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SUMARY

Int J Cardiovasc Sci. 2021; 34(6):597-598

EDITORIAL

Sex and Gender Equity in Research and Publishing: International Journal of Cardiovascular Sciences endorses SAGER Guidelines

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"I raise up my voice - not so I can shout, but so that those without a voice can be heard...we cannot succeed when half of us are held back."

Malala Yousafzai

According to the recently published "Cardiovascular Statistics – Brazil 2020",[1] mortality from cardiovascular diseases (CVD) is proportionally higher in women compared to men. The INTERHEART study demonstrated that the population attributable risk for myocardial infarction associated with modifiable risk factors of smoking, alcohol use, high-risk diet, and physical inactivity, was significantly higher among women than men.[2] Evidence from the VIRGO study (Variation in Recovery: Role of Gender on Outcomes of Young Acute Myocardial Infarction [AMI] Patients) indicates that both health professionals and women are unaware or neglect the development of cardiovascular heart disease (CHD) and the presence of cardiovascular risk factors in women.

Women are underrepresented in cardiovascular disease trials despite known sex differences across a broad range of risk, prevention, treatment, and outcome parameters. Gender influences many aspects of disease like its pathophysiology and clinical presentation, response to treatment, clinicians' behavior, and access to health care,[3,4] and now it is clear that research must consider this to promote better diagnosis and treatment, and gender equity in health care.

How can scientific journals strengthen sex and gender equity in research and publishing? In many ways, like promoting research in the field. Recently the International Journal of Cardiovascular Sciences made a call for articles about cardiovascular diseases in women and published an entire edition dedicated to subject. In that edition, Meira Ferreira et al.,[4] published a review article about closing the gender gap in ischemic heart disease (IHD) and myocardial infarction. These authors showed that the prevalence of IHD increased in both sexes from 1990 to 2017 in Brazil, with differences in sex distribution among geographical regions. For example, there were 22% more IHD cases in women in the southeast region than in women in the northeast region.[4] In the same edition, Gazzilli[5] highlighted the increase in annual proportional mortality from IHD in women in recent years, with an age-standardized incidence of 104 per 100,000 population for males and 58 per 100,000 population for females.[5]

Another important step in the promotion of gender equity is the adoption of guidelines to improve the reporting of sex and gender in research across disciplines. A panel of 13 experts developed the SAGER (Sex and Gender Equity in Research) guidelines to guide authors in preparing manuscripts and editors in assessing the inclusion of sex and gender into manuscripts as an integral part of the editorial process.[6] Table 1 lists a summary of recommendations from the SAGER guidelines that may be easily adopted by authors. The International Journal of Cardiovascular Sciences is including the SAGER guidelines in its policy and will encourage the submitting

Keywords

Cardiovascular Diseases/mortality; Risk Factors; Epidemiology; Humans; Gender Indentity; Social Determinants of Health; Female; Women´s Health Services.

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Table 1 – Sex and Gender Equity in Research (SAGER) guidelines

General principles	
• Use the words *sex* and *gender* carefully. • Use the term *sex* in animal studies. • Where subjects can be differentiated by gender, research should take this into account.	
Recommendations per section of the article	
Title and Abstract	• the title and the abstract of articles should specify the sex /gender of research subjects • specify the sex of cells and tissues in cell biological, molecular biological, and biochemical studies
Introduction	• authors should report if sex/gender differences may be expected.
Methods	• authors should describe how sex/gender was determined (self-report, examination, genetic testing) • in medical device testing, explain whether the device will be used by all genders and if it has been tested with this in mind
Results	• data should be routinely presented disaggregated by sex • sex- and gender-based analyses should be carried out, if appropriate, and reported regardless of positive or negative outcome.
Discussion	• implications of sex and gender on study results and analysis should be discussed. If a sex and gender analysis was not conducted, the rationale should be given, and authors should discuss the implications of the lack of such analysis in interpreting the results.

Adapted from Heidari ,et al.[6]

authors to follow these recommendations. We will make progressive changes in the Scholar One submission system to increase the compliance to these guidelines and promote educational activities to revisors and authors to facilitate the adherence to the SAGER guidelines.

There is a lot yet to be done to close the gap of sex and gender equity in research, publication, and in many other aspects of life. Women need to be included, respected, empowered, and adequately represented in many aspects of the scientific community.[7,8] Men and women publish a comparable number of papers per year and have equivalent career impact for the same total number of publications. The decrease in productivity observed in women can be largely explained by different publishing career length and dropout rates.[9]

We must use our knowledge and wisdom to offer opportunities to close the gender gap to researchers and to our patients. The International Journal of Cardiovascular Sciences is making this call to the cardiovascular scientific community.

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Int J Cardiovasc Sci. 2021; 34(6):599-607

ORIGINAL ARTICLE

Family Functioning of Adolescents with Congenital Cardiopathy in a Sample from Public Schools in Porto Alegre - RS

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Abstract

Background: The impact of chronic diseases on the patient and the family ranges from minimal to severe distress. Family functioning has been often investigated as a psychosocial measure having an essential role for social adjustment in chronic diseases.

Objectives:: To compare family functioning among families of adolescents with congenital heart disease (CHD) and healthy controls (H) in relation to cohesion, adaptability, and family risk.

Method: Cross-sectional exposed-control study with 2 groups of adolescents (12 -18 years). The exposed group included adolescents with congenital heart disease (CHD), from a specialized public health system hospital (SUS), and adolescents from 7 public schools, considered healthy, composed the control group. In the hospital, the data collection was individual, before the medical consultation. In schools, the collection took place in groups. Adolescents and parents responded to the FACES III scale. The following statistical tests were used: Pearson's chi-square, Fisher's test, T-test for independent samples, Poisson multivariate regression analysis with 95% reliability, significance established at 5% and a statistical power at 99% (ß = 0.01).

Results: A total of 161 (41.6%) adolescents with CHD and 226 (58.4%) healthy adolescents participated. There was greater family cohesion among adolescents with CHD, with a higher frequency of connected families, while among healthy adolescents, there are more families of the disengaged type. Regarding adaptability, a higher proportion of families of the chaotic type were found among healthy adolescents compared to adolescents with CHD. A higher frequency of high-risk families was identified among healthy adolescents (16.8%).

Conclusion: The families of the adolescents with CHD have a more balanced functioning and low risk when compared to the families of healthy adolescents; with greater cohesion between the members and greater adaptability. Congenital heart disease was not an independent factor for high-risk family.

Keywords: Heart Defects, Congenital; Adolescent; School Health Services; Social Cohesion; Compliance; Academic Performance.

Introduction

In situations of affected health, parents and children may have difficulties to overcome adversities for a good psychological and social adjustment[1,2] and family functioning is important to predict psychosocial results. Chronic diseases shed light on changes in family functioning,[1] as well as family interaction influences health care.[3] It is not clear whether families of children with congenital heart disease have more difficulties in family functioning than families of healthy children.

Congenital heart diseases accounts for 15% of infant deaths. [4] Adolescents can be affected in their

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development, health perception, cognitive and relational skills, daily activities, adherence to treatment, and transition to adulthood,[5] have a greater risk for a healthy emotional[6] and behavioral development, as well as greater difficulties in adaptation.

Olson et al., [7-10] consider 2 factors to diagnose family functioning: cohesion (bond and autonomy between members) and adaptability (how the family reacts to situations). The combination of factors defines family risk. This study compared family functioning between adolescents with congenital heart disease and healthy adolescents to support the treatment of these children and adolescents and their families.

Methods

Cross-sectional, exposed-control study with adolescents (12 to 18 years of age), approved by the Research Ethics Committee of the Fundação Universitária de Cardiologia - Porto Alegre, state of Rio Grande do Sul, Brazil. The exposed group, with congenital heart disease (CHD), attended a specialized hospital, while the control group, with healthy adolescents (H), included students from public schools. Once the exposed group came from the public health system, it was defined the public education system as one of the criteria for the control group, minimizing possible biases related to the socioeconomic condition of the adolescents' families.

Adolescents with cognitive difficulties or other chronic illnesses were excluded.

Adolescents with CHD, authorized by their parents by the informed consent form (ICF), answered a sociobiodemographic questionnaire and the FACES-III scale (Family Adaptability and Cohesion Evaluation Scale) at the hospital's outpatient clinic. The parents also answered the FACES III scale. Of the 7 participating schools, 2 were suggested by the Municipal Education Secretariat (only elementary school) and the other state schools, were selected by convenience in different areas of the city of Porto Alegre. Data collection was made according to the school calendar. All students attending the grades with adolescents within the stipulated age group were invited and each one took home an envelope containing the ICF for parents and the FACES-III scale, so that a parent or guardian could respond. Participants included students who agreed to participate, brought the signed authorization, responded to the FACES III scale, and met the inclusion criteria. The school provided a list of students considered special, with cognitive difficulties, to control the sample. The collection was made in groups of students, in a specific room for this purpose. Parents answered the FACES-III scale at home.

Family functioning was identified using 2 dimensions (cohesion and adaptability) of the FACES III scale. [9] The values were obtained by adding the odd items for cohesion and the even items for adaptability. In cohesion, families can be agglutinated (high cohesion), connected (medium / high cohesion), separated (medium / low cohesion), and disconnected (low cohesion). The sample's mean values define the center point. Up to a standard deviation (SD) on the left (-1 SD) are the separated families, on the right (+1 SD) are the connected families and, from standard deviation (SD), the disconnected and joined families, respectively. A similar classification was used for adaptability in which families are chaotic (high adaptability), flexible (medium / high adaptability), structured (medium / low adaptability), or rigid (low adaptability). For adaptability, the values up to 1 SD, to the left of the midpoint (-1SD) are the flexible families and to the right (+1 SD), the structured families. In addition to a standard deviation, families are chaotic or rigid. One considers a functional family if it is not included in the extremes of these levels. The combinations between the 2 dimensions define the family risk: low, medium, and high. Low risk is the combination of families with connected or separate cohesion and separate or flexible type adaptability. High risk is defined for families with disconnected or bonded cohesion and with rigid or chaotic adaptability. Other combinations between dimensions are medium-risk families. FACES III [11]was identified through the average responses given by the adolescent and their guardian.

Symptoms related to physical limitation had 4 classifications and were analyzed based on 4 questions: 1. If the adolescent had medical restrictions to the practice of physical activities; 2. What physical activities they practiced besides school; 3. What is the weekly frequency of sports practice, and 4. If the patient had "shortness of breath or felt very tired" even when at rest. Therefore, adolescents who practiced mainly aerobic sports, and with frequency above 2 weekly hours, obtained a rating of 1. And those who only performed activities such as reading, table games, computer or walking had a rating of 2. Those who mentioned medical restrictions had a rating of 3 or 4 according to reports of fatigue at rest.

Statistical analysis: SPSS for Windows, version 24, was used. The Shapiro-Wilks test was used to assess the normality of the continuous variables. As they all

presented normal distribution, their description was made based on the average and standard deviation. Categorical variables were described using frequency and standard deviation. The following tests were used: Pearson's chi-square, Fisher's exact test, t test for independent samples, and multivariate Poisson regression analysis with 95% reliability. The sample was calculated to detect a difference of 0.5 in the standard deviation of the average and standard deviation of the family functioning scores; significance was set at 5%, and statistical power at 99% (ß = 0.01). It was estimated that at least 97 adolescents per group would be evaluated. [11]

Results

Participants included 387 adolescents, 161 (41.6%) with CHD and 226 (58.4%) healthy adolescents (H). Table 1 reveals the characteristics of the study population and Table 2 shows the prevalence of family types according to cohesion, adaptability, and degree of family risk. There were significant differences in the averages of cohesion and adaptability, in the frequency of the types of family functioning in each dimension, and in relation to the degree of risk between the groups. There was greater cohesion in the families of adolescents with CHD, with a higher frequency of connected families than among controls (H), which had more disconnected families. As for adaptability, there was a higher proportion of families with chaotic functioning among controls (H) than among adolescents with CHD. There were more low-risk families among CHD adolescents, and more high-risk families among H adolescents.

Among adolescents with CHD, there is greater cohesion in 2-parent families and with mothers with elementary education. Adaptability showed, among the exposed (CHD), a borderline difference for maternal age (p = 0.051).

In the comparison between groups according to family risk, it was found that in high-risk families, mothers have a lower level of education, there are more adolescents with tiredness or dyspnea, and fewer adolescents playing sports among the CHD. It is understood that the focus of clinical interventions should be on high-risk families. In this sense, after a bivariate analysis between low and medium risk families (grouped) with high-risk families, considering the general population and their family characteristics, we identified that high-risk families had a higher proportion of healthy adolescents, between 15 and 18 years old; females, from 2-parent families, and 25% had no siblings. Other variables were not significant for high-risk families. Multivariate regression analysis (Table 3) shows that being healthy represents a 148% increase in chances for high risk compared to CHD adolescents; being female increases the chance by 120% compared to males; being an only child increases by 101%, and living with both parents increases the chances of having a high-risk family functioning by 114%.

Discussion

The values of cohesion and adaptability were close to Olson's,[12] normative values of family functioning, of a non-clinical population, and the values of the exposed group (CHD) were higher than the controls (H), with a significant difference in the investigated dimensions and degree of risk.

Studies with children and adolescents with CHD are scarce and it is essential to conduct them because the epidemiological profile is specific and with different severity than heart disease in adults. [13] The identification of behavioral factors that can be targeted in the intervention for families at risk for cardiovascular disease (CVD) has become a priority,[14] and this concern extends to families where heart disease has been present from birth. The family environment is the cradle of the development of behaviors and psychosocial aspects that aim at the adaptation of the individual and affect his or her Quality Of Life (QOL). The psychological resources of parents, the child, and family functioning contribute to the child's adaptation to the disease.

Most families of adolescents with CHD presented connected functioning, suggesting that members care about each other and have a certain emotional dependence between them. Among H adolescents, more families of the disconnected type were observed, in which there is less affective connection and more emotional independence. It may be that care for the member with a chronic illness favors a more cohesive family environment and, if so, CHD may represent an integrating function among members. On the other hand, studies on QOL in children with CHD have identified that the autonomy domain is one of the most compromised due to the overprotection of parents, developed during treatment, and can contribute to a relationship of dependency among children. [15]

In the adaptability dimension, H adolescents revealed more chaotic families. This result denotes that when faced with the unforeseen, there may be a certain

Table 1 - Sample Characterization

Characteristics	Adolescents			p
	Total 387 (100.0) n (%)	Bank account 161 (100.0) n(%)	H 226 (100.0) n(%)	
Sex				0.006
Male	187 (48.3)	91 (56.5)	96 (42.5)	
Female	200 (51.7)	70 (43.5)-	130 (57.5)	
Age – M (sd)	15.3 (1.6)	14.8 (1.7)	15.7 (1.5)	< 0.001
12 to 14 years old	147 (38)	91 (56.5)	56 (24.8)-	< 0.001
15 to 18 years old	240 (62)	70 (43.5)	170 (75.2)+	
Schooling (n = 386)				< 0.001
Primary education	256 (66.3)	127 (79.4)+	129 (57.1)	
High School	130 (33.7)	33 (20.6)-	97 (42.9)	
Family configuration				0.001
Biparental family	195 (50.4)	97 (60.2)+	98 (43.4)-	
Monoparental family	55 (14.2)	22 (13.7)	33 (14.6)	
Reconstituted family	123 (31.8)	34 (21.1)-	89 (39.4)+	
Living with other relatives	14 (3.6)	8 (5.0)	6 (2.7)	
Only child	54 (14.0)	25 (15.5)	29 (12.8)	0.451
Father's age (n = 338)				0.653
Up to 40 years old	102 (30.2)	45 (30.8)	57 (29.7)	
41 to 50	141 (41.7)	57 (39.0)	84 (43.8)	
Over 50	95 (28.1)	44 (30.1)	51 (26.6)	
Mother's age (n = 371)				0.771
Up to 40	175 (47.2)	77 (49.4)	98 (45.6)	
41 to 50	131 (35.3)	53 (34.0)	78 (36.3)	
Over 50	65 (17.5)	26 (16.7)	39 (18.1)	
Father's schooling (n = 342)				< 0.001
Up to complete primary education	193 (56.4)	104 (69.3)+	89 (46.4)-	
Complete secondary education	102 (29.8)	39 (26.0)	63 (32.8)	
Complete higher education	47 (13.7)	7 (4.7)-	40 (20.8)+	
Mother's schooling (n = 375)				< 0.001
Up to complete primary education	198 (52.8)	114 (72.6)+	84 (38.5)-	
Complete secondary education	120 (32.0)	39 (24.8)-	81 (37.2)+	
Complete higher education	57 (15.2)	4 (2.5)-	53 (24.3)+	
BMI – M (sd)	55.9 (32.1)	55.3 (32.7)	56.4 (31.8)	0.733
Regular	284 (73.4)	120 (74.5)	164 (72.6)	0.666
Overweight	103 (26.6)	41 (25.5)	62 (27.4)	
Health				
Cardiac surgery	88 (54.7)	88 (54.7)	-	
Congenital heart disease				
Cyanotic	43 (11.1)	43 (26.7)	-	
Acyanotic with repercussion	77 (19.9)	77 (47.8)	-	
Acyanotic without repercussion	41 (10.6)	41 (25.5)	-	
Symptoms for physical limitation				< 0.001
1 - Asymptomatic	329 (85.0)	118 (73.3)-	211 (93.4)+	
2 – Symptoms in everyday activities	50 (12.9)	35 (21.7)+	15 (6.6)-	
3 – Symptoms in effortless activities	7 (1.8)	7 (4.3)+	0(0)-	
4 – Symptoms at rest	1 (0.3)	1 (0.6)	0 (0)	

Note: CC: Congenital heart disease; H: Healthy;
Symbols + and - mean respectively significantly higher and lower than expected percentage of cases for the category (+: adjusted standardized residuals > +1.96; - : adjusted standardized residuals < -1.96;
M (sd) = Average (standard deviation)
Pearson's chi-squared, Student's t

Table 2 - Cohesion, adaptability, and family risk in different groups of adolescents

Dimensions	Adolescents			
	Total 387 (100.0%) n (%)	Bank account 161 (100.0%) n (%)	H 226 (100.0%) n(%)	p
Cohesion – M (sd)	36.7 (4.9)	37.5 (3.9)	36.1 (5.5)	0.004
Types of cohesion				0.002
Disengaged*	56 (14.5)	12 (7.5)-	44 (19.5)+	
Separate	122 (31.5)	50 (31.1)	72 (31.9)	
Connected	152 (39.3)	77 (47.8)+	75 (33.2)-	
Enmeshed*	57 (14.7)	22 (13.7)	35 (15.6)	
Adaptability – M (sd)	26.2 (5.0)	26.9 (4.4)	25.7 (5.8)	0.026
Adaptability – Types				0.002
Chaotic*	61 (15.8)	12 (7.5)-	49 (21.7)+	
Flexible	133 (34.4)	61 (37.9)	72 (31.9)	
Structured	134 (34.6)	62 (38.5)	72 (31.9)	
Rigid*	59 (15.2)	26 (16.1)	33 (14.6)	
Family risk				0.001
Low risk	202 (52.2)	99 (61.5)+	103 (45.6)-	
Average risk	137 (35.4)	52 (32.3)	85 (37.6)	
High risk	48 (12.4)	10 (6.2)-	38 (16.8)+	

Note: CC: Congenital heart disease; H: Healthy. Symbols + and - mean respectively significantly higher and lower than expected percentage of cases for the category (+: adjusted standardized residuals > +1.96; - : adjusted standardized residuals < -1.96;
** Dysfunctional types of cohesion or adaptability*
Pearson's chi-squared, Student's t; m: mean; sd: standard deviation

disorganization of these families, with possible absence of leadership or rules for facing changes, with an excessive change in the roles of members and discipline tends to be irregular,[16] since families of adolescents with CHD revealed more capacity to adapt to the unforeseen, characterizing the 'functional flexibility'. Research has shown that having a child with a chronic disease results in improvement in certain areas of family functioning such as solving health-related challenges, since living with the disease makes them more proficient in these issues. [1,17]

Results of studies[18,19] on family functioning and the upbringing of children with chronic diseases are controversial. Some found deficits in family cohesion, family adaptability, parent-child interactions, family conflict and problem-solving skills while others[20] did not identify significant differences in family functioning when compared to healthy families. Such differences in results can be attributed to the diversity of measures, the specificities of the diseases, or to the fact that they are studies focused on the perception of parents and not on the carrier of the disease, whether a child or adolescent. In this case, maladjustments may be more related to the way the family perceives the disease than to the child's own behavior, related to the disease. [21] It is unusual to verify the perception of the disease from the patient's perspective, which results in discrepancies in response and clinical evolution.[22,23] One of the prerogatives of this study was to seek the evaluation of family functioning using the joint responses of 2 members - the teenager and one of the parents - for a broader perception of the family.

In the combinations between cohesion and adaptability in the groups studied, it was identified

Table 3 - Prevalence of high-risk functioning families and factors independently associated with high family risk

Variables	Prevalence of high-risk functioning families	Factors independently associated with high family risk		
	N(%)	p	PR	CI 95%
Congenital heart disease				
Yes	10 (6.2)		1	
No	38 (16.8)	0.015	2.48	1.193 – 5.142
Gender: female				
Male	13 (7.0)		1	
Female	35 (17.5)	0.013	2.20	1.184 – 4.083
Age				
12 to 14 years old	12 (8.2)		1	
15 to 18 years old	36 (15.0)	0.280	1.44	0.745 – 2.774
Only child				
No	36 (10.8)		1	
Yes	12 (22.2)	0.012	2.01	1.165 – 3.475
Family configuration				
Biparental	32 (16.4)	0.008	2.14	1.222 – 3.763
Other	16 (8.3)		1	

Note: Dependent variable: High Family Risk - Extreme Cohesion and Adaptability
PR: prevalence ratio,
CI: 95% confidence interval

a higher frequency of high-risk family among H adolescents compared to those with CHD, and that being healthy is independently and positively associated with high family risk . When it comes to a study on family functioning associated with chronic diseases, there are many variables to be considered. [1,14] Due to this complexity, studies related to family functioning need to unravel parts that integrate the whole. In a review study, the domains of communication, interpersonal involvement, discipline management, and role definition were significantly lower in families with chronic diseases compared to families with healthy children. [1] This study, however, makes reservations about issues such as instruments, severity and lifespan with the disease, whether they are hereditary or genetic, having other family members with the disease, whether data were collected from all members, and it does include congenital heart diseases.

On the other hand, there are studies that analyzed QOL in children with chronic diseases and found satisfactory values, despite the aspects inherent to the pathology. [22,24] There are QOL factors that are related to family dynamics, indicating their proper functioning.[25] The fact that families of adolescents with CHD proved to be more functional than families of control adolescents (H) may be associated with these factors and assume a satisfactory QOL, suggesting further investigation of this relationship.

Many aspects may have contributed to the result of this study: CHD is present since birth and, therefore, the lifetime with the disease makes the demands of the disease and treatment part of everyday reality, implying the strengthening of family bonds and favoring interactions. Compared to the reality of healthy adolescents, adolescents with CHD have already overcome adversities and risks of the disease from an early age, including the imminence of death. Nevertheless, treatments (surgery or other procedures) were successful and it is possible that they have developed capacities to deal more resiliently with situations of uncertainty or risk.

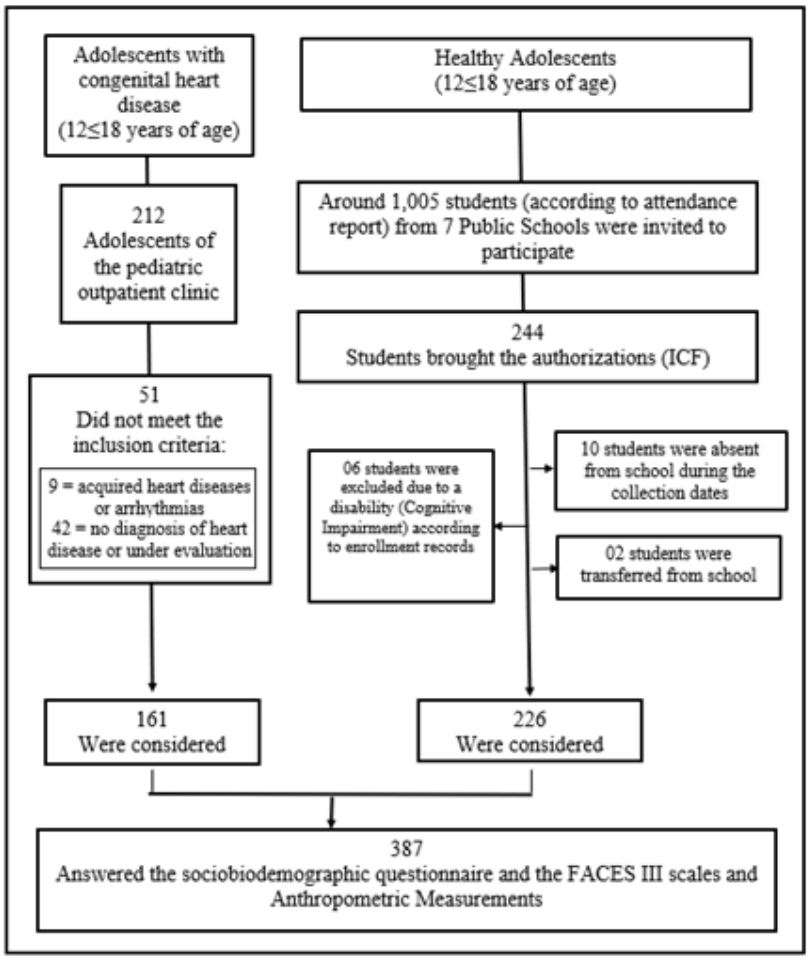

Figure 1 – Data collection flowchart.

Another relevant point is that, although there are authors who recognize that hospitalization, catheterization, anesthesia, surgical procedures, and the various experiences inherent to the course of heart disease, affect children and their families,[24] there are studies that highlight that there were few deviations in the normal behavior of children in the postoperative period, whether immediate or late. [24] The fact that adolescents with CHD and their families remain under medical and health care since birth, in systematic and regular care with a multidisciplinary team, promotes feelings of care and protection, in addition to the bond established with some of these professionals throughout their lives. Such feelings can contribute to the dynamics of a more balanced family functioning.

This study showed a small number of adolescents with severe physical limitations (only 4.9% of the congenital). A study with children with CHD, pre and post-surgical, identified cases in which deficits in child psychomotor development were determined by the variables sex, age and socioeconomic status and were not related to the treatment of heart disease, information, understanding of the disease, and the way parents treat their children. [26] A study, however, points out that the way the disease is perceived by individuals influences the way they act on it[27] and the perception of physical and health limitations on the part of the patient and/or parents affects the family functioning. [24] Adolescents with CHD recognize their physical and emotional limitations as part of their condition and rely on the support of their family and social network as a protective factor, remembering that physical exercise limitations are for different reasons, sometimes with very small dimensions, not bringing early repercussions, with normal development and absence of symptoms,[28] not restricting activities that give

them pleasure. Caregivers only perceive the disease when it manifests; children without symptoms and who are able to perform daily activities are not considered sick.

This study showed that there are no differences in the levels of cohesion in the families of adolescents with CHD when considering the age of the patient. This result was reversed in a study of children (6 to 16 years old) with juvenile rheumatoid arthritis (JRA)[1] in which this difference was found in families with only younger children when compared to families without JRA. Our results suggests that, health care demands are prioritized, depending on the disease, according to the child's developmental stage and over other related demands and they define the level of interaction between people over the period. In the families of H adolescents, the search for greater autonomy can be an alert factor for parents to the needs of their children, increasing cohesion. The greater adaptability in this age group is justified by the need for greater coping capacity related to phase changes.

The education of mothers in the control group (H) was higher compared to mothers of adolescents with CHD among high-risk families. The assumption that the higher the level of education, the lower the chances of risk is not valid when it is understood that education or knowledge is not always associated with behaviors and attitudes. Studies reveal that the level of education or information about diseases is not associated with the importance attributed or even with learning itself. [29] In this sense, being aware of family functioning associated with the family's ability to understand the disease is important for the efficacy and effectiveness of treatment.

It was found that being healthy, female, living with both parents, and being an only child proved to be positively associated factors, independently, for high family risk, characterizing the dysfunctional family dynamics. In families of the agglutinated type, among adolescents with CHD, 77.3% were girls. We can consider the multiple roles that contemporary women have played in society; girls with CHD may need more support and support from their families for these achievements. Such data deserves further study.

Living with both parents was positively associated with an increased family risk, which is surprising considering the belief that the joint participation of parents in the education of their children requires more balanced families. There are few studies on this aspect; however, a review on marital adjustment identified results without significant differences in divorce rates between groups with and without children with chronic diseases; 4 out of 7 studies showed that marital distress was increased in parents of children with chronic illnesses, stating that additional studies are needed to understand marital adjustment to chronic childhood illnesses. [30] Such studies demonstrate the effects of chronic disease on parental conjugality, however, they do not focus on the reverse relationship, on how relationships or marital conflicts affect the patient with chronic disease, or more specifically, with CHD. Being an only child was also associated with a high family risk, which suggests that the presence of other healthy children can be an element of balance in living with the disease.

In terms of the limitations of this study, as it is transversal, the groups, collected in different environments (hospital and school), showed significant differences, limiting the comparative results. Another limitation was the finding that studies on family functioning have a variety of measurement instruments with specific factors, which made it difficult to compare results among studies. Still, most studies involving younger children focus on the parents' perception of their children's adjustment and do not include the child's perception. Another difficulty in the comparisons is that many studies on family functioning are conducted with several chronic diseases, and few exclusively on CHD.

Conclusion

The results obtained in the present sample suggest that congenital heart disease does not represent a factor associated with high-risk family functioning and that the families of these adolescents with CHD are generally considered to have a balanced functioning and lower risk when compared to the family of healthy adolescents. The results are not in line with the paradigms that define chronic disease as a family dysfunction factor.

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Author Contributions

Conception and design of the research: Piccoli AB, Neiva-Silva L, Pellanda LC. Acquisition of data: Piccoli

AB. Analysis and interpretation of the data: Piccoli AB, Neiva-Silva L, Pellanda LC. Statistical analysis: Piccoli AB, Neiva-Silva L. Writing of the manuscript: Piccoli AB. Critical revision of the manuscript for intellectual content: Piccoli AB, Neiva-Silva L, Pellanda LC. Ângela Piccoli, Lucas Neiva-Silva, Lucia Campos Pellanda

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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This study was approved by the Ethics Committee of the *Instituto de Cardiologia/FUC* under the protocol number 5041/14. 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

Family Functioning and Congenital Heart Disease

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Editorial referring to the article: Family Functioning of Adolescents with Congenital Cardiopathy in a Sample from Public Schools in Porto Alegre – RS

In the last decades, we have been watching a remarkable increase in survival of children with congenital heart disease (CHD), due to advances in surgical and medical management, leading to a significant growth in the number of adolescents and young adults with the disease.[1] In developed countries, the number of adults with CHD surpasses the number of children with CHD.[2]

Unfortunately, prolonged survival has been achieved at a high cost, as an expressive number of patients continue to suffer from significant medical, psychological and social issues.[3] The knowledge that CHD brings an individual burden is not a new concept. In 1964, Glaser[4] concluded that "Despite benefits derived from these remarkable therapeutic gains, children with CHD face many difficulties in their efforts toward social and emotional adjustment."[5]

The change in the prognosis of these previously fatal diseases has required a broader understanding of outcomes for a better quality of life, including physical, psychological and social issues.

In this context, a review published in Arquivos Brasileiros de Cardiologia in 2014[6] evaluated health-related quality of life in childhood and adolescence, with emphasis on CHD patients. The authors found conflicting results and suggested the need for further investigation such as parental life style, social support and coping strategies.

Keywords

Heart Defects, Congenital; School Health Services; Patient Compliance; Family Health; Social Cohesion; Family Health; Adolescent; Quality of Life.

In this recent paper, Piccoli et al.,[7] studied the family functioning of adolescents with CHD. The study included 387 adolescents, 161 (41.6%) with CHD and 226 (58.4%) healthy adolescents from a public specialized hospital and public schools, respectively, through a socio-bio-demographic questionnaire and the Family Adaptability and Cohesion Evaluation Scale III (FACES III). They analyzed responses from the adolescents and from one of the parents to evaluate family functioning to have a better perception and evaluation of the families. The authors did not find an association between the presence of CHD and high-risk family functioning, and interestingly, the families of adolescents with CHD had a balanced functioning and lower risk when compared to families of healthy adolescents. The authors discussed several aspects of CHD families, such as a lifetime with the disease, development of abilities to deal with health challenges, close follow-up with a multidisciplinary team, among others. In addition, cohesion in the families of adolescents with CHD was higher compared with controls, mainly in two-parent families. Surprisingly, the mother's educational level did not show a direct relationship with the level of family cohesion. All these data reinforce the complexity of the nature of this type of study and the difficulties in understanding the various factors involved in this subject and the relationship between them.

The authors conclude that their "results are not in line with the paradigms that define chronic disease as a family dysfunction factor", thereby demonstrating the uniqueness of the family functioning of CHD patients and the need for further studies in this very important field.

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ORIGINAL ARTICLE

Hypertension and Different Levels of Body Mass Index and Cardiorespiratory Fitness Amongst Adolescents

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Abstract

Background: Hypertension is an increasingly common problem in adolescents; amongst the associated factors, physical inactivity and obesity are increasing the risk of developing cardiovascular diseases.

Objective: To verify whether there is an association between higher blood pressure levels amongst adolescents with the relationship between different levels of body mass index (BMI) and cardiorespiratory fitness (CRF).

Method: Cross-sectional study consisting of 860 adolescents. Higher blood pressure (BP) was considered as borderline and hypertension as the classification. BMI was categorized as low-normal weight and overweight-obesity. The CRF was assessed by a nine-minute run/walk test and classified into low or appropriate levels (less and more favorable to health, respectively). Later, BMI and CRF were grouped into one categorical variable: (I) low/normal weight and appropriate CRF levels; (II) low/normal weight and low CRF levels; (III) overweight/obesity and appropriate CRF levels; and (IV) overweight/obesity and low CRF levels. Data were analyzed using Poisson regression, through the prevalence ratio (PR) and 95% confidence intervals (CI). The p-values of $p<0.05$ were considered significant.

Results: Adolescents with overweight/obesity and low CRF levels had a 22% higher BP prevalence. Moreover, children with overweight/obesity, but with appropriate CRF levels, have a 15% higher BP prevalence.

Conclusion: Adolescents with overweight/obesity had a higher prevalence of BP, regardless of CRF levels. It is suggested that maintaining normal BMI is a protective factor for less favorable BP.

Keywords: Hypertension; Blood Pressure, Adolescent, Cardiorespiratory Fitness; Obesity; Exercise; Exercise Therapy; Body Mass Index.

Introduction

Obesity and hypertension have become a public health problem worldwide and are now present in both children and adolescents.[1] Amongst adolescents, the higher levels of blood pressure (BP) is associated with sex, obesity, family history of hypertension,[2] and waist/height ratio.[3] These also tend to increase with age, body mass, height, and body mass index (BMI).[4]

The prevalence of prehypertension amongst overweight individuals suggests the need for the early clinical detection of BP changes, as well as possible intervention in this condition, by making changes in lifestyle, particularly in body weight control.[5] The association between excess body mass and hypertension highlights the urgent need to implement strategies to prevent cardiovascular disease on a large scale,[6,7] continuously and over the long term.[8]

In a survey of English schoolchildren, Ogunleye et al.,[9] found that cardiorespiratory fitness (CRF) attenuates the association between BMI and BP levels; however, amongst obese students, this attenuation was

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not as relevant as amongst normal weight students. Previous findings demonstrated that CRF can reduce the risk of hypertension in children and adolescents when associated with a favorable nutritional status, but it is not yet known whether good CRF is able to attenuate the chances of high BP in individuals with excess body mass.[10,11] From this perspective, there is still a gap in the literature concerning the concurrent relationship between excess weight and CRF levels with hypertension.

Therefore, it could be easily postulated that the identification of potential protection parameters against the development of hypertension among youth populations would present great importance to decide what should be the focus in preventions and health promotion strategies. The present study aims to verify whether there is an association between higher BP levels amongst adolescents with the relationship between different levels of BMI and CRF.

Method

This was a cross-sectional study using a sample comprised of 860 adolescents (480 girls), aged from 10 to 17 years. All participants were randomly selected from 18 public and private schools of Santa Cruz do Sul, RS, Brazil. The sample was selected by conglomerates, encompassing all municipality regions (center, north, south, east, and west) from urban and rural areas. This study is part of a larger research called "Schoolchildren's Health - Phase II" developed at the University of Santa Cruz do Sul (UNISC). It was approved by the UNISC Committee of Ethics in Research with Human Subjects, logged under protocol number 3044/11. The study included all students whose parents or guardians signed the informed consent form.

The program G*Power 3.1 (Heinrich-Heine University - Düsseldorf, Germany) was used for the sample size estimator, using the Poisson regression as a statistical test (dependent variable as dichotomous) and the test procedure described by Demidenko,[12] with variance correction. The following parameters were established: a power of the test (1 - β) = 0.95, a significance level of $\alpha = 0.05$, an effect size – Exp(β1) of 1.15, and a base rate exp(β0) of 0.70. The sample size was estimated at 784 schoolchildren.

The evaluation of BP levels was performed early in the morning by trained health professionals using a stethoscope and sphygmomanometer, in a quiet room, with participants resting for five minutes in a sitting position, with their backs resting on the chair and their feet resting on the floor. The systolic (SBP) and diastolic (DBP) blood pressure were later classified following criteria established in the VI Brazilian Guidelines on Hypertension,[13] considering sex, age, and height. The BP level was considered highly altered when SBP and/or DBP were classified as borderline or hypertensive.

The BMI was calculated to assess the adolescent's body composition and classified by the cutoff points established by the Centers for Disease Control and Prevention/National Center for Health Statistics,[14] considering sex and age. Low weight (<p5), normal weight (≥p5 and <p85), overweight (p≥85 and <p95), and obesity (≥p95) were considered. Subsequently, data were dichotomized as low weight/normal weight or overweight/obesity. The CRF level was assessed using the nine-minute run/walk test, described by *Projeto Esporte Brasil* (PROESP-BR)[15], which was validated for use with this population.[16] Data were obtained in meters performed with subsequent classification into appropriate or low CRF levels, as established by the PROESP-BR cutoff points for the Brazilian children and youth population, considering sex and age. Subsequently, the measures of BMI and CRF were unified into a single categorical variable and classified as (I) low/normal weight and appropriate CRF levels; (II) low/normal weight and low CRF levels; (III) overweight/obesity and appropriate CRF levels; or (IV) overweight/obesity and low CRF levels.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS), software version 23.0 (IBM, Armonk, NY, USA), was used for statistical analysis. Descriptive statistics were used to characterize the sample, using the frequency and percentage values. The association between the outcome variable (higher BP levels) and the BMI/CRF relationship was tested using Poisson regressions and expressed as prevalence ratio (PR) values and 95% confidence intervals (CI), with adjustment for the biological gender variable. Values of $p<0.05$ were considered significant in all analyses.

Results

Table 1 shows the descriptive characteristics of the subjects. There was a high prevalence of overweight and obese adolescents (24.8%) and low CRF levels (53.7%), and 19.4% had high BP levels (borderline and hypertension).

Figure 1 presents the percentage of BP levels amongst adolescents with different BMI/CRF relationship classifications. Adolescents with low/normal weight had a lower percentage of higher BP, regardless of the CRF levels (appropriate: 14.6%; low: 15.7%). By contrast, the percentage was higher amongst overweight/obese adolescents: 29.3% for those with appropriate CRF levels and 34.1% for those with low CRF levels.

The regression models demonstrated that adolescents with overweight/obesity and low levels of CRF had a 22% higher prevalence of higher BP. Students with overweight/obesity and appropriate CRF levels also presented a higher prevalence (15%) of less favorable BP levels (Table 2).

When SBP and DBP were analyzed separately (Table 3), similar findings to those presented in Table 2 were observed. However, the prevalence of alteration was slightly higher for SBP amongst those students with overweight/obesity, regardless of the CRF level.

Discussion

The present study aimed to assess the association between levels of BP and BMI/CRF of schoolchildren. Previous studies assessed the association of BP with obesity and CRF indicators separately. In a systematic review, Corrêa Neto and Palma[17] stated that there is not

Table 1 – Descriptive characteristics of the subjects. Santa Cruz do Sul, RS, 2011-2012

	n (%)
BMI	
Low weight/normal weight	647 (75.2)
Overweight/Obesity	213 (24.8)
CRF	
Appropriate levels	398 (46.3)
Low levels	462 (53.7)
BMI/CRF	
Low/normal weight and appropriate CRF levels	323 (37.6)
Low/normal weight and low CRF levels	324 (37.7)
Overweight/obesity and appropriate CRF levels	75 (8.7)
Overweight/obesity and low CRF levels	138 (16.0)
Blood pressure	
Normal	693 (80.6)
Borderline and hypertension	167 (19.4)
Systolic blood pressure	
Normal	707 (82.2)
Borderline and hypertension	153 (17.8)
Diastolic blood pressure	
Normal	699 (81.3)
Borderline and hypertension	161 (18.7)

BMI: body mass index; CRF: cardiorespiratory fitness;

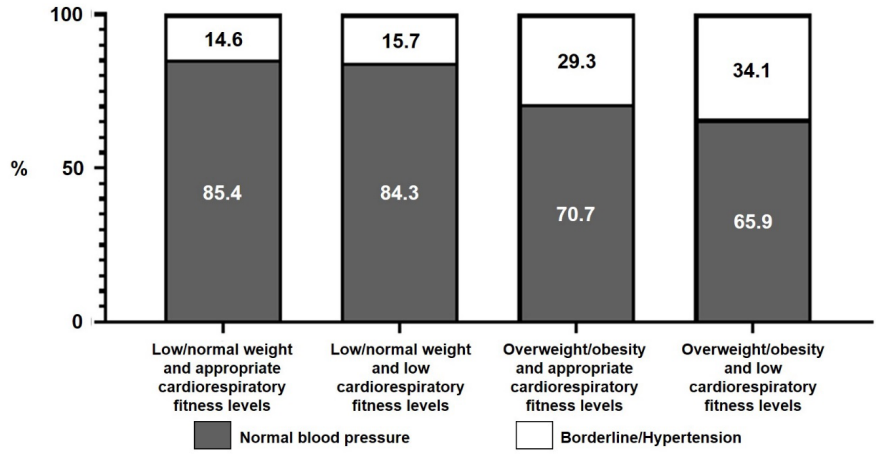

Figure 1 – Relationship between BP levels and BMI/CRF classification

Table 2 – Association between less favorable blood pressure levels and different levels of BMI/CRF in adolescents (n=860)

	Borderline and hypertension	
	PR (95% CI)	*p*
Low/normal weight and appropriate CRF levels	1	
Low/normal weight and low CRF levels	1.02 (0.97 to 1.08)	0.433
Overweight/obesity and appropriate CRF levels	1.15 (1.03 to 1.28)	0.015
Overweight/obesity and low CRF levels	1.22 (1.11 to 1.33)	<0.001

BMI: body mass index; CRF: cardiorespiratory fitness; PR: prevalence ratio; 95% CI: 95% confidence interval; Poisson regression considering two categories for outcome variable (normal blood pressure versus higher blood pressure); analyses adjusted for sex.

Table 3 – Association between SBP and DBP, and different levels of BMI/CRF in adolescents (n=860)

	Higher SBP		Higher DBP	
	PR (95% CI)	*p*	PR (95% CI)	*p*
Low/normal weight and appropriate CRF levels	1		1	
Low/normal weight and low CRF levels	1.03 (0.98 to 1.09)	0.245	1.03 (0.97 to 1.08)	0.370
Overweight/obesity and appropriate CRF levels	1.16 (1.04 to 1.29)	0.008	1.13 (1.02 to 1.26)	0.022
Overweight/obesity and low CRF levels	1.23 (1.12 to 1.34)	<0.001	1.19 (1.09 to 1.29)	<0.001

SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; CRF: cardiorespiratory fitness; PR: prevalence ratio; CI: 95% confidence interval; Poisson regression considering two categories for outcome variable (normal blood pressure versus higher blood pressure); analyses adjusted for sex.

always a well-defined link between higher BP levels and physical inactivity/obesity, which demonstrates a need for greater considerations on the subject. Corrêa-Neto et al.,[18] identified an association between hypertension and obesity in a study with adolescents in Rio de Janeiro, Brazil, but the authors did not consider physical inactivity.

The data presented in the current study suggest that normal BMI is an important protective factor against increased BP, regardless of CRF levels. These findings run in line with the results obtained in a study with children and adolescents, which demonstrated that thinner boys and girls with lower CRF levels have a better cardiometabolic risk profile compared to their peers who are obese and who present appropriate CRF levels. Moreover, Wang et al.,[19] showed that children and adolescents with excess weight and low CRF also present a higher cardiometabolic risk. These results emphasize the importance of maintaining adequate weight to prevent the development of cardiometabolic risk during childhood and youth.[20,21]

Accordingly, Pozuelo-Carrascosa et al.,[22] observed higher BP levels in children with excess weight and low CRF levels in the provinces of Ciudad Real and Cuenca, Spain. Díez-Fernández et al.,[23] also found that BP was worse amongst overweight students and better amongst those with higher CRF levels. Both aforementioned studies demonstrated BMI as a mediator in the association between CRF and BP. Fernandes et al.,[24] also suggest that the association between CRF and BP is mediated by body composition. Additionally, Müller et al.,[25] identified body weight as an independent determinant of SBP, whereas CRF did not show an association with SBP. These findings demonstrate the importance of maintaining a healthy weight for the prevention of high levels of BP.[26] Therefore, as suggested by the present and previous studies, excess weight should be considered when looking at preventing hypertension development among youth, especially for Brazilian children and adolescents, which has an estimation of a quarter presenting excess weight.[27]

By contrast, Yang et al.,[28] highlight better levels of CRF associated with normal BP levels. Obese students with low CRF levels present a higher prevalence of hypertension (OR: 3.98; 95% CI: 2.92 to 5.41) compared to obese students with better CRF levels (OR: 1.75; 95% CI: 1.10 to 2.79), which suggests that CRF may attenuate the relationship between obesity and less favorable BP levels.[9] This positive influence of CRF on BP was also demonstrated by Burgos et al.,[29] Students with better CRF had better SBP and DBP results. The authors also observed a gradual increase in the number of students with normal BP as the CRF level increased. Additionally, Ruiz et al.,[30] showed that markers of total and central adiposity were associated with BP only in children with low levels of CRF, which also demonstrates that more favorable CRF levels can attenuate the association between body fat and BP in children. Lastly, Silva et al.,[31] exposed that children and adolescents with low CRF levels, with or without the presence of central adiposity, demonstrated a higher cardiometabolic risk than individuals with better CRF levels and normal central adiposity. These findings suggest that low CRF levels can increase BP, regardless of BMI, and it should be considered when targeting BP levels. Therefore, physical activity should be promoted as much as preventing excess weight, especially at higher intensities.[32]

The current study has strengths, such as the fact that it presents a representative sample of adolescents from Santa Cruz do Sul. Moreover, to the best of our knowledge, few studies, especially in Brazil, have assessed the association of excess weight and CRF with hypertension in schoolchildren. However, we also highlight some limitations, mainly concerning the methodological design, which cannot establish a causal relationship between the variables. Although the municipality of the study was from German colonization and the sample had a higher percentage of Caucasian students,[33] ethnic aspects were not included in the analyzed models, nor was pubertal status.

Conclusion

Overweight and obese adolescents, regardless of CRF levels, have a higher prevalence of altered BP. It is also suggested that maintaining adequate body mass may well be better in preventing BP changes than improving CRF levels in adolescents would be.

Author contributions

Conception and design of the research: Bertollo C, Burgos LT, Reuter CP. Acquisition of data: Bertollo C, Barbian CD, Schneiders LB, Silveira JFC, Burgos LT, Reuter CP. Analysis and interpretation of the data: Bertollo C, Barbian CD, Schneiders LB, Silveira JFC, Vogt BD, Mello ED, Burgos LT, Hobkirk JP, Reuter CP. Statistical analysis: Schneiders LB, Silveira JFC, Reuter CP. Obtaining financing: Barbian CD, Schneiders LB, Silveira JFC. Writing of the manuscript: Bertollo C, Barbian CD, Schneiders LB, Silveira JFC, Vogt BD, Mello ED, Burgos LT, Hobkirk JP, Reuter CP. Critical revision of the manuscript for intellectual content: Bertollo C, Barbian CD, Schneiders LB, Silveira JFC, Vogt BD, Mello ED, Burgos LT, Hobkirk JP, Reuter CP. Supervision / as the major investigador: Burgos LT, Reuter CP.

