003
	Male ≥ 55 and Female ≥ 65 yo	131	(78.4)	70	(70.7)	61	(89.7)	

** Chi-square test (descriptive statistics)*
yo - years old
† No data available in six subjects
‡ No data available in two subjects

Mean age of all patients at IHD diagnosis was 66.9 ± 10.6 years old (range, 40–90 years old); 65.4 ±11.5 years old in group D, and 69.0 ± 8.8 years old in group G. The difference was statistically significant (p=0.025), four years on average, as shown in Figure 2 as a normal curve and a cumulative normal curve.

We then sought to determine whether there were associations between age at diagnosis and gender or initial symptoms. We found significant differences by age and sex groups (Table 4). We also evaluated differences in age at diagnosis among descendants according to ancestry, and found that in the 70 descendants with only one German parent, mean age was 64.2 ± 11.9 years old, and in the 29 descendants with two German parents, mean age was 68.3 ± 11.3 years old (p = 0.02).

We did not observe any interaction between age at diagnosis and initial symptoms by sex or other variables (p = 0.574), including interaction between the class of angina and age at diagnosis with IHD.

Discussion

Previous studies have examined populations that emigrated from other countries to countries in the Americas. This study is the first to explore IHD in German immigrants living outside their country of origin in a confined area in Brazil. This allowed the evaluation of IHD manifestations in German immigrants and their descendants without a strong cultural interference.

An important difference observed between Germans and their descendants was age at the time of the first diagnosis of IHD symptoms. Mean age was four years higher in the first generation of immigrants compared as descendants, even though both populations may have maintained their eating habits and other habits of life.

There was no difference in other IHD characteristics, such as coronary anatomy and disease extension, or the occurrence of AMI with or without ST segment elevation. We did not observe differences between the groups in the incidence of systemic arterial

Table 2 – Description of clinical presentation according to the study group

		Study cohort		Group				
Variable		(n=167)		Descendants (n=99)		Germans (68)		p
Acute myocardial infarction (AMI)‡								0.264(*)
	No	94	56.6%	59	60.2%	35	51.5%	
	Yes	72	40.9%	39	40.21%	33	49.25%	
ST elevation AMI								0.366(+)
(n=72)	No	5	6.9%	4	10.3%	1	3.0%	
	Yes	67	93.1%	35	89.74%	32	96.97%	
Angina §								0.526(*)
	No	19	11.6%	12	12.4%	7	10.5%	
	I	17	10.4%	7	7.2%	10	14.9%	
	II	22	13.4%	12	12.4%	10	14.9%	
	III	14	8.5%	8	8.3%	6	9.0%	
	IV	92	56.1%	58	59.8%	34	50.8%	
Development of								0.962(*)
CF	No	120	71.9%	71	71.7%	49	72.1%	

** Chi-square test*
+ Fisher's exact test
‡ No data available in one subject
§ No data available in three subjects
CF: Cardiac Failure

Table 3 – Low-density lipoprotein (LDL)-cholesterol levels by study group and time of assessment

	Group	
Time	Descendants	Germans
Initial	158.6 + 47.8 mg/dl	154.9 + 42.5 mg/dl
Final	96.9 + 31.1 mg/dl	100.7 + 39.3 mg/dl

*ANOVA with repeated measures: Group*Time, p=0,355; Grupo=0,999; Time: p<0,001*

hypertension, DM and smoking, which would be expected according to other published studies.[8,14,24] Probably we did not find the same results because our population was concentrated in Blumenau area without major external interferences. Blood test results were also similar, except for HDL cholesterol, which was higher in Germans than their descendants.

Except for the differences we observed in HDL cholesterol levels and age at the first manifestation of disease, no other variable was different in the univariate analysis, so we did not perform a multivariate regression. Such analysis would be justified if we wanted to correct for a confounding factor. We used the analysis of variance of two factors (sex and age) when

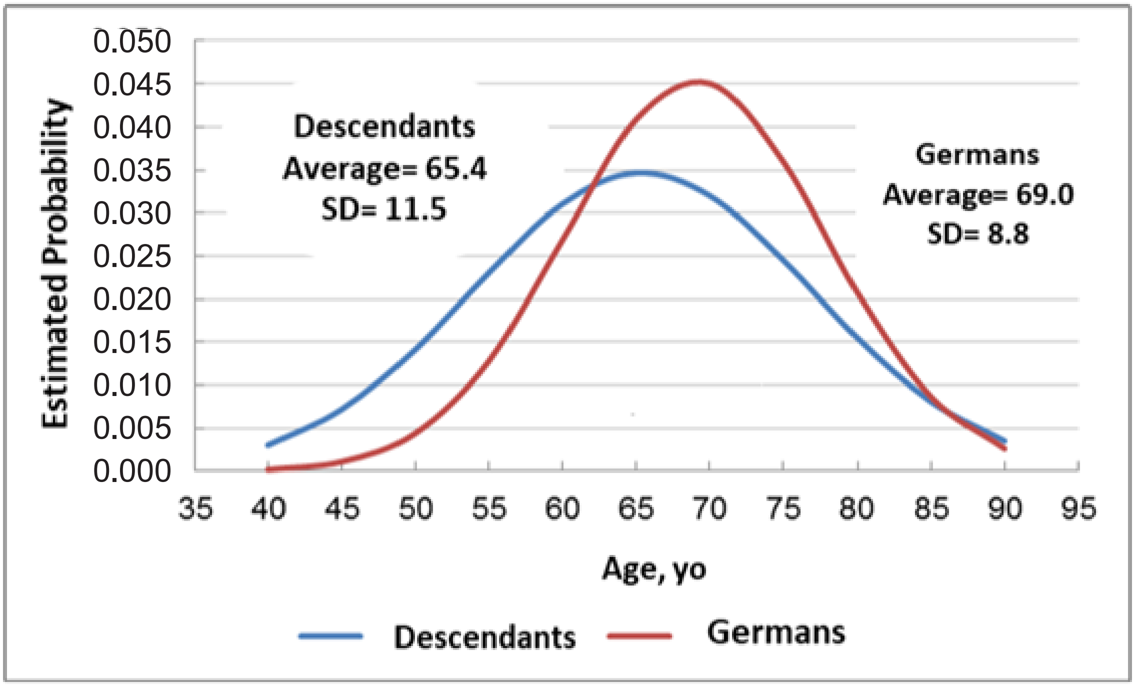

Figure 2 – Distribution of age at diagnosis of coronary heart disease in Germans and descendants

Table 4 – Association of age at diagnosis with study group and sex

	Cohort	Group	
Sex		Descendants	German
Female	72.2 ± 10.9	70.7 ± 11.8	75.5 ± 8.3
Male	65.0 ± 9.9	63.0 ± 10.7	67.6 ± 8.2
Cohort		65.3 ± 11.5	69.1 ± 8.8

*Two-factor ANOVA: Group*Sex, p = 0.950; Group = 0.015, Sex: p < 0.001*

we assessed the relationship of the two variables with the response variable.

In our study, to explain why descendants experienced IHD earlier than German immigrants, one hypothesis is that they seek medical assistance earlier than people from Germany. Perhaps the latter group had difficulties in communication (language), limited access to healthcare, or poor knowledge about how the health system works. Nevertheless, although these factors would be important in IHD diagnosis, they seemed to have low or no impact in our sample, since the number of Germans who presented with myocardial infarction was proportionally similar to that reported in their descendants. In fact, 83% of the German cohort presented with AMI as the first manifestation of the disease, and we could not determine if the reason for this difference was that they sought help at a later time.

German immigrants had to work hard to survive and build new lives outside their homeland. It is important to note that although they have preserved strong cultural and culinary habits, including a high-fat diet, they presented with IHD at older ages compared with their descendants. Also, health resources were not the same as those disponible for their descendants. To explain the significantly higher HDL levels in Germans than descendants, a more intense legwork may have contributed to it.

There are some limitations needed to be addressed. First, in the region of Blumenau, where this survey was performed, periodic floods occur because of intense rains that overflow the rivers. Hence, many patient records were missing, and for this reason, we were unable to include in this cohort a larger number of cases, especially those related to patients who originated from Germany.[25] Second, the number of patients were small, despite representative of Blumenau population. Third, not all data were available from the medical records of patients, which is seen the variation of "N" in the tables. Finally, we do not know the age of patients who died from AMI, and therefore we do not know whether Germans died at an early age or had a higher prevalence of cardiovascular risk factors.

Conclusion

Mean age at the first diagnosis of IHD was four years higher in German immigrants than in the first-generation descendants. German patients had higher HDL-cholesterol levels, which may be explained by the fact that these individuals did more legwork than their descendants.

Potential Conflict of Interest

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

Sources of Funding

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Study Association

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Ethics approval and consent to participate

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

Author contributions

Conception and design of the research: Zimmermann SL. Cesar, LA. Acquisition of data: Zimmermann SL, Starke S. Analysis and interpretation of the data: Zimmermann,SL. Statistical analysis: Zimmerman SL, Cesar LA. Writing of the manuscript: Zimmermann SL, Moretti MA. Critical revision of the manuscript for intellectual content: Vianna CB, Mansur AP, Cesar LA.

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EDITORIAL

Immigrants, Descendants and the Risk of Coronary Heart Disease

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Editorial referring to the article: Ischemic Heart Disease in German Immigrants and Their Descendants in a Region of Southern Brazil: A Comparison of Initial Symptoms Reported between Two Generations

Cardiovascular disease remains the leading cause of death worldwide and in all regions of Brazil.[1] Racial, cultural, and environmental factors contribute to different prevalence rates of risk factors and presentations of the disease. Differences have been found between Whites, Hispanics, Asians, and Afro-descendants, and even within each race, due to migratory movements.[2,3]

Changes in the socio-demographic profile of migrant populations have resulted in health transitions, considering the country of origin (some of them with a high risk for certain diseases) and changes in lifestyle and diet in the new country. Several studies have found a significant linear relationship between migration and acculturation, alcohol consumption, lipid profile, blood pressure, body mass index and physical activity.[4-6]

Brazil is one of the countries with the greatest cultural diversity that is explained by the origin of its population. Brazil has absorbed numerous nationalities and cultures throughout its historical formation resulting from intense immigration, especially at the turn of the 19th century and in the 1920s.[7]

For example, new geographic and cultural contexts due to the immigration from Germany to Brazil have changed the disease profile of these immigrants and their descendants. The study "Ischemic Heart Disease in German Immigrants and Their Descendants in a Region of Southern Brazil: A Comparison of Initial Symptoms Reported between Two Generations" by Zimmermann et al.,[8] published in this issue compared age at diagnosis and manifestations of ischemic heart disease (IHD) between German immigrants and their first-generation descendants through the review of hospital records in the city of Blumenau, Brazil. The authors found that at the time of the first diagnosis of IHD, the mean age of participants born in Germany was significantly higher than the group of descendants and concluded that the earlier disease onset may be partly due to changes in the lifestyle of their children, including changing in eating habits characterized by high consumption of saturated fats.

Another Brazilian study also assessed the differences in the presentation of IHD between immigrants and their descendants. Amato et al.[9] carried out a retrospective analysis of the clinical manifestations of coronary artery disease and the prevalence of risk factors, comparing 128 Japanese immigrants (Japanese group) with 304 Japanese descendants (Nisei group). The authors found that, despite a similar clinical presentation, the onset of coronary heart disease was nearly 12 years earlier in the Nisei group (mean = 53 years) compared to the Japanese group (mean = 65 years) ($P < 0.001$).

Interestingly, these studies did not find differences regarding risk factors, LDL levels or clinical and angiographic manifestations of the disease between immigrants and their descendants. Maybe, this can be explained by the retrospective, cross-sectional nature of the studies that evaluated initial manifestations of coronary heart disease. Even so, it may be assumed that Brazilian descendants were exposed earlier and perhaps more intensely to risk factors for IHD. To confirm this possibility, prospective cohort studies would be interesting, especially if including, in addition to body mass index, waist circumference and blood pressure measurements, laboratory tests, validated questionnaires on quality of life, and assessment of physical activity

Keywords

Atherosclerosis; Coronary Artery Disease; Imigrants and Descendants; Risk Factors; Epidemiology.

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level and eating habits, to confirm whether the earlier manifestation of IHD is associated also with an earlier onset of risk factors like diabetes, hypertension and dyslipidemia. Healthy habits combined with a regular diet are fundamental for an adequate control of risk factors to prevent premature occurrence of cardiovascular disease.

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ORIGINAL ARTICLE

Predictive Value of Myocardial injury in Patients with COVID-19 Admitted to a Quaternary Hospital in the City of Rio de Janeiro

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Abstract

Background: In Brazil the factors involved in the risk of death in patients with COVID-19 have not been well established.

Objective: To analyze whether elevations of high-sensitivity troponin I (hTnI) levels influence the mortality of patients with COVID-19.

Methods: Clinical and laboratory characteristics of hospitalized patients with COVID-19 were collected upon hospital admission. Univariate and binary logistic regression analyzes were performed to assess the factors that influence mortality. P-value<0.05 was considered significant.

Results: This study analyzed192 patients who received hospital admission between March 16 and June 2, 2020 and who were discharged or died by July 2, 2020. The mean age was 70±15 years, 80 (41.7%) of whom were women. In comparison to those who were discharged, the 54 (28.1%) who died were older (79±12 vs 66±15years; P=0.004), and with a higher Charlson´s index (5±2 vs 3±2; P=0.027). More patients, aged≥60years (P <0.0001), Charlson´s index>1 (P=0.004), lung injury>50% in chest computed tomography (P=0.011), with previous coronary artery disease (P=0.037), hypertension (P=0.033), stroke (P=0.008), heart failure (P=0.002), lymphocytopenia (P=0.024), high D-dimer (P=0.024), high INR (P=0.003), hTnI (P<0.0001), high creatinine (P<0.0001), invasive mechanical ventilation (P<0.0001), renal replacement therapy (P<0.0001), vasoactive amine (P<0.0001), and transfer to the ICU (P=0.001), died when compared to those who were discharged. In logistic regression analysis, elevated hTnI levels (OR=9.504; 95% CI=1.281–70.528; P=0.028) upon admission, and the need for mechanical ventilation during hospitalization (OR=46.691; 95% CI=2.360–923.706; P=0.012) increased the chance of in-hospital mortality.

Conclusion: This study suggests that in COVID-19 disease, myocardial injury upon hospital admission is a harbinger of poor prognosis.

Keywords: COVID-19; SARS-CoV-2; Mortality; Myocardial Contusions; troponin I.

Introduction

Since the first reported cases in Wuhan, China, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread rapidly worldwide. According to the World Health Organization (WHO), on October 9, 2020, there were 36,754,395 confirmed cases of COVID-19 in the world, with 1,064,838 deaths, while in Brazil there were 5,028,444 confirmed cases with 148,957 deaths.[1]

Although SARS-CoV-2 explicitly refers to an aggression in the lungs, often inducing acute respiratory distress syndrome (ARDS), it also affects other organs, including blood vessels, brain, gastrointestinal tract, kidneys, heart, and liver,[2] and cardiovascular complications are manifestations that contribute significantly to the mortality of these patients.[3]

Several biomarkers of myocardial injury are elevated in patients with COVID-19, and a rise in troponin levels

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have been associated with the prediction of malignant cardiac arrhythmias,[4] and the need for mechanical ventilation (MV).[3,5-8]

This study sought to verify whether the elevation of high-sensitive troponin I (hTnI) levels upon hospital admission is an independent predictive factor of higher mortality in hospitalized patients with COVID-19.

Methods

This retrospective study involved a cohort of patients over 18 years of age who received hospital admission between March 16 and June 2, 2020, with a diagnosis of COVID-19, confirmed by nasopharyngeal reverse transcription-polymerase chain reaction (RT-PCR), or IgM and IgG measurement by chemiluminescent microplate immunoassay technique, and who were discharged or died by July 2, 2020.

The following characteristics were routinely collected upon hospital admission: sex, age, symptoms, comorbidities, blood count, biochemistry, prothrombin time with INR (INR), ultrasensitive PCR, D-dimer, simple X-ray, and chest computed tomography (CT) scan. hTnI (VITROS® High Sensitivity Troponin I assay), N-terminal prohormone of brain natriuretic peptide (Roche NT-proBNP), fibrinogen, and transthoracic echocardiogram (TTE) were not collected in all patients upon hospital admission. The laboratory tests were those collected within 24 hours of the patients' admission.

Comorbidities and clinical manifestations were collected by the physician responsible for hospital admission and were described, non-systematically, in the research forms from which the data were extracted for analysis.

The need for invasive MV, renal replacement therapy (RRT), extracorporeal membrane oxygenator (ECMO), the development of acute left ventricular systolic dysfunction (LVSD), or acute cor pulmonale, and the transfer to the intensive care unit (ICU) due to the worsening of the clinical condition during hospitalization, were also collected. Worsening of the clinical condition meant persistent desaturation, despite oxygenation by a high-flow nasal catheter, endotracheal intubation, resuscitation after cardiorespiratory arrest, and shock of any nature requiring vasoactive amines.

To analyze the chest CT scan, exams performed in the first 24 hours of hospitalization were included, and those with a “ground glass” infiltrate pattern, compatible with SARS-CoV-2 infection,[9] were considered positive. All chest CT reports were reviewed by a senior radiologist, with an emphasis on compatible changes and the percentage of pulmonary parenchymal involvement.

TTE were performed following the recommendations of the Department of Cardiovascular Imaging (DIC, in Portuguese) of the Brazilian Society of Cardiology (SBC, in Portuguese) to perform cardiovascular imaging tests during the COVID-19 pandemic,[10] prioritizing the analysis of the left ventricular systolic dysfunction (LVSD) and the presence of acute cor pulmonale. The degree of LVSD was assessed visually. These analyzes were performed within the first 48 hours of hospitalization, and all tests were reviewed and validated by a senior echocardiographer.

The review of the imaging exams was carried out without the doctors having any knowledge of the clinical, laboratory, or patient outcomes.

Symptoms and comorbidities were those reported by patients or provided by family members, caregivers, or companions depending on the degree of interaction of the patients at the time of hospital admission.

The comorbidities presented by the patients were assessed using the Charlson’s comorbidity index.[11]

This study was approved by the institution’s Ethics Committee (number 31543220.1.0000.5533).

Statistical analysis

Data were collected directly from the medical records by an independent clinical research team and subsequently included in the SPSS statistical package, version 22 (IBM SPSS®).

Continuous variables were exposed by mean and standard deviations, and categorical variables by numbers and the appropriate proportions. The unpaired Student t test was used to compare continuous variables, and the Fisher's exact test or the Chi-square method was used to verify the existence of the association between categorical variables.

Binary logistic regression analysis was used to define which factors independently influenced mortality. To be included in this analysis, it was necessary that in the univariate analyses conducted by the Student’s t test, Fisher exact test, or Chi-square test, the P-values were ≤ 0.05. Two-tailed P-values < 0.05 were considered statistically significant.

Results

During the study period, 339 consecutive patients were admitted to cohort units for SARS-Cov-2 infection, of whom 205 had a confirmed diagnosis. Among the 205, 192 (93.6%), who either died or were discharged by July 2, 2020, were included in this analysis.

Of the 192, 80 (41.7%) were women, aged 70 ± 15 years and Charlson's index of 3 ± 2. This study included 135 patients aged ≥60 years (70.3%), and 61 (31.8%) were aged ≥80 years. Charlson's index >1 was observed in 133 (69.3%) patients.

During the study period, 54 (28.1%) patients died.

Table 1 shows that, on average, deceased patients were 13 years older than those who were discharged and with a significantly higher Charlson's index.

Of the 54 who died, 27 (50%) received palliative care during hospitalization. In 7 of the 27 (25.9%), no invasive procedures, endotracheal intubation, renal replacement therapy, or resuscitation procedures were used, and the deaths occurred in semi-intensive care units.

As shown in Table 1, more patients of ≥60 years, and with Charlson's index >1 died when compared to those who were discharged. Table 1 also shows that patients who died had more than 50% of the pulmonary parenchyma compromised, a previous history of

Table 1 – Factors involved in mortality upon hospital admission in a univariate analysis

Characteristics	Discharged (N=138)	Died (N=54)	p-value	OR	95% CI
Age ≥ 60 years, N (%)	84 (60.9)	51 (94.4)	<0.0001	10.929	3.247–36.779
Charlson's index >1, N (%)	121 (87.7)	54(100)	0.004	1.446	1.310–1.547
Men, N (%)	81 (58.7)	31 (57.4)	0.672	1.054	0.558–1.994
Obesity, N (%)	37 (26.8)	14 (25.9)	1.0	0.995	0.467–1.954
SAH, N (%)	79 (57.2)	40 (74.1)	0.033	2.134	1.064–4.279
Diabetes, N (%)	48 (34.8)	20 (37.0)	0.867	1.103	0.573–2.121
CAD, N (%)	26 (18.8)	18 (33.3)	0.037	2.154	1.060–4.375
Stroke, N (%)	7 (5.1)	10 (18.5)	0.008	4.253	1.527–11.848
COPD, N (%)	11 (8.0)	8 (14.8)	0.181	2.008	0.760–5.303
CHF, N (%)	4 (2.9)	9 (16.7)	0.002	6.700	1.968–22.814
CRF, N (%)	7 (5.1)	6 (11.1)	0.197	2.339	0.749–7.310
CT pulmonary>50%, N (%)	30 (21.9)	22 (41.5)	0.011	2.531	1.282–4.997
Leukocytosis, N (%)	16 (11.6)	11 (20.4)	0.164	1.951	0.840–4.530
Lymphocytopenia, N (%)	63 (45.7)	35 (64.8)	0.024	2.193	1.143 4.206
Thrombocytopenia, N (%)	44 (31.9)	21 (38.9)	0.398	1.360	0.707–2.614
D-dimer≥500ng/mL, N (%)	108 (80.0)	48 (91.4)	0.024	4.000	1.157–13.827
hsRCP-t>0.5ng/mL, N (%)	135 (97.8)	54 (100)	0.560	0.978	0.954–1.003
hTnI≥34pg/mL, N (%)	11 (10.8)	18 (48.6)	<0.0001	7.837	3.192–19.345
INR>1.3, N (%)	21 (15.3)	19 (35.8)	0.003	3.087	1.489–6.398
Creatinine>1.3mg/dL, N (%)	29 (53.7)	28 (20.6)	<0.0001	4.474	2.273–8.809

SAH: systemic arterial hypertension; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; CHF: congestive heart failure; CRF: chronic renal failure; CT pulmonary: pulmonary parenchymal alterations in chest computed tomography; hsCRP: high-sensitive C-reactive protein; hsTnI: high-sensitivity troponin I; INR: international normalized ratio; Leukocytosis means white blood cell count ≥10500/L; Lymphocytopenia, lymphocyte count <900/L; thrombocytopenia, platelet count <150000/L.

coronary artery disease (CAD), stroke, congestive heart failure (CHF), and systemic arterial hypertension (SAH), as well as lymphocytopenia, higher levels of creatinine, D-dimer, INR, and hTnI upon hospital admission than those who survived and were discharged.

The average length of stay was not different between those who died and those who were discharged (14 ± 13 days vs 14 ± 11 days; P=0.174).

No difference in mortality was found between men and women (27.7% vs 28.7%, respectively; P=0.872).

Table 2 shows that during hospitalization, more patients who died received invasive MV, RRT, vasoactive amine, and transfer to the ICU compared to those who were discharged.

There was no difference between those who died and those who were discharged with regard to the development of acute LVSD during hospitalization (10.6% vs 2.7%; P=0.109).

Table 3 shows that, in the binary logistic regression analysis, it was found that elevated hTnI levels upon hospital admission, and the need for invasive MV during hospitalization, increased the chance of hospital mortality.

Patients with hTnI elevation upon hospital admission are more likely to have previous CHF (17.2% vs 2.7%; P=0.010; OR=7.431; 95% CI=1.661 – 33.243), COPD (20.7% vs 6.4%; P=0.029; 95% CI= 1.179 – 12.497), and the need for invasive MV during hospitalization (55.2% vs 21.8%; P=0.001; OR=4.410; 95% CI=1.865 – 10.426) as compared to patients who have normal hTnI levels.

No difference was found in relation to previous history of stroke (13.3% vs 9.1%; P=0.49), CAD (27.6% vs 23.6%; P=0.63), SAH (72.4% vs 60,0%; P=0.28), diabetes (44.8% vs 33.6%; P=0.28), and the development of acute LVSD (7.7% vs 6.3%; P=1.0) during hospitalization between patients with high and normal TnI levels, respectively, upon hospital admission.

Discussion

According to the findings of this study, it is suggested that, in a selected population of symptomatic hospitalized adult patients with a confirmed diagnosis of COVID-19, the presence of myocardial injury, characterized by high levels of hTnI upon hospital admission, is associated with an increased risk of death.

There is growing evidence of an association between myocardial injury and an increased risk of death in patients with COVID-19. Several studies involving patients with confirmed COVID-19 have implied the elevation of serum hTnI not only with mortality,[4,12-19] but also criticality.[8,14,16]

Although some investigators[4,14,16,18] have found an association between inflammatory biomarkers with poor prognosis, in the present study, only higher levels of hTnI were independently associated with mortality (table 3).

Another finding of this study, unlike others,[6,12,13,18] is that the presence of cardiovascular comorbidities was not independently associated with higher mortality (Table 3). In addition, it was demonstrated (table 3) that there was no independent association between older age (>60year-old) and mortality as has been demonstrated in other studies.[12,14,16] In the present study, the mortality of patients aged ≥ 60years of age was 37.8%, while the mortality of

Table 2 – Factors involved in mortality during hospitalization in univariate analysis

Characteristics	Discharged (N=138)	Died (N=54)	p-value	OR	95% CI
LVSD, N (%)	2 (2.7)	5 (10.6)	0.109	4.226	0.785–22.758
RRT, N (%)	2 (1.4)	11 (20.4)	<0.0001	17.395	3.710–81.562
Transfer to ICU, N (%)	17 (12.3)	19 (35.2)	0.001	3.864	1.817–8.219
Vasoactive amine, N (%)	20 (14.5)	30 (55.6)	<0.0001	7.375	3.604–15.092
MV, N (%)	16 (11.6)	41 (75.9)	<0.0001	24.048	10.667–54.214

LVSD: left ventricular systolic dysfunction; RRT: renal replacement therapy; ICU: intensive care unit; MV: invasive mechanical ventilation;

Table 3 – Results of binary regression analysis

Characteristics	OR	95% CI	p-value
Age ≥ 60 years	6.305	0.501 – 79.403	0.154
CAD	8.093	0.944 – 69.376	0.056
Stroke	13.980	0.327 – 597.291	0.169
CHF	8.567	0.426 – 172.445	0.161
INR>1.3	6.221	0.765 – 50.613	0.087
D-dimer>500ng/mL	1.507	0.034 – 66.740	0.832
Creatinine >1.3mg/dL	1.206	0.196 – 7.404	0.840
hTnI >34pg/mL	9.504	1.281 – 70.528	0.028
CT pulmonary alterations >50%	3.878	0.502 – 29.943	0.194
MV	46.691	2.360 – 923.706	0.012
Vasoactive amine	0.843	0.113 – 6.262	0.867
Transfer to ICU	3.231	0.153 – 68.109	0.451
RRT	10.175	0.800 – 129.444	0.074

CAD: coronary artery disease; CHF: congestive heart failure; CT pulmonary: pulmonary parenchymal alterations in chest computed tomography; hTnI: high-sensitivity troponin I; MV: invasive mechanical ventilation; ICU: intensive care unit; RRT: renal replacement therapy.

patients with higher hTnI was 69.4% (data not shown). In other words, it is suggested that myocardial injury upon hospital admission is much more dangerous than older age or cardiovascular comorbidities in the population with COVID-19 reported in this study.

Therefore, according to the findings of the present study and data collected from recent literature, it seems clear that the presence of myocardial injury in hospitalized adult patients with COVID-19 was associated with an increased risk of death. The pathophysiological substrate of myocardial injury produced by SARS-CoV-2 is not yet well defined, but it is speculated that an imbalance between myocardial demand and supply due to tachycardia, hypotension, and hypoxemia resulting in type 2 myocardial infarction, acute coronary syndrome due to a virally induced thrombotic and inflammatory state, microvascular dysfunction due to diffuse microthrombi or vascular injury, stress-related cardiomyopathy (Takotsubo syndrome), nonischemic myocardial injury due to hyperinflammatory cytokine storm, or a direct viral cardiomyocyte toxicity and myocarditis may be involved.[5,20]

Although no association was found between a rise in troponin upon hospital admission and the development of acute LVSD, it must be taken into account that there was no analysis of the evolution of hTnI levels during hospitalization.

Another finding of the present study is the independent association of the need for invasive MV during hospitalization, and an increased chance of death. Patients who required MV had a much higher chance of death when compared to those who did not require MV (Table 2 and Table 3). Of 57 patients that needed MV, 41 died (71.9%). This association has been reported by other studies, which have demonstrated that the mortality involved in the need for invasive MV varied from 33.9% to 90%.[16,21-24]

The finding of an association between the need for MV and increased mortality seems obvious, as it implies greater severity of the disease, especially acute respiratory distress syndrome. In the studied population, patients who required MV present greater lung injury (40.4% vs 21.8%; P = 0.013), higher hTnI (40% vs 13.1%; P = 0.001), a greater need for ECMO (5.3% vs 0%; P = 0.025), and RRT (21.1% vs 0.7%; P <0.0001) than those that did not require MV.

Limitations

Like any retrospective study, this study suffers from the lack of systematization in the registration of clinical and laboratory characteristics of patients, implying that the associations between these data and mortality are suggestive and require external validation, involving a larger number of patients with similar clinical and laboratory characteristics.

Laboratory changes that occurred during the course of hospitalization were also not routinely analyzed, which could somehow modify the results of the study.

This is a study of a quaternary heart center, which increases the chance of involving more patients with heart diseases, although no difference was found in the presence of previous CAD, stroke, chronic kidney dysfunction, SAH, diabetes or the development of acute LVSD among those with and without myocardial injury.

Conclusions

In a selected population of symptomatic hospitalized adult patients with COVID-19, the presence of myocardial injury upon hospital admission was independently associated with increased mortality. Therefore, it was suggested that hospitalized COVID-19 patients should have troponin levels measured routinely upon hospital admission in order to stratify the risk of death.

Author contributions

Conception and design of the research: Rocha ASC, Volschan A, Coelho RPS, Thielmann DCA. Acquisition of data: Rocha ASC, Volschan A. Analysis and interpretation of the data: Rocha ASC, Volschan A, Campos LAA, Thielmann DCA, Ferreira CALC, Colafranceschi AS. Statistical analysis: Rocha ASC, Volschan A. Writing of the manuscript: Rocha ASC, Volschan A. Critical revision of the manuscript for intellectual content: Rocha ASC, Volschan A, Campos LAA, Thielmann DCA, Ferreira CALC, Colafranceschi AS.

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 Pró-Cardíaco* under the protocol number 31543220.1.0000.5533. 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

Cause or Consequence? What is the Relationship between Cardiac Injury and COVID-19 Severity?

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Editorial referring to the article: Predictive Value of Myocardial injury in Patients with COVID-19 Admitted to a Quaternary Hospital in the City of Rio de Janeiro

"I know nothing and my heart aches"

Fernando Pessoa, The Book of Disquiet

In most patients, coronavirus disease-2019 (COVID-19) causes minor respiratory symptoms or even no symptoms. SARS-CoV-2 infection can also cause extrapulmonary manifestations and complications. COVID-19 is more severe and fatal among patients with pre-existing cardiovascular risk factors or diseases.[1] Increases in cardiac troponin (cTn) are indicative of myocardial injury and frequently found in patients with COVID-19.[2] The Chinese Center for Disease Control and Prevention published a survey demonstrating that among patients diagnosed with COVID-19, 13% had hypertension, 5% had diabetes mellitus, and 4% had a history of cardiovascular disease. However, in this same cohort, among patients who had not survived, 40% had hypertension, 20% had diabetes, and 22% had pre-existing cardiovascular disease.[3] Patients with cardiovascular disease had the highest case fatality rate (10.5%).

In this issue of the International Journal of Cardiovascular Sciences, Rocha et al. ,[4] studied 192 patients admitted with COVID-19 in a quaternary care cardiac hospital in Rio de Janeiro, Brazil. Mortality rate was 28%. Multivariate analysis demonstrated that elevated cTnI levels (OR=9.504; 95% CI=1.281–70.528; P=0.028) upon admission and the need for mechanical ventilation during hospitalization (OR=46.691; 95% CI=2.360–923.706; P=0.012) were independent predictors of death during hospitalization.[4] The main limitations of the study are a sample from a single Brazilian metropolitan region and a short follow-up period. However, these limitations do not invalidate the main message of the study: the measurement of cardiac troponin at hospital admission may be useful for identification of high-risk patients infected by SARS-CoV-2.

Cardiac troponins are not specific markers of ischemic injury of the heart. The Fourth Universal Definition of Myocardial Infarction defines myocardial injury (acute or chronic) as cTn concentrations >99th percentile upper reference limit (URL). While dynamic changes in cardiac troponins characterize acute injury, patients without these changes have chronic injury.[5] Patients with COVID-19 have several conditions that may be associated with myocardial injury such as myocarditis, stress cardiomyopathy, acute heart failure, pulmonary embolism, critical illness, and sepsis.[2] Garcia de Guadiana-Romualdo et al.,[6] demonstrated that elevated troponin levels were common in patients with COVID-19. These authors found abnormal levels of cTn in 26.9% of the patients and in 30% when sex-specific cut-offs were used to detect myocardial injury.[6] Some factors increase the risk of abnormal cTn levels, including older age and the type of troponin measured (troponin T is associated with higher levels). Nascimento et al.,[7] studied 61 patients admitted to intensive care unit with COVID-19 in a Brazilian hospital and found a high incidence of myocardial infarction in patients with severe COVID-19, with impact on in-hospital mortality.[7]

COVID-19 can damage the cardiovascular system in many ways. A myocardial oxygen supply-demand

Keywords

Cardiovascular Diseases/complications; COVID-19/complications; SARS-CoV-2; Risk Factors; Hypertension; Diabetes Mellitus; Troponin I; Hospitalization; Mortality.