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 Unisc under the protocol number 3044/11. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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EDITORIAL

Weight Excess: The Great Villain in the Development of Hypertension in Adolescents

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Editorial referring to the article: Hypertension and Different Levels of Body Mass Index and Cardiorespiratory Fitness Amongst Adolescents

The relationship between arterial hypertension (AH) and excess weight in young populations is well established. This association involves several conditions including hyperinsulinemia, altered adipokine profile, elevated markers of subclinical inflammation, and inadequate habits, including physical inactivity.[1-5]

In a study[3-5] conducted in the city of Rio de Janeiro, Brazil, an increased body mass index in adolescents was correlated with a higher prevalence of elevated blood pressure (BP) and higher risk of developing AH at young adult age. From a longitudinal perspective, an interesting aspect in the assessment of cardiovascular risk factors is the tracking effect, in which children and adolescents with altered clinical and metabolic parameters (BP, body mass index and cholesterol levels) are likely to maintain an abnormal profile of these variables throughout life and become adults at increased cardiovascular risk.[1-5] This fact highlights the continuous, unfavorable impact of persistent obesity from childhood to adulthood on cardiovascular risk factors.

The prevalence of physical inactivity at leisure times is very high in Brazilian adolescents (54.3%. 95%CI 53.4-55.2), especially among girls. One fourth of the adolescents (26.5%; 95%CI 25.8-27.3) reported to be physically inactive at leisure times (girls 39.8%, 95%CI 38.8-40.9 vs. boys 13.4%, 95%CI 12.4-14,4).[6] Although these prevalence data have indicated a correlation between excess weight, physical inactivity, and hypertension in young individuals, there are still important evidence gaps regarding this association.[1-5]

In the current issue of the International Journal of Cardiovascular Sciences, Bertollo et al.,[1] explored the interrelationship between obesity, cardiorespiratory fitness, and hypertension in 860 adolescents. The authors found a prevalence of 22% of elevated BP in overweight/obese individuals with low cardiorespiratory fitness, and a prevalence of 15% in those overweight with adequate cardiorespiratory fitness. In underweight and normal weight adolescents, the frequency of hypertension was relatively lower, and independent of the cardiorespiratory fitness level (14.6% and 15.7% in those with adequate and low cardiorespiratory fitness levels, respectively).[6] Thus, cardiorespiratory fitness had no effect on the positive correlation between excess weight and the presence of hypertension. This study adds information about the relationship between BP, excess weight, and physical fitness in adolescents, which is of particular importance considering the scarcity of studies on this subject with individuals in this age range in Brazil. However, the cross-sectional nature of the study precludes establishing a causal relationship between these variables as well as analyzing the impact of a higher cardiorespiratory fitness in a longer-term perspective.

Likewise, in a cross-sectional study, Briggs et al.,[7] evaluated the relationship between cardiorespiratory fitness, prevalence of cardiovascular risk factors, and risk of metabolic syndrome in 183 young obese individuals. Of the study individuals, 30% had metabolic syndrome, but no differences were

Keywords

Hypertension; Adolescents; Sedentarism; Physical Activity; Exercise; Quality of Life; Risk Factors; Obesity.

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observed in the prevalence of cardiovascular risk factors or metabolic syndrome between individuals with higher and lower cardiovascular fitness.

Martínez-Vizcaíno et al.,[8] evaluated the effects of a physical activity program on indicators of obesity, cardiorespiratory fitness, and BP in children. This was a crossover randomized clinical trial including 1,434 children (4-7 years old). The intervention consisted of three 60-minute sessions per week on weekdays between October 2013 and May 2014. Despite improvements in cardiorespiratory fitness seen in both girls ($p<0.001$) and boys ($p<0.001$), there were no significant improvements in overweight/obesity with the intervention compared with the control group in both sexes. Also, the intervention did not alter other adiposity indicators or BP parameters.

Therefore, studies with individuals in this age range have suggested that body composition is the key point in the relationship between BP and physical fitness and is sufficient grounds for promoting the regular practice of physical activity. However, excess weight seems to play a fundamental role in the development of hypertension and of an abnormal metabolic profile in children and adolescents. Long-term, longitudinal studies may help to understand the impact of regular physical activity and higher cardiorespiratory fitness in early stages of life on BP and other cardiovascular risk factors.

In a modern view of AH and cardiovascular risk, vascular injury and an accelerated vascular aging are seen as indicators of increased risk of cardiovascular morbidity and mortality since early age.[2]

The study conducted in Rio de Janeiro was one of the pioneers in the evaluation of the relationship between arterial stiffness and excess weight in the young. The study participants (n=96) were stratified into three groups according to the pulse wave velocity tertile for each sex. The group in the highest tertile showed higher mean values for body mass index, BP, systolic and diastolic BP, insulin, and HOMA-IR, lower adiponectin levels, and higher prevalence of diabetes mellitus, glucose intolerance and hyperinsulinemia. Pulse wave velocity showed a significant positive correlation with body mass index, systolic and diastolic BP, mean BP, pulse pressure and low-density lipoprotein cholesterol levels, and a significant negative correlation with high-density lipoprotein-cholesterol and adiponectin. In the multiple regression model, after adjustment for HDL-cholesterol, LDL-cholesterol and adiponectin by sex, age, body mass index and mean BP, only male sex and mean BP remained significantly correlated with pulse wave velocity.[9]

The association between body composition, cardiorespiratory fitness and arterial stiffness in young Swedish adults was investigated by Fernberg et al.,[10] The authors found a negative correlation of body mass index/cardiorespiratory fitness with pulse wave velocity. Young adults with obesity and low cardiorespiratory fitness had significantly higher pulse wave velocity than non-obese young adults with medium or high cardiorespiratory fitness. In the multiple regression analysis, cardiorespiratory fitness had a stronger effect on arterial stiffness as compared with body mass index.

This association between low cardiorespiratory fitness and arterial stiffness was also observed by Haapala et al.,[11] in a study with children with chronic diseases. In their study, low cardiorespiratory fitness and increased waist circumference were associated with increased arterial stiffness in children and adolescents with chronic diseases and physical disabilities.

The role of physical exercise in vascular health is still controversial. Intense resistance training, without additional aerobic exercises, can increase pulse wave velocity in healthy young individuals. However, aerobic exercise seems to be a strategy capable of maintaining or restoring healthy arterial aging. This favorable effect of aerobic exercise on vascular health seems to occur regardless of its effect on BP; it involves anti-inflammatory and anti-proliferative effects and influences vasodilation of small and medium-sized vessels that directly affect wave reflection, and consequently augmentation index and central systolic pressure.[12]

The meta-analysis by Cote et al.,[13] compared arterial stiffness measures of obese children and adolescents with those of a control group with normal body mass index. The authors demonstrated a significant effect of obesity on pulse wave velocity, indicating greater arterial stiffness in children and adolescents with obesity than controls.

Therefore, overweight seems to be the key element associated with different clinical scenarios including elevated BP, inadequate habits, altered metabolic profile, cardiovascular risk factors and subclinical vascular abnormalities. Maintenance of an adequate body weight should be one of the pillars of primary prevention strategies in young populations.

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ORIGINAL ARTICLE

Effect of the Brazilian Cardioprotective Nutritional Program on the Quality of Life of Atherosclerotic Disease Patients

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Abstract

Background: Cardiovascular diseases (CVD) accounted for 27% of deaths in Brazil in 2017. Most of the recorded deaths caused by CVD would be preventable if patients controlled risk factors including inadequate diet. The Brazilian Cardioprotective Nutritional Program (Dica Br) adapted the Mediterranean diet pattern to Brazilian typical foods and evaluated the effectiveness of a nutritional program based on cardioprotective foods on cardiovascular events and death of patients with cardiovascular diseases.

Objectives: To evaluate the effect of Dica Br on the QoL of patients with atherosclerotic disease from two health centers in the city of Rio de Janeiro.

Method: Randomized clinical trial with 273 participants of both sexes, over 45 years old, followed for four years. The intervention group (IG) received individualized dietary prescription, educational program, individual and group consultations, and phone calls. The control group (CG) received general dietary guidance. The SF-36 was used to assess QoL. The Student's t-test and the Mann-Whitney test was used to compare means between the groups. The mixed model test was used to compare the course of variables over time between the groups. Statistical significance was set at 5%.

Result: Most patients were male, with an average age of 64.2 ± 8.2 years in the IG and 65±9.5 years in the CG. Most were physically inactive, overweight, and had incomplete elementary school. The most prevalent comorbidity was systemic arterial hypertension, followed by dyslipidemia. QoL improved in both groups at four years. Waist circumference decreased in both groups over time, and low-density lipoprotein cholesterol (LDL-C) levels decreased in the IG but not in the CG after four years of follow-up.

Conclusion: The cardioprotective diet was effective in reducing LDL-C in the IG, and an improvement in QoL was observed in both intervention and control groups.

Keywords: Quality of life; Diet, Atherosclerosis; Cardiovascular diseases; Disease Prevention.

Introduction

Cardiovascular diseases (CVD) accounted for 45% of deaths in the world in 2015, causing a great impact on statistics.[1] In Brazil, mortality rates from diseases of the circulatory system are also high and represented 28% of deaths in 2017.[2] Therefore, CVD is considered a major public health problem. Most of the recorded deaths caused by CVD would be preventable if patients followed the prescribed medical treatment and controlled risk factors, including inadequate diet, smoking, obesity, physical inactivity, high blood pressure and high cholesterol levels.[3]

CVDs are debilitating conditions, with a progressive course and multiple factors, such as physical limitation and risk of death, that affect the improvement of the

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diseases and patients' quality of life (QoL).[4] A poor QoL is associated with depression, social exclusion, anxiety, and consequently worsening of diseases, leading to an increased use of medications and increased incidence of CVD, leading to a vicious cycle.[5–7]

The main risk factor for CVDs is unhealthy eating, and the relationship between dietary patterns and the disease has been studied in recent years. One of these patterns, called the "western diet", is rich in total fats, cholesterol and refined sugar, and poor in dietary fiber. It is closely related to a sedentary lifestyle and the occurrence of chronic non-communicable diseases.[8–10] Meanwhile, the Mediterranean diet[11–14] has been shown to have a consistent and positive association with cardiovascular and metabolic health, [9,15,16] as well as with higher rates of QoL.[17,18]

The multicenter clinical trial Dica Br evaluated the effectiveness of implementing a nutritional program based on cardioprotective foods on cardiovascular events and death in patients with established CVD. The trial adapted the Mediterranean diet pattern to Brazilian typical foods that are easily accessible, low cost, and clearly prescribed, respecting regional characteristics, thus favoring adherence by the Brazilian population.[19–22]

The objective of this study was to assess the effects of the Dica Br on the QoL and nutritional status of participants over a four-year follow-up period.

Methods

Study Design

This is a randomized clinical trial conducted at the National Institute of Cardiology (INC) and at the Piquet Carneiro Polyclinic (PPC-UERJ). This study is an integral part of the Dica Br, whose design has been described and published previously.[20]

The study protocol was approved by the Research Ethics Committees of the INC and the Pedro Ernesto University Hospital of the State University of Rio de Janeiro (HUPE), in accordance with Resolution No. 466 of December 12, 2012, of the National Health Council (approval numbers 03218512.0.2006.5272 and 03218512.0.2002.5259, respectively). All participants were informed about the procedures and signed an informed consent form.

The participants received personalized dietary guidance and food calorie distribution according to the Dica Br food groups. They also received educational guidance, individual and group consultations, and a cookbook. The control group received a generalized guidance only, with a list of foods to be avoided, and no caloric value.

Participants

The trial was initially carried out with 273 participants from two study centers. Inclusion criteria were adults of both sexes, aged 45 or over; with previously documented CAD, stroke, myocardial revascularization and/or angioplasty, peripheral arterial disease, or hospitalization for unstable angina.

Exclusion criteria were inability to eat by mouth; clinical suspicion or diagnosis of hepatic encephalopathy or other liver diseases; cancer patients; patients who underwent gastroplasty; patients with previous organ transplantation; wheelchair users; patients in the immediate postoperative period of cardiac surgery (up to 30 days after surgery); patients diagnosed with heart failure at any stage of the disease.

Randomization

Eligible participants were randomly assigned (1: 1) to the intervention group (IG) or the control group (CG). Randomization was performed in blocks with stratification by study location. The allocation concealment was guaranteed through an automated centralized system, available on the web 24 hours a day.

Intervention

The intervention consisted of three components: (a) dietary prescription; (b) educational program based on playful educational strategies and suggestions of food choices; and (c) individual interviews, group sessions and contact by telephone. Participants received a booklet with information on the diet they should follow, including caloric value, distribution, portions and food groups, recipes, tips and general information about the program, in addition to the cookbook.

The foods were divided into three groups according to the following criteria: no added sugar; low calories; no nutrients that increase cardiovascular risk (cholesterol, saturated fat, and sodium), and the presence of cardioprotective nutrients (antioxidants and fibers). This qualitative selection generated a list containing skim milk and yogurt, fruits and vegetables, and beans. This group was called "green". The cutoff point was established based on a caloric density ≤1.11 kcal/g, fatty

acids ≤0.001 g/g, cholesterol ≤0.04 mg/g and sodium ≤2.01 mg/g.[23] Foods containing one or two nutrients above the cutoff point were allocated to the yellow group, and those containing three or four nutrients above the cutoff point were categorized in the blue group.

The green color occupies the greatest area on the flag, which correlates with the green food group that should be consumed in greater quantity. Yellow comes in second place, suggesting a lower intake, and the blue, which is in a small part, an even more restricted intake. The red group consists of foods containing trans fat, refined sugar, artificial sweeteners and preservatives, as well as ultra-processed foods, and their consumption has been totally discouraged. As the red group is not shown on the flag, the food in that group should not be consumed.

The total energy value (TEV) was calculated using the formula of 20 kcal/kg of the current weight for weight loss (obesity and overweight), and 25 kcal/kg/weight for normal-weight patients.[20] Aiming to promote adherence to the diet, dietary prescriptions contained the numbers of food portions of the green, blue and yellow groups by meals. All participants were seen individually every six months. In the first two years, once a month, participants received a telephone call to reinforce their understanding of the program and reinforce dietary points. In the third and fourth years they received a call every four months. Participants also attended group meetings every four months, from the 28th to the 44th month, with lectures with topics on nutritional and motivational education prepared by the program to increase adherence.

Control

Participants were instructed to follow a diet based on low-fat and low-sodium foods. They all received a folder containing a list of foods that should be avoided and foods that should be preferred. It was a qualitative diet, without calculation of the TEV. Caloric restriction was made by replacing high-energy-density foods by low-energy-density foods. These participants were seen in face-to-face, individual sessions every six months for four years. Anthropometric data and blood samples were collected, the 24-hour food recall was applied and information on lifestyle habits and QoL was collected.

Study steps

During their half-yearly visits to the data collection sites, participants underwent individual interviews, blood collection for biochemical analysis, anthropometric analysis, physical activity assessment questionnaire, a 24-hour dietary recall, and the Medical Outcomes Study 36-item Short-Form Healthy Survey (SF-36) questionnaire, and received guidance regarding diet, as shown in Figure 1.

Sample

A convenience sampling was used to recruit 273 patients in the two study centers, over the period of one year.

Anthropometric assessment

Body weight was measured in kilograms (kg), using an electronic body weight scale (Líder®) with a stadiometer, with a maximum of 200 kg, precision of 100 g and accuracy of 1 mm, positioned on a flat surface. The patients were weighed barefoot. Height was measured in meters (m), with participants barefoot, with the head in the Frankfurt plane, and arms extended along the body. Weight and height measurements were used to calculate the body mass index (BMI).

Waist circumference (WC) was measured with a flexible, inelastic measuring tape to the nearest 0.1 cm, with the subject in an upright position, abdomen relaxed, arms alongside the body and feet together. The measurement was taken at the midpoint between the last rib and the iliac crest, and the result expressed in centimeters (cm).

Biochemical evaluation

Blood collection was performed by a trained technician, after a 12-hour fast. Blood samples were collected in a tube containing coagulant. After 30 minutes of coagulation at room temperature, they were centrifuged at 4000 rpm for 15 minutes to obtain serum. The samples obtained were analyzed by the hospital biochemical analysis laboratory on the same day of collection.

Quality of Life Assessment

To assess QoL, the SF-36 questionnaire[24,25] was used. This questionnaire was chosen because it is more extensive and not specific to a given population. It consists of 36 items distributed in eight domains: functional capacity, physical aspects, pain, general health, vitality, emotional aspect, social aspect, and mental health. Domains 1 to 4 deal with physical aspects, while domains 5 to 8 measure

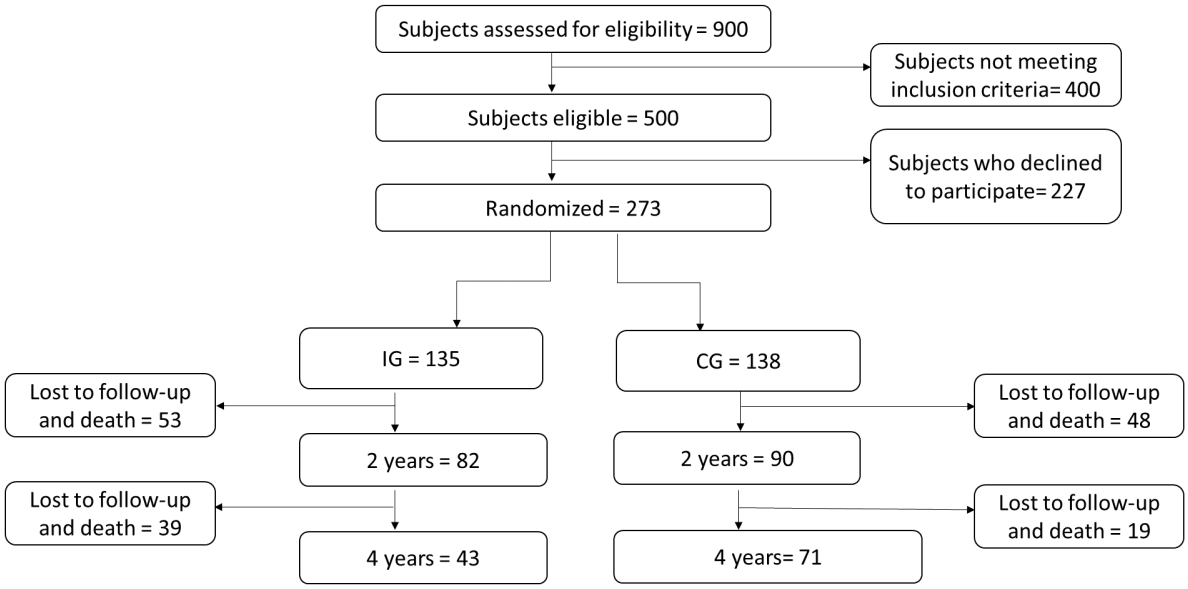

Figure 1 – Flowchart of patient selection.

emotional characteristics. For each parameter, the scores were coded, added and transformed on a scale from 0 (the worst possible condition) to 100 (the best possible condition). In the case of body pain domain, a score of 100 means complete tolerance or absence of pain. Each dimension is analyzed separately, there is no single value that summarizes the entire assessment, translating into a better or worse general health condition. The purpose is to avoid, on an average of values, failure to identify the actual problems related to the interviewee's QoL and health, or underestimate them. For the analysis of the SF-36 questionnaire, the free app Qualipes, available at https://app.qualipes.com.br, was used.

Financial resources

This study was funded by the Heart Hospital (HCor), as part of the program "Hospitals of Excellence in Health Services (PROADI-SUS)", in partnership with the Ministry of Health of Brazil.

Statistical analysis

The data were evaluated using the statistical program Statistical Package for the Social Sciences® (SPSS) version 23.0 (SPSS Incorporation), GraphPad Prism version 8.3.0.538 and Stata Corp LLC (Stata 13) Texas, USA. Data are expressed as mean (standard deviation) for variables with normal distribution, median (P25-75) for nonparametric variables, and percentages for dichotomous variables. The Kolmogorov-Smirnov normality test was used to verify the distribution the continuous variables. The chi-square test was used to compare dichotomous variables. The student's t-test or the Mann-Whitney U test was used to compare means between the groups. Differences in the responses of QoL domains between different intervention protocols (control and intervention groups) were evaluated by linear mixed models,26,27 with the inclusion of the variables time, protocol, and interaction term (time*protocol), which estimates the response rate of the outcome over time (term of interest). The significance value was set at 5%.

Results

Two hundred seventy-three subjects started the study, but only 114 reached the end, representing a percentage loss of 58.3%. Subjects were diagnosed with atherosclerotic disease documented in medical records, 142 of whom were followed at the INC and 131 at the PPC. They are all part of the national multicenter study entitled "Effect of the Brazilian Cardioprotective Nutritional Program to reduce events and risk factors in secondary prevention for cardiovascular disease: a randomized clinical trial".

Nine hundred medical records were selected, of which 400 did not meet the eligibility criteria. Of this total, 273 patients agreed to participate in the trial. After electronic randomization, the subjects were divided into two groups, 135 in the IG and 138 in the CG. In the second year of the study, there were 53 dropouts or deaths in the IG and 48 in the CG. At the end of the study, 43 subjects in the IG and 71 in the CG had completed it, that is, a percentage of 32% and 71% respectively (Figure1).

Table 1 compares the subjects who completed the trial and those who dropped out. Besides having similar quality of life scores, no differences were found in age, weight, sex, BMI, education and physical activity between these subgroups. Those who dropped out had higher HDL, lower cholesterol and glucose levels.

Table 2 shows general characteristics of participants by study group. Mean age of CG was 64.2 ± 8.2 years and 65 ± 9.5 years in the IG. Most participants were male (82% in the CG and 63.7% in the IG), physically inactive (65.2%

Table 1 – Comparison of demographical, laboratory and quality of life data between participants who finished and dropped out of the study

Variables	Finished	Dropped out	p
n (%)	114 (42%)	159 (58%)	
Age (years)[b]	64.15 ±7.61	64.95 ±9.69	0.720
Weight[b]	76.88 ±14.48	77.04 ±15.24	0.459
Body mass index[b]	29.6 ±4.80	29.40 ±5.23	0.664
Gender - male[t]	61.06 (69)	61.88 (99)	0.892
Marital status - married[t]	52.68 (59)	53.46 (85)	0.668
Incomplete elementary school[t]	28.57 (32)	33.96 (54)	0.430
Physically inactive[t]	67.86 (76)	70.51 (110)	0.642
Ex-smoker[t]	62.73 (69)	54.84 (85)	0.439
Ex-alcoholic[t]	37.50 (42)	35.48 (55)	0.629
Total cholesterol (mg/dL)[a]	167.0 (138.5-206.0)	170.5 (137.0-205.2)	0.792
LDL-C (mg/dL)[a]	91.0 (74.0-118.5)	94.5 (72.8-122.0)	0.641
HDL-C (mg/dL)[a]	39.0 (33.0-45.0)	44.0 (36.0-55.5)	0.001*
Triglycerides (mg/dL)[a]	152.0 (104.5-207.5)	114.0 (88.5-165.5)	0.000*
Glucose (mg/dL)[a]	122.0(102.0-166.0)	108.5 (97.3-134.0)	0.001*
Glycated hemoglobin (%)[a]	6.7 (5.8-8.2)	6.0 (5.7-6.7)	0.000*
Physical functioning[a]	53 (30-75)	55 (30-85)	0.454
Role physical[a]	25 (90-75)	50 (0-81)	0.441
Bodily pain[a]	52 (31-72)	51 (30-84)	0.860
General health[a]	67 (42-87)	67 (49-82)	0.839
Vitality[a]	60 (35-80)	65 (40-80)	0.443
Social functioning[a]	75 (50-100)	75 (50-100)	0.401
Role emotional[a]	100 (0-100)	66 (33-100)	0.481
Mental health[a]	76 (48-88)	72 (52-85)	0.750

*Values expressed as means ± standard deviation, median (P25-75) and percentage (n). LDL: low-density lipoprotein; HDL: high-density lipoprotein; Student's t-test[b], Mann-Whitney[h] test and chi-square test[t]. * Statistical difference (p <0.05).*

Table 2 – General characteristics of study participants by randomization group

Variable (n)	Control group	Intervention group	p value
n	138	135	
Age (years)[b]	64.2 (± 8.2)	65 (± 9.5)	0.448
Gender - male % (n)[ǂ]	82 (59.4)	63.7 (86)[ǂ]	0.535
Marital status - married % (n)[ǂ]	55.1 (76)	51.13 (68)	0.647
Incomplete elementary school % (n)[ǂ]	33.3 (46)	30.01 (40)	0.649
Physically inactive% (n)[ǂ]	65.2 (90)	73.85 (96)	0.116
Ex-smoker[ǂ]	60.6 (83)	55.5 (71)	0.595
Ex-alcoholic[ǂ]	39.0 (53)	35.6 (44)	0.398
Overweight % (n)[ǂ]	46.7 (63)	38.7 (53)	0.434
Hypertension % (n)[ǂ]	95.6 (131)	97.0 (131)	0.535
Dyslipidemia % (n)[ǂ]	94.2 (129)	88.1 (119)	0.159
Diabetes mellitus % (n)[ǂ]	54.7 (75)	53.3 (72)	0.596
Acute heart attack % (n)[ǂ]	62.8 (86)	67.4 (91)	0.427
Angina % (n)[ǂ]	51.1 (70)	54.8 (74)	0.438
Myocardial revascularization surgery %(n)[ǂ]	43.8 (60)	42.2 (57)	0.793
Weight (kg)[b]	77.3 (± 14.5)	78.4 (± 15.4)	0.548
Waist circumference (cm)[b]	100.8 (± 13.2)	100.7 (± 12.2)	0.934
Total cholesterol[a]	171 (137-206.7)	165.5 (140.2-204)	0.534
HDL-C[a]	40 (33-48)	40 (34-50)	0.958
LDL-C[a]	94 (73-119)	94 (76-120)	1
Triglycerides (mg/dL)[a]	130.5 (96.5-191.2)	141 (95-201)	0.418
Glucose (mg/dL)[a]	117 (101.50-153)	113 (99.5-153.5)	0.802
Glycated hemoglobin (%)[a]	6.3 (5.7-7.5)	6.3 (5.8-8.2)	0.751
Physical functioning[a]	55 (37.50-80)	50 (30-75)	0.945
Role physical[a]	25 (0-100)	25 (90-75)	0.680
Bodily pain[a]	51 (31-74)	52 (30-72)	0.856
General health[a]	67 (46-83.50)	67 (45-87)	0.966
Vitality[a]	60 (37.50-80)	60 (40-80)	0.578
Social functioning[a]	75 (50-100)	75 (50-100)	0.497
Role emotional[a]	66 (0-100)	100 (33-100)	0.364
Triglycerides (mg/dL)[a]	72 (52-88)	72 (48-88)	0.953

Values expressed as means ± standard deviation, median (P25-75) and percentage (n).
*T-Student test[b], Mann-Whitney[a] test and Q-square test[ǂ]. * Statistical difference (p <0.05).*

CG and 73.8% IG), and 33.3% in the CG and 30% in the IG had incomplete elementary education. Among the most reported diseases, systemic arterial hypertension was the most prevalent (97% of patients in the IG and 95.6% in the CG), followed by dyslipidemia (88.1% in the IG and 94.2% in the CG). A high rate of overweight, a known risk factor for CVD, was found among study participants of both groups. No difference in QoL scores or in any other variable was found between the groups.

Figure 2 shows the impact of the intervention on anthropometric and biochemical data over the four years of study. Although no changes in body weight and BMI were observed in the groups, WC showed a significant reduction over time, with no statistical difference between the groups though. LDL and total cholesterol levels significantly reduced in the IG but not in the CG, leading to a significant difference between the groups. Glycated hemoglobin levels also decreased in the IG, and no differences in HDL, triglycerides or glucose levels were observed between the groups.

Figure 3 shows the graphs with the analysis of the QoL scores. All domains and subdomains, except mental health, showed improvement over time, but no statistical difference was found between groups.

Table 3 presents the linear regression analysis of QoL domains in IG and CG at 2 and 4 years of follow-up. In the first analysis, results of the SF-36 were compared between the groups without adjustments, and in second the comparison, results were adjusted for BMI, age, and sex. No differences were found in neither analysis between groups over time.

Discussion

In recent years, eating patterns have changed in almost every nation in the world. At the same time, the science of nutrition has advanced remarkably. The importance of adopting an adequate dietary pattern for the prevention and treatment of atherosclerotic disease is clear.

The present study evaluated the effects of the cardioprotective diet on the QoL of atherosclerotic disease patients participating in the multicenter clinical trial Dica Br over four years of intervention. An improvement in the general QoL of participants was observed after the dietary intervention. Studies using dietary patterns have shown an improvement in QoL associated with improvements in the quality of the diet.[28–30]

Study participants were on average 65 years old, mostly married men with incomplete elementary education. We found some studies in the literature with a population similar to ours, but with a much higher number of participants, such as the study by

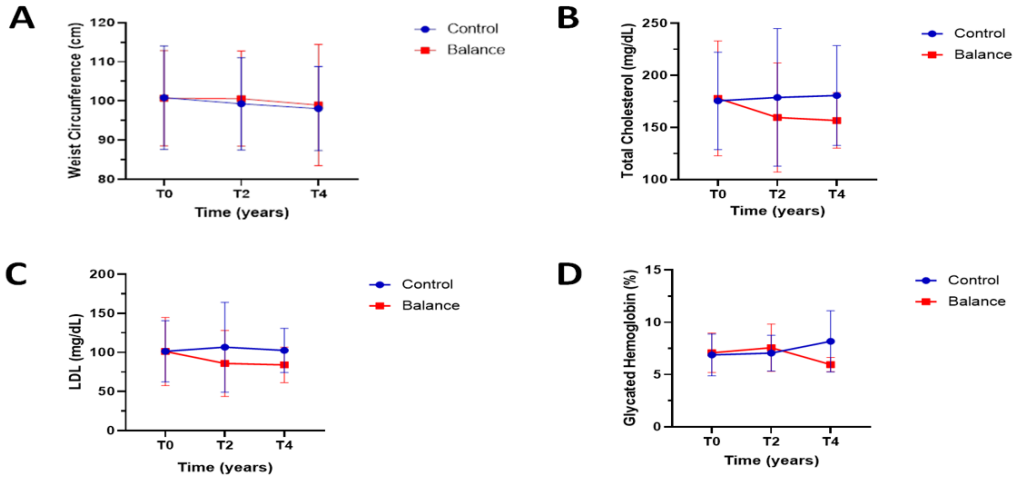

Figure 2 – Graphs respresenting the analysis of waist circumference, total cholesterol,low-density lipoprotein (LDL)-cholesterol and glycated hemoglobin at baseline, two years and four years of follow-up in the intervention group and control group. A. waist circumference: time = p=0.0001; group p=0.470; time x group p=0.1559; B. total cholesterol: time p=0.2048; group p=0.1268; time x group p=0.0462; C LDL: time p=0.3498; group p=0.0437; time x group p=0.0222; D glycated hemoglobin: time p=0.7801; group p=0.2035; time x group p=0.0224. Linear mixed model test

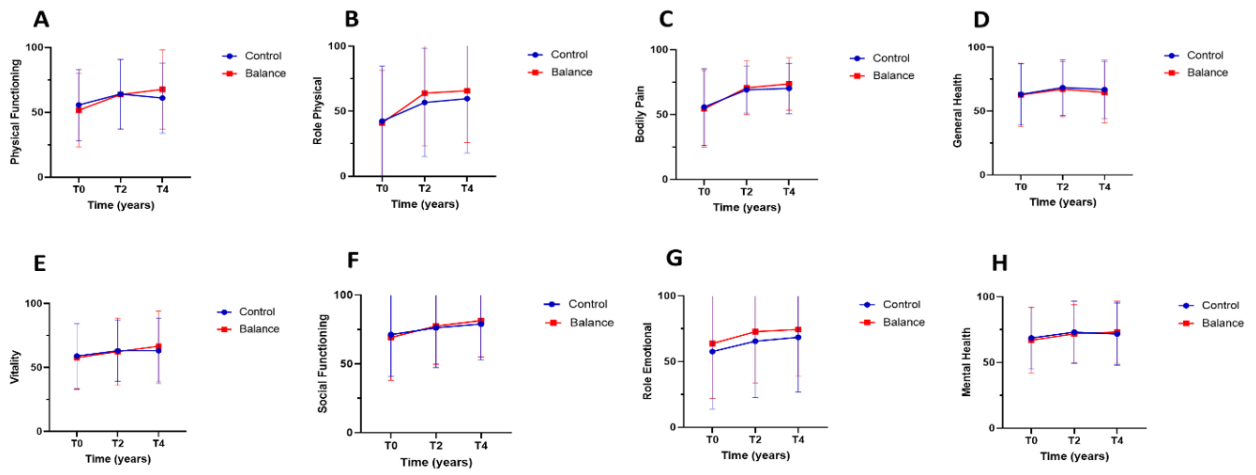

Figure 3 – Graphs representing the analysis of quality of life domains obser the four years of study. A physical functioning: time p=0.0001, group p=0.9745, time x group p=0,1613; B role physical: time p=0,0001, group p=0,3813, time x group p=0,4102; C bodily pain: time p=0,0001, group p=0,6404, TxG p=0,5727; D general health: time p=0,0488, group p=0,5744, time x group p=0,8771; E vitality: time p=0,0329, group p=0,8942, time x group p=0,7134; F social functioning: time p=0,0009, group p=0,9025, time x group p=0,6666; G role emotional: time p=0,00086, group p=0,1449, time x group p=0,9963; H mental health: time p=0,0542, group p=0,7604, time x group p=0,8802. Lineal Mixed

Milte et al.,[31] in Australia, with 2,457 patients between 55 and 65 years old, where they evaluated adherence to a Mediterranean diet and association with QoL.[31] In the study by Pérez-Tasigchana et al.[14] in Spain, 2,376 elderly people were enrolled, and most had completed high school; adherence to the Mediterranean diet was associated with QoL.[14] Our study is part of the Dica Br study,[19] and our population representative of the Dica Br program.

Our study focused on tertiary prevention in sample of CVD patients with hypertension, diabetes, and dyslipidemia as the most prevalent comorbidities. When performing the cardiovascular risk assessment using anthropometric and biochemical indices, we observed that our participants were classified as at increased risk. It is worth mentioning that all patients in the study presented a previous cardiovascular event, and most of them were overweight, physically inactive and hypertensive. Characteristics of our population were similar to that in the study by Jahangiry et al.,[32] in Iran, where most patients were overweight, had increased WC and hypertension.

WC is a simple measure that has a close correlation with central adiposity and is therefore a good marker of cardiovascular risk. In our study we found a significant reduction in WC in the participants of both intervention and control groups. Renzo et al.,[11] evaluating the effects of a dietary intervention in 188 subjects, for four weeks in Italy, demonstrated a decrease in gynoid body adiposity in the group that underwent intervention with an isocaloric Mediterranean diet.

In our study, the IG showed a significantly greater reduction in serum LDL-C levels after four years of intervention when compared to the CG. At the end of the study, total cholesterol and glycated hemoglobin showed differences between the groups. In their clinical trial, Castres et al.[33] also observed a decrease in serum LDL-C levels after six months of intervention with a balanced diet and a program of 10,000 steps per day. Estruch et al.[13] found an increase in serum HDL-C levels in subjects undergoing a Mediterranean-style dietary intervention. In our study, the improvement in serum LDL-C levels in the IG can be justified by the recommendation to not consume ultra-processed products, in accordance with the guidelines for the treatment and prevention of dyslipidemia.[15,16,34] In addition, a guideline from the American College of Cardiology (ACC) and the American Heart Association (AHA), published in early 2019, points to lifestyle change as an extremely important item in the prevention and treatment of CVD.[16] Then, in addition to dietary practices, other lifestyle changes such as regular exercise, smoking cessation, meditation

Table 3 – Assessment of quality of life domains (SF-36 questionnaire) between the groups over the four years of the study

	Without adjustment			Adjusted for BMI, age and sex		
Variable	β	95%CI	p value	β	95% CI	p value
Physical Functioning						
Time 2	4.45	-2.52 11.43	0.210	4.39	-2.58 11.37	0.217
Time 4	7.76	-0.66 16.19	0.071	7.56	-0.95 16.07	0.082
Role Physical						
Time 2	8.77	-4.67 22.22	0.201	8.05	-5.45 21.55	0.242
Time 4	6.85	-9.25 22.95	0.405	7.96	-8.38 24.29	0.340
Bodily Pain						
Time 2	3.34	-4.95 11.63	0.429	3.51	-4.76 11.78	0.406
Time 4	4.76	-5.16 14.67	0.347	3.63	-6.32 13.59	0.474
General Health						
Time 2	-1.25	-7.98 5.47	0.715	-0.86	-7.63 5.90	0.803
Time 4	-1.95	-10.05 6.16	0.638	-3.52	-11.77 4.71	0.401
Vitality						
Time 2	1.42	-5.95 8.79	0.706	1.53	-5.75 8.80	0.681
Time 4	3.72	-5.15 12.60	0.411	2.59	-6.26 11.45	0.566
Social Functioning						
Time 2	2.67	-6.56 11.89	0.571	3.03	-6.29 12.36	0.524
Time 4	4.86	-6.21 15.93	0.389	4.44	-6.85 15.13	0.440
Role Emotional						
Time 2	0.08	-13.60 13.77	0.990	0.19	-13.49 13.86	0.979
Time 4	0.72	-15.67 17.10	0.932	0.65	-15.86 16.16	0.938
Mental Health						
Time 2	0.40	-5.95 6.76	0.901	0.63	-5.74 7.02	0.847
Time 4	1.97	-5.69 9.640	0.614	1.48	-6.30 9.67	0.709

**Statistical difference ($p < 0.05$). Mixed linear regression. B: Beta coefficient, CI: Confidence Interval, BMI: Body mass index.*

and others, should be incorporated into the Dica Br program to improve cardiovascular outcomes.[19]

Appropriate dietary recommendations can play an essential part in the prevention and treatment of chronic diseases and consequently in the improvement of QoL. Authors have consistently demonstrated this association in intervention and observational studies. For example, in a randomized clinical trial with dietary intervention with postmenopausal women in the United States, with individual monitoring by a nutritionist and group consultations, showed a slight but significant improvement in the rates of quality of life.[30] Another study, also in the United States, with obese adults of both sexes, with group consultations, dietary guidance and physical activity, showed an improvement in QoL of participants.[35] There was an improvement in the QoL of our participants after four years of dietary intervention, with individual and group consultations. However, such improvement was not different as compared with the CG.

Regarding the most studied dietary patterns, the Mediterranean pattern stands out in the scientific literature[8,14,36,37] for its role in the prevention and treatment of CVD in many parts of the world, including Brazil.[15,16,34,38,39] However, the foods that make up this diet are typical of countries bathed by the Mediterranean Sea and are not usually consumed in Brazil, where they are often expensive. With the clear objective of adapting the Mediterranean diet to Brazilian food standards, the Cardioprotective Diet study considered the access to food, the cost and the clear understanding of the program by the participants.[20] The nutritional strategy was an attempt to increase accessibility to the diet, by adapting the menu to cultural specifications and encouraging the consumption of local products. In addition to fruits and vegetables, the consumption of larger amounts of other cardioprotective foods was recommended. However, despite the recommendation to consume locally produced food, some participants may have considered it as a costly option, which may have contributed to drop-out or low adherence. The program, with individual and group consultations, telephone calls and a cookbook, with the intention of holding participants' attention and facilitating adherence to the program, was intended to prevent cardiac events – stroke, infarction, angina and death – and improve QoL of these patients.[40] Also, the low adherence to the program and the advanced age of the participants may have contributed to a loss to follow-up of 58.3% at the end of four years (68.1% in the IG and 48.5% in the CG), in contrast to other studies on dietary intervention in diabetic, hypertensive, dyslipidemic patients that showed lower loss rates.[11,36]

In a four-year cohort study with 2,376 elderly participants in Spain, Pérez-Tasigchana et al. observed that there was no association between high adherence to diet and improved QoL.[14] Torres et al.,[41] in a study in Australia with 100 elderly women with a mean age of 60 years, evaluating the effects of a high-protein diet and physical activity program, showed that there was no significant difference in the QoL between intervention and control groups, despite the higher scores in the physical domains obtained by the group undergoing the high protein diet.[41]

We believe that the fact that these patients were already in tertiary prevention, that is, they had previously been advised about their diet, might be one of the factors that can explain the absence of significant difference between the CG and IG in our study.

The loss to follow-up was one of the main limitations of our study and may have been caused by the low level of education of the participants, which may have led to difficulties in understanding the program. Another possible contributing factor was the fact that they had atherosclerotic disease, often a limiting condition, considering the distance between their home and the hospital.

Conclusion

At the end of these four years of study, we could observe that the QoL of the participants improved, but we did not find any difference between the IG and the CG. There was also an improvement in the LDL-cholesterol fraction and total cholesterol in the IG, which did not occur in the CG. Participants in both groups had a reduction in WC, but apparently, it was not enough to decrease the cardiometabolic risk.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Instituto Nacional de Cardiologia* and the *Hospital Universitário Pedro Ernesto da Universidade do Estado do Rio de Janeiro* under the protocol number 03218512.0.2006.5272 and 03218512.0.2002.5259, respectively. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Author contributions

Conception and design of the research: Weber B, Moreira ASB. Acquisition of data: Martins PRT. Analysis and interpretation of the data: Martins PRT. Statistical analysis: Martins PRT, Santos EM, Rodrigues Junior LF. Obtaining financing: Weber B. Writing of the manuscript: Martins PRT. Critical revision of the manuscript for intellectual content: Moreira ASB, Santos EM.

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EDITORIAL

The Present and Future of the Cardioprotective Food Model for the Brazilian Population

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Editorial referring to the article: Effect of the Brazilian Cardioprotective Nutritional Program on the Quality of Life of Atherosclerotic Disease Patients

In recent decades, researchers have found important changes in the health pattern and food consumption of the Brazilian population. These changes have been associated with chronic non-communicable diseases, especially cardiovascular disease.[1]

The Global Burden of Disease Study (2019), which analyzed data on chronic non-communicable diseases in 204 countries and territories between 1990 and 2019, estimated that cardiovascular disease, which is attributable to modifiable risk factors such as cholesterol level, is the main health care burden worldwide. High LDL cholesterol and its associated mortality remain a major threat to public health. The report recommends that national health systems focus on new approaches that can reverse these trends, since there is an urgent need to implement effective policies and interventions to achieve a 30% reduction in premature mortality from non-communicable diseases.[2]

In this context, the World Health Organization recommends public policies focused on health strategies and periodic updating of national guidelines on food and nutrition that consider changes in eating habits and the health conditions of the population. Countries should invest in cost-effective programs and clinical interventions not only to address modifiable risks, but also to promote healthy aging, reducing disability and premature death from cardiovascular disease.[1,3]

The Mediterranean diet is the only diet that health and nutrition research has found to be effective in reducing cardiovascular events. However, in view of the social transformations in Brazil, which have impacted its health and nutrition conditions, the Brazilian Cardioprotective Diet (*Dieta Cardioprotetora Brasileira* – DICA-BR) was created to adapt Mediterranean diet standards to typical Brazilian foods in an effort to protect the population's heart health. The DICA-BR is in line with the recommendations of the Food Guide and addresses the consumption of natural, minimally processed, and processed foods. However, individuals with some cardiovascular risk should receive specific guidance about managing their diet.[1,3]

The DICA-BR was based on the typical Brazilian diet, using the colors of Brazilian flag to classify food groups. The largest area of the flag is green, followed by yellow and blue, and the food groups follow this same logic. Since foods in the green group are cardioprotective, including vitamins, minerals, fiber, and antioxidants, and have no nutrients that can harm the heart, such as saturated fat, cholesterol, and sodium, they should be consumed in greater quantities. Foods in the yellow group should be consumed in moderation, since they have more calories, fat, or salt than the green group. Blue group foods should be consumed in yet smaller quantities, because they contain saturated fat, salt, and cholesterol, nutrients that can harm heart health. A red group was also created to include ultra-processed foods, whose consumption is not encouraged.[3]

A total of 35 reference centers for CVD treatment participated in the DICA-BR study to determine the efficacy of a typically Brazilian diet for preventing and reducing risk factors for cardiac events, including hypertension and high levels of total cholesterol, LDL, and triglycerides, as well as changes in blood glucose, weight, and waist circumference.[3,4]

Keywords

Quality of Life; Diet; Cardiovascular Diseases/prevention and control; Cardiotonic Agents/administration and dosage; Public Health; Epidemiology; Diet, Food and Nutrition/habits.

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The DICA-BR diet is a balanced distribution of cardioprotective nutrients, prioritizing the most common and accessible foods in Brazil. The researchers evaluated 2,534 patients with heart disease, who were monitored by nutritionists who assessed regional consumption habits and adapted them to a culturally and economically accessible cardioprotective diet.[3,4]

A recent study tested the DICA-BR diet in 273 participants with heart disease and dyslipidemia. The intervention group received individualized diet guidance, educational programs, telephone calls, and individual and group consultations. The control group received general dietary guidance. The results indicated that the DICA-BR was effective in reducing LDL-C and improving quality of life in the intervention group.[5]

Brazilian cardioprotective diet guidelines have been developed to encourage healthy eating practices, and this diet model is very effective because it values, recognizes, and considers the regional eating habits of the Brazilian population in its strategy to protect cardiovascular health. However, global research is needed to improve our understanding of LDL-cholesterol and determine treatment gaps in this persistent worldwide threat to health.

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ORIGINAL ARTICLE

Implementation of a Home-based Exercise Program for Cardiopulmonary Rehabilitation Patients during the SARS-CoV-2 Pandemic

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Abstract

Background: In pandemic times, social isolation is of utmost importance to minimize the spread of the SARS-Cov-2 virus. At times like these, home fitness becomes extremely necessary to avoid sedentarism and decompensation in chronic disease patients.

Objectives: Evaluate the engagement of rehabilitation patients to a tele- oriented exercise program at home (TOEP).

Materials and Methods: 66 of 94 patients (63.8% males; 65.5±14 years old; 5.2±2.6 months in rehabilitation) agreed to take part. Subjects were grouped in three levels of functionality to guide the exercise prescription. Weekly Training Rates (WTR) were compared using the Friedman test and corrected by Dunn's test. A multivariate logistic model was designed to determine independent predictors in program engagement. Statistical significance was determined by a $p<0.05$.

Results: TOEP provided WTR similar to the pre-quarantine values of 2.8/week ($p>0.05$), and 91.8% of patients took part until the end of those 5 weeks. The presence of diabetes was a predicted factor for low engagement to TOEP with relative risk of 0.41 (CI95%: 0.25 to 0.66).

Conclusion: TOEP provided satisfactory engagement in rehabilitation patients. Most of them increased WTR during quarantine. Patients with diabetes displayed lower engagement to the minimum standard frequency.

Keywords: Home Officer; Rehabilitation-Orientation/telemedicine; Rehabilitation Cardiac; Health Services/telemedicine.

Introduction

Ever since infectious disease transmission mechanisms became known, social isolation has been a strategy to control most epidemics.[1] This strategy has been adopted against 2019 SARS-COV2 pandemic in most countries worldwide, with varied rigorousness depending on the region. What seems to be unanimous is the directive for total social isolation for the elderly and chronicle disease patients. The reasons behind this recommendation are the ever-so-great number of recent publications pointing out the unfavorable evolution of COVID-19 among this population. Wu and McGoogan analyzed more than seventy thousand cases of COVID-19, reporting that the mortality rate by COVID-19 was 10.5% for cardiovascular disease patients and 6% for hypertensive patients.[2] These rates were higher than the 2.3% rate noticed in the same sample by the general population. In the same publication, death rate was 8 and 14.8% for individuals between 70 and 79 years old and over 80 years old, respectively. Patients with cancer presented an even higher risk of morbimortality.[3]

Home-based rehabilitation strategies with or without remote monitoring have already been classified as an urgent matter with regard to patients' engagement in rehabilitation programs.[4] Telemedicine strategies have

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been used with this purpose.[5] A meta-analysis including 11 studies concludes that it is at least as effective as a center-based rehabilitation in improving modified risk factors and aerobic capacity.[6]

In pandemic times, keeping chronic disease patients at home with their compensated illnesses is an extremely important clinical and epidemiological measure. Physical exercise becomes imperative in this process. Given the circumstances, remote-based guiding and surveillance strategies supported by technological resources are the only possible tools.[9] This study aims at evaluating the engagement of center-based rehabilitation patients in a tele- oriented exercise program at home (TOEP).

Materials and Methods

Sample

On March 18th, immediately after Health authorities declared social isolation as a sanitary measure to control the pandemic, our rehabilitation center suspended its face-to-face activities. All patients taking part in different kinds of rehabilitation programs were invited to join the Exercise Centre. A total of 94 patients were invited (63.8% men, mean age: 69.0 [58.7; 75.0] years old, and median time at rehabilitation: 5.3 [2.9; 7.4] months). Patients displayed different comorbidities, such as cardiovascular disease, lung disease, cancer, and diabetes. Some of those patients were fragile elderly with sarcopenia or other muscle-skeleton conditions and prehabilitation.

The sudden closing of all establishments made it necessary a fast implementation of a strategy that would enable patients to keep up with the rehabilitation regimen. The proposal should be effective in providing physical activities and either improve or, at best, maintaining patients' physical aptitude. It was also necessary to be easily accessible, so that patients could immediately perform their activities at home, using minimum resources, in a safe way, to ensure no harm to the physical integrity, as well as to respect their level of autonomy and the previously evaluated physiopathological limitations. Lastly, it was of utmost importance that the strategy was sustainable, due to an undetermined staff reduction and limited working hours, while preserving their safety.

Exercise prescription

To make the program viable to all patients, the exercise team elaborated different plans for all three levels of functionality, considering falling risks, degree of autonomy, and patient-training experience (Figure 1). Once the plans were elaborated, to better adapt to the exercises, patients were analyzed one by one and then classified in accordance with plans A, B, and C. Some patients who required specific attention beyond the three plans were allocated in a special plan (SP). Based on the Rockwood et al.[10] protocol, patients' individual frailty level was verified after group distribution.

Exercises were prescribed using body weight, whole body, or most of the muscle groups. Isolated upper-body exercises were not prescribed due to the difficulty of performing them without additional equipment. The number of exercises, the execution (stable positioning), the use of support and the speed to execute were differentiating issues between plans.

Training load progression was based on volume increase during the weeks, being adjusted by changing the number of repetitions, bout duration and number of series in each session or adjusting recovering interval between series in each suggested band (Figure 1). Demonstrative videos were recorded to help patients understand each exercise. Each exercise plan was designed to last 30 to 45 min. Patients with access to ergometers or open spaces would be instructed to choose a free complementary aerobic exercise such as a 10-30-minute additional walk. To maintain low intensity, we used as reference anaerobic Heart rate predetermined in a cardiopulmonary exercise test or effort subjective perception <5 in a 0-10 scale.

Surveillance

Patients were distributed among team professionals, considering one professional assigned to each patient as a reference to contact during social isolation. This professional was in charge of communicating daily with their patients, introduce the program, address doubts, and make themselves available for remote supervision, whenever necessary. A flow of communication was established, where each professional should send their patients a standardized initial message, introducing themselves. Once participation in the program was confirmed, exercise plans A, B, C, or SP were sent with specifications according to each case, as well as explanatory exercise videos. These professionals were responsible for keeping in touch with patients, three times a week, through text messages or email, with a conference call every fifteen days. Weekly reports were

	PLAN A	PLAN B	PLAN C
Functional class	Frail patients with a higher risk of fall or special clinical limitation.	patients with a low risk of fall and few exercise experience or reduced exercise capacity.	Patinets with advanced fitness for reabilitation.
Exercises	A1. Stationary walk (s) A2. Single leg chair Knee extension (R) A3. Isometric pelvic Bridge (s) A4. Hip abduction (R) A5. Front Planck with straight elbow and hands on a bed (s) A6. Calf rise (R) A7. Hip adduction (sited on a chair) (s)	B1. Stationary walk (s) B2. Chair Sit and rise(R) B3. Dynamic pelvic bridge (R) B4. Hip abduction (R) B5. Front plank with straight elbow and hands on a bed (s) B6. Calf rise (R) B7. Hip adduction (sited on a chair) (s) B8. Stationary walk (s)	C1. Stationary Run (s) C2. Chair Sit and rise (R) C3. Lunge (R) C4. Single leg Isometric pelvic Bridge (s) C5. Stationary Run (s) C6. Hip adduction (sat on a chair) (s) C7. Hip adduction (sat on a chair) (s) C8. Front planck (s) C9. Calf rise (R) C10. Bird-dog (s) C11. Stationary Run (s)
Volume range	Sets: 2 to 3 Duration: 6 to 12 (R) or 15 to 30 (s) Rest: 20 to 60 (s) Frequency: 3 to 5 days/ week	Sets: 2 to 3 Duration: 8 to 20 (R) or 20 to 40 (s) Rest: 20 to 60 (s) Frequency: 3 to 5 days/ week	Sets: 2 to 4 Duration: 8 to 20 (R) or 20 to 60 (s) Rest: 20 to 60 (s) Frequency: 3 to 5 days/ week

Figure 1 – Exercise plans general scope.
Source: the author (2020). Exercises with volume based on duration in seconds (s) and on the number of repetitions (R). Unilateral (UL)

added to the database system, stating the number of exercise sessions done in the past week, as well as a brief well-being and symptom evaluation. Since most patients were in the COVID-19 risk group, in case any of them displayed COVID-19 symptoms, exercising would be immediately suspended, and an assistant doctor would be notified.

Complementary assistance

In addition to three doctors and two physical educators in the staff for exercise prescription and control, the program also involved two nutritionists and a psychologist for further complementary assistance. These professionals were able to offer regular online support to patients. Besides physical training, healthy eating behavior and stress control are of utmost importance in these times. Therefore, patients were offered additionally a "healthy entertainment" program, with live videos, where the team of professionals tackled topics regarding food storage and re-use, as well as eating behavior during isolation, exercise recommendation classes, and meditation and mindfulness workshops, aiming at helping to control anxiety.

Statistical analysis

The data distribution was tested using the Kolmogorov-Smirnov test. Continuous variables related to the characteristics of the population were expressed in median and interquartile interval and compared through U-Mann-Whitney test. Age comparison and frailty between training plans was made using the Kruskal-Wallis test. The categorical variables were expressed in percentage and compared through chi-square test or Fisher exact. The variations in weekly training rate (WTR) pre-quarantine and along the five-week TOEP were compared using the Friedman test. Pairwise comparison post-hoc between weeks was made by Dunn's test. Variations in attendance were tested considering a WTR ≥3 per week throughout the weeks and compared by the McNemar test.

It was considered satisfactory engagement WTR≥3 per week in at least 4 out 5 weeks of training. A multivariate logistic regression model was created to determine independent engagement predictors containing age and variables with an error probability alfa ≤10% in the univariate analysis (chi-square and Mann-Whitney U). The statistical significance was defined by an alfa <5% probability error. The statistical analysis was conducted using a SPSS program (SPSS 22.0 for Windows, IBM SPSS, IL, US). This research was approved by the *Hospital Federal Cardoso Fontes* ethical and research committee under the protocol 36149020.6.0000.8066 and 4.258.930. All the procedures are in accordance with the Helsinki declaration 1975, updated in 2013.

Results

Table 1 presents the characteristics of the sample and engagement rate by gender and clinical conditioning. By comparing individuals who participated or not, there was no difference in age, gender-prevailing illnesses and training characteristics. Frailty was the only different variable, with participants frailer than the non-participants.

The distinction between patients in exercise plans A, B, and C enabled effective distinction according to age and patient functionality (Table 2). Individuals classified as plan C were significantly younger than the others. With regard to frailty, group distribution provided the expected distinction, confirmed by the analysis of the Rockwood scale[10], so there was no overlapping in the group distribution.

TOEP had 91.8% engagement among participant patients. With respect to WTR, in the face-to-face physical training program previously adopted by patients, the average was of 2.7±0.1 sessions per week (Figure 2). Since the implementation of home-based exercise program, the same previous average of 2.8±0.2 sessions of weekly training were kept. It was possible to notice no evolution each week. In the beginning, there was a reduction in WTR followed by a rise in the second week, for values higher than the previous average, which was sustained until the end.

WTR≥3 trains per week was observed in 27.9; 77.0; 60.7; 67.2 and 72.1% of participants in weeks 1 and 5, respectively. Variations were significant between weeks 1 and 2 (p<0.001) and weeks 2 and 3 (p=0.007).

Table 1 - Sample characteristics

	Total	Non-Participant	Participant	p value
Patients (n)	94	33	61	
Male (%)	62.8%	60.6%	63.9%	0.75&
Age (years)	69.0(58.7; 75.0)	70.0(61.5; 77.0)	67.0(51.5; 75.0)	0.17*
Hypertension (%)	59.6%	72.7%	52.5%	0.056&
DM (%)	27.7%	30.3%	26.2%	0.673&
AMI (%)	20.2%	18.2%	21.3%	0.718#
Heart failure (%)	9.6%	6.1%	11.5%	0.486#
Angioplasty (%)	33.0%	39.4%	29.5%	0.331&
CABG (%)	11.7%	6.1%	14.8%	0.318#
COPD (%)	13.8%	15.2%	13.1%	0.785#
ILD (%)	4.3%	6.1%	3.3%	0.524#
Cancer (%)	22.3%	33.3%	16.4%	0.06&
Frailty	8.0(7.0; 8.0)	7.0(6.5;8.0)	8.0(7.0; 9.0)	0.004*
WTR	3.0(2.0; 3.0)	2.0(2.0;3.0)	3.0(2.0; 3.0)	0.065*
Rehabilitation time (months)	5.3(2.9; 7.4)	5.1(2.8;7.4)	5.3(3.0;7.5)	0.924*

*Source: the author (2020). DM: Diabetes Mellitus; AMI: Acute Myocardial Infarction; CABG: Coronary Artery Bypass Graft; COPD: Chronic Obstructive Pulmonary Disease; ILD: Interstitial Lung Disease; WTR: Weekly Training Rate; &: Chi-square test; #: Fisher exact test; *: Mann-Whitney-U test*

Table 2 – Age and frailty comparison among exercise groups

	Plan A	Plan B	Plan C	Special Plan	p
Age	74(71;78)	74(68;78)	54(46;63)	64(52;66)	<0.001
Frailty	6(6;6)	8(7;8)	9(8;9)	8(7;8)	<0.001

Source: the author (2020). Median values (interquartile amplitude). Significance determined by the Kruskal-Wallis test.

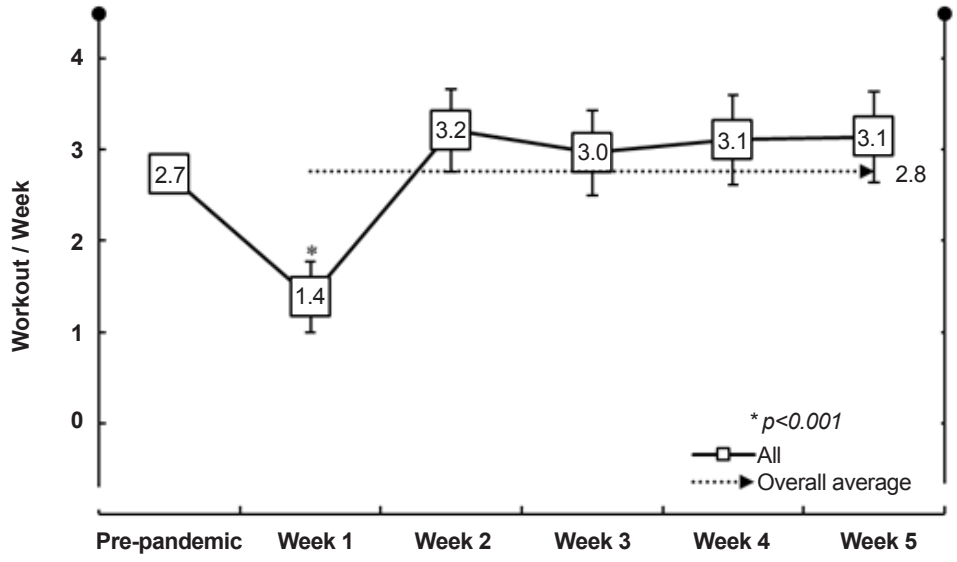

Figure 2 – Evolution in all patients' weekly training average.
Significance determined by the Friedman test (p<0.001) and Dunn's post-hoc (p<0.004 for all).
Source: the author (2020).

While comparing the fifth week with the previous training period (pre-quarantine) 29.5% of patients reduced 13.1% kept and 57.4% had a significant increase in WTR.

Multivariate analysis is show on Table 3. DM was the only independent predictor of engagement equal or higher than three training sessions per week within at least 4 weeks in the program. Figure 3 illustrates the evolution of WTR in stratified patients through the presence/absence of DM.

Discussion

In this study, after moderated engagement in the remote rehabilitation program (63.9%), participants' involvement was considered good. By the end of the fifth week, 91.8% kept in touch with the program. Several rehabilitation centers interrupted their face-to-face activities during the pandemic and invited their patients to join remote rehabilitation programs,[11,12] but in the light of the authors' knowledge, this is the first publication that describes patient engagement and commitment to the home-based tele-oriented exercise program.

The highest multicentric register so far (1,653 patients with heart failure) reported an engagement of 85.6% right at the beginning of the program.[13] At the end of the 24 weeks, only 55% of the patients kept in touch with the telemonitoring system. Stampehl et al.[14] presented that at the end of 31 days, there were 66.7% of participant patients

Table 3 – Predictors of more than 4 weeks with minimum 3 training sessions/week

	Present	Absent	*Univariate RR (IC95%)*	*Multivariate RR (IC95%)*
Male	53,8%	54,5%	0,99 (0,61; 1,60)	
Age ≤65 y/o	55.2%	53.1%	0.95 (0.55; 1.65)	
SAH	53.1%	55.2%	0.95 (0.55; 1.65)	
DM	18.8%	66.7%	0.41 (0.25; 0.66)	0.097 (0.02; 0.44)
AMI	69.2%	50.0%	1.62 (0.69; 3.85)	
CHF	71.4%	51.9%	1.68 (0.50; 5.60)	
Angioplasty	61.1%	51.2%	1.25 (90.62; 2.41)	
MRS	66.7%	51.9%	1.44 (0.55; 3.80)	
COPD	62.5%	52.8%	1.25 (0.49; 3.20)	
ILD	50.0%	54.2%	0.91(0.22; 3.76)	
Cancer	50.0%	54.9%	0.90 (0.45; 1.80)	
Frailty	50.0%	54.9%	0.90 (0.45; 1.80)	
Rehabilitation time < 3 months	50.0%	55.8%	0.90(0.52; 1.52)	

Source: the author (2020). SAH: Systemic Arterial Hypertension; DM: Diabetes Mellitus; AMI: Acute Myocardial Infarction; CHF: Congestive Heart Failure; MRS: Myocardial Revascularization Surgery; COPD: Chronic Obstructive Pulmonary Disease; ILD: Interstitial Lung Disease.

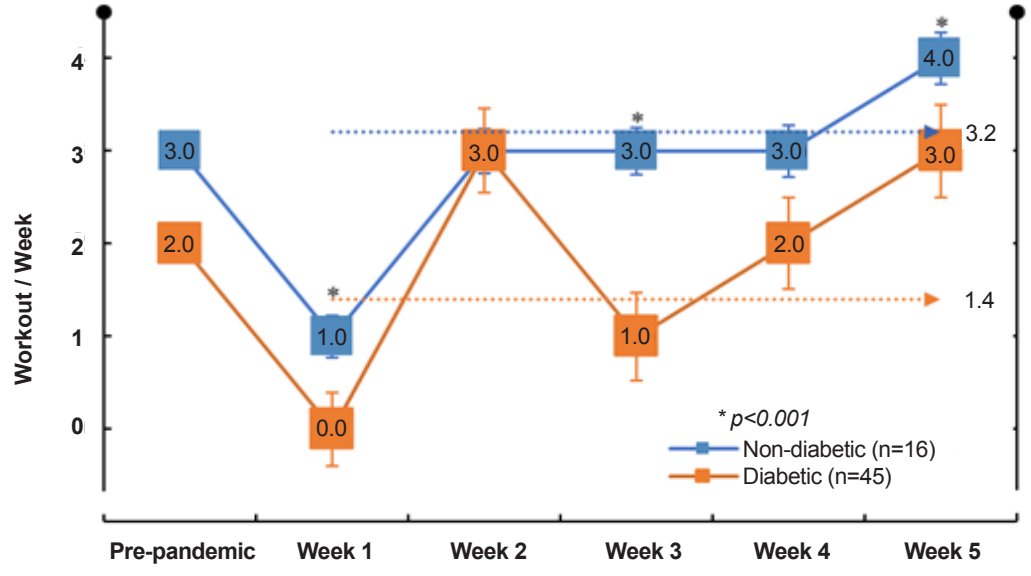

Figure 3 – Weekly training rate in patients stratified by absence/presence of diabetes.
Significance referred to Mann-Whitney U test. Source: the author (2020).

engaged in the program. Unfortunately, the DIAL study,[15] which included 1,518 patients with heart failure, excluded physical exercise from its engagement criterion.

Although engagement criteria and monitoring plan may vary across studies, in both cases a larger rate of engagement has been related to a lower number of events in this population.

Beyond the satisfactory engagement rate, the main finding in this study is the efficiency in keeping patients exercising. A 2.9 days per week WTR average was observed, with more than 70% of patients exercising more than 3 days a week after 5 weeks of quarantine, which can be considered a good result. Besides, more than half of the patients exercised 3 or more days/week in 4 out of 5 weeks, and 57.4% were exercising more than they did before isolation. Some studies have already evaluated the rate of exercising during telemonitored home-based rehabilitation sessions. Kraal et al.[16] and Laustsen et al.[17] after 12 weeks of training, reported WTR 2±0.6 and 2.6±0.5 days/weeks, respectively. Another group has published a similar result of WTR 2.5±0.3 days/weeks within 12 weeks using a cell phone based exercise plan.[18]

The presence of diabetes was the only independent predictor of exercise engagement within the analyzed period. Only 18.8% of the patients with diabetes were able to exercise 3 times a week in 4 out of 5 weeks. The low engagement to exercise programs by patients with diabetes in different countries has been known for years,[19,20] and their rate vary around 60% of inactivity after adjustments. Reasons for that include difficulty to engage and fatigue, among others.[21] Many studies have used telemedicine exercise plans to boost physical activity engagement in patients with diabetes,[22,23] successfully. Duruturk and Özköslü[24] performed a random study including 44 patients with diabetes where participants were offered a 6-week home-based exercise program (an average of 2.66 sessions per week), with the support of a physiotherapist by video-conference. Participants not only showed significant improvement in fitness, but also improved glycemic control and reduced symptoms of depression.

Diabetes is a risk factor for COVID-19 mortality.[2] Thus, we believe that isolation may be recommended for a longer period for this population,[25] even after flexibilization may reach the general population. On the other hand, sedentarism and low physical exercise engagement are risk factors for the development of macro and microvascular events in patients with diabetes.[26]

The difficulty for full individualization of TOEP exercise prescriptions may be a limiting factor for its efficacy. However, TOEP was a fast-solution plan in order to keep patients engaged in physical activities, while allowing them to manage their clinical conditions. To evaluate patients' points of view regarding the program would help understand its efficacy. This type of analysis demands the use of mixed methods of investigation. Considering the urgency of the program, there was no available time to develop an evaluation tool that could reflect perception and individual satisfaction.

Moreover, to ensure efficacy, it would have been necessary that patients go through a pre- and post-intervention for cardiopulmonary performance. In these regards, the exercise plan has data of previous evaluations for each patient and will soon be reevaluated. WTR is the main measure of attendance and was based on patients' personal feedback. Pre-pandemic frequency was based on the program in which patients were enrolled, and not in attendance.

Conclusion

In this small sample, the development of a fast-tracking remote rehabilitation program, comprised by center-based rehabilitation concepts and data, was well-received by the participants. The exercise plans were adequate, and patients were able to maintain good exercise rates after 5 weeks of quarantine. Patients with diabetes showed lower engagement and deserve special attention in future exercise plans. In pandemic times, developing efficient and safe tele-rehabilitation plans must be regarded as a scientific urgent matter.

Author contributions

Conception and design of the research: all authors. Acquisition of data: Espinosa G, Toledo L, Prado C, Moraes G, DOmecg F, Facio M. Analysis and interpretation of the data: Espinosa G, Braga F. Statistical analysis: Braga F. Writing of the manuscript: Espinosa G, Toledo L, Prado C, Moraes G, DOmecg F, Facio M. Critical revision of the manuscript for intellectual content: Espinosa G, Braga F.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Hospital Federal Cardoso Fontes* – HFCF under the protocol number 4.258.930. 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 Rehabilitation at Distance: A New Moment

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Editorial referring to the article: Implementation of an Exercise Program at Home for Patients Undergoing Cardiopulmonary and Metabolic Rehabilitation during the SARS-CoV-2 Pandemic

Cardiovascular rehabilitation consists of a non-pharmacological intervention process in individuals with metabolic, pulmonary, or cardiovascular disorders, aiming at reducing symptoms, quality of life improvement, and the possible increase in life expectancy. [1]

It consists, predominantly, in the practice of regular, individualized physical exercises, in addition to guidance concerning other risk factors, including physical inactivity, as well as nutritional and psychological support, intending to slow down and cause possible regression of the patient's pathology.[2,3]

The COVID-19 pandemic made face-to-face rehabilitation sessions impossible due to the risk of contamination. Thus, to continue such a necessary treatment, the implementation of exercise programs at home for these patients started.[4]

The study presented emphasized home strategies to keep in activity patients with different clinical conditions, with distance guidance, to assess Internet-oriented patients' adherence.[5] This program's feasibility was very well-designed, consisting of three exercise plans based on the patient's level of functionality.[6]

It is worth mentioning the prescription of exercises according to the individual's body structure, allowing them to exercise with the largest muscle groups due to the impossibility of performing them without additional equipment. We consider the subjective effort perception scale ≤ 5 to be adequate (in Borg scale from 0 to 10).[7]

We believe that the patient control strategy, distributed among the team's professionals, individually, can result in more safety and adherence. No less important was the complimentary assistance by two nutritionists and a psychologist. Food and emotional balance are of great importance in the current phase when anxiety and depression can interfere with the continuation of physical activity.

It is worth mentioning the statistical treatment of this study, in which was created a multivariate logistic regression model to determine independent predictors of satisfactory adherence. We can point out the "fragility" prevalent in the elderly, a reason for increased attention.

The adherence of 91.8% of the patients can be credited to the participating professionals.

The variation in the frequency of weekly training of patients and the absence/presence of diabetes require a broad study related to the disease's pathology. In patients with heart failure, there was a higher percentage of those present (71.4%) compared to absent (51.9%). We consider that it can be attributed to the possible longer duration of the disease, better awareness, good results already observed before the pandemic, and the need to continue rehabilitation.

This publication, considered the first in our country to describe participants' adherence under current conditions, is an example of conduct useful for future studies, since in bibliographic references, there is a strong predominance of international presentations.

Keywords

COVID-1; Betacoronavirus; Pandemia; Exercise Tolerance; Cardiac Rehabilitation; Physical Therapy Modalities; Guidelines; Physical Exertion; Telerehabilitation.

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ORIGINAL ARTICLE

Effects of Breaking up Deskwork with Physical Activity Combined with Tea Consumption on Cerebrovascular Function, Mood, and Affect

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Abstract

Background: Prolonged sitting, typical of desk work, decreases cerebral blood flow (CBF), mood and affect. Conversely, short physical activity breaks from sitting may prevent these detrimental effects and provide cardiometabolic benefits.

Objective: We evaluated the effect of interrupting prolonged sitting with short breaks of light physical activity combined with tea consumption on CBF, cerebral autoregulation (CA), mood, and affect in desk workers.

Methods: Nineteen healthy desk workers (ten male, 27±10 years) performed desk work in a laboratory for six hours on two separate intervention days: tea breaks (TEA-BREAK: short walk combined with ingestion of one cup of tea every hour) and sedentary (SED: ingestion of one cup of water every hour, while seated). Before and after desk work, we assessed mean arterial pressure (MAP), middle cerebral artery blood velocity (MCAv) and CA. Questionnaires were used to assess mood (Bond & Lader, PANAS) and affect (Affect grid) before and after the intervention. Data are expressed as mean ± standard deviation. Two-way ANOVA with repeated measurements followed by Sidak post hoc test was used for data analysis. Paired Student's t-test was also used to compare changes (Δ) between trials. Statistical significance was at $p<0.05$.

Results: Desk work increased MAP (4.6±4.6 Δ mmHg; $P<0.05$), and decreased MCAv (-5.2±7.0 Δ cm/s; $P<0.05$), with no difference between interventions in these parameters. TEA-BREAKS, but not SED, decreased gain (-0.08±0.12 Δ $cm.s^{-1}.mmHg^{-1}$) and increased phase (5.26±8.84 Δ radians) at very low frequency ($P<0.05$), but not at low frequency. Small changes in positive affect were found after the six hours of desk work (-5.5±7.3 Δ scale; $P<0.05$), with no differences between interventions.

Conclusion: Changes in MCAv and positive affect induced by prolonged desk work could not be prevented by TEA-BREAKS. However, TEA-BREAKS improved CA, suggesting a higher efficiency in maintaining MCAv in response to blood pressure fluctuations.

Keywords: Tea; Black Tea; Blood Pressure; Risk Factors; Homeostasis Cerebral; Cerebrovascular Circulation.

Introduction

Modern lifestyle is marked with unhealthy habits, including a sedentary behavior characterized by several hours of low energy expenditure, such as prolonged uninterrupted sitting.[1] Sedentary lifestyle is a worldwide public health problem,[2] primarily due to its association with increased risk of chronic diseases, such as type 2 diabetes, cancer, osteoporosis and cardiovascular disease (CVD).[3-5] In addition, prolonged sitting decreases cerebral blood flow (CBF) and function,[6] and may also impair affective and cognitive measures related to mood, affect, and alertness.[7]

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Public health recommendations suggest reducing sedentary time and increasing physical activity whenever possible.[2] It has been demonstrated that frequent short-duration walking breaks (mor than walking breaks), can prevent CBF decreases, promote metabolic benefits (e.g. insulin sensitivity), and enhance mood.[6-8] However, one potential limitation of these studies is the fact that they used controlled physical activity interventions, which may not be applied to a real-life situation. Usually, in real time situations, physical activity breaks are short and with a very low intensity (i.e., standing), and are often combined with consumption of a beverage.

Epidemiological studies have suggested that regular consumption of tea, one of the most consumed beverages in the world, may improve cardiovascular health and affective function.[9,10] In fact, recent studies have confirmed that the consumption of black tea is an effective approach to improve cardiovascular function.[11,12] Furthermore, daily consumption of tea seems to reduce the risk for heart disease and ischemic stroke.[13] Tea consumption has also been linked to benefits related to attention, alertness, mood and creativity.[9]

Although taking a break for a hot drink is a typical behavior among office-based workers, there is no study examining the effect of this behavior on cerebrovascular and affective function in a research setting. Therefore, this exploratory study evaluated the effects of light, short physical activity breaks with tea consumption at regular intervals during prolonged sitting in healthy, young office workers. We hypothesized that regular breaks associated with tea consumption would prevent prolonged sitting-induced decreases in CBF, and improve cerebral autoregulation (CA), mood and affect.

Methods

Participants

Nineteen sedentary desk workers (10 males) aged 20-55 years old were recruited. Participants were screened for the following exclusion criteria: physical exercise ≥4 hours per week, participation in night shift work two weeks prior to screening or during the study, use of dietary supplements, use of prescribed or over-the-counter medication, smoking and history of CVD. The sample size calculation was based on a residual standard deviation of 12 $cm.s^{-1}$ in CBF and a correlation of 0.7 between pre- and post-treatment scores reported in a previous study.[6] With 19 participants in this cross over design, we anticipated *a priori* that our sample size would be sufficient to detect a difference in middle cerebral artery blood velocity (MCAv) of 10% between the uninterrupted sitting and the tea break intervention, assuming a power of 0.80 and significance level of 0.05 (2-sided). Study procedures were approved by the Ethics Committee of Liverpool John Moores University (19/SPS/023). Fully informed written and verbal consent was obtained from all participants. Each participant received £50 for their participation in the study. The study has been registered as a clinical trial in ClinicalTrials.gov (NCT03953391).

Design and experimental procedures

Participants attended the laboratory at the same time of day (7:00 –8:00 A.M.) on two separate occasions (two interventions). The trials were separated by a 2 to 7 day wash-out, and participants were randomly allocated to one of the interventions: *1.* tea break intervention (TEA-BREAKS), where, during the sedentary work (desk work, for 6 hours), participants were instructed to have regular breaks (5 minutes every hour) from sitting desk work, walk a short distance and prepare and consume tea; or *2.* sedentary intervention (SED), where participants were offered water every hour while seated in upright posture at their desk. The randomization sequence was created using Excel 2016 (Microsoft, Redmond, WA, USA) with a 1:1 allocation using random block to ensure a balanced distribution between the two intervention. The hourly breaks were chosen based on previous work,[6] and on the real-world situation. The duration of breaks (5 minutes) in TEA-BREAKS was determined based on the pilot study conducted in our laboratory to evaluate the feasibility of the study. Testing procedures were the same on all test days. As participants arrived at the laboratory, body mass and height were measured. Then, after 20 minutes of supine rest, MCAv, blood pressure (BP), and heart rate (HR) were assessed, and subsequently participants underwent measurements of CA. After baseline measurements, three questionnaires assessing mood and affect were administered. Then, participants performed either the TEA-BREAKS or the SED. At the end of the six hours of desk work, the questionnaires, and MCAv and CA measurements were repeated (Figure 1).

Interventions

SED: 150 mL of tap water at room temperature were provided by the researcher once every hour (total of 5) to participants while sitting at their desks.

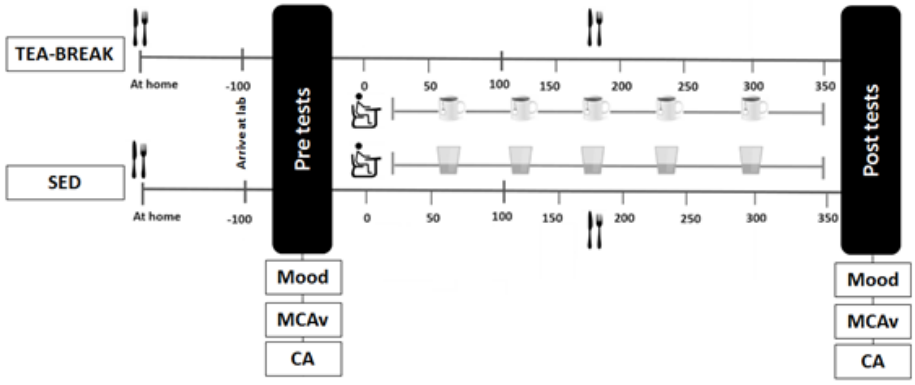

Figure 1 – Experimental design. TEA-BREAK, 6h of deskwork with tea breaks every hour. SED, 6h of deskwork sedentary intervention drinking water every hour. MOOD, mood questionnaires. MCAv, medium cerebral artery velocity. CA, cerebral autoregulation. Knife and fork represent breakfast and lunch.

TEA-BREAK: Participants were instructed to leave their desk for approximately 5 minutes once every hour. During this period, the subjects were instructed to walk 150 meters at their preferred walking speed to the tea brewing area. Participants were instructed to prepare a black tea (PG Tips pyramid bags, Unilever UK Ltd), by putting the teabag into 150 mL of boiling water and leaving it to steep for three minutes without stirring. Adding milk and/or sugar was not permitted. Participants then returned to the desk and drank the tea.

Participants were asked to refrain from vigorous exercise for at least 24 hours prior to the sessions and to avoid dietary products that may affect endothelial function, such as caffeine, alcohol, chocolate, and vitamin C for at least 18 h.[14,15] A standardized breakfast was provided to all participants to be consumed at home one hour prior to laboratory visit, and on both study days, all participants received lunch at the end of the third hour of intervention. Both meals were composed of a medium banana and porridge (Oat So Simple 57g, Quaker, Leicester, UK). For lunch, participants walked to a next-door room to eat their lunch sitting at a table within a 30-minute period. Participants were allowed to move their legs and feet while sitting, to mimic a real-world situation and to prevent the decline in leg blood flow and reduce the risk of thrombus formation.[16] Participants were instructed to perform only low cognitively demanding desk-based activities, such as reading or completing simple work tasks on a computer. Demanding tasks such as gaming and taking phone calls were not permitted. Participants performed comparable desk-based activities on both test days. Participants were supervised at all times and asked to avoid standing or walking. All participants were asked to visit the toilet before the start of the intervention and at the lunch break. If needed, more toilet breaks were allowed, and participants were taken to the restroom on a wheelchair. Women were evaluated in the early follicular phase of the menstrual cycle to control for hormonal fluctuations.

Measurements

All measurements were continuously acquired using an analogue-to-digital converter (PowerLab ML880; ADInstruments, Colorado Springs, CO, USA) and displayed in real time on a computer with commercially available software (LabChart version 7.0; ADInstruments).

Blood pressure

Arterial blood pressure (BP) was measured with an automated sphygmomanometer (Dinamap Procare 100 GE Medical Systems Ltd., Buckinghamshire, UK) [17] on the left arm while the participant was lying supine. This measure was used to determine resting BP and to calibrate the beat-to-beat BP, which was measured by finger photoplethysmography (Finometer, Finapres Measurement Systems, Arnhem, Netherlands). A cuff was attached to the second phalanx of the right index or middle finger placed at heart level.[18]

Middle cerebral artery blood flow velocity

Continuous bilateral transcranial Doppler ultrasound (TCD) (ST3; Spencer Technologies, Redmond, WA) was used to measure the left and right MCAv. A 2-MHz Doppler probe was positioned over the temporal window, located above the zygomatic arch, and was secured using an adjustable headband (Marc 600 Headframe; Spencer Technologies). Each MCA was identified based on the signal depth, peak, and mean blood flow velocity as previously described.[19] Once optimal signals had been obtained, the transducers were secured in position, and the signal parameters were recorded to ensure within-subject consistency between tests. Mean MCAv was calculated from the envelope of the velocity tracing using a weighted mean (1/3 maximum 2/3 minimum) to account for the relative time spent in systolic and diastolic pressures.[20] Supine MCAv was acquired for 5 minutes before and at the end of the intervention. Cerebral conductance index (CVC_i) was calculated by dividing MCAv by mean arterial pressure (MAP). Partial pressure of end-tidal CO_2 ($PETCO_2$) was sampled with a mouthpiece and monitored via an online gas analyzer (ML206; ADInstruments, Colorado Springs, CO).

Cerebral autoregulation

Participants completed two repeated cycles of squatting and standing to induce oscillations in BP. Sets were performed at low frequency (LF; 0.1 Hz; 5 seconds of squatting, followed by 5 seconds of standing) and very low frequency (VLF; 0.05 Hz; 10 seconds of squatting, followed by 10 seconds of standing), for 5 minutes each, with a 5-minute rest interval.[21] MCAv and BP were continuously assessed.

Data were analyzed using transfer function analysis (TFA) as previously described.[6,21] Briefly, beat-to-beat MCAv and BP signals were spline interpolated and resampled at 4 Hz for spectral and TFA based on the Welch algorithm. The five-minute data were subdivided into five successive windows that overlapped 50%. Data contained in each window were linearly detrended and passed through a Hanning window. Then, the discrete Fourier transform was applied. The cross-spectrum between MCAv and BP was determined and divided by the autospectrum of mean arterial pressure (MAP) to derive the TFA coherence, gain, and phase.[6,21] Phase shift is considered an alternative measure for the time delay of the autoregulatory reactivity, with rises in phase indicating a more efficient CA. Gain describes how changes in BP are transmitted into MCAv, with lower gain indicating a higher CA sensitivity. Coherence labels the linearity of the relationship between the fluctuations in MCAv and BP, with a coherence value approaching one indicating a linear relationship.[22,23] Coherence values were used to accept the validity of gain and phase estimates, with cut-off values for inclusion set at 0.5.[23] TFA is a frequency-dependent phenomenon and, as a result, the frequency ranges have different responses and are likely controlled by different mechanisms. The regulation of CBF is efficient in the LF range of BP oscillations but not in the high frequency range due to the time delay in initiating cerebrovascular adaptations to the changes in perfusion pressure. CA therefore allows rapid BP changes to be transmitted to CBF, whereas slow BP changes are filtered.[22,23] Data were processed and analyzed in agreement with standardized TFA guidelines for the two frequency domains: VLF (0.02–0.07 Hz) and LF (0.07– 0.2 Hz).[23]

Mood and affect

Three different questionnaires were used to evaluate mood and affect 1. Positive and Negative Affect Schedule (PANAS): consists of a list of ten positive and ten negative feelings and emotions (e.g., active, determined, afraid, irritable). Participants were instructed to rate the extent to which they were currently feeling each emotion on a scale of 1 (very slightly or not at all) to 5 (extremely);[24] 2. Bond-Lader Visual Analogue Scale: this scale comprises of 16 items consisting of an adjective pair (e.g. tense/relaxed) and a 100 mm line. Participants were asked to mark on line to what extent the described state was appropriate to them at that moment.[25] 3. The Affect grid: this is a single-item measure of the two affect dimensions of pleasure and arousal, designed as a 10x10 grid. The horizontal line represents the degree of pleasure (ranging from unpleasant to very pleasant), while the vertical line represents the degree of arousal (ranging from sleepy to very active).[26] Participants were asked to check a cell in the 10x10 grid that best represented how they were feeling in relation to the two dimensions at the moment.

Statistical analysis

Data are expressed as mean ± standard deviation (SD) and were analysed using statistical software (Graph Pad Prism 6.0, San Diego, CA, USA). Data were initially tested for normality using the Kolmogorov-Smirnov test. Two-way ANOVA with repeated measurements followed by Sidak post hoc test was used to analyse all variables. Paired Student's t-test was also used to compare changes

(Δ) between interventions. Statistical significance was set at $p<0.05$.

Results

Descriptive statistics are presented in Table 1.

Baseline cardiorespiratory and hemodynamic parameters

The two-way ANOVA analysis showed a significant time effect for systolic arterial pressure (SAP), diastolic arterial pressure (DAP), MAP, MCAv, CVC_i, and HR. We found increases in SAP, DAP and MAP and decreases in MCAv, CVC_i, and HR after 6 hours of sitting. However, no effect of the intervention was observed on any of these parameters. Analysis of peak MCAv and MCAv corrected for baseline values also showed a decrease in these parameters over time with no significant difference between the interventions (data not shown). Also, comparisons of MCAv were made between men and women, and no significant differences were observed (data not shown). There was also a significant time effect, and an interaction effect for $PETCO_2$, but no effect of the intervention (Table 2). Sidak's post-hoc test revealed decreases in $PETCO_2$ in the TEA-BREAK intervention. Student's t-test analysis showed a greater decline in relative $PETCO_2$ after the TEA-BREAK intervention compared to SED.

Cerebral autoregulation

The two-way ANOVA analysis showed a time effect in the VLF for gain but not for phase, and no effect (either for gain or phase) of intervention. An interaction effect was observed in VLF for both phase and gain, with post hoc analysis showing decreases in gain after the TEA-BREAK trial, but not after SED. Student's t-test analysis showed decreases in the relative gain and increases in phase in the TEA-BREAK intervention compared to SED intervention in the VLF (Figure 2). In LF, no effect of time, intervention or interaction effects on gain or phase was detected by the two-way ANOVA or the Student's t-test (Figure 3). Mean coherence values were 0.8 in the VLF and 0.6 in the LF (pre- and post-intervention).

Mood and affect questionnaires

The two-way ANOVA showed a time effect in The PANAS questionnaire for positive affect, with Sidak's post hoc analysis showing decreases in affect from pre- to post-SED intervention. Student's t-test analysis showed no differences between TEA-BREAK and SED for affect. No other significant effects were observed (Table 3).

Discussion

The purpose of this study was to assess the effects of sitting breaks combined with tea consumption during prolonged sitting (every hour for six hours), reflective of a sedentary desk work, on CBF and function, affect, and mood, in healthy young workers. We found that prolonged desk work decreased CBF (measured by MCAv) and positive affect, but regular breaks with physical activity (short walk) and tea consumption were not able to prevent these changes. However, work sitting breaks with a short walk and tea consumption increased phase and reduced gain in CA, reflecting a quicker and

Table 1 – Characteristics of participants (n=19)

	Mean ± SD
Age (years)	27 ± 10
Body mass (kg)	70 ± 11
Height (m)	1.7 ± 0.1
Body mass index (kg/m²)	23 ± 3
Systolic arterial pressure (mmHg)	114 ± 7
Diastolic arterial pressure (mmHg)	65 ± 6
Mean arterial pressure (mmHg)	81 ± 5
Heart rate (bpm)	63 ± 11

Table 2 – Baseline cardiovascular and hemodynamic parameters

	SED			TEA-BREAK		
	Pre	Post	Δ	Pre	Post	Δ
SAP (mmHg)	114 ± 7	118 ± 8*	3.7 ± 6.5	114 ± 7	118 ± 7*	4.0 ± 7.4
DAP (mmHg)	65 ± 6	70 ± 6*	5.5 ± 5.3	65 ± 6	71 ± 8*	5.8 ± 7.8
MAP (mmHg)	81 ± 5	86 ± 6*	4.6 ± 4.6	81 ± 5	87 ± 7*	5.2 ± 6.8
HR (bpm)	63 ± 11	53 ± 10*	-10 ± 6	66 ± 10	56 ± 9*	-10 ± 7
MCAv (cm/s)	68 ± 9	63 ± 8*	-5.2 ± 7.0	62 ± 12	58 ± 9*	-4.4 ± 6.6
CVC_i ($cm \cdot s^{-1}.mmHg^{-1}$)	0.85 ± 0.13	0.74 ± 0.09*	-0.11 ± 0.09	0.77 ± 0.15	0.67 ± 0.11*	-0.10 ± 0.10
$PETCO_2$ (mmHg)	40 ± 2	39 ± 2	-0.62 ± 1.88	39 ± 2	37 ± 2*	-2.2 ± 1.2#

*The results are presented as means ± SD. n=19. Pre- and post-intervention data were analyzed using two-way ANOVA with repeated measurements followed by Sidak post hoc test. Changes (Δ) data were analyzed using paired Student t test. * different from PRE; # different from SED; P<0.05. CVC_i, cerebral vascular conductance index; DAP, diastolic arterial pressure; MAP, mean arterial pressure; MCAv, medium cerebral artery velocity; $PETCO_2$, partial pressure of end-tidal CO_2; SAP, systolic arterial pressure; TEA-BREAK, six hours of desk work with walking and tea breaks every hour; SED, sedentary intervention: six hours of desk work with drinking water (while seated) every hour*

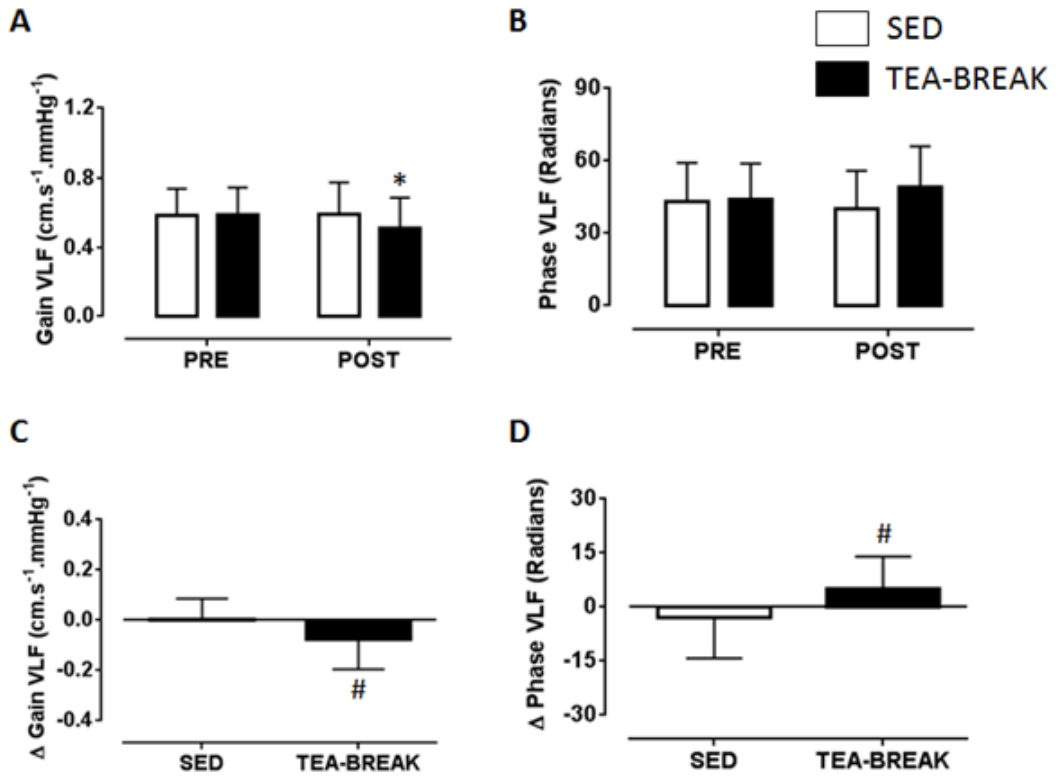

Figure 2 – Cerebral autoregulation in very low frequency (VLF). Absolute values of A) Gain VLF, and B) phase VLF pre and post 6-hour of deskwork with tea breaks every hour (TEA-BREAK) or sedentary intervention drinking water every hour (SED). Changes in C) Gain VLF, and D) Phase VLF in response to 6-hour of deskwork in TEA-BREAK or SED intervention. The results are presented as the means ± SD. n=19. In A and B data were analysed using two-way ANOVA followed by Sidak post hoc test. In D and E data were analysed using paired Student t test. * different from PRE; # different from SED; P<0.05.

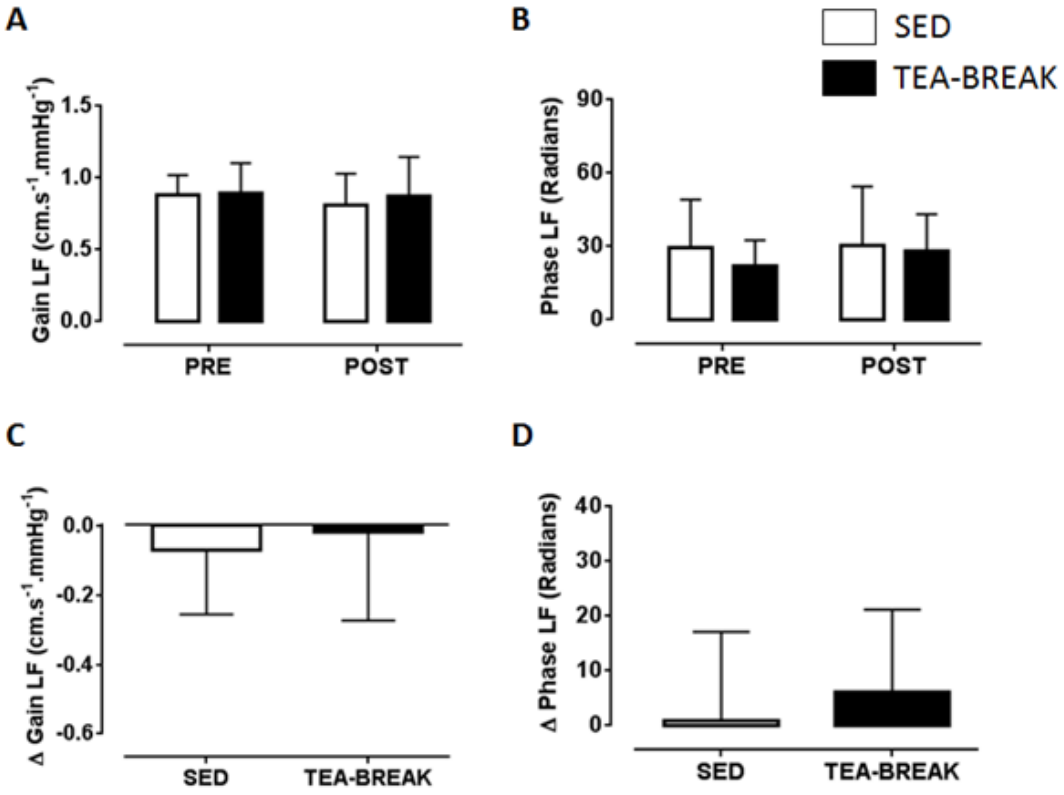

Figure 3 – Cerebral autoregulation in low frequency (LF). Absolute values of A) Gain LF, and B) phase LF pre and post 6-hour of deskwork with tea breaks every hour (TEA-BREAK) or sedentary intervention drinking water every hour (SED). Changes in C) Gain LF, and D) Phase LF in response to 6-hour of deskwork in TEA-BREAK or SED intervention. In A and B data were analysed using two-way ANOVA followed by Sidak post hoc test. In D and E data were analysed using paired Student t test. * different from PRE; # different from SED; P<0.05.

more efficient cerebrovascular response to BP changes, while no such effects were found with prolonged sitting. Taken together, these findings confirm the deleterious effects of sedentary work on CBF and affect. Although short breaks with physical activity and tea could not prevent these effects, they significantly improved cerebrovascular function in healthy volunteers.

It is well established that sedentary behavior, which is characterized by little physical movement and low energy expenditure, including prolonged sitting, leads to deleterious health outcomes, including impairment of cardiovascular function.[27] Indeed, it has been shown that continuous sitting is associated with lower MCAv, but also with lower BP and impaired peripheral vascular function.[6,28] Our data confirms previous findings in that prolonged desk work lowers blood flow through the middle cerebral artery (MCA). This decline in the CBF may be a consequence of endothelial dysfunction in cerebral blood vessels due to a lower nitric oxide availability as a result of prolonged sitting.[29,30] Further work should explore potential mechanisms underlying this consistent observation in humans.