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mismatch (type 2 myocardial infarction) can result from an imbalance between high metabolic demand and low cardiac reserve, systemic inflammation and thrombogenesis, in addition to direct cardiac damage from the virus.[8] Cardiovascular complications occur mainly in patients with cardiovascular risk factors (advanced age, hypertension and diabetes) or preexisting cardiovascular diseases. There are few reports of COVID-19 patients who presented with acute ST-segment elevation myocardial infarction (STEMI) that the final diagnosis was myocarditis. This diagnosis is supported by elevated cardiac troponins, moderate decrease of left ventricular ejection fraction, and absence of flow-limiting coronary artery disease by invasive coronary angiography.[9] Autopsy findings support the concept that the pathogenesis of severe COVID-19 involves a virus-induced injury of multiple organs, including heart and lungs, coupled with the consequences of a procoagulant state with coagulopathy, although overt myocarditis is very rare.[10] Together, these data suggest that in most cases, myocardial injury detected by increased cardiac troponins are not causes of severe COVID-19, but rather consequences/effects of high risk COVID-19.

Type I myocardial infarction is not commonly associated with COVID-19 and some studies have shown even a decreased incidence of hospitalization for acute myocardial infarction during the Covid-19 pandemic. Solomon et al.,[11] reported a decrease by up to 48% in weekly rates of hospitalization for acute myocardial infarction during the COVID-19 period.[11] De Filippo et al.,[12] found similar reductions in 15 hospitals in northern Italy. This decrease may also be associated with the anxiety and fear of catching COVID-19 in the emergency department, commonly seen among patients during the initial months of the pandemic. Consequently, parallel to this decrease in myocardial infarction hospitalizations, a transient increase in the incidence of out-of-hospital cardiac arrest (AOHCA) was observed when compared with the equivalent time period in previous years with no pandemic.[13] The same trend was demonstrated in a Brazilian study by Guimarães et al.,[14] who found a proportional increase of 33% of home deaths in March 2020, which is when the World Health Organization declared the COVID-19 pandemic.[14] The increase of AOHCA can be linked to COVID-19 infections and to the potential increase of patients with acute cardiac diseases that did not seek emergency care.

We are entering a new phase of the COVID-19 pandemic. The United Kingdom's Medicines and Healthcare products Regulatory Agency has issued temporary authorization of the antiviral drug molnupiravir for the treatment of mild to moderate COVID-19 in adults with at least one risk factor for severe illness.[15] The approval of effective oral drugs, combined with the use of effective vaccines against COVID-19, can potentially change the scenario and contribute to a consistent decrease in the number of cases and the adverse effects of SARS-COV-2 infections.[16,17] However, we must remember that there is a long way to go to let our guard down. Science needs to be protected and valued; now more than ever.

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ORIGINAL ARTICLE

Lifestyle Intervention in Reducing Cardiometabolic Risk Factors in Students with Dyslipidemia and Abdominal Obesity: A Randomized Study

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Abstract

Background: The long incubation periods of cardiovascular diseases offer opportunities for controlling risk factors. In addition, preventive interventions in childhood are more likely to succeed because lifestyle habits become ingrained as they are repeated.

Objective: To investigate the effects of recreational physical activities, in combination or not with a qualitative nutritional counseling, in cardiometabolic risk factors of students with dyslipidemia and abdominal obesity.

Methods: Students (8-14 years old) were randomly divided into three groups (n=23 each): *i*) Control; *ii*) PANC, students undergoing Physical Activity and Nutritional Counseling, and *iii*) PA, students submitted to Physical Activity, only. Blood samples (12-h fasting) were collected for biochemical analysis and anthropometric markers were also assessed. Two-Way RM-ANOVA and Holm-Sidak's test, and Friedman ANOVA on Ranks and Dunn's test were applied. $P \leq 0.05$ was considered significant. Effect sizes were evaluated by Hedges' g and Cliff's δ for normal and non-Gaussian data, respectively.

Results: Compared to the control group and to baseline values, both interventions caused significant average reductions in total cholesterol (11%; $p < 0.001$), LDL-c (19%; $p = 0.002$), and non-HDL-c (19%; $p = 0.003$). Furthermore, students in the PANC group also experienced a significant decrease in body fat compared to baseline ($p = 0.005$) and to control (5.2%; $g = 0.541$).

Conclusions: The proposed strategies were effective to reduce cardiometabolic risk factors in children and adolescents. The low cost of these interventions allows the implementation of health care programs in schools to improve the students' quality of life.

Keywords: Child; Adolescent, Students; Exercise; Dyslipidemias; Obesity; Risk Factors; Lifestyle; Nutritional Orientation; Glycemic Profile.

Introduction

Despite remarkable advances in cardiovascular health promotion over the past decades, cardiovascular diseases (CVD) remain the leading cause of death worldwide.[1-3] It is estimated that behavioral risk factors may be responsible for about 80% of CVD and are associated with metabolic and physiological changes like overweight, hyperlipidemia, and hyperglycemia, which may have multiple effects.[1,2,4,5]

Over the last decades, the increased prevalence of overweight, obesity, and dyslipidemias in children and adolescents has placed concern on the health conditions of this population.[1-3] Additionally, the increased knowledge about the long-term effects of exposure to risk factors and concern about the epidemic of pediatric obesity led to the urgency of primordial and primary prevention strategies during childhood.[3,6] Therefore, in addition to the early detection of the metabolic disorders, it is important to establish preventive strategies for reducing these emerging epidemics.

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In this context, there are increasing evidences that physical inactivity in children and adolescents, which promote decrease in energy expenditure, is closely associated with the current prevalence of overweight, obesity, and dyslipidemias.[1,6-8] Therefore, in order to prevent and treat these disorders, there is a growing interest for approaches based on physical activity improvement.[1,6,9,10] According to the WHO, ideally, children and adolescents should accumulate 60 min of daily moderate to vigorous-intensity physical activity, and to improve biomarkers of cardiovascular health they should incorporate vigorous activities three times per week.[9,10]

In addition to physical activities, dietary patterns can modulate various aspects of cardiovascular risk, such as dyslipidemia, insulin resistance (IR), hyperglycemia, hypertension and inflammation.[8,11] Healthful dietary patterns are important for primary prevention of risk factors related to CVD from childhood through adulthood. Evidence of the effectiveness of dietary intervention for reducing risk factors in children is limited, but ample data suggest that changes in specific dietary macronutrients (e.g., fat and carbohydrates) and micronutrients (e.g., sodium and calcium) have a great positive impact.[2,8]

Herein, we hypothesized that recreational physical activities that are normally carried out in schools as obligatory curriculum, in combination or not with qualitative nutritional counseling, could promote the improvement of cardiovascular risk factors in children and adolescents with dyslipidemias and abdominal obesity. The primary endpoints were serum lipid profile and anthropometric parameters, while secondary endpoints were glycemic profile and subclinical inflammation markers.

Materials and Methods

Subjects

This is a parallel randomized with control group study. The Ethical Committee for Human Research of the Federal University of Santa Catarina approved the study (CAAE: 03626512.4.0000.0121). All participants and their legal guardians provided written informed consent before any procedure. Students (n=450; 8-14 y) of a public school in Guabiruba-SC, Southern Brazil, who were able to practice physical activities, were invited to participate. The studied school was chosen for having numerous students, an easy access location, and a number of children and adolescents with risk factors for CVD identified in our previous study.[12] Therefore, sampling for convenience or accessibility was used. Initially, blood samples were collected from 173 volunteers for biochemical analyses and waist circumference (WC) was measured. Based on the results, 114 students had abdominal obesity (WC cut off stratified by sex and age)[13] and dyslipidemias.[14] Volunteers were stratified according to sex and age, and were counterbalanced randomized (Website Research Randomizer®, 2008) into three groups (n=38 each): *i*) Control, whose members were not subjected to any intervention; *ii*) PANC (Physical Activity and Nutritional Counseling), whose students participate in a physical activity program and qualitative nutritional counseling; and *iii*) PA (Physical Activity), whose students participated in physical activities only.

The interventions were performed during 4 months and data were obtained in the beginning and at the end of study.

Lifestyle intervention

Physical activities were held at school in extracurricular period and consisted of soccer and basketball games or dance, which were developed during 1 h, twice a week, with the goal of approaching the WHO recommendation *i.e.*, 60 min of daily moderate to vigorous-intensity physical activities, three times per week.[9,10]

Qualitative nutritional counseling was performed by a nutritionist, without adopting specific or individualized diet and encouraging healthy eating based on increased consumption of fruits and vegetables and decreased consumption of sweets and fried food. The counseling was held collectively for student participants only, with meetings every three weeks, totaling four meetings, using videos, competitions, and practical activities in order to know and to give instruction about the amount of sugar, salt, and fat in foods regularly consumed by the students. In addition, the participants received instructions for preparing healthy snacks. Food consumption habits were assessed using a questionnaire for 24 h dietary recall (24HR), on two different days (one of which was a weekend day). The 24HR aims to report the intake of all foods and beverages consumed over a period of 24 h.[15] The 24HR was administered at the beginning and at the end of interventions and assessed using Avanutri® software, version 4.0 (Rio de Janeiro-RJ, Brazil).

Biochemical analysis

Blood sample was collected (12-h fasting) in tubes without anticoagulant and serum was obtained by centrifugation (750 x g, 10 min). Determinations of total cholesterol (TC), triglycerides (TG), glucose, uric acid, and high-density lipoprotein-cholesterol (HDL-c) were performed using routine methods (Labtest Diagnostic, Lagoa Santa-MG, Brazil) in automated Cobas Mira Plus® (Roche Diagnostics, Basel, Switzerland). The low-density lipoprotein-cholesterol (LDL-c) was estimated by the Martin equation [TC - (HDL-C - TG/×)], with "×" being the factor resulting from non-HDL-c and TG concentrations.[16] The non-HDL-c was estimated by the difference between TC and HDL-c. The Castelli I index [TC/HDL-c] and Castelli II index [LDL-c/HDL-c] were also evaluated.[17] The small, dense-LDL (sd-LDL) subclass was determined by procedure previously described for sd-LDL-cholesterol[18] and the LDL particle size was estimated using the equation [26.262 - 0.776 (TG $mmol.L^{-1}$/HDL-c $mmol.L^{-1}$)].[19] Quantification of insulin was carried out using chemiluminescence (Immulite 2000, Siemens Healthcare Diagnostics Inc. – USA) and the IR was identified by the homeostasis model assessment (HOMA-IR) index according to the equation [HOMA-IR = fasting insulin (μUI/mL) x fasting glucose (mg/dL)/405].[20] The levels of high-sensibility C-reactive protein (hs-CRP) and tumor necrosis factor-alpha (TNF-α) were measured by immunonephelometry (Nephelometer Behring BN, II Siemens Healthcare Diagnostics Products GMBH-Germany) and enzyme linked immune assay (BD OptEIA Human TNF ELISA Set, BD Biosciences-USA), respectively.

Anthropometric analyses

Weight (kg) and height (m) were measured (Welmy Equipment, São Paulo, Brazil), and the body mass index (BMI) was estimated by [weight/height^2]. Inelastic tape with a scale of 0.1 cm was used to the measurement of hip circumference and WC, that was performed at the midpoint between the last rib and the iliac crest.[13] Skinfolds were measured with adipometer (Scientific Cescorf, Porto Alegre-RS, Brazil) with a scale of 0.1 cm, amplitude of 88 mm and pressure of 10 g/mm^2. The measurement of triceps skinfold (TS) was performed on the posterior aspect of the arm, at the half distance between the superolateral border of the acromion and the olecranon. Subscapular skinfold (SS) was measured obliquely to longitudinal axis, following the costal arches, two inches below the scapula inferior angle. The percentage of body fat was estimated using TS and SS as described by Slaughter.[21]

Statistical analysis

We used sampling of convenience or accessibility. Results are presented as mean ± standard deviation or median and 25-75% interquartile interval (IQI). Data distribution was assessed by the Shapiro-Wilk test. Data that were not normally distributed were log-transformed whenever possible. Differences were detected by the Two-Way RM-ANOVA and Holm-Sidak's *post-hoc* test for normal (or normalized after log-transformed) data, and by the Friedman ANOVA on Ranks and Dunn's test for data with non-Gaussian distribution. The differences between variations in the three groups, based on the percentage changes (Δ%) to baseline values [((4-month x 100)/baseline) – 100], were analyzed using the One-Way ANOVA and Holm-Sidak's test for normal data and Kruskal-Wallis One-Way ANOVA on Ranks and Dunn's test for non-Gaussian data. When groups were stratified by sex, the differences in the percentage changes (Δ%) were detected by the Two-Way ANOVA and Holm-Sidak's test, and Kruskal-Wallis ANOVA on Ranks and Dunn's test for normal and non-Gaussian data, respectively. The chi-square test was used to compare baseline biodemographic features between the three groups. $P \leq 0.05$ was considered significant. All analyses were performed using SigmaPlot software v. 12.0 (Systat Software Inc., San Jose-California, USA).

To obtain a standardized measure of the magnitude difference between treatments for each variable, effect sizes were estimated. For normal distribution data, the effect size was calculated using Cohen's d statistic, with Hedges' g-average correction, and 95% confidence interval (CI), and interpreted as trivial (<0.20), small (0.20 to 0.49), medium (0.50 to 0.79), and large (> 0.80).[22] For non-Gaussian data, Cliff's delta (δ) effect size was calculated, which is classified as negligible (<0.147), small (0.148-0.32), medium (0.33-0.474), and strong (> 0.474).[23]

Results

During the study period, 40 students did not attend the final data collection for personal reasons and were thus excluded from the study. Therefore, 74 students effectively participated in the study (28 control, 23 PANC, and 23 PA groups). However, for appropriating paired statistical analysis, five students in the control group were additionally randomly (Website Research Randomizer®, 2008) excluded, retaining 23 participants per group (Supplemental File 1).

The main clinical and biodemographic features of students in the baseline period are shown in Supplemental File 2. The baseline values of lipid and glycemic profiles and anthropometric parameters are shown in Tables 1 and 2. Inflammatory marker levels are presented in Supplemental File 3. In spite of randomization, students of the control group had significantly lower levels of serum lipids (TC, LDL-c, non-HDL-c, and TG) and glucose (Tables 1 and 2).

Serum lipid profile

The physical activity intervention, with or without nutritional counseling, promoted similar and significant effects on serum lipid parameters (Tables 1 and 3). Students in the PANC and PA groups showed significant reductions in the absolute values of TC, LDL-c, and non-HDL-c, with a medium effect size for PA, in comparison to the respective baseline values (Table 1). Interventions did not change HDL-c and TG levels. Normalizing data to the respective baseline values, i.e., relative changes (Δ%), we also observed significant decreases in TC, LDL-c, and non-HDL-c of PANC and PA students in comparison to the control group, with medium and strong effect sizes (Table 3). Additional lipid parameters such as Castelli I and II indexes, and the small dense-LDL fraction (sd-LDL-cholesterol and LDL size) did not modify after interventions (results not shown).

Stratification by sex showed that male students in the PANC group experienced the most relevant, although not significant, relative reductions in TC, LDL-c, and non-HDL-c, with strong effect size, in comparison to male control (Table 4). Students in the PA group, regardless of sex, also showed percentage reductions in total- and lipoproteins-cholesterol in comparison to male and female controls, with strong effect size. On the contrary, male students in the control group had increased triglyceride levels after 4 months, with a strong effect size, in comparison to control females and to the male students in the PANC and PA groups (Table 4).

Anthropometric characteristics

After four months of intervention, all students maintained their BMI and WC values (Table 1). However, students in the PANC group showed a significant decrease in body fat, compared to the respective baseline values (Table 1) and to control students, with a strong effect size (Table 3).

Stratification by sex showed that female students in the PANC group had a significant decrease in body fat (in the percentage of baseline) compared to PANC male, with a large effect size (Table 4). Although not significant, a large effect size was also observed for a reduction in body fat of female PANC students in comparison to female students in the control group. Female students in the PA group also showed a significant body fat reduction in comparison to male students in this group, with a medium effect size (Table 4).

Glycemic profile

Regarding glycemic parameters, students in the control group showed a significant increase in the fasting glucose concentration, with a medium effect size in comparison to baseline values (Table 2). On the other hand, PANC and PA students showed no alterations in glucose levels. However, PA students experienced a significant and a medium effect size increase in the insulin and HOMA-IR values in comparison to baseline (Table 2), and the variation of insulin (Δ%) compared to the control group (Table 3). Taking into account the variation in relation to the respective baseline values (Δ%), the percentage reduction of glucose after the intervention was significant and with a strong effect size for PANC students, in comparison to control participants (Table 2).

Although not significant, the stratification by sex showed that male students in the PANC group showed a reduction in the fasting glucose levels, as a percentage of baseline (Δ%), that was more expressive than both female PANC and male control students, with strong effect sizes (Supplemental File 4). Male PA students also reduced glucose (in the percentage of baseline) compared to male control, with a strong effect size. On the other hand, male students in the PA group had increased levels of insulin compared to both female PA and male control, with medium and strong effect sizes, respectively (Supplemental File 4). Female PA students also showed increased percentage levels of insulin, with a medium effect size, in comparison to female control. Consequently, male PA students also experienced elevated HOMA-IR values, in the percentage of baseline, in comparison to male control students, with a medium effect size (Supplemental File 4).

Table 1 – Effect of physical activity and nutritional counseling on the serum lipid and anthropometric parameters of children and adolescents

Parameters	Control	Physical Activity and Nutritional Counseling		Physical Activity	
TC (mg/dL)			P^2		P^2
Baseline	158.5 ± 26.9[a]	206.3 ± 57.3[b]	0.009	197.4 ± 34.3[b]	**0.037**
4 months	164.4 ± 31.0[a]	184.3 ± 48.8[a]	0.229	176.1 ± 34.0[a]	0.517
P^1	0.961	0.007		0.009	
Effect Size	0.103	-0.399		-0.602	
LDL-c (mg/dL)*					
Baseline	99.5 ± 21.4[a]	137.1 ± 51.6[b]	**<0.001**	132.0 ± 30.4[b]	**<0.001**
4 months	103.9 ± 27.7[a]	117.6 ± 41.4[a]	0.362	114.1 ± 29.6[a]	0.358
P^1	0.455	0.004		0.002	
Effect Size	0.095	-0.391		-0.576	
HDL-c (mg/dL)					
Baseline	47.0 ± 12.6[a]	52.0 ± 17.5[a]	0.158	51.6 ± 10.4[a]	0.195
4 months	47.8 ± 10.2[a]	50.5 ± 15.9[a]	0.190	49.4 ± 10.6[a]	0.226
P^1	0.554	0.277		0.465	
Effect Size	0.067	-0.086		-0.202	
N-HDL-c (mg/dL)*					
Baseline	111.5 ± 22.8[a]	154.3 ± 56.0[b]	**0.001**	145.8 ± 32.1[b]	**0.001**
4 months	116.1 ± 29.2[a]	133.9 ± 45.8[a]	0.231	126.7 ± 31.4[a]	0.417
P^1	0.422	0.007		0.003	
Effect Size	0.161	-0.402		-0.597	
TG (mg/dL)*					
Baseline	60.1 ± 22.9[a]	85.8 ± 42.3[b]	**0.006**	68.7 ± 21.7[a,b]	0.418
4 months	63.4 ± 18.6[a]	81.5 ± 35.4[a]	0.165	63.2 ± 20.8[a]	0.435
P^1	0.502	0.429		0.398	
Effect Size	0.205	-0.060		-0.231	
BMI (kg/m²)					
Baseline		20.1 ± 3.6	0.874	18.9 ± 2.7	0.845
4 months		19.7 ± 3.7	0.901	19.1 ± 3.0	0.936
P^1		0.858		NS	
Effect Size		0.105		0.068	
Body fat (g%)*					
Baseline		19.3 ± 8.3	0.689	16.9 ± 5.0	0.594
4 months		17.8 ± 6.5	0.714	16.1 ± 4.4	0.908
P^1		0.005		0.964	
Effect Size		0.142		0.159	
WC (cm)*					
Baseline		70.6 ± 11.4	0.712	66.0 ± 7.2	0.893
4 months		70.7 ± 11.2	NS	66.1 ± 7.1	0.902
P^1		0.985		0.934	
Effect Size		0.008		0.013	

*Results are expressed as mean ± standard deviation (n=23 each group). TC: total cholesterol; HDL-c: high-density lipoprotein-cholesterol; LDL-c: low-density lipoprotein-cholesterol; BMI: body mass index; WC: waist circumference. *Log-transformed data. P^1 = Comparison to the respective baseline values and P^2 = Comparison between groups; different upper script letters in the same row mean significant differences (Two-way RM-ANOVA and Holm-Sidak post-hoc test). Effect size, comparisons between 4-month and baseline values of the same group. Hedges' g effect size for Gaussian paired-samples = trivial (<0.20), small (0.20 to 0.49), medium (0.50 to 0.79), and large (>0.80). Effect size between groups for baseline values were small or large, while effect size for 4-month values were trivial or small (not shown).*

Table 2 – The effect of physical activity and nutritional counseling on the glycemic profile of children and adolescents

Parameters	Control	Physical Activity and Nutritional Counseling		Physical Activity	
Glucose (mg/dL)			P[2]		P[2]
Baseline	81.9 ± 14.5 [a]	94.5 ± 11.9 [b]	**0.005**	90.9 ± 14.0 [a,b]	0.057
4 months	91.5 ± 15.1 [a]	91.8 ± 9.0 [a]	0.948	90.4 ± 11.4 [a]	0.951
P[1]	**0.002**	0.297		0.874	
Effect Size[1]	**0.626 (0.19 – 1.10)**	-0.244 (-0.20 – 0.71)		0.037 (-0.42 – 0.50)	
Insulin (μU/L)*					
Baseline	6.5 ± 5.1 [a]	7.3 ± 5.3 [a]	0.567	4.2 ± 2.6 [a]	0.199
4 months	6.6 ± 4.1 [a]	8.5 ± 4.6 [a]	0.449	7.4 ± 3.8 [a]	0.564
P[1]	0.836	0.144		**0.001**	
Effect Size[1]	0.021 (-0.32 – 0.28)	0.020 (-0.34 – 0.31)		**0.698 (0.62 – 1.34)**	
HOMA-IR*		7.3	8.5		
Baseline	1.4 ± 1.3 [a]	1.7 ± 1.3 [a]	0.343	1.0 ± 0.7 [a]	0.450
4 months	1.6 ± 1.4 [a]	1.9 ± 1.1 [a]	0.717	1.6 ± 0.9 [a]	0.133
P[1]	0.256	0.257		**0.002**	
Effect Size[1]	0.142 (-0.11 – 0.40)	0.158 (-0.19 – 0.52)		**0.679 (0.38 – 1.09)**	

*Results are expressed as mean ± standard deviation (n=23 each group). HOMA-IR, insulin resistance index; *Log-transformed data. P[1] = Comparison to the respective baseline values and P[2] = Comparisons between groups; different upper script letters in the same row mean significant differences (Two-Way RM-ANOVA and Holm-Sidak post-hoc test). Effect size[1], comparisons between 4-month and baseline values of the same group. Hedges' g for Gaussian paired-samples = trivial (<0.20), small (0.20 to 0.49), medium (0.50 to 0.79), and large (>0.80). Effect size between groups was trivial or small (not shown).*

Table 3 – Changes (Δ) in the serum lipid and glycemic parameters and body fat of children and adolescents after 4-month interventions

	Control (n=23)	PANC (n=23)		PA (n=23)		
Parameters	**Δ %**	**Δ %**	**Effect Size[1]**	**Δ %**	**Effect Size[1]**	**p**
Total Cholesterol	2.3 (-2.9 – 8.3) a	-11.2 (-20.6 – 0.0) b	**-0.537**	-13.2 (-22.6 – -1.4) b	**-0.586**	**< 0.001**
LDL-c	4.5 (-10.0 – 12.5) a	-19.5 (-29.8 – -4.8) b	**-0.490**	-16.8 (-26.5 – -9.2) b	**-0.573**	**0.002**
Non-HDL-c	5.3 (-10.2 – 12.0) a	-18.7 (-27.8 – 0.7) b	**-0.463**	-15.2 (-27.4 – -1.3) b	**-0.550**	**0.003**
HDL-c	-7,4 (-14,3 – 21,0) a	-2,9 (-13,3 – 2,4) a	0.004	-7,8 (-11,4 – 7,4) a	-0.066	0.905
Triglycerides	11.9 (-30.8 – 59.5) a	-4.5 (-15.4 – 50.9) a	-0.130	-0.0 (-37.0 – 15.4) a	-0.229	0.389
Glucose	5.4 (-1.3 – 15.6) [a]	-4.7 (-9.8 – 9.6) [b]	**-0.482**	-1.0 (-13.6 – 10.7) [a,b]	-0.291	**0.022**
Insulin	6.8 (-24.2 – 49.1) [a]	48.2 (-24.8 – 92.1) [a]	0.229	67.8 (12.6 – 156.2) [b]	**0.471**	**0.017**
HOMA-IR	11.9 (-30.8 – 59.5) [a]	-4.5 (-15.4 – 50.9) [a]	-0.108	0.0 (-37.0 – 15.4) [a]	**-0.353**	0.389
Body Fat	1.3 ± 12.6 [a]	-5.2 ± 10.3 [a]	**-0.541**	-3.0 ± 12.5 [a]	-0.328	0.178

Results are expressed as median (25-75% IQI) and mean ± standard deviation. Δ = 4 months minus the respective baseline values, in percentage. PANC: Physical activity and nutritional counseling; PA: Physical activity. LDL-c: low density lipoprotein-cholesterol, HDL-c: high-density lipoprotein-cholesterol; HOMA-IR: insulin resistance index. Different upper script letters mean significant differences (One-Way ANOVA and Holm-Sidak's test or Kruskal-Wallis One-Way ANOVA on Ranks and Dunn's test). Effect size: Hedges' g for normal data = trivial (<0.20), small (0.20 to 0.49), medium (0.50 to 0.79), and large (>0.80); Cliff's δ for non-Gaussian data = trivial (<0.147), small (0.148 – 0.32), medium (0.33 – 0.474), and strong (>0.474). Effect size[1], compared to the control group. The effect size between PANC and PA groups was trivial or small (not shown).

Table 4 – Changes (Δ) in serum lipid and anthropometric parameters of male and female students after 4-month interventions

	Control	Physical Activity/Nutritional Counseling		Physical Activity		
Parameters	**Δ %**	**Δ %**	**Effect Size¹**	**Δ %**	**Effect Size¹**	**P²**
Total Cholesterol						
Male	2.3 (-0.6 – 5.0)	-15.4 (-20.3 – 8.6)	**0.812 (0.26 – 0.96)**	-8.5 (-21.5 – -1.7)	**0.681 (0.08 – 0.92)**	NS
Female	0.6 (-6.6 – 19.3)	-4.4 (-24.3 – 8.6)	0.290 (-0.20 – 0.29)	-14.2 (-22.8 – -0.2)	**0.562 (0.11 – 0.82)**	NS
P¹	NS	NS		NS		
Effect Size²	-0.052 (-0.49 – 0.40)	0.265 (-0.28 – 0.67)		-0.061 (-0.52 – 0.43)		
LDL-c						
Male	-1.9 (-5.1 – 11.8)	-20.7 (-30.3 – -11.5)	**0.810 (0.26 – 0.96)**	-16.8 (-25.6 – -2.2)	**0.587 (-0.03 – 0.88)**	NS
Female	6.3 (-11.3 – 22.1)	-5.1 (-29.8 – 20.2)	0.261 (-0.23 – 0.65)	-16,1 (-27.3 – -8.3)	**0.563 (0.12 – 0.82)**	NS
P¹	NS	NS		NS		
Effect Size²	0.143 (-0.34 – 0.57)	0.333 (-0.20 – 0.71)		0.063 (-0.52 – 0.42)		
Non-HDL-c						
Male	5.3 (-0.92 – 17.8)	-19.9 (-30.0 – -6.1)	**0.786 (0.24 – 0.95)**	-14.9 (-26.4 – 1.4)	**0.683 (0.10 – 0.92)**	NS
Female	5.0 (-11.8 – 11.9)	-7.7 (-27.8 – 15.9)	0.239 (-0.25 – 0.63)	-16.9 (-28.1 – -5.4)	**0.491 (0.04 – 0.77)**	NS
P¹	NS	NS		NS		
Effect Size²	-0.054 (-0.50 – 0.41)	0.242 (-0.26 – 0.64)		-0.048 (-0.51 – 0.43)		
HDL-c						
Male	-11.6 (-15.8 – 21.0)	-2.1 (-12.2 – 2.9)	-0.100 (-0.62 – 0.48)	-4.2 (-18.9 – 8.9)	0.050 (-0.52 – 0.59)	NS
Female	-3.6 (-13.8 – 18.8)	-3.0 (-13.3 – 0.1)	0.062 (-0.37 – 0.48)	-8.0 (-10.5 – 7.5)	0.081 (-0.33 – 0.47)	NS
P¹	NS	NS		NS		
Effect Size²	0.210 (-0.32 – 0.63)	-0.08 (-0.52 – 0.39)		0.110 (-0.40 – 0.57)		
Triglycerides						
Male	59.4 (15.1 – 111.1)	-5.4 (-19.9 – 41.7)	**0.670 (0.12 – 0.90)**	0.1 (-23.3 – 6.3)	**0.650 (-0.01 – 0.92)**	NS
Female	1.6 (-31.7 – 26.9)	-4.5 (-14.0 – 52.4)	-0.100 (-0.51 – 0.35)	-8.1 (-39.8 – 22.7)	0.031 (-0.38 – 0.43)	NS
P¹	NS	NS		NS		
Effect Size²	-0.610 (-0.86 – -0.11)	0.110 (-0.37 – 0.54)		-0.060 (-0.51 – 0.41)		

Results are expressed as median and (25%-75% IQI) and mean ± standard deviation. Δ = 4 months minus the respective baseline values, in percentage. Number of Male/Female = Control: 7/16; Physical activity and nutritional counseling: 12/11; Physical activity: 9/14. LDL-c: low-density lipoprotein-cholesterol, HDL-c: high-density lipoprotein-cholesterol; BMI: body mass index; WC: waist circumference. NS, not significant. P¹, comparison between sexes of the same group and P², comparisons between groups (Kruskal-Wallis ANOVA on Ranks and Dunn's test). Effect size (CI 95%): Hedges' g for normal distribution data = trivial (<0.20), small (0.20 to 0.49), medium (0.50 to 0.79), and large (>0.80). Cliff's δ = trivial (<0.147), small (0.148 – 0.32), medium (0.33 – 0.474), and strong (>0.474). Effect size¹, comparisons between intervention groups and control. Effect size comparisons between interventions groups were trivial or small. Effect size², comparisons between male and female students of the same group.

Inflammatory markers

The interventions did not promote significant changes in inflammatory markers, but an increase in the TNF-α level was observed in students in the control and PA groups in comparison to the respective baseline levels, with a medium effect size. In addition, a medium effect size was observed for hs-PCR decrease in students in the control group in relation to the baseline levels (Supplemental File 3).

Diet profile

Table 5 and Supplemental File 5 show the main nutritional parameters considered in this study at the baseline and 4-month periods. At baseline, students in the PANC group had a significantly increased intake of energy and total fat, in comparison to control participants with a large effect size. However, after a 4-month intervention, students in the PANC group significantly decreased the ingestion of total calories, total fat, and cholesterol, and increased the protein intake, with a large effect size. Although not significant, but with a large effect size, the PANC students also reduced the intake of SAT, PUFA, MUFA (Table 5). On the other hand, students in the control group significantly increased the intake of total fat, PUFA, and cholesterol, with a large effect size, while reduced the intake of protein, carbohydrates, and fiber (Table 5). Students in the PA group did not change their diet profile (Table 5 and Supplemental File 5). Similar results were found when data in the PANC group were normalized to the respective baseline values and the variation (in the percentage of baseline) was compared to control and PA groups (Supplemental File 5).

Discussion

Diet, physical activity, and sedentary behaviors should be considered simultaneously for preventing CVD. Herein, we showed that regular practice of recreational physical activities, associated or not with nutritional counseling for four months, promoted a significant decrease in TC (11.2%), LDL-c (19.5%), non-HDL-c (18.7%), and body fat (5.2%) in children and adolescents with dyslipidemia and abdominal obesity, with medium or large effect size. According to our results, male students were more prone to reduce serum cholesterol, while female students showed the most prominent decrease in body fat.

In general, lifestyle changes improved serum lipid profile at different extents, corroborating our findings.[24-28] Lifestyle changes had a significant impact on the total and LDL-c and triglycerides in the short-term (4-6 months) and long-term (1-2 years), without differences for HDL-c.[25] Interestingly, our results were contrary to those reported by Rosini et al. (2014),[29] where the authors found a significant reduction in triglycerides and an increase in HDL-c, but no change in total- and LDL-c. The type of physical activity applied, and the extent of dyslipidemias may play a role to explain the different results.

The sd-LDL subclass has been considered to be more atherogenic than the large, buoyant LDL particles.[29-32] Herein, our short-term interventions did not decrease the sd-LDL-c levels or increase the LDL particle size. However, previous studies showed improvement in the sd-LDL subclass after intervention with physical activities and nutritional counseling in obese adolescents.[24,28]

In general, physical activities when associated with dietary interventions promoted greater reductions in TC, LDL-c, and triglycerides, without effect for HDL-c.[33] However, in our study, nutritional counseling was not effective for superior benefits on serum lipid profile, despite the significantly decreased intake of total calories, total fat, SFA, PUFA, MUFA, and cholesterol, associated to increase the ingestion of fiber, which could improve the serum lipid profile.[34] Altogether, the controversial and inconclusive results are probably due to differences in study designs, sample size, exercise intensity, and type of nutritional counseling.[35] The underlying heterogeneity in the response to interventions in lifestyle and the fact that young people do not respond the same way, need to be further elucidated and will help to refine the interventions on target populations.[28-]

Low levels of physical activity are considered a fundamental factor for elevated glucose and insulin levels and, increased risk of diabetes mellitus.[35] In fact, in our study, students in the control group tended to increase glucose by 5.4%, in the median, with strong effect size, while those who were on physical activities and nutritional counseling reduced glucose by 4.7%, in the median, particularly male students in the PANC and PA groups. Poeta et al.[27] reported that glucose levels did not change in students on physical activities, while students in the control group showed a significant increase. Moreover, a significant decrease in fasting glucose was observed in obese children on physical activities.[36] Interestingly, for unknown reasons, insulin levels and IR increased in students who underwent physical activity, especially male students. Park et al.[37] did not observe changes in glucose and insulin in

Table 5 – Effect of physical activity and nutritional counseling on the diet parameters of children and adolescents

Parameters	Control	PANC		PA	
Energy (kCal)			P²		P²
Baseline	1747.6 ± 399.2[a]	1937.9 ± 237.0[b]	**<0.001**	1806.1 ± 192.4[a,b]	0.189
4 months	1663.7 ± 374.9[a]	1321.1 ± 590.7[a]	0.089	1819.2 ± 240.5[a]	0.219
P¹	0.586	**<0.001**		0.884	
Effect Size	-0.198	**-1.229**		0.052	
Protein (%)					
Baseline	16.3 ± 4.2 [a,b]	12.8 ± 2.0 [a]	0.075	15.7 ± 5.9 [a]	0.056
4 months	13.5 ± 4.0 [a]	15.6 ± 3.4 [a]	0.358	17.9 ± 2.6 [a]	0.252
P¹	**0.020**	**0.023**		0.513	
Effect Size	**-0.624**	**0.864**		0.392	
Carbohydrates (%)					
Baseline	49.7 ± 8.9 [a]	47.8 ± 5.4 [a]	0.578	51.6 ± 8.4 [a]	0.812
4 months	44.6 ± 4.3 [a]	48.6 ± 5.7 [a]	0.239	52.6 ± 6.7 [a]	0.068
P¹	**0.004**	0.647		0.550	
Effect Size	**-0.589**	0.131		0.142	
Total Fat (%)					
Baseline	63.9 ± 22.4 [a]	84.9 ± 12.7 [b]	**0.002**	71.3 ± 18.2 [a]	0.792
4 months	76.0 ± 14.1 [a]	63.3 ± 13.2 [b]	**0.044**	67.6 ± 9.6 [a,b]	0.874
P¹	**0.010**	**<0.001**		0.506	
Effect Size	**0.558**	**-1.524**		-0.210	
SFA (%)					
Baseline	14.8 ± 6.0 [a]	19.0 ± 3.8 [a]	0.069	16.7 ± 4.7 [a]	0.519
4 months	16.7 ± 4.6 [a]	15.3 ± 4.8 [a]	0.469	16.0 ± 2.1 [b]	0.802
P¹	0.311	0.057		0.957	
Effect Size	0.324	**-0.756**		-0.166	
PUFA (%)					
Baseline	15.5 ± 7.3 [a]	17.8 ± 2.6 [a]	0.204	16.3 ± 2.5 [a]	0.487
4 months	21.9 ± 4.7 [a]	15.0 ± 2.9 [b]	**0.001**	16.9 ± 3.5 [a,b]	0.354
P¹	**0.001**	0.113		0.771	
Effect Size	**0.939**	**-0.930**		0.177	
MUFA (%)					
Baseline	14.7 ± 6.4 [a]	15.9 ± 3.7 [a]	0.496	13.9 ± 4.5 [a]	0.221
4 months	16.8 ± 3.7 [a]	13.2 ± 3.4 [a]	0.107	14.8 ± 4.2 [a]	0.301
P¹	0.196	0.080		0.451	
Effect Size	0.352	**-0.693**		0.189	
Cholesterol (mg)					
Baseline	145.6 ± 76.8[a]	155.1 ± 46.4[a]	0.730	135.3 ± 59.7[a]	0.093

4 months	189.9 ± 60.8[a]	126.2 ± 42.7[a]	0.086	152.3 ± 77.1[a]	0.334
P[1]	**0.005**	**0.051**		0.162	
Effect Size	**0.578**	**-0.587**		0.223	
Fiber (g)					
Baseline	21.8 ± 23.6 [a]	13.6 ± 8.8 [a]	0.274	23.1 ± 9.3 [a]	0.806
4 months	9.7 ± 9.0 [a]	15.8 ± 10.2 [a]	0.476	20.6 ± 7.0 [b]	0.159
P[1]	**0.003**	0.551		0.505	
Effect Size	-0.385	0.210		-0.273	

Results are expressed as mean ± standard deviation (n=23 each group). PANC, physical activity and nutritional counseling; PA, physical activity; SFA, saturated fatty acids; PUFA, polyunsaturated fatty acids; MUFA, monounsaturated fatty acids. P^1 = Comparison to the respective baseline values and P^2 = Comparison between groups; different upper script letters in the same row mean significant differences (Two-way RM-ANOVA and Holm-Sidak post-hoc test). Effect size, comparisons between 4-month and baseline values of the same group. Hedges' g effect size for Gaussian paired-samples = trivial (<0.20), small (0.20 to 0.49), medium (0.50 to 0.79), and large (>0.80). Effect sizes between groups were trivial or small (not shown), except for PANC vs. Control: Total Fat baseline (g = 1.046); Total Fat 4-month (g = -0.850); PUFA 4-month: (g = -1.631); and Cholesterol 4-month (g = -1.117).

adolescents doing exercises for 12 weeks. Physical activity was unassociated with glucose and IR, independent of nutritional status, sexual maturation, food intake, and sex.[35] One possible explanation for our results is the small number of students with blood glucose higher than reference values. Moreover, according to a meta-analysis, significant improvement in insulin levels was observed only after intervention exceeding 12 months, with no change in glucose levels.[25] However, a study with obese students found a reduction in glucose, insulin, and IR after 6 months of intervention with diet to reduce sugar and fat intake, instructions in physical exercise as part of everyday life, reducing screen time and doing behavioral therapy.[38] Improvement of IR was also found in obese students on aerobic and resistance exercises. Thus, improvement in glycemic profile seems to occur only in children and adolescents with high levels of these parameters, particularly in obese students.[39]

Although physical activity and diet adjustment separately promoted beneficial effects on inflammation markers, combined programs are the most promising approach.[40] However, herein we did not find changes in the hs-CRP, uric acid, and TNF-α levels after interventions. Similar findings were described by Poeta et al.[27] It is noteworthy that, in general, the students had normal levels of the inflammatory biomarkers. On the other hand, six months of combined intervention decreased hs-CRP in obese students, suggesting that the duration of activity and the type of nutritional counseling may be relevant.[38] It has been reported that decreasing intake of SFA, MUFA, and PUFA may also reduce hs-CRP concentration in children.[3] However, herein, regardless of a decrease in the intake of all fatty acids by students in the PANC group, a similar improvement of inflammatory markers was not observed. Thus, additional studies are needed to establish a better intervention to reduce subclinical inflammation in children and adolescents.

Abdominal obesity in childhood seems to be more related to CVD and diabetes mellitus in adulthood than general obesity.[41] In this study, physical activity and nutritional counseling did not promote significant changes in abdominal obesity measured by WC. Similarly, no reduction in abdominal obesity was seen in our previous study with participants of the same downtown.[29] Decrease of WC and WC/height ratio was observed and associated with improvement of insulin sensitivity in students after 40 weeks of a lifestyle intervention: individual nutritional counseling, with 60 min weekly training at school and 90 min weekly training with their families.[42] On the opposite, reports are suggesting that the absence of WC improvement after lifestyle interventions may be due to the intensity of physical activity and/or adherence to dietary modifications.[36,38,39] On the other hand, herein the physical activity associated with nutritional counseling was highly effective for body fat reduction by 5.2%, consistent with previous results.[36,38]

Despite the small number of individuals here studied, which might be considered a limitation of this study, we may suggest that the regular practice of recreational physical activities and qualitative nutritional counseling for children and adolescents with dyslipidemia and abdominal obesity promoted significant improvements in the serum lipid profile and body fat percentage.

Such benefits proved to be an effective and low-cost strategy for reducing risk factors in this population. Furthermore, the greatest strength of this study, which also differentiates it from other studies, was the presence of a control group, the absence of a specific or restrictive diet, and no vigorous physical activities nor parents' participation, proving that is an effective strategy to be applied in schools as a regular part of the curriculum.

Conclusion

Regular recreational physical activities at school associated with nutritional counseling reduced total cholesterol, non-HDL-cholesterol, and LDL-cholesterol, and body fat in children and adolescents with dyslipidemias and abdominal obesity. In addition, students also decreased the intake of total calories, total fat and saturated, monounsaturated, and polyunsaturated fatty acids, and cholesterol, and increased the ingestion of protein and fiber. It is suggested that early adoption of a healthy lifestyle should be considered as a basic component for prevention, reduction, and treatment of cardiometabolic factors for CVD in childhood and adolescence.

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Author contributions

Conception and design of the research: Pamplona-Cunha H, Rosini N, Caetano R, Silva EL. Acquisition of data: Pamplona-Cunha H, Rosini N, Caetano R, Silva EL. Analysis and interpretation of the data: Pamplona-Cunha H, Machado MJ, Silva EL. Statistical analysis: Pamplona-Cunha H, Machado MJ, Silva EL. Obtaining financing: Pamplona-Cunha H, Rosini N, Silva EL. Writing of the manuscript: Pamplona-Cunha H, Rosini N, Caetano R, Machado MJ, Silva EL. Critical revision of the manuscript for intellectual content: Pamplona-Cunha H, Silva EL.

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 Santa Catarina* under the protocol number CAAE: 03626512.4.0000.0121. 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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*Supplemental Materials

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ORIGINAL ARTICLE

Emergency Department Visits and Deaths from Cardiovascular Diseases at a Referral Center for Cardiology During the COVID-19 Pandemic

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Abstract

Background: The COVID-19 pandemic has imposed measures of social distancing and, during this time, there has been an elevation in cardiovascular mortality rates and a decrease in the number of emergency visits.

Objectives: To assess and compare in-hospital mortality for cardiovascular diseases and emergency department visits during the COVID-19 pandemic and the same period in 2019.

Methods: Retrospective, single-center study that evaluated emergency visits and in-hospital deaths between March 16, 2020 and June 16, 2020, when the steepest fall in the number of emergency admissions for COVID-19 was registered. These data were compared with the emergency visits and in-hospital deaths between March 16 and June 16, 2019. We analyzed the total number of deaths, and cardiovascular deaths. The level of significance was set at $p < 0.05$.

Results: There was a 35% decrease in the number of emergency visits and an increase in the ratio of the number of deaths to the number of emergency visits in 2020. The increase in the ratio of the number of all-cause deaths to the number of emergency visits was 45.6% and the increase in the ratio of the number of cardiovascular deaths to the number of emergency visits was 62.1%. None of the patients who died in the study period in 2020 tested positive for COVID-19.

Conclusion: In-hospital mortality for cardiovascular diseases increased proportionally to the number of emergency visits during the COVID-19-imposed social distancing compared with the same period in 2019.

Keywords: Cardiovascular Diseases; Emergency Service, Hospitalar; COVID-19; Betacoronavirus/complications; Hospitalization; Visitors to Patients; Hospitals, Packaged; Pandemics.

Introduction

In December 2019, in the city of Wuhan, capital of Hubei Province, in China, the first cases of a new disease that would reach global proportions and become devastating in many aspects were identified.[1-3] The world has watched the spread of this disease caused by the new coronavirus (COVID-19) from Asia to Europe and then to the Americas in less than three months. On March 11, 2020, the World Health Organization (WHO)[1] announced the COVID-19 outbreak a pandemic.

In addition to its rapid transmission, even by presymptomatic and asymptomatic infected individuals, the SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) has significantly higher mortality as compared with other coronaviruses associated with

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respiratory diseases and may progress to pneumonia and acute respiratory distress syndrome (ARDS), notably in elderly patients and in those with comorbidities.[4] Global mortality rate has varied from 1 to 5%, with more than 600,000 deaths registered on 20 July, 2020. The number of confirmed cases surpasses 14 million.[5]

The effects of COVID-19 go beyond the respiratory tract, affecting the cardiovascular and the nervous system also.[4,6-9] The psychological and economic impacts of social distancing policies have been a challenge to health system and financial managers worldwide.[10,11]

Patients have avoided medical care due to concerns about viral exposure in the hospitals. New York city and other cities severely hit by the COVID outbreak have reported an elevation in the number of deaths from acute myocardial infarction (AMI) and other cardiovascular diseases, and a drastic reduction in the number of emergency admissions for these conditions.[12,13]

Thus, our objective was to assess in-hospital mortality from cardiovascular diseases in relation to the number of emergency visits for these conditions during the SARS-CoV-2 pandemic, and to compare these data with those of the same period in 2019 in a cardiology referral center in Santa Catarina, in southern Brazil.

Methods

This was a retrospective, single-center study of the analysis of emergency records and in-hospital deaths at the participating institution, which is a referral center for treatment of highly complex cases in cardiology in the state, and sees patients through the unified health system (SUS) only. Approximately 10,900 visits are made to the emergency department annually, mostly for cardiovascular diseases, and 272 patients underwent primary angioplasty in 2019 at this hospital.

Emergency visits and in-hospital deaths registered between March 16, 2020 and June 16, 2020 (period when there was a drastic reduction in emergency visits because of the pandemic-induced social distancing) were included in the analysis. These data were compared with the emergency visits and in-hospital deaths registered between March 16, 2019 and June 16, 2019.

All-cause mortality and cardiovascular mortality during these periods were analyzed. Cardiovascular mortality was defined according to the International Classification of Diseases, tenth revision (ICD-10), as available, and by review of medical charts.

Cardiovascular causes of death were determined using the circulatory system diseases listed in the ICD-10 code range I00-I99. After analysis of the incidence of overall and cardiovascular deaths in proportion to the number of emergency visits, we analyzed the incidence of deaths by cardiovascular cause, notably AMI (ICD-10 I21), heart failure (HF) (ICD-10 I50), stroke (ICD-10 I60-I64) and subcategories. Exclusion criteria were lack of data on emergency admissions in the hospital statistical report, and restrict access to the electronic medical records for analysis of the medical history of patients who had died.

The number of all-cause and cardiovascular deaths and the number of emergency visits were analyzed weekly during the periods of study (total of 13 weeks/year), so that curves of the course of these variables, and curves of the relationship between deaths and emergency visits over time were constructed.

The following variables were compared between the two periods of study (2019 vs. 2020): number of all-cause deaths, number of cardiovascular deaths, demographic profile (age and sex) of participants who died, number of emergency visits, ratio of the number of all-cause deaths to the number of emergency visits, and ratio of the number of cardiovascular deaths to the number of emergency visits. We also analyzed the number of beds in intensive care unit (ICU) between 2019 and 2020 and the possible increase in the number of patients referred to the institution in this period.

The study was approved by the ethics committee of the institution (approval number 34042720.5.1001.0113). All study procedures were conducted according to the Helsinki declaration (2013 version). Written informed consent was waived due to the retrospective nature of the study.

Statistical Analysis

Data were stored in an Excel spreadsheet and then exported to IBM SPSS Statistics® 18.0. Categorical variables were presented as frequencies (absolute and relative) and continuous variables as mean and standard deviation. In the bivariate analysis, Pearson chi-square test was used for categorical variables, and the independent t-test was used for continuous variables, depending on data normality, which was tested by the Kolmogorov-Smirnov test. Values of $p<0.05$ were considered statistically significant.

Analysis of temporal trends of the number of emergency visits per week was conducted by simple linear regression, with construction of an estimated model using the formula Y = b0 + b1X, where Y = standard coefficient, b0 = mean coefficient for the period, b1 = mean annual increment and X = year; a $p<0.05$ was considered statistically significant. All assumptions for conducting the simple linear regression were previously checked.

Results

There was an increase in the number of beds in ICU from 2019 to 2020; new beds were placed in ICU on April 04, 2020, indicating an elevation in the number of beds for severely ill patients during nearly two-thirds of the study period (Figure 1). No expansion in the health service coverage or in coverage area was observed from 2019 to 2020.

Mean age of patients who died in 2019 and 2020 was 74.1 years (standard deviation, SD 11.2 years) and 70.0 years (SD 11.1years), respectively, with no statistical difference (p=0.067). Analysis of the number of deaths by age range (< 65 years, ≥ 65 and < 75 years, ≥ 75 and < 85 years and ≥ 85 years) in 2019 and 2020 showed no statistical difference in the incidence of deaths by age group between the two years.

Most deaths occurred in male patients – 51.9% of deaths in 2019 and 58.8% of deaths in 2020 (p = 0.473) – and due to cardiovascular causes (Figure 2). This is in agreement with the mortality profile of patients seen in the institution. No statistical difference was seen in the proportional incidence of cardiovascular deaths between 2019 and 2020 (p=0.326). The medical history of all patients who died in this two-year period could be accessed through the electronic medical records.

The total number of emergency visits decreased from 2019 to 2020, leading to an elevation in the ratio of the number of deaths to the number of emergency visits in 2020. The ratio of all-cause deaths to emergency visits and the ratio of cardiovascular deaths to emergency visits increased by 45.6% and 62.1%, respectively in 2020 (Table 1).

Figures 3-5 show the weekly course of the number of emergency visits, ratio of all-cause deaths to emergency visits, and the ratio of cardiovascular deaths to emergency visits in 2019 and 2020. The relation of in-hospital deaths to emergency visits was expressed as percentage.

Analysis of temporal trends revealed a stable pattern in emergency visits per week in 2019 (p=0.981) and a

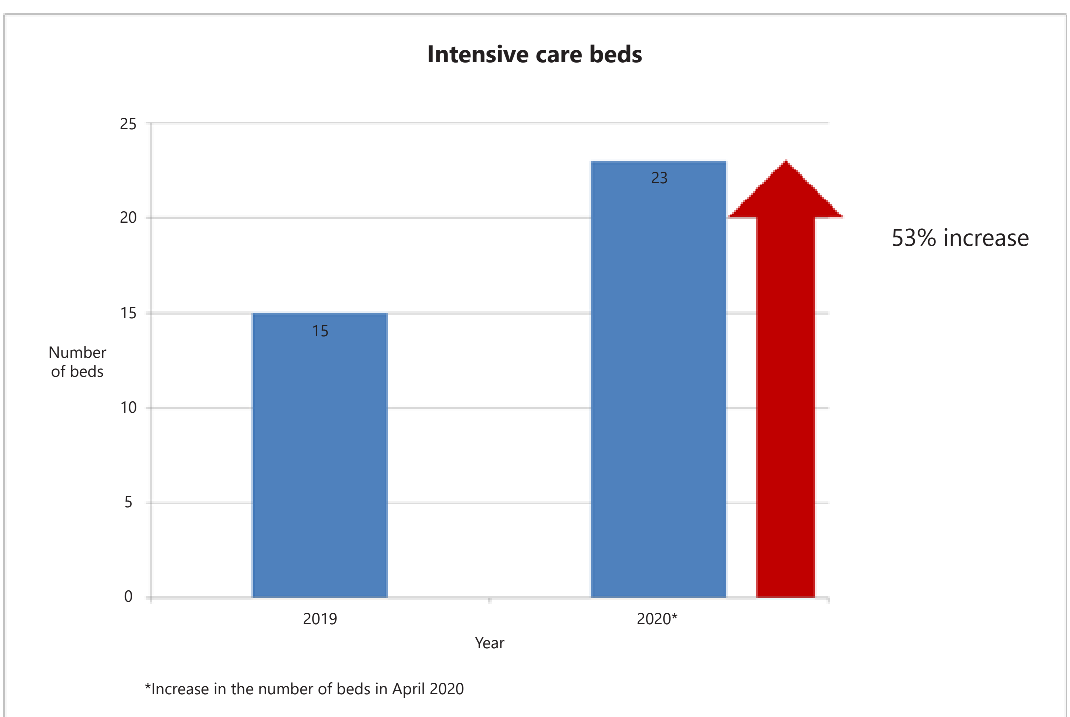

Figure 1 – Number of ICU beds in 2019 and 2020.

Table 1 - Total deaths, cardiovascular deaths, emergency visits, ratio of all-cause deaths to emergency visits, ratio of cardiovascular deaths to emergency visits and difference in percentages between 2020 and 2019

	Year					
	2019		2020		Difference 2020-2019	
	n	%	n	%	%	p
Total deaths	54	100.0%	51	100.0%	-5.6%	-
CV* deaths	39	72.2%	41	80.4%	5.1%	0.326
Emergency visits	2732	100.0%	1772	100.0%	-35.1%	-
All-cause deaths / EMG†	-	1.98%	-	2.88%	45.6%	-
CV* deaths/EMG†	-	1.43%	-	2.31%	62.1%	-

*CV: cardiovascular; †EMG: emergency visits

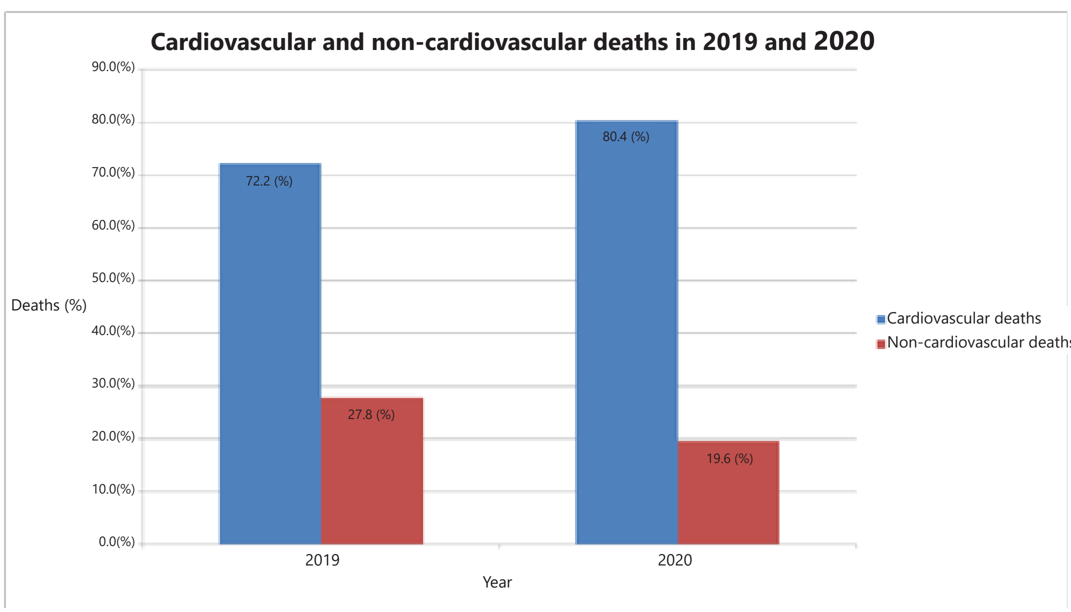

Figure 2 – Proportion of deaths from cardiovascular and non-cardiovascular causes in 2019 and 2020.

tendency of increase by 8.5 emergency visits per week in 2020 ($p<0.001$).

When only cardiovascular deaths were analyzed, we found an increase in the proportion of deaths related to AMI and a decrease in the proportion of deaths related to heart failure in 2020 compared with 2019, with no statistical difference. The number of deaths related to stroke was not significant in our institution in the study period (Table 2).

Other forms of heart diseases, including advanced atrioventricular and left bundle-branch block, aortic aneurysm rupture, aortic dissection, and infectious endocarditis accounted for 28% of cardiovascular deaths in 2019 and 22% in 2020.

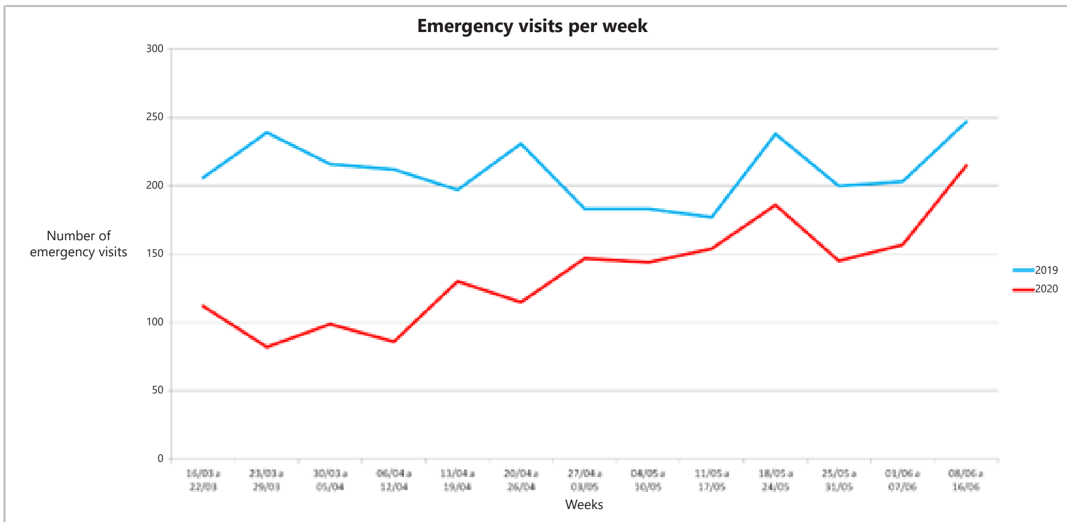

Figure 3 – Graph showing the evolution of the number of emergency visits per week in 2019 and 2020.

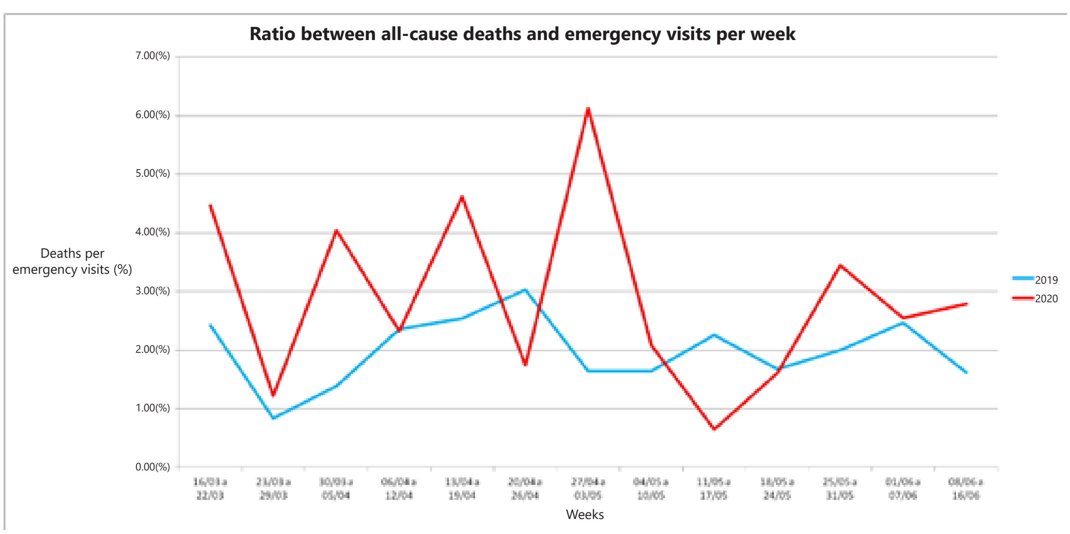

Figure 4 – Graph showing the evolution of the ratio of total deaths / emergency visits per week in 2019 and 2020.

Regarding non-cardiovascular deaths, septicemia was the main cause of deaths in 2019 and 2020. Less frequent causes included upper digestive hemorrhage, acute renal failure, severe bronchospasm, and stage IV cancer. None of the patients who died in 2020 in the study period had a positive COVID-19 test.

Discussion

On March 17, 2020, the government of Santa Catarina state declared a state of emergency and established social distancing norms because of the COVID-19 pandemic. In the beginning, a strict social distancing was imposed,

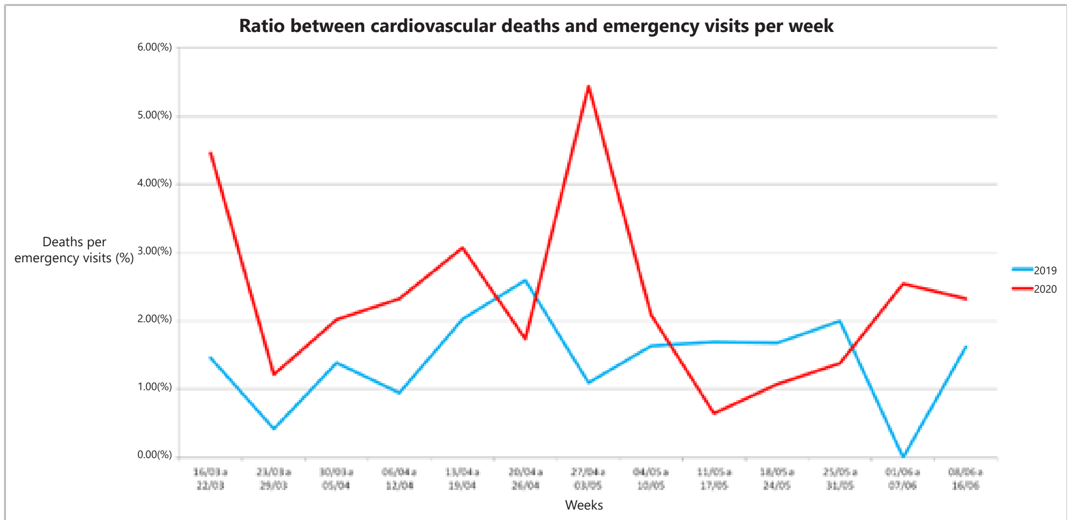

Figure 5 – Graph showing the evolution of the cardiovascular deaths / emergency visits ratio per week in 2019 and 2020.

Table 2 - Distribution of cardiovascular deaths by specific causes in 2019 and 2020

	Year				
	2019		2020		
Cause of cardiovascular death	**n = 39**	**%**	**n = 41**	**%**	**p**
AMI*	18	46.1%	24	58.5%	0.268
HF†	9	23.1%	8	19.5%	0.697
Stroke	1	2.6%	0	0.0%	-

**AMI: acute myocardial infarction; †HF: heart failure; values expressed as absolute number and proportion of total cardiovascular deaths*

with ban of public transportation, and closing of hotels, gyms, malls, and stores. Government officers warned and pled for people to stay home, which was effective to reduce COVID-19 transmission. The fear of exposure to the new coronavirus was felt by the entire population, especially by the elderly, and may have caused negligence of cardiovascular symptoms . Cardiovascular diseases are the main cause of death worldwide, accounting for 31% of global deaths.[14]

In the local context, the strategy to reduce coronavirus transmission to improve the infrastructure of health care for patients with ARDS was effective at first, with public policies aimed at assigning resources for providing ICU beds, so that 21.7% of the intensive care beds would be occupied by patients with suspected or confirmed COVID-19. In our institution, there was a 50% increase in the number of intensive care beds, and the quality of care of patients without suspected COVID-19 was preserved. Despite this increase in the number of beds, the area covered by the institution did not change in 2020, and hence the increase in the ratio of the number of deaths to the number of emergency visits was not caused by an elevation in the referral of severely ill patients. The absence of deaths from COVID-19 in the analyzed period in 2020 reinforces that there was no significant change in the sample profile. The fact that the study was conducted in a specialized, tertiary-care center allowed an analysis of specific effects of social distancing on the cardiovascular system.

During this pandemic, we found that despite the well-known financial difficulties of SUS and the heterogeneity among the states, the number of ICU beds in Brazil is the third highest in the world, lower only than the United States and Germany. Brazil had advantageous strategies to fight the pandemic and its consequences, especially the time to prepare the health system and knowledge about the disease. However, limitations in the number of diagnostic tests and identification of transmitters have affected our epidemiological viewpoint and we have stuck to social distancing and its consequences.[15]

In light of the need to reduce the likelihood of virus transmission, the demand for diagnosis and treatment of cardiovascular events has decreased.[16-18] This becomes clear in the comparison of the number of tests and procedures performed in the institution between 2019 and 2020. A total of 1,870 echocardiograms and 1,210 catheterizations were performed in the three-month period (March – June) of analysis in 2019, whereas in the same period of 2020, 870 echocardiograms and 979 catheterizations were performed.