In contrast to our hypothesis, breaking up prolonged sitting with light physical activity accompanied by tea consumption did not prevent the decline in MCAv and increase in MAP. This is somewhat surprising, since previous work on the effects of walking breaks during prolonged sitting prevented decreases in MCAv.[6] A possible explanation for the conflicting results is the longer sitting time in our protocol, which could have made it more difficult for short breaks with light physical activity to prevent these decreases. Previous studies demonstrating benefits of physical activity breaks typically adopted more frequent (every 30 min) and more intense exercise[6,7] compared with the present study. Therefore, positive metabolic and cardiovascular

Table 3 – Mood and affect questionnaires (n=19)

	SED			TEA-BREAK		
	Pre	Post	Δ	Pre	Post	Δ
PANAS						
Positive affect	27 ± 7	22 ± 6*	-5.5 ± 7.3	29 ± 5	26 ± 9	-2.9 ± 7.1
Negative Affect	12 ± 3	11 ± 2	-1.2 ± 3.3	13 ± 4	12 ± 3	-0.3 ± 4.0
AFFECT GRID						
Pleasure-displeasure	6 ± 1	6 ± 1	-0.2 ± 2.2	6 ± 1	5 ± 1	-0.7 ± 1.6
Arousal-steepness	4 ± 1	4 ± 2	0.2 ± 2.8	5 ± 1	5 ± 2	0.7 ± 2.2
BOND & LADER						
Alert	49 ± 5	50 ± 7	0.6 ± 7.6	47 ± 6	50 ± 6	3.1 ± 6.7
Content	53 ± 5	51 ± 6	-1.5 ± 5.4	54 ± 5	56 ± 6	1.2 ± 5
Calm	54 ± 13	53 ± 8	-1.3 ± 11.1	50 ± 8	49 ± 14	- 0.8 ± 16

*The results are presented as means ± SD. Pre- and post- intervention data were analyzed using two-way ANOVA with repeated measurements followed by Sidak post hoc test. Changes (Δ) data were analyzed using paired Student t test. * different from PRE; P<0.05. TEA-BREAK, 6-hour of deskwork with tea breaks every hour; SED, sedentary intervention: six hours of desk work with drinking water (while seated) every hour; PANAS, Positive and Negative Affect Schedule.*

effects, induced by physical activity, that can improve cerebrovascular function may be intensity- and frequency-dependent. In addition, prolonged sitting seems to increase postprandial glycemia,[31] resulting in decreases in MCAv,[32] and frequent physical activity breaks seem to prevent it.[31] Also, pre-clinical and clinical studies have shown that physical activity causes an increase in CBF by a cholinergic receptor mechanism.[33-35] Further studies are needed to directly evaluate the effects of different levels of physical activity breaks on cardiovascular and metabolic mechanisms involved in the CBF regulation.

Additionally, the fact that our experimental design included healthy participants and acute tea ingestion makes it difficult to compare the cardiovascular response with previous studies. The consumption of black tea has been shown to be effective in improving cutaneous vascular function and flow-mediated dilation of the brachial artery.[11,12] These benefits on peripheral vessels seem to be mediated by tea flavonoids by improving the bioactivity of the endothelium-derived vasodilator nitric oxide.[36]

Nevertheless, there is no conclusive evidence for the impact of tea on cerebral perfusion during prolonged sitting. For instance, black tea flavonoids did not alter CBF.[30] At least, data from our study suggests that, in a real-world setting, breaking sedentary work time with low-intensity physical activity combined with tea ingestion does not prevent the impact of prolonged sitting on cerebral perfusion. Importantly, we found a slight reduction in $PETCO_2$ (-2.2 mmHg) after the TEA-BREAKS, which could promote a reduction in the MCA diameter resulting in changes in the MCAv. Nevertheless, a model based on data from studies that evaluated the influence of changes in MCA diameter on the validity of TCD during changes in $PETCO_2$ showed that substantial changes in MCA diameter occur with changes in $PETCO_2$ ≥ 7.5 mmHg.[37]

Although the TEA-BREAKS did not induce changes in MCAv, we found that this intervention improved CA, by reducing gain and increasing phase in response to BP fluctuations using the 10 s squatting-standing protocol (VLF). A lower gain denotes a more efficient CA, since for a certain change in BP, lower changes in MCAv would be required.[22] In other words, these data indicate a greater ability of cerebral vessels to prevent large fluctuations in CBF. The higher phase is related to a faster response of cerebral blood vessels to BP variations, which is linked to the efficiency of the system.[22] These benefits of physical activity breaks combined with tea ingestion

were not observed when more rapid fluctuations in BP were adopted (i.e. LF). The higher coherence in VLF compared to LF may contribute to this observation. Our findings fit with a previous study showing that walking breaks also enhanced the VLF phase compared with uninterrupted sitting.[6] In contrast, in a previous work, acute tea ingestion had no effect on CA.[38] This suggests that physical activity may have a greater impact than tea on CA. However, we could not demonstrate the relative contribution of physical activity or tea in preventing the detrimental effects of prolonged sitting. This represents an important limitation of the present study. Future work is required to better understand these effects.

In the present investigation, prolonged sitting impaired positive affect. Among the different parameters related to mood, we found a decrease in PANAS positive affect after six hours of desk work, but not in PANAS negative affect, Bond & Lader questionnaire or the Affect grid. The different findings between questionnaires might be attributable to the relatively small number of participants. Nonetheless, the decrease in affect fits with previous work that also linked sedentary behavior to decreases in mood and affect.[7] In our study, we found no evidence for the ability of waliking breaks combined with tea ingestion to prevent the decline in affect and mood during prolonged sitting. Possibly, the intensity and frequency of walking breaks in our study were not sufficient to enhance affect and mood.[7]

Conclusions

The results of the present study add to the growing body of literature that prolonged desk work leads to unhealthy outcomes, including an increase in MAP, decreases in MCAv, and lower affect status. Repeated exposure to such physiological disturbances may increase the risk for cardiovascular disease, although future work is required to better understand this link. These effects could not be significantly altered by short walking breaks combined with tea ingestion in healthy individuals. However, tea breaks improved CA, indicating a higher efficiency in maintaining CBF in response to BP changes. These findings further support the importance of lifestyle changes to prevent the detrimental effects of prolonged, uninterrupted sitting.

Author contributions

Conception and design of the research: Thijssen DH, Hopkins N, and Low D. Acquisition of data: Speretta GF, Fornasiero A, and John JA. Statistical analysis: Speretta GF. Obtaining financing: Thijssen DH, Hopkins N, and Low DA. Writing of the manuscript: Speretta GF. Critical revision of the manuscript for intellectual content: Thijssen DH, Hopkins N, Low DA, Fornasiero A, and John JA.

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 Liverpool John Moores University under the protocol number 19/SPS/023. 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

Small Exercise Breaks can Save your Brain from Prolonged Sitting

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Editorial referring to the article: Effects of Breaking up Deskwork with Physical Activity Combined with Tea Consumption on Cerebrovascular Function, Mood, and Affect

A sedentary lifestyle is one of the major risk factors for the development of cardiovascular diseases.[1] For instance, in 2019, stroke was the second-leading cause of death, as well as the primary cause of death and disability combined in the world.[2] Active commuting to work is one strategy to decrease sedentary time and its impact,[3] and the COVID-19 pandemic has changed work and daily routines worldwide. Moreover, the necessary social distancing has led to increased sedentary time,[4] especially for those who are engaged in office desk work .[5]

Acute prolonged sitting seems to lead to transient impairment of the endothelial function in the healthy population,[6] whether this phenomenon is related to cardiovascular or cerebrovascular events is unknown. Nonetheless, prolonged sitting impairs the cerebrovascular function.[7,8] Conversely, exercise breaks from prolonged sitting seem to restore the endothelial [9] and cerebrovascular function.[7] Therefore, active breaks from prolonged sitting could be a good strategy to mitigate the effects of sedentary time. However, the ideal duration and intensity need further investigation. Additionally, the difficulty to implement exercise breaks as a daily routine for office workers must be considered.

In this sense, the effect of walk breaks from prolonged sitting on the cerebral vascular function was investigated, simulating a real-life routine.[10] Hence desk workers took breaks from prolonged sitting to prepare tea every hour for six hours.[1] After six hours of sitting, medium cerebral artery blood flow velocity (MCB_V) decreased, and the small walk breaks (e.g.; five breaks of 150 meters of slow walking) were insufficient to re-establish MCB_V. The authors also observed an increased phase and reduced gain in very low frequency in cerebral autoregulation, which would indicate an improvement in cerebral autoregulation. However, the results concerning cerebral vasculature are difficult to interpret due to the decrease in the partial pressure of end-tidal carbon dioxide after the tea-break session ($PETCO_2$). The partial pressure of arterial carbon dioxide ($PaCO_2$) is the most potent regulator of cerebral blood flow, where small fluctuations evoke significant changes in cerebral blood flow.[11]

Furthermore, the walk breaks were followed by black tea consumption, but acute ingestion of tea seems to increase the endothelial function,[12] and therefore the effect of the walk breaks cannot be isolated from the effect of the tea on the vascular function. Finally, the energy expenditure during those small walk breaks was not measured, but there is a possibility that higher energy expenditure is needed so that the exercise can exert a systemic vascular effect.

The study conducted by Speretta et al.[10] does not allow a more thoughtful interpretation of the effect of small walk breaks or tea consumption on the possible cerebrovascular risk caused by prolonged sitting. However, the literature does support the conclusion that active breaks from a sedentary time are important in order to decrease vascular risks, but activities that produce higher energy expenditure than small walks must be considered.

Keywords

Exercise; Sedentarism; Lifestyle; Cerebrovascular Circulation; Stroke, Risk Factors; COVID-19; Pandemics; Physical Activity.

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ORIGINAL ARTICLE

Cardiac Remodeling in Obesity-Resistance Model is not Related to Collagen I and III Protein Expression

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Abstract

Background: As some individuals present resistance to obesity development, experiments have been trying to understand their susceptibility to cardiometabolic diseases.

Objetive: To evaluate if the cardiac remodeling was related to collagen protein expression change.

Methods: Male Wistar rats were randomized into two experimental groups: control diet (CD, n=15) or high-fat diet (HFD, n=15) for 30 weeks. Rats fed with HFD were ranked based on their adiposity indexes and classified as obese (Ob, n = 8) or obesity-resistant (ROb, n = 6). Rats that failed to present the normal characteristic of the control group while fed with CD were excluded (Control, n = 8). Nutritional profile, comorbidities (dyslipidemia, hypertension, glucose metabolism, hyperleptinemia), cardiac remodeling, and collagen protein expression were evaluated. The groups were compared by One-Way ANOVA, together the Tukey post hoc test, with $p<0.05$ considered significant.

Results: The Ob rats presented an increased adiposity index when compared to C and ROb. Both groups Ob and ROb presented increased low-density lipoprotein (LDL), insulin, homeostatic model assessment of insulin resistance (HOMA- IR) and systolic blood pressure (SBP), and low high-density lipoprotein (HDL) levels when compared to the control group. The levels of triglycerides, non-esterified fatty acid (NEFA), and leptin were lower in ROb as compared to Ob, but higher than the control group. The Ob and ROb groups presented cardiac remodeling, evidenced by echocardiographic and *post-mortem* analysis. The collagen protein expression did not differ among the groups.

Conclusion: The ROb animals present cardiac remodeling that is not related to collagen type I and III protein expression change.

Keywords: Obesity; Adiposity; Diet.

Introduction

Obesity is a chronic metabolic disease characterized by an excessive adipose tissue accumulation.[1] It is considered a global epidemic and a major public health problem,[2] since this disease can lead to nutritional, metabolic, hormonal, and cardiovascular changes, increasing the population's morbidity and mortality, and reducing life expectancy.[3–5]

The literature reports that the cause of main obesity, currently, is the inadequate dietary habits, with increased carbohydrate and/or fat consumption.[6,7] However, some individuals seem to present resistance to the development of obesity. Within this context, experiments using animals fed with a high-fat diet try to understand the pathophysiological susceptibility of obesity-resistant individuals to cardiometabolic diseases.[8–10]

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Cardiac remodeling is well established in obesity conditions, since research has shown the relationship between time of obesity and myocardial collagen type I and III expression.[11] However, no studies have evaluated the contribution of collagen expression to cardiac remodeling in obesity-resistant animal models, and the few studies that evaluated the cardiac changes in this condition found divergent results. Sá et al.[9] found isolated papillary muscle contraction impairment, while Carroll et al.[10] found cardiac no abnormalities in obesity-resistant animals fed with a high-fat diet.

Considering this situation, the primary aim of this study was to verify the presence of cardiac remodeling in obesity-resistant animals fed with a high-fat diet. An additional aim was to evaluate if the cardiac remodeling was related to collagen I and III protein expression change.

Methods

Animals and experimental protocol

Male Wistar rats (60-day-old) were randomly divided into two experimental groups to receive a control diet (CD, n=15) or a high-fat diet (HFD, n=15) for 30 weeks. The sample size and the experimental period were based on previous studies conducted by our research group.[9,11,12] Animals were kept in individual cages with controlled temperature (24 ± 2 ºC), humidity (55 ± 5%), and light (12-h light/dark cycle). The diet and water were *ad libitum*. The experimental procedures were performed according to the "Guide for the Care and Use of Laboratory Animals"[9,13] and approved by the Animal Ethics Committee of the Botucatu Medical School (991/2012). At the end of the experimental protocol, after 8h fasting, the animals were euthanized by decapitation after intraperitoneal anesthesia with a mixture of ketamine (1 mg/kg) and xylazine (100 mg/kg) (Syntec, Rhobifarma Indústria Farmacêutica Ltda., Hortolândia, São Paulo, Brazil). The blood and the cardiac samples were collected and stored at −20°C for further analysis.

Diet composition

The diets used in this study have been described elsewhere[11,12,14,15] and the composition followed AIN93 recommendations, consisting of the following ingredients: corn bran, soybean hull, soybean bran, dextrin, salt, vitamin and mineral complex, palm kernel oil, and soybean oil. The CD contained 31.0% of kcal from protein, 51.6% from carbohydrates, and 17.4% from fat. The HFD contained 18.7% of kcal from protein, 41.6% from carbohydrates, and 39.7% from fat. The content of saturated/unsaturated fatty acids was 61.5% / 38.5% in CD and 64.8% / 35.2% in HFD. The energetic densities from the diets were: HFD = 3.85 kcal/g and CD = 3.10 kcal/g.

Nutritional profile

The nutritional profile was determined by food and calorie intake, feed efficiency, final body weight, and adiposity index. Dietary intake and body weight were measured weekly. The calorie intake was determined by the following formula: weekly food intake multiplied by the energy value of each diet (g × kcal). To analyze the animal's capacity to convert the consumed food energy in body weight, feed efficiency was calculated by dividing the total body weight gain (g) by the total energy intake (kcal). The total body fat was obtained by the sum of epididymal, retroperitoneal, and visceral deposits. The adiposity index was calculated by the total body fat divided by the final body weight and multiplied by 100.[15,16]

Determination of Obesity and Obesity Resistance

A criterion based on the adiposity index was used to determine the occurrence of obesity and obesity resistance according to several authors.[10,17-19] After 30 weeks, the rats that consumed HFD were ranked based on their adiposity indexes. Therefore, the animals that received HFD and presented the highest adiposity indexes were classified as obese (Ob, n = 8); the animals that consumed a high-fat diet and presented adiposity indexes similar to control animals were classified as obesity-resistant (ROb, n = 6). Rats that failed to present the normal characteristic of the control group, while fed with a standard diet, were excluded (n = 8).

Metabolic and hormonal evaluation

The metabolic evaluation included plasma lipid and glucose levels, as well as insulin resistance, whereas the hormonal evaluation was assessed by the concentrations of leptin and insulin.

The triglycerides, total cholesterol (TC), high- and low-density lipoprotein (HDL and LDL) levels were determined using a specific kit (BIOCLIN®, Belo Horizonte, MG, Brazil) and analyzed by the automated

enzymatic colorimetric method (Chemistry Analyzer BS-200, Mindray Medical International Limited, Shenzhen, China). The non-esterified fatty acid (NEFA) concentrations were evaluated by colorimetric kit (WAKO Pure Chemical Industries Ltd., Osaka, Japan).

Glycemia was analyzed in blood samples collected from the tails of the animals, using a handheld glucometer (Accu-Chek Go Kit, Roche Diagnostic Brazil Ltda, São Paulo, SP, Brazil). The homeostatic model assessment of insulin resistance (HOMA-IR) was used as an insulin resistance index, calculated according to the formula: HOMA-IR = [fasting glucose (mmol/L) x fasting insulin (μU/mL)]/22.5[7].

The insulin and leptin levels were analyzed by the enzyme-linked immunosorbent assay (ELISA) method (EMD Millipore Corporation, Billerica, MA, USA). The reading was performed using a microplate reader (Spectra MAX 190, Molecular Devices, Sunnyvale, CA, USA).

Echocardiographic Study

The analysis was performed with live animals by transthoracic echocardiography, using a Vivid S6 system equipped with a multifrequency ultrasonic transducer 5.0 to 11.5 MHz (General Electric Medical Systems, Tirat Carmel, Israel). The animals were lightly anesthetized by intraperitoneal injection with a mixture of ketamine (50mg/kg) and xylazine (1mg/kg) and put in left decubitus position. Only one examiner performed all of the exams. The heart image structural measurements were obtained in one-dimensional mode (M-mode) guided by the images in two-dimensional mode with the transducer in the parasternal position, minor axis. Left ventricular (LV) evaluation was performed with the cursor M-mode just below the mitral valve plane at the level of the papillary muscles. The echocardiographic analysis was performed according to that established in prior studies.[19-21]

Morphometric variables

- Maximum left atrium diameter (LA, cm);
- Left ventricular diastolic and systolic diameters of the left ventricle (LV, mm): LVDD and LVSD, respectively;
- Interventricular septum diastolic thickness (IVSDT) and posterior wall diastolic thickness (PWDT) of the LV (mm): IVSDT and PWDT, respectively;
- Relative thickness of the LV (LVRT) = (2 × PWDT)/ LVDD;
- Left ventricular mass (LVM, g) = 0.8 × {1.04 × [(IVSDT + PWDT + LVDD)^3 − LVDD^3]} + 0.6;
- LVM index (LVMI, g/m$^{2.7}$) = LVM/Height$^{2.7}$ where LVMI is LV mass indexed to height.

Systolic function variables

- Cardiac output (CO) was calculated by multiplying the systolic volume by the heart rate.

Diastolic function variables

- Maximum early ventricular filling velocity (E wave peak, cm/s): obtained by spectral Doppler recording of the transmitral diastolic flow;
- Maximum late filling velocity during atrial contraction (A wave peak, cm/s): obtained by spectral Doppler recording of the transmitral diastolic flow;
- E-wave deceleration time (ms) corresponding to the time between the initial velocity peak of the mitral transvalvular flow and its extrapolation to the baseline.

Systolic blood pressure

The Systolic blood pressure (SBP) was measured by tail plethysmography, using a Narco Bio-System® Electro-Sphygmomanometer, model 709-0610 (International Biomedical, Austin, TX, USA). The animals were warmed in a wooden box (50 × 40 cm) between 38–40°C for 4–5 min to stimulate arterial vasodilation. After this procedure, a cuff with a sensor was placed in the proximal region of the tail, coupled to the electro-sphygmomanometer. The cuff was inflated to 200 mmHg pressure and subsequently deflated.[15,16] The arterial pulsations were recorded in a computerized data acquisition system (AcqKnowledge ® MP100, Biopac Systems Inc., Santa Barbara, CA). The average of two readings was recorded for each measurement.

Post-Death Morphological Analysis

After euthanasia, the animals were submitted to thoracotomy, and the hearts, ventricles, and tibia were separated, dissected, weighed, and measured. Cardiac remodeling was determined by analyzing the weight of the heart and the left (LV) and right (RV) ventricles, and their correlation with the tibial length.

Myocardial collagen types I and III protein expression

The Western Blot analysis was performed to evaluate the types I and III collagen protein expression. Briefly,

the LV samples were rapidly frozen in liquid nitrogen and subsequently homogenized in a solution containing RIPA buffer (Amresco LLC, Solon, OH, USA), together with protease (Sigma-Aldrich, St. Louis, MO) and phosphatase (Roche Diagnostics, Indianapolis, IN, USA) inhibitors. The samples were subjected to SDS-PAGE in 10% polyacrylamide gel and were then electrotransferred to a nitrocellulose membrane (Amersham Biosciences, Piscataway, NJ, USA). The blotted membrane was blocked (5% nonfat dry milk, 20 mmol/L Tris-HCl pH 7.4, 137 mmol/L NaCl and 1% Tween 20) for 2h at room temperature and then incubated overnight at 4–8°C with primary antibody against collagen type I (1:10000) and collagen type III (1:10000) (Abcam, Cambridge, MA, USA). The immunoblots were washed three times with TBS-T and incubated for 1.5h with peroxidase-conjugated anti-rabbit secondary antibody (1:2000) (Abcam, Cambridge, MA, USA), and then washed again three times with TBS-T and incubated with ECL (Enhanced Chemi-Luminescence, Amersham Biosciences, Piscataway, NJ, USA) for chemiluminescence detection. Blots were analyzed on Scion Image software (Scion Corporation, Frederick, MD, USA) and protein expressions were normalized to β-actin expression (1:1000) (Santa Cruz Biotechnology, Santa Cruz, CA, USA).

Statistical analysis

The data were submitted to Kolmogorov-Smirnov normality test. Parametric variables were compared by One-Way analysis of variance (ANOVA) and complemented with the Tukey post hoc test for multiple comparisons when significant differences were found ($p< 0.05$). All the results are presented as mean ± standard deviation. Statistical analyses were performed using Sigma Stat for Windows Version 3.5. (Systat Software, Inc., San Jose, CA, USA). The level of significance considered was 5%.

Results

Table 1 presents the nutritional profile of the groups. It is possible to verify that both Ob and ROb groups presented lower food intake compared to the control group. Feed efficiency, final body weight, weight gain, and adiposity index were higher in the Ob group when compared to the control group. The ROb presented only a reduced adiposity index when compared to the Ob group, with no difference in the other variables.

The metabolic, cardiovascular, and hormonal parameters are presented in Table 2. Both groups, Ob and Rob, presented increased LDL, insulin, HOMA- IR and SBP, and low HDL levels when compared to the control group. The triglycerides, NEFA, and leptin levels were lower in the Rob group when compared to the Ob group, but higher than the control group.

The echocardiographic parameters are presented in the Figure 1. The Ob and ROb groups presented cardiac remodeling, characterized by increased LVDD, LVSD, left atrium, and estimated LV mass when compared to the control group. The systolic dysfunction, characterized by reduced cardiac output, was detected in both the Ob and

Table 1 – Nutritional profile

Variables	C (n=8)	Ob (n=8)	ROb (n=6)
Food intake (g/day)	25.1 ± 2.3	21.1 ± 1.8*	20.2 ± 1.4*
Calorie intake (kcal/day)	74.2 ± 7.1	76.9 ± 6.7	73.9 ± 5.1
Feed efficiency (%)	1.45 ± 0.08	1.82 ± 0.20*	1.64 ± 0.14
Final body weight (g)	506 ± 46.9	592 ± 60.2*	546 ± 36.4
Weight gain (g)	226 ± 21,3	296 ± 51,2*	255 ± 24,3
Adiposity index (%)	5.91 ± 0.59	10.21 ± 1.41*	6.31 ± 0.51#

*Data presented as mean ± standard deviation. n: Number of animals; C: control; Ob: obese; ROb: obesity-resistant. *versus C; $p < 0.05$; #versus Ob, $p< 0.05$; One-way ANOVA for independent samples and Tukey's post hoc test.*

Table 2 – Metabolic, cardiovascular, and hormonal parameters

Variables	C (n=8)	Ob (n=8)	ROb (n=6)
Triglycerides (mg/dL)	50.1 ± 10.3	99.6 ± 19.8*	73.1 ± 10.6*#
NEFA (mmol/L)	0.345 ± 0.033	0.642 ± 0.037*	0.462 ± 0.034*#
HDL (mg/dL)	28.7 ± 2.2	22.1 ± 2.6*	22.3 ± 2.9*
LDL (mg/dL)	19.9 ± 2.1	33.4 ± 5.1*	30.9 ± 3.7*
Glucose (mg/dL)	117 ± 13	169 ± 13*	136 ± 17#
Insulin (ng/mL)	3.39 ± 0.49	9.18 ± 2.14*	7.91 ± 2.12*
HOMA-IR	18.6 ± 4.5	75.1 ± 14.2*	21.1 ± 8.6*
Leptin (ng/mL)	4.23 ± 1.11	27.34 ± 3.36*	10.76 ± 3.21*#
SBP (mmHg)	116 ± 7	135 ± 3*	133 ± 12*

*Data presented as mean ± standard deviation. n: Number of animals; C: control; Ob: obese; ROb: obesity-resistant. TC: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein; NEFA: non-esterified fatty acids; HOMA-IR: Homeostatic Model Assessment - Insulin Resistance; SBP: Systolic blood pressure. *versus C; p < 0.05; #versus Ob, p< 0.05; One-way ANOVA for independent samples and Tukey's post hoc test.*

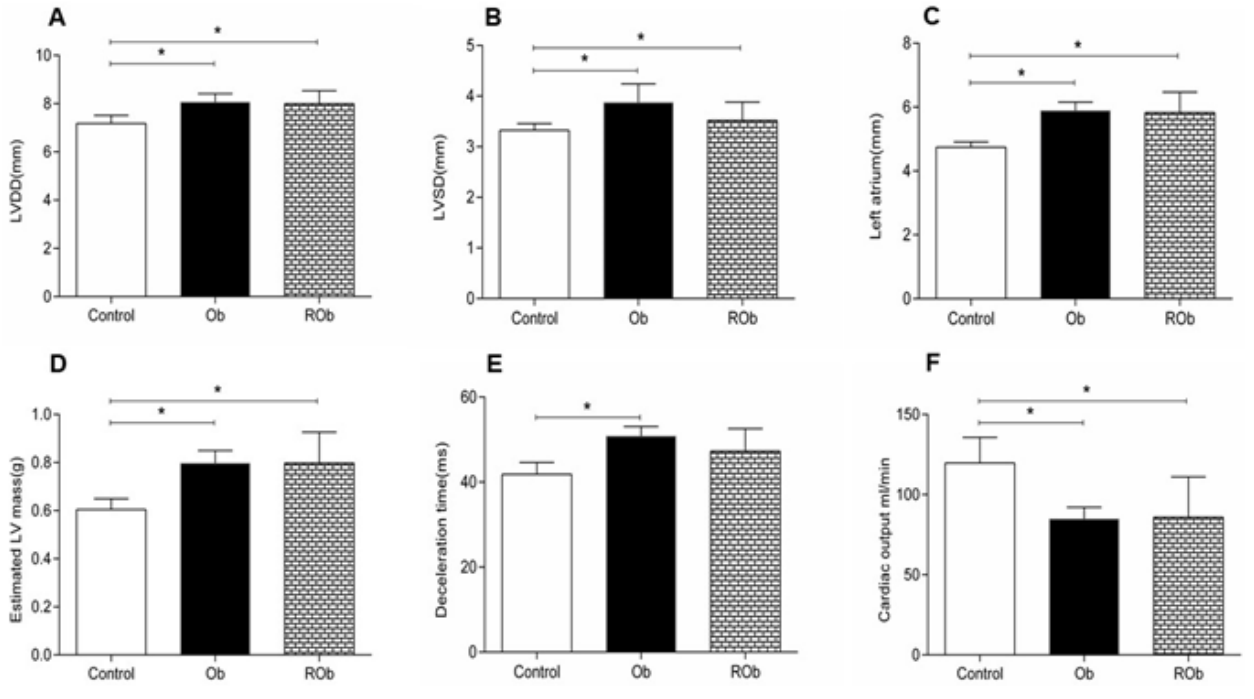

Figure 1 – Echocardiographic parameters. LVDD: left ventricular diastolic diameter (A), LVSD: left ventricular systolic diameter (B), Left atrium (C); Estimated left ventricular mass (D), Deceleration time (E), and Cardiac output (F). Control (C, n=8), Obese (Ob, n=8) and Obesity-resistant (ROb, n=6). Data presented as mean ± standard deviation. *versus C; p < 0.05; #versus Ob, p< 0.05; One-way ANOVA for independent samples and Tukey's post hoc test.

ROb groups. The diastolic dysfunction appeared only in the Ob group (increased deceleration time).

Cardiac remodeling was also confirmed in both the Ob and ROb groups by the cardiac post-mortem analysis, as these animals presented higher heart weight, LV weight, RV weight, heart/ tibia length, LV/ tibia length, and RV/ tibia length when compared to the control group (Figure 2).

Figure 3 shows the collagen type I (figure 3A) and the collagen type III (figure 3B) protein expression. No difference was found among the groups.

Discussion

Since obesity and its related disorders are becoming increasingly prevalent, several researchers have been using high-fat diet models to induce obesity, typically characterized by weight gain and increased body fat.[7,15,22,23] In the present study, we chose ~40% of kcal from fat, as we believe this is closer to what is consumed by humans. However, some individuals remain resistant to becoming obese, a condition also observed in some animals' fed with high-fat diets, which are defined as obesity-resistant animals.[8-10,24,25] Within this context, some authors have reported that around 40% of the animals fed with a high-fat diet are classified as ROb.[8-10,23] Some possible pathways to explain the obesity resistance include: increased expression of some thermogenic enzymes and decreased expression of lipogenic enzymes in adipose tissues of ROb rats, as well as the suppression of lipogenesis and the acceleration of fatty-acid oxidation in visceral fat.[8]

Several experiments have demonstrated that obese rats due to a high-fat diet intake develop obesity-related disorders that are similar to human disorders, such as glucose intolerance, insulin resistance, hypertension, and dyslipidemia.[16,22,26] However, in ROb models, there are controversies regarding the presence of comorbidities.[9,10,23,27] In the current study, the ROb group presented relevant metabolic, hormonal, and cardiovascular changes commonly found in obesity and associated with increased adiposity.[28] As the ROb group presented a weight gain and an adiposity index similar to the C group, it demonstrates that all the disorders were independent of adiposity gain. According to the literature, the intake of processed foods rich in fats, especially saturated fat, is one of the main causes for

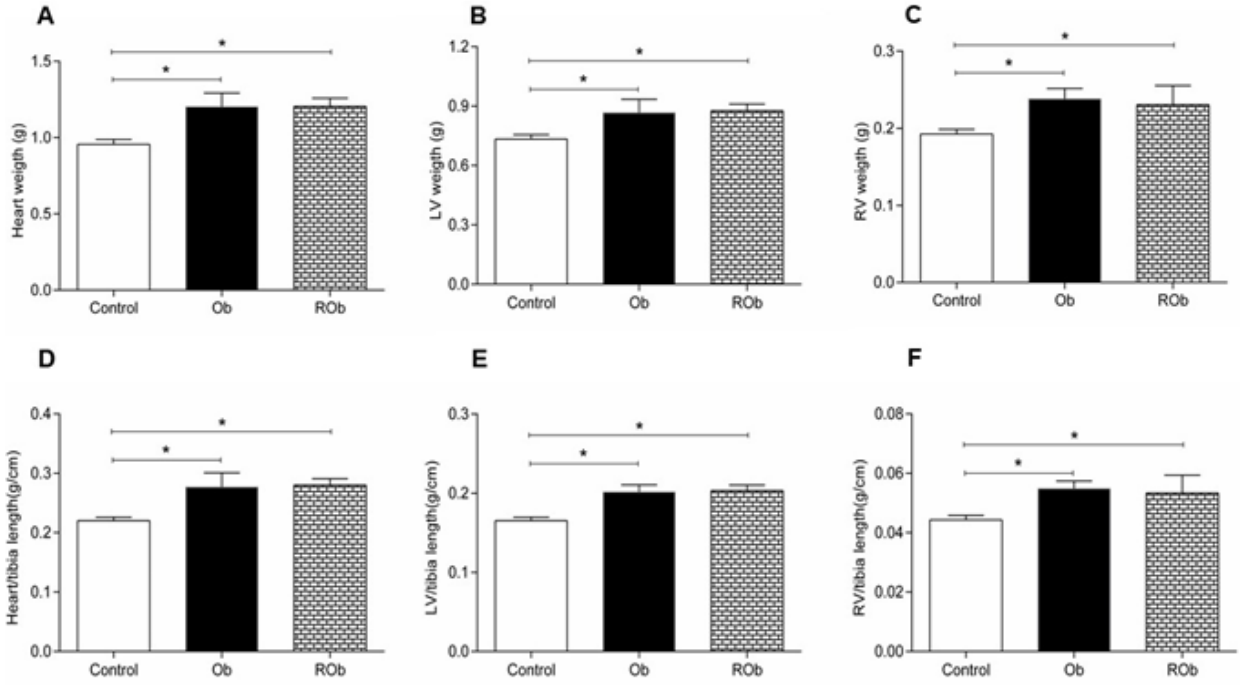

Figure 2 – Cardiac remodeling. Heart weight (A), LV: left ventricle weight (B), RV: right ventricle weight (C); Heart/tibia length (D), LV/ tibia length (E), and RV/tibia length (F). Control (C, n=8), Obese (Ob, n=8), and Obesity-resistant (ROb, n=6). Data presented as mean ± standard deviation. *versus C; p < 0.05; #versus Ob, p< 0.05; One-way ANOVA for independent samples and Tukey's post hoc test.

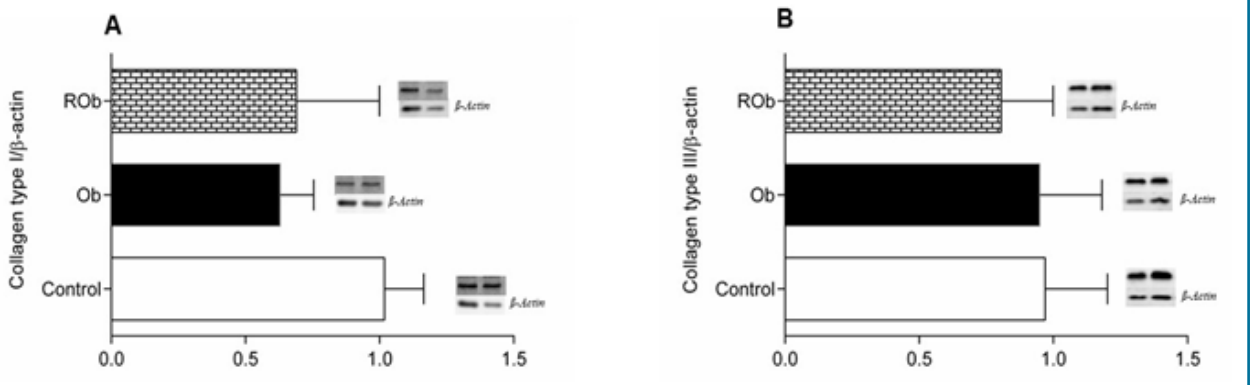

Figure 3 – Western blot analysis of collagen type I (A) and type III (B) in the hearts of the control (C, n=4) and obese I (Ob, n=4) and II (ROb, n=4) rats. Western blot bands were normalized by β-actin. Data presented as mean ± standard deviation. n: Number of animals; C: control; Ob: obese; ROb: obesity-resistant. *versus C; p < 0.05; #versus Ob, p< 0.05; One-way ANOVA for independent samples and Tukey's post hoc test.

obesity and is considered an isolated cause of metabolic disorder development due the pro-inflammatory effect of this nutrient.[29] Corroborating this finding, the ROb group presented increased an HOMA-IR index when compared to the control group, indicating impairment in carbohydrate metabolism as well as dyslipidemia, characterized by increased triglycerides and LDL, and reduced HDL.

Increased leptin and insulin are common in obesity.[16,22] However, the present study also observed this condition in the ROb animals. Increased insulin can be due to insulin resistance or elevated gastric inhibitory polypeptide levels induced by high-saturated fatty acid intake.[30] At the same time, hyperinsulinemia stimulates and increases the leptin secretion by adipose tissue through the PI3K/Akt/mTOR pathway, which can explain the increased leptin levels in the ROb animals that did not present increased body fat.[31]

The metabolic responses to hyperinsulinemia and hyperleptinemia are well established in the literature.[22,26] Nevertheless, these conditions also promote responses in other target organs, such as the heart.[16,32] In obesity, the high hormone levels trigger hypertrophic responses in the heart by activating specific signaling pathways.[33-36] However, in obesity-resistance models, the establishment of cardiac remodeling seems controversial.

Our results confirm the primary aim of this experiment, since the presence of cardiac remodeling in the ROb animals was verified by both echocardiographic and morphological post-mortem analysis,. The majority of cardiac diseases are followed by heart mass and morphologic changes. Due to the cardiac cell's incapacity to divide into the adult phase, the remodeling process usually occurs because of cardiomyocytes hypertrophy in response to a hemodynamic overload.[37]

Hemodynamic and hormonal changes promote extracellular matrix remodeling, altering its gene expression.[38,39] There are two main types of collagen in the heart, types I and III, which are responsible by cardiac rigidity.[40] However, different obesity models have demonstrated controversial results about collagen synthesis and degradation in the heart.[38,39,41] In this sense, this study had as secondary aim to evaluate if the cardiac remodeling was related to collagen I and III protein expression changes. Our results showed that no difference was found in the collagen protein expression among the groups. Thus, other pathways that influence cardiac remodeling and should be addressed in future studies include insulin/ PI3k/Akt/ PKB,[33,37] leptin/ RhoA/ ROCK/ p38,[34,35] oxidative stress,[42] and inflammation.[43]

Study Limitations

Limitations of this study include the absence of histological analysis for collagen evaluation and the small sample size.

Conclusion

Considering the results presented in this study, it is possible to conclude that obesity-resistant animals present cardiac remodeling that is not related to collagen type I and III protein expressions.

Author contributions

Conception and design of the research: Oliveira SM and Cicogna AC. Acquisition of data: Oliveira SM, Campos DHS, Silva-Bertani DCT and Vileigas DF. Analysis and interpretation of the data: Oliveira SM, Vileigas DF, Ferron AJT, Silva-Bertani DCT and Corrêa CR. Statistical analysis: Francisqueti-Ferron FV, Ferron AJT and Padovani CR. Obtaining financing: Oliveira SM and Cicogna AC. Writing of the manuscript: Oliveira SM, Garcia JL, Francisqueti-Ferron FV, Ferron AJT and Cicogna AC. Critical revision of the manuscript for intellectual content: Ferron AJT, Corrêa CR and Cicogna AC.

Potential Conflict of Interest

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

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee on Animal Experiments of the FMB-UNESP under the protocol number 991/2012.

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ORIGINAL ARTICLE

Electromyographical and Physiological Correlation in Patient with Heart Disease

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Abstract

Background: Walking is an economic activity, the more efficient the mechanical contribution, the less metabolic energy is necessary to keep walking. Patients with chronic heart failure and heart transplant present peripheral musculoskeletal disorders, dyspnea, and fatigue in their activities.

Objective: In this scenario, the present study sought to verify the correlations between metabolic and electromyographic variables in chronic heart failure, heart transplant patients, and healthy controls.

Methods: Regression and correlation between cost of transport and electromyographic cost, as well as correlation between oxygen consumption and muscle coactivation in patients and controls at five different walking speeds have been performed, with alpha = 0.05.

Results: Strong correlation values (r controls: 0.99; chronic heart failure: 0.92; heart transplant: 0.88) indicate a linear relationship between the cost of transport and electromyographic cost. Oxygen consumption was significantly correlated to muscle activation in all groups.

Conclusion: These results suggested that dynamic muscle coactivation was an important factor, especially for CHF and HT. These data support the idea that peripheral muscle limitations play an important role in people with CHF and HT. These findings indicate a strong relation between metabolic and electromyographic variables. For chronic heart failure and heart transplant patients, it can help to explain some difficulties in daily activities and aid in physical rehabilitation.

Keywords: Heart Failure; Heart Transplantation; Electromyographic/methods; Transportation; Costs and Analysis; Gait; Walking; Running.

Introduction

Walking and running are the most common human gaits. Humans walk at low speed and change gait to increase their locomotion speed, minimizing the energy expenditure. Thus, at speeds below walk-run transition speed, the oxygen consumption of walking is lower than that of running, while at higher speeds the relationship is reversed.[1] The energetic cost to travel a given distance is called the cost of transport (C), and has long been known to strongly depend on speed in human walking.[2,3] The cost is minimized at intermediate walking speeds of 4.5–5.4 km·h^{-1} (or 1.25–1.5 m·s^{-1}) and grows as speed increases above or decreases below this optimum value. This trend is related to the pendular transfer of kinetic and potential energy, which is greater at intermediate speeds, [4] reducing the total mechanical work that must be performed by muscles at these speeds. Equally, the described energetically optimal walking speeds are in accordance with the contractile physiology of skeletal muscle and the biomechanical models of terrestrial locomotion.[5]

Humans are exceptionally economical walkers [2, 6] with their long legs and capacity to store and recover elastic strain energy.[7] If the activity of individual muscles is minimized at intermediate walking speeds, as suggested above, we would expect the various

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muscles of the human locomotor system to be tuned to the same optimal speed to reduce the energetic cost of locomotion.[5]

Patients with chronic heart failure (CHF) and heart transplant (HT) experience fatigue and dyspnea during daily activities as well as during maximal exercise testing.[8, 9] HT is the preferred therapeutic strategy for the treatment of end-stage CHF. HT patients have different responses to physical exercise because of sustained pre-transplant physical conditions. Wilson el al.,[8] suggested that nutritive flow to skeletal muscles was defective in patients with CHF, and that their diminished maximal exercise capacity was correlated to the degree of impairment of nutrient flow. The exertional fatigue suffered by these patients was attributed to skeletal muscle underperfusion.[8, 10] However, Wilson et al.,[11] demonstrated that patients with CHF and exertional fatigue were limited by skeletal muscle abnormalities rather than by skeletal muscle underperfusion. Further studies indicated that early skeletal muscle anaerobic metabolism, with lactate production, is the primary factor limiting exercise performance in patients with this disorder.[9, 11] The skeletal muscle metabolic response to exercise is altered in patients with CHF.

Studies with EMG activity in CHF patients demonstrated that surface EMG can be used to detect skeletal muscle fatigue, altered muscle activity and atrophy.[12, 13] Information of muscle activity in groups of CHF and HT showed high coactivation and high "global" EMG (called electromyographic cost) when compared to healthy controls.[14] The correlation between metabolic and electromyographic variables can help to understand the changes in patients walking parameters and propose adequate goals during physical rehabilitation.

It is known that patients with cardiac diseases undergo musculoskeletal peripheral disorders, as well as anomalies in oxygen consumption, cost of transport, electromiographic activity and muscular coactivation.[11, 13] In a previous study, it has been shown that ventilatory efficiency disorders in CHF patients could explain some changes during physical activity.[15] However, others factors should be taken in account, like the connection between metabolic and electromyographic variables proposed in the present study.

The aim of this study was to verify correlations between metabolic (oxygen consumption and cost of transport) and electromyographic (coactivation and electromyographic cost) variables, as well as to obtain the regression equation over a range of walking speeds in CHF and HT patients and healthy controls. A strong positive correlation was hypothesized between cost of transport and electromyographic cost, and between oxygen consumption and the main muscle coactivations in all of the experimental and control groups.

Methods

Participants

In the sample calculation, a 20%difference was considered between the groups of cases (CHF) and the control group, with a statistical power of 80% and a significance level of 0.05.[15] The statistical program used was Winpepi, based on data from the study by Figueiredo et al.,[15] and the effect of the sample size was 0.67. For the HT group, all transplant recipients (in the hospital) who were able to walk on the treadmill were invited to participate in the study. The sample was consisted of two experimental groups (CHF and HT patients) and a control group. The first group (n = 12) included patients with a previous history of stable symptomatic CHF due to left ventricular systolic dysfunction (left ventricular ejection <45%). Patients with angina, uncontrolled hypertension, renal or pulmonary disease, recent myocardial infarction (previous 3 months), decompensated heart failure, neuromuscular disease, and smokers were not included. The second group (n = 5) included all the HT patients of the hospital where the study was carried out. The control group (n = 12) included individuals matched for age and sex, with a normal medical history and physical examination, as well as with normal resting and exercise ECG. The Institutional Ethics Committee approved the protocol (number 00788512.9.0000.5327), in accordance to the Helsinki Declaration, and all individuals signed an informed consent form (complying with resolution 466/2012).

Study Design

This was a cross-sectional study, following the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) checklist.[16] Each participant performed an incremental cardiopulmonary exercise test, whose details are given in Bona et al. (2017),[14] and, at least 48h after, to a walking cost test.

Cost of transport protocol

Each experimental session started with 5 minutes of resting VO_2 assessment *(m102/(kgmin))* in orthostasis. The Self-Selected Walking Speed (SSWS), a comfortable speed that could be sustained for a prolonged period, of each subject was determined according to Figueiredo et al. (2013)[15] and Bona et al.[17] Data acquisitions on treadmill were performed at five different speeds (SSWS; +/- 20%; +/- 40%), whose sequence was randomized. Each trial lasted 5 minutes in order to reach a steady state for VO_2. Between each speed, the subjects were allowed to rest until the oxygen consumption levels were close to the values of VO_2 in orthostasis . Respiratory gas was analyzed breath by breath with a validated system (system (Metalyzer 3B, CPX System; Cortex, Leipzig, Germany), and the cost of transport (C) was estimated from the data collected during the last 2 minutes, by dividing the measured net VO_2 (total-resting), adjusted for the respiratory quotient, by the progression speed.

Walking EMG protocol

Electromyographic signals were collected for 3-5 minutes during each trial, by four miotools 400 (Miotec Biomedical Equipments Ltd, Porto Alegre, Brazil), with a sampling rate of 2,000 Hz per channel. EMG records were synchronized with digital videos, collected with two CASIO cameras (Exilim FH25; 120 fps). All procedures recommended by[18] were strictly observed. Fourteen muscles were monitored on the right side of the body: tibialis anterior (TA), gastrocnemius medialis (MG), vastus lateralis (VL), rectus femoris (RF), biceps femoris (long head, BF), gluteus medius (GM), deltoideus anterior (DA), external oblique (OE), internal oblique (OI), latissimus dorsi (LD), iliocostalis (IC), erector spinae (ES) recorded at T1, T9, rectus abdominis superior portion (RAS), and trapezius ascending portion (TRAP). Recommended position for electrodes according to SENIAM 2008, except for ES, RAS,[19] and OE[20] were used.

The electromyographic data were analyzed with a custom-written MATLAB program (version 7.1; MathWorks, Inc.), as described in Bona et al. (2016).[14]

Walking EMG analysis

The EMG data were bandpass filtered with a zero-lag, third-order Butterworth filter with cut-off frequencies at 10 and 500 Hz, and the integral of the rectified EMG (iEMG) signal was determined for each muscle at each phases, with time interpolated over base with 200 points.[21]

The EMG signal was normalized by the peak value of the EMG data. Step phase onsets and offsets were defined using the video recording cameras and three reflective markers (on the fifth metatarsal, calcaneus, and greater trochanter). Sampling of EMG and video recording data were synchronized. For EMG cost, the step was divided by onset, which happened when the heel stuck and offset happened in mid-stance (first stance phase – eccentric contraction), onset happened at mid-stance and offset happened at forefoot lift-off (second stance phase - concentric contraction). The balance phase was defined as the interval between the forefoot lift off the ground and the following heel-strike (isometric contraction).[22] The mean EMG signal was subtracted by the iEMG activity in orthostasis. iEMG signal were converted into count units (100 counts correspond to 1 $mV.s^{-1}$).[23] EMG eccentric (EMG_{neg}), EMG concentric (EMG_{pos}), and EMG isometric (EMG_{iso}) were obtained in the counts. The metabolic equivalent was obtained through a linear regression equation of previous experimental study,[23] as follows:

$$Vo_{2neg}(ml) = 0.0015.EMG_{neg} + 0.3353 \quad \text{Equation 1}$$

$$Vo_{2pos}(ml) = 0.0042.EMG_{pos} + 0.1493 \quad \text{Equation 2}$$

$$Vo_{2iso}(ml) = 0.0042.EMG_{iso} + 0.1394 \quad \text{Equation 3}$$

VO_{2neg} is the oxygen consumption for negative mechanical work, VO_{2pos} is the oxygen consumption for positive mechanical work, and VO_{2iso} is the oxygen consumption for isometric contraction.

Finally, the sum of metabolic equivalent was converted into Joules using an energetic equivalent. This was obtained adjusting the respiratory quotient.[24] Subsequently, this value was divided by step length to determine the walking EMG cost in joules per meter (equation 4).

$$CEMG\,(J/m) = EQ[(VO_{2neg1} + VO_{2neg2} \cdots + VO_{2neg14}) + (VO_{2pos1} + VO_{2pos2} \cdots + VO_{2pos14}) + (VO_{2iso1} + VO_{2iso2} \cdots + VO_{2iso14})].SL^{-1} \quad \text{Equation 4}$$

EQ is the energetic equivalent, SL is the stride length.

The percentage of coactivation was defined by the onset of the stance phase, when the calcaneus touched the ground, and the offset, when the forefoot lifted off the ground; the balance phase was defined as described above.[23] Coactivation was analyzed for five pairs of muscles, DA-LD, IC-OI, ES-RAS, TA-GM, and RF-BF, by the quotient between antagonistic iEMG and agonistic iEMG (as follows) at each phase described above.[25]

$$Coactivation = \frac{iEMGantagonist}{iEMGagonist} X100 \quad \text{Equation 5}$$

Data analysis

Data analysis was based upon a linear model. The relation between CEMG and C was analysed through a standard major axis (SMA) linear regression model, following the recommendations of Sokal and Rohlf.[26] The four assumptions associated with a linear regression model were verified as follows:

1) Normality: by means of the Shapiro-Wilk test.
2) Homoscedasticity: by means of the Levene test.
3) Linearity: through the analysis of the Akaike Information Criterion (AIC) for linear and non-linear models.
4) Independency: by the Durbin-Watson statistics, testing the autocorrelation of the residuals.

All the tests gave no significant results at alpha = 0.05, and all the best likelihood of AIC were in favor of linear models. Therefore, SMA linear regression equations were calculated using the mean values of CEMG and C. The regression equation (y = a + bx; where" b" is the slope) was obtained by estimating CEMG ($J \cdot kg^{-1} \cdot m^{-1}$) from C for the general population and for each group of this study. Due to the properties of SMA linear regression, where x and y are interchangeable, the equations can be adjusted to estimate C from CEMG as well[26]The results of regression equations are dependents of the C speed used during walking.

Pearson's correlation coefficient (r) was used to assess the linear relationship between oxygen consumption and coactivation.

One-way ANOVA was carried out to test for differences between groups for each anthropometric, cardiopulmonary, and cost measures. Normality and homoscedasticity of all variables was verified as specified above, and the sphericity by the Mauchly test. When appropriate, multiple comparisons were made with Bonferroni correction. Continuous variables are presented in mean and standard deviation , categorical (gender and medicine) data were described in absolute frequencies.

Analyses have been performed using the SPSS statistical package (IBM, USA), version 13.0, and R, version 3.6.3, with alpha = 0.05.

Results

Participants' characteristics

As shown in Table 1, the age and gender of CHF patients and controls were well matched. All patients with HT in Hospital de Clínicas de Porto Alegre (Clinical Hospital of Porto Alegre, Brasil) participated in this study. HT Patients presented a higher mean weight than did CHF patients (P=0.006), and a higher height than the controls and CHF patients (P=0.003 and 0.001, respectively). CHF Patients showed a moderate reduction in the left ventricular systolic function and a mild impairment in functional capacity. SSWS of CHF and HT patients was lower than that of the controls (P = 0.001/0.001), while C was higher in the same groups (P = 0.001/0.001). All CHF patients were studied under currently recommended medical therapy. VO_{2peak} was higher in the control group (P = 0.001). The VE/VCO_{2slope} was significantly higher in CHF and HT patients (P = 0.049/0.027). Peak heart rate and % of predicted and peak heart rate were higher in the control group (0.001/0.001). The VE/VCO_2 was higher in the HT group. As expected, controls presented the lowest C and CEMG at the SSWS (P = <0.001/0.001 and <0.001/<0.001).

Data are mean ± SD or number of subjects. CHF, chronic heart failure; HT, heart transplant; f/m, female/male; ACE-I, angiotensin-converting enzyme inhibitor; ARA, angiotensin receptor antagonist; VO_2 peak, peak oxygen uptake; $VE(VCO_2)$ slope, minute ventilation to carbon dioxide production slope; OWS Froude, OWS calculated by Froude number; 220 - age, 220 minus the subject's age; SSWS self-selected walking speed; C cost of transport; CEMG electromyographic cost. Symbols identify statistical significance in the Bonferroni test: ** differences between HT and others; *** differences between controls and others; **** difference between HT and CHF. * identifies statistical significance; † differences between HT and controls; ‡ differences between HT and CHF; § differences between controls and CHF; Data source: B ona et al. 2017.[14]

Walking EMG: correlations and regression

The values of Pearson's correlation coefficients between oxygen consumption and muscle coactivation, during stance and balance phases at five walking speeds are shown in Table 2 . Coactivation were determined between five couples of muscles (deltoideus anterior - latissimus dorsi; iliocostalis - internal oblique; erector spinae - rectus abdominis; tibialis anterior - gastrocnemius; rectus femoris - biceps femoris) . Values of Pearson's correlation coefficient (r) were around 0.87 and 0.98, classified as strong correlation,[27] for tree groups (controls, CHF, and HT patients), and was significant according the table. For information about CA comparisons between groups (see supplementary document and Bona et al., 2017).

Table 1 – Characteristics of controls and CHF and HT patients

	Controls	CHF	HT	p-value
	(n=12)	(n=12)	(n=5)	
Age (yr)	57 ± 11	59 ± 10	57 ± 6	
Weight (kg)	70.3 ± 14	66 ± 12	82 ± 7****	0.006
Gender (f/m)	4/8	4/8	1/4	
Height (cm)	166 ± 11	160 ± 12	180 ± 10**	0.003 †/0.001‡
BMI (kg/m²)	25.51 ± 6.1	25.78 ± 5.9	25.30 ± 7.2	0.1
Time after HT (yr)	-	-	1.7 ± 1	
Left ventricular ejection fraction (%)	-	33 ± 3	70 ± 9	
Beta-blockers	-	12	5	
Diuretics	-	10	3	
ACE-I/ARA	-	12	5	
Digoxin	-	7	-	
Anticoagulants	-	8	5	
Immunosuppressor	-		5	
VO_2 peak (mL.kg^{-1}min^{-1})	32.1 ± 6.3 *	23.9 ± 5.1	19.3 ± 2.9	0.001
VE(VCO_2) slope	28 ± 2 ***	32 ± 1	35 ± 4	0.049§/0.027//
Peak expiratory exchange ratio	1.22 ± 0.07	1.15 ± 0.05	1.27 ± 0.03	0.073
Peak heart rate, % of predicted (220-age)	110 ± 3 ***	87 ± 2	76 ± 2	0.001§/0.001//
Peak heart rate (bpm)	179 ± 3***	139 ± 2	124 ± 4	0.001§/ 0.001//
Peak VE(VCO_2)	31.11 ± 4.1	32.83 ± 3.9	38.86 ± 3.2**	0.022 †/ 0.028‡
SSWS (m.s^{-1}) on treadmill	1.04 ± 0.4 ***	0.75 ± 0.3	0.85 ± 0.3	0.001§/ 0.011//
C at the SSWS (J.kg.m-1)	1.93±0,71 ***	3.04 ± 0.8	3.01 ± 0.31	<0.001§/0.001//
CEMG at the SSWS (J.m^{-1})	2.77±0.9***	3.52±1.2	3.16±1.3	<0.001§/<0.001//
VO_2 at the SSWS (mL.kg^{-1}min^{-1})	11.77 ± 0.6	10.59±0.9	11.53 ± 0.9	0.26

*Data are mean ± SD or number of subjects. CHF, chronic heart failure; HT, heart transplant; f/m, female/male; ACE-I, angiotensin-converting enzyme inhibitor; ARA, angiotensin receptor antagonist; peak, peak oxygen uptake; () slope, minute ventilation to carbon dioxide production slope; OWS Froude, OWS calculated by Froude number; 220 - age, 220 minus the subject's age; SSWS self-selected walking speed; C cost of transport; CEMG electromyographic cost. Symbols identify statistical significance in the Bonferroni test: ** differences between HT and others; *** differences between controls and others; **** difference between HT and CHF. * identify statistical significance; † differences between HT and controls; ‡ differences between HT and CHF; § differences between controls and CHF; Data source: Bona et al. 2017.*[14]

Correlation coefficient between the oxygen consumption and coactivation of DA-LD (deltoideus anterior - latissimus dorsi), IC-OI (iliocostalis - internal oblique), ES-RAS (erector spinae - rectus abdominis superior portion), TA-GM (tibialis anterior - gastrocnemius medialis), RF-BF (rectus femoris - biceps femoris long head) during stance and balance phases at five walking speeds.

Differences between groups for CA (see supplementary document) were discussed in Bona et al., 2017.[14]

The regression equations for estimating CEMG (J·kg^{-1}·m^{-1}) from C, in a range of speed around the SSWS, were calculated in four models:

i) general equation: CEMG = 0.547 + 0.921(C);

ii) controls: CEMG = -0.091 + 1.209 (C);

Table 2 – shows the Pearson correlation between oxygen consumption (VO_2) and coactivation (CA) - stance and balance phases

	Controls		CHF		HT	
Correlation	*r*	p	*r*	p	*r*	p
VO_2 and CA Stance Phase						
DA-GD	0.91	*0.001*	0.84	*0.033*	0.94	*0.024*
IL-OI	0.95	*0.038*	0.70	*0.04*	0.78	*0.03*
ES-RAS	0.96	*0.032*	0.87	*0.026*	0.96	*0.001*
TA-GM	0.95	*0.001*	0.90	*0.001*	0.98	*0.001*
RF-BF	0.92	*0.001*	0.89	*0.034*	0.94	*0.002*
VO_2 and CA Balance Phase						
DA-GD	0.92	*0.03*	0.8	*0.03*	0.98	*0.001*
IL-OI	0.98	*0.001*	0.82	*0.032*	0.92	*0.001*
ES-RAS	0.90	*0.002*	0.86	*0.041*	0.88	*0.01*
TA-GM	0.87	*0.035*	0.90	*0.021*	0.92	*0.026*
RF-BF	0.94	*0.001*	0.93	*0.04*	0.89	*0.039*

Correlation coefficient between the oxygen consumption and coactivation of DA-LD (deltoideus anterior - latissimus dorsi), IC-OI (iliocostalis - internal oblique), ES-RAS (erector spinae - rectus abdominis superior portion), TA-GM (tibialis anterior - gastrocnemius medialis), RF-BF (rectus femoris - biceps femoris long head) during stance and balance phases at five walking speeds. CHF - chronic heart failure; HT - heart transplant. r is Pearson's correlation coefficient. P significant correlation values.

iii) CHF: CEMG = 0.630 + 0.871(C);

iv) HT: CEMG = 0.221 + 1.047(C);

where CEMG is the electromyographic cost and C is the cost of transport.

Linear regression graphs are presented in figure 1. All values for R^2 were between 0.88 and 0.99, which validated the model. For controls, the linear model explains 99% for the C values, 92% for CHF, and 88% for HT.

Discussion

Better understanding of complex interactions involved in measuring mechanical work and efficiency might best be obtained using a multidisciplinary approach.[28] The present study proposed an evaluation of the relationship between electromyographic and physiological variables, using specific (coactivation percentage) and global (C and CEMG) measures. The global measures reflect the sum of more localized contributions throughout the body.

The linear regression analyses showed a strong relationship between CEMG and C in the three analyzed populations. However, the metabolic cost appears slightly underestimated in the controls, but the CEMG seems to be a bit overestimated, with HT set in between, with the slope at nearly 1 (Figure 1). As shown, it is possible to estimate the C towards the CEMG in the three analyzed populations. CEMG could replace C in some clinical situations: when a gas analyzer is not available, when using a mask is not recommended (like in cerebral palsy), or when the population present some alteration in respiratory parameters (like in a respiratory disease), which could to change the real values.

A strong and significant correlation was found in all the analyzed groups, between the CEMG and the metabolic C, and between oxygen consumption and the main muscle coactivation. According to Bona et al.[17] the mechanical work was higher, while the mechanical efficiency was lower in CHF and HT, when compared with the controls. Those differences were partially due to differences of SSWS. However, muscle activation and CEMG also play a secondary role.[14] According to Williams (1985),[28] muscular efficiencies are typically between 20-35% for walking. Mechanical efficiency during walking was near 25% at SSWS. For CHF and

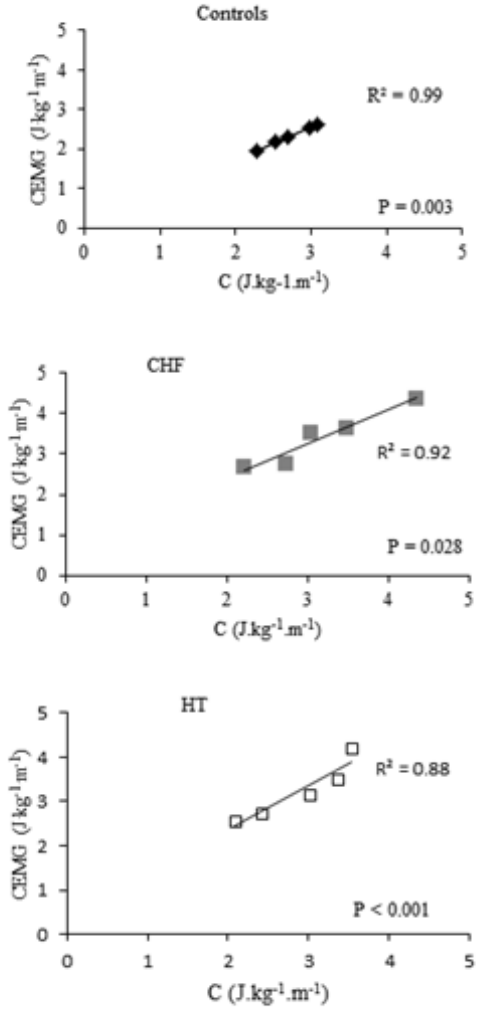

Figure 1 – C is the cost of transport, CEMG is the electromyoghraphic cost, CHF is chronic heart failure, HT is heart transplant. R2 is the determination coefficient. Significant correlation (p<0.05).

HT, the mechanical efficiency during walking achieve values near 20% at the same speed of the control group.[17]

The EMG technique presents some limitations, much like other physiological evaluations. EMG recordings provide a local quantitative measure of total muscle fiber activity, and changes in total rate of oxygen uptake result primarily from changes in the oxygen uptake of the general working of muscles.[23] A strong relationship was reported between EMG data and mechanical work.[29] Decrease in the recovery index and increase in the external mechanical work in CHF and HT patients is determined by a reduction in the pendulum-like energy interchange due to an altered trajectory of the COMB.[17] The authors suggest that the reported differences in external mechanical work and recovery could determine an increased muscle activity to sustain locomotion. All these data confirm the relationship between EMG data and biomechanical parameters during walking.

Analysis of the energy recovery showed that, according to literature, the exchange between kinetic energy and potential energy was limited, especially at slow speeds, while it reached maximum values at the higher walking speeds.[30-32] By optimizing the system conversion, less metabolic energy is needed to keep walking. The SSWS adopted by CHF and HT patients directly determines the efficiency of the pendulum mechanism (recovery). Reducing their speed, patients increase the stability of walking, but increase the variability of movements as well,[33, 34] a factor that could affect the muscular activity and, therefore, the C. Improvements in walking speed,

leading to the optimal walking speed, would increase the vertical displacement of the COMB, providing larger oscillations of kinetic energy and potential energy of the COMB and, generally, an improvement of the efficiency of the pendulum mechanism of walking.

The rate of oxygen consumption was significantly correlated to leg, trunk, and arm muscle activation in all groups, suggesting that these are key factors affecting exercise performance. This finding suggests that dynamic muscle coactivation was an important factor specific to CHF and HT as a quality of movement index. The authors estimated coactivations in both stance and balance phases of walking, and at specific phases and requests of movement. These data support the idea that peripheral muscle limitations play an important role in people with CHF and HT, confirming and extending prior studies.[14, 17] The same behavior has been shown for a number of other muscles and for a variety of different types of dynamic contractions.[29]

There is compelling evidence that skeletal muscle dysfunctions play an important role in exercise intolerance in CHF. The problem involves the large muscles of locomotion, small muscles of the arms, and even respiratory muscles. These changes lead to increased muscle fatiguability, decreased oxidative metabolism, increased oxidative stress, and ineffective high energy phosphate, most likely resulting in an early accumulation of lactate during walking.

The beneficial effect of exercise training on reducing skeletal muscle alterations in these patients demonstrates that this process is reversible.[35] The changes lead to an improvement in peak VO_2 and lactate threshold, and delayed onset of anaerobic metabolism. Exercise training also has anti-inflammatory effects, and, as described above, can increase local expression of the anabolic peptide insulin-like growth factor 1. Additionally, reduced sympathetic hyperactivation and improved endothelial dysfunction with exercise training contribute to improved muscle blood flow and clinical performance.[35]

One recent study[36] found increased coactivation in people with multiple sclerosis when compared to healthy subjects walking at similar speeds. This fact appeared not to be due to different gait velocities for this population; by contrast, it was likely an adopted strategy, suggesting that this mechanism may be part of a characteristic implemented pattern that may explain differences in gait ability. For CHF and HT patients, this increase in percentage of coactivation may well contribute to higher C and CEMG,[14] lower recovery, and mechanical efficiency at SSWS.[17]

Another study[37] analyzed the activity of agonist and antagonist muscles during gait in patients with multiple sclerosis, demonstrating that abnormal lower limb muscle coactivation occurs during the stance phase of gait. This increased lower limb muscle coactivation during gait is an adaptive strategy that tends to compensate for muscle weakness. The relationship between muscle coactivation during gait and disability, postural stability, joint stiffness, and gait performance are regulated by variations in the forces produced. This is important, since an inappropriate coactivation (excessive and/ or prolonged) reduces gait performance by reducing gait speed and increasing metabolic cost. The results of the present study increase understanding of the function of coactivation in cardiac patients.

Research in medicine sports for decades has demonstrated that the skeletal muscle function improved through exercise training, which reduces the debilitating symptoms of chronic heart failure through its effects on the cardiovascular and musculoskeletal systems. Analysis of muscle activation can provide important clinical information and the ability of patients to produce a desired functional outcome.[36] In these way, mortality and hospital admission are significantly reduced after exercise training in patients with CHF, and this benefit was not restricted to any particular subgroup of patients.

The present study proposes that for CHF and HT patients who have SSWS lower than OWS, rehabilitation programs should focus on improving the speed of exercise, such as dynamic muscle contraction (and coactivation) for a better efficiency and economy of movement. Thus, further studies are necessary to evaluate other populations, like chronic obstructive pulmonary disease, multiple sclerosis, or cerebral palsy with these methods.

It is important to consider some limitations of the present study. The SSWS on the ground, for all groups, was greater than SSWS on the treadmill. This, as described by Figueiredo et al. (2013),[15] may have affected the results (see Table 1). SSWS are expected to be lower on the treadmill than on the ground, hence the control group's lower SSWS. The assessment of the SSWS is an important task in an attempt to define the characteristics of walking and the physical tolerance of each group. Our CHF patients showed only a slight decrease in function capacities and, for this reason, our outcomes cannot be extended to patients with more severe CHF. However, with the current clinical therapies, more and more patients of CHF clinics have a profile equivalent to that of our group.

Conclusion

The aim of this study was to verify the correlation between oxygen consumption and coactivation, as well as the correlation between C and CEMG in CHF and HT patients and healthy controls. Accordingly, the results highlighted complementary strategies to reduce the C caused by muscle economy denominated CEMG, in addition to the inverted pendulum mechanism. More specifcially, muscle coactivation seemed to play a role in the increase of oxygen consumption throughout postural stability, stance, and balance phases for the entire gait cycle to determine total body energy consumption. Identification of inappropriate activation and how this may lead to specific locomotor deficits could lead to more effective training interventions.

Clinical Messages

Strategies to increase muscle economy and stability, reducing muscle contraction, can help the physical condition and locomotion of patients with heart disease.

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Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Hospital de Clínicas de Porto Alegre / Plataforma Brasil* under the protocol number 00788512.9.0000.5327. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Author contributions

Conception and design of the research: Bona RL, Bonezi A, Castro FAS, Clausell N. Acquisition of data: Bona RL, Bonezi A. Analysis and interpretation of the data: Bona RL, Bonezi A, Biancardi CM, Castro FAS, Clausell N. Statistical analysis: Bona RL, Biancardi CM. Obtaining financing: Bona RL, Clausell N. Writing of the manuscript: Bona RL, Bonezi A, Biancardi CM, Castro FAS, Clausell N. Critical revision of the manuscript for intellectual content: Bona RL, Bonezi A, Biancardi CM, Castro FAS, Clausell N.

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ORIGINAL ARTICLE

Analysis of Diastolic Left Ventricular Function in Adolescents with Juvenile Systemic Lupus Erythematosus

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Abstract

Background: Juvenile systemic lupus erythematosus (JSLE) is a chronic inflammatory disease that affects the heart in 50% of cases. The behavior of diastolic function in adolescents and the predictors of its occurrence by conventional echocardiography are poorly established.

Objectives: This study aimed to evaluate diastolic function in adolescents with JSLE and to identify possible predictors of its occurrence by conventional echocardiography.

Methods: Cross-sectional, observational, control group study in a tertiary hospital of 49 adolescents with JSLE and 49 controls, using the EACVI 2016 guideline classification. Statistical methods used were Fisher and Mann-Whitney tests. Multivariate logistic regression models were constructed. A significance level of 5% was adopted.

Results: Among 98 patients, the JSLE group had higher indexed left atrial volume ($p < 0.001$), lower lateral E' value ($p<0.001$) and lower E/A ratio value ($p<0.001$). The diagnosis of JSLE was associated with a higher chance of increased left atrial index volume (OR 3.3; p value 0.03).

Conclusions: Based on the 2016 guideline, no diastolic dysfunction was found in JSLE. However, differences in the analyzed echocardiographic parameters were found in these adolescents.

Keywords: Lupus Erythematosus, System; Ventricular Dysfunction, Left; Adolescent; Echocardiography/methods.

Introduction

Juvenile systemic lupus erythematosus (JSLE) is an inflammatory disease involving multiple organs and systems. The average age at onset is between 11 and 12 years old, approximately 80% of patients are female.[1, 2] It usually has a more severe clinical course raising morbidity and mortality rates.[1-3] Cardiovascular complications occur in 50% of patients, and are the third leading cause of death, requiring special attention.[3,4] They normally present heart failure (HF) and preserved ejection fraction (HFpEF), and initially manifest as subclinical diastolic dysfunction (DD).[4] The early diagnosis of this dysfunction is fundamental, since at this early stage of DD, factors that interfere with the progression of HF can be modified. This recognition is a complex process that requires a systematized evaluation. Echocardiography is the mainstay of DD evaluation, as it is noninvasive and available.[5,6] In adolescents, studies are scarce, and little is known about LV function in JSLE. [7]

Given the importance of the topic, this study used echocardiography to assess left ventricular (LV) diastolic function in JSLE, based on the hypothesis that the inflammatory process arising from pathogenesis and/or treatment would be associated with the occurrence of subclinical LV DD due to a complex interplay of factors leading to chronic inflammation, deposition of immune

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complexes, and chronic infiltrates that result in impaired LV relaxation and distensibility as early as adolescence.[8,9]

Methods

This was a cross-sectional, observational, control group study conducted with patients of the NESA-HUPE/UERJ, Rio de Janeiro, Brazil, from March 2017 to June 2019. Echocardiographic tests were performed at Lup Dup and Babycor Pediatric and Fetal Cardiology Clinics, for routine and/or sports practice evaluation.

Inclusion criteria were adolescents aged 10 to 20 years, diagnosed with JSLE, in follow-up at NESA-HUPE/UERJ, and healthy adolescents of the same age group, who had routine echocardiograms. Laboratory tests of the control group (complete blood count, lipid count, coagulogram, biochemistry, urea, creatinine, TSH and free T4 tests), echocardiogram and ECG were normal. The exclusion criteria were patients diagnosed with cardiac arrhythmia, congenital heart disease, systolic dysfunction, and inadequate echocardiographic window. The data were obtained from medical records that were reviewed by the same pediatric rheumatologist to obtain clinical, laboratory and therapeutic management data. Disease activity was determined according to the SLE Disease Activity Index 2000, revised in 2012 (SLEDAI-2K).[4,10] A SEDAI-2K value > 4 was defined as an indicator of disease activity. All patients completed a clinical questionnaire at the time of examination.[10]

Two-dimensional color transthoracic Doppler echocardiography, M-mode, with tissue Doppler was performed using a Philips HD 11 (Philips, Andover MA, USA) device and 3 to 5 MHz transducers. The echocardiogram was performed in the left lateral decubitus position. All images were recorded. All echocardiographic examinations were performed and interpreted by the same observer and according to the recommendations of the American Society of Echocardiography.[9] The echocardiographic variables studied were septal annular velocity E' or lateral E', mean E/E' ratio (lateral E' + septal E'/2), indexed left atrial volume (iVLA) by body surface area (BS), maximum reflux speed through the tricuspid (VT), mitral Doppler (E/A ratio), LV systolic diameter (LVDd), posterior wall in systole (PWs), aortic root.

For the purpose of identifying diastolic function, the 2016 recommendation cites four items: septal E' speed less than or equal to 7 cm/sec. or lateral E' ≤10 cm/m, mean E/E' ratio >14; reflux speed through the tricuspid 2.8 m/sec; and indexed LA volume >34 ml/m². If three or more items are negative, diastolic function is normal. If half is negative and half is positive, the diastolic function is indeterminate. If three or more items are positive, diastolic dysfunction is present.[11] (Figure 1). Based on the diagnosis of JSLE, two groups were created: A- cases of JSLE (subdivided by disease activity, yes or no) and B- control group, composed of healthy adolescents and comparisons were made between the groups.

All Doppler measurements were averaged over 3 heartbeats, to minimize variations with breathing. Pulsed Doppler (PW) was used for accurate definition of ventricular interval times.[12] Simultaneous electrocardiograms helped correlate flow timing with electrical changes.

Indexed Left Atrial Volume

The anteroposterior diameter of the left atrium was obtained by M-mode echo. Using two-dimensional echo, the indexed left atrial volume (iVLA) was gauged using the biplane Simpson technique on apical 4- and 2-chamber sections followed by indexing by body surface area.[11-13] (Figure 2). The cut-off value indicating abnormality is iVLA > 34 ml/m².[11]

Tissue Doppler imaging of mitral annular velocities: septal and lateral

PW Tissue Doppler imaging (TDI) was performed on the apical section to acquire mitral annular velocities. (Figures: 3, 4 and 5) Measurements reflected the average of ≥3 consecutive cardiac cycles.

E/A ratio; Pulsed wave (PW) Doppler was performed in the apical 4-chamber view to obtain mitral inflow velocities to assess LV filling. Color flow imaging was used for optimal Doppler beam alignment (Figure 6).[11,13]

Tricuspid flow velocities

The peak velocity of the tricuspid valve regurgitant jet was performed by positioning the sample volume in the reflux vena contracta. By continuous Doppler, the pulmonary systolic pressure was quantitatively estimated (Figures 7 and 8).[11-14]

Aortic root: Location of measurements performed were the aortic valve annulus (point of articulation of the aortic leaflets), the sinuses of Valsalva, the sinotubular junction, and the proximal ascending aorta.[11-14]

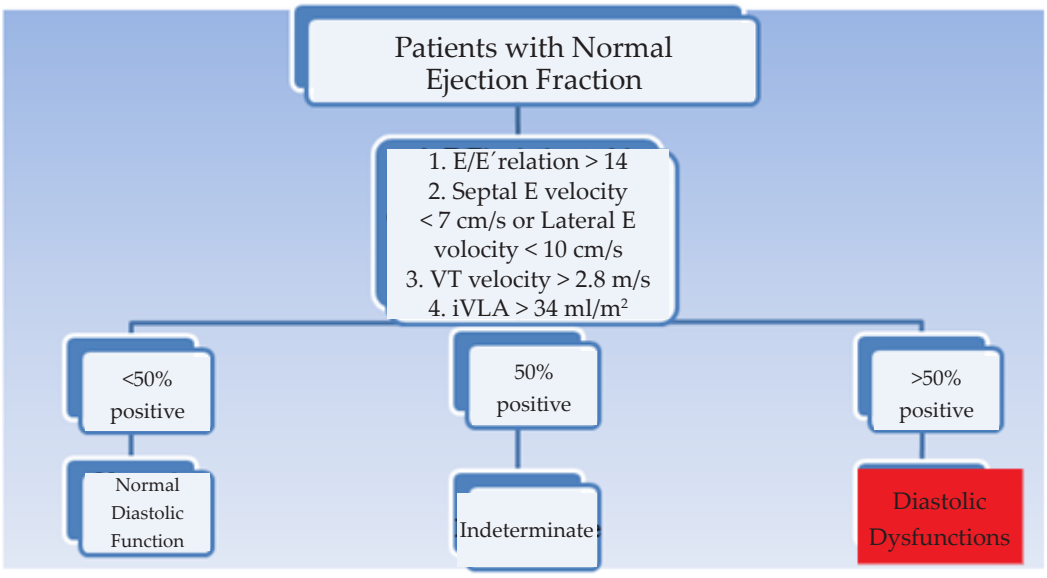


Figure 1 – Algorithm of diastolic function evaluation 2016.11
Source: prepared by the author. Based on the Journal of the American Society of Echocardiography 2016 29, 277-31411.
**(VT) velocity through the tricuspid; > 2.8 to 2.9 m/s, corresponding to *(PSAP) pulmonary artery systolic pressure of approximately 36 mmHg.*[11]

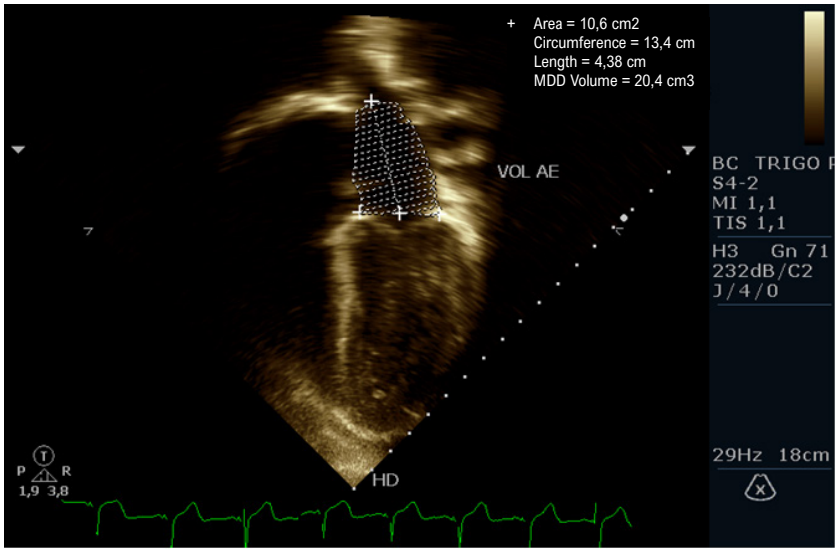


Figure 2 – Indexed volume of the left atrium. (iVLA)
Personal file
Planimetry of the area of the left atrium in the apical 4 chambers.

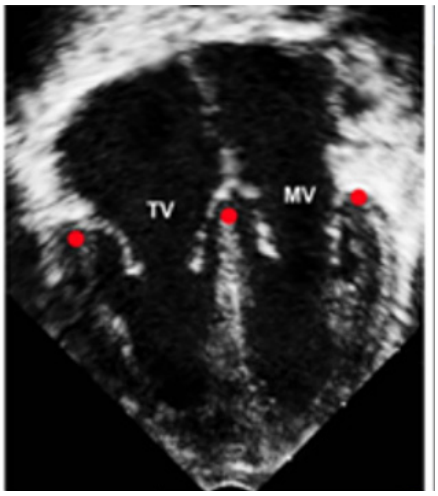
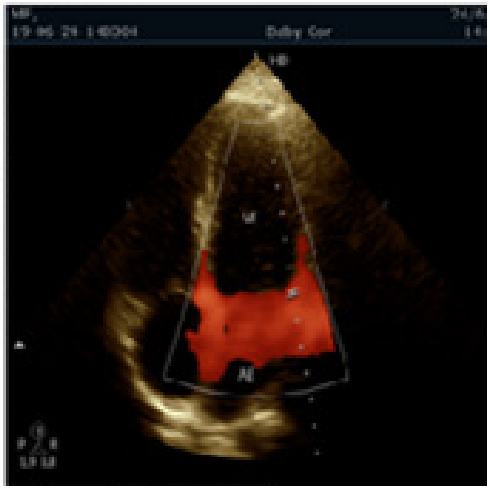
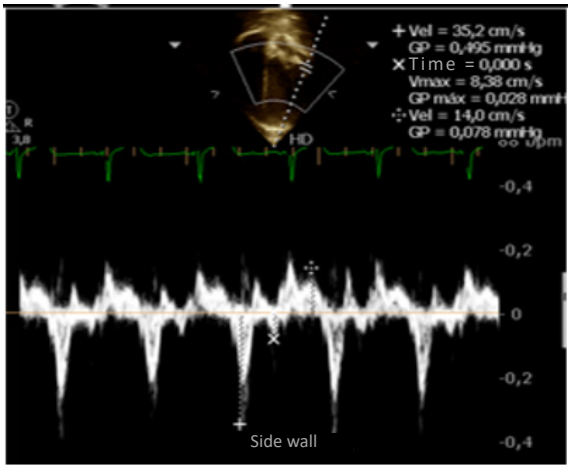


Figure 3 – Position of the sample volume in TDI and tissue Doppler evaluation at color
Personal file
Nagueh et al. 201611





Figures 4 and 5 – Tissue Doppler, lateral E′ wave. Pulsed Doppler analysis of mitral flow velocities.

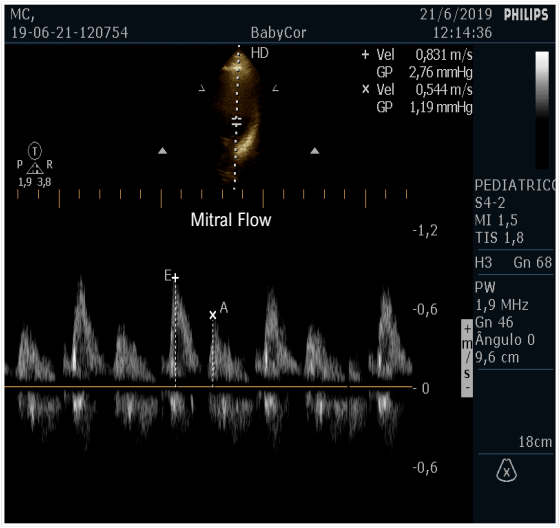
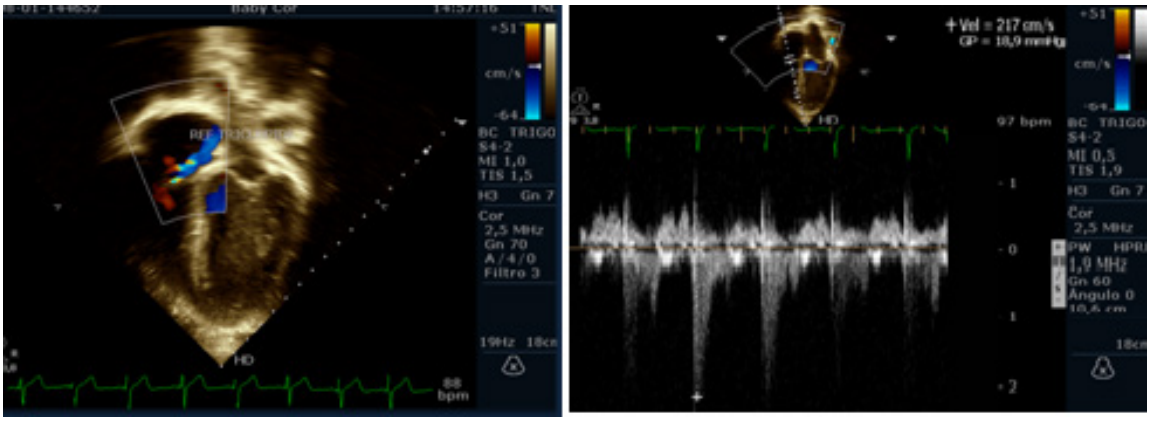


Figure 6 – Mitral valve Doppler
Personal file.
Normal mitral flow pattern acquired by PW Doppler. Mitral E velocity and A velocity



Figures 7 and 8 – Tricuspid flow velocities at color and tricuspid flow velocities at pulsed Doppler.
Personal file.
Color Doppler of reflux through the tricuspid (left); Doppler of tricuspid regurgitant jet (right).

Two-dimensional echocardiography

The dimensions of the cardiac chamber were obtained by M-mode in the parasternal long axis section, guided by two-dimensional (2D) echocardiography following the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging from March 2015.[14,15] The dimensions of the left ventricle, interventricular septum, and posterior wall both at systole and diastole; aorta and left atrium were measured.

Statistical analysis

The Stata program version 13.0 (Stata Corp) was used for statistical analysis. A significance level of 5% ($p<0.05$) was adopted for all analyses. The data did not show normal distribution (Shapiro Wilk test; p value=0.02). In the bivariate analyses, Mann-Whitney and Kruskal-Wallis tests were used for continuous variables, and for categorical variables, Fisher's exact test was used. Continuous variables were presented

Table 1 – Clinical characteristics and echocardiographic data according to the diagnosis of JSLE (n=98)

Variable	JSLE Diagnosis		p value*
	Yes	No	
Age (years)	14 (12-16)	14 (13-15)	0.43
BS (m^2)	1.0 (0.8-1.2)	1.1 (0.9-1.2)	0.55
Females (%)	83.6	24.4	<0.001#
Ind. Vol. Left Atrium	15.7 (12.7-18.9)	12.2 (10.0-15.0)	<0.001
Aortic root	23.0 (22.0-25.0)	22.0 (20.0-25.0)	0.11
LA	26.0 (23.0-29.0)	27.0 (23.3-29.0)	0.42
PWd	10.0 (9.0-11.5)	10.0 (8.5-12.0)	0.87
Lv Systolic Diameter	24.0 (23.0-25.5)	23.0 (20.0-26.0)	0.18
E' Septal line	0.18	18.1 (15.4-20.9)	0.13
E' Lateral line	24.7 (20.1-32.7)	28.3 (23.6-35.2)	0.01
E' Medium Septal line	6.0 (4.8-6.8)	5.7 (4.8-7.3)	0.97
E' Lateral line	3.9 (3.3-4.6)	3.5 (3.2-4.7)	0.30
E line	4.7 (3.8-5.4)	4.3 (4.0-5.2)	0.42
E'/A ratio	1.6 (1.3-2.1)	1.9 (1.7-2.2)	0.001
TV	1.9 (1.7-2.2)		0.20

**Mann-Whitney test; Fisher's exact test.*
LA: left atrium, PWd: left ventricular posterior wall in diastole, LV: left ventricle, TV: tricuspid jet velocity. Tissue Doppler: E' septal and E' lateral.

Table 2 – Echocardiographic findings in patients with JSLE according to disease activity (n=49)

Variable	Disease activity		p value*
	Yes	No	
Ind. Vol. Left Atrium	15.7 (13.0 - 18.5)	15.8 (10.8 - 19.0)	0.70
Aortic root	22.0 (21.0 - 25.0)	24.0 (22.5 - 26.5)	0.03
LA	26 (24.0 - 28.0)	26.0 (22.0 - 29.0)	0.93
PWd	10.0 (9.0 - 11.5)	10.0 (8.8 - 11.2)	0.69
Lv Systolic diameter	25.0 (23.0 - 26.0)	24.0 (22.0 - 25.0)	0.55
E' Septal line	16.4 (13.4 - 18.8)	17.9 (15.9 - 20.1)	0.26
E' Lateral line	23.6 (18.7 - 29.1)	29.2 (22.0 - 34.7)	0.15
E' Medium Septal Line	6.0 (4.8 - 6.8)	5.7 (4.8 - 7.3)	0.74
E' Medium Lateral line	4.0 (3.3 - 4.8)	3.6 (2.8 - 4.4)	0.35
E line	4.8 (4.0 - 5.6)	4.5 (3.7 - 5.4)	0.60
E'/A ratio	1.5 (1.3-2.0)	1.7 (1.4-2.2)	0.21
TV	1.9 (1.7-2.2)	1.8 (1.5-2.1)	0.18

**Mann-Whitney test.*
LA: left atrium, PWd: left ventricular posterior wall in diastole, LV: left ventricle, TV: tricuspid jet velocity. Tissue Doppler: E' septal and E' lateral.

Table 3 – Echocardiographic parameters in patients with JSLE, according to corticosteroid use (n=49)

Variable	Corticosteroid use		p value*
	(yes)	(no)	
Age (years)	14 (12 - 16)	15 (13 - 17)	0.13
BS (m^2)	1.07 (1-1.23)	1.05 (0.94 – 1.21)	0.38
Ind. Vol. Left Atrium	15.23 (12.69 - 18.5)	16 (12.7 - 19.2)	0.93
Aortic root	23 (22 - 26)	23 (22 - 25)	0.67
LA	26.75 (24 - 29)	25 (22.7 - 28)	0.31
PWd	10 (9 - 11.5)	10 (8.5 - 11.5)	0.57
Lv Systolic diameter	24 (23 - 26)	24 (23 - 25)	0.66
E' Septal line	15.75 (13.2 - 18.4)	17.9 (16.2 - 20.4)	0.03
E' Lateral line	22.3 (17 - 30.6)	25.5 (22 - 33.5)	0.12
E' Medium Septal Line	6.38 (5.13 - 7.54)	5.55 (4.57 - 6.42)	0.09
E' Medium Lateral line	4.31 (3.37 - 5.44)	3.7 (2.81 - 4.27)	0.18
E line	5.18 (4.38 - 6.0)	4.38 (3.59 - 5.0)	0.05
E'/A ratio	1.52 (1.31 - 2.19)	1.72 (1.33 - 2.18)	0.71
TV	21.35 (17 - 28.5)	20 (13 - 22.5)	0.12

**Mann-Whitney test.*
LA: left atrium, PWd: left ventricular posterior wall in diastole, LV: left ventricle, TV: tricuspid jet velocity. Tissue Doppler: E' septal and E' lateral.

Table 4 – Logistic regression model for indexed Vol LA and variables (n=98)

Variable	OR	IC 95%	Standard Error	p value
JSLE	3.3	1.10-9.9	1.86	0.03

Model adjusted by sex.

by medians and interquartile range (IQ). Categorical variables were presented by frequencies and 95% confidence intervals (95% CI). Multivariate logistic models were constructed to test echocardiographic parameters and possible associations. All variables with $p<0.20$ in the bivariate analysis were tested in the model.

This research was approved by the Research Ethics Committee (Opinion number 2.385.087). Informed consent was obtained from legal guardians as well as from the patients themselves.

Results

Ninety-eight patients were included. Of these, 49 patients diagnosed with JSLE and 49 healthy and asymptomatic adolescents. All patients had normal ejection fraction. Based on the 2016 guideline, no diastolic dysfunction was found in adolescents with JSLE. The median age was 14 years (IIQ 12-16) and body mass index (BMI) 21.2 (IIQ 19.3-23.6). The clinical characteristics and echocardiographic parameters of

the study sample revealed a female in those diagnosed with JSLE, larger index volume of the left atrium, smaller lateral E' and lower E/A ratio (Table 1).

Among adolescents with JSLE 44 (89.7%) had a history of disease of less than 5 years, and 33 children (67.34%) were in disease activity. Comparisons were made among patients diagnosed with JSLE according to disease activity. In those with disease activity, less aortic root was observed (Table 2).

Comparisons were made between echocardiographic parameters in patients with JSLE taking or not taking corticosteroids. In those taking this medication, lower septal E's were observed (Table 3).

To construct logistic regression models, echocardiographic parameters with statistical significance were categorized and distributed according to the 50th percentile of the control group. Three models were calculated: Ind. Vol. LA (> 12), E' lateral line (> 28), and E'/A ratio (> 1.9). The only model that revealed statistical significance was the variable JSLE as a predictor of higher indexed Vol LA (Table 4).

The regression model for the variable E lateral line did not result in any predictor variable with statistical significance. The regression model of the variable E'/A ratio resulted in a marginal result for the variable JSLE (OR 0.36; p value 0.05).

Regarding the use of hydroxychloroquine, only 2 (4.08%) of patients with JSLE did not use it during the study period.

Discussion

The main result found in this study was the presence of normal diastolic function according to the criteria of the 2016 guideline. However, when compared to normal adolescents, there was a significant difference in some parameters of diastolic function assessment. The presence of JSLE influenced the following parameters: index volume of the larger LA, smaller lateral line E' and smaller septal E', due to the influence of corticoid use, smaller E'/A ratio, and finally, lower aortic root values were observed in patients who were active. The sample size of this study, the short time of disease and follow-up may have interfered with this result.

This analysis of cardiac function by echocardiography enabled early evaluation of the heart of patients with JSLE with normal ejection fraction. JSLE patients had worse indices than controls, even though they were within normal values. Thus, this study highlights the need for monitoring diastolic function after the diagnosis of JSLE. In a study that evaluated function, Petri et al.,[4] showed that 4 to 71% of adults with lupus have some degree of diastolic dysfunction, with few or no associated comorbidities.[4]

In this casuistry, patients with JSLE had higher indexed LA volume values. In 2017, Singh et al.,[16] reinforced that LA strain could be used to detect diastolic dysfunction.[16] Assessment of left atrial function provides important information related to diastolic dysfunction, as increased LA is usually associated with increased LV stiffness. In this study, the values were higher in subjects with JSLE regardless of disease activity or not, and in multivariate analysis the presence of JSLE was associated with higher values of indexed LA volume. The main role of the left atrium is to modulate left ventricular filling through adaptive changes in its mechanics and structure in the various LV filling patterns. Chronic or prolonged elevation of left atrial pressure may also be associated with natriuretic peptide elevation, left atrial remodeling, and increased risk of death.[14] Currently, three-dimensional echo (3D-E) and myocardial strain imaging are being used promisingly for LA volume assessment, as they correlate well with cardiac computed tomography and nuclear magnetic resonance imaging.[17]

Regarding the E' lateral line, patients with JSLE had a lower value. The lower values are justified because the lateral line E' parameter is used to identify and measure the speed of myocardial movement, and this movement can be slowed down or delayed in the setting of dysfunction. As a result, the restoring forces in the myocardium increase the stretching load and tend to compensate for the deficit through compensatory mechanisms. Thus, lateral line E' wave analysis is a relatively insensitive measure of LV preload and has been shown to be useful in predicting higher LV filling pressure.

Regarding the E'/A ratio patients with JSLE showed lower values when compared to controls. The diagnosis of JSLE was not a predictor of lower E/A ratio values. Marginal statistical significance was observed. In this case, the sample size may have influenced the result; had the sample been a little larger, this index might have obtained statistical relevance. Lower E'/A ratio occurs when the LV presents progressing diastolic dysfunction.[14] Impaired relaxation with normal LA size would ideally fall under diastolic dysfunction, but under the new scheme the classification would be

considered indeterminate in the absence of an elevation in peak RT velocity.[14,18] Therefore, it is possible that the updated 2016 guideline for the assessment of diastolic function creates a situation where diastolic dysfunction may be underdiagnosed.

Although no association between JSLE and aortic root has been reported in the literature, lower aortic root values have been observed for patients with JSLE in disease activity. This can be understood as higher aortic root stiffness representing structural and functional changes of the vessel wall caused by vasculitis.[17,19] The replacement of the elastic band by the stiffer fibrous scar during the repair process, and the induction of metalloproteinases by inflammatory mediators may be cited as causes.[20] Thus, although there is no description of the relationship between echocardiographic measurements of the aortic root and JSLE, it is suggested that aortic elasticity indices should be emphasized in patients. Persistent low-grade inflammation and endothelial dysfunction, which are interrelated, may also explain, at least in part, the JSLE-related increased arterial stiffness.[20,21] Increased arterial stiffness increases the risk of cardiovascular disease by increasing blood pressure, increasing ventricular hypertrophy, decreasing coronary perfusion, and increasing the risk of stroke.[22,23] Arterial function in adolescents and young adults with JSLE has not been studied to date and should be the subject of future research.

Limitations of this study are the short follow-up time, the sample size, and the absence of sequential examinations for evolutionary comparison. We suggest that the parameters of the EACVI 2016 guideline[11] should be used along with those of the EACVI 2009 guideline[15] in a thorough and systematic manner, at the very first moment of evaluation, as they are important for the assessment of ventricular diastolic function. Assessment of diastolic function in JSLE is a recognized prognostic severity marker, and changes may be early and subclinical. We suggest that echocardiography be performed early in these patients.

Conclusions

No changes in FD following EACVI guidelines were detected in adolescents with JSLE and ejection fraction was normal. However, among patients with JSLE, there was a higher prevalence of higher indexed LA volume, lower lateral E' values and lower E'/A ratio. Aortic root measurements were smaller in patients with active JSLE.

Author contributions

Acquisition of data: Loureiro TN. Analysis and interpretation of the data: Loureiro TN. Statistical analysis: Valete COS. Writing of the manuscript: Loureiro TN. Critical revision of the manuscript for intellectual content: Sztajnbok FR e Castier MB.

Potential Conflict of Interest

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

Sources of Funding

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Study Association

This article is part of the thesis of master submitted by Talita Nolasco Loureiro, from *Universidade do Estado do Rio de Janeiro*.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Hospital Universitário Pedro Ernesto/ Universidade do Estado do Rio de Janeiro* under the protocol number 2.385.087. 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

Inflammation and Nocturnal Pattern of Blood Pressure in Normotensives

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Abstract

Background: In most healthy individuals, blood pressure (BP) shows a circadian rhythm. Being non-dipper increases cardiovascular risk in normotensive and hypertensive individuals. Nocturnal dipping shows a correlation with the state of inflammation.

Objetive: To investigate the relationship between inflammation-based indexes and nocturnal BP pattern in normotensive individuals.