In a context of drastic reduction in the number of emergency visits, the number of deaths per number of emergency visits serves as a parameter for analysis of the incidence of in-hospital deaths. This is of particular importance in an institution where most patients are admitted through the emergency department, including by self-referral, even being a tertiary hospital.

The increase by 62.1% in the ratio of the number of cardiovascular deaths to the number of emergency visits in 2020 is mainly related to the delay in seeking emergency care due to social distancing policies and reductions in the number of emergency department admissions for less severe illnesses. In addition, interruption of outpatient follow-up has contributed to the increase in cardiovascular mortality.[15] Similar phenomena have been observed in large urban centers like New York and northern Italy.[12,13] In an article published in The New York Times in April 2020, Dr. Harlan M. Krumholz calls attention to the sharp fall in the number of hospital admissions for AMI and stroke, and reports a 40-60% drop in admissions for AMI in the USA according to informal analyses.[19] The hypothesis is that many symptomatic people are opting to remain at home rather than seek medical care or dying before receiving medical attention. Patients with cardiovascular disorders who seek medical attention only after their condition has worsened are at increased risk of in-hospital death.

An analysis of the Brazilian Society of Cardiology revealed a 30% increase in the number of cardiovascular deaths occurring at home between March and May 2020 as compared with the same period in the previous year.[20] While Brazil registered almost 80 thousand deaths from COVID-19 (WHO),[21] the Brazilian Society of Cardiology estimated that the number of people who died from cardiovascular diseases by July 2020 was almost three times higher, 224 thousand.[22] Today the number of deaths from COVID-19 in Brazil exceeds 353 thousand according to the WHO.

The low incidence of stroke-related deaths in the study hospital may be related to the existence of public referral centers for cerebrovascular events in the region.

Considering the increasing number of coronavirus infected, proportional increase in cardiovascular deaths and uncertainties in the duration and consequences of the pandemic, we should be prepared to deal with potential deleterious effects of COVID-19 on the cardiovascular system of patients severely affected by the disease. Late myocardial dysfunction, for example, deserves attention and investigation.[23]

Limitations of the present study include the short period of analysis, which did not represent the whole period of the pandemic and social distancing, and its retrospective single-center design, reflecting the reality of a public, tertiary, specialized hospital. Also, we did not evaluate the reasons for emergency visits or the severity of the cases. Besides, it was not possible to analyze the time from symptom onset to hospital presentation, which could explain at least in part the increase in the ratio of cardiovascular deaths to emergency visits in 2020, due to the time-sensitive nature of cardiovascular events. Further studies are needed to elucidate the cardiovascular implications of social distancing in other contexts and regions of Brazil.

Conclusion

During the COVID-19-related social distancing, in-hospital mortality for cardiovascular diseases increased proportionally to the number of emergency visits when compared with the same period in 2019.

Author Contributions

Conception and design of the research: Luciano LSC, São Thiago LEK. Acquisition of data: Luciano LSC. Analysis and interpretation of the data: Luciano LSC, São Thiago LEK, Back IC. Statistical analysis: Luciano LSC, Back IC. Writing of the manuscript: Luciano LSC. Critical revision of the manuscript for intellectual content: Luciano LSC, São Thiago LEK, Back IC, Waldrich L, São Thiago LB, Alves AR, Comelli BC, Santos MJ, Giuliano LC.

Potential Conflict of Interest

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

Sources of Funding

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Instituto de Cardiologia de Santa Catarina* under the protocol number 34042720.5.1001.0113. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Written informed consent was waived due to the retrospective nature of the study.

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ORIGINAL ARTICLE

Predictors of Hospitalization in Vitamin K Antagonist Users Presenting with Bleeding at the Emergency Department

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Abstract

Background: Vitamin K antagonists (VKA) are indicated for the prevention of thromboembolic events and reduction of mortality in patients with atrial fibrillation and patients with valvular prostheses. However, their use is associated with bleeding complications and hospitalizations. Predictors of hospital admission for bleeding in these patients are poorly known.

Objectives: To define the predictors for hospitalization of VKA users who seek emergency care due to bleeding.

Methods: Single-center, cross-sectional study, with retrospective analysis of electronic medical records from 03/01/2012 to 02/27/2017. Clinical and laboratory variables were compared between patients who were hospitalized and those who were not. A logistic regression model as used, in which the variables were included using the Backward stepwise method, with a p value of 0.05 as the input criterion, a removal value of 0.20 and a confidence interval of 95%. The p-value was considered statistically significant when <0.05.

Results: A total of 510 patients with bleeding were included, of whom 158 were hospitalized. Predictors of hospitalization were: INR at supratherapeutic levels (OR 3.45; P <0.01; 95% CI 1.58 - 7.51), gastrointestinal bleeding (OR 2.36; P <0.01; CI 95% 1.24 - 4.50), drop in hemoglobin (OR 6.93; P <0.01; 95% CI 3.67 - 13.07), heart failure (OR 1.96; P 0.01; 95% CI 1.16 - 3.30) and need for blood transfusion (OR 8.03; P <0.01; 95% CI 2.98 - 21.64).

Conclusion: Drop in hemoglobin, heart failure, INR at supratherapeutic levels, gastrointestinal bleeding and need for blood transfusion were associated with hospitalization. Identification of these factors in the initial evaluation would help to define which patients will demand more intensive care.

Keywords: Hemorrhage; Emergencies; Warfarin; Platelet Aggregation.

Introduction

Vitamin K antagonists (VKA) are indicated for the prevention of thromboembolic events and reduction of mortality in patients with atrial fibrillation (AF) and patients with prosthetic heart valves.[1-4] However, hemorrhagic complications of VKA therapy are frequent, due to genetic polymorphisms of VKA enzymes in the liver, or pharmacological and dietary interactions.[5]

VKA is still the only option for patients with mechanical prostheses and valvular AF.[3,4,6,7] Warfarin is the only VKA currently available in the United States, and here in Brazil, phenprocoumon, a long-acting oral anticoagulant, has been also used. Bleeding in patients treated with VKA is a common cause of unscheduled emergency room visits and consequent hospitalization,[8] with a significant impact on social healthcare costs.[9]

The number of studies on VKAs has been decreasing in recent years. In particular, studies reporting the prevalence and management of hemorrhagic complications (such as stroke) in emergency services are scarce, with high methodological heterogeneity.[10-15] To date, there is little knowledge about the reasons of hospitalization among these patients. Thus, this study aims to evaluate the

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predictive factors of hospitalization in VKA users who seek emergency care due to bleeding.

Methods

This was a single-center, cross-sectional study carried out in a tertiary cardiology hospital, with retrospective analysis of electronic medical records. Emergency room recorded from 03/01/2012 to 02/27/2017 were reviewed if the following ICD-10 codes where entered: coumarin poisoning (T 45.5), bleeding esophageal varices (I 85.0), acute post-hemorrhagic anemia (D 62.0), acute hemorrhagic gastritis (K 29.0), hematemesis (K 92.0), conjunctival hemorrhage (H 11.3), upper gastrointestinal bleeding (K 92.2), upper gastrointestinal bleeding due to duodenal ulcer (K 26.0), upper gastrointestinal bleeding due to gastric ulcer (K 25.0), lower gastrointestinal bleeding (K 92.2), unspecified non-traumatic intracranial hemorrhage (I 62.9), unspecified respiratory tract bleeding (R 04.9), retinal hemorrhage (H 35.6), subarachnoid hemorrhage (I 60.9), melena (K 92.1), adverse effect of coumarins (Y 44.3), epistaxis (R 04.0) and long-term use of oral anticoagulants (Z 92.1). Data collection was carried out by trained medical students and cardiology fellows.

Patients older than 18 years who had bleeding while using VKA were included. Those with bleeding not related to the use of the drugs in question, those with supratherapeutic international normalized ratio (INR) without bleeding, with inadequately filled medical records and new visits to patients who had already been selected were excluded. Patients included in the study were divided into two groups according to the need for hospitalization or not.

The risk of thromboembolism and bleeding in patients with non-valvular AF was estimated by the CHA2DS2-VASc (congestive heart failure / left ventricular dysfunction, hypertension, age> 75, diabetes mellitus, stroke / transient ischemic attack / thromboembolism, vascular disease [prior myocardial infarction, peripheral artery disease, or aortic plaque], age 65-74, and sex category [female gender]) and the HAS-BLED (hypertension, abnormal renal and liver function, stroke, bleeding, labile INRs, elderly, and drug or alcohol consumption). Bleeding severity was assessed using the BARC (Bleeding Academic Research Consortium) and GUSTO (The Global Use of Strategies to Open Occluded Arteries) scores, and medications that could interact with VKA, increase the risk of bleeding, and gastric protectors were reviewed.

Recommendations for conducting cross-sectional studies were followed according to the STROBE Statement (https://www.strobe-statement.org). The study was approved by the institutional ethics committee.

Statistical Analysis

Continuous variables were described by means and standard deviations and categorical variables as absolute and relative frequencies. The Shapiro-Wilk test was used to assess the normality of quantitative variables. For comparison between categorical variables, the chi-square test or Fisher's exact test was used, when appropriate. For comparisons of continuous variables between the groups, the unpaired Student's t test was used. The p-value was considered statistically significant when <0.05.

A binary logistic regression model was performed, and the variables were included using the backward stepwise method (probability), using a p-value of 0.05 as the inclusion criterion, a removal value of 0.20 and a confidence interval of 95%. The variables with a statistically significant difference in the comparative analysis between the groups and those considered relevant by the researchers were selected to enter the model. Statistical analyses were performed using the Statistical Package for the Social Science version 25 (SPSS).

Results

Of the 145,122 patient visits in the emergency department during the analyzed period, 1,823 were screened. After applying the exclusion criteria, 510 patients were included in the study. Of these, 44.8% required hospitalization.

Table 1 describes the main clinical characteristics of patients admitted or discharged from the emergency department. Most patients were women (52.7%) and elderly, with an average age of 65.3 years, with no difference between the groups. There was a high prevalence of heart failure, renal failure, and coronary artery disease (CAD) among the hospitalized patients. The main antiplatelet drugs prescribed for outpatients were acetylsalicylic acid and clopidogrel. The most used VKA was warfarin (77.3%), with no difference between groups.

VKAs were mainly indicated for patients with AF or atrial flutter, with no difference between groups; however, venous thromboembolism was found to be significantly more common in outpatients than hospitalized patients (Table 2).

Table 1 – Clinical characteristics of patients who were hospitalized or not after emergency care (n = 510)

	Discharged from the mergency department (n = 349)	Hospital dmission (n = 161)	p
Female gender, n (%)	185 (53)	84 (52)	0.92
Age	66.8 (+13.6)	64.6(+12.3)	0.08
Diabetes mellitus (%)	64 (18.3)	39 (24.2)	0.12
Systemic arterial hypertension, n (%)	264 (75.6)	132 (82)	0.13
Stroke or TIA, n (%)	34 (9.7)	15 (9.3)	1.00
Heart failure, n (%)	149 (39.8)	85 (52.8)	<0.01
Ejection fraction%, mean (DP)	57.9(+14.4)	55.7(+17.1)	<0.01
PAD, n (%)	10 (2.9)	8 (5.0)	0.30
Renal Failure, n (%)	20 (5.7)	26 (16.1)	<0.01
Liver Disease, n (%)	3 (0.9)	5 (3.1)	0.11
Smoking, n (%)	105 (30.1)	59 (36.6)	0.15
Alcoholism, n (%)	5 (1.4)	7 (4.3)	0.05
Lipid disorder, n (%)	115 (33)	63 (39.1)	0.19
Coronary heart disease, n (%)	101 (28.9)	68 (42.2)	<0.01
HCM, n (%)	2 (0.6)	2 (1.2)	0.59
COPD, n (%)	14 (4)	10 (6.2)	0.36
CHA2DS-VASC2, média (DP)	4.14 (+1.47)	3.67 (+1.36)	0.01
HASBLED, média (DP)	3.73 (+1.25)	3.11 (+1.2)	<0.01
Antiplatelet use, n (%)	158 (45.3)	39 (24.2)	<0.01
ASA	148 (42.4)	37 (23)	<0.01
Clopidogrel	40 (11.5)	6 (3.7)	<0.01
Ticagrelor	1 (0.3)	0	1.00
Ticlopidine	2 (0.6)	1 (0.6)	1.00
Anticoagulant n (%)			0.36
Warfarin	274 (78.5)	120 (74.5)	
Phenprocoumon	75 (21.5)	41 (25.5)	
Current medications, n (%)			
Amiodarone	42 (12)	12 (7.5)	0.12
NSAID	4 (1.1)	2 (1.2)	1.00
Calcium channel blocker	12 (3.4)	8 (5)	0.46
Anticonvulsant	3 (0.9)	1 (0.6)	1.00
Antibiotics	5 (1.4)	2 (1.3)	1.00
Statin	205 (58.7)	81 (50.3)	0.08
Digoxin	52 (14.8)	29 (18.4)	0.18
Fibrate	6 (1.7)	1 (0.6)	0.44

TIA: Transient Ischemic Attack; SD: Standard Deviation; PAD: Peripheral Obstructive Arterial Disease; COPD: Chronic Obstructive Pulmonary Disease; AF: Atrial Fibrillation: VKA: Vitamin K antagonists; ASA: Acetylsalicylic acid; NSAID: Non-steroidal anti-inflammatory drugs; HCM: Hypertrophic cardiomyopathy.

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Original Article

Table 2 – Reason for anticoagulation of patients who were hospitalized or not after emergency care (n = 510)

Reason for anticoagulation, n (%)	Discharged from the mergency department (n = 349)	Hospital dmission (n = 161)	p
Atrial fibrillation or flutter	238 (68,2)	121 (75,2)	0,11
Prosthetic heart valve	119 (34,1)	50 (31,1)	0,54
Venous thromboembolism	23 (6,6)	3 (1,9)	0,02
Left ventricular thrombus	11 (3,2)	5 (3,1)	1,00
AMI; low EF	5 (1,4)	2 (1,2)	1,00
Others	6 (1,7)	5 (3,1)	0,33

EF: ejection fraction, VKA: Vitamin K antagonists; AF: Atrial Fibrillation; AMI: Acute Myocardial Infarction.

Gastrointestinal, intra-abdominal, and central nervous system bleeding were more frequent in patients who were hospitalized. Genitourinary bleeding, epistaxis, oral cavity, and conjunctival bleeding were more prevalent in those who did not require hospitalization (Table 3).

Most patients had supratherapeutic INR levels, especially among those who were hospitalized. Drop in hemoglobin levels, use of vitamin K, blood transfusions and use of plasma, as well as more important bleeding were also more frequent in this group (Table 4).

Figure 1 shows the results of the binary logistic regression between the groups, identifying the variables with the strongest association with the need for hospitalization by VKA users experiencing bleeding. Predictors of hospitalization were: INR at supratherapeutic levels (OR 3.45; P <0.01; 95% CI 1.58 - 7.51), gastrointestinal bleeding (OR 2.36; P <0.01; CI 95% 1.24 - 4.50), drop in hemoglobin (OR 6.93; P <0.01; 95% CI 3.67 - 13.07), heart failure (OR 1.96; P 0.01 ; 95% CI 1.16 - 3.30) and need for blood transfusion (OR 8.03; P <0.01; 95% CI 2.98 - 21.64).

Discussion

Our study reports the experience of an emergency department regarding the management of hemorrhagic complications in anticoagulated stroke patients by means of a five-year retrospective review. According to the study by Shehab et al.,[8] for every 1,000 patients who seek emergency care in the United States in 2013-2014, four were due to adverse medication events, mainly bleeding complications of oral anticoagulants, especially warfarin. Furthermore, there was a need for hospitalization in practically half of the cases.[8]

In our registry, the main reasons of hospitalizations for bleeding were gastrointestinal bleeding, followed by spontaneous bleeding, and genitourinary and cutaneous hematomas. These data are in line with other studies on the subject.[8,10,12,14,16,17] Gastrointestinal bleeding site was a predictor of hospitalization, probably due to its higher severity and the need for diagnostic or therapeutic endoscopic procedures.

With regard to comorbidities, heart failure was associated with a greater need for hospitalization. This finding may be explained by the fact that heart failure patients usually have more severe conditions, with more comorbidities, hence requiring greater care.

The intensity of anticoagulation is one of the factors that increase the risk of bleeding.[5,7] This fact may justify the higher hospitalizations of patients with INR at supra-therapeutic levels. Real-life reports show that 34% to 51% of stroke patients who seek emergency care, have an INR above the recommended level.[12-14,18,19] In our study, these numbers were even higher, probably because we only evaluated patients presenting with bleeding. Considering that an inadequate anticoagulation control can lead to higher morbidity and an increase in public health expenditures, population educational strategies, in addition to a close and continuous medical follow-up are essential, especially at the primary care level.

Anticoagulation reversal is necessary in patients with very high INR or active hemorrhage who will undergo urgent, invasive procedures. In this regard, low doses of vitamin K can be used in conjunction with the suspension of anticoagulation in patients taking VKAs.[3,5,7] Despite the few studies in the reviewed literature, the prescription of

Table 3 – Bleeding site of patients who were hospitalized or not after emergency care (n = 510)

	Discharged from the emergency epartment (n = 349)	Hospital Admission (n = 161)	p
Bleeding site, n (%)			
Gastrointestinal	42 (12)	85 (52.8)	<0.01
Spontaneous cutaneous hematoma	95 (27.2)	31 (19.3)	0.06
Central nervous system	0	5 (3.1)	<0.01
Abdominal	0	4 (2.5)	0.01
Genitourinary	94 (26.9)	22 (13.7)	<0.01
Soft tissue after trauma	8 (2.3)	5 (3.1)	0.56
Epistaxis	63 (18.1)	16 (9.9)	0.01
Hemoptysis	5 (1.4)	2 (1.2)	1.00
Oral cavity	60 (17.2)	10 (6.2)	<0.01
Hemarthrosis	0	2 (1.2)	0.09
Conjunctival	24 (6.9)	1 (0.6)	<0.01
Ear	6 (1.7)	0	0.18
Operative wound	2 (0.6)	3 (1.9)	0.18

vitamin K in cases of bleeding during the use of VKA ranges from 19% to 27%.[12,19] In our institution, it was used in 50% of cases.

The independent variables with stronger association with hospitalization were drop in hemoglobin and need for blood transfusion. This is probably explained by the fact that more severe bleeding requires more medical care and an increased observation period.

Our study is subject to some limitations. The fact that this was a single-center, cross-sectional study, including a convenience sample by the review of electronic medical records, may be associated with registration bias. In addition, bleeding complications among VKA users may be been underestimated, since the study was conducted in a cardiology hospital, and many patients may have sought general hospitals for these events.

Conclusion

Drop in hemoglobin, heart failure, supra-therapeutic INR, gastrointestinal bleeding, and need for blood transfusion were associated with the need for hospitalization by VKA users who seek emergency care due to bleeding. Identification of these factors in the initial evaluation would help to define which patients will demand more intensive care.

Author contributions

Analysis and interpretation of the data: Chiaparini AF, Rabaioli PSB, Slaviero JV, Tem-Pass CS, Fontana Filho HA. Statistical analysis: Chiaparini AF, Almeida ED, Leiria TLL. Writing of the manuscript: Chiaparini AF, Leiria TLL, Castro I. Critical revision of the manuscript for intellectual content: Chiaparini AF, Leiria TLL, Castro I. Acquisition of data: Slaviero J. Analysis and interpretation of the data: Slaviero J.

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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Table 4 – Bleeding characteristics of patients who were hospitalized or not after emergency care (n = 510)

	Discharged from the emergency department (n = 349)	Hospital Admission (n = 161)	p
Therapeutic range of INR, n (%)			<0.01
Subtherapeutic	27 (7.7)	8 (5.0)	
Therapeutic	76 (21.8)	7 (4.3)	
Supratherapeutic	246 (70.5)	146 (90.7)	
Drop in hemoblogin, n (%)	27 (7.7)	107 (66.5)	<0.01
Use of vitamin K, n (%)	136 (39)	121 (75.2)	<0.01
Blood transfusion, n (%)	6 (1.7)	77 (47.8)	<0.01
Plasma, n (%)	1 (0.3)	38 (23.6)	<0.01
BARC			<0.01
I	171 (49)	3 (1.9)	
II	170 (48.7)	69 (42.9)	
IIIa	7 (2)	47 (29.3)	
IIIb	1 (0.3)	30 (18.6)	
IIIc	0	6 (3.7)	
IV	0	0	
Va	0	5 (3.1)	
Vb	0	1 (0.6)	
GUSTO			<0.01
Mild	343 (98.3)	73 (45.3)	
Moderate	6 (1.7)	55 (34.2)	
Severe	0 (0.9)	33 (19)	

INR: International Normalized Ratio

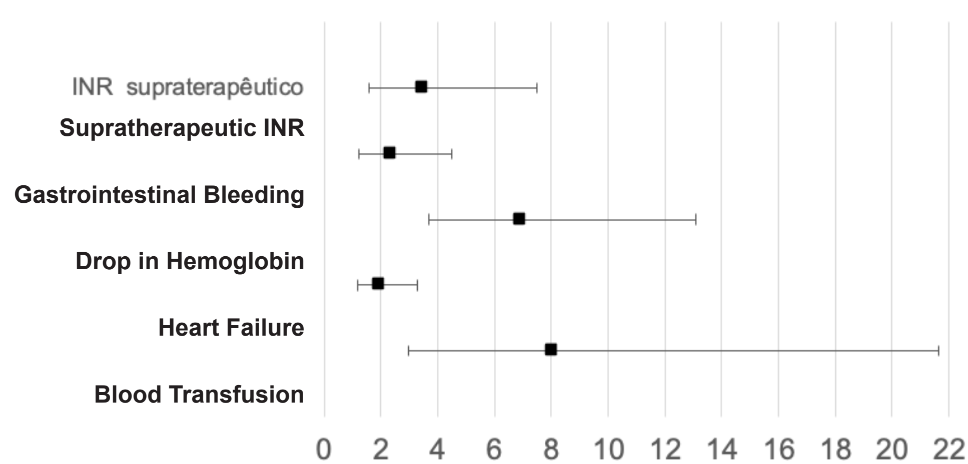

Figure 1 – Forest Plot representing the Odds Ratio and confidence interval (95%) of the predictive factors for hospitalization of vitamin K users who sought emergency care for bleeding

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the IC/FUC under the protocol number 4.225.884. 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

Cardioprotective Effects of Sodium-glucose Cotransporter 2 Inhibitors Regardless of Type 2 Diabetes Mellitus: A Meta-analysis

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is an independent risk factor for cardiovascular impairment, increasing the rates of atherosclerotic and non-atherosclerotic events. Additionally, adverse kidney events are directly linked with T2DM and cardiovascular diseases. In this context, the sodium-glucose cotransporter 2 inhibitors (SGLT2i) have demonstrated both cardioprotective and renoprotective effects in patients with or without T2DM. Therefore, the present meta-analysis aims to evaluate cardiovascular outcomes involving SGLT2i as monotherapy or other add-on antidiabetic agents (ADA) in patients with or without T2DM.

Objetive: The present meta-analysis aims to evaluate cardiovascular outcomes involving SGLT2i as monotherapy or add-on other ADA in patients with or without T2DM.

Methods: The entrance criteria to SGLT2i studies were: describing any data regarding cardiovascular effects; enrolling more than 1,000 participants; being approved by either the FDA or the EU, and having available access to the supplementary data. The trial had to exhibit at least one of the following results: major adverse cardiovascular events (MACE), cardiovascular death or hospitalization for heart failure, cardiovascular death, hospitalization for heart failure, renal or cardiovascular adverse events, or non-cardiovascular death. The significance level of 0.05 was adopted in the statistical analysis.

Results: Nine trials with a total of 76,285 participants were included in the meta-analysis. SGLT2i reduced MACE (RR 0.75, 95% CI [0.55-1.01]), cardiovascular death or hospitalization for heart failure (RR 0.72, 95% CI [0.55-0.93]), cardiovascular death (RR 0.66, 95% CI [0.48-0.91]), hospitalization for heart failure (RR 0.58, 95% CI [0.46-0.73]), renal or cardiovascular adverse events (RR 0.55, 95% CI [0.39-0.78]), and non-cardiovascular death (RR 0.88, 95% CI [0.60-1.00]).

Conclusions: Conjunction overall data suggests that these drugs can minimize the risk of cardiovascular events, thus decreasing mortality in patients, regardless of the presence of T2DM.

Keywords: Sodium-Gucose Transport Protein II; Heart Failure;Hospitalization; Reproducibility of Results; Outcome Assessment (Health Care); Diabetes Mellitus; Meta-Analysis.

Introduction

Around 63 million people present heart failure worldwide,[1,2] and this condition costs billion dollars to health care,[3] This syndrome is associated with high morbidity and mortality rates, since it has a poor prognosis due to the difficulty in recognizing high-risk and pre-clinical stage patients linked to the problem of an appropriate early treatment.[1,4,5] Despite many designed trials, no adequate pharmacological treatment was found for heart failure with preserved ejection fraction (EF>50%)[6–8], which most likely represents 65% of heart failure in 2020.[1,6]

Among the remarkable consequences of heart failure is the cardiorenal syndrome.[9] This link is attributed to renal hypoperfusion, which is caused by high venous pressure

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and low cardiac output, leading to renal inflammation; sympathetic overstimulation; elevated sodium and consequent fluid retention; as well as atherosclerosis, anemia, and the of uremic toxins.[1,9] Altogether, these pathological mechanisms enhance the risk of cardiovascular adverse events, worsening heart failure.[1]

Type 2 diabetes mellitus (T2DM) is a specific risk factor for atherosclerotic and non-atherosclerotic impairment responsible for myocardial diseases, such as myocardial infarction and heart failure. Furthermore, T2DM is, together with hypertension, the leading cause of chronic renal disease.[1,10,11] This metabolic condition is capable of promoting injuries and alterations in the kidneys, hormone control, hepatic function, lipid metabolism, and vascular control, as well as in overstimulating the sympathetic nervous system and increasing the blood pressure.[1,12]

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) comprise one of the newest antidiabetic agents (ADA).[13] Recent studies have shown SGLT2i benefits in T2DM, such as lowering sodium and glucose retention, promoting glycosuria and weight loss, reducing glycemia, and the glycated hemoglobin (HbA1c), as well as autonomic symptoms and blood pressure and the enhancement of the renal function.[12] Moreover, cardiovascular benefits were seen in recent cardiovascular outcome trials (CVOTs).[14–22] Such services may be attributed to SGLT2i ability to reduce left ventricular mass,[23] improve systolic and diastolic functions,[24] endothelial function, and cardiac output[25] to reduce preload and afterload,[26] to raise erythropoietin[1] and to inhibit cardiac fibrosis.[27,28]

According to a recent paper published by the European Society of Cardiology in association with the Heart Failure Association,[29] SGLT2i have proven to be the most effective ADA at reducing hospitalization for heart failure. It was demonstrated that Empagliflozin, Canagliflozin, and Dapagliflozin were responsible for decreasing hospitalization for heart failure by 35%, 33%, and 27%, respectively. Moreover, Empagliflozin lowered the risk of cardiovascular death by 38% and presented similar performance to Canagliflozin in reducing the risk of major adverse cardiovascular events (MACE), a composite of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke in 14%.

Approved by the Food and Drug Administration (FDA), Canagliflozin (Invokana®)[13], Dapagliflozin (Forxiga®)[13], and Empagliflozin (Jardiance®)[13] were the SGLT2i tested in CVOTs. The cardioprotective effect of Ertugliflozin (Steglatro®)[30], the most recent SGLT2i approved by the FDA, is underway through the ongoing trial VERTIS-CV (Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial)[31]. In turn, Sotagliflozin (Zynquista®),[32] recently approved by the European Medicines Agency (EU), but not by the FDA, is the first dual sodium-glucose cotransporter 1 and 2 inhibitors) and its probable cardiovascular effects are reliant on the ongoing SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening).[33]

Most importantly, the SGLT2i effects are seen both in patients with T2DM and without T2DM. Thus, the SGLT2i benefits are independent of glucose levels. Intending to test this hypothesis, the DAPA-HF trial (Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure)[18] portrayed outstanding results in its analysis through the demonstration that Dapagliflozin 10 mg could also reduce hospitalization for heart failure regardless of the presence of T2DM.[34–36]

Furthermore, some ongoing trials, with more than 2,000 participants, will present their outcomes regarding patients with or without T2DM and heart failure with reduced (HFrEF – FE<40%)[1] or preserved ejection fraction (HFpEF), such as EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction)[37], EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction)[38] and DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure).[1] Another two ongoing trials were designed to evaluate the cardioprotective benefit of SGLT2i in chronic kidney disease patients with or without T2DM, such as DAPA-CKD (Dapagliflozin and Prevention of Adverse outcomes in Chronic Kidney Disease trial)[39] and EMPA-KIDNEY (The Study for Heart and Kidney Protection with Empagliflozin)[40].

Hence, this present meta-analysis aims to evaluate and compare the available data from the published trials regarding the cardioprotective effects of SGLT2i in patients either in the presence or absence of T2DM.

Methods

Search and Selection Strategy

First, a search was conducted on the Google Scholar, Scielo, and PubMed databases using the keywords:

“sodium-glucose cotransporter 2 inhibitors”, “heart failure”, “hospitalization", and "cardiovascular outcomes". From the recovered articles of these databases, the following data were gathered: (I) author; (II) year; (III) title of the trial; (IV) the number of participants in each trial; (V) the number of participants who received the drug; (VI) the number of participants who matched placebo or other ADA; (VII) the events of MACE or hospitalization for heart failure or cardiovascular death; (VIII) the results of renal or cardiovascular adverse events [End-stage Kidney Disease, Renal Death, ≥ 40% Decrease in estimated glomerular filtration rate (eGFR) to <60 mL/min/1.73m^2, renal replacement therapy or hospitalization for heart failure, cardiovascular death, MACE]; and (IX) non-cardiovascular death.

Eligibility Criteria

The eligibility criteria of this analysis required four obligatory entrance criteria: studies with any of the SGLT2i describing any data regarding any cardiovascular effect; having enrolled more than 1,000 participants; being approved by the FDA and/or the EU; and the available access to the supplementary data. Afterward, the trial had to exhibit at least one of these following criteria: major adverse cardiovascular effects (MACE – cardiovascular death, non-fatal myocardial infarction or non-fatal stroke); a composite of cardiovascular death or hospitalization for heart failure; cardiovascular death; hospitalization for heart failure; renal or cardiovascular adverse events (End-stage Kidney Disease, Renal Death, ≥ 40% decrease in estimated glomerular filtration rate (eGFR) to <60 mL/min/1.73m^2, renal replacement therapy or hospitalization for heart failure, cardiovascular death, MACE); or non-cardiovascular death. Figure 1 summarizes the flow of the selection of articles.

Statistical Analysis

The R software[41] with the “Metafor” package was used to analyze the Relative Risk (RR) among the trials to random effect through the DerSimonian method,[42] classifying them in six patterns: MACE; cardiovascular death or hospitalization for heart failure; cardiovascular death; hospitalization for heart failure; renal or cardiovascular adverse events; and non-cardiovascular death. Thus, the SGLT2i group was compared to the placebo group. In addition to RR's cumulative effect, the heterogeneity index (H^2) was also analyzed for each predetermined pattern. The significance level of 0.05 was adopted in the statistical analysis.

Results

Studies Characteristics

The search retrieved ninety-three studies, nine of which fulfilled the eligibility criteria and were included

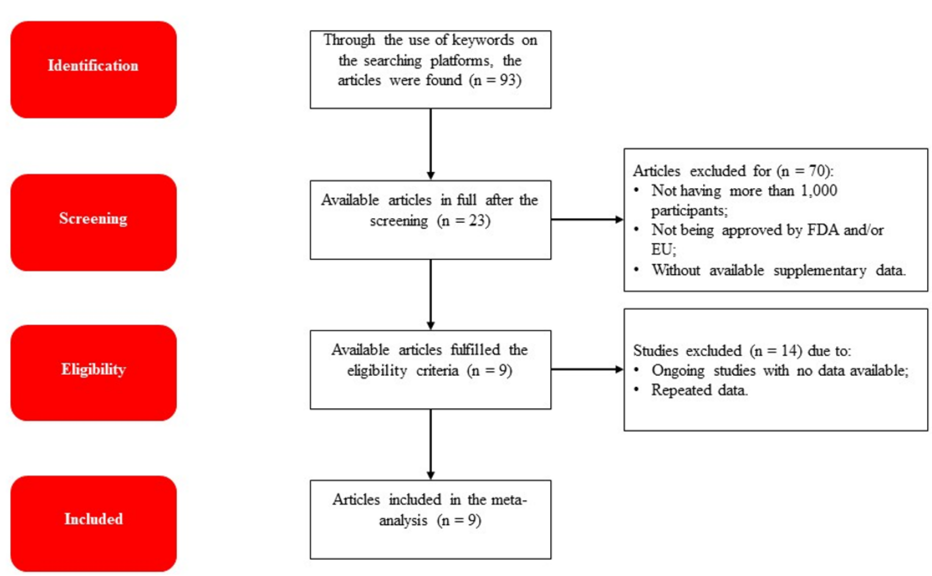

Figure 1 – Flowchart of the analyzed studies included.

in this analysis, enrolling 76,285 participants, of whom 2,605 (approximately 3.4%) did not have T2DM.

Of the nine studies analyzed, five investigated SGLT2i as a monotherapy: Fitcher et al.[15] (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients Removing Excess Glucose - EMPA-REG OUTCOME)[15]; Mahaffey et al.[14] (Canagliflozin Cardiovascular Assessment Study - CANVAS)[14]; Perkovic et al.,[16] (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation - CREDENCE);[16] Wiviott et al.,[17] (Dapagliflozin Effect on Cardiovascular Events – Thrombolysis in Myocardial Infarction 58 - DECLARE-TIMI 58),[17] and McMurray et al.,[18] (Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure - DAPA-HF).[18]

Three of them studied SGLT2i add-on metformin vs. other ADAs: Levalle-González et al.,[19] (Canagliflozin Treatment and Trial Analysis – DDP-4 Inhibitor Comparator Trial - CANTATA-D)[19]; Ridderstrale et al.,[20] (Efficacy and Safety of Empagliflozin With Metformin in Patients With Type 2 Diabetes - EMPA-REG H2H-SU)[20] and Patel et al.,[21] (Canagliflozin Treatment And Trial Analysis-Sulfonylurea - CANTATA-SU).[21] Comparing Empagliflozin versus other Sitagliptin, EMPRISE (Empagliflozin Comparative Effectiveness and Safety) had their first analysis published by Patorno et al.,[22] The overall study characteristics are gathered in Table 1.

Major Adverse Cardiovascular Effects

Seven of the nine selected trials have analyzed the rate of MACE. Among these trials, the studies that used SGLT2i as monotherapy presented more robust and significant results than those using SGLT2i add-on metformin, as shown in Figure 2. Mahaffey et al.,[14] (CANVAS)[14] and Perkovic et

Table 1 – Characteristics of the included studies at baseline

Author/ Year	Trial*	Follow-up (weeks)	Mean age (years)	SGLT2inhib	ADM	Exposed	Compare	Control	Total
Mahaffey et al., 2018[14]	CANVAS	338	63.3	CANA	MONO	3,756	PBO	2,039	5,795
Fitcher et al., 2016[15]	EMPA-REG OUTCOME	162	63.1	EMPA	MONO	4,687	PBO	2,333	7,020
Perkovic et al., 2019[16]	CREDENCE	42	63.0	CANA	MONO	2,202	PBO	2,199	4,401
Wiviott et al., 2018[17]	DECLARE-TIMI 58	206	63.9	DAPA	MONO	8,582	PBO	8,578	17,160
McMurray et al., 2019[18]	DAPA-HF	72	66.0	DAPA	MONO	2,373	PBO	2,371	4,744
Levalle-González et al, 2013[19]	CANTATA-D	52	55.4	CANA	Add-on MET	735	SITA	549	1,284
Ridderstrale et al., 2018[20]	EMPA-REG H2H-SU	104	55.9	EMPA	Add-on MET	765	GLIM	780	1,545
Patel et al., 2016[21]	CANTATA-SU	104	56.2	CANA	Add-on MET	968	GLIM	482	1,450
Patorno et al., 2019[22]	EMPRISE	48	59	EMPA	MONO	16,443	SITA	16,443	32,886
Total	-	1128	60.6	-	-	40,551	-	35,774	76,285

SGLT2 inhib: Sodium-glucose Cotransporter 2 Inhibitor; EMPA: Empagliflozin; CANA: Canagliflozin; DAPA: Dapagliflozin; ADM: Administration; MONO: Monotherapy; MET: Metformin; PBO: Placebo; SITA: Sitagliptin; GLIM: Glimepiride.
** p<0.05 was the level of significance adopted by all articles*

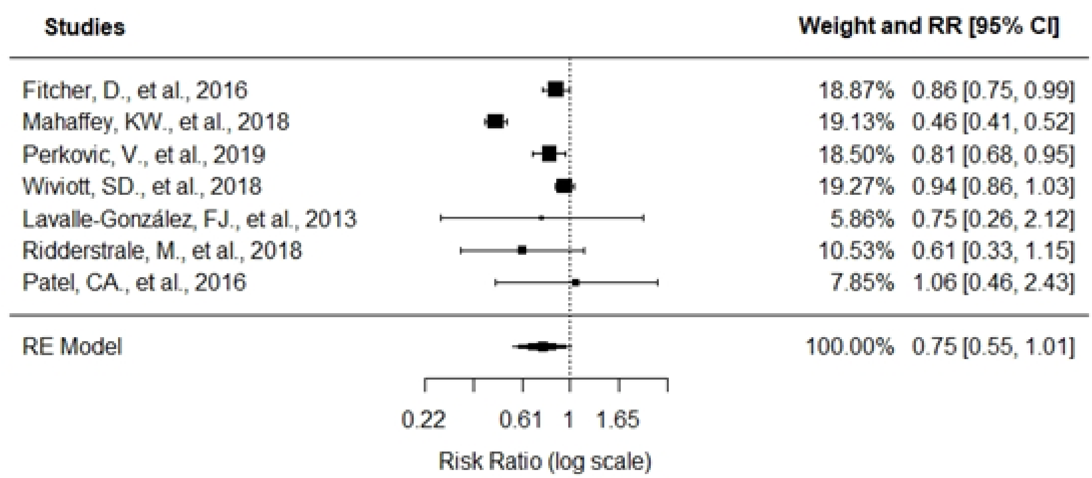

Figure 2 – Major Adverse Cardiovascular Effects (MACE).

al.,[16] (CREDENCE)[16] showed the more significant and more reliable reductions of MACE with Canagliflozin 100 or 300 mg than placebo. Similarly, Empagliflozin 10 or 25 mg and Dapagliflozin 10 mg also reduced this event as shown by Fitcher et al.,[15] (EMPA-REG OUTCOME)[15] and Wiviott et al.,[17] (2018) (DECLARE-TIMI 58).[17]

On the other hand, SGLT2i add-on metformin therapy vs. other ADA decreased MACE episodes, which can be noticed through Levalle-González et al.,[19] (CANTATA-D)[19] with Canagliflozin 100 or 300 mg add-on metformin vs. Sitagliptin 100 mg and Ridderstrale et al.[20] (EMPA-REG H2H-SU)[20] with Empagliflozin 25 mg add-on metformin vs. Glimepiride 1 to 4 mg. However, these two studies had a large range of confidence intervals. In turn, Patel et al.,[21] (CANTATA-SU)[21] displayed that Canagliflozin 100 or 300 mg add-on metformin did not show to be effective at reducing MACE when compared with Glimepiride 6 to 8 mg.

In general, SGLT2i performed further effectiveness at reducing MACE than control, placebo, or other ADA, RR 0.75, 95% CI [0.55-1.01]. The heterogeneity (I^2) found was 94.02%.

Cardiovascular Death or Hospitalization for Heart Failure

Five of the analyzed trials presented the data regarding cardiovascular death or hospitalization for heart failure; all employed SGLT2i as monotherapy. At first, Canagliflozin 100 or 300 mg was more effective in lowering this parameter than the placebo through the data presented by Mahaffey et al.,[14] (CANVAS)[14] and Perkovic et al.,[16] (CREDENCE).[16] Likewise, Wiviott et al.,[17] (2018) (DECLARE-TIMI 58)[17] and McMurray et al.,[18] (2019) (DAPA-HF)[18] showed a reduction of the episodes of cardiovascular death or hospitalization for heart failure with Dapagliflozin 10 mg as well. By contrast, Fitcher et al.,[15] (EMPA-REG OUTCOME)[15] did not observe a significant decrease in these events by the administration of Empagliflozin 10 or 25 mg. Considering all the five studies together, there was a reduction of cardiovascular death or hospitalization for heart failure (RR 0.72, 95% CI [0.55-0.93]) generally (Figure 3), and the heterogeneity (I^2) was 93.72%.

Cardiovascular Death

Eight of all the selected studies evaluated the cardiovascular death parameter. The greater power among the studies involving the evaluation of cardiovascular death was assured by the SGLT2i-monotherapy studies and the most significant reductions. Regarding SGLT2i-monotherapy studies, Canagliflozin 100 or 300 mg and Empagliflozin 10 or 25 mg proved to be the most effective at reducing cardiovascular death events according to Mahaffey et al.,[14] (CANVAS)[14] and Fitcher et al.,[15] (EMPA-REG OUTCOME).[15] In the same manner, Mahaffey K

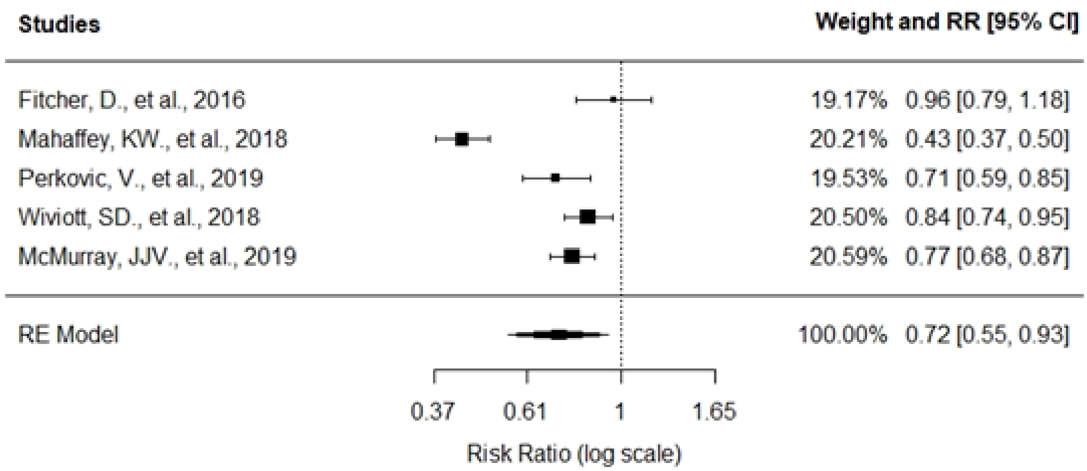

Figure 3 – Cardiovascular Death or Hospitalization for Heart Failure.

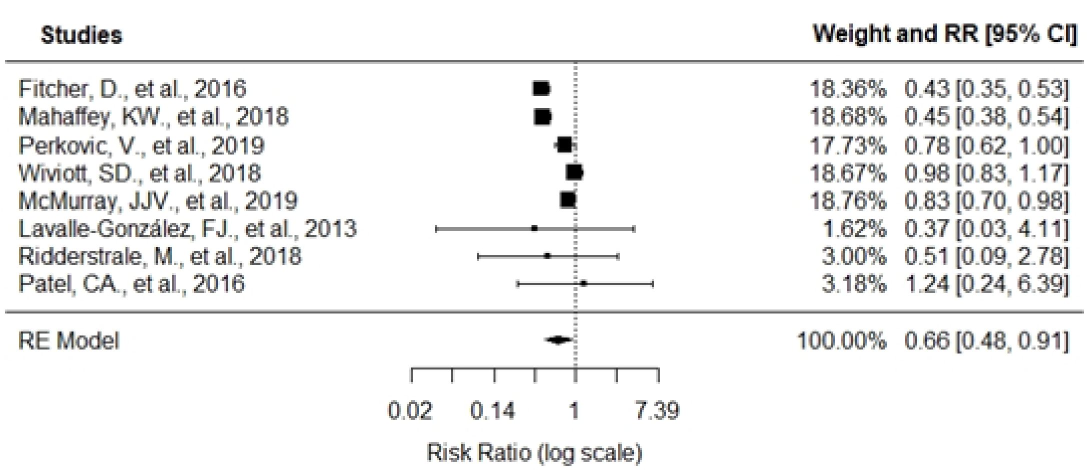

Figure 4 – Cardiovascular Death.

et al.,[16] (CANVAS),[16] Perkovic et al.,[16] (CREDENCE)[16] presented a consistent reduction in cardiovascular death promoted by Canagliflozin 100 or 300 mg. However, the use of Dapagliptin 10 mg did not result in a consistent reduction of this event, as demonstrated by Wiviott et al.,[17] (DECLARE-TIMI 58)[17] and McMurray et al.,[18] (DAPA-HF).[18]

Despite the apparent benefit of SGLT2i add-on metformin, the studies using a combined therapy had a wide confidence interval. This is shown with the use of Canagliflozin 100 or 300 mg add-on metformin vs Sitagliptin 100 mg demonstrated by Levalle-González et al.,[19] (CANTATA-D),[19] Empagliflozin 25 mg add-on metformin vs Glimepiride 1 to 4 mg by Ridderstrale et al.,[20] (EMPA-REG H2H-SU)[20] and Canagliflozin 100 or 300 mg add-on metformin vs Glimepiride 6 to 8 mg by Patel et al.,[21] (CANTATA-SU).[21]

Although the heterogeneity (I^2) among the data was 89.43%, the general evaluation showed that the use of SGLT2i causes a significant reduction in cardiovascular deaths (RR 0.66, 95% CI [0.48-0.91]) (Figure 4).

Hospitalization for Heart Failure

Seven of the evaluated studies displayed the hospitalization for heart failure parameter. In general, SGLT2i administration led to a lower rate of hospitalization for heart failure (RR 0.60, 95% CI [0.47-0.77]) (Figure 5). Ridderstrale et al.,[20] (EMPA-REG H2H-SU)[20] was the only SGLT2i add-on metformin study to evaluate this parameter. In its data, Emplagliflozin 25 mg add-on metformin compared to Glimepiride 1 to 4 mg showed a broad confidence interval in reducing this event as.

By contrast, SGLT2i, as a monotherapy, presented more consistent and significant results. At first, Canagliflozin 100 or 300 mg showed the highest reduction in hospitalization for heart failure among the SGLT2i, according to the data from Mahaffey et al.,[14] (CANVAS).[14] Similarly, Patorno et al.,[22] (EMPRISE)[22] reported a substantial reduction of hospitalization for heart failure through the use of Empagliflozin 25 mg, revealing a superiority of SGLT2i over Sitagliptin. Perkovic et al.,[16] (CREDENCE)[16] also demonstrated that Canagliflozin 100 or 300 mg resulted in a lower hospitalization for heart failure. Similarly, Fitcher et al.,[15] (EMPA-REG OUTCOME)[15] reported a reduction in hospitalization for heart failure with Empagliflozin 10 or 25 mg.

In turn, Dapagliflozin 10 mg administration decreased hospitalization for heart failure, producing similar results to those obtained by Wiviott et al.,[17] (DECLARE-TIMI 58)[17] and McMurray J et al.,[18] (DAPA-HF),[18] highlighting the fact of McMurray et al.,[18] (DAPA-HF)[18] enrolled only 45% of T2DM participants (Table1), indicating the potential benefit of this medication to prevent and treat heart failure events, regardless of T2DM presence. The heterogeneity identified was 82.99%.

Renal or Cardiovascular Adverse Events

Four of the selected studies, all of which were SGLT2i monotherapy studies, evaluated the renal or cardiovascular adverse events. In general, SGLT2i reduced these outcomes in 45% (RR 0.55, 95% CI [0.39-0.78]) (Figure 6). The most effective medications at reducing this outcome were Empagliflozin 10 or 25 mg and Canagliflozin 100 or 300 mg as highlighted by Fitcher et al.,[15] (EMPA-REG

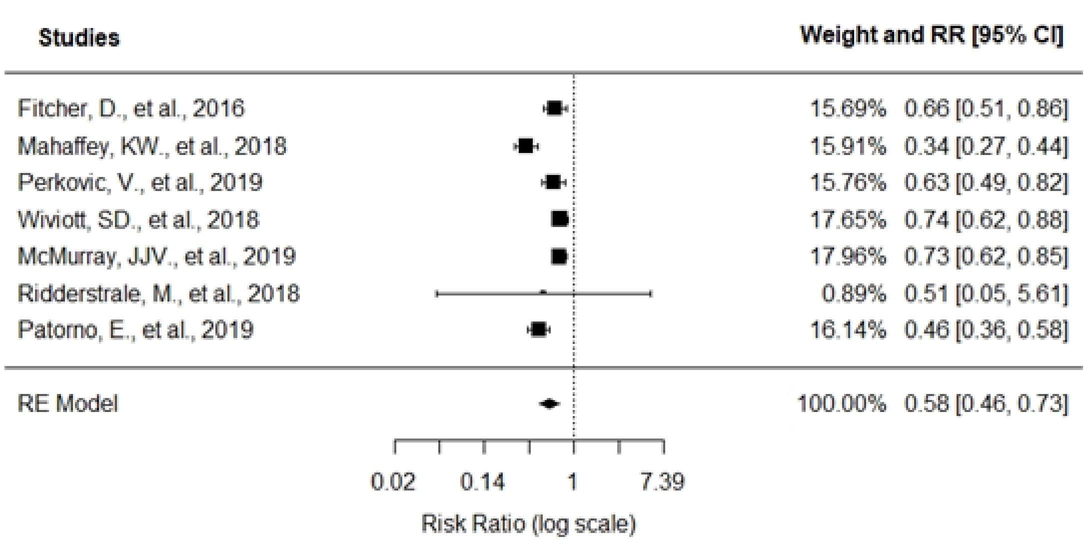

Figure 5 – Hospitalization for Heart Failure.

OUTCOME)[15] and Mahaffey et al.,[14] (CANVAS).[14] Perkovic et al.,[16] (CREDENCE),[16] despite showing a smaller protective effect as compared to the studies cited above, also showed a consistent reduction with Canagliflozin 100 or 300 mg, similarly to Empagliflozin 10 or 25 mg by Wiviott et al.,[17] (DECLARE-TIMI 58).[17] The heterogeneity found was 96.77%.

Non-cardiovascular Death

Four of the trials registered non-cardiovascular deaths, all four of which were SGLT2i-monotherapy studies. Although the results were not the most consistent, SGLT2i seemed to reduce non-cardiovascular death (RR 0.88, 95% CI [0.60-1.00]), especially Dapagliglozin 10 mg, as reported by Wiviott et al.,[17] (DECLARE-TIMI 58)[17] (Figure 7). However, McMurray et al.,[18] (DAPA-HF),[18] using the same dose of this medication, did not present such promising results. Fitcher et al.,[15] (EMPA-REG OUTCOME)[15] and Perkovic et al.,[16] (CREDENCE)[16] presented similar effects regarding non-cardiovascular death. No heterogeneity was found due to the overlap of the confidence interval between studies ($I^2 = 0\%$).

Discussion

SGLT2i presents promising effects concerning the protection of the cardiovascular system.[1,13] This class of drugs lowered MACE, the composite of cardiovascular death or hospitalization for heart failure, cardiovascular death, hospitalization for heart failure, and non-cardiovascular death. All these reductions were seen in patients with cardiovascular and/or kidney injuries and in patients with a high risk for these conditions, which shows that these drugs can be used in primary prevention. Still, it is essential to highlight that the SGLT2i monotherapy studies exerted the most noteworthy outcomes.

Regardless of T2DM presence, McMurray et al.,[18] (DAPA-HF)[18] showed that the use of Dapagliflozin 10 mg reduced the composite of cardiovascular death or hospitalization for heart failure, cardiovascular death, hospitalization for heart failure and non-cardiovascular death. In accordance with Milder et al.,[43] and Heerspink et al.,[44] such benefits can be elucidated due to the dissociation between hypoglycemic and cardioprotective effects exerted by SGLT2i. The probable mechanisms are weight loss,[43,45] reduced blood pressure,[43,46–49] reduced preload and afterload,[23,26,43,50,51] natriuresis, and osmotic diuresis,[23,43] inhibition of sodium-hydrogen exchanger in the myocardium,[43,52–54] induced ketone bodies for cardiac metabolism,[43,55] reduced cardiac fibrosis,[27,28,43] and reduced adipose inflammatory cytokines.[43,56] All these mechanisms are uncoupled from glycemic levels and kidney function. However, Vallon et al.,[57] and Chao E,[58] showed that the natriuresis and osmotic diuresis caused by glycosuria are the most robust mechanisms in reducing cardiovascular adverse events.

Although SGLT2i lowered all the analyzed parameters, the monotherapy study outcomes[14–18,22] seemed to be

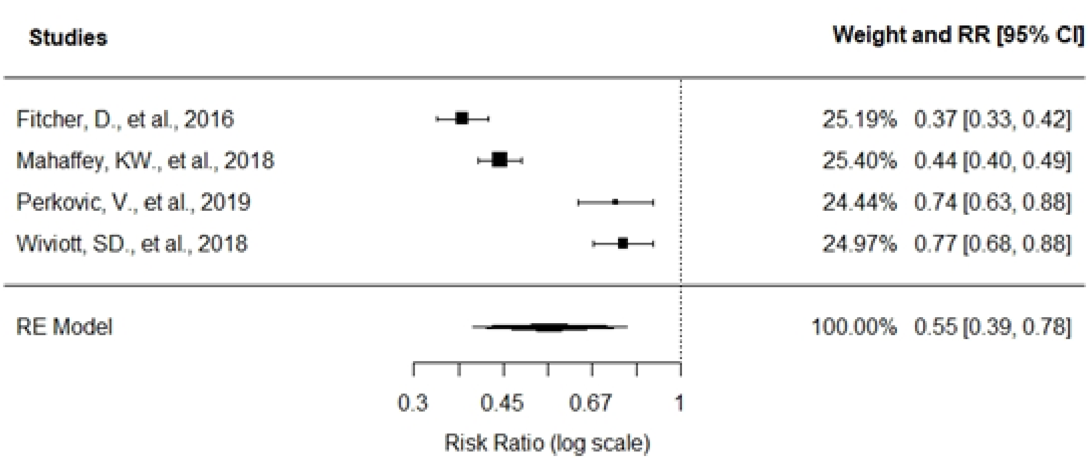

Figure 6 – Renal or Cardiovascular Adverse Events.

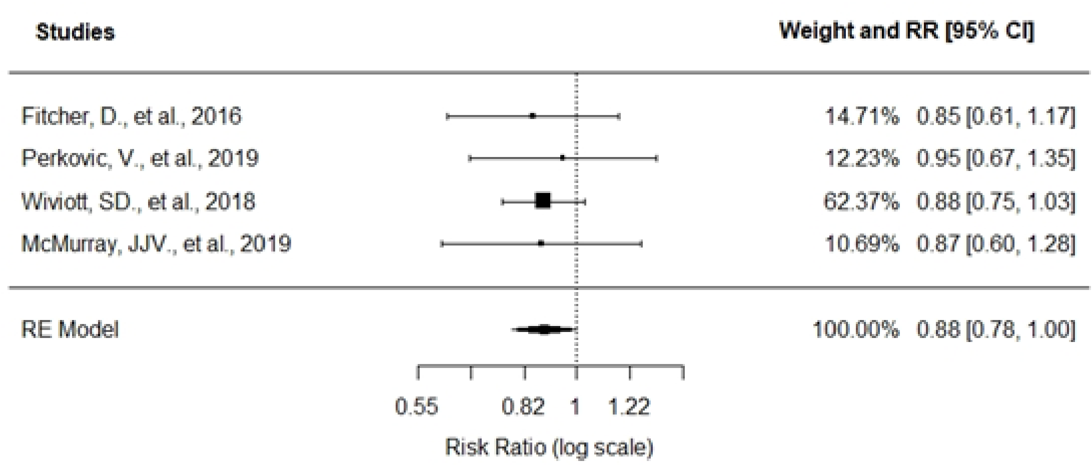

Figure 7 – All-cause of Death.

superior to SGLT2i add-on metformin study outcomes.[19–21] However, to date, there is no evidence proving that monotherapy is more promising than add-on therapy. There is a lack of robust CVOTs evaluating SGLT2i add-on therapy's effect, and no medical association[1,2,8,9,29] has described either of them. The majority of SGLT2i add-on therapy studies[19–21] were designed to assess this therapy's impact regarding glycemia, glycated hemoglobin, and blood pressure reductions, which indirectly affects the cardiovascular system. Therefore, the direct cardiovascular effects of SGLT2i add-on therapy have not yet been consistently proven.

Regarding the benefits of SGLT2i in treating cardiovascular autonomic neuropathy in T2DM patients, Spallone V,[12] showed that these drugs could improve the signs and symptoms of sympathetic overstimulation. The improvement of cardiovascular system effects would occur through natriuretic development, glycosuria, weight-loss, anti-inflammatory action, tyrosine hydroxylase, and kidney and heart noradrenaline inhibition, reducing hypertension, tachycardia, exercise intolerance, and orthostatic symptoms at rest.

Saleem,[13] and Fioretto et al.,[59] found that the SGLT2i could perform protection in the kidney and heart through a minor risk of atherosclerotic events, volume contraction and blood pressure, and preload and afterload reduction. The authors also presented that dapagliflozin could be well-tolerated when co-administered with common medications to treat other comorbidities and could benefit from low and high cardiovascular risk profiles. By contrast, no reduction in stroke events was noticed by the use of SGLT2i.

Moreover, Elmore et al.,[60] presented that the SGLT2i would be involved in several biochemical mechanisms, which reduced cardiovascular events, such as MACE, atherosclerotic diseases, and hospitalization for heart failure, including the possible reduction of left ventricular ejection fraction. On the other hand, Canagliflozin did not display an improvement in cardiovascular diseases, and its side and adverse effects did not surpass its efficacy (Mosleh et al.,[61]) Comparing the results of Dipeptidyl Peptidase 4 (DPP-4) Inhibitor studies to SGLT2i studies, the Savarese et al.,[62] meta-analysis, evaluating 157 trials, showed that the use of DPP-4 Inhibitors did not result in a reliable reduction into all-cause death, cardiovascular death, myocardial infarction and hospitalization for heart failure. Still, they could decrease stroke events, mostly as compared to placebo. Conversely, SGLT2i reduced all-cause death, cardiovascular death, myocardial infarction, and hospitalization for heart failure. However, a higher risk of non-fatal stroke was associated with SGLT2i use.

Similarly, Wu et al.,[63] portrayed, through 57 studies and six regulatory submissions included within their meta-analysis, the benefits of SGLT2i to MACE, cardiovascular death, hospitalization for heart failure, and all-cause of death. Furthermore, they reported the potential higher risk of non-fatal stroke due to SGLT2i administration and no statistical effect related to myocardial infarction. Meanwhile, a meta-analysis employing 71 studies designed by Monami et al.,[64] showed that SGLT2i lowered the all-cause death, cardiovascular death, and myocardial infarction, whereas no significant reduction was seen in stroke.

Recently, Zelniker et al.,[65] in their meta-analysis of three SGLT2i trials vs. placebo, found that SGLT2i had a powerful effect in reducing MACE, myocardial infarction, cardiovascular death, hospitalization for heart failure, all-cause of death, and the composite of worsening of renal function, end-stage renal disease or renal death, and hospitalization for heart failure in those participants with a worse estimated glomerular filtration rate (eGFR). However, these remarkable results were better seen in the subgroup of patients with the atherosclerotic disease than the subset of patients with multiple risk factors, and no benefit was found in reducing rates of stroke.

Cai-Yan Zou et al.,[66] in their meta-analysis involving 42 studies about SGLT2i and their benefits to the cardiovascular system showed that 37 studies showed the SGLT2i, mostly add-on metformin, reduced MACE, whereas 25 SGLT2i studies, primarily as monotherapy and add-on metformin vs. other ADA, reduced myocardial infarction events. Twenty-six studies pointed out that SGLT2i was not effective at reducing stroke episodes. SGLT2i lowered cardiovascular death, mostly as a monotherapy and add-on metformin vs. other ADA, and all-cause mortality, primarily as monotherapy, through the analysis of thirteen and twenty-five studies, respectively. Similarly, our study also evaluated the impact of SGLT2i on MACE, but not apart from cardiovascular death, non-fatal stroke, and non-fatal myocardial infarction. On the other hand, our study evaluated this class's effect regarding hospitalization due to heart failure, which is widely investigated today by a wide range of ongoing trials, including the possible benefit regardless of T2DM presence.

Birkeland et al.,[67] brought some data from the CVD-REAL Nordic, a multinational analysis of data collected from Denmark, Norway, and Sweden Health Care System. In this article, 22,830 participants started to use SGLT2i and 68,490 participants in other ADA. Cardiovascular death, MACE, hospitalization for heart failure, and all-cause death rates were decreased after the administration of SGLT2i. However, the same was not observed with non-fatal myocardial infarction and non-fatal stroke.

Regarding the high heterogeneity index observed in the present study for all the evaluated parameters, except for the analysis of non-cardiovascular death, several variables justify these values, such as the different medicines employed in the studies (Canagliflozin, Empagliflozin, Dapagliflozin) as monotherapy or other add-on ADAs, in various specific dosages (300, 100, 25, and 10 mg), administered to different population groups (high-risk factors, presence of atherosclerotic disease, with or without heart failure and with or without diabetes), and low k-study values, such as these are recent clinical trials. On the other hand, it is important to emphasize that the 9 studies analysed enrolled a total of 76,285 participants. Besides, in order to increase the reliability of the study, we selected the studies which comprehended over 1,000 participants.

Conclusion

SGLT2i is a promising class of drugs, since it is related to favorable cardiovascular outcomes. Thus, this class is a potent treatment candidate for cardiovascular illnesses and hopefully will soon be available for this goal if future trials continue to present such benefits.

Author contributions

Conception and design of the research: Sousa LS, Nascimento FA, Rocha J, Rocha-Parise M. Acquisition of data: Sousa LS, Nascimento FA. Analysis and interpretation of the data: Sousa LS, Nascimento FA. Statistical analysis: Nascimento FA. Writing of the manuscript: Sousa LS, Rocha J, Rocha-Parise M. Critical revision of the manuscript for intellectual content: Rocha J, Rocha-Parise 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 article does not contain any studies with human participants or animals performed by any of the authors.

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REVIEW ARTICLE

Effectiveness of Mindfulness Meditation Programs in the Promotion of Quality of Life in Patients with Heart Failure: A Systematic Review

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Abstract

Background: Despite optimal *medical treatment*, many heart failure (HF) patients continue to show a high prevalence of symptoms, which contributes to a high morbidity and poor health-related quality of life (HRQL). Mindfulness meditation may be effective in improving the quality of life in these patients.

Objective: A systematic review was conducted to evaluate if mindfulness meditation programs are effective in promoting and improving the quality of life in patients with heart failure.

Methods: The PubMed (MEDLINE), Cumulative Index of Nursing and Allied Health (CINAHL), LILACS, Cochrane Library, and Scopus databases were searched between October and November of 2019. Articles were selected if they evaluated mindfulness intervention, with an experimental or quasi-experimental design, in adults with heart failure and measured health-related quality of life.

Results: This systematic review identified 108 studies through database searches. After applying the inclusion and exclusion criteria, a total of three studies were considered qualified. These studies took place in the Netherlands, the USA, and Brazil, and occurred between 2005 and 2015. Sample sizes varied from 19 to 215, and the average range of participants within each study varied from 43.2 to 75.4 years. Compared to control programs, mindfulness-based meditation programs improved the quality of life in two studies ($p= 0.041$ and $p=0.03$).

Conclusion: Mindfulness-based meditation programs improved the quality of life in patients with HF. Therefore, there is limited data to strengthen this recommendation to this population, and future research is warranted in order to present consistency in the intervention protocols.

Keywords: Heart Failure; Awareness; Mindfulness; Knowledge; Meditation; Quality of life.

Introduction

Heart failure (HF) is a disabling illness with significant morbidity and mortality, affecting at least 26 million people worldwide, and is increasing in prevalence.[1]

In spite of optimal *medical treatment*, many patients continue to show a high prevalence of symptoms,[2-6] including dyspnea, fatigue, edema,[7] as well as psychosocial distress.[8-11] This burden of symptoms contributes to a high morbidity and poor health-related quality of life – HRQoL.[7,12,13] The HF patient's quality of life itself is associated with prognosis, hospitalizations, and mortality.[14,15]

Mindfulness is described as the ability to pay attention in a particular way: on purpose, at the present moment, and non-judgmentally.[16] Mindfulness-based intervention (MBI) includes meditative exercises, using focused breathing as a tool, and has been effective in reducing stress, anxiety, and depressive symptoms,[17,18] as well as in improving physical functioning[17,19,20] and decreasing cardiovascular sympathetic activity in randomized controlled trials- RCTs.[19, 20]

Over the past decade, many RCT's have presented evidence on the effectiveness of MBI in several chronic conditions, such as cancer, depression, chronic pain,

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and eating disorders.[21-24] However, few studies have specifically explored this kind of intervention in HF patients.

Therefore, the aim of this article is to provide information regarding an additional treatment option for patients with heart failure – mindfulness meditation programs – and to evaluate their effectiveness. A systematic review was conducted to answer the PICO[25] (Problem/Population, Intervention, Comparison, and Outcome) question: "How are mindfulness meditation programs effective in promoting and improving the quality of life in patients with heart failure?"

Methods

Search strategy and selected studies

The PubMed (MEDLINE), Cumulative Index of Nursing and Allied Health (CINAHL), LILACS, Cochrane Library, and Scopus databases were searched between October and November of 2019, using the Descriptors in Health Sciences (DeCS) and MeSH (Medical Subject Headings) terms.

The following controlled descriptors cited below were used for all databases equally, using the boolean "and" operators for search: *heart failure*, *mindfulness*, *meditation*, and *quality of life*. Due to the specific characteristics of each database, search strategies were adapted according to the purpose and inclusion criteria of this study.

This study's population included adults over 18 years of age, with heart failure, whether hospitalized or in outpatient follow-up, who evaluated mindfulness meditation programs that have been effective in patients' quality of life.

Study quality evaluation

Due to the need to evaluate only the interventions with better methodological rigor and effective results in the presented outcomes, this systematic review performed only quantitative content analysis of the following studies: those with an experimental or quasi-experimental design, such as studies without randomization with a single pre- and post-test; time series or control case; indexed in databases published in English, Spanish, or Portuguese, with a temporal cut between 2004 and 2019. The exclusion criteria were studies with no clear determination of methodology, theses and dissertations, and online publications that were impossible to access or print.