Method: This is a retrospective study that included patients evaluated with ambulatory BP monitoring (ABPM). A total of 131 normotensive individuals were included and grouped as dippers and non-dippers. The normality of the data was verified with a Shapiro-Wilk test. We compared ABPM variables and inflammation-based indexes derived from blood tests (monocyte to high-density lipoprotein ratio [MHR], platelet to lymphocyte ratio [PLR], neutrophil to lymphocyte ratio [NLR], and systemic immune-inflammation index [SII]) between groups. The independent samples t-test and Mann-Whitney U test were used for comparing variables with normal and non-normal distributions, respectively. The Pearson's chi-squared test was used to compare categorical variables, and Spearman's correlation coefficient was used to examine the relationships between variables. A receiver operating characteristic (ROC) curve was used to evaluate the diagnostic performances of inflammation-based indexes. The level of statistical significance was 5%.

Results: The study included 131 patients (mean±standard deviation [SD] age 49.2±15.1 years, 58 [76.0%] of which were women). SII was significantly higher in the non-dipper group (p=0.033). Significant negative correlations were observed between the change in systolic BP [ΔSBP] and SII (r=-0.172, p=0.049) and between ΔSBP and PLR (r=-0.179, p=0.040).

Conclusion: SII is a predictor of nocturnal BP pattern in normotensives.

Keywords: Inflammation; Monocytes; HDL Cholesterol; Hypertension.

Introduction

Blood pressure (BP) normally decreases during sleep, and certain metabolic and cardiovascular alterations may affect this circadian pattern.[1] Leading reasons for a non-dipping BP pattern are obesity, sleep disorders, obstructive sleep apnea, chronic kidney disease, excessive salt consumption, diabetes mellitus, orthostatic hypotension, autonomic dysfunction, and advanced age.[2] An arbitrary cut-off point has been proposed to define patients as "dippers" if their nocturnal BP falls by ≥10% of the daytime mean BP value.[2] A non-dipper BP pattern is associated with high cardiovascular mortality and morbidity in people with both normal BP and hypertension.[3,4]

In recent years, hematological parameters such as the neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), monocyte to high-density lipoprotein (HDL) cholesterol ratio (MHR), and systemic immune-inflammation index (SII) have been investigated in different systemic diseases as indicators of inflammation.[5-12] Although studies are searching for

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the relationship between inflammation and nocturnal BP pattern in hypertensive patients,[13,14] to the best of our knowledge, these easily accessible parameters have not been used in studies with normotensive individuals. Hence, in this study we aimed to investigate the relationship between inflammation-based indexes and nocturnal BP pattern in normotensive individuals.

Materials and Methods

Study Population

Patients admitted to the outpatient cardiology clinic at Hospital were retrospectively screened. Those who were evaluated with ambulatory BP monitoring (ABPM) to confirm/reject a hypertension diagnosis were enrolled. Our sample represented patients aged 18 years or older, without a history of hypertension or treatment with antihypertensives, and with ABPM findings compatible with normotension in consistence with the European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines[2] (daytime threshold for hypertension: systolic BP [SBP] ≥ 135 mmHg and/or diastolic BP [DBP]≥85 mmHg; nighttime: SBP≥120 mmHg and/or DBP≥70 mmHg; overall 24-hour mean: SBP≥130 mmHg and/or DBP≥80 mmHg). Exclusion criteria were pregnancy; history of drug/alcohol abuse; having a night shift job; chronic inflammatory disease; kidney failure; thyroid function disorders; connective tissue disease; chronic liver disease; acute infection; sleep disorders; malignancy; use of antinflammatory drugs, statins, or drugs that may increase BP (such as steroids); and intolerance to ABPM. The sample size was defined for convenience. A total of 131 patients were included. Participants represented a consecutive series of patients fulfilling these exclusion/inclusion criteria and were divided into 2 groups (dippers vs non-dippers) according to the decline in nighttime SBP. The dipper group was defined as patients with a nocturnal dip of ≥10% in SBP. The non-dipper group was defined as patients with a nocturnal dip of <10% in SBP.[2]

This study was approved by the local ethics committee of Istanbul Bakirkoy Dr Sadi Konuk Training and Research Hospital (20.05.2019, 2019-10-10).

ABPM Assessment

A portable recording device (Suntech Bravo 24-HR ABP) was used to record 24-h ABPM values. The cuff was placed on the patient's non-dominant arm. Overall, the nighttime and daytime SBP and DBP of each participant were automatically measured every 20 min between 07:00 and 23:00 h and every 30 min during the night. Daytime and nighttime periods were defined using fixed time periods for all patients. Participants were asked to continue performing their usual activities. Data was analyzed using SunTech AccuWin Pro v3 ABPM software. Mean SBP and DBP values, as well as mean arterial pressure (MAP), were separetely calculated for nighttime and daytime periods. BP series were excluded if ≤70% of the measurements were valid. The percentage of nocturnal BP decline was calculated using the following formula: nocturnal BP decline (%)=(daytime BP- nocturnal BP)×100 / daytime BP.

Study Parameters

Data regarding patient demographics, blood biochemistry (total cholesterol, triglycerides, low-density lipoprotein cholesterol, HDL), complete blood count at admission, and ABPM results were obtained from the medical records. The 24-hour, nighttime, and daytime ABPM values of SBP, DBP and MAP, as well as the mean nocturnal declines in SBP, DBP, and MAP, were recorded for all patients.

SII (calculated as platelet count x neutrophil count / lymphocyte count), NLR, PLR, and MHR were constructed as inflammation-based indexes in accordance with previous studies.[9-12,15,16]

Statistical Analysis

Our statistical analysis was performed using IBM SPSS Statistics version 21 and MedCalc version 12.3.0.0. The normality of the data was tested with the Shapiro-Wilk test. Normally distributed variables were presented as means ± standard deviations (SDs); non-normally distributed variables were reported as median (interquartile range [IQR]) values. Independent samples t-tests and Mann-Whitney U tests were used for comparing normal and non-normal variables, respectively, between the 2 indepedent groups. Categorical variables were presented as frequencies and percentages (n, %), and Pearson's chi-squared tests were used to compare categorical variables between groups. The Spearman's correlation coefficient was used to examine the relationships between variables. A receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performances of inflammation-based

indexes. The Youden's J index was used to obtain the optimal cut-off value. The level of statistical significance adopted for our analyses was 5%.

Results

This single-center, retrospective study included 131 patients (mean±SD age 49.20±15.09 years, 58 (76.0%) of which were women). Among these 131 patients, 55 (42.0%) were included in the dipper group and 76 (58.0%), in the non-dipper group. Baseline charecteristics and laboratory findings of the groups are summarized on Table-1. No significant differences were noticed between groups in terms of patient characteristics.

ABPM results of both groups were summarized on Figures-1 and -2. A significant difference was observed between dippers and non-dippers in terms of daytime and nighttime SBP and DBP. The difference between dippers and non-dippers in terms of daytime SBP was (mean±SD) 121.24±7.43 vs 114.25±7.46, respectively, p<0.001, while for daytime DBP it was (mean±SD) 73.20±6.11 vs 68.46±5.68, p<0.001. The difference between dippers and non-dippers in terms of nighttime SBP was (median [IQR]) 102 (15.0) vs 109 (9.8), respectively, p<0.001, and in terms of nighttime DBP it was (median [IQR]) 60.0 (8.0) vs 63 (5.8), p<0.001. The difference between dippers and non-dippers in terms of daytime MAP was (median [IQR]) 90.0 (9.33) vs 84.0 (9.08), respectively, p<0.001, and that for nighttime MAP was (median [IQR]) 73.33 (9.0) vs 78.5 (6.5), p<0.001; these were also statistically significant.

MHR, PLR, and NLR were similar between dippers and non-dippers (p=0.929, p=0.110, and p=0.152, respectively). However, SII was significantly higher in the non-dipper group than in the dipper group (median [IQR]): 457.4 (233.5) vs 391.4 (266.6), respectively, p=0.033 (Table-2). When we investigated the correlations between the change in systolic BP (ΔSBP) and inflammation-based indexes, we found significant negative correlations between ΔSBP and SII (r=-0.172, p=0.049) and between ΔSBP and PLR (r=-0.179, p=0.040) in non-dipper normotensives. On the other hand, correlations between ΔSBP and MHR (p=0.768) and between ΔSBP and NLR (p=0.320) were not significant in non-dipper normotensives.

Table 1 – Baseline charecteristics and laboratory findings of dipper and non-dipper groups

	Dipper (n=55)	Non-dipper (n=76)	p-value
Age (years)*	49.7±14.1	48.8±15.9	0.743
Gender (female)&	40 (41.7)	56 (58.3)	1.000
Total cholesterol (mg/dL)*	202.1±42.1	206.1±37.6	0.570
TG (mg/dL)#	133 (103)	105 (82.3)	0.408
HDL (mg/dL)#	50 (16)	51 (17.8)	0.879
LDL (mg/dL)*	123.7±36.7	128.7±29.7	0.390
WBC (x 10^9/L)#	7.59 (3.29)	7.45 (2.45)	0.928
Neutrophil (x 10^9/L)#	406 (186)	419.50 (204.3)	0.509
Monocyte (x 10^9/L)#	61 (39)	59 (27)	0.946
Lymphocyte (x 10^9/L)#	244 (131)	241.50 (84.3)	0.475
RDW %#	13.40 (1.3)	13.50 (1.65)	0.931
PLT(x 10^9/L)*	256.6±62.9	269.7±58.3	0.223
MPV# (fL)	10.20 (1.3)	10.25 (1.18)	0.814

*Data presented as *mean±standard deviation, #median (interquartile range [IQR]), or &n(%) values.*
LDL: low-density lipoprotein; TG: triglyceride; HDL: high-density lipoprotein; WBC: white blood cell; PLT: platelet; RDW: red cell distribution width; MPV: mean platelet volume; fL: femtoliter.

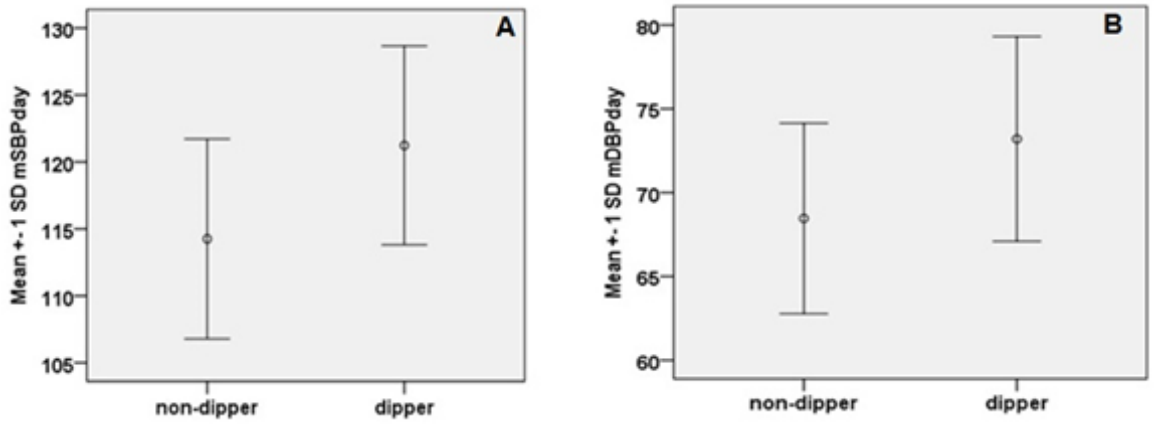

Figure 1 – Difference between dippers and non-dippers in terms of daytime blood pressure. A) Systolic blood pressure; B) Diastolic blood pressure (mSBP: mean systolic blood pressure; mDBP: mean diastolic blood pressure; SD: standard deviation). Error bars represent 1 SD, data present mean ± SD values.

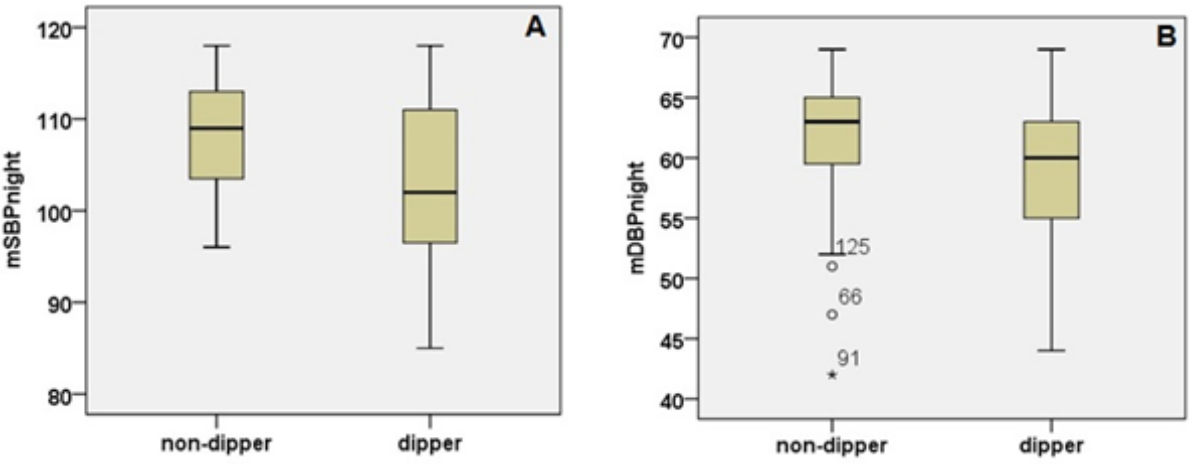

Figure 2 – Difference between dippers and non-dippers in terms of nighttime blood pressure A) Systolic blood pressure B) Diastolic blood pressure (mSBP: median systolic blood pressure; mDBP: median diastolic blood pressure; IQR: interquartile range). º: outliers; *: extreme values. Data presented as median [IQR] values.

In our ROC curve analyses, we found a significant diagnostic performance for SII in discriminating between dippers and non-dippers (area under the ROC curve [AUC]=0.610, p=0.031). The optimal cut-off point for non-dippers was >373.23, corresponding to a 78.95% (95% confidence interval [CI]: 68.1–87.5) sensitivity and a 49.09% (95% CI: 35.4–62.9) specificity. AUCs for MHR (p=0.932), PLR (p=0.118), and NLR (p=0.149) were not statistically significant (Figure-3).

Discussion

In this study, we found that among the studied parameters, only SII differed significantly between groups. Moreover, SII and PLR were negatively correlated with a nocturnal decline of SBP in non-dipper normotensives. MHR, NLR, and PLR values were similar between dipper and non-dipper normotensives.

Table 2 – Inflammation-based indexes derived from laboratory tests

	Dipper (n=55)	Non-dipper (n=76)	p-value
SII	391.4 (266.6)	457.4 (233.5)	0.033
MHR	1.18 (1.0)	1.21 (0.71)	0.929
PLR	0.96 (0.44)	1.09 (0.34)	0.110
NLR	1.68 (0.86)	1.89 (1.0)	0.152

Data presented as median (interquartile range [IQR]) values.
MHR: monocyte to high-density lipoprotein ratio; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; SII: systemic immune-inflammation index.

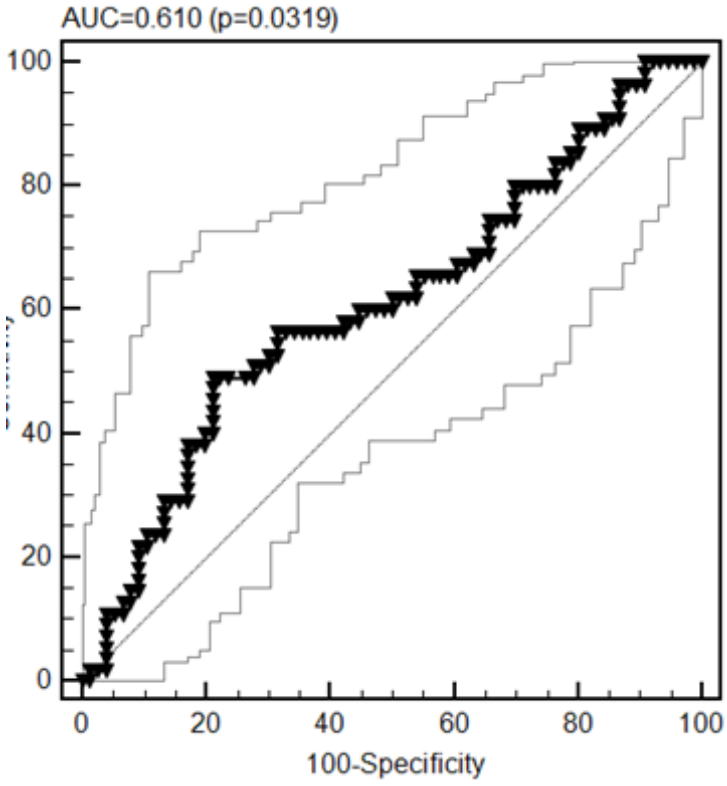

Figure 3 – Receiver operating characteristic curve for the systemic immune-inflammation index in predicting non-dippers. AUC: area under the receiver operating characteristic curve.

Increased inflammation may increase neutrophil and platelet counts while decreasing lymphocyte count.[17] Inflammatory cytokines are secreted by monocytes as a result of inflammatory reactions, whereas HDL has anti-inflammatory effects. MHR has been identified as an easy cardiovascular prognostic marker indicating the intensity of inflammation.[11]

High levels of inflammatory markers were described in hypertensive patients with non-dipper BP.[18,19] Inflammation may play a role in individuals being non-dipper, even if they are normotensive. Therefore, the patients' inflammatory conditions should be considered. Due to expensive and time-consuming procedures, the measurement of cytokines, adhesion molecules, and chemokines to assess

inflammatory status is difficult. On the other hand, SII, MHR, PLR, and NLR are inflammation-based indexes that are cost-effective and can be easily obtained by routine blood tests. Based on this, we searched for an easy and accesible inflammation-based index to distinguish patients who may be non-dipper even if they are normotensive and who should be confirmed with an ABPM evaluation.

Previous studies have investigated the cardiovascular effects of a nocturnal decline in BP in normotensives,[4,20] as well as in hypertensive patients.[21,22] Cardiovascular mortality among dipper hypertensive patients and non-dipper normotensive patients is similar,[23] and it is unknown if non dipper normotensives are candidates to being hypertensive. Therefore, diagnosing and managing non-dippers not only among hypertensives but also among normotensives is important. If their dipping status is not determined early enough, non-dipper normotensive individuals may not have the chance to receive an antihypertensive medication despite a higher cardiovascular risk. Hence, an SII cut-off may be useful to select patients who need to be evaluated with ABPM regarding their nocturnal BP pattern among those defined as normotensive according to office BP measurements.

Although in previous studies the association of inflammation with being non-dipper has been investigated in hypertensive patients,[24,25] as far as we know, our study is the first to investigate the relationship between nocturnal BP pattern and inflammation-based indexes derived from complete blood count and biochemical test results in normotensive individuals.

Limitations

Firstly, we only searched for the relationship between dipping status and inflammation-based indexes derived from complete blood count and biochemical test results. Apart from these study parameters, we did not measure other inflammatory markers such as C-reactive protein or interleukin-6. Another limitation of our study is the lack of data on salt consumption on the day of measurement, the menopausal status of female participants, and sleep diaries including sleep-wake hours.

Conclusion

We observed a significant relationship between SII and a nocturnal decline of SBP in normotensives. SII may be a predictive parameter for non-dipper normotensive individuals and may be useful to distinguish those who should be confirmed with ABPM in terms of dipping status before target organ damage develops. Further studies are needed on how to distinguish non-dipper individuals among normotensives both correctly and easily in daily practice.

Acknowledgement

From the bottom of my heart, I would like to express my special thanks to my father (M.Ugur Gunay), who has supported me throughout my life and has just passed away because of an incurable disease, unfortunately.

Author contributions

Conception and design of the research: Gunay S, Caliskan S. Acquisition of data: Caliskan S, Gunay S. Analysis and interpretation of the data: Gunay S. Sigirli D. Statistical analysis : Sigirli D. Writing of the manuscript : Gunay S. Critical revision of the manuscript for intellectual content : Gunay S.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Istanbul Bakirkoy Dr Sadi Konuk Training and Research Hospital under the protocol number 2019-10-10. 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

Cost-Effectiveness Analysis of Implantable Cardioverter Defibrillator Therapy for Primary Prevention Patients with Additional Risk Factors in Brazil

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Abstract

Background: Implantable cardiac defibrillators (ICDs) therapy for primary prevention (PP) of sudden cardiac arrest (SCA) is well-established but underutilized globally. The Improve SCA study has identified a cohort of patients called 1.5 primary prevention (1.5PP), based on PP patients with the presence of documented risk factors: non-sustained ventricular tachycardia, frequent premature ventricular contractions, left ventricular ejection fraction < 25%, and pre-syncope or syncope.

Objective: This study evaluated the cost-effectiveness of ICD therapy compared to no ICD among 1.5PP patients in the Brazilian public healthcare system.

Methods: Modified inputs to a published Markov model were applied to compare costs and outcomes of ICD therapy to no ICD therapy from the Brazilian payer's perspective. Mortality and utility estimates were obtained from the IMPROVE SCA trial. Additional effectiveness inputs were sourced from the literature. Cost inputs were obtained from the Brazilian Unified Health System and the Ministry of Health. Costs were discounted at 4.7%; quality-adjusted life years (QALYs) were discounted at 1.45%. This study applied a willingness-to-pay (WTP) value of three times Brazil's gross domestic product (GDP) in 2017, R$105,723 (Brazilian Real).

Results: The total discounted lifetime costs for ICD therapy were R$100,920 compared to R$43,866 for no ICD therapy. Total discounted QALYs for ICD therapy and no ICD therapy were 9.85 and 7.15, respectively. The incremental cost effectiveness ratio was R$21,156 per QALY and less than the R$105,723 WTP threshold. Results from sensitivity analyses were consistent with base case results.

Conclusions: ICD therapy compared to no ICD therapy is cost-effective in the 1.5PP population in Brazil.

Keywords: Cardiovascular Diseases/prevention andcontrol; Defibrillators,Implantable/economy; Cost-Effectiveness Evaluation; Technology Assessment, Biomedical; Death, Sudden Cardiac; Health Evaluation.

Introduction

Evidence for the use of implantable cardioverter defibrillators (ICDs) for primary prevention of sudden cardiac arrest (SCA) in patients with moderately symptomatic heart failure and reduced systolic function has been well-established through multiple randomized clinical trials [1,2] and confirmed in real-world observational evidence.[3] This evidence has led to strong recommendations for ICD use in society guidelines[4,5] and has been leveraged to establish the cost-effectiveness of ICD therapy in multiple healthcare systems.[6,7] Despite this strong evidence base, ICD therapy remains underutilized globally, due at least in part to cost considerations and the lack of reimbursement.[8]

The Improve SCA study has identified a high-risk subset of primary prevention patients called 1.5 primary prevention (PP) based on the presence of at least one of the following documented risk factors: non-sustained ventricular tachycardia (NSVT), frequent premature

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ventricular contractions (PVCs) >10/h, left ventricular ejection fraction (LVEF) <25%, pre-syncope, or syncope.[9] Improve SCA patients with 1.5 PP characteristics were found to have a higher rate of treatment with appropriate therapy than PP patients, and when treated with an ICD, 1.5 PP patients experienced a 49% relative risk reduction in all-cause mortality compared to normal PP patients.[10]

While the cost-effectiveness of ICD therapy for primary prevention patients has been established, the cost-effectiveness of ICD therapy for 1.5 PP patients is not well-known. The 1.5 PP cohort could be used to prioritize health care resources in geographies where such resources are insufficient to cover the full PP population. To that end, this study sought to estimate the lifetime cost and benefits of ICD therapy in the 1.5 PP patient population in Brazil, where ICD therapy is underutilized but may be cost-effective.[11] To the best of our knowledge, this is the first evaluation of the cost-effectiveness of ICD therapy compared to no ICD therapy among 1.5 PP patients from the perspective of the Brazilian public healthcare system.

Methods

An existing Markov decision model was applied to estimate the lifetime cost, quality of life, survival, and incremental cost-effectiveness of ICD therapy versus no ICD therapy for a Brazilian population at risk for SCA (1.5 PP).[6] No ICD therapy was selected as the control, rather than pharmacologic therapy, based on SCD-HeFT study findings that indicated no significant difference in the risk of death between treatment with amiodarone and treatment with a placebo.[1] This evaluation was conducted in the setting of the Brazilian public healthcare system, where health technology assessments are overseen by the National Commission for the Incorporation of Technology (CONITEC).[12] Model inputs are shown in Table 1, and the model analysis was performed in Microsoft Excel, the details of which are described below.

Model Structure

The model follows a simulated cohort of 1,000 patients with a standard indication for PP ICD therapy and at least one 1.5 PP risk factor. The model is structured as a decision tree with two treatment arms, ICD therapy or no ICD therapy, followed by consecutive Markov models (Figure 1). Patients who enter the model in the ICD arm are at an initial risk of operative death or survival. Patients who survive the ICD surgery enter the Markov model in the well state. From the well state, ICD patients stay well or progress to ICD complications, sudden cardiac death, non-sudden cardiac death, non-cardiac death, or unknown death. Patients remain in the same state or progress to a different state at the beginning of each cycle, except for the complication state. Patients who experience an ICD complication remain in the complication state for only one cycle, then progress to continued ICD therapy or discontinued ICD therapy. In the event of therapy discontinuation, ICD patients stay well without ICD treatment or progress to sudden cardiac death, non-sudden cardiac death, non-cardiac death, or unknown death. Patients in the no ICD arm enter the model in a healthy state and remain well or progress to sudden cardiac death, non-sudden cardiac death, non-cardiac death, or unknown death.

Patients incur costs and effects by progressing through the model in monthly increments over a lifetime (420 months); a lifetime perspective allows the model to account for all costs incurred by patients that survive without a sudden cardiac arrest event. Patients in both treatment arms incur monthly inpatient and outpatient costs. In the ICD therapy arm, patients also incur the cost of the device and ICD implant procedure. ICD patients who remain alive long enough to require a device replacement incur additional device and procedure costs at the time of replacement. ICD patients may receive an inappropriate shock or other ICD-related complication that incurs a cost and affects treatment adherence. After experiencing an inappropriate shock or other ICD-related complication, patients remain in the ICD therapy arm, receiving ICD treatment, or progress to discontinued use of ICD therapy. In this study it was assumed that ICD patients who discontinue their use of ICD therapy have the same mortality risk as patients in the no ICD arm.

Clinical Data

Clinical inputs to the model were based on Improve SCA clinical study results, the United States (US) National ICD registry, literature, and administrative claims-based analyses. Improve SCA[10] is the largest ICD study conducted in emerging markets and has enrolled patients from 17 different countries. The non-randomized study tracked outcomes in patients with primary, secondary, and 1.5 PP indications for ICD therapy. The probability of implant-related operative death (0.0002) was based

Table 1 – Model Input Parameters

Model Parameters	Base Case Value	Standard Error	Distribution	Reference
Monthly Risk of Mortality (ICD Therapy)				
Sudden cardiac death	0.0007	0.0003	Beta	(10)
Non-sudden cardiac death	0.0014	0.0004	Beta	
Non-cardiac death	0.0005	0.0003	Beta	
Unknown death	0.0013	0.0003	Beta	
Monthly Risk of Mortality (No ICD Therapy)				
Sudden cardiac death	0.0028	0.0005	Beta	(10)
Non-sudden cardiac death	0.0021	0.0004	Beta	
Non-cardiac death	0.0010	0.0004	Beta	
Unknown death	0.0014	0.0004	Beta	
ICD-Related Probabilities				
Initial operative death	0.0002	0.00002	Beta	(13)
Continue ICD therapy after shock	0.0034	0.0002	Beta	(2,14,15,19,35,36)
Discontinue ICD therapy after shock	0.0001	0.00007	Beta	
Lead replacement (initial implant)	0.0004	0.0005	Beta	(18,22)
Lead replacement (replacement implant)	0.0008	0.0009	Beta	(23)
Lead dislodgement (initial implant)	0.018	0.0012	Beta	(18,22)
Lead dislodgement (replacement implant)	0.005	0.0009	Beta	(23)
ICD infection (initial implant)	0.0244	0.0049	Beta	(17)
ICD infection (replacement implant)	0.0432	0.0064	Beta	(20)
Costs, 2018 Brazilian Reals (R$)				
ICD implant procedure (initial)	R$1,738			(37)
ICD implant procedure (replacement)	R$1,738			
Lead replacement	R$827			
ICD generator removal	R$742			
ICD lead dislodgement	R$742			
ICD inappropriate shock	R$500			
ICD infection	R$30,000			
Monthly inpatient cost	R$166			
Monthly outpatient cost	R$354			
Utility				
Annual utility of heart failure patient	0.837	0.007	Beta	(10)
ICD complication state	0.7408	0.0112	Beta	

Abbreviations: ICD, Implantable Cardioverter-Defibrillator

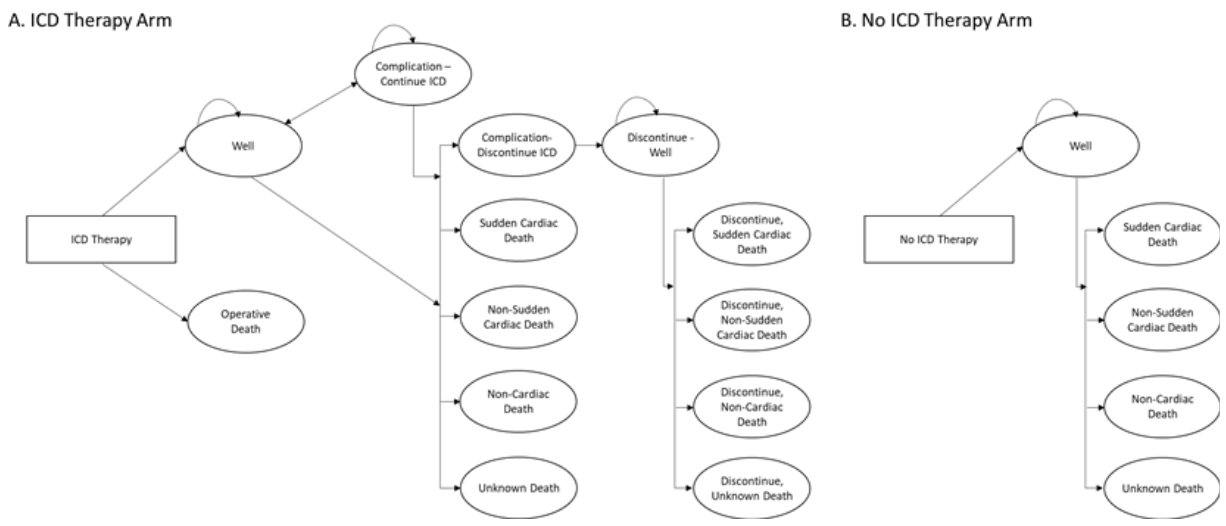

Figure 1 – Model schematic. Model states are represented by ovals; arrows indicate transitions between states. ICD, implantable cardioverter defibrillator. Panel A shows model states in ICD therapy arm. Panel B shows model states in the control arm.

on the US National ICD Registry and applied only to the ICD treatment arm.[13] The probabilities of sudden cardiac death, non-sudden cardiac death, non-cardiac death, or unknown death were based on results from the Improve SCA study. Inappropriate shock probability was derived from a weighted average based on the MADIT RIT, ADVANCE III, PROVIDE, and PainFree SST clinical trials that demonstrated a reduction in inappropriate shock rates due to device programming. [2,14-16] Probabilities of lead failure or dislodgement after initial implant were based on studies of annual incidence of lead failure and ICD lead dislodgement at one year after implant, 0.45% and 1.8% respectively.[17,18] Probability of lead dislodgement or replacement after ICD replacement was based on data from the REPLACE registry, which reported a 1% combined dislodgement and replacement rate.[19]. It was assumed that half of the combined rate reported in the REPLACE registry could be attributed to lead failure (0.5%) and half could be attributed to lead dislodgement (0.5%). The one-year probability of lead infection after initial implant (1.22%) and device replacement (2.16%) was also estimated by means of a retrospective data analysis based on administrative claims from a large US insurance company.[20] The lifetime risk of lead infection after the first year of an initial or replacement implant was double the value of the one-year claims-based probability.[17,18]

Economic Data

Device related costs and long-term health care use costs associated with heart disease were modeled over a lifetime. To represent the perspective of the Brazilian public healthcare system, several cost inputs to the model were based on the medical procedure price list published by the Brazilian Unified Health System in 2017.[21,22] The 2017 costs were updated to 2018 Brazilian Reals (R$) using the Brazil-specific average inflation rate based on the consumer price index, 3.66%. The cost of inappropriate shock was derived from an analysis of procedures commonly performed at encounters for shocks.[23] Long-term inpatient and outpatient costs were estimated from a publication on the costs of heart failure in Colombia .[24] To obtain ICD-specific costs, the long-term inpatient costs were multiplied by the average number of hospitalizations per year for patients recommended for ICD therapy based on the SCD-HeFT trial. Costs were discounted at 4.7%; quality-adjusted life years (QALYs) were discounted at 1.45%, according to CONITEC guidelines.[25].

Health-Related Quality of Life

Quality of life was based on an analysis of EQ-5D data collected in the PainFree SST clinical trial. Brazil-specific utilities were derived by mapping each

patient's EQ-5D state, using country specific societal preferences.[26] The baseline utility for both treatment arms was assumed to be the same. Patients who experienced an ICD-related complication received a short-term utility decrement of 0.096, which is equivalent to 3.5 days.[27]

Construction of the ICER (w/WTP) and Sensitivity Analysis

Total lifetime costs and quality-adjusted life years (QALYs) between ICD therapy and no ICD therapy were simulated to calculate the incremental cost effectiveness ratio (ICER). Both undiscounted and discounted results were calculated to best represent the time value of costs and outcomes. One-way sensitivity analysis and probabilistic sensitivity analysis were conducted to assess the impact of model inputs and parameter uncertainty. A willingness-to-pay (WTP) threshold value of R$105,723 was used for this model. Our WTP value reflects an amount equal to three times the per capita gross domestic product (GDP) in Brazil in 2018, as recommended by the World Health Organization (WHO).[28]

Results

Base case scenario

Table 2 shows the results of the base-case scenario. ICD therapy for 1.5 prevention resulted in a benefit of 11.79 (discounted) and 13.41 (undiscounted) life-years saved, while no ICD therapy resulted in a benefit of 8.54 and 9.46 life-years saved, respectively. Measured in QALYs, the discounted benefit from ICD therapy is 9.85 and 7.15 from no ICD therapy, resulting in an incremental effectiveness of 2.70 QALYs. Discounted costs from ICD therapy and no ICD therapy account for R$100,920 and R$43,866, respectively. The ICER for ICD therapy is R$21,156 per QALY; ICD therapy for 1.5 prevention is cost-effective at R$105,723, three times the Brazilian GDP per capita WTP threshold in the base case scenario. Moreover, ICD therapy is *highly* cost-effective at the R$35,241 threshold of one GDP per capita.

Sensitivity analyses

Results of the one-way sensitivity analyses show that costs per QALY are more responsive to the

Table 2 – Base case scenario results

Base Case Scenario Results		ICD therapy	No ICD Therapy
Undiscounted	Aggregated costs	R$139,120	R$59,008
	Differential cost	R$80,112	
	Effectiveness (life-years saved)	13.41	9.46
	Effectiveness (QALY saved)	11.20	7.91
	Differential effectiveness (QALY)	3.28	
	ICER (costs per QALY saved)	R$24,413	
Discounted	Aggregated costs	R$100,920	R$43,866
	Differential cost	R$57,055	
	Effectiveness (life-years saved)	11.79	8.54
	Effectiveness (QALY saved)	9.85	7.15
	Differential effectiveness (QALY)	2.70	
	ICER (Costs per QALY saved)	R$21,156	

Abbreviations: ICD: Implantable Cardioverter-Defibrillator; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio.

discount rate, age at implant, and conventional mortality (Figure 2); however, the low values of the discount rate resulted in a change in costs per QALY, which proved to be substantially lower than those resulting from the high value. No values of the one-way sensitivity analysis are under the incremental costs per QALY above the WTP thresholds of one or three times the Brazilian GDP per capita.

Figure 3 shows the simulated costs per QALY of the probabilistic sensitivity analysis, where each dot corresponds to the resulting cost per QALY of a model iteration, and the continuous line shows the WTP threshold of R$105,723 per QALY. Results show a mean cost per QALY of R$21,258 (median cost per QALY of R$21,250, 95-percent Credible Interval [R$15,293 – R$46,619] per QALY) after 1,000 iterations; 99.8% and 92.9% of the simulations result in costs per QALY below the three (long-dashed lined in Figure 3) and one (short-dashed line in Figure 3) times GDP per capita WTP threshold, respectively.

Discussion

Our results indicate that ICD therapy is highly cost effective for 1.5 PP patients in the Brazilian healthcare system, which at an ICER of R$21,156 per QALY is less than one-third the WTP value of R$105,723 (three times GDP per capita). This finding is robust, with a sensitivity analysis indicating that the cost effectiveness is preserved in virtually all reasonable variations of model inputs.

Prior estimates of the cost effectiveness of ICD therapy have been performed in the broader primary prevention population. Mark et al.[7] performed an analysis of the randomized SCD-HeFT trial and found ICD therapy to be economically attractive at $41,530/QALY (at a WTP of $100,000) in the US healthcare system. An analysis in the healthcare system of a European country using a meta-analysis of six randomized PP trials and the same model used in this study showed similar results.[6]). The cost-effectiveness of ICD therapy has also been confirmed in

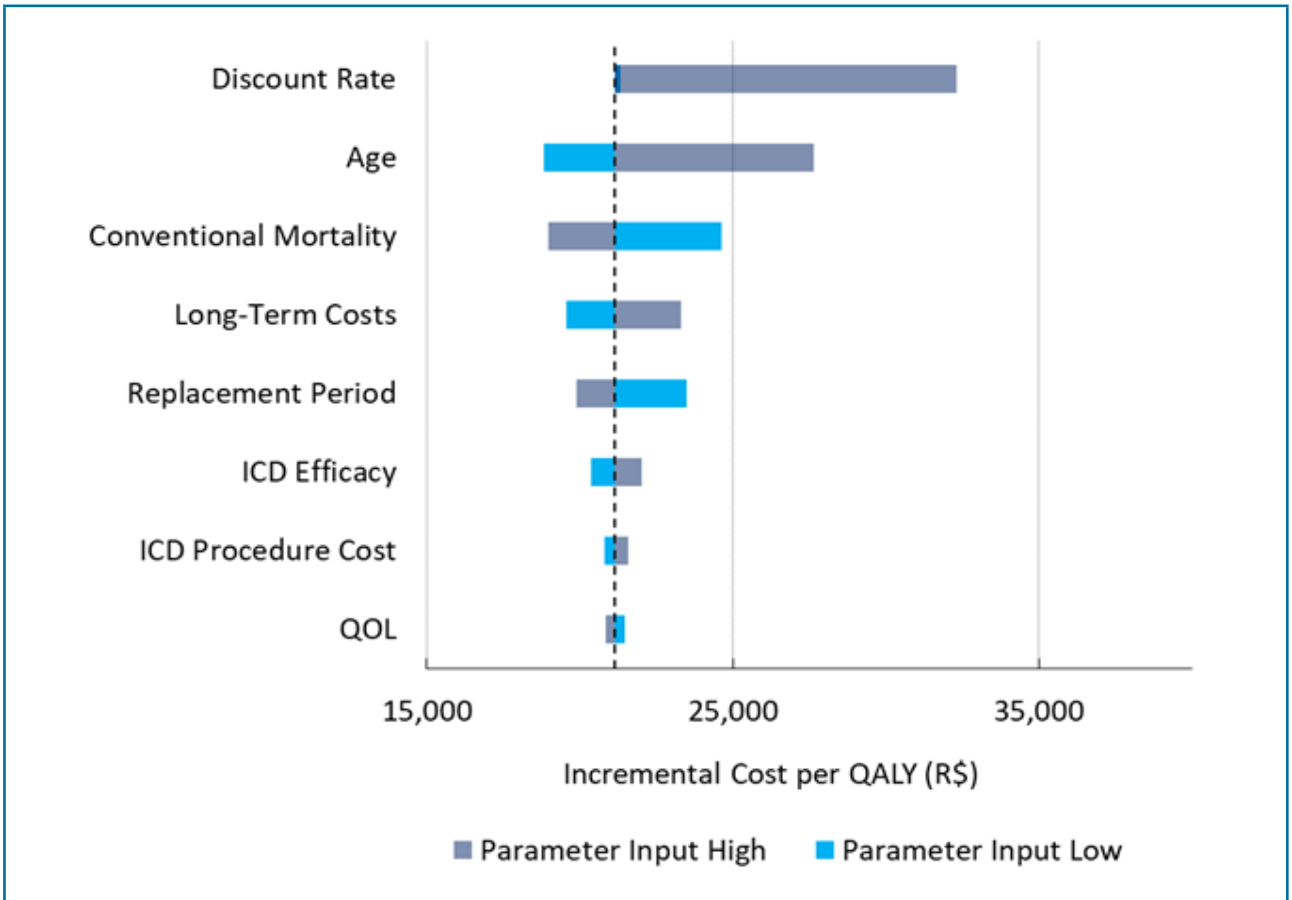

Figure 2 – One-way sensitivity tornado chart. A tornado chart of the range of ICER across high and low parameter input values. Each input was varied, with all others held constant. All ICER values remained below the willingness to pay threshold.

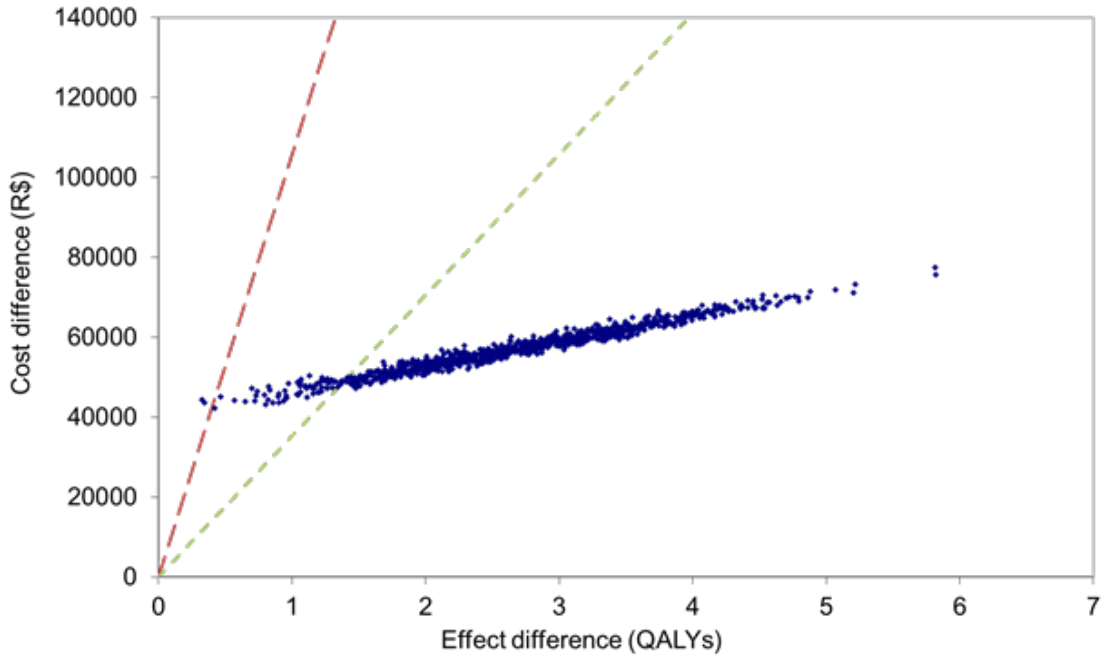

Figure 3 – Probabilistic Sensitivity Analysis scatterplot. The range of ICER given probabilistic variation in model inputs. All ICER values remained below the willingness to pay threshold. Dots represent individual ICER data points, the green dashed line represents WTP at 1x GDP per capita, the red dashed line represents WTP at 3x GDP per capita.

a real world setting outside of clinical trials.[29] However, Ribeiro et al.[30] performed an evaluation specific to the Brazil healthcare system, concluding that the ICER was elevated in both the public (R$68,318/QALY) and private (R$90,942/QALY) perspectives relative to the WTP, based on three times GDP per capita in 2007 (R$40,545).

The cost effectiveness of ICD therapy in Brazil has clearly improved since the 2010 assessment, and this can be explained by several factors. First, the model is highly sensitive to the longevity of ICD therapy, which has improved significantly over time. Ribeiro et al.[30] assumed a replacement interval of five years, based on expectations of devices manufactured in the 1990's, while the current model assumes a median replacement interval of 9.5 years, reflecting advancements in device longevity reported in both the literature and recent product performance reports from device manufacturers.[21,31] Extended longevity results in fewer ICD reimplantation costs in the model. Second, while this report has used the same approach as the WTP (WHO recommendation of three times GDP per capita), the GDP per capita in Brazil indicates a WTP that has more than doubled when compared to 2007 levels (R$105,723 versus R$40,545). Economic growth increases the ability to extend one's life saving benefits of ICD therapy to more people. Third, the model is sensitive to the efficacy of ICD therapy, which has improved relative to the prior report, reducing the number needed to treat in order to save one life from 13 to 10[10,32]. Other factors, such as the cost of devices and related hospitalizations may also have contributed to the observed differences between the current and former reports of cost-effectiveness.

Despite convincing evidence from multiple randomized clinical trials [1,3,33], strong recommendations in international society guidelines,[4], and corroboration of mortality benefits in the Brazilian healthcare system,[11] ICD therapy remains underutilized. In a seven-year period, 3,295 ICD implants were reported within the Brazilian National Health System .[11] placing the annual rate of ICD use at 2-3 implants per million in the Brazilian population. By comparison, the average rate of ICD implantation in Europe is approximately 100 implants per million.[34] To the extent that economic factors play a role, this study provides information for decision makers to direct

scarce resources first toward those who can benefit the most. While it remains cost effective to treat the PP population with ICD therapy, from an economic standpoint, a priority should be placed on treating patients with a 1.5 PP indication.

It is important, however, to acknowledge the limitations of this analysis. The Improve SCA trial was not randomized, but the mortality analysis from the trial adjusted for baseline characteristics are likely to have an impact on mortality, and the effectiveness of ICD therapy has been replicated in non-randomized observational trials. Costs and benefits were modeled beyond the timeline of direct observation in the Improve SCA trial; however, this is a standard approach in economic modeling and necessary for the proper perspective for decision makers. Patients in the Improve SCA trial were not all from Brazil, yet they were from countries of similar economic development. Further, ICD therapy application is well developed and largely standardized around the world. Conclusions from this report are not generalizable beyond the 1.5 PP population in the Brazilian public healthcare system.

Conclusion

Developments over time, including identification of the 1.5 PP population of high-risk patients, improved ICD longevity, and economic growth has led to improved cost effectiveness of ICD therapy. ICD therapy in this context should be considered highly cost effective and represents an economically efficient way to address the underutilization of ICD therapy in indicated patients in Brazil.

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Medtronic; DA. Rodriguez: proctor/lecture fees: Boston Scientific, proctorship: Biosense Webster, St. Jude Medical/ Abbott, steering committee fees: Medtronic.

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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: Wherry K, Holbrook R. Acquisition of data: Fujii F. Analysis and interpretation of the data: Wherry K, Holbrook R, Fujii F. Statistical analysis: Wherry K, Holbrook R, Higuera L. Writing of the manuscript: Wherry K, Holbrook R, Higuera L. Critical revision of the manuscript for intellectual content: Rodriguez D, Fujii F.

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REVIEW ARTICLE

Autonomic Innervation Evaluation in Cardiac Disease

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Abstract

Cardiovascular diseases are among the leading causes of mortality and morbidity in the world. In different cardiac diseases, the neuronal function of the heart is impaired. Nevertheless, the development of a simple method to assess the autonomic effects on the heart and/or autonomic dysfunction is a challenge. The evaluation of autonomic innervation in cardiac diseases has helped to improve the knowledge of the pathophysiology of these conditions, as well as to provide information on their prognosis. Single photon emission computed tomography (SPECT) and positron emission tomography (PET) are currently the only imaging methods that allow *in vivo* assessment of cardiac innervation. The majority of SPECT and PET radiotracers evaluate sympathetic neuronal integrity using presynaptic imaging agents that are either labeled as endogenous transmitters or analogues. Postsynaptic imaging agents have also been developed to study sympathetic neuronal integrity, as well as tracers to investigate the parasympathetic nervous system. These methods may be used to analyze the innervation of the heart and allow for early detection of abnormalities caused by, for example, ischemia, heart failure, cardiomyopathies, cardiotoxicity, and arrhythmogenic disorders. This review provides an overview of cardiac innervation evaluation and their application in the assessment of heart disease.

Keywords

Autonomic Denervation; Heart Failure; Diagnostic, IImaging; Myocardial Ischemia; Autonomic Nervous System.