In order to reduce the risk of publication bias, full articles were made available for two evaluators to carry out an independent analysis. For this assessment, the Joana Briggs Institute Checklists[26,27] were used and those articles with a maximum of 3 negative items were deemed eligible.

Of three selected articles, two studies completed 11 items out of the 13 approved in the Randomized Controlled Trials (RCT) Checklist [26] and 1 article completed 8 items out of the 11 approved in the Cohort Study Checklist. [27]

Data extraction and Analysis

The titles and abstracts were evaluated separately by two independent evaluators. A database was constructed with the following information of each article found: year, journal / author, objectives, methods, interventions performed, sample size, evaluated outcomes, results, and conclusion, as well as the final evaluation of the inclusion or exclusion of justified studies, according to the criteria described above.

A descriptive analysis of the results found in the selected articles was performed, including study objectives, type of intervention, scenarios, sample characteristics, follow-up time, and outcomes.

Registration

This systematic review was registered on PROSPERO (International Prospective Register of Systematic Reviews) platform under the number CRD42020153597.

Results

Search results

This systematic review identified 108 studies through database searches. After applying the inclusion and exclusion criteria, a total of 3 studies were qualified for this review,[20,28,29] revealing a limited number of studies addressing QoL as an outcome in patients undergoing a mindfulnessbased intervention. The higher scores meant a better methodological quality and are represented in Table 1.

Table 1 – Summary of studies reviewed and Quality scores of reviewed studies. Potential range 0-13 for randomized controlled trials and 0-11 for cohort study

Author/ Year	Sample	N	Intervention	Dose	QoL Measures	Effect	Quality Score
Curiati[28] 2005	Elderly with HF classes I-II	19 Intervention =10	Group meditation, including mindfulness techniques	2 hours of learning technique class, plus daily audio guided meditation for 30 minutes twice per day for 12 weeks	Minnesota Living with Heart Failure Questionnaire	Significant improvement in the meditation group (p =0.047)	11 (13)
Sullivan[29] 2009	Adults with HF classes I-IV, FE ≤40%	208 Intervention =108	Mindfulness-based psychoeducational support group	2.25-hour group session, weekly for 8 weeks, plus daily audio guided meditation for 30 minutes	Kansas City Cardiomyopathy Questionnaire (KCCQ)	Significant difference over time in favor of the treatment (p< 0.033)	8 (11)
Younge[20] 2015	Adults with Heart Disease, including HF	324 Intervention =215	Structured standardized online mindfulness program	12-week structured standardized online program for self-directed training, practical assignments, and daily meditations	Visual Analogue Scale (0 -100)	No significant effect on Quality of Life	11 (13)

A Preferred Reporting Items for Systematic review and Meta-Analysis (P.R.I.S.M.A.) flow diagram outlining the research results is presented in Figure 1.

Study design and samples

All three of the analyzed studies used controlled groups. Two were randomized controlled trials and one was a cohort study, using a geographic control group (> 90 miles from the treatment center).[29] The studies took place in the Netherlands, the USA, and Brazil, between 2005 and 2015. Sample sizes varied from 19 to 215, and the average range of participants within each study varied from 43.2 to 75.4 years. In two studies, the subjects were exclusively heart failure patients, most of whom were of the NYHA class I and II. In the third study, the patients presented heart failure and other kinds of cardiomyopathy, including ischemic, valvular, and congenital.[20]

Quality of Life measures

The QoL was measured with different instruments, including the Minnesota Living with Heart Failure Questionnaire (MLHFQ), the Kansas City Cardiomyopathy Questionnaire (KCCQ), and the Visual Analogue Scale (VAS), which assessed the subjective, self-reported QoL, in which the patients described themselves in terms of overall "quality of life", ranging from 0 to 100, as represented in Table 1.

Intervention

The study intervention varied. Curiati et al used a meditation program including mindfulness exercises, such as conscious breathing, body scan, and simple self-compassion meditation, and included a relaxation-response technique.[28] Sullivan et al., developed a mindfulness psychoeducational support group,[29] while Younge et al., worked with a web-based mindfulness intervention. including meditations, self-reflection, and yoga.[20] Patients had to complete practical questions and assignments in order to be monitored in terms of adherence.

Two studies provided face-to-face meditation sessions ranging from 2 to 2.5 hours plus at least 30 minutes of audio for guided meditation during 8 to 12 weeks. One was an online program of 12 weeks designed to be self-directed.[20]

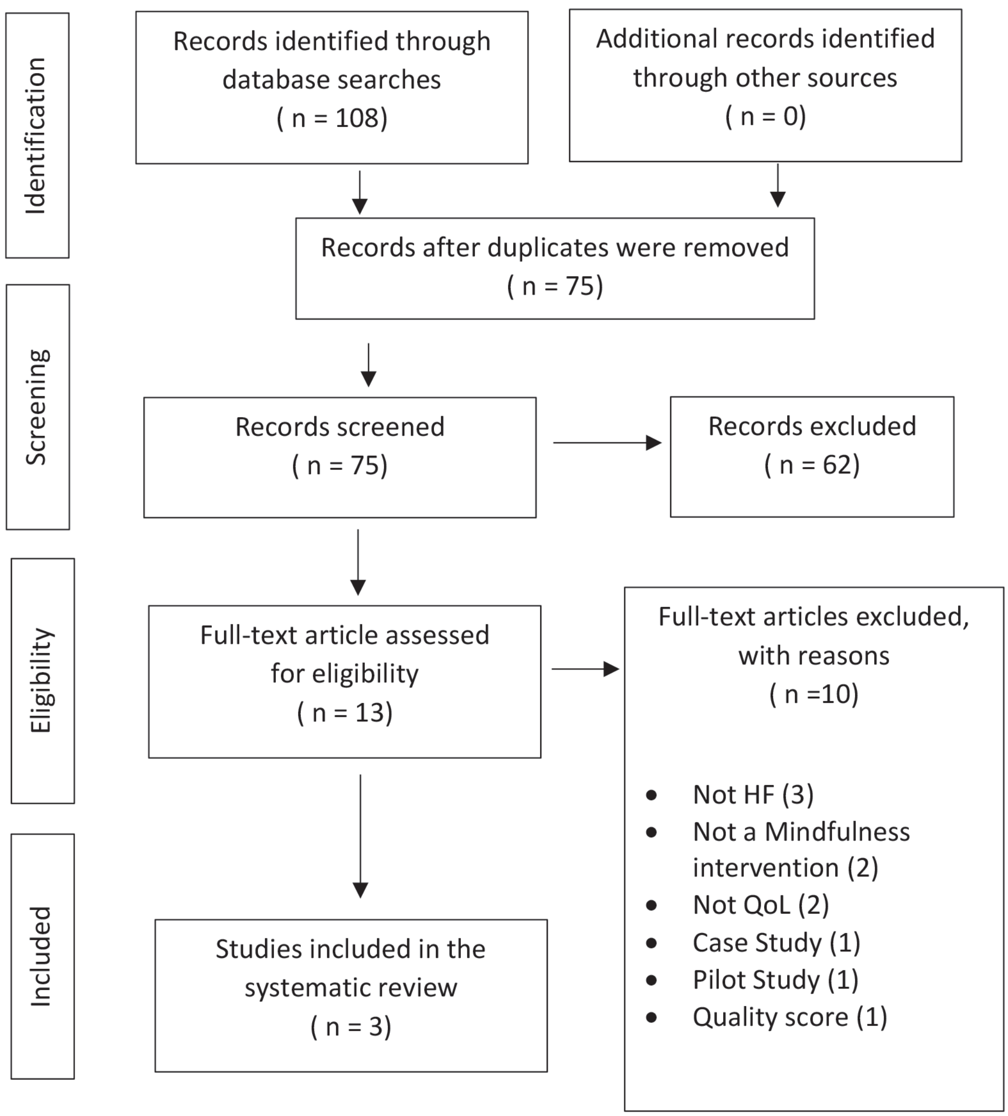

Figure 1 – Preferred Reporting Items for Systematic Review and Meta-Analysis flow diagram. HF indicates heart failure, QoL indicates Quality of life.

Treatment effects

The two face-to-face studies[28,29] showed significant improvement in QoL (p = 0.047 and p = 0.033), while the web-based study did not.[20] In addition to QoL, a wide range of outcomes were found, including exercise capacity, biomarkers, psychosocial, death and hospitalizations. This fact limited the comparison between studies.

Discussion

This systematic review evaluated three studies assessing the impact of mindfulness-based meditation programs on the QoL of patients with HF. Besides the relevant fact that quality of life is associated with prognosis, hospitalization, and mortality in HF patients,[14] previous studies have shown that these subjects prefer quality of life over longevity.[30]

Out of the three evaluated studies, only two showed a significant impact on QoL. The web-based mindfulness program[20] showed no improvement in QoL or in the other psychological outcomes, although it has presented small positive changes in physiological parameters (functional capacity and heart rate).

Previous studies using web-based mindfulness training was modestly effective in subjective outcomes.[31-33] The authors consider that the impact of the online training could be lower than that of personal in-group training. Nevertheless, online training has the potential to provide easy access and can reach a larger number of people.

The in-person interventions, on the other hand, presented positive trends towards HF patients' QoL, after the mindfulness-based intervention program (p = 0.047 and p =0.033)

In the Brazilian study, the total score of QoL improvement was even similar to those obtained with enalapril, suggesting that nonpharmacologic interventions may be as effective as medical treatment.[34]

The American study also showed a significant reduction in anxiety and depression, which may well have contributed to improvement in QoL.[29] Luskin et al., demonstrated that a psychosocial treatment applying stress management improved this population's quality of life.[35] In chronic HF, psychosocial copings are strong predictors of quality of life and symptoms regardless of the patient's physiological state.[36, 37]

A recent study conducted by Rechenberg et al., showed that total mindfulness (measured by the Five Facets of Mindfulness Questionnaire) was significantly associated with lower anxiety ($\beta = -0.491$, $P < .01$), which was in turn associated with greater total QoL ($\beta = 0.488$, $P < .01$). The author concluded that Mindfulness might be a way of improving this population's QoL.[38]

Limitations

The small number of studies evaluating the impact of mindfulness-based programs in the QoL of HF patients was a limitation in this systematic review.

The sample size of the studies also limited the recommendation of mindfulness-based intervention to improve the QoL in HF patients. The variation in the intervention protocols, including different techniques, length of the programs, daily dose of meditation, and type of interaction (in person or online) also limited the generalization of such interventions in this population.

Conclusion

According to the reviewed studies, mindfulness-based meditation programs can be useful to improve the QoL of patients with HF.

Coats suggested that this kind of intervention can play an important role in HF treatment programs,[39] Therefore, future studies are warranted so as to present consistency in the intervention's methodology in order to generalize the recommendation of this type of behavioral intervention for HF patients.

Author contributions

Conception and design of the research: Cavalcante VN. Acquisition of data: Cavalcante VN. Analysis and interpretation of the data: Tinoco JVMP, Figueiredo LS. Writing of the manuscript: Cavalcante VN. Critical revision of the manuscript for intellectual content: Mesquita ET, Cavalcanti ACD.

Potential Conflict of Interest

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

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Study Association

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Erratum

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In Original Article "Effectiveness of Mindfulness Meditation Programs in the Promotion of Quality of Life in Patients with Heart Failure: A Systematic Review", with DOI number: https://doi.org/10.36660/ijcs.20200135, published in the journal International Journal of Cardiovascular Sciences, 35(1):107-142, in page 107, correct the Keywords "Heart Failure awarence; Mindfulness; Knowledge; Meditation; Quality of life" to "Heart Failure; Awareness; Mindfulness; Knowledge; Meditation; Quality of life".

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REVIEW ARTICLE

Reperfusion Strategies in Acute Myocardial Infarction: State of the Art

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Abstract

ST elevation myocardial infarction (STEMI) is a highly prevalent condition worldwide. Reperfusion therapy is strongly associated with the prognosis of STEMI and must be performed with a high standard of quality and without delay. A systematic review of different reperfusion strategies for STEMI was conducted, including randomized controlled trials that included major cardiovascular events (MACE), and systematic reviews in the last 5 years through the PRISMA (*Preferred Reporting Items for Systematic Reviews and Meta-Analysis)* methodology. The research was done in the PubMed and Cochrane Central Register of Controlled Trials databases, in addition to a few manual searches. After the exclusion criteria were applied, 90 articles were selected for this review. Despite the reestablishment of IRA patency in PCI for STEMI, microvascular lesions occur in a significant proportion of these patients, which can compromise ventricular function and clinical course. Several therapeutic strategies – intracoronary administration of nicorandil, nitrates, melatonin, antioxidant drugs (quercetin, glutathione), anti-inflammatory substances (tocilizumab [an inhibitor of interleukin 6], inclacumab, P-selectin inhibitor), immunosuppressants (cyclosporine), erythropoietin and ischemic pre- and post-conditioning and stem cell therapy – have been tested to reduce reperfusion injury, ventricular remodeling and serious cardiovascular events, with heterogeneous results: These therapies need confirmation in larger studies to be implemented in clinical practice

Keywords

Acute Myocardial Infarction/therapy; Myocardial Reperfusion; Myocardial Stunning; Ventricular Remodeling; Morbidity and Mortality.

Prevalence

The worldwide prevalence of ischemic heart disease is approximately 111 million cases, with 7.3 million cases of fatal acute myocardial infarction (AMI) in 2015. The inadequate treatment of patients with AMI is associated with significant increases in morbidity and mortality.[1]

Objectives

The objective of this systematic review is to evaluate the evidence of different reperfusion therapies in ST-segment elevation AMI (STEMI), selecting mainly randomized controlled trials and systematic reviews that address major cardiovascular clinical outcomes.

Methods

The review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). We searched the PubMed database for the terms "acute myocardial infarction" and "reperfusion therapy", which yielded 9,885 results. After applying the following search filters – type of abstract: "text and full text"; type of article: "meta-analysis, review, systematic review and randomized clinical trial", and date of publication: "last 5 years", and language: "English" – 127 articles were obtained. In addition, research was conducted at the Cochrane Central Register of Controlled Trials using the terms "acute myocardial infarction" and "reperfusion therapy", in English, between 2018 and 2020, which revealed 64 clinical trials, already excluding duplicates. Of the 191

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articles, nine articles were selected manually and added to the review, as they were considered of high relevance to the topic. Of the 200 articles, 92 were removed after analysis of the abstracts and, after reading the full texts, 18 (12 in PubMed and 6 in the Cochrane database) of the 108 remaining were excluded for not addressing reperfusion, yielding a total of 90 references, which were included in this review.

Results

Revascularization Strategies

The invasive strategy is the treatment of choice for reperfusion of patients with high-risk non-ST elevation AMI (STEMI).[1,2] Delays in reperfusion therapy for patients with STEMI cause significant impairments in myocardial reperfusion.[3]

Patients with acute coronary syndrome (ACS), who had transient ST elevation, were analyzed before reperfusion, and no differences were found in the size of the infarction or in the rates of serious ischemic events.[4]

Hospital interventions for qualitative improvement in the care of patients with STEMI can improve myocardial reperfusion.[5] Difficulties in implementing reperfusion therapy include: delay in seeking care, absence of adequate pre-hospital emergency systems, absence of trained emergency services, inadequate hospital structure, absence of quality improvement and rehabilitation programs.[6]

Thrombolytics

Thrombolytics are indicated for patients with STEMI in the first 12 hours of symptom onset, in cases where percutaneous coronary intervention (PCI)-related delay would be 120 minutes or more. Thrombolytics can be administered in the first 30 minutes of first medical contact, with no contraindications. Streptokinase is associated with higher mortality rates and lower reperfusion rates as compared with tissue plasminogen activator (tPA) and its recombinant forms – alteplase, tenecteplase (TNK) and reteplase. Therefore, a fibrin-specific agent should be chosen, since, although the administration of TNK in a single bolus is equivalent to accelerated tPA, in terms of reducing mortality in 30 days, it is safer in reducing non-cerebral hemorrhages and preventing blood transfusions, with easier administration.[1,3]

Percutaneous Coronary Intervention (PCI) x Thrombolysis

In STEMI without previous fibrinolytic therapy, PCI is the best strategy for reperfusion of AMI when performed by experienced operators, ideally within the first 90 minutes of admission. Although thrombolysis allows early vascular reperfusion, with an average rate of infarct-related artery (IRA) patency of 50%, in PCI the rates are greater than 90%, with a reduction in the incidence of reinfarction.[7]

Pharmacoinvasive Therapy

When a delay to primary PCI is suspected, fibrinolytic therapy should be immediately followed by the transfer, between 2 hours and 24 hours, to a coronary intervention center, for coronary angiography and PCI of the IRA, a strategy called “pharmacoinvasive therapy”, or for rescue angioplasty if there are no signs of reperfusion.[1,2] Although a superiority of the pharmacoinvasive strategy over thrombolysis with Tenecteplase has been shown, no differences were found after 8 years regarding major cardiovascular events (MACE).[8] Compared with primary PCI, the pharmacoinvasive strategy showed no differences in the occurrence of MACE in 30 days.[9,10] The pharmacoinvasive strategy using streptokinase reduced the size of the infarction and MACE, compared to conventional thrombolysis.[11] The effectiveness of the pharmacoinvasive strategy does not depend on initial troponin levels,[12] and the radial access was considered safe and effective in the pharmacoinvasive strategy.[13]

The EARLY-MYO Study demonstrated that in patients with STEMI presenting less than 6 h after symptom onset and expected delay to PCI, the pharmacoinvasive strategy with half-dose of alteplase was not inferior to PCI in complete epicardial and myocardial reperfusion evaluated defined as thrombolysis in myocardial infarction (TIMI) grade 3, TIMI perfusion grade 3 and resolution of the ST segment ≥70% in 60 minutes.[14] In patients who admitted within 6 hours of STEMI and underwent PCI, intracoronary administration of low doses of alteplase had no effect on the degree of microvascular obstruction or on clinical outcomes.[15]

Electrocardiogram on Reperfusion

The reduction in QRS duration immediately after and 60 minutes after reperfusion was associated with its success, but the presence of QRS fragmentation had

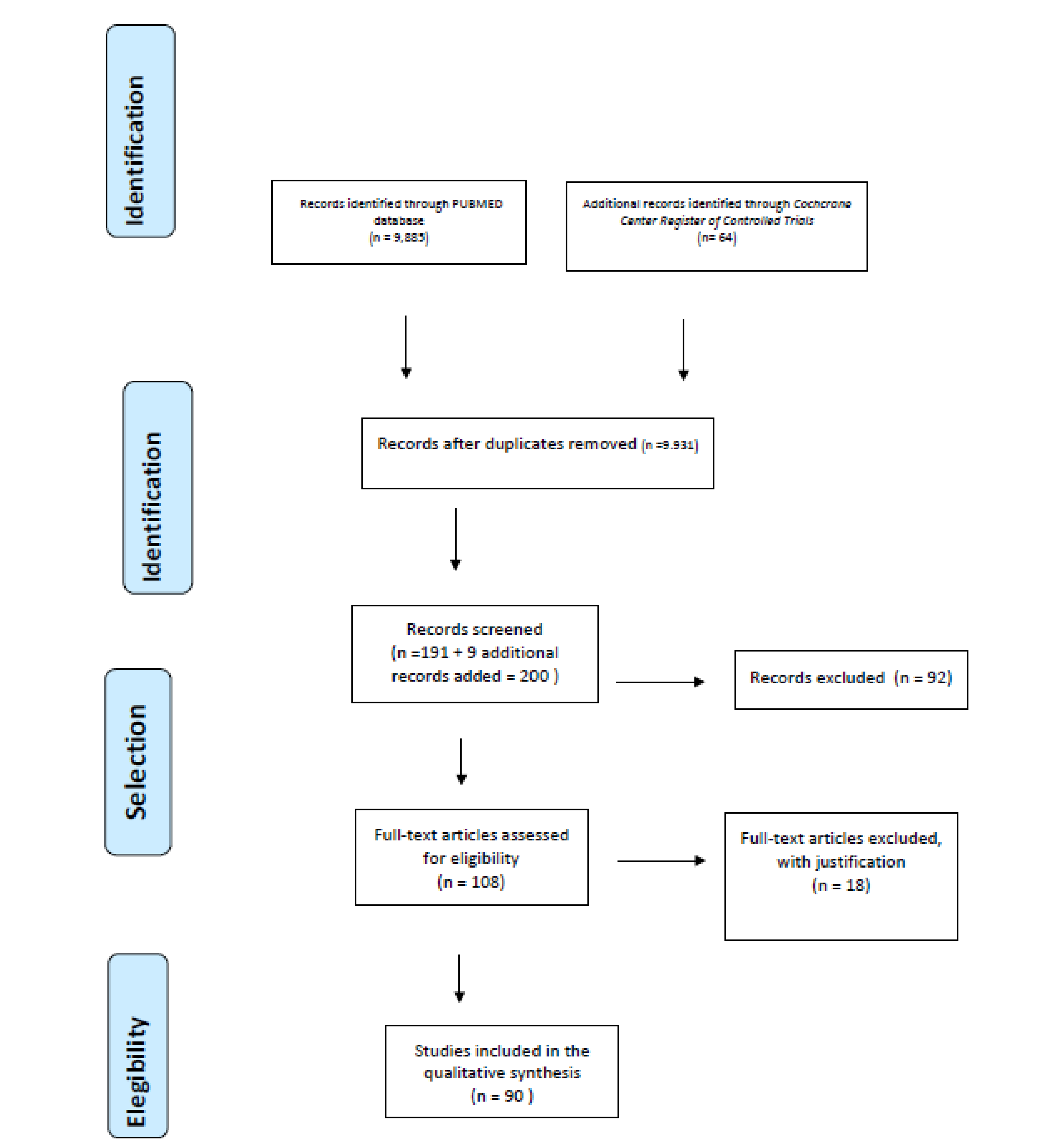

Figure 1 – Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram

an inverse correlation.[16] Incomplete resolution of ST-segment depression (reciprocal image of ST elevation) 90 minutes after PCI was correlated with larger infarctions and MACE.[17] The absence of ST resolution was poor prognostic factor after primary PCI, but complete resolution of the ST elevation was associated with an increased risk of ST elevation at the time of discharge.[18] The complete resolution (≥ 70%) of the ST elevation, 60 minutes after PCI, was associated with greater reduction of MACE; however, the presence of diabetes mellitus and delay in reaching the hospital were deleterious to reperfusion.[19] Distortion of the terminal portion of the

QRS was associated with cardiac dysfunction.[20] The presence of Q wave on the initial ECG was associated with mortality, regardless of the time interval to peripheral PCI.[21] Early HR elevation ≥ 100 bpm was an independent prognostic marker.[22] Reperfusion arrhythmias, defined by accelerated idioventricular rhythm and ventricular extrasystoles with long periods of coupling, are well tolerated and may be related to the infarction size and reperfusion injury.[23] The peak of plasma troponin T occurs after 12 hours of type 1 AMI and after 6 hours of AMI successfully reperfused, with a second peak after 24 hours.[24]

Coronary flow (TIMI flow grades 0 or 1) before PCI is an independent risk factor for microcirculatory obstruction and size of AMI.[25]

Thrombectomy in PCI

Embolization of thrombus fragments in PCI can lead to microcirculatory obstruction, with impacts on myocardial remodeling and prognosis.[26] In patients with a high thrombotic load in the IRA undergoing PCI, there was an improvement in coronary flow after the intervention with aspiration catheter, but without differences in the VCTs .[26] There were no differences regarding the effectiveness of coronary reperfusion between manual and mechanical methods[27]. The procedure should be reserved for patients with high thrombotic burden, and its routine use is not recommended, since it did not reduce MACE and increased the risk of stroke.[1]

Stents at Primary PCI

There was a reduction in the target vessel revascularization rate, in favor of drug-eluting stents in relation to conventional stents in PCI, in addition to MACE reduction,[27] leading to the recommendation of eluted stent implantation as a preferred strategy.[28] The option of late stent implantation in PCI, with the objective of reducing microvascular obstruction, had no effect in reducing MACE, but increased the rate of revascularization of the target vessel.[29]

Antiplatelet Therapy

The loading dose of acetyl salicylic acid (162 mg to 325 mg) should be administered shortly after the diagnosis of AMI, followed by low maintenance doses (75-100 mg) indefinitely, as they are equally effective as larger doses for MACE reduction, but causing less bleeding.[1]

$P2Y_{12}$ Inhibitors

Clopidogrel is an irreversible inhibitor of the adenosine diphosphate (ADP) platelet receptor P2Y12, being recommended in acute coronary syndromes (ACSs), regardless of the performance of primary PCI. The addition of clopidogrel reduces the risk of CVMS in patients with SCASST , treated or not with PCI.[30,31] In patients with STEMI treated with thrombolysis, clopidogrel also significantly reduces MACE, without increasing hemorrhagic outcomes.[32,33] A loading dose of clopidogrel (300 mg) is recommended in patients <75 years of age, after fibrinolysis.[34]

Clopidogrel requires conversion of hepatic cytochromes to the active form. The activity of the C19 allele has great variation in the population, increasing the risks of thrombotic events. Clopidogrel has a relatively small antiplatelet potency and a slow onset of action, which is a disadvantage, especially in patients treated with PCI, who have considerable thrombotic burden. The onset of action of ticagrelor and prasugrel is, respectively, 30 minutes and 60 minutes.[7] Prasugrel was shown to be superior to clopidogrel in patients with ACS undergoing PCI, with reductions in the rates of death from cardiovascular causes, infarction, stroke, and a 52% relative reduction for stent thrombosis. However, rates of major bleeding and life-threating bleeding were greater in patients receiving prasugrel compared with clopidrogrel. There were no benefits in patients with cerebrovascular disease, individuals older than 75 years or those with a body weight less than 60Kg.[35] Ticagrelor, a direct-acting and reversible P2Y12 inhibitor, with a shorter duration of action, was superior to clopidogrel in ACS, both in invasive and conservative strategies, with a decrease in MACE and mortality (by 22%) rates, but higher rate of major bleeding not related to CABG. Although not significantly, there was a higher incidence of sinus pauses and dyspnea in patients taking ticagrelor than in those taking clopidogrel.[36] Another study obtained favorable results for ticagrelor administered before PCI.[37]

Morphine prolongs gastric emptying and delays the onset of action of prasugrel, ticagrelor and clopidogrel.[7] In the absence of contraindications, ticagrelor and prasugrel are recommended, preferably, in ACSs.[1,2,38]

There were no differences in reperfusion rates before PCI when ticagrelor was initiated in the ambulance (prehospital treatment) than in the catheterization laboratory; but prehospital treatment reduced rates of stent thrombosis and MACE.[39] Diabetics had lower rates of reperfusion and a higher incidence of MACE, with a large increase in stent thrombosis.[40] The comparative analysis of the administration of clopidogrel, prasugrel or ticagrelor in the emergency room in patients treated with PCI, showed a superiority of prasugrel and ticagrelor over clopidogrel, regarding reperfusion rates pre- and post-PCI.[41] In STEMI, the administration of intravenous agents that are extremely fast and potent, such as cangrelor, may be advantageous for patients who have not received P2Y12, patients with hemorrhagic complications or for whom surgery is indicated.[7,38] In patients with STEMI, when compared with ticagrelor, cangrelor produced greater inhibition of P2Y12 receptors, but there were no differences regarding coronary microvascular function and infarct size.[42,43] The TREAT study compared clopidogrel with ticagrelor after fibrinolytic therapy, with no differences in the incidence of VCT or severe bleeding after one year, which suggests the use of ticagrelor 24 hours after STEMI, initially treated with chemical thrombolysis.[44]

GPIIbIIa (IGP) Inhibitors

PGIs (abcxicimab, tirofiban and eptifibatide) are potent and fast inhibitors. There is no evidence of the benefits of the administration of PGI with contemporary dual oral antiplatelet therapy in patients with ACS; however, as it can increase the bleeding risk, PGIs are recommended in situations where there is a significant thrombotic burden in PCI.[7,37] The inability to reperfuse a myocardial region, despite the opening of the IRA, is an independent prognostic factor, whose mechanisms are microembolization, reperfusion injury, endothelial dysfunction, myocardial edema, microcirculation vasospasm, and neutrophil aggregates.[45] Selective injection of tirofiban through a catheter showed improvement in reperfusion in patients with STEMI and high thrombotic load, but without differences in VCT.[46] The intracoronary (ic) injection of tirofiban was superior to intravenous administration regarding reperfusion parameters, left ventricular ejection fraction (LVEF), but with no differences in VCT or hemorrhagic outcomes.[47] Another study compared intralesional versus intracoronary administrations of PGI in patients with ACS and demonstrated a superiority of the first strategy.[45] The COCKTAIL II trial[48] also showed advantages of the intralesional administration of abciximab over intracoronary injection, in terms of better reperfusion.[48]

Statins and Reperfusion

A meta-analysis of treatment with high-dose statins before PCI revealed improvement in reperfusion and a 47% reduction in MACE with atorvastatin in ACS patients, who had not received statins previously. No benefits were found with rosuvastatin.[49] A study showed that the administration of 80 mg of atorvastatin before PCI reduced the incidence of no-reflow and MACE, and increased survival.[50]

Reperfusion Injury

Despite the restoration of the IRA patency in PPCI, microvascular lesions occur in a large proportion of these patients, which can compromise ventricular function and clinical outcome. The REDUCE-MVI trial showed no differences in microcirculatory resistance rates in patients undergoing PCI and treated with ticagrelor or prasugrel, resulting in similar infarction sizes.[51]

The ic administration of adenosine or sodium nitroprusside in patients with STEMI did not reduce the size of the infarction or the degree of microvascular obstruction.[52] The ic infusion of insulin-like growth factor after primary PCI improved ventricular remodeling.[53] Several trials have shown that both intravenous and ic administration of nicorandil in primary PCI improved reperfusion, left ventricular function and MACE[54-57] rates.

A meta-analysis of experimental studies demonstrated benefit with treatment with nitric oxide in reducing reperfusion injury and size of AMI.[58] The ic administration of nitrate reduced systemic inflammatory activity.[59] There was a reduction in the incidence of ventricular tachycardia with the use of ic nitrite in patients undergoing PCI.[60]

Liraglutide administered 30 minutes before PCI reduced the no-reflow rates and decreased the concentration of C-reactive protein, however, there was no difference in the incidence of ECVM.[61]

Intravenous or ic administration of melatonin was not associated with a reduction in the size of AMI and increased left ventricular remodeling;[62] however, when administration was early, it reduced the size of the infarction.[63]

The ic injection of morphine did not reduce the size of the AMI in patients undergoing PCI PCI[64]. There was no reduction in the size of AMI in patients treated with a mineralocorticoid receptor antagonist before reperfusion, but there was an improvement in left ventricular remodeling.[65]

There was no reduction in MACE with the administration of intravenous erythropoietin after reperfusion.[66] In addition, the ic injection of erythropoietin, before reperfusion, did not reduce the size of the AMI or the left ventricular remodeling.[67]

In patients undergoing PCI, intravenous injection of cyclosporine did not reduce MACE or left ventricular remodeling.[68] Other trials have also failed to demonstrate a favorable impact of intravenous cyclosporine administered prior to PCI.[69-71]

The intravenous infusion Quercetin (antioxidant) during reperfusion of ARI improved the clinical course of the disease, accelerating the onset of reperfusion[72].

An experimental study showed attenuation of reperfusion myocardial injury with artesunate administration (an antimalarial substance).[73]

The infusion of Glutathione (antioxidant), before PCI, showed a reduction in the production of hydrogen peroxide and an increase in nitric oxide, which may improve cardiomyocyte survival.[74]

It was found that the monoclonal antibody against P-Selectin (Inclacumab), administered before PCI, reduced the size of the infarction. The ic administration of anisodamine improved reperfusion and reduced MACE.[75]

Also, interleukin-6 (IL-6) can participate in reperfusion injury. The IL-6 receptor antagonist, tocilizumab, was tested in STEMI, before coronary angiography, with a reduction in the systemic inflammatory response and troponin release.[76]

Stem Cells

The administration of granulocyte-colony stimulating factor (G-CSF) did not influence the size of the AMI, left ventricular function or ECV in patients with AMI that underwent PCI.[77]

The ic infusion of autologous bone marrow stem cells (ABMC) 24 hours after PCI did not increase LVEF, but increased the rate of myocardial salvage.[78] The ic injection of primitive stromal cells after reperfusion increased the viability in the AMI territory and LVEF.[79] The TECAM trial [80] analyzed the ic injection of ABMC or subcutaneous G-CSF in the STEMI and showed no differences in left ventricular function.

A meta-analysis on ABMC to treat AMI showed that the ic infusion of ABMC led to an increase in LVEF and reduction of ventricular remodeling in up to 12 months, and was considered a safe and effective treatment in patients with AMI.[81]

In addition, a laser therapy applied to the tibia bone before and 24 and 72 hours after PCI reduced the troponin-T levels, with few adverse effects, but no differences were found in LVEF.[82]

Ischemic Postconditioning

Ischemic postconditioning was assessed for recanalization of the IRA, through four repetitions of balloon occlusion, with no reductions in mortality and hospitalization rates for heart failure.[83] Another study on remote ischemic postconditioning in the upper limb, after PCI, demonstrated a reduction in the plasma release of CK-MB and an increase in LVEF and glomerular filtration rate.[84] Another study on ischemic postconditioning showed improvement in reperfusion and size of AMI.[85] Remote ischemic preconditioning uses brief cycles of cuff insufflation and deflation to protect the myocardium from reperfusion injury. A meta-analysis showed favorable results for this strategy, including higher myocardial salvage rate, reduced infarct size and reduced MACE.[86] The increase in plasma concentrations of the soluble tumor necrosis factor (TNF)-related apoptosis-inducing ligand (sTRAIL) after reperfusion was related to a reduction in the size of AMI and improvement in LVEF.[87] There were reductions in the size of AMI and reperfusion injury with ischemic postconditioning, in patients admitted for less than four hours.[88] A trial on remote ischemic preconditioning did not show changes in the rates of death and heart failure at 12 months of follow-up.[89]

Multivessel Coronary Artery Disease

The AIDA STEMI trial analyzed patients with STEMI and multivessel coronary artery disease and found a higher prevalence of diabetes and advanced age when compared to patients with single-vessel disease. There were no differences in the reperfusion rates between the two groups, but those with multivessel disease had higher MACE rates over a year.[90]

Conclusions

An effective reperfusion of STEMI, in a timely manner, defines the prognosis. Patients should be selected for primary angioplasty or thrombolysis, followed by PCI in 24 hours (pharmacoinvasive therapy). Fibrin-specific agents are superior to streptokinase. Anticoagulant and dual antiplatelet therapy have evolved substantially in recent years, with a reduction in severe ischemic outcomes, such as death, reinfarction and stroke. The time factor and the experience of the interventionists are paramount in decision making for primary PCI. PCI has advanced in recent years, notably with the development of state-of-the-art drug-eluting stents. Even with an adequate opening of the IRA in PCI, there may be a failure in coronary microcirculatory reperfusion. Several clinical trials have tested different substances and different strategies, with inconclusive results regarding the improvement of tissue reperfusion, preservation of ventricular function and reduction of serious ischemic outcomes. Larger randomized controlled studies will be needed to test these therapeutic possibilities.

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Conception and design of the research: Rangel FO. Acquisition of data: Rangel FO. Analysis and interpretation of the data: Rangel FO. Writing of the manuscript: Rangel FO. Critical revision of the manuscript for intellectual content: Rangel FO.

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VIEWPOINT

Physical Activity, Obesity, and COVID-19: What can we Expect from his Relationship?

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The COVID-19 pandemic is a public health problem, whose first cases were found in Wuhan, China, in December, 2019, and which is currently present around the world.[1] COVID-19 is caused by the new coronavirus (SARS-CoV-2), which shows a high potential of contamination. Its transmission occurs through droplets during unprotected proximity with an infected person and contact with contaminated environmental surfaces, which are the main systemic and respiratory symptoms.[1,2]

To date, there is no pharmacological treatment that has proven to be effective, or a vaccine for the prevention or treatment of COVID-19. Thus, a non-pharmacological strategy of public health, which has shown effectiveness in the exponential control of the disease, is social distancing, which encompasses the isolation of cases, quarantine of contacts, and the voluntary practice of not going to crowed places.[3] These measures have demonstrated that they can reduce mortality rates during the pandemic, and they have helped in governmental decision-making.[3, 4]

Although the lethality rate of COVID-19 varies among countries, mortality most commonly occurs among the elderly or people with comorbidities, such as cardiovascular diseases, diabetes, cancer, and chronic pulmonary diseases.[5,6] In a recent study in the city of Wuhan, China, obesity was not reported as a pre-existing comorbidity, which favored the increase in the general lethality rate in patients with COVID-19.[5]

However, a study conducted in New York pointed out that approximately 41.7% of all hospitalized patients were obese, it being among the three most common comorbidities of the infected people.[7] This divergency of data among the countries can be justified by the demographic characteristics and prevalence of comorbidities of each population.[8] The Center for Disease Control and Prevention (CDC) considers that people with severe obesity (Body Mass Index (BMI) ≥40 Kg/m²), can present greater risks for the worsening of COVID-19.[9]

Some common connections between SARS-CoV-2 and obesity are respiratory problems. It is well-known that there is a positive correlation among asthma, acute lung injury, obstructive sleep apnea syndrome, acute respiratory distress syndrome, and being overweight.[10] Obesity is associated with a decrease in functional capacity, as well as with a compliance of the respiratory system and the expiratory reserve volume.[11]

In France, data from patients that made use of invasive mechanical ventilation have shown that individuals with severe obesity (BMI ≥ 35Kg/m²) presented impaired respiratory patterns in relation to the patients with BMI ≤ 25Kg/m².[12] In this scenerio, obesity represents an independent risk factor for the respiratory hypoventilation syndrome, a potential aggravating factor for complications related to respiratory insufficiency in patients who are admitted to intensive care units.[13]

Beyond respiratory complications, another liaison with COVID-19 is inflammation. Obesity causes an increase of secretion of pro-inflammatory cytokines in the adipose tissue, which can worsen if infected by COVID-19.[10,11,14] High serum levels of interleukin-6 (IL-6) have been reported in patients who passed away

Keywords

COVID-19; Coronavirus; Exercise; Obesity.

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due to COVID-19.[6] In addition to IL-6, the receptors of interleukin-2 and the tumor necrosis factor-alpha can also take part in endothelial dysfunction.[15]

Another important point to be highlighted is the relationship between obesity with cardiovascular diseases/events, such as hypertension, stokes, heart failure, and coronary artery disease, as well as diabetes. However, what has most called attention in this scenario is thrombosis, since obesity can increase the risk of developing this type of blood clot, and, together with COVID-19, it can further aggravate the situation through intravascular coagulation and an increase in the rates of venous thromboembolism.[10] Moreover, a high incidence of cardiovascular symptoms can be observed due to the systemic inflammatory response and the changes caused by the immune system during the course of COVID-19.[16]

Thus, the reduction of body weight, despite not reducing the risk of infection, seems to be an important preventive and protective measure against serious cases of SARS-CoV-2, as it favors a decrease in inflammatory processes caused by obesity. Despite the need for more consistent evidence of the protective effect of the regular practice of physical activity and healthy diets in a population contaminated by SARS-CoV-2,[17] these types of behaviors are acknowledged in the literature as effective for the control of obesity in the general population.[18] It has also been speculated that individuals with desirable levels of cardiorespiratory aptitude tend to show a higher protection against the symptoms caused by the SARS-CoV-2 infection, mainly due to an enhanced immunological resistance.[19]

Another issue that requires close attention is the possibility of an increase in sedentary behaviors, such as sitting in front of a TV or spending time with electronic gadgets, as these seem to be associated with various chronic non-communicable diseases and cardiovascular mortality.[20]

Thus, with the needed recommendations of social distancing, it is feared that the population may reduce the practice of physical activity and increase sedentary behaviors and body weight, even further worsening the scenario of a global endemic of obesity, which could, in the mid-term, at least while there is not a more efficient treatment or the discovery of a definitive vaccine, increase the risk of more complications because of the disease and cause an overload in the health system. Moreover, it is still true that the recommendation of global scientific and health entities is to avoid agglomerations in situations with a high possibility of the transmission of the virus, such as gyms and sports centers, in municipalities and regions that need interventions to flatten the contagion curve.

In this sense, the stimulus for the practice of regular outdoor, or in-home, physical activities for all ages must be better widespread and conveyed, respecting the advice from health authorities and governmental decrees regarding the continuance of social distancing. This is an important message of public health in order to maintain physical and mental health and to cope with this moment of generalized anxiety and the feeling of hopelessness.

There are many alternatives for the practice of physical activities – ones that do not require the use of equipment and that can be done in a family and household environment; however, people need to be encouraged and properly advised. Such activities include aerobic activities, such as dancing, stationary racing, and walking up and down stairs, as well as activities of muscular strength/resistance, which make use of different areas of the body, including yoga, Pilates, and training with body weight (squatting, burpees, sit-ups, ground support, etc.).

Many physical education professionals are already using messages in mobile phones, apps, e-mails, or video calls to prescribe and monitor exercises individually.[21] There are also free initiatives for the guidance of physical activities on the internet, many of which are connected to universities or non-governmental organizations, according to guidelines set forth by the World Health Organization (WHO),[22] for example, which could be implemented by governments, with mass educational campaigns, freely broadening this message to the entire population.

It is is also important to highlight the need for the maintenance of the practice of physical activity for the elderly, as they tend to have a higher number of chronic, primarily cardiovascular, diseases, and they are more vulnerable to complications caused by SARS-CoV-2. Nevertheless, if symptoms related to COVID-19 appear, the practice of physical activity should be interrupted, regardless of the age group.[21,23] The Pre-Exercise Screening Questionnaire (PESQ), considering the presence of signs and symptoms, was proposed to the current context as an additional tool for initial screening for a safer practice of telepresence exercise.[21]

Therefore, it seems that the regular practice of physical activities can aid in the control of obesity, beyond favoring an enhanced immunological response for the current moment of the COVID-19 pandemic. Public health policies should provide assistance not only for individuals, but also for the public in general. They should help people either to continue or become physically active, encouraging people's autonomy and independence, taking into consideration the differences between groups and iniquities in health. These policies are emerging, are of utmost importance and, will become an ever-increasingly important part of the "new normal".

Finally, this moment of the COVID-19 pandemic may be an opportunity for reflection on our behaviors and individual and collective care related to health. In general, periods of social distancing are not experienced over the long term; however, the decision-making concerning our choices can and should be undertaken throughout our entire life.

Author contributions

Conception and design of the research: Queiroz CO, Conceição AF, Aristides PRS, Alves, LS, Almeida RT. Acquisition of data: Queiroz CO, Conceição AF, Almeida RT. Writing of the manuscript: Queiroz CO, Conceição AF, Almeida RT Critical revision of the manuscript for intellectual content: Queiroz CO, Conceição AF, Aristides PRS, Alves, LS, Almeida RT.

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VIEWPOINT

Smartphone-Based Screening for Cardiovascular Diseases: A Trend?

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Abstract

Cardiovascular diseases are the leading cause of death in the world. People living in vulnerable and poor places such as slums, rural areas and remote locations have difficulty in accessing medical care and diagnostic tests. In addition, given the COVID-19 pandemic, we are witnessing an increase in the use of telemedicine and non-invasive tools for monitoring vital signs. These questions motivate us to write this point of view and to describe some of the main innovations used for non-invasive screening of heart diseases. Smartphones are widely used by the population and are perfect tools for screening cardiovascular diseases. They are equipped with camera, flashlight, microphone, processor, and internet connection, which allow optical, electrical, and acoustic analysis of cardiovascular phenomena. Thus, when using signal processing and artificial intelligence approaches, smartphones may have predictive power for cardiovascular diseases. Here we present different smartphone approaches to analyze signals obtained from various methods including photoplethysmography, phonocardiograph, and electrocardiography to estimate heart rate, blood pressure, oxygen saturation (SpO_2), heart murmurs and electrical conduction. Our objective is to present innovations in non-invasive diagnostics using the smartphone and to reflect on these trending approaches. These could help to improve health access and the screening of cardiovascular diseases for millions of people, particularly those living in needy areas.

Keywords

Smartphone/trends; Artificial Intelligence/trends, Computers System/trends; Cardiovascular Diseases/diagnóstico; COVID-19/diagnóstico; Smartphone/trends; Diagnostic; Imaging/methods; Telemedicine.

Introduction

Cardiovascular diseases (CVD) are the leading cause of death in the world. According to the World Health Organization (WHO), in 2016, it was estimated that 17.9 million people died from conditions related to CVD, representing 31% of all global deaths. Over 75% of deaths from CVD occur in low- and middle-income countries. About 6.2 million premature deaths (under the age of 70) from non-communicable diseases are caused by CVD, which include coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis, and pulmonary embolism. Heart attacks and strokes are the most serious acute events that lead to death.[1]

Increasing researches on technology and communication have been conducted in medicine. Advances in mobile health (mHealth) have helped health professionals in the prevention and early detection of diseases, remote diagnosis, and self-care management,[2] and significantly reduced the amount of money spent on diagnosing and treating heart diseases.

Telemedicine combines information technology, telecommunication, and data analysis in consultations (teleconsultation), diagnostics (telediagnosis), and robotic surgery (telesurgery). Also, cardiological telemedicine or telecardiology have been expanded, and a wide range of cardiological investigations have been performed remotely, accelerating the flow of information.

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Electrocardiograms (ECGs), X-ray, ultrasound, and other test results are transmitted for evaluation by specialists (teleconsultants), who provide quick and accurate diagnostics in primary health care (PHC).[3] The Federal Council of Medicine (CFM) in Brazil indicated the use of digital resources in health and possible introduction of telemedicine during the pandemic, through the letter dated 19th March 2021.[4]

Furthermore, considering the current context of the new coronavirus pandemic (SARS-Cov-2) which causes COVID-19 and the recommendations for social isolation, the use of telemedicine has grown exponentially,[5] which includes the developement of non-invasive tools for health monitoring of patients with COVID-19.[6]

Countries with a continental territorial dimension, such as Brazil, have great difficulties in providing a comprehensive and decisive service to the entire population. Therefore, telemedicine and mHealth have emerged as opportunities to improve health access for thousands of people,[3] including underprivileged areas such as slums, rural areas, and remote locations.

In 2018, the number of mobile phones exceeded 5 billion, indicating that almost 70% of the world population had access to a smartphone. A projection pointed out by the Getúlio Vargas Foundation indicated that in 2018, there were more smartphones than inhabitants in Brazil, with about 220 million devices.[7]

Smartphones are equipped with cameras, flashlights, microphones, processors, internet connection, and function like a computer. Mobile applications have advanced quickly, allowing access to different information about a person's health, from diseases such as anemias,[8] diabetes,[9] to cardiovascular conditions.[10]

Measuring vital signs with smartphone

Vital signs are the first clinical parameters assessed in a health facility. Studies have shown that smartphone applications that use the photoplethysmography (PPG) technique are capable of monitoring heart rate with a quality similar to commercial devices. Smartphone-based photoplethysmography (spPPG), a technique similar to pulse oximetry, is based on obtaining a video of patient's fingertip. The flashlight of the smartphone lights up the patient's fingertip, and the camera detects the reflected color. As the heart contracts, the blood reaches the fingertip, and a video of the fingertip allows recording of the blood perfusion and analysis the color/signal intensity per unit of time (photoplethysmographic waves).[9] When processing the signals obtained by a smartphone or a computer, it is possible to analyze the quantity and morphological characteristics of these pulse waves and to estimate heart rate, oxygen saturation, and blood pressure.[9,11] Figure 1 shows how PPG technology works.

Schoettker et al.,[11] compared blood pressure measurements from a smartphone application that analyzes optical PPG signals (OptiBP) with blood pressure measurements by the conventional auscultatory method. After testing 50 patients, it was demonstrated that the OptiBP application is capable of accurately measuring blood pressure in an outpatient setting, making it an important tool for detecting hypertension.

Ridder et al.,[12] published a meta-analysis that included 14 studies that compared heart rate measured by applications and heart rate measured by equipment, and concluded that there was no significant difference between the results obtained by the smartphone and by commercial equipment, indicating a reliable use in adults. However, further studies are needed for children. Mitchell et al.,[13] analyzed 111 individuals who used Azumio®'s Instant Heart Rate apps on Android® and iOS® compared to an FT7 Polar® heart rate monitor and found an acceptable test-retest reliability at rest and post-exercise using the smartphone.

Nemcova et al.,[10] developed an Android™ application that used smartphone accessories, such as camera, flashlight, and microphone to predict heart rate, percentage of oxygen saturation (SpO_2%), and blood pressure. Thirteen different smartphone models were used, and 65 signals from 22 individuals were obtained. Photoplethysmography was used to estimate heart rate and SpO2%. lood pressure was estimated using pulse transit time values. These were calculated by PPG and phonocardiogram (PCG), with cardiac sounds recorded by the smartphone placed on the chest, with a built-in microphone area pressed perpendicularly against to the cardiac auscultation point (Figure 2A). The App proved to be an alternative to estimate heart rate, SpO_2, and blood pressure, indicating their relevance in mobile point of care Apps.

Phonocardiogram with smartphone

Cardiopathies such as heart valve diseases are often manifested by murmurs and sounds that can be heard during auscultation.[14] Recently, a smartphone and a microphone were used to record sounds and heart murmurs to generate PCGs, which are graphs plotted with the variations of sounds over time.[15]

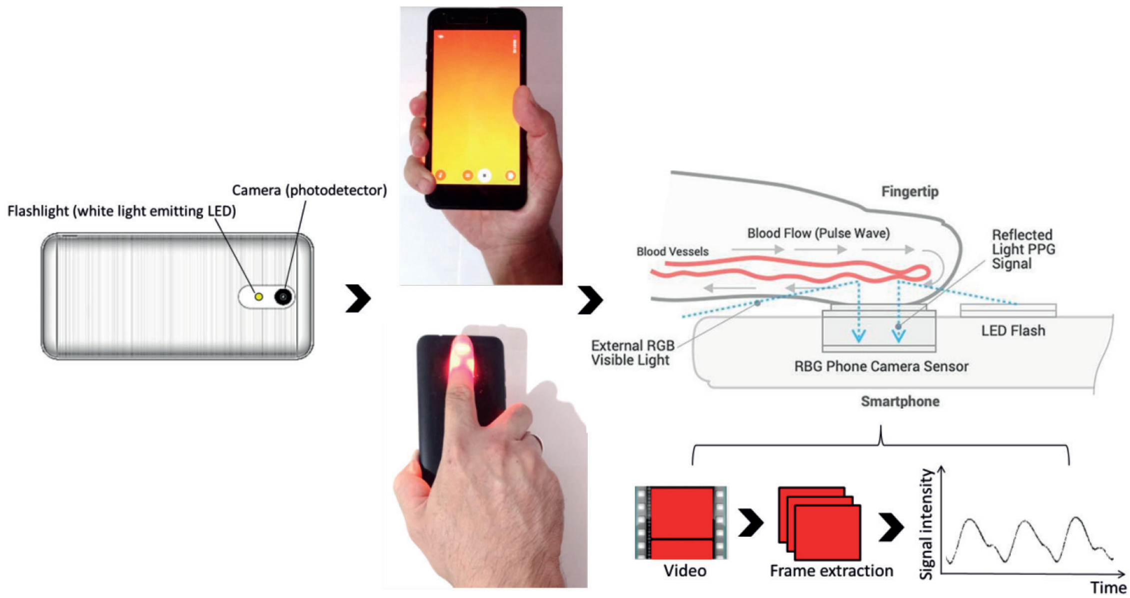

Figure 1 – A schematic detail of the smartphone-based photoplestimography technique. The flashlight functions as a light emitter, and the camera, as a photodetector. The light from the flashlight lights up the blood capillaries of the finger and the camera captures the reflected signal. Then, the frames are extracted from the videos and the signal is processed. Reproduced from Mazzu-Nascimento et al.,[8] and Schoettker et al.,[11] with permission from Creative Commons Attribution 4.0 International License.

It is possible to record cardiac sounds using stethoscopes attached to microphones or only microphones placed at the cardiac auscultation point to send the sounds to the smartphone for recording and processing the data. Thoms et al.,[15] were able to plot a PCG using the smartphone and a microphone through sound vibrations captured by the microphone. Researchers demonstrated that it is possible to determine heart rate and arrhythmias, but emphasized that background noises, breathing sounds, and noises produced by microphone motion can interfere with the quality of sound acquisition.

Kang et al.,[16] developed a smartphone android app (CPstethoscope) to perform cardiac auscultation using a smartphone and a built-in microphone to identify heart murmurs and physiological sounds. In 46 participants, three different smartphone models were used to capture the cardiac sounds recorded when the smartphone was placed at cardiac auscultation points on patient's chest (Figure 2A). Using a machine learning model, convolutional neural networks (CNNs) were used to process and classify sounds. Because the model only used the smartphone's built-in microphone, 16 sounds could not be interpreted due to capture failures. Of the 30 interpretable sounds, the classification accuracy was around 90%, showing the viability of the app for cardiac auscultation.

Mamorita et al.,[17] developed a smartphone application capable of hearing and recording sounds and heart murmurs in real-time using a smartphone and an external microphone attached to a stethoscope. A simulator was used to generate the reference sounds (normal and pathological) and compare them with the sounds recorded by the smartphone. The results showed that the smartphone/microphone set obtained sound waves similar to the simulator, serving as an important tool to identify sounds and murmurs of the heart in real-time. Figure 2B shows the profiles of cardiac pathological sounds captured by the microphone.

Electrocardiogram with smartphone

The use of smartphones to perform an ECG can increase the accessibility to medical exams in even the most remote locations and a reduction of expenses when compared to the conventional exam.[18]

In the light of the pandemic caused by COVID-19, the Food and Drug Administration (FDA) authorized the use of the KardiaMobile-6L mobile device, produced by Alivecor, to detect atrial fibrillation. Giudicessi et al.,[19] pointed out

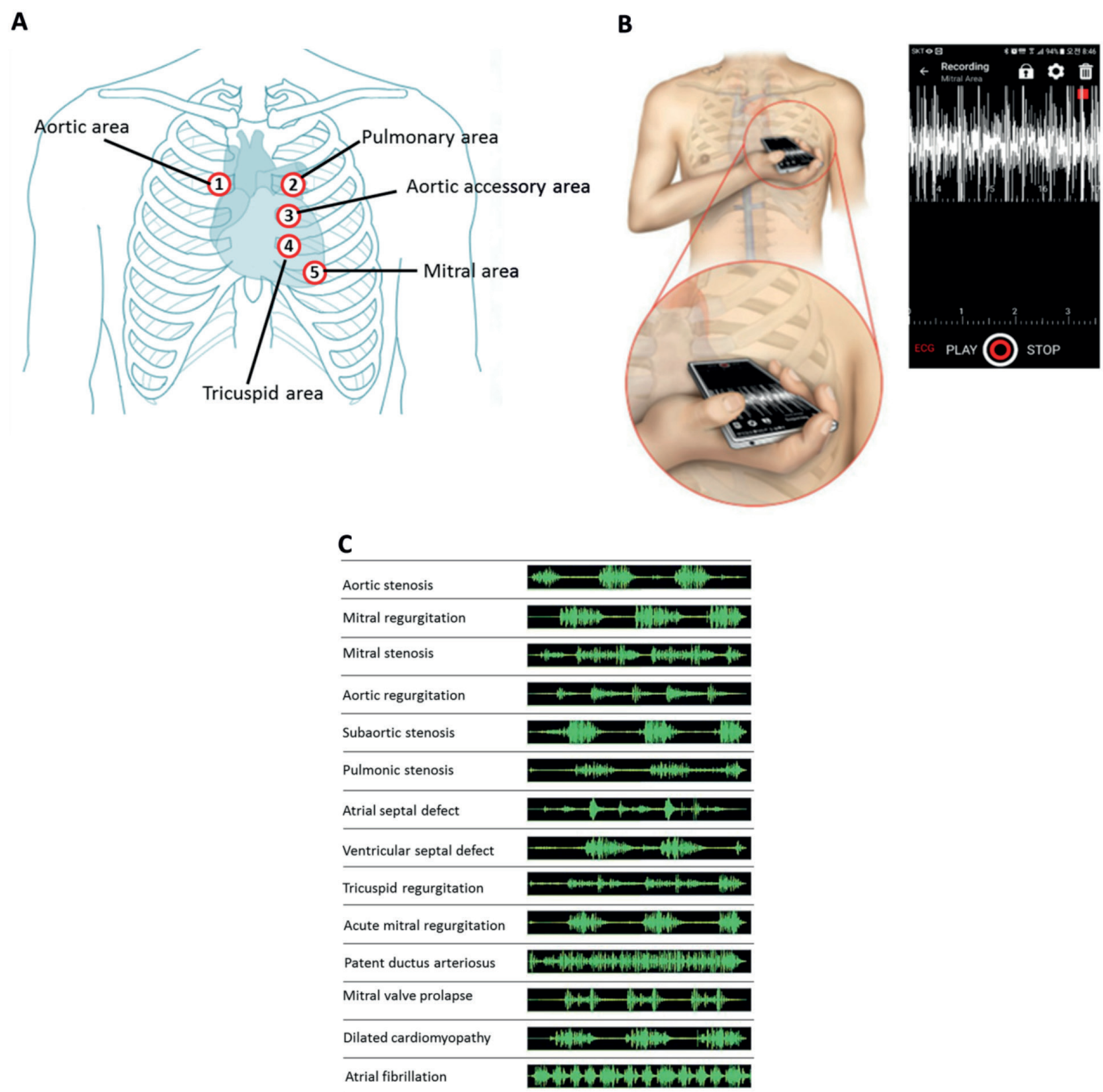

Figure 2 – Capture of cardiac sounds using a microphone and smartphone. A) Auscultation points. B) Use of the smartphone's built-in microphone over the cardiac auscultation points. Reproduced from Kang et al.[16] with permission from Creative Commons Attribution 4.0 International License. C) Profiles of sound characteristics of cardiac pathologies captured by the external microphone. Reproduced in part from Mamorita et al[17] with permission from Karger Publishers.

the importance of using this model to remotely assess the cardiac condition of isolated patients diagnosed with COVID-19 to reduce the risk of contamination due to the lower exposure of health professionals. Also, the device does not require trained technicians to perform the exam. In this portable ECG device, the patient places his fingers on the device and in less than a minute, the ECG is obtained on the smartphone screen (Figure 3A).

Recently, in Canada, in a pilot study carried out in PHC, KardiaMobile devices were distributed to 184 doctors over a period of three months to investigate atrial fibrillation in 7,585 individuals. Atrial fibrillation was detected in 471 patients, showing an acceptable performance of the device in screening, and its potential as a clinical alternative in medical care in the future.[20]

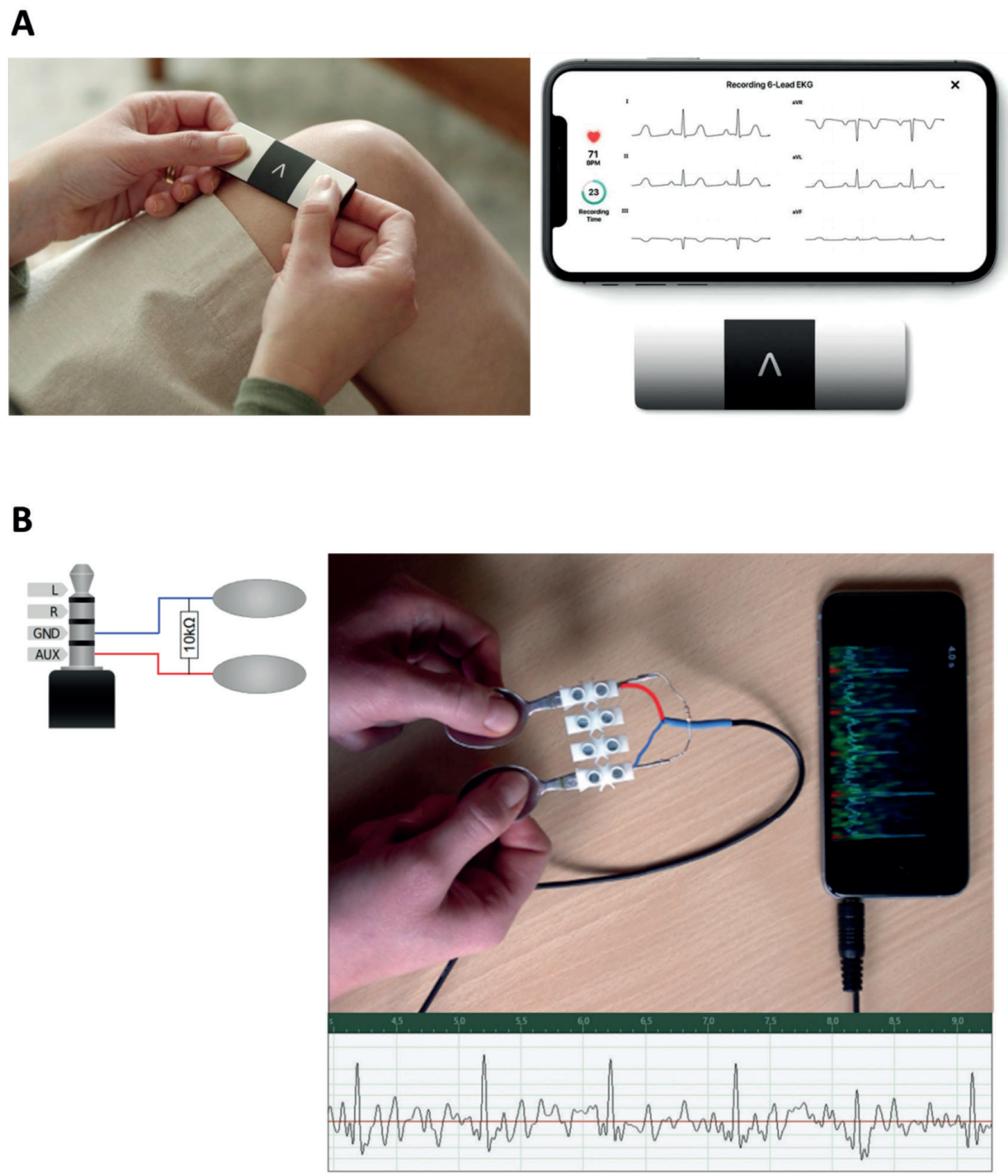

Figure 3 – Electrocardiograms obtained using a smartphone. A) KardiaMobile-6L commercial model used for remote monitoring of patients with COVID-19. Image reproduced with permission from AliveCor. B) Electronic scheme and electrocardiographic pattern generated by the low-cost sensor for electrocardiogram with the smartphone. Reproduced from Thoms et al.,[22] with permission from the American Association of Physics Teachers.

It is also possible to build an ECG device in a simple and low-cost way using electrodes, capacitors, and a smartphone, and a tutorial is available for this.[21] As the cardiac impulse spreads through the heart, the electrical current also spreads from the heart to the surrounding tissues, reaching the body's surface. Therefore, by attaching two electrodes on the skin surface on opposite sides of the heart, it is possible to capture the electrical potentials generated by the dipole field,[22] similar to what happens with the Alivecor Kardia Mobile mobile device. Thoms el al.,[22] put this device into practice by using a cable and the earphone socket, two stainless steel plates functioning as electrodes making contact with the body, plus a 10 kΩ resistor connected in parallel with the input to reduce the polarization voltage. This circuit was tested on iPhone 6s and Samsung Galaxy S8, and it was possible to obtain the ECG at an experimental level (Figure 3B).

Is it time to use artificial intelligence?

Artificial intelligence (AI) is incorporated in software and functions like the human brain to make intelligent decisions, identify patterns, objects, and sounds,[23] to encompass constant learning based on the most varied data sources through the use of algorithms, robotics, and artificial neural networks.[24] Machine learning is part of the artificial intelligence approach inspired by human learning through examples and errors. A machine can recognize patterns and, at the end of the process, give a predictive answer to a complex question. One set of data is used to train the algorithms and another set to perform the tests to verify the model's accuracy.[24,25]

In cardiology, machine learning has been used in electrocardiography and echocardiography for automatic pattern recognition and classification of abnormal rhythms, interpretation of images, in nuclear cardiology to predict myocardial revascularization, among other approaches.[26]

Strategies to capture signals (image and sounds) from a smartphone's source have advanced rapidly, and several applications are capable of performing these tasks. It is noted that the biggest challenges in signal processing are eliminating noise, and improving prediction accuracy.[27] Hence, it is necessary to explore different approaches to AI. Some of the techniques involving smartphones described above are already benefiting from AI.

Deep learning is a type of Machine Learning that learns through a taxonomy of functions distributed in layers, which allow meaningful learning of complex tasks. Different approaches using deep learning are being applied to filter out the noise and improve predictive power. Long Short-Term Memory (LSTM) networks employ a strategy based on forgetting long-term learning and have been very suitable for classifying, processing, and predicting time series.[28] This approach has shown promising results in analyzing characteristics of ECG waves, which are temporal waves.[29,30]

A Brazilian study used more than two million ECG exams from 811 municipalities in the state of Minas Gerais using the Minas Gerais Telehealth Network (TNMG) for the automatic diagnosis of the 12-lead ECG using a deep neural network. It was demonstrated that Deep Neural Networks (DNNs) can accurately recognize anomalies such as bundle branch block, left bundle branch block, sinus bradycardia, atrial fibrillation, and sinus tachycardia more efficiently than medical doctors and residents. This approach shows that the use of DNN for ECG interpretation can increase the quality of the analysis and increase the population's access to diagnosis.[31]

Botina-Monsalve et al.,[32] used LSTM with a set of public data to filter PPG waves, to improve signal quality and increase the accuracy of heart rate measurements. Also, Liang et al.,[33] used a pre-trained CNN (GoogLeNet) to improve the classification and assessment of hypertension using PPG.

Recently, many studies have used two datasets with cardiac sounds to apply different processing techniques and classifications of cardiac sounds, the PhysioNet / CinC (2016) and the PASCAL (2011).[34] The Short-time Fourier Transform (STFT), Wavelet transform, and Mel Frequency Cepstral Coefficients (MFCC) are widely used for the processing of cardiac sounds. The reason for processing a raw cardiac sound is to decompose a temporal signal (cardiac sounds over a period of time) into frequencies, to filter the sound and extract characteristics before classification. For classification, different machine learning approaches such as the Support Vector Machine (SVM) and the CNNs are being used for sound recognition and heart murmurs.[35] Pre-trained CNN also serves as an option for classifying heart sounds. These networks are first trained with a dataset, then refinement and adjustments are applied to the layers of this pre-trained network. In addition, another dataset is used to train and perform the classifications. This strategy is very useful because deep-learning approaches need big data. Khan et al.,[36] used this approach by varying the use of the PhysioNet and PASCAL datasets and achieved an accuracy of 98.29% for classifying heart sounds.