Introduction

Cardiovascular diseases (CVD) have been considered the leading cause of death and one of the most critical global public health problems. Although cardiovascular mortality in high-income countries is decreasing, sudden cardiac death (SCD) still constitutes a substantial part of cardiovascular mortality, with an estimated 4 to 5 million cases per year worldwide.[1]

Sympathetic innervation plays an important role in controlling myocardial blood flow, heart rate, and contraction of heart performance. In several cardiac diseases, the neuronal function of the heart is altered and neuronal cardiac imaging can help to improve the knowledge of the pathophysiology of these diseases, especially in SCD.

Single photon emission computed tomography (SPECT) and positron emission tomography (PET) are currently the only imaging methods that allow for an *in vivo* assessment of cardiac innervation. The majority of SPECT and PET radiotracers evaluate sympathetic neuronal integrity, using presynaptic imaging agents that are either labeled as endogenous transmitters or analogues. Postsynaptic imaging agents have also been developed to study sympathetic neuronal integrity, as well as tracers to investigate the parasympathetic nervous system. Several diagnostic methods that do not involve imaging have also been applied in the assessment of cardiac dysautonomia.

The purpose of this article is to provide a review of published data on the evaluation of cardiac autonomic innervation by image and its application in various heart diseases.

Autonomic Nervous System

The autonomic nervous system (ANS) is broad and extends to most organic systems. Therefore, the study of

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autonomic function is usually linked to a final organ of specific interest. Functional autonomic outputs, defined by the sympathetic and parasympathetic systems provide a strongly integrated combination of homeostasis control.[2]

The ANS is closely linked to many behaviors, emotions, and the immune system. Some examples include changes in the cardiorespiratory response orchestrated during exercise, when trying to escape from a threatening environment, when facing a situation of fear, during an inflammatory response, or even when simply moving from the supine to the vertical position. In the heart, cardiac sympathetic and parasympathetic nervous systems (SNS) work by exerting essentially opposite responses. These branches differ in their neurotransmitters and use stimulatory or inhibitory effects on the target tissue through adrenergic and muscarinic receptors [2] (Figure 1).

The two mediators of the SNS, norepinephrine (NE) and epinephrine are derived from two main sources in the body: the sympathetic nerve endings, which release NE directly into the synaptic cleft, and the adrenal medulla, whose chromatin cells predominantly synthesize, store and release epinephrine,[3] NE is released in the synaptic clefts in response to neuronal stimulation through the fusion of presynaptic storage vesicles with the neuronal membrane. It stimulates presynaptic cardiac α2 adrenergic receptors (ARs), which provide negative feedback on exocytosis and postsynaptic β-ARs. In the synaptic cleft, most NE undergoes resorption at the nerve terminals by the NE presynaptic transporter and recycles into vesicles or is metabolized in the cytosol by the monoamine oxidase enzyme. The overflow of NE can also be measured in the blood and used to infer a sympathetic flow to the heart.[4]

Acetylcholine (ACh), the neurotransmitter of the parasympathetic system, is stored in the vesicles and is released by parasympathetic stimulus, activating the muscarinic and pre-ganglionic postsynaptic receptors. Parasympathetic stimulation decreases the heart rate, reducing the discharge rate of the sinoatrial node and the conduction velocity of the atrioventricular node, with minimal or no effect on cardiac contractility.[5]

ANS dysfunction may result from primary disorders of the autonomic nerves or secondarily in response to heart or systemic diseases. These changes can occur in several interrelated cardiac conditions, including hypertension, myocardial ischemia, heart failure (HF), cardiac arrhythmias and SCD.[6] Adrenergic beta-blockers are the most established autonomic intervention. Other interventions (for example, cardiac sympathetic denervation) have shown promise for the treatment of refractory ventricular arrhythmias.[7]

Much has been studied about the complex interactions along the neuroaxis and its role in cardiac control. However, the development of a simple method to assess the autonomic effects on the heart and/or autonomic dysfunction is a challenge. There are several exams that evaluate the autonomic function. Even though many methods have demonstrated some prognostic value, none have yet been implemented in clinical practice.

Flowchart of research execution

Methodology

A comprehensive literature review of articles published in the following databases was performed: PubMed and Medline. The following terms used were: autonomic innervation evaluation (AND) cardiac disease. Through the evaluation of abstracts, articles that were not related to the topic were excluded.

Results

The search with the combination of all the terms listed above returned 602 articles in a search carried out until May 15, 2020. Only articles in the English language and human species were selected. A total of 184 articles were selected according to the visual analysis of correlation with the topic studied between the years 1980 and 2020, after excluding duplicate articles. Approximately 50% of the articles were published in the last 10 years.

Imaging techniques used to assess autonomic innervation:

The following imaging techniques have been used to assess ANS activity: SPECT and PET.

Metaiodobenzylguanidine (^{123}I-MIBG) Single-Photon Emission Computed Tomography (SPECT)

Metaiodobenzylguanidine (MIBG) was discovered in 1980 to search for tumors of the adrenal medulla. MIBG is an NE analogue with a similar molecular structure. It is captured via the norepinephrine transporter 1 (uptake-1 mechanism) and stored in presynaptic neurosecretory vesicles.[8] After adrenergic stimulation, MIBG is

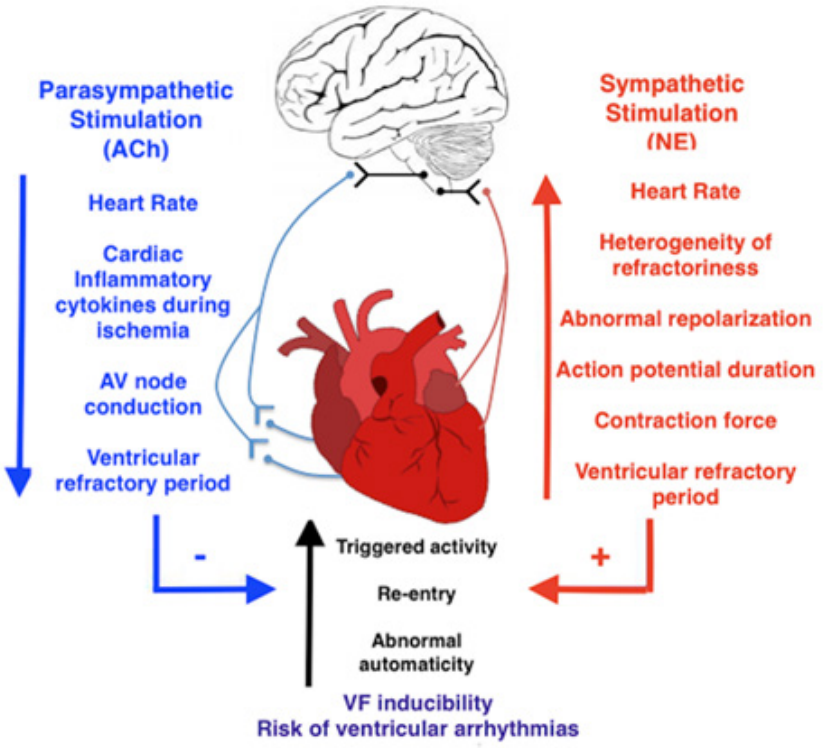

Figure 1 – The sympathetic and parasympathetic nervous system - arrhythmogenic effects on the heart. Adapted from Franciosi et al. [17]

released into the synaptic cleft, but it has low affinity for postsynaptic receptors without pharmacological action and is not metabolized by monoamine oxidase (MAO) nor catechol-o-methyltransferase (COMT) enzymes. In contrast to NE, MIBG is stored for several hours without being metabolized, allowing the acquisition of images. MIBG uptake has been shown to correlate with NE concentration *in vivo*, representing cardiac SNS innervation under physiological and pathological conditions[9,10] (Figure 2).

Iodine-123-labeled MIBG (^{123}I-MIBG) allows for the visualization of cardiac sympathetic innervation by SPECT technology and makes it possible to evaluate and quantify the radiotracer distribution in the myocardium. Calculations of early and late heart-mediastinum ratio (HMR) and washout rate (WO) are performed.

Early HMR represents the integrity of the presynaptic nerve terminals and the density of β-ARs; late HMR combines neural function information, including NE uptake, release, and storage in presynaptic vesicles; and the WO reflects the adrenergic tone.[11]

The role of ^{123}I-MIBG has been well studied in several clinical conditions, with prognostic value in heart failure, ischemic heart disease, ventricular arrhythmias, and cardiomyopathies.

Positron Emission Tomography (PET)

PET imaging offers several advantages over SPECT, including superior image resolution, allowing for a more specific regional analysis of the function of cardiac neurons.[12] The PET examination facilitates the combined assessment of myocardial viability and perfusion together with innervation. It also offers the potential for imaging using autonomic receptors, as well as the global quantification of cardiac sympathetic and parasympathetic activity.

The most studied radiotracer for the neuronal evaluation conducted by the PET technique in humans is carbon-11 (^{11}C)-labeled meta-hydroxyephedrine (^{11}C-HED), an analogue to NE and ^{123}I-MIBG, which is transported by the uptake-1 mechanism.

Other agents have been researched for their role in the direct visualization of adrenergic receptors. Examples include ^{11}C-CGP12177 and ^{11}C-CGP12388. Both analogues were studied for their role in assessing the density of β-ARs in normal and diseased hearts using PET images, and are promising in predicting results and guiding treatment in ischemic heart disease and HF.[13, 14]

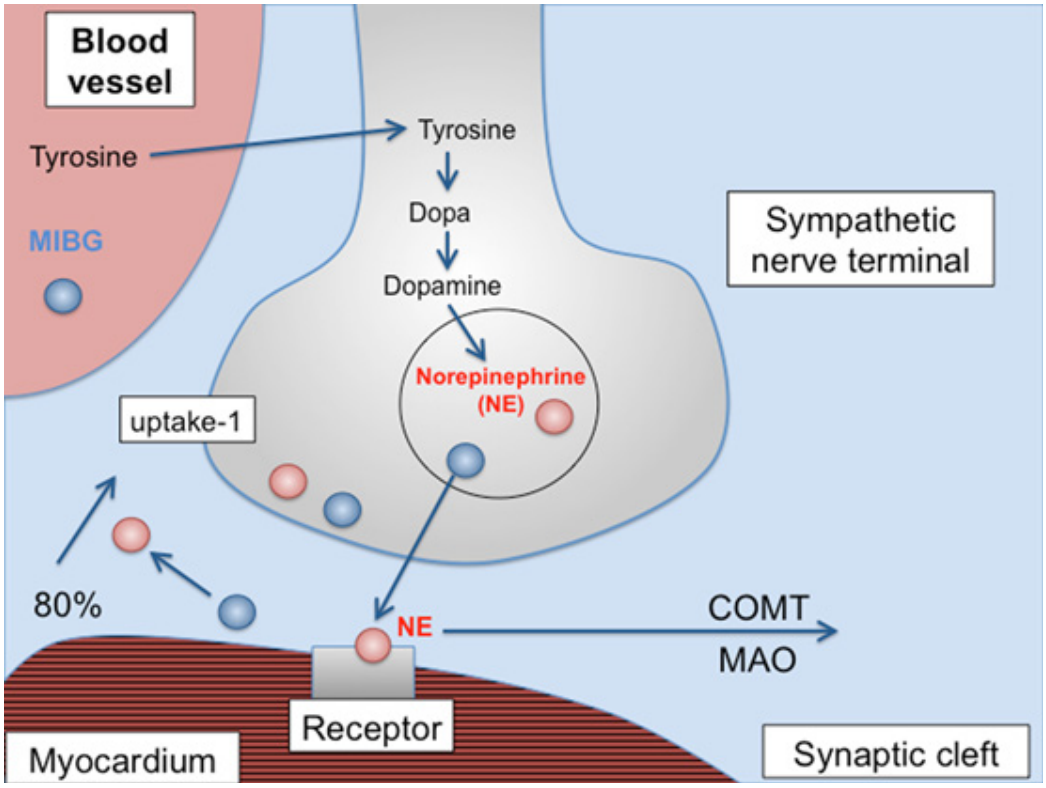

Figure 2 – Norepinephrine and MIBG metabolic pathways in the sympathetic cardiac nerve terminal.

However, the main current limitations for assessing innervation by PET technology are the higher costs when compared to SPECT and shorter half-lives of radioisotopes, some of which require on-site cyclotrons for production, such as ^{11}C.[15] Consequently, very few centers perform cardiac sympathetic neuroimaging using the PET scan.

Neuronal imaging in heart disease

Heart Failure (HF)

In HF, it is possible to maintain blood flow to the vital organs during states of low cardiac output thanks to the activation of the sympathetic nervous systems, renin-angiotensin-aldosterone, and antidiuretic mechanism.[16]

Prolonged exposure to NE leads to peripheral vasoconstriction, sodium and water retention, activation of the renin-angiotensin neurohumoral system, and desensitization of β-adrenergic postsynaptic receptors, which can cause malignant arrhythmias and SCD, or ventricular remodeling with insufficiency progression due to direct toxicity, interleukin, and TNFα system expressions and consequent apoptosis. When facing persistent high concentrations of circulating NE, the heart undergoes blockage of its β-adrenergic agonist receptors. Several mechanisms can contribute to this phenomenon, such as β-adrenergic receptor down regulation, non-coupling of β-receptor subtypes, upregulation of the β-adrenoreceptor kinase enzyme, increased G-protein and reduced adenylcyclase activity. Ventricular remodeling itself, which involves hypertrophy and myocyte apoptosis caused by NE, is associated with the re-expression of fetal genes with consequent downregulation of adult genes. This demonstrates the toxicity of chronic direct stimulation of β-adrenergic receptors in myocytes and fibroblasts and contributes to several biochemical and structural changes in HF.[17-21]

^{123}I-MIBG SPECT is characterized by reduced uptake and increased washout of the radiotracer in patients with HF compared to healthy individuals.

Several prognostic studies have shown that abnormal HMR as well as accelerated washout are independent

Table 1 – Applications of ^{123}I-MIBG in Heart Failure patients - Pooled or Multicenter Analyses in North America, Japan, and Europe

Study	Year	Nº of patients	Subjects included	Follow-up (mean)	HMR threshold on123I-MIBG studies	Multivariate analysis	Endpoint	Cardiac events	Cardiac death
Jacobson et al. (41)	2010	961	NYHA class 2 or 3; LVEF <35%	17 mo	1.60	HMR; LVEF; NYHA class; BNP	Death; progressive HF; life threatening arrhythmia	ACD: 81; CD: 53; arrhythmia: 64	5.5%
Nakata et al. (26)	2013	1,322	6 cohort studies; pooled data	77.6 mo	1.68	NYHA class; age; HMR on 123I-MIBG studies; LVEF	Death	ACD: 326; CD: 263	24.7%
Verschure et al. (31)	2014	636	8 studies for meta-analysis	36.9 mo	Continuous variable	HMR; LVEF; age for ACD	Death; life-threatening arrhythmia; heart transplant	ACD: 83; CD: 67; arrhythmia: 33; heart transplant: 56	10.5%

CD: cardiac death; ACD: all-cause death; HMR: heart-mediastinum ratio; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; BNP: brain natriuretic peptide; HF: heart failure

predictors of death in patients with left ventricular (LV) dysfunction, even better than left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) functional class, the size of the ventricle, and plasma NE values.[22-29]

A meta-analysis of 18 studies, including 1,755 patients, indicated that HF patients with reduced late ^{123}I-MIBG HMR or increased WO had a worse prognosis when compared to those with normal ^{123}I-MIBG uptake and WO.[30]

This same group demonstrated the independent prognostic value of increased cardiac sympathetic activity by the late HMR as a measure of ^{123}I-MIBG myocardial uptake when used as a continuous parameter in another meta-analysis of multiple single-centre cohort studies.[31]

Table 1 shows pooled or multicenter analyses of ^{123}I-MIBG SPECT in the evaluation of HF patients' prognosis in North America, Japan, and Europe.

Regarding the therapeutic evaluation of ventricular dysfunction, numerous studies using ^{123}I-MIBG imaging have shown that the use of beta-blockers, ACE inhibitors, and spironolactone can significantly improve SNS activity, with a significant impact on prognosis.[23,24,30-35]

Gould et al.,[36] investigated whether the use of the biventricular pacemaker would affect sympathetic activity in HF patients. The results showed that the use of the pacemaker increased early and late ^{123}I-MIBG uptakes. These authors concluded that the use of this device in HF patients is associated with a significant improvement in cardiac SNS activity, and this must be the potential mechanism of benefits regading morbidity and mortality.[36]

Some authors have also correlated adrenergic denervation on ^{123}I-MIBG imaging with abnormal heart rate recovery,[37] heart rate variability, and SCD in patients with left ventricular dysfunction, even in those with mild dysfunction and NYHA class I.[29,38,39] Akutsu et al.,[40] demonstrated that changes in the SNS were independent predictors of ventricular tachycardia (VT) and ventricular fibrillation (VF) recurrence in patients with a previous history of these arrhythmias. The authors concluded that the ^{123}I-MIBG image may be a good option for screening high-risk patients of SCD.[40]

Finally, after the prospective and multicenter ADMIRE-HF trial results, ^{123}I-MIBG was approved by the US Food & Drug Administration for use in NYHA

class II or III HF patients with LVEF = <35%. The trial results showed that patients with a late HMR <1.6 (low MIBG uptake) had a cardiac death rate of 19.1% versus 1.8% in the group with a late HMR >= 1.6 (high uptake of MIBG), with a negative predictive value for this outcome, in two years, of 98.8%, thus permitting the identification of individuals with a worse prognosis[41] (Figure 3).

Ischemic heart disease

The exact mechanisms of ventricular arrhythmias in ischemic heart disease have been debated, and it has been recognized that scar tissue and the presence of myocardial ischemia may serve as a substrate. In myocardial infarction, ischemia acts as a trigger for ventricular arrhythmias by inducing electrical instability. Areas of slow conduction facilitate the development of reentrant tachycardia in the scar from the infarction.

Sympathetic neurons have proven to be more sensitive and take longer to recover from ischemic injury when compared to myocardial tissue. It has been postulated that denervated myocardial regions with preserved blood flow and viability may predispose to fatal ventricular arrhythmias.[42] Although the pathophysiology is not yet clear, it has been suggested that denervated but viable myocardium may be hypersensitive to circulating catecholamines and may respond differently to sympathetic activation with more automaticity[17,43] (Figure 4).

Klein et al.,[44] demonstrated the feasibility of integrating ^{123}I-MIBG SPECT with voltage mapping for VT ablation in post-infarction patients. The areas defined as denervated by ^{123}I-MIBG were 2.5 times larger than the scar identified by the mapping of bipolar tension, and all sites of VT ablation showed abnormal denervation defined by the ^{123}I-MIBG SPECT.[44]

The PARAPET study sought to predict arrhythmic events using a ^{11}C-HED PET study in 200 patients with ischemic cardiomyopathy. This study demonstrated that arrhythmic death or shock from the implanted cardiac defibrillator (ICD) for VT or VF was directly related to the severity/extent of abnormalities in ^{11}C-HED PET scans, regardless of brain natriuretic peptides (BNP), clinical symptoms, or LVEF.[45]

The new European Society of Cardiology guidelines included the use of myocardial perfusion SPECT or PET to assess ischemia and myocardial viability. However, there is no mention of the possible usefulness of cardiac innervation tests.[46] Despite several promising studies, there is a consensus that the data are still insufficient to replace those established in the guidelines.

Ventricular Arrhythmias

It is well-known that ventricular arrhythmias and SCD occur frequently in the vulnerable cardiac substrate context with a triggering event and can be induced by an increased sympathetic tone.[17, 43, 47]

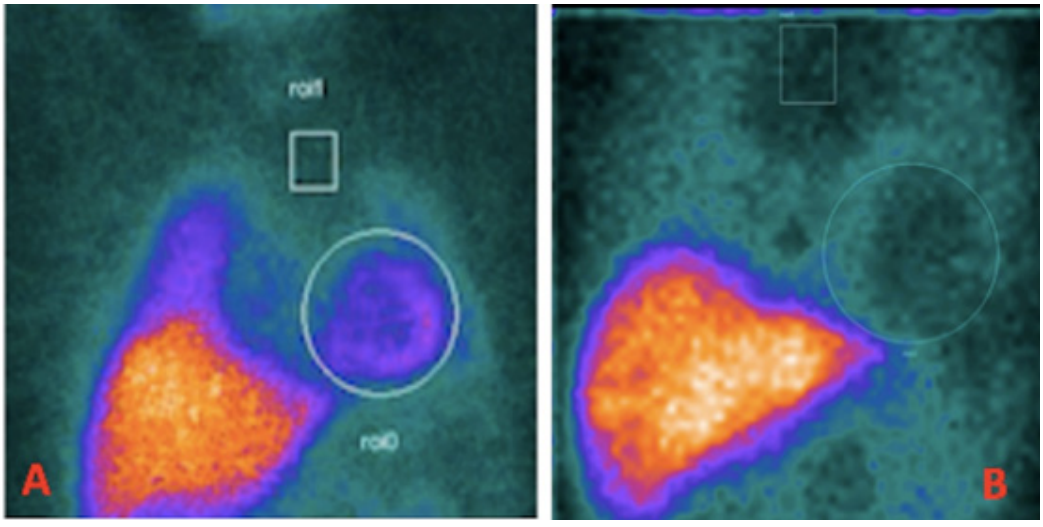

Figure 3 – ^{123}I-MIBG imaging. Planar anterior chest images demonstrate: (A) normal uptake of the radiotracer; (B) absence of radiotracer uptake in cardiac topography in a patient with heart failure.

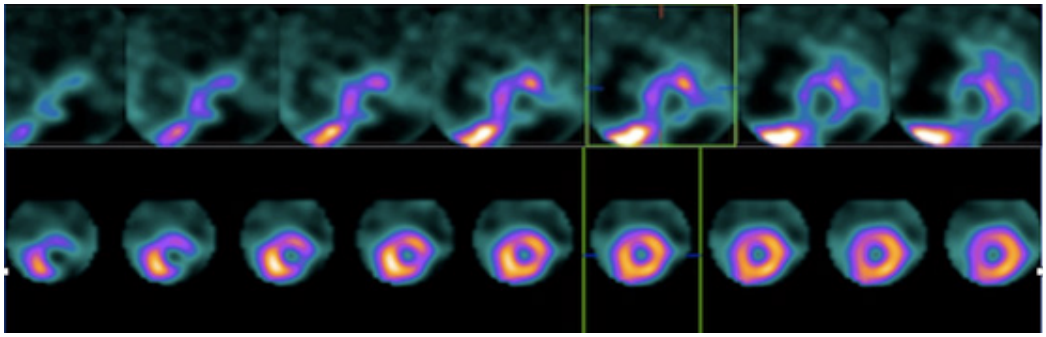

Figure 4 – Cardiac imaging in a patient with reduced innervation but relatively preserved perfusion. (A) short axis images of myocardial perfusion (lower row) and (B) ^{123}I-MIBG uptake (upper row) indicate a lack of innervation in the apical, inferior, and lateral segments.

Current methods to identify risk of fatal arrhythmias are neither sensitive nor specific, and current patient selection practices for ICD are expensive. ^{123}I-MIBG imaging was studied as a potentially useful tool in the prediction of ventricular arrhythmias and has shown promise in HF patients regarding the selection of defibrillator implantation.

Nagahara et al.,[48] investigated the role of ^{123}I-MIBG imaging to predict arrhythmias in the setting of ICD therapy. In one study, ICD discharge was predicted by a combination of late HMR <1.95 together either LVEF <50% or elevated BNP level.[48] A second, prospective study from the same group examined the value of simultaneous innervation and perfusion imaging to predict arrhythmia, quantifying both ^{123}I-MIBG and ^{99m}Technetium-tetrofosmin uptakes in 60 patients. Patients that received ICD shocks during follow-up presented a significantly lower HMR and more abnormal perfusion scores.[49] Boogers et al. demonstrated that regional sympathetic denervation on late MIBG SPECT images was significantly associated with ventricular arrhythmia and appropriate ICD shock. In this study, the uptake defect score on ^{123}I-MIBG late SPECT images was an independent predictor for adequate therapy with ICD. The risk for appropriate ICD shocks was 13 times higher in patients with large ^{123}I-MIBG uptake defects than those with small defects.[50]

The subanalysis study of ADMIRE-HF also demonstrated that combined arrhythmic events (self-limited VT, resuscitated cardiac arrest, and appropriate ICD discharges) were more common in individuals with an HMR <1.60 (10.4%) than those with HMR > or = 1.6 (3.5% P <0.01).[41]

Thus, cardiac ^{123}I-MIBG imaging may enable cardiologists to identify patients who are most susceptible to lethal arrhythmias and event risks, and who can actually benefit most from device therapy by overcoming the limitations of current device therapy criteria, most of which consist of surrogate markers of lethal events, such as symptoms (NYHA class), clinical backgrounds, and LVEF. Nonetheless, this will depend on improvements in the technical consistency of clinical ^{123}I-MIBG exams and a prospective generation of data documenting a positive effect of this procedure in clinically relevant situations.

Takotsubo cardiomyopathy

Takotsubo Cardiomyopathy (TC) also known as acute stress-induced cardiomyopathy is defined as a clinical condition characterized by an acute and transient (<21 days) LV systolic dysfunction that occurs mainly in post-menopausal women after emotional or physical distress. The classic pattern of regional LV wall motion abnormality is the apical (apical ballooning) with basal hyperkinesis present in up to 75-80% of the cases.[51,52]

It was originally recognized as a benign disease because of its typical transient nature; however, nowadays, non-negligible rates of life-threatening complications are also recognized. Moreover, the frequency of recurrence is practically irrelevant (1-2% per-patient year) happening early or much later (up to 10 years) after the primary episode.[53]

Clinical manifestations are similar to acute coronary syndrome. Hence, a detailed anamnesis is essential to suspect TC, especially when an echocardiogram reveals a typical wall motion abnormality beyond the territory

perfused by a single coronary artery. Nonetheless, most patients underwent coronary angiography to rule out obstructive coronary disease as the cause of acute systolic dysfunction.[51-53]

Non-invasive methods, such as echocardiogram and cardiac magnetic resonance (CMR) have been used to assist in the diagnosis and follow-up of TC patients.[53,54] The precise pathophysiology of this cardiomyopathy has not been completely understood. Nevertheless, a link between brain and heart has long been recognized. Hyperactivity of the SNS is the cornerstone in TC.[51-53] Emotional or physical distresses are triggers, and high plasma catecholamines levels are identified in the acute phase of the disease. Overload of catecholamines might be linked to cardiomyocyte cardiotoxicity and stunning. Results from animal studies displayed a higher density of β2-AR in apical than in basal ventricular cardiomyocytes. Thus, apical stunning could be evoked by excessive catecholamine stimulation. Therefore, stress cardiomyopathy represents a form of neurocardiogenic myocardial stunning, and nuclear medicine may play an important role in its evaluation.[55]

^{123}I-MIBG imaging is usually performed in the sub-acute phase of TC. Typical findings include impaired late HMR and WO obtained from planar imaging and reduced apical uptake on SPECT images correlating to impaired LV segments in the acute phase.[56] More recently, some follow-up studies have unveiled promising data. One such study showed, after some months impaired, that a late HMR was increased and WO decreased significantly, while impaired apical uptake was not present. These findings reinforce the hypothesis that TC might be related to neurogenic myocardial stunning. The phenomenon underlying persistent reduced uptake on SPECT images is still unknown. The increased density and sensitivity of apical β2-AR to catecholamines may well prolong downregulation and consequently impair the uptake-1 mechanism. Whether those findings could be related to an increased chance of relapse or if β-blockers may be appropriate in the treatment is still undetermined[54,57,58] (Figure 5).

Ideally, a rest perfusion should also be performed mostly when CMR is not available. Normal or mild reduction of uptake is likely. Of note, ^{11}C-HED PET data are scant.[53,54,57]

Hypertrophic Cardiomyopathy

Hypertrophic Cardiomyopathy (HC) is the most common heritable cardiomyopathy and is characterized by LV hypertrophy in absence of other possible causes. The anatomic hallmark of HC is a non-uniform LV hypertrophy, mainly of the interventricular septum. Several mutations in genes encoding sarcomere proteins have been uncovered, which impact phenotypic expression and prognosis. Diastolic dysfunction, dynamic LV outflow tract (LVOT) obstruction, mitral regurgitation, myocardial ischemia and arrhythmias are interrelated abnormalities commonly observed in HC patients.[59]

The echocardiogram has long been used to assess LV hypertrophy severity, a predictor of SCD risk. CMR should be considered as a baseline assessment of HC patients because of its superior spatial resolution, more accurate volumetric evaluation, better identification of apical aneurysms often related to ventricular

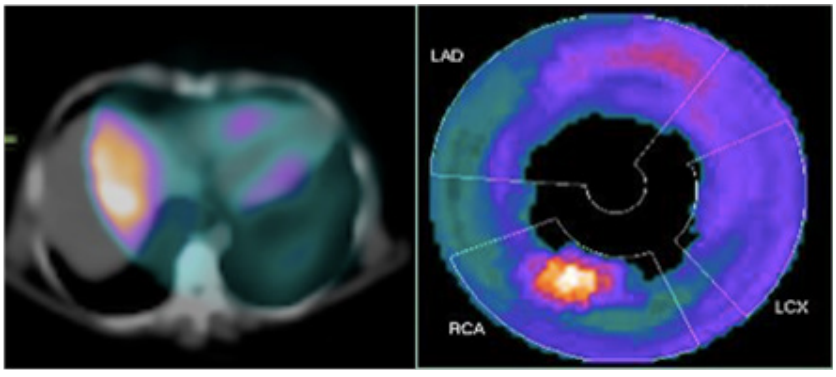

Figure 5 – Cardiac imaging in a patient with Takotsubo cardiomyopathy. (A) SPECT/CT showing ^{123}I-MIBG distribution and the absence of apical uptake; (B) bulls-eye image showing ^{123}I-MIBG distribution and the absence of apical uptake. LAD: left anterior descending coronary artery, RCA: right coronary artery, LCX: left circumflex coronary artery.

arrhythmias, and, particularly, tissue characterization by late gadolinium enhancement (LGE). Prevalence of LGE is as high as 80% and a patchy, multifocal mid-wall LGE pattern in areas of hypertrophy suggests HC. Previous studies have revealed that LGE is useful in predicting cardiovascular mortality, but current data do not support LGE as an independent predictor of SCD risk.[59]

SCD may be the first manifestation in asymptomatic patients. The use of ICD for secondary prevention carries a class I indication in international guidelines. However, its use for primary prevention remains controversial. HC Risk-SCD Calculator incorporates LV hypertrophy, but not LGE.[60,61]

Clearly, it is mandatory to improve risk stratification in order to detect new outcome predictors. ^{123}I-MIBG scintigraphy might be helpful in this scenario. Cardiac sympathetic activity is known to be impaired in HC, and some studies have indicated a correlation between WO and echocardiogram features, such as hypertrophy severity, septum thickness, LVOT, and diastolic dysfunction. It is interesting to note that late HMR increased and consequent WO decreased in the months after septal ablation.[55, 62]

Cardiotoxicity evaluation

The past years have led to significant improvements in cancer treatment. Nevertheless, old and novel therapies are known to cause cardiotoxicity. Among cancer survivors, secondary malignancies are reported as the leading cause of morbidity and mortality, followed closely by cardiotoxicity. Cardio-oncology is a developing specialty dedicated to understanding and preventing cardiovascular disease in cancer patients. In this context, non-invasive methods capable of screening subclinical cardiotoxicity are most needed.[63,64]

At first, cancer therapeutics-related cardiac dysfunction (CTRCD) was used to be allocated into two major groups: type I, related to cell death, irreversible, and normally dose dependent (anthracyclines), and type II, associated with myocyte dysfunction rather than apoptosis, potentially reversible, and not dose-dependent (trastuzumab). This kind of classification demonstrates that, initially, patient evaluation was solely related to LV dysfunction, but nowadays, other relevant parameters are also crucial.[63,64]

MUGA, echocardiogram, and CMR are recommended by several guidelines to regularly monitor LV function during chemotherapy. Since LV dysfunction is a late manifestation of cardiotoxicity, methods that precisely evaluate molecular damage might be extremely helpful [63,64].

CTRCD induces a compensatory adrenergic response and ^{123}I-MIBG imaging can identify it in advance detecting patients at increased risk. Some studies have shown reduced MIBG uptake in a dose-dependent way in patients receiving anthracycline treatment even before slight changes in LVEF. Two mechanisms might be involved: destruction of adrenergic nerve tissue or functional impairment. Another study valued the use of ^{123}I-MIBG imaging in accessing trastuzumab-related CTRCD. In case of persistent CTRCD, the ^{123}I-MIBG scan results might indicate whether recovery will occur and may be treatment reinitiated.[65-67]

Nowadays, ^{18}F-fluorodeoxiglucose (^{18}F-FDG) PET has been an extremely valuable technique in diagnosis, prognosis, and management treatment in cancer patients. However, clinical data assessing the role of PET in detecting CTRCD is still scarce. ^{11}C-HED, ^{11}C-epineiphrine, and ^{18}F-6-fluordopamine and (3H) CGP12177 might be beneficial in the future.[68]

Chagas Cardiomyopathy

Chagas disease is a serious health problem in endemic Latin America countries; an estimated six million people are infected with *Trypanossoma cruzi*, leading to significant morbidity and mortality. Due to migratory waves, infected individuals have spread worldwide. Chronic Chagas' cardiomyopathy (CC) is the most severe and frequent manifestation, occurring in 25-30% of all infected people.[69] Patients may develop severe clinical manifestations, such as congestive HF, malignant arrhythmias, or thromboembolism. Chronic CC carries a worse prognosis when compared to ischemic and non-ischemic HF.[70] The presence of persistent myocardial inflammation plays a central role in the genesis of arrhythmias due to irreversible cell damage, fibrosis, and scar formation. Ventricular arrhythmias are a major cause of morbidity and mortality in patients with Chagas disease and may occur even before significant LV systolic dysfunction, leading to SCD.[71]

Miranda et al. showed that regional myocardial sympathetic denervation assessed with ^{123}I-MIBG SPECT is associated with sustained VT in CC, concluding that viable, although denervated, myocardial areas were associated with the genesis of sustained ventricular arrhythmias.[72] Furthermore, researchers have been searching for active inflammation as a trigger for

reentry and VT. In this scenario, ^{18}F-FDG PET may be a promising tool to monitor disease activity and risk stratification of patients with CC. Future studies should address these new potential clinical applications of PET imaging[73,74] (Figure 6).

Limitation of the studies

Some limitations affect the quality of our review on autonomic innervation evaluation in cardiac disease, such as the lack of prospective multicenter studies and the heterogeneity of the studies for autonomic dysfunction assessment in the diverse cardiac syndromes.

Conclusions

The autonomic nervous system plays a central role in the cardiac function. Cardiac neuronal imaging can be used to visualize the sympathetic innervation of the heart and allows for the early detection of these abnormalities caused by, for example, ischemia, heart failure, cardiomyopathies, cardiotoxicity, and arrhythmogenic disorder.

It is important to continue research in the field of cardiac autonomic innervation evaluation while exploring its clinical utility, as it has the potential to provide novel insights into pathophysiology of this cardiac disease and potentially lead to the development of novel therapies to improve prognoses.

Author contributions

Conception and design of the research: Xavier de Brito AS. Acquisition of data: Xavier de Brito, AS, Glavam A, Bronchtein AI. Analysis and interpretation of the data: Xavier de Brito AS, Rosado-de-Castro PH. Statistical analysis: Xavier de Brito AS, Rosado-de-Castro PH. Writing of the manuscript: Xavier de Brito AS, Glavam A. Critical revision of the manuscript for intellectual content: Rosado-de-Castro PH.

Potential Conflict of Interest

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

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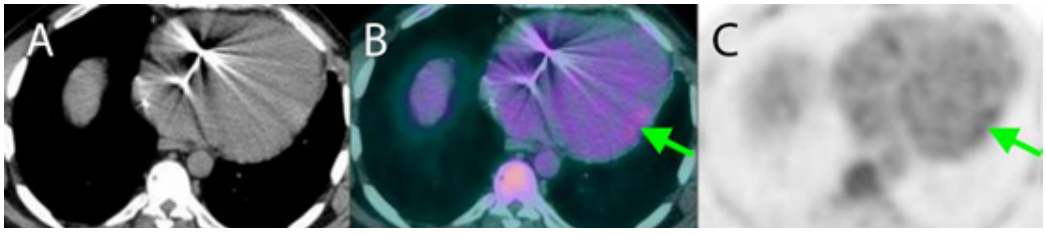

Figure 6 – ^{18}F-FDG PET-CT in a patient with chagasic cardiomyopathy and pacemaker (A, axial CT; B, axial PET-CT; C, axial PET). Mild uptake was observed in the basal anterolateral segment. This finding could potentially indicate mild ventricular inflammation.

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EDITORIAL

Assessment of Cardiac Sympathetic Activity by Nuclear Medicine: Many Clinical Benefits but Weak Recommendation

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Editorial related to the article: Autonomic Innervation Evaluation in Cardiac Disease

The autonomous nervous system (ANS) regulates important cardiac functions, including heart rate, ventricular contractility, QT interval and systemic vascular resistance. ANS dysfunction, known as dysautonomia, can lead to many clinical manifestations, some of them severe and debilitating.[1] Dysautonomia is often underdiagnosed and detected at late stages, due to its wide phenotypic variability and the poor familiarity of the physicians with the disease, leading to higher cardiovascular mortality and morbidity.[2]

The diagnostic and prognostic potential of nuclear cardiology in the assessment of the ANS has increased. In addition, there is growing evidence that the use of scintigraphy in the evaluation of cardiac innervation can help in cardiovascular risk stratification, therapy selection, and evaluation of potential benefits of new therapeutic approaches.[3,4] However, there is increasing need for physicians with experience with this method, and hence, scientific studies that synthesize and discuss its applications, advantages, and disadvantages would contribute to the effective implementation in clinical practice.[5]

In this issue, Brito et al.[4] present an interesting review on the use of scintigraphic imaging in the assessment of autonomic innervation in cardiac diseases. The article provides an overview of the use of nuclear medicine and different radiotracers in various clinical settings. Despite the unquestionable potentiality of the technique for a non-invasive, objective, imaging diagnosis of cardiac dysautonomia, each section of the review presents clear limitations for its routine recommendation. The authors point out problems involved in the standardization, low availability, and high cost of the method as the main challenges to be overcome.

Among the scintigraphic techniques addressed in the review, we believe that the cardiac 123I-metaiodobenzylguanidine (^{123}I-mIBG) scintigraphy is the most feasible for practical application. Its implementation in clinical practice would help in solving the issue of underdiagnosing of dysautonomia, and in promoting better medical care for these patients. However, for this purpose, all those limitations should be overcome.

The study is a review of the literature and presents, in a didactic way, the main clinical applications of scintigraphy in the study of cardiac autonomic denervation. The use of this technique started in the early 80s, i.e., 41 years of experience have been accumulated (Figure 1). Undoubtedly, cardiac scintigraphy with ^{123}I-mIBG and its parameters – the late heart-to-mediastinum ratio (HMR) of ^{123}I-mIBG uptake and its clearance rate – is the most supported by currently available data.[6] Results of these indexes indicate, respectively, the integrity of presynaptic terminals and the adrenergic tone.[7]

Figure 2 summarizes the clinical settings that would most benefit from cardiac ^{123}I-mIBG scintigraphy. In heart failure a reduced HMR is an independent marker of mortality and a predictive marker of arrhythmic events.[8] Besides, observational studies have shown its applicability in cardiac resynchronization therapy[9] and cardiac defibrillator implantation,[10]

Keywords

Scintigraphy/methods; Single photon emission computed tomography/methods; Nuclear Medicine; 123I-mIBG.

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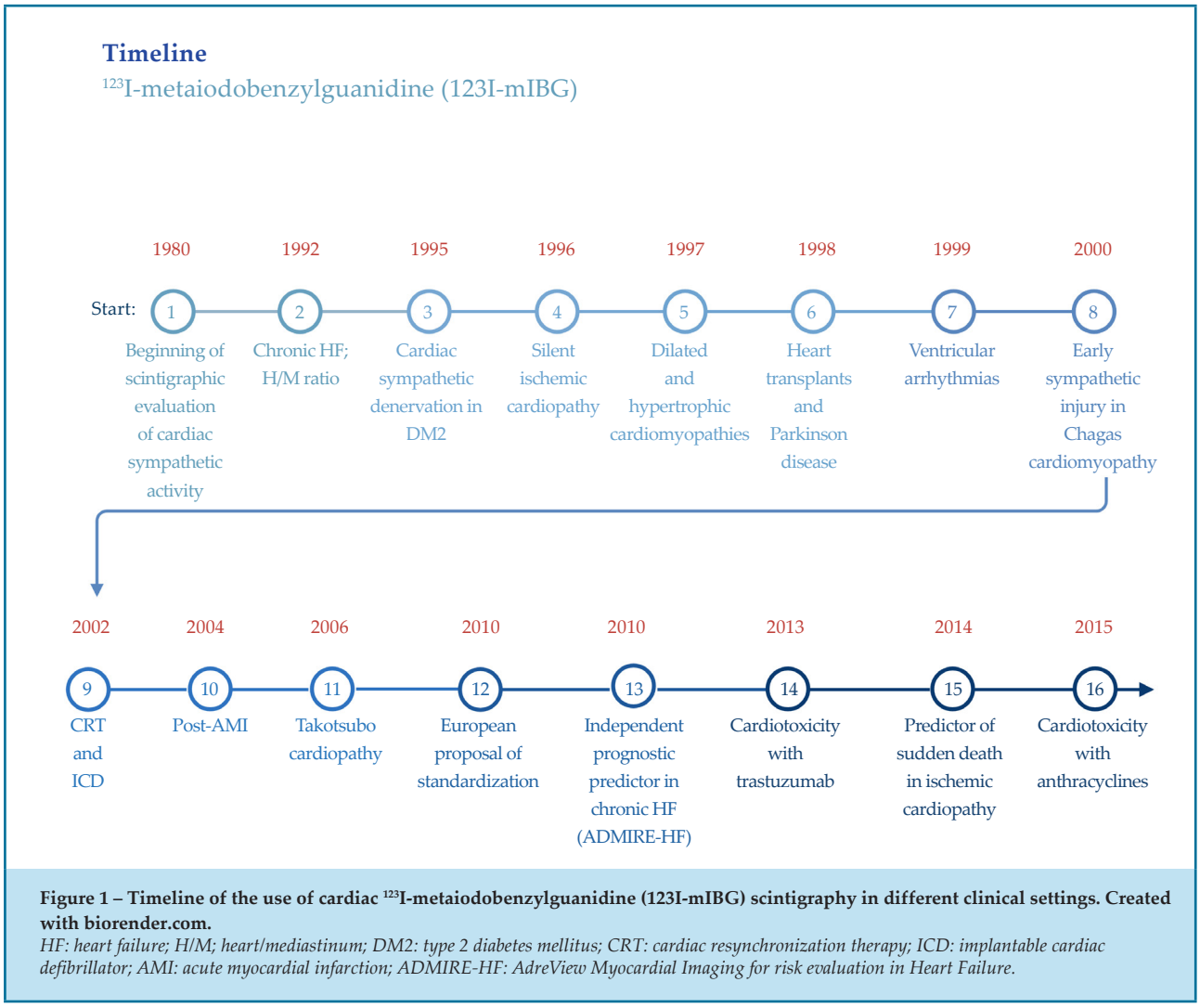

Figure 1 – Timeline of the use of cardiac ^{123}I-metaiodobenzylguanidine (123I-mIBG) scintigraphy in different clinical settings. Created with biorender.com.
HF: heart failure; H/M; heart/mediastinum; DM2: type 2 diabetes mellitus; CRT: cardiac resynchronization therapy; ICD: implantable cardiac defibrillator; AMI: acute myocardial infarction; ADMIRE-HF: AdreView Myocardial Imaging for risk evaluation in Heart Failure.

focusing on refining the indication criteria for these expensive therapies and making them more cost-effective.

Other applications include cardiovascular risk stratification in Chagas cardiomyopathy, hypertrophic cardiomyopathy, Takotsubo cardiomyopathy, early detection of cardiotoxicity, cardiac amyloidosis, and dysautonomia secondary to neurodegenerative diseases and diabetes mellitus, as well as therapeutical monitoring in several cardiac conditions.[4,5,11,12] In many of these situations, mapping of myocardial denervated areas can help in the identification of arrhythmogenic foci and prediction of arrhythmic events,[8] and consequently in better establishing patient risk and appropriate therapy. In addition, monitoring of recovery from myocardial injury by cardiac ^{123}I-mIBG scintigraphy helps in the evaluation of therapy effectiveness.[4]

However, despite the well-established pathophysiological foundation and numerous studies supporting the benefits of scintigraphy in the evaluation of cardiac sympathetic activity, the scientific community still recommends the development of large prospective randomized clinical trials before including the method in clinical guidelines.[11]

The main limitations of the method, discussed in the article, are the scarcity of cost-effectiveness data, the high cost of the technique, poor familiarity of physicians with the method, and the lack of multicenter studies evaluating the role of cardiac ^{123}I-mIBG scintigraphy in each of the clinical conditions above mentioned. In addition, the technique as well as the interpretation results (or cutoff points) in different clinical settings still need standardization.[6] The overcoming of these limitations will advance the use of nuclear imaging in dysautonomia and its full implementation in clinical practice.

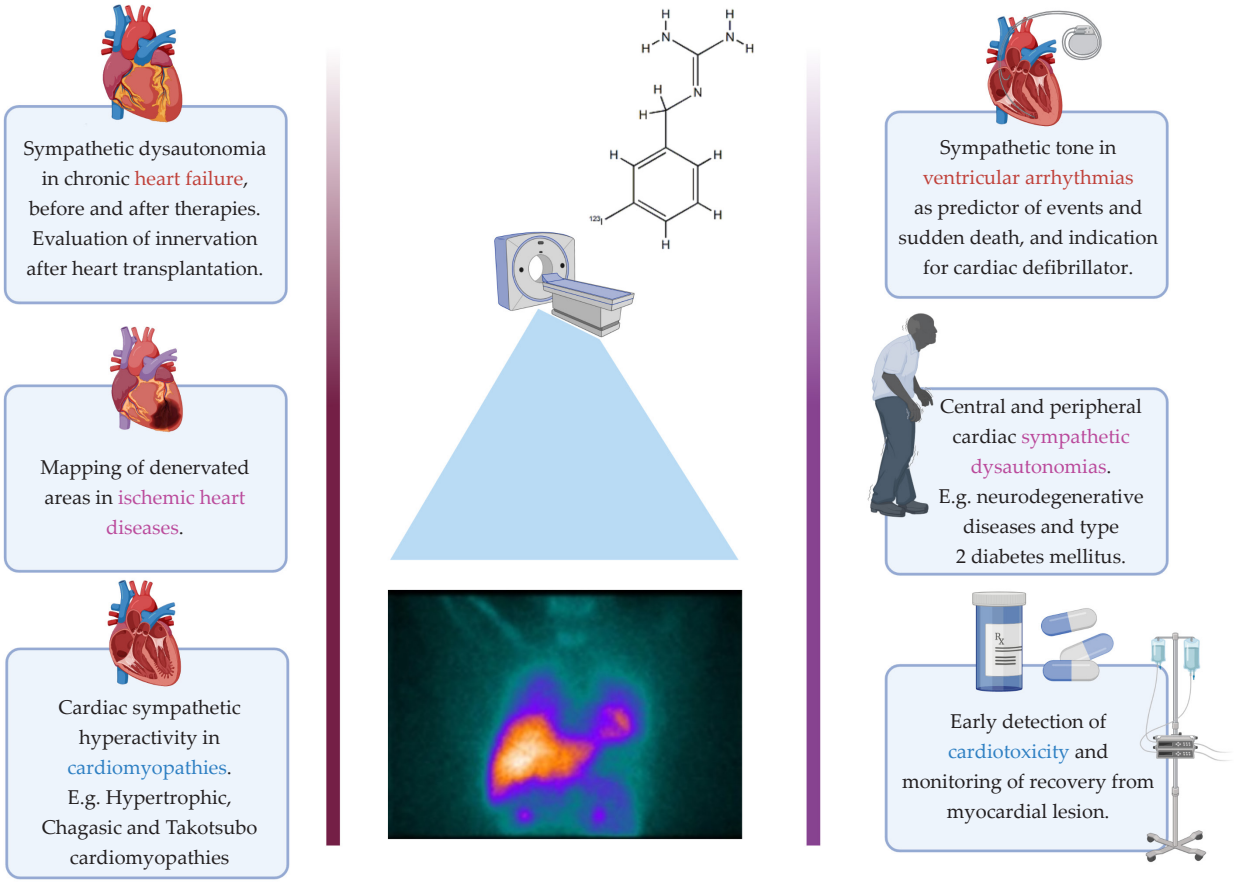

Figure 2 – Main clinical applications of cardiac ^{123}I-metaiodobenzylguanidine (123I-mIBG) scintigraphy. Created with biorender.com.