Deep-learning has been recognized as a powerful approach that seems capable of providing the necessary accuracy to smartphones for screening cardiovascular diseases. The different architectures allow noise filtering, signal amplification, and increased predictive power. Considering the advances in mobile health, in the future, a multiparameter application can be created combining the analysis of different cardiovascular parameters to increase access to screening tests in underprivileged populations, such as people living in slums and rural areas with difficult access to health. A smartphone can hence analyze different signals, including PPG, PCG, and ECG to provide parameters such as heart rate, blood pressure, and SpO_2, in addition to analyzing heart murmurs and electrical conduction of the heart. This app can be used directly in the population by trained personnel. People with urgent health needs can be referred to a hospital, and people with less serious health needs can be referred to PHC services. After the specialist care, patients can return to primary care facilities for health monitoring and treatment. Figure 4 illustrates this process.

A question that arises is: What is the effective way to handle big data in healthcare? The answer is by using cloud technology, since different algorithms can be implemented in the storage and processing of big data. Cloud technology in health has been used in the COVID-19 pandemic[37] and emerged as a possibility that could be implemented in health systems such as the Brazilian Unified Health System (SUS).

Considering the advances in the use of AI, it is important to consider the ethical aspects regarding the use of data, which can generate doubts regarding the responsibilities of the doctor and about the software.[26] Nevertheless, technological tools are available to help but not replace clinical practice.

In Europe, on May 25, 2018, the new General Data Protection Regulation (GDPR) came into force, and in Brazil, there is the General Personal Data Protection Law (LGPD - Law No. 13.709 / 2018), which regulates the processing of personal data.[38] With the action of AI and access to data for incorporation of these technologies, it is important to consider the security of this information. Authors have been suggesting improvements in data protection systems, especially in systems such as the Unified Health System (SUS) with the use of personal data stores (PDS), which would be owned and controlled by the user, who would hold an user identifier composed of an

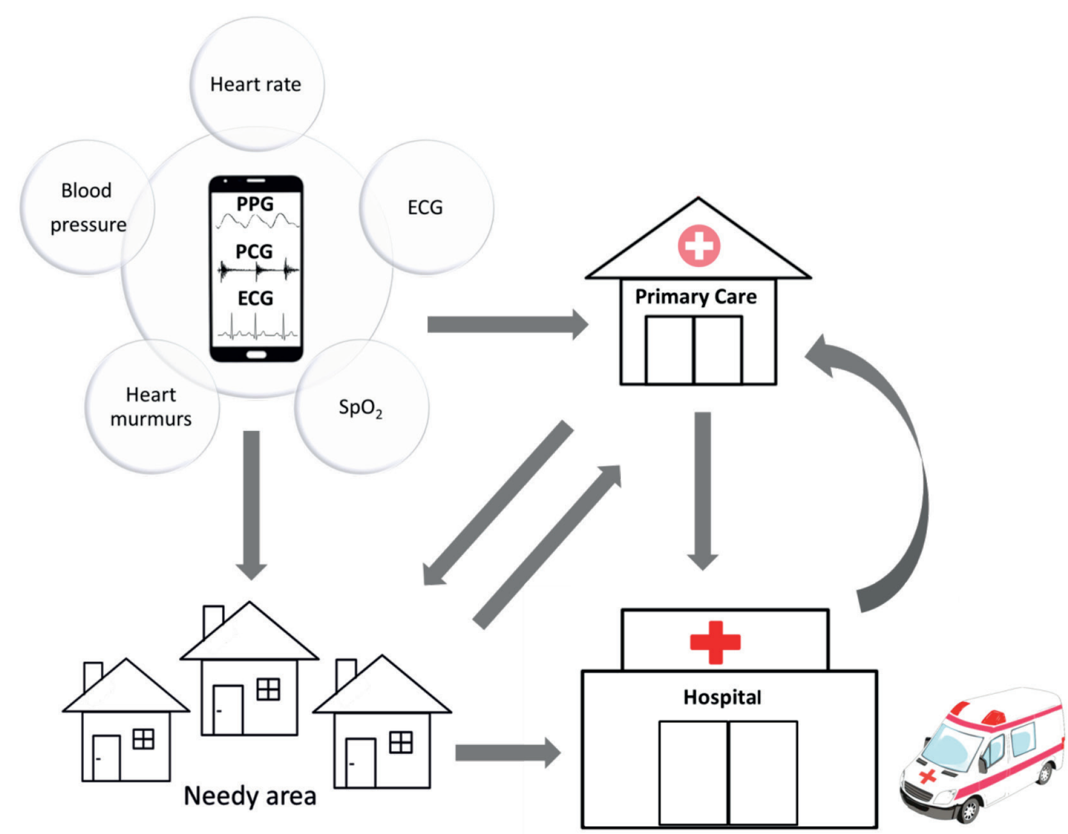

Figure 4 – Measurement of different cardiovascular parameters using a smartphone and flow of screening and care for a population in an underprivileged area.

alphanumeric code to access exams. Despite the massive data access necessary for using AI, this does not seem to overshadow its incorporation in the health field.[39]

Final considerations

Given the COVID-19 pandemic scenario and the growing demand for telemedicine and telecardiology solutions, it is essential to invest in health technology. Note the great potential of using smartphones in cardiology. The heart is a pump capable of working with three physical phenomena: optical, electrical, and acoustic. The techniques described here work exactly on the measurement of signals from these phenomena – cardiac frequency, blood pressure, and SpO_2 (optical field), PCG (acoustic field), and ECG (electrical field). The use of smartphones for screening cardiovascular diseases is promising, however, advances in this area are necessary, including noise elimination, signal amplification, and improvement of predictive accuracy. The use of deep learning significantly improves the power of smartphones to analyze these parameters and appears as a fundamental technique to allow the use of smartphone in clinical screening on eliminating noise a large scale. The creation of applications or a multiparameter application proves to be very useful to increase access to people's health, especially in needy populations. We hope that in the near future the use of deep learning to improve mobile tools and development of multiparameter apps to enhance technology achievement will intensify.

Author contributions

Conception and design of the research: Mazzu-Nascimento T and Evangelista DN. Analysis and interpretation of the data: Mazzu-Nascimento T, Evangelista DN, Abubakar O. Writing of the manuscript: Mazzu-Nascimento T, Evangelista DN, Abubakar O, Roscani MG, Aguilar RS, Chachá SGF, da Rosa PR, Silva DF. Critical revision of the manuscript for intellectual content: Mazzu-Nascimento T, Evangelista DN, Abubakar O, Roscani MG, Aguilar RS, Chachá SGF, da Rosa PR, Silva DF.

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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CASE REPORT

Isolated Left Ventricular Apical Hypoplasia without Lamin A/C Gene Mutation

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Abstract

Isolated left ventricular apical hypoplasia is a rare cardiomyopathy, with a broad range of clinical presentations. Since this entity was already described in association with osteomuscular diseases, mutation in the Lamin A/C gene has been regarded as a possible cause of this disease. This study describes the case of an asymptomatic teenager with isolated left ventricular apical hypoplasia and arthrogriposis but with no mutations in the entire Lamin A/C gene.

Introduction

Isolated left ventricular apical hypoplasia is a very rare anomaly with a broad range of clinical presentations. Mutation in the Lamin A/C gene has been regarded as a possible cause of this heart disease. The present study describes the case of an adolescent with isolated left ventricular apical hypoplasia and arthrogryposis without mutation in the Lamin A/C gene and conducts a review of the literature on this cardiomyopathy.

Case presentation

An asymptomatic 13-year-old boy was diagnosed with a mild systolic murmur during a routine evaluation. He also presented arthrogryposis multiplex congenita with mild spine deviation, as well as scapular and wrist deformities. He had been previously submitted to three right foot procedures due to clubfoot. ECG showed sinus bradycardia (HR = 50 bpm) with no conduction disturbances or left ventricular hypertrophy. Although our patient presented sinus bradycardia, he did perform well in a cardiopulmonary test. A transthoracic echocardiogram identified a mild left ventricular systolic dysfunction and an abnormal papillary muscle resembling a parachute mitral valve with no obstruction to left ventricular inflow. The patient was then started on enalapril.

One year later, a new routine echocardiogram identified a spherical left ventricle with an ejection fraction of 51%, with no signals of diastolic dysfunction, parachute mitral valve without dysfunction, and banana-shaped right ventricle (Figure 1A). Therefore, a cardiac MRI was performed.

The cardiac MRI identified an isolated left ventricular apical hypoplasia. It demonstrated the diagnostic aspects of the disease: spherical left ventricle configuration, fatty material at its apex, right ventricle elongation wrapping the deficient left ventricle apex, and both mitral papillary muscles originating in the flattened anterior apex (Figure 1B); however, it failed to confirm the presence of a parachute mitral valve. At his last medical visit, after a five-year follow-up or six years after initial diagnosis, the patient was asymptomatic and had sinus rhythm (Figure 2). However, a 24-hour Holter showed one episode of atrial tachycardia and two episodes of non-sustained ventricular tachycardia. The ejection fraction remained about 54% without diastolic dysfunction.

Because the patient presented arthrogryposis and cardiomyopathy, it was believed that this could be due to a laminopathy phenotype. Therefore, Sanger sequencing was performed for all 12 Lamin A/C gene exons in the proband and his parents, but no mutations were detected.

Keywords

Isolated Left Ventricular/abnormalities; Cardiomyopathies/ physiopathology; Lamin Type A/C/genetics.

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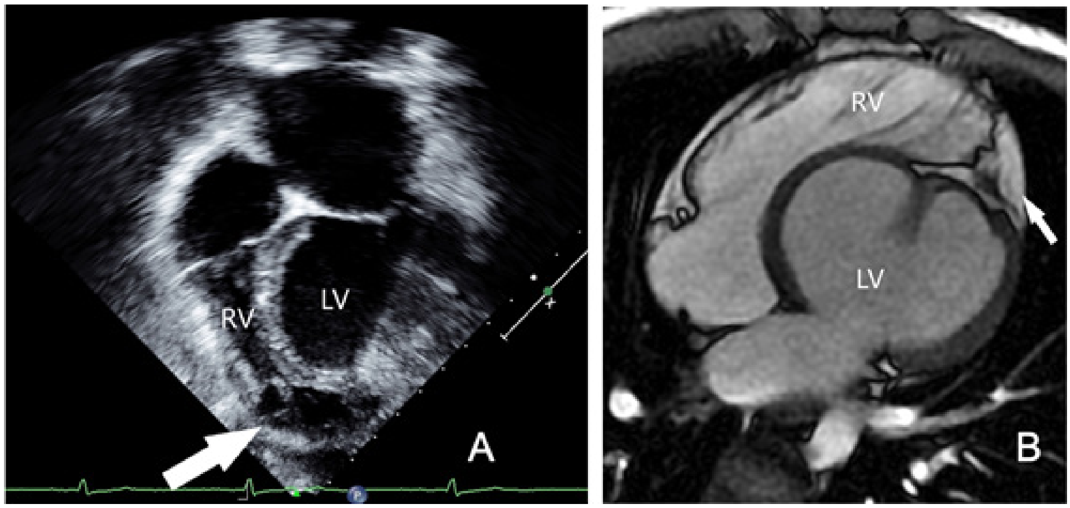

Figure 1 – A-Echocardiogram (four-chamber view) showing the right ventricle (RV) (arrow) wrapping the left ventricle (LV). B-Cardiac MRI (four-chamber view) showing spherical LV configuration, fatty material at LV apex (arrow), RV elongation wrapping the deficient LV apex.

Discussion

Isolated left ventricular apical hypoplasia is a very rare disease. There have been no more than 50 reports since its first description in 2004.[1] Diagnosis age ranges from three months to 66 years.[2]

In most patients, including our case, the condition is discovered incidentally. Because isolated left ventricular apical hypoplasia is very rare, initial echocardiographic diagnosis may appear as a dilated cardiomyopathy.[1] A wrapping right ventricle, a bulging ventricular septum toward the right ventricle, and an abnormal papillary muscle aroused the suspicion of this diagnosis and showed the need for a cardiac MRI.

There is no report in the literature of a single pattern regarding the ECG of patients with isolated left ventricular apical hypoplasia: the ECG may present right or left deviation. Poor R progression across the chest leads and left bundle block have also been described. In addition, non-sustained ventricular tachycardia and atrial tachycardia have been reported in these patients,[3] as was also detected in our patient during a recent 24-hour Holter.

Clinical evolution may also vary from asymptomatic or mild clinical impairment to fatal arrhythmia. Therefore, the patient should be followed up to monitor the emergence of heart failure and arrhythmias.

To date, no clear cause for this disease has been established. The apical trabecular component, which is most universally present in normal and in malformed and incomplete ventricles, and which most readily differentiates right from left ventricles from a morphological standpoin,t is notably lacking in this disease. In most congenital left ventricle heart diseases, the apical component exists as an incomplete ventricle, even when the left ventricle sometimes lacks both the inlet and outlet components.[4]

We are not sure if this disease is part of some kind of genetic syndrome, but our patient also has arthrogryposis, as described by others.[5] This association of cardiopathy and muscular dystrophy led us to hypothesize that this entity may be related to the Lamin A/C gene, which underlies the so-called laminopathies. One study has described a specific mutation in the Lamin A/C gene (p.Arg644Cys) associated with this cardiopathy.[6] Mutations may be present in up to 40% of cases previously classified as idiopathic dilated cardiomyopathy.[7] In this picture, geneticists and cardiologists have been working together and establishing more accurate diagnoses.

The Lamin A/C gene encodes Lamin A and Lamin C. Mutations in this gene may lead to cell and tissue fragility, mainly in tissues submitted to mechanical stress, like heart and muscle.[8] A previous case report has described an association of arthrogryposis with this cardiomyopathy,[5] with a mutation in the Lamin A/C gene (p.Arg644Cys), which is considered to be the potential genetic cause.[6] This mutation is found not only in patients

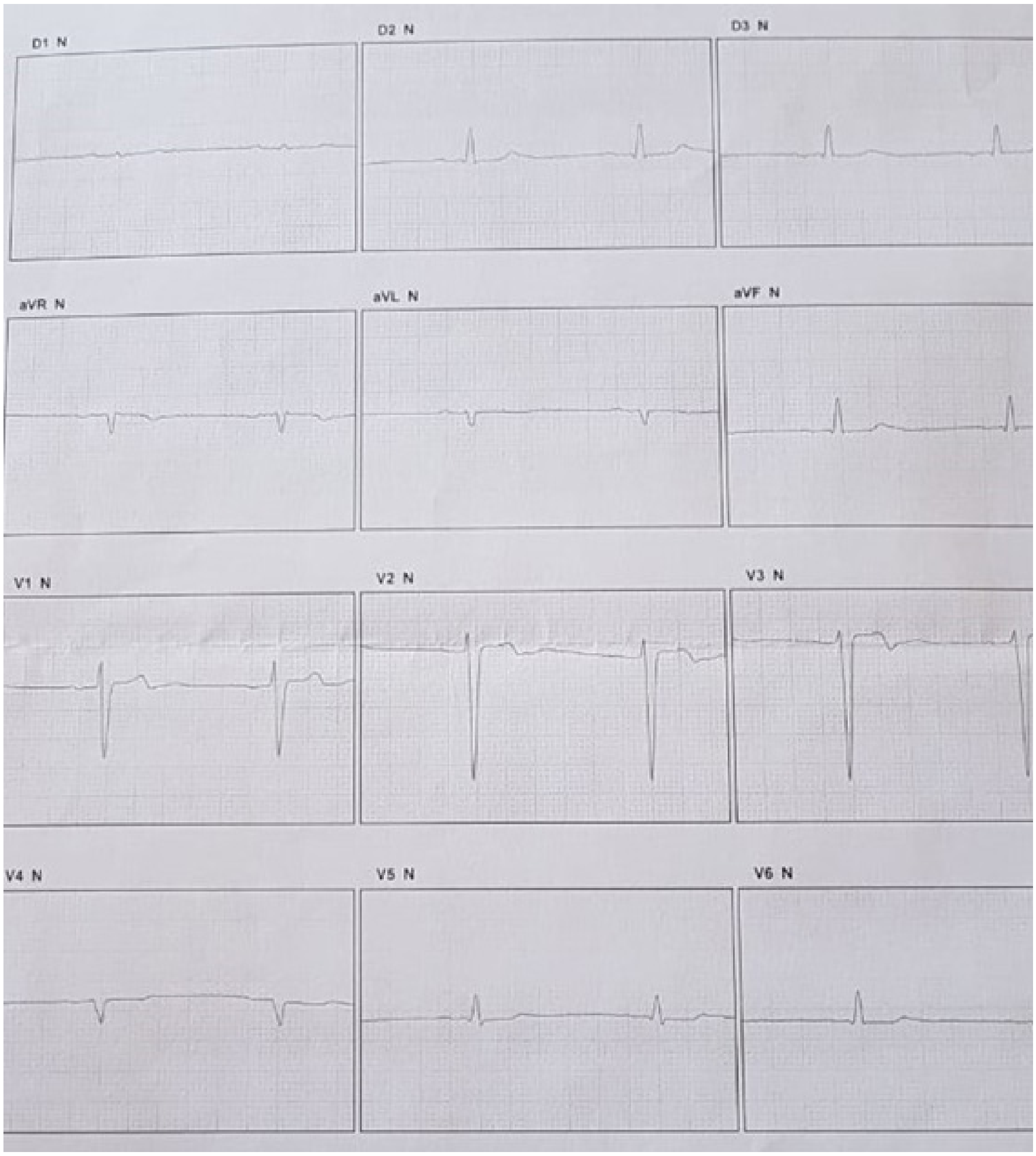

Figure 2 – 12-Lead Electrocardiogram showing sinusal bradycardia

with cardiomyopathy, but also in patients with muscular and osteoarticular diseases[9].

In the present case, no mutation in the Lamin A/C gene could be found; it is not surprising that, much like with most cardiomyopathies, more than one gene mutation may well be involved in causing this phenotype.

Conclusion

Isolated left ventricular apical hypoplasia is a very rare disease, with multiple clinical and electrocardiographic presentations. Close surveillance regarding heart failure and arrhythmias seems desirable. Although echocardiography may diagnose this entity, cardiac MRI is an invaluable tool in this diagnosis. Lamin A/C gene mutations alone may not account for this presentation.

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Author contributions

Conception and design of the research: Manso PH, Jurca MC, Trad HS. Acquisition of data: Manso PH, Suazo VK, Jurca MC, Trad HS. Analysis and interpretation of the data: Manso PH, Suazo VK, Jurca MC. Writing of the manuscript: Manso PH, Amaral FTV, Trad HS. Critical revision of the manuscript for intellectual content: Manso PH, Amaral FTV.

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

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Hospital das Clínicas* FMRP-USP under the protocol number 05001218600005440. 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

Pulmonary Embolism in Patients with Covid-19 in Direct Oral Anticoagulant

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Introduction

The global pandemic caused by the new coronavirus (COVID-19) has been promoting major challenges and unprecedented clinical decisions in the medical scenario. Currently, according to the World Health Organization, the disease affects over 185 countries, with over 12 million people infected and nearly 500 thousand deaths.[1]

Among the most serious manifestations of the syndrome, the high prevalence of thromboembolic events, up to 31% of the patients hospitalized in intensive care units, according to an international series, calls attention.[2-4] Different mechanisms of action related to the infection by SARS-CoV-2 may be related to thrombosis: excessive inflammation, tissue hypoxia, immobilization, and disseminated intravascular coagulation (DIC); however, one question remains: Is the etiology linked to some specific effect of the virus or a reflex of the severity of the case?[5] Despite the anticoagulant therapy emerging as a major weapon in the therapeutic arsenal, data is still scarce in the literature regarding the efficacy and safety of warfarin or direct oral anticoagulants (DOAC) in this specific setting.[6] It should be highlighted that, of the 1.5 million people currently infected in Brazil,[1] a significant number present a history of cardiovascular disease and are presently taking anticoagulants. This class of drugs may show serious interactions with investigational therapies currently employed for COVID-19, which could increase the risk of thrombotic or hemorrhagic events. In this context, it becomes imperative to highlight that the thrombosis associated with COVID-19 and anticoagulant therapy is a unique scenario and must be investigated.

In this light, the report below presents the case of a patient diagnosed with COVID-19 with a medical history of chronic atrial fibrillation (CAF) and who, despite his regular use of DOACs, has evolved to pulmonary embolism and deep venous thrombosis.

Keywords

COVID-19; Pandemics; Respiratory Acute Syndrome; Pulmonary Embolism; Anticoagulants.

Case Report

A male, 46-year-old Japanese patient was admitted to the emergency room of the hospital, reporting a condition of non-specific malaise, associated with fever peaks and body aches for 3 days. The patient presented a medical history of obesity (BMI-38.1 kg/m^2); systemic high blood pressure, treated with losartan, 50 mg/day; diabetes mellitus, treated with metformin, 1000 mg/day; and a diagnosis of atrial fibrillation for approximately 3 years, treated with apixaban, 5 mg twice a day, and metoprolol, 50 mg twice a day. Physical examination upon hospital admission showed: BP: 130 x70 mmHg, HR: 93bpm, O2 Sat: 94% Axillary temperature: 37.8 degrees (despite using antipyretic medication). The patient also presented hyperemic oropharynx, but with no secretion, a moderate pain upon palpation of the facial sinuses, and cardiorespiratory auscultation with no significant change. The Padua score is meant to risk stratify patients who have a potential risk for VTE. The Padua Score has 11 baseline features, and patients ≥4 tend to present a high risk of VTE. In this case, the PADUA score was 5 (decreased mobility-3, obesity-1, active infection-1).

The admission electrocardiogram (ECG) confirmed the diagnosis of atrial fibrillation and diffuse changes of ventricular repolarization (Figure 1)

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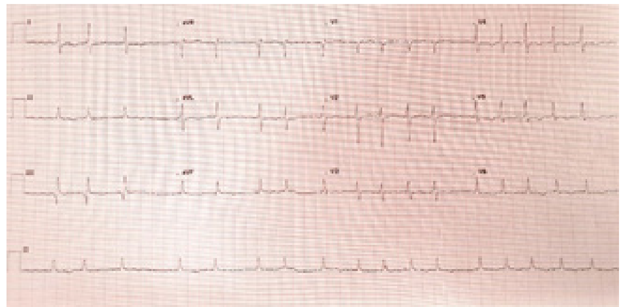

Figure 1 – Admission ECG with atrial fibrillation rhythm and diffuse change of repolarization.

Initial lab tests revealed leukopenia and thrombocytopenia, and after 48 hours, a D-dimer increase of almost 3 times the baseline value and maintenance of thrombocytopenia was idenitified (Figure 2).

The chest computed tomography (CT) imaging showed ground-glass opacities and bilateral consolidation foci, predominant in peripheral regions (Figure 3A), estimating a 25% to 50%-involvement of the pulmonary parenchyma. Due to the patient's clinical condition, together with the tomographic imaging suggesting viral pneumonia, the patient was started on Oseltamivir, venous hydration, and symptomatic care. The next day after hospitalization, the RT-PCR for COVID-19 was confirmed, and hydroxichloroquine (800 mg on the first day, followed by 400 mg on subsequent days), associated with clarithromycin (500 mg twice a day) was administered. Due to atrial fibrillation with a high ventricular response (FC around 130 bpm), the resumption of metoprolol, 50 mg twice a day, was chosen. On the fifth day of hospitalization (eight days after the onset of symptoms), a significant worsening was observed in the patient's respiratory condition, with a worsening of saturation and tachypnea; as a result, methylprednisolone, 40 mg twice a day, was introduced. Concurrently to the clinical deterioration, a significant increase in D-dimer (above 10,000 ng/ml) was also observed. Therefore, the decision was made to perform a chest CT, respecting the protocol for pulmonary embolism (Figure 3B), and the diagnosis of pulmonary thromboembolism (PTE) was confirmed, with bilateral segmental and subsegmental involvement. Antibiotic spectrum was expanded to Tazobactam and Linezolide due to the worsening in the radiological imaging and suspected bacterial association. Subsequently, a combination of lopinavir and ritonavir was started.

The anticoagulant scheme was changed with the interruption of apixaban and the start of intravenous unfractioned heparin with aPTT control (target 1.5 to 2.5 times the normal value). Echocardiography showed satisfactory ventricular performance: left ventricle ejection fraction of 58%, pulmonary artery pressure: 35 mmHg, and no right ventricle impairment. No troponin increase was observed; however, there was a BNP peak of 231 (TN 100 pg/ml). Deep venous thrombosis was observed in the left gastrocnemius vein, identified in the lower limb doppler.

After the institution of therapy and intensive support care, the patient experienced stabilization and posterior gradual improvement of the respiratory and infectious condition, with the normalization of lab tests, and after 15 days of hospitalization, the patient was discharged and medicated with rivaroxaban, 15 mg twice a day for a 21-day period. After this period, the dose was changed to 20 mg once a day. At Day 30 follow-up, the patient returned to the outpatient clinic in good clinical condition, with no complaints, maintaining outpatient follow-up with the cardiologist and infectologist.

Discussion

Since the beginning of the course of the COVID-19 pandemic in Brazil, on February 26, 2020, some international studies were already highlighting different cases of pulmonary embolisms in patients with COVID-19 and a general incidence of around 23% to 31%.[7-9]

In a survey of 328 patients who had a positive RT-PCR, 22% were diagnosed with pulmonary embolism. In this sample, patients with a body mass index above 30 kg/m2 were more frequently diagnosed (58% vs.

Table 1 – Laboratory test results

Test	03/24	03/25	03/26	03/27	03/28	03/29	03/30
Hemoglobin (g/dL)	16.2	15.0	14.5	15.2		14.8	14.9
Leukocytes/mm³	3,080	3,340	2,960	3,800		5,240	7,390
Platelets/mm³	68,000	74,000	73,000	86,000		94,000	115,000
D-dimer (ng/mL)	408	1041	1116	1702	4596	>10,000	
Ferritin (mg/dL)	3576	4646	4170	4774	3603		3384
Troponin (ng/mL)	<0.16			< 0.16			
BNP (pg/mL)					174		
PCR (mg/dL)	3.0	3.88	5.53	7.65	4.48	10.6	
Creatinine (mg/dL)	0.84	0.89	0.79			0.75	0.85
Arterial pH				7.44		7.47	
Arterial pO2 (mmHg)				80		63	
Lactate (mg/dL)	11.3	20.4		25.3			

Test	03/31	04/01	04/02	04/03	04/04	04/05	04/06
Hemoglobin (g/dL)	14.7		14.5		15.3	15.1	14.0
Leukocytes/mm³	8,210		8,500		8,980	9,450	8,540
Platelets/mm³	99,000		130,000		164,000	171,000	159,000
D-dimer (ng/mL)	>10,000	>10,000	>10,000	5285	3958	3465	1712
Ferritin (mg/dL)	783	3675	3382	3425			
Troponin (ng/mL)	<0.16		<0.16			<0.16	<0.16
BNP (pg/mL)			231	99			
PCR (mg/dL)	2.73	1.56	1.24	1.69	1.23	0.46	0.25
Creatinine (mg/dL)			0.87	0.84	0.95		
Arterial pH				7.48	7.46	7.46	
Arterial pO2 (mmHg)				60	75	72	
Lactate (mg/dL)			2.3			38.6	

g/dL: grams per deciliter; mm³: cubic milimeters; ng/mL: nanogram per mililiter; mg/dL: miligrams per deciliter; pg/mL: picogram per mililiter; BNP: Brain natriuretic peptide; PCR: polymerase chain reaction; PH: potential of hydrogen; mmHg: milimeters of mercury; pO2: oxygen pressure.

44%). Both the mean D-dimer was (9.33 mcg/ml vs 2.54 mcg/ml, p = 0.001) as well as oxygen supplementation were higher in this group diagnosed with pulmonary embolism (4.3 vs 2.7, p = 0.007). Regarding the location of the thrombi, 51% are segmental, 31% lobar, 13% central, and 5.5% subsegmental.[8]

The case reported here follows a profile of patients at higher risk due to obesity and an increase in dimer. Moreover, the CT scan is in accordance with that found with a higher prevalence in the literature, that of segmental and subsegmental involvement.

The presence of pulmonary embolism and venous thromboembolism is a prognostic marker, increasing mortality by 3.3 fold. This fact increases the discussion of the early use of anticoagulants in these patients. D-dimer variation has been considered to be one of the possibilities for therapeutic recommendation; however, there is still no general consensus.[10,11] In this case, after the diagnosis

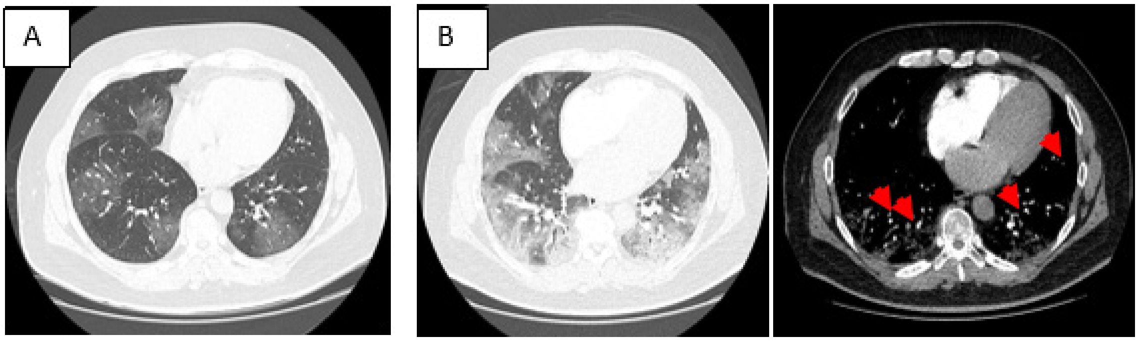

Figure 2 – A) Admission chest CT with ground-glass opacities
B) Chest CT on the fifth day of hospitalization with worsening of ground-glass imaging pattern and diagnostic angiotomography for pulmonary embolism

of an embolism, the patient experienced a significant worsening in his general health and was admitted to the ICU on oxygen supplementation.

Regarding the prophylaxis of thrombotic events, a retrospective study at the Tongji hospital, in Wuhan-China, 449 patients with a severe course of COVID-19, only 99 (22%) received heparin (both low molecular weight and unfractionated) for 7 days or longer. The 28-day mortality was higher in the group not receiving anticoagulants[12-14] The patient was initially managed with the maintenance of DOACs, as he was already taking apixaban, at the therapeutic dose, to prevent embolic events during atrial fibrillation. However, after the confirmation of the pulmonary embolism and venous thrombosis of the lower limbs, apixaban was interrupted, and unfractionated heparin was started, with seeking to promote a lab control of anticoagulation through aPTT and to produce the potential benefit of pleiotropic actions ascribed to heparin, primarily due to the description, in COVID-19, of the action of pro-inflammatory cytokines, such as: IL-2, IL6, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1ª, and TNF-α.[15] Another key factor associated with the trend of replacing DOACs by heparin is that this procedure showed a change in DOAC blood levels with the concurrent use of antivirals, such as lopinavir/ritonavir.[16]

The option to use rivaroxaban upon hospital discharge was due to the proof of efficacy and safety shown in Einstein-PE and Einstein-VTE[16,17] studies, with a higher dose in the first 21 days (15 mg twice a day), followed by 20 mg on an ongoing basis due to the presence of atrial fibrillation.[18] The logic associated with the higher initial dose was considered beneficial, as it could enhance the anticoagulant action in the initial post-COVID-19 recovery phase, a regression point of the inflammatory condition but still of unknown pro-thrombotic extension.

Even though DOACs have been approved for the treatment of pulmonary embolism and VTE prevention in the general population, their efficacy in this specific situation is still unknown and thus impossible to affirm. It should be noted that the mechanism of thrombosis is still relatively unknown and may well be related to the activation of multiple coagulation pathways, which can lead to the assumption that DOAC does not in fact provide full coverage.

It is also important to highlight that, even when there is no thrombotic event, as in the case reported here, some societies have been adopting a favorable position regarding continuous prophylactic anticoagulation. In a recent publication, the Italian Society on Thrombosis and Hemostasis (SISET), suggests the maintenance of the extended prophylaxis at home for 7–14 days after discharge. This Italian guideline also reinforces that patients with therapeutic doses of heparin or DOAC must have the renal function, as well as an anti-Xa factor,[15] monitored.

Conclusion

Pulmonary embolism is a frequent complication in patients diagnosed with COVID-19 and is a severity marker, highlighting the pro-thrombotic status present in this illness. Patients with cardiovascular disease, who are treated with the chronic use of antiplatelets and oral anticoagulants, makes it difficult to define anticoagulation during the period of a thrombotic storm imposed by the Sars-Cov-2 infection. Many questions related to anticoagulation, thrombotic events, and COVID-19 still remain. While we wait for the randomized studies promoting such answers, the guidance based on the already established anticoagulation guidelines and on the individualization of the benefit and risk associated with each patient must guide the treatment in such cases.

Author Contributions

Acquisition of data: De Luca FA, Arruda G, Sousa IB, Brandao JC, Garcia RM. Conception and design of the research: De Luca FA, Arruda G, Esteves V, Souza O, Feldman A. Analysis and interpretation of the data: De Luca FA, Arruda G, Esteves V, Souza O, Feldman A. Writing of the manuscript: De Luca FA, Arruda G, Sousa IB. Critical revision of the manuscript for intellectual content: De Luca FA, Arruda G, Esteves V, Souza O, Feldman A.

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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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