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REVIEW ARTICLE

Cardiac Arrhythmias and Covid-19

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Abstract

Cardiovascular manifestations of COVID-19 include cardiac rhythm disturbances, whose mechanisms, incidence, and most common types are not well established in this population. Intense inflammatory response and metabolic activity contribute to recurrence of pre-existing arrhythmias, and other arrhythmias can occur due to myocardial injury, acute coronary insufficiency, and electrolyte disturbances. Brady- and tachyarrhythmias, as well as conduction disorders have been described. QT interval prolongation and fatal ventricular arrhythmias (*Torsades de Pointes*) may result from the pathological process or adverse effect of drugs (antiarrhythmics, chloroquine / hydroxychloroquine, azithromycin and antivirals). Patients with congenital heart disease and hemodynamic repercussions, patients with signs of heart failure, pulmonary hypertension, cyanosis, hypoxemia, and those who underwent heart transplantation and immunosuppression are at greater risk. In patients with implantable cardioverter-defibrillators (ICDs), the risk depends on the presence of structural heart disease. In the course of COVID-19, in-person assessment of these patients should be limited to high-risk situations, including syncope, worsening of heart failure and shock delivery by ICDs. Likewise, cardiac implantable electronic device implantation or replacement surgery should be limited to emergency and urgent cases, including symptomatic high-degree atrioventricular block, ICD for secondary prevention and pulse generator replacement due to battery drain.

Keywords

Coronavirus Infections; Cardiac Arrhythmias; Artificial Pacemaker.

Introduction

The infection by SARS-CoV-2, the virus that causes COVID-19, may lead to clinical manifestations that directly affect several organs and systems. Although the COVID-19 is a primarily respiratory disease, many studies have suggested a cardiovascular involvement, especially in the group of patients who require hospitalization.[1,2] Clinical presentation and cardiac involvement may vary from asymptomatic disease to development of myocardial disease, hemodynamic instability, and rhythm disturbances.

Regarding cardiac arrhythmias, the real incidence, and the more common types of arrhythmias in SARS-CoV-2 infection is still unknown. So far, due to limited information on cardiac electrical disturbances related to COVID-19, current recommendations on the management of arrhythmias during the infection are based on existing evidence before the pandemic.

The current review aims to explore the pathophysiological mechanisms involved in arrhythmogenic cardiomyopathy, as well as clinical and therapeutic features of adult and pediatric COVID-19 patients, and patients with implantable cardiac electronic devices.

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Pathophysiology

Elevation of troponin in up to 30% of patients in the early stages of COVID-19 is an indication for cardiac stress and injury. Increased levels of brain natriuretic peptide (BNP) levels have been reported in similar proportions.

Cardiovascular damage induced by COVID-19 has not been fully elucidated, and several mechanisms have been proposed:

a) Intense systemic inflammatory response, with increased cytokine levels (particularly interleukin 6, IL6), which may lead to injury of multiple organs, including myocardial cells;

b) Myocardial injury resulting from an imbalance between an increased cardiometabolic demand and reduced oxygen supply due to significant hypoxemia induced by severe pneumonia; myocarditis, microvascular injury and stress-related cardiomyopathy may also be involved in the development of myocardial injury;

c) Acute coronary syndrome caused by atherosclerotic plaque rupture. Plaque instability and rupture may be caused by viral infection and consequent systemic inflammatory response, culminating in acute myocardial infarction. Likewise, dysregulation of the renin-angiotensin-aldosterone system may predispose to plaque rupture. Type 2 infarction is observed in some patients, as a result of hypoxemia induced by an increased oxygen demand by the myocardium and hypotension.[3,4]

Based on current knowledge, cardiac arrhythmias in COVID-19 patients seem to be caused by multiple factors from intense inflammation and metabolic activity, which favor the recurrence of arrhythmias, until the emergence of new arrhythmias induced by myocardial injury and acute coronary failure. IL-6, TNFα and IL-1 have been found to prolong the ventricular action potential duration, modulating the expression and/or function of cardiomyocyte ion channels, specifically potassium and calcium channels (inflammatory cardiac channelopathies).[5]

In addition to direct cardiac effects, systemic inflammation can also predispose to QT interval

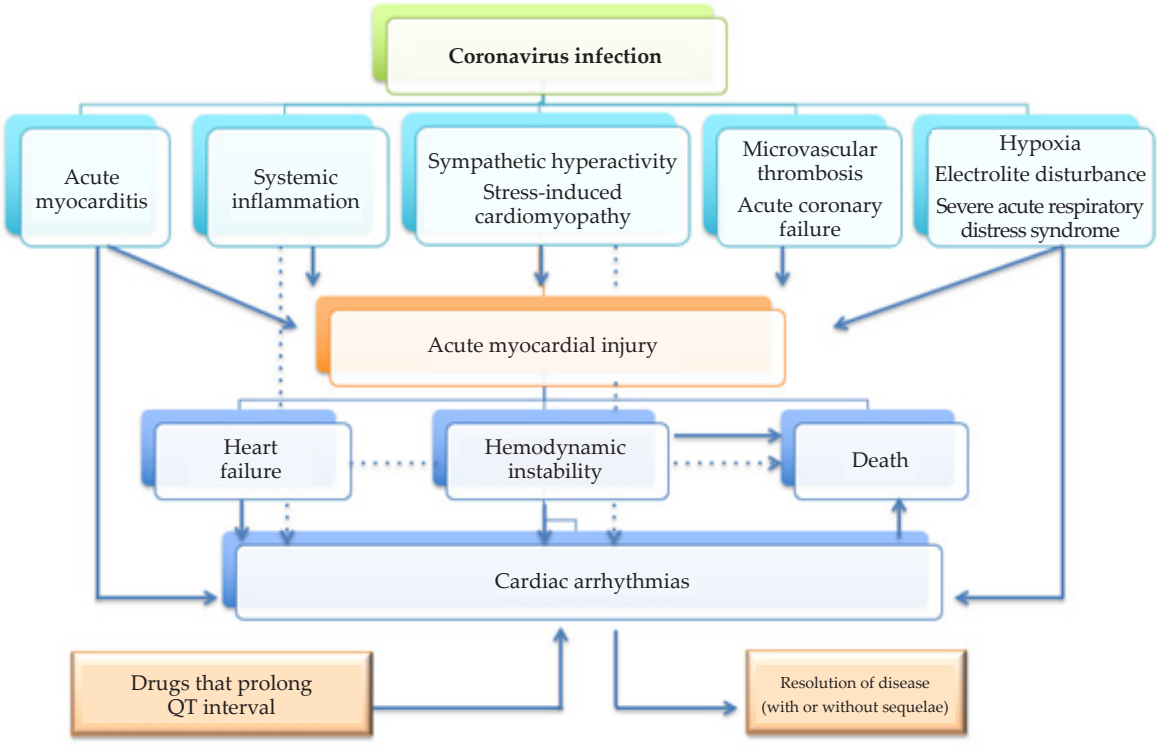

Figure 1 – Possible pathophysiological mechanisms of cardiac arrhythmias in COVID-19

prolongation and consequently polymorphic ventricular tachycardia – *Torsades de Pointes* (TdP). Inflammatory cytokines can cause hyperactivation of cardiac sympathetic nervous system, mediated by hypothalamus (inflammatory reflex), and of the peripheral system (with activation of left stellate ganglion). These processes are recognized as triggers to arrhythmic events and life threat in patients with long QT syndrome. In addition, IL-6 inhibits p450 cytochrome, mainly the CYP3A4, which enhances the bioavailability of several drugs, including those that prolong the QT interval.

Experimental studies in rats infected by SARS-Cov-2 have also demonstrated changes in cardiac conduction system secondary to myocarditis and ventricular dysfunction.[6] Bradycardia has also been reported in critically ill patients, as a result of increased vagal tone.[7] So far, there is no report on the direct involvement of the conduction system in COVID-19 in humans.

Electrolyte disturbances, direct effects of cytokines, and drugs that prolong the QT interval may favor the occurrence of arrhythmias, particularly high-risk arrhythmias such as TdP. Thus, the combined use of chloroquine with azithromycin, associated with predisposing factors such as ventricular dysfunction, concomitant use of antiarrhythmic drugs (e.g. magnesium and potassium deficiency), older age, among others, can contribute to the development of polymorphic ventricular tachycardias (TdP). In a retrospective study, Wang et al. showed that 23 (16.7%) of 138 hospitalized patients with COVID-19 developed some form of arrhythmia. The incidence of arrhythmia was higher in more severely ill patients, treated in the intensive care unit (44% vs. 6.9%). The authors did not specify the types of arrythmia detected.[2]

These factors, either alone or together, may culminate in the emergence of atrial and ventricular tachyarrhythmias; the involvement of the cardiac excito-conductor system, combined with sinus bradycardia, atrioventricular, interventricular, and intraventricular block may also occur.

Bradyarrhythmias

Bradyarrhythmias are common in many clinical scenarios, varying from structural defects of cardiac conduction system, physiological adaptations to transient mechanisms (vagal modulation, pharmacological effects, ischemia, inflammatory activity) to pathological conditions.

Patients with previous structural heart disease are at higher risk for complications of COVID-19, with potentially fatal outcome. Many of these patients have a history of bradycardia or of use of medications with negative chronotropic effect. The use of beta-blockers, dihydropyridine calcium channel blockers, amiodarone, digoxin, among others, is common among hypertensive patients with heart failure or coronary artery disease. Also, an exacerbated inflammatory response, with myocardial involvement, may cause bradyarrhythmias with potential hemodynamic instability, even transient ones.

In general, sinus bradycardia, junctional rhythm, first- and second-degree atrioventricular block (Mobitz I, with a narrow QRS complex), are related to reflex and adaptative mechanisms, or to structural disease at the atrioventricular node level, above the bundle of His. These changes seem to have better prognosis and better response to vasoactive agents and atropine and are usually transient. Advanced or third-degree atrioventricular block reflect reflects a more severe involvement of the infra-Hisian conduction and usually requires artificial cardiac stimulation, even temporarily.

Therefore, COVID-19 patients with bradyarrhythmias may require special attention regarding the prevention of complications of systemic inflammatory response, worsening of arrythmia by iatrogenic effect and eventual need of pacemaker (PM).

Atrial fibrillation

The incidence of atrial fibrillation (AF) and atrial flutter (AFL) is unknown in patients with COVID-19.[30] Based on previous studies, it is known that, in critically ill patients with SARS or septicemia, AF is not uncommon and is associated with higher mortality rates.[8,9,10]

Similar to patients without COVID-19, the treatment of AF and AFL should be based on the control of ventricular response and heart rhythm, and prevention of thromboembolic events.

Electrical cardioversion (ECV) is indicated for patients with hemodynamic instability. In the context of COVID-19, it is important to highlight the need for protecting health care workers involved in this procedure, especially in cases of orotracheal intubation due to the high risk of aerosol contamination.[11]

Amiodarone is the drug of choice for COVID-19 patients, either for reversion of stable AF or to avoid recurrence after ECV. It is important to identify and correct factors that can increase the risk for proarrhythmic

effects, such as electrolyte disturbance, and concomitant use of drugs that increase QT interval. Despite the absence of robust scientific evidence on their efficacy in the treatment of COVID-19, the combination of hydroxychloroquine with azithromycin has been used in these patients. However, it is worth to mention that these medications can cause QT interval prolongation, which could, in theory, exacerbate the effect.[12,13] Also, other drugs previously tested and currently used against the SARS-CoV-2 infection, may also affect the QT interval and lead to more severe arrhythmias like the TdP. An updated list of drugs that cause QTc prolongation is available at online databases (e.g. the CredibleMeds® - https://crediblemeds.org/pdftemp/pdf/CombinedList.pdf).

It is of note that the more severe forms of SARS-CoV-2 infection could, in theory, contribute to the development and persistence of AF. In addition, maintenance of sinus rhythm may be challenging in the presence of acute respiratory failure, severe inflammation, metabolic and electrolyte disturbances, as well as increased sympathetic tone activation. In this critical scenario, the choice for the primary control of heart rate without ECV attempts for atrial fibrillation until stabilization of patient's clinical status should be considered.[13]

As above mentioned, attention should be paid to interactions of drugs that increase the risk of QT interval prolongation and the occurrence off potentially fatal arrhythmias. In this regard, it is crucial to assess the degree of risk/benefit of continuing or temporarily discontinuing antiarrhythmic drugs during the acute phase of COVID-19. For example, hemodynamically stable patients with AF, receiving antiviral treatment, discontinuation of antiarrhythmic agents should be considered to prevent the risk of proarrhythmic effects. In this case, the use of beta-blockers (if not contraindicated) may be a good alternative for the control of ventricular rate.

Finally, electrocardiographic monitoring of QT interval and electrolyte disturbances (especially potassium and magnesium) should be conducted with appropriate corrections before and after the use of drugs that prolong QT interval is initiated.

Anticoagulation is indicated to both valvular AF (patients with metallic prosthetic valves or moderate/severe mitral stenosis) and non-valvular AF. In the latter, anticoagulation has been advocated for patients with $CHA_2DS_2VASC \geq 2$ for men and ≥ 3 for women. In hemodynamically stable patients with nonvalvular AF and no mechanical ventilatory support, direct oral anticoagulants are the drugs of choice, whereas for patients with valvular AF, warfarin is indicated. Possible drug interactions that could affect both the efficacy of anticoagulants and the risk of bleeding complications (e.g. antiviral drugs and direct anticoagulants) should be evaluated.

Subcutaneous low-molecular-weight heparin or intravenous unfractionated heparin molecular should be preferred for hemodynamically unstable patients and those on ventilatory support with orotracheal intubation.

As previously mentioned, these recommendations have been developed on the basis of accumulated knowledge before the COVID-19 pandemic. Thus, a better understanding of the pathophysiology of COVID-19 should, in near future, help in the management of these patients including on the choice of prophylactic anticoagulation for prevention of thromboembolic events in AF and AFL. Critically-ill patients with COVID-19 are at higher risk for thrombotic complications, which is particularly important in AF.

Due to the lack of controlled randomized clinical trial that would help in defining the best therapeutic approaches in each clinical situation, a systematic prevention of thromboembolic phenomena should be implemented. It is worth pointing out that computed tomography has been shown as an effective alternative to echocardiography for detection of thrombus in the left atrium. Such strategy may be valuable for COVID-19 patients, to mitigate the risk of upper airway contamination.[14]

Ventricular tachycardia and ventricular fibrillation

The incidence of malignant ventricular arrhythmias, such as ventricular tachycardia (VT) and ventricular fibrillation (VF) in COVID-19 is still unknown. The risk of VT and VF is believed to be higher in more severely ill patients, reflected by the higher intensity of metabolic derangement, hypoxemia, neurohumoral and inflammatory stress, and greater myocardial injury. Besides, due to infection, these conditions may be even more complicated in patients with previous cardiovascular disease or ventricular arrhythmias.[30]

A recent study showed a 5.9% incidence of VT or VF in patients hospitalized for COVID-19, with higher frequency in those with elevated troponin.[15] In fact, increased troponin levels seem to be a marker of severity of COVID-19 and are associated with hemodynamic instability and cardiac arrhythmias.

While hemodynamically unstable patients with VT or VF should be submitted to ECV or defibrillation, for patients with polymorphic VT and QT interval prolongation (TdP), other strategies including intravenous administration of lidocaine and/or magnesium sulfate, elevation of heart rate with isoproterenol administration (except patients with long-QT syndrome), PM implantation, in addition to discontinuation of negative inotropic agents and drugs that prolong QT interval, and maintenance of serum potassium levels > 4.5 mEq/L must be considered.

For patients with sustained monomorphic VT, without hemodynamic instability, ECV (particularly intubated patients and those on artificial ventilation); intravenous lidocaine (especially patients with prolonged QT interval and/or use of drugs that prolong the QT interval), and intravenous amiodarone (for those with structural heart disease and ventricular dysfunction) should be considered. Amiodarone should be avoided in patients with prolonged QT interval or those using drugs that prolong the QT interval.

Electrical storm

Electrical storm is defined as three or more episodes of sustained VT or VF within 24 hours. It is a serious condition with high mortality rates. Electrical storm is more commonly seen in patients with structural heart disease, and the main predictive factors include severity of ventricular dysfunction, older age and previous VT or VF.[16]

When an electrical storm occurs, in addition to the above-mentioned therapeutic strategies for VT/VF, the use of intravenous lidocaine and beta-blockers (Esmolol) must be considered for patients in whom amiodarone therapy was unsuccessful or its use is contraindicated. Deep sedation with orotracheal intubation and artificial ventilatory support (again highlighting the importance of protecting the health care workers from the risk of aerosol transmission), and transient PM aiming at reversing the arrhythmia by rapid ventricular stimulation and acting as an adjuvant to pharmacological therapy should also be useful.

Children and congenital heart diseases

Severe SARS-CoV-2 infection has been rarely found in children, who have usually presented a milder form of the disease, with better prognosis. So far, risk of vertical transmission by SARS-CoV-2 is probably very low,compared with adults.[6, 17, 18, 19]

The largest study involving children with COVID-19 included 2,143 patients. Most of them (94.1%) were asymptomatic, or had mild or moderate symptoms and, for this reason, the actual infection rate is believed to be much higher.[20]

Recent data have suggested that asymptomatic or oligosymptomatic individuals have potentially infectious particles of SARS-CoV-2 in nasopharyngeal secretions, which favors the transmission to close contacts. Another important finding in COVID-19 transmission was the detection of the virus in fecal samples from asymptomatic children, with longer virus shedding period compared to the upper respiratory samples, suggesting a prolonged fecal-oral transmissibility for COVID-19.[20] The presence of SARS-CoV-2 for a long period in nasal secretion and feces from infants and children has important implications for dissemination of the virus in nurseries and schools, and even at home. Consequently, infants and children may play an important role in community transmission of COVDI-19.

Individuals younger than 18 years old represent less than 2% of severely infected patients.[17] The reason why children are less likely than adults to be infected and harmed by SARS-CoV-2 has not been elucidated yet. Two hypotheses have been proposed to this fact: first, children, especially younger ones, would have higher immunity against the SARS-CoV2 virus due to repetitive exposure to different viruses, and second, the lower presence of angiotensin-converting enzyme 2, which has a high affinity for the viral protein.

The main symptoms found in children with COVID-19 are fever, dry cough, and fatigue. Few children have upper respiratory symptoms including nasal congestion and runny nose, and some patients also have gastrointestinal symptoms, including abdominal pain and discomfort, nausea, vomiting and diarrhea. Chest X-ray findings in these patients are normal or reveal unspecified pulmonary changes, with unilateral or bilateral lesions. Most children have normal chest computed tomography (CT) scans. Abnormal findings observed in critically ill adult patients, including lung consolidation, pleural effusion and enlarged lymph nodes, have been rarely found in children with COVID-19.[18]

Laboratory test results in the initial phase of COVID-19 show normal or low white cell count, with low lymphocyte count. Levels of hepatic and muscle enzymes, and myoglobin are elevated in some patients.

In moderately ill patients, elevation of C-reactive protein and erythrocyte sedimentation rate and normal procalcitonin is seen in most of them. Severely ill patients have increased d-dimer levels and low lymphocyte count. Complete blood count, urine and stool tests, coagulation test, biochemical tests, and identification of biomarkers of infection were performed in children with SARS-CoV-2 infection, with normal results in almost all of them. Few children, in contrast to adult patients, had leukopenia, leukocytosis, lymphopenia, or elevated transaminases.[18]

In the largest study on the severity of COVID-19 in children, Dong et al. reported that the infants were more vulnerable to severe SARS-CoV-2 infection (10.6% of all pediatric patients), and symptoms like pneumonia, central cyanosis (8.7% of the cases), and acute respiratory distress syndrome (ARDS), requiring mechanical ventilation (1.8% of the cases).[21] The proportion of severe and critical cases was 10.6 % in infants, 7.3% for the age group of 1-5 years, 4.3% for the age group of 6-15 years, and 2.8% for ≥16 years.

Children that are more susceptible to developing severe infection are those with developmental disabilities, children with congenital heart diseases, and other underlying diseases, including type 1 diabetes mellitus, cancer, and chronic pulmonary disease (e.g. asthma).

Of 345 children with confirmed COVID-19, the CDC (Centers for Disease Control and Prevention) reported that the most common underlying conditions were: chronic pulmonary disease (11.6%), cardiovascular disease (7.2%) and immunosuppressive conditions (2.9%).[21] The authors also reported an overall low mortality rate in children (0.18%) compared with adults (4.3%).[6, 22]

Despite the risk of contamination, breastfeeding should be encouraged since it is the best source of nutrients and antibodies, and so far, COVID-19 virus has not been detected in the breast milk. SARS-CoV-2–infected mothers should wash their hands frequently with soap and water or use alcohol-based hand sanitizer and wear a face mask. If a mother is too tired to breastfeed, milk should be expressed using a manual or an electric breast pump so that a healthy family member or caregiver may feed the infant.

According to the Brazilian Pediatric Society, COVID-19 patients with congenital heart disease and hemodynamic repercussion or manifestations of heart failure are more likely to have an unfavorable outcome. The clinical course tends to be benign in patients without hemodynamic repercussion and patients in stable clinical conditions or no signs of cardiac decompensation after cardiac surgery or catheterization.

Children with unoperated congenital heart disease, significant hemodynamic repercussion (including signs of heart failure, pulmonary hypertension, cyanosis, and hypoxemia following) surgical correction of congenital heart defects, immunosuppressed children, and children submitted to cardiac transplantation are at increased risk for an unfavorable outcome in infectious diseases. Likewise, although specific data on pediatric patients with COVID-19 are still lacking, a strict social isolation is recommended for this population.[23]

Congenital heart disease patients considered at high risk of becoming seriously ill from COVID-19, according to the British Congenital Cardiac Association, are listed in Table 1.[24]

Similar to what has been observed in adults, the pathophysiology of COVID-19 in children may involve the development of cardiac arrhythmias due to intense inflammation and, eventually, myocarditis. Studies have suggested that inflammation is an important risk factor for long QT syndrome and TdP, mainly by direct electrophysiological effects of cytokines in the myocardium.[6] Also, changes in ventricular repolarization and QT interval prolongation, and consequent risk of proarrhythmia, may be caused by drugs like antiarrhythmic agents, azithromycin, hydroxychloroquine or chloroquine, and antivirals.[18]

The incidence of cardiac arrhythmias is not well established in SARS-Cov-2-infected children. Arrhythmias may occur due to primary diseases, individual or familial genetic disorders, or secondary to toxic and metabolic disorders, drug effects or current heart disease.

During an infection, several factors can trigger arrhythmias, which can be of difficult control. Clinical history and examination are essential for adequate diagnosis and management. Electrocardiographic monitoring of arrhythmia, especially by 12-lead electrocardiogram, can reduce the need for complementary tests. Correction of electrolyte disturbances should be the first step, combined with improvement of metabolic conditions, particularly hypoxia and anxiety

A careful pharmacological approach of arrhythmia should be performed due to the risk of proarrhytmia.[18] In this regard, a multidisciplinary team is needed and, in special situations, an arrhythmia specialist should be consulted.

Table 1 – Congenital heart conditions associated with high risk of unfavorable outcome in COVID-19

Single ventricle; Fontan circulation (total cavopulmonary connection)
Infants younger than one year with congenital heart disease, who require surgical repair or catheterization (e.g. interventricular communication, atrioventricular septal defect, Fallot tetralogy)
Chronic cyanosis (oxygen saturation persistently <85%)
Severe cardiomyopathies that require drug therapy
Congenital heart disease and use of medications to improve cardiac function
Pulmonary hypertension that requires drug therapy
Patients undergoing cardiac transplantation
Congenital heart disease and comorbidities like chronic renal disease and chronic pulmonary disease

https://www.bcca-uk.org/documents/my_files/COVID_BCCA_Vulnerable_groups_FINAL-18_March_2020.pdf

Patients with cardiac implantable electronic devices (CIEDs)

Pacemakers (PM), implantable cardioverter defibrillators (ICDs) and cardiac resynchronization therapy (CRT).

The use of CIEDs *per se* does not imply an increased risk of unfavorable outcome in COVID-19. This risk depends essentially on the presence of structural heart disease.[13] In PM patients with neurally mediated syncope, for example, the prevalence of structural heart disease is low. On the other hand, in patients undergoing CRT, the presence of dilated cardiomyopathy and reduced left ventricular ejection fraction is a prerequisite for PM implantation and put them at high risk. In patients with ICDs, there are two possible scenarios: (1) patients with structural (anatomical) heart disease and (2) ultrastructural changes (electrical, mainly channelopathies). Although the prevalence of severe outcomes is higher in the first group, special considerations should be made for channelopathies.[5]

Patients with CIEDs and suspected or confirmed COVID-19

The real incidence and the types of cardiac arrhythmias that may be related to COVID-19 are not known.[13] A study[2] has reported a prevalence of 16.7%, 7% in ward patients and 44% in ICU patients

The pathophysiology of arrhythmias is complex and multifactorial. Due to few available data on the management of arrhythmias and ICDs in the context of the COVID-19 pandemic, consensus based on limited information and on treatment of arrhythmias associated with other conditions has been used. New information may become available at any time, since attention of all medical societies is turned to this infection.

The general principles of the management of patients with CIEDs during the pandemic are directed towards managing financial resources to provide adequate treatment of all patients with COVID-19, minimize the risk of in-hospital infection among noninfected patients and health care workers, and continue to provide high-quality emergency care for CIED patients with life-threatening arrhythmias.[13]

Cardiac arrhythmias in COVID-19 patients with CIED may occur in three situations:

1. Exacerbation of previous arrhythmias: in this case, the treatment of underlying disease and the use of antiarrhythmic agents are essential;
2. Arrhythmias caused by QT interval prolongation (TdP): in this case, it is recommended to correct electrolyte disturbances and hypoxemia; discontinue nonessential medications, evaluate the risk/benefit of the use of drugs that prolong the QT interval (such as chloroquine and azithromycin), and elevate heart rate (temporary PM insertion or reprogramming of permanent pacemaker by telemetry);
3. Development of new arrhythmias: after correction of systemic and metabolic causes, the presence of myocarditis, systemic inflammation, and myocardial ischemia should be considered.

The routine evaluation of patients with CIEDs should be postponed. In-person visits should be limited to patients with new symptoms (such as syncope, worsening of heart failure in patients on CRT, inappropriate shock delivery by ICDs), tonal or vibration alerts, suspicious of broken electrode, battery depletion, and abnormal heart rhythm (ICU, ward or remote monitoring).

Local protocols are recommended for the use of unique, dedicated programmers, with proper storage in designated areas, thorough cleaning before and after each use, and single-use personal protective equipment. Patient interview should be preferable performed via wireless communication technology, thereby avoiding person-to-person contact.

Invasive procedures using CIED should also be avoided until the infection is controlled and the patient shows clinical improvement.

Pacemakers

Although there are no reports on PM failure in COVID-19, possible situations of PM malfunction are listed in Table 2.

Implantable cardioverter defibrillators

Although there are no consistent data on the incidence of ventricular arrhythmias in COVID-19 patients, one center retrospectively reported an incidence of 5.9% of sustained VT and VF in hospitalized patients. Myocardial injury, diagnosed by elevation of Troponin I, was more prevalent in the subgroup of patients with malignant arrhythmias (17.3%) compared with the subgroup without malignant arrythmias (1.5%).[29] This finding suggests that the development of new malignant ventricular arrythmias is a marker of myocardial injury and indicates the need for antiviral treatment and a more aggressive immunosuppressive therapy. Patients receiving ICD for secondary prophylaxis may experience exacerbation of VT/VF episodes precipitated by COVID-19. In addition, despite the absence of data on patients with COVID-19, correlations between seasonal influenza activity with the incidence of ventricular arrythmias requiring therapy in patients with an ICD has been reported.[29] Based on the therapies delivered by the ICD, some situations may occur, and its differentiation may require electronic assessment (Table 3).

Cardiac resynchronization therapy (CRT)

There are no reports on failure of CRT or on the outcome of CRT patients in COVID-19. However, due to reduced LVEF, there is a greater risk of severe outcomes. Considering the worsening of LEFV during the course of disease, an electronic evaluation of CRT is needed. Besides, continuous electrocardiographic monitoring of multiple channels and its comparison with telemetry data is useful. Finally, programming of CRT by transthoracic echocardiography may be useful in nonresponders.

Table 2 – Possible pacemaker malfunction related to Covid-19.

Increased atrial stimulation rate	Relative bradycardia, similar to what has been reported in typhoid fever.[, 12] Prone ventilation may also cause a fall in heart rate.[26, 12]
Increased ventricular stimulation rate	In animal experiments, the coronavirus infection caused second-degree atrioventricular block (AVB), secondary to myocarditis and heart failure.[7] Some drugs used in the treatment of COVID-19 (e,g, chloroquine) may cause distal AVB.[7]
Increased stimulation threshold and loss of capture	Caused by electrolyte disturbances, hypoglycemia, hypoxemia, drugs, myocarditis, and inflammatory state. Electronic programming is required.
AHRE (Atrial High Rate Episodes)	Atrial arrhythmias, combined with hypercoagulability may increase the incidence of thromboembolic events. In addition to the $CHADS_2VASC_2$ score, a SIC (Sepsis-Induced Coagulopathy score) ≥ 4 and elevation of d-dimer (more than five times the normal level or > 3μg/mL)[28] should be used to determine the initiation of anticoagulation.
Need for reprogramming of the stimulation rate	Due to inflammatory state and/or TdP, an elevation of heart rate may be needed to meet the metabolic demand and inhibit the formation of ectopic foci. Stimulation rates of 90 - 110ppm are usually applied. Eventually, the magnet mode is turned on with application of a magnet over the pulse generator, which, in most PMs, leads to a stimulation frequency of 90-110ppm and may be an useful strategy when the electronic programming is not available.

Patients with CIEDs without suspected or confirmed Covid-19

Routine assessment

Whenever possible, remote monitoring of patients with CIED should be preferred during the COVID-19 pandemic. When the remote evaluation is not possible, in-person visits are recommended in the following situations:

- New symptoms (syncope, worsening of heart failure in CRT patients, and shock delivery by ICD);
- Tonal or vibration alerts;
- Suspicious of broken electrode;
- Battery depletion (based on last evaluation)
- Abnormal heart rhythm (ICU, ward or remote monitoring).

Invasive procedures

All patients should be considered potentially infected, and hence adequate protection and cleaning measures should be applied . Only in rare cases of patient and physicians with two consecutive negative PCR results within 48 hours, the facility is classified as free of COVID-19, and level A protection and cleaning measures should be routinely applied.[13]

Surgical procedures can be classified as urgent, semi-urgent and elective, according to the severity of the condition and time to surgery (Table 4).

Final Considerations

The SARS-CoV-2 infection can cause cardiovascular changes that culminate in arrhythmias or worse outcomes of patients with previous heart disease. There is a wide variety of cardiac rhythm disturbances, and their presence does not necessarily imply a worse prognosis for SARS-CoV-2-infected patients. Underlying cardiac disease, *i.e.* cardiac "health", is the main factor that influences cardiovascular outcomes. Likewise, there is no evidence that the presence of an electronic device *per se*, such as a PM or an ICD, is sufficient to influence the prognosis, without considering patient's cardiac condition.

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Table 3 – Possible effects of COVID-19 in patients with implantable cardioverter defibrillators

Inappropriate therapy	Sinus tachycardia, atrial tachyarrhythmias, internal interference (disruption of the electrode cable) and external interference (myopotentials, electromagnetic interferences). In these cases, treatment of the causes is required.
Sustained monomorphic ventricular tachycardia	Commonly seen in patients with structural heart disease. The treatment aims to inhibit the arrhythmogenic activities with amiodarone, beta-blockers, lidocaine, procainamide, cervical ganglion infiltration, radiofrequency ablation.
Polymorphic ventricular tachycardia in patients with channelopathies	Triggers should be corrected. *Brugada syndrome*: control fever; *Congenital long QT syndrome* (cLQTS): optimize the dose of beta-blockers, switch off stimulation algorithms that may cause pacing pauses (hysteresis, intrinsic atrioventricular conduction search), drugs that prolong QT interval, correct thyroid dysfunction. Catecholaminergic polymorphic ventricular tachycardia (CPVT): beta-blockers, flecainide; sympathomimetics and adrenergics should be used with caution.
Polymorphic ventricular tachycardia associated with QT prolongation (*Torsades de Pointes*)	Multifactorial disease, mainly secondary to drug-drug interaction: discontinue nonessential drugs that prolong QT interval, correct ions and hypoxemia, evaluate risk/benefit of chloroquine/azithromycin, elevate the heart rate to 90-110 bpm (attention: in contrast to pacemakers, the application of a magnet on ICD pulse generators has no effect on magnetic heart rate and temporarily deactivates anti-tachycardia therapies).
Polymorphic ventricular tachycardia associated with normal QT interval	Usually secondary to myocardial ischemia or myocarditis. Specific imaging tests are useful.

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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: Fagundes AA, Melo SL, Armaganijan LV, Kuniyoshi RR, Moraes LGB, Teixeira RA, Teixeira RA. Acquisition of data: Fagundes AA, Melo SL, Armaganijan LV, Kuniyoshi RR, Moraes LGB, Borges VAG, Scanavacca MI, Martinelli Filho M, Teixeira RA. Analysis and interpretation of the data: Fagundes AA, Melo SL, Armaganijan LV, Kuniyoshi RR, Moraes LGB, Borges VAG, Scanavacca MI, Martinelli Filho M, Teixeira RA. Writing of the manuscript: Fagundes AA, Melo SL, Armaganijan LV, Kuniyoshi RR, Moraes LGB, Borges VAG, Scanavacca MI, Martinelli Filho M, Teixeira RA. Critical revision of the manuscript for intellectual content: Fagundes AA, Melo SL, Armaganijan LV, Kuniyoshi RR, Moraes LGB, Teixeira RA. Supervision / as the major investigador: Teixeira RA.

Table 4 – Classification of surgical procedures in patients with implantable cardioverter defibrillators according to priority criteria

Urgent (days)	• Pacemaker implantation for symptomatic, high-degree atrioventricular block; • Pacemaker implantation for sinus node dysfunction with symptomatic pauses; • ICD implantation for secondary prophylaxis (recovered cardiac arrest or sustained ventricular tachycardia); • Replacement of pulse generators (PM/ICD) in dependent patient and in case of end-of-life battery; • Electrode revision in symptomatic patients; • Extraction of the electrodes due to infection.
Semi-urgent (< 3 months)	• Replacement of PM/ ICD/ CRT generator due to battery depletion detected by the elective replacement indicator (ERI); • ICD implantation for primary prophylaxis in high-risk patients; • PM implantation for sinus node dysfunction without pauses.
Elective (≥ 3 months)	• PM implantation for neurally mediated syncope; • ICD implantation for primary prophylaxis; • CRT implantation; • Upgrade to ICD; • Extraction of electrodes without infection; • Electrode revision in asymptomatic patients.

ICD: implantable cardioverter defibrillators; PM: pacemaker; CRT: cardiac resynchronization therapy

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BRIEF COMMUNICATION

Increased Maximal Expiratory Pressure, Abdominal and Thoracic Respiratory Expansibility in Healthy Yoga Practitioners Compared to Healthy Sedentary Individuals

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Abstract

Background: Increasing thoracic expansion is effective at reducing blood pressure in hypertensive subjects. Yoga prescribes many respiratory techniques with a growing number of practitioners. However, very little is known whether sedentary or yoga practitioners show measurable differences in their respiratory patterns.

Objective: This study aims to demonstrate differences between healthy sedentary individuals and healthy yoga practitioners regarding maximal respiratory pressures and thoracic and abdominal respiratory expansibility.

Methods: Maximal inspiratory and expiratory pressures (MIP and MEP, respectively) were evaluated by manovacuometry, while respiratory expansion was assessed by the cirtometry of abdominal (CA), thoracic xiphoidal (CTX), and thoracic axillary (CTA) circumferences at rest (end expiratory moment) and at full inspiration in healthy sedentary individuals (SED) and yoga practitioners (YOGA). A *delta* derived from rest and full inspiration measures (ΔCA, ΔCTX, and ΔCTA, respectively), followed by a percentage of each item (ΔCA/CA, ΔCTX/CTX, and ΔCTA/CTA) was then calculated. Groups were compared by means of an unpaired Student's t-test, with a significance level $p < 0.05$.

Results: All respiratory expansion measures were significantly higher in in the YOGA group. A significantly higher MEP (cmH_2O) was also detected in yoga practitioners: SED 89.3 ± 19.3 and YOGA 114.7 ± 24.8 ($p = 0.007$), along with decreased heart rate at rest (bpm): SED 84±6 and YOGA 74±15 ($p = 0.001$).

Conclusions: Yoga practitioners have shown greater thoracic and abdominal expansion and increased MEP, when compared to healthy sedentary individuals, as well as significantly lower heart rates at rest and body mass index (BMI). However, whether or not these findings are related to respiratory patterns is uncertain.

Keywords: Yoga; Breathing Exercises; Sedentarism; Maximal Respiratory Pressures; Heart Rate; Blood Pressure.

Background

Respiratory exercises have proven to be an effective non-pharmacologic intervention for the treatment and prevention of hypertension[1] and psychological states, such as anxiety and depression.[2] However, not much has been demonstrated concerning respiratory patterns that could be considered critical parameters for health issues.

Most respiratory evaluations are related to pulmonary function (spirometry) or respiratory muscle strength (maximal inspiratory and expiratory pressure) and made by means of a mouth device that could interfere with most people's natural breathing.[3] Abdominal cavity and rib cage movements involved in respiration have the potential to be evaluated (piezoelectric belts), but

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there is no scientific consensus as to acceptable values, on the variation of respiratory movements at rest and in an orthostatic position, or in differences between healthy individuals and those presenting pathologies or comorbidities.

Rib cage expansion assessed by cirtometry has been used to evaluate responses to a one-month respiratory exercise program involving hypertensive subjects and has demonstrated not only enhanced thoracic expansion, but also lower blood pressure and increased heart rate variability, a reliable index of vagal modulation.[4]

Yoga is an ancient philosophy based on physical and non-physical techniques to reach an elevated state of consciousness. Among the physical components, respiratory exercises, or *pranayamas*, are known to influence both physiological and psychological states, and are widely practiced by its adherents.[5]

Therefore, the aim of this study was to investigate whether differences in abdominal and rib cage expansion and maximal inspiratory and expiratory pressures could be found between yoga practitioners and healthy sedentary individuals.

Methods

Study Design

A cross sectional study approved by the local ethics committee (UP 4802/12) took place at the Clinical Investigation Laboratory of Instituto de Cardiologia do Rio Grande do Sul, in Porto Alegre, Brazil, from July to October 2014. Healthy yoga practitioners, constituting the Yoga group (YOGA), and healthy sedentary individuals, constituting the Sedentary group (SED), were recruited from the social media network. They were to be between 20 and 47 years of age, non-smokers, and non-obese (BMI ≤ 29.9). Additionally, they were to have practiced yoga at least twice a week for at least one year (YOGA) or not engaged in any form of exercise at all (SED). If they met the inclusion/exclusion criteria, they were sent information on the study and invited to participate. All participants signed an informed consent and were assessed between 2:00pm and 4:00pm on weekdays.

Evaluations and Measurements

Systolic and diastolic blood pressure (SBP and DBP, respectively) and resting heart rate (HR) were assessed in accordance with Brazilian Hypertension Guidelines (OMROM Automatic Blood Pressure Monitor Model HEM-711).

Respiratory rates were assessed by three consecutive measures at rest in the supine position, using the visual method. The mean of three values was considered for analysis. Maximal inspiratory and expiratory pressure (MIP and MEP, respectively), as performed by manovacuometry (Globalmed MDI Model MVD 300) with five measurements of each variable and then taking the mean of the values, was also considered for analysis.

Based on the method applied by Pinheiro, et al.[4], measurements of circumferences at rest, including respiratory maneuvers, were used to detect respiratory expansion at three different levels of the abdomen and thorax. Abdominal expansion was taken at the mean distance between the iliac crest and the last rib, and thoracic expansion was measured in the xiphoidal process and at the axillary level. Measurements were taken in the orthostatic position after full exhalation and at maximal inspiratory retention. Three consecutive measures have been taken and the mean of these has been considered for analysis. A delta was derived from the resting and full inspiration measurements (ΔCA, ΔCTX, and ΔCTA, respectively) to standardize measurements as a percentage of expansion, and a percentage of each item (ΔCA/CA, ΔCTX/CTX, and ΔCTA/CTA) was then calculated.

All measurements were taken by the same trained investigator.

Statistical Analysis

As a novel approach to investigative study, this study has gathered a convenience sample of subjects. Collected data have been processed by the SPSS 25.0 for Windows. Normality of data have been tested by the Kolmogorov–Smirnov test, and all variables fulfilled normality criteria. Groups were compared by means of an unpaired Student´s t-test. Data are presented as the mean (M) ± standard deviation (SD) for a significance level of $p < 0.05$.

Results

Twenty-six individuals were enrolled in YOGA (n = 15) and SED (n=11). No significant differences were observed between the two groups in terms of age, systolic and diastolic pressure, and respiratory rate. However, the BMI was significantly lower in YOGA than SED: 22.5 ± 2.0

versus 25.3 ± 2.2 (p = 0.031). The waist-height ratio proved to be higher in SED than in YOGA (0.5 ± 0.05 versus 0.4 ± 0.03 p = 0.004). The resting heart rate was lower in YOGA than in SED (74±15 beats per minute versus 84±6 beats per minute, p = 0.031). No significant differences were found in respiratory variables between the groups for MIP, but YOGA presented a significantly higher MEP than in SED: 114.7 ± 24.8 cmH_2O versus 89.3 ± 19.3 cmH_2O (p = 0.009). All values for abdominal and thoracic expansion were significantly higher in YOGA than in SED. Results are summarized in Table 1.

Discussion

This study demonstrated that the MEP was significantly higher in YOGA than in SED, although there were no differences in the MIP and respiratory rate between the two groups, which is in accordance to another study that showed no changes in respiratory rates among healthy individuals after eleven months of yoga.[6]

The main finding of this study was that all respiratory movements of the abdominal cavity and rib cage assessed by cirtometry were significantly greater in YOGA than in SED. This calls attention to the fact that the inspiratory abdominal values of the SED group were lower than at rest, suggesting a squeezing displacement of the abdominal cavity to attend inspiratory demands. Electromyographic analysis demonstrated greater demands of the abdominal muscles during respiration in the orthostatic position, when compared to the supine position, which suggests that this "maneuver" of squeezing the abdominal cavity as a synergistic action of these muscle and diaphragm is supposed to happen in healthy individuals.[7] The respiratory muscle pump for venous return is well described in the literature,[8] which could be related to the lower resting heart rate found in

Table 1 – Characterization of participants

	SED (n=11)	YOGA (n=15)	p
Age (years)	33.2 ± 8.7	36.8 ± 7.4	0.315
SBP (mmHg)	117.8 ± 7.7	113.1 ±7.4	0.185
DBP (mmHg)	75.3 ± 8.9	72.3 ±5.5	0.297
HR (bpm)	84 ± 6	74 ± 15	0,031*
RR (cpm)	11.9 ± 6.5	11.0 ± 3.9	0.658
BMI (kg/m^2)	25.3 ± 2.2	22.5 ± 2.0	0.031*
W-H ratio	0.5 ± 0.05	0.44 ± 0.03	0.004*
Δ CA (cm)	-0.67 ± 1.4	1.3 ± 1.8	0.007*
ΔCA/CA	-0.09 ± 0.02	0.02 ± 0.03	0.008*
ΔCTX (cm)	1.3 ± 1.1	4.0 ± 1.7	0.002*
ΔCTX/ CTX	0.02 ± 0.01	0.06 ± 0.04	0.002*
ΔCTA (cm)	2.08 ± 1.08	3.23 ± 1.74	0.028*
ΔCTA/CTA	0.02 ± 0.01	0.04 ± 0.01	0.012*
MIP (cmH_2O)	78.3 ± 18.8	91.2 ± 29.9	0.161
MEP (cmH_2O)	89.3 ± 19.3	114.7 ± 24.8	0.009*

SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, HR: Heart rate at rest, bpm: beats per minute, RR: Respiratory rate at rest, cpm: cycles per minute, BMI: Body Mass index, W-H ratio: Waist-Height ratio, Δ CA: Delta value from rest and full inspiration measures for abdominal circumference ΔCA/CA percentage value of expansion of abdominal circumference, ΔCTX: Delta value from rest and full inspiration measures for xiphoidal circumference, ΔCTX/ CTX: percentage value of expansion of xiphoidal circumference, ΔCTA: Delta value from rest and full inspiration measures for axillary level thoracic circumference, ΔCTA/CTA: percentage value of expansion of axillary level thoracic circumference, MIP: Maximal Inspiratory pressure, MEP: Maximal expiratory pressure.

** Significant differences between groups after Student´s t-test ($p < 0.05$)*

YOGA as compared to SED.[9] To what extend HR can be modified by yoga respiratory techniques warrants further investigation.

No differences between the groups was detected in SBP or DBP. Nevertheless, the waist-height ratio, as a marker of abdominal fat and cardiovascular risk[10] and BMI, were significantly lower in YOGA. Whether or not these differences have been determining factors for differences found in other outcomes demands further elucidation, and whether or not these findings are related to respiratory pattern is still uncertain.

Furthermore, it is unclear whether the cirtometry of respiratory movements may be considered an accurate method to analyze breathing patterns and contribute to the early detection of improper respiratory patterns. Hence, more studies are needed to explain the effects of yoga and its respiratory exercises on healthy individuals.

As a limitation, this study has not tested the reproducibility and reliability of cirtometry evaluations.

Conclusion

MEP, abdominal and thoracic expansion were significantly enhanced in yoga practitioners as compared to sedentary individuals. The resting heart rate and BMI were also significantly lower in the former group. As no significant differences were detected in the respiratory rate, it is plausible to question whether or not the respiratory pattern rather than the respiratory rate may be modified by yoga.

Author contributions

Literature search: Fetter C, Souza LA and Schein A. Conception and design of the research: Fetter C, Dartora DR, Casali K and Irigoyen MC. Acquisition of data: Fetter C, Souza LA, Schein A and Casali K. Analysis and interpretation of the data: Fetter C, Dartora DR and Eibel B. Writing of the manuscript: Fetter C, Eibel B and Souza LA. Critical revision of the manuscript for intellectual content: Dartora DR, Casali K and Irigoyen MC.

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 IC/FUC under the protocol number 4802/12. 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

Breathing and Cardiovascular Patterns: What can we Learn from Respiratory Exercises?

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Editorial referring to the article: Increased Maximal Expiratory Pressure, Abdominal and Thoracic Respiratory Expansibility in Healthy Yoga Practitioners Compared to Healthy Sedentary Individuals

In the current issue of the International Journal of Cardiovascular Sciences, Fetter and colleagues[1] found that respiratory movements of the abdominal cavity and rib cage, evaluated by circumferences measurements, were higher in Yoga practitioners than in an age-matched sedentary group. Also, the study confirmed that Yoga practitioners showed higher maximal expiratory strength and lower heart rate at rest than non-practitioners.

Yoga has been recommended as a non-pharmacological therapy to control cardiovascular risk factors.[2] Respiratory exercises are part of the Yoga program that includes abdominal and rib cage expansion by rhythmic movements.[1-3] It was demonstrated that four months of Yoga respiratory training improved inspiratory and expiratory muscle strength, forced vital capacity and quality of life in healthy elderly. Another study demostrated that Yoga influenced cardiorespiratory control, affecting the resting sympatho-vagal balance, with a shift from vagal to sympathetic predominance, reflecting a sympathetic withdrawal.[3] Several disease subsets are marked by autonomic dysfunction characterized by sympathetic overactivity at rest, and in this context, respiratory exercises such as Yoga may be a potential countermeasure.

Keywords

Breathing; Cardiovascular Diseases; Breathing Exercises; Yoga; Physical Therapy Modalities; Continuity of Patient Care.

As regards respiratory influences on hemodanymic, acute changes in spontaneous respiratory pattern at rest[4,5] or during orthostatic stress[5] cause a great impact on cardiovascular and cerebrovascular regulation. These changes seem to be influenced by a combination of neural and non-neural mechanisms, such as changes in heart rate variability, respiratory sinus arrhythmia,[4,6] and mechanical contributions of the respiratory muscle pump on venous return, stroke volume, and cardiac output.[5]

Inspiratory muscle training (IMT) is another respiratory training modality that was proposed in the current literature as a plausible method to improve respiratory muscle strength in healthy individuals and patients with cardiovascular and respiratory diseases. Recently, it was suggested that IMT is a feasible method to enhance cardiovascular control at rest[6-8] and post-exercise,[6] and cerebrovascular and postural control during orthostatic stress[9] in older women. In particular, IMT reduced postural instability and the time to cerebral blood flow recovery in the initial phase of orthostatic stress,[9] suggesting that IMT could be a potential intervention to prevent fall accidents in this population.

Therefore, further studies could investigate the impact of novel combinations of breathing maneuvers during respiratory exercise programs, on putative mechanisms of changes in spontaneous breathing patterns, and of cardiovascular and cerebrovascular responses in healthy and cardiopulmonary disease individuals. Thus, answering the question posed in the title, we are still learning about respiratory and cardiovascular patterns from respiratory exercise programs.

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VIEWPOINT

Physical Exercise, Energy Expenditure and Weight Loss: An Assumption not Always Observed in Practice

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The increased prevalence of overweight and obesity observed in recent decades has been attributed mainly to behavioral changes, such as excessive food consumption and reduction in physical activity level over time, leading to a positive energy balance. Due to the technological advances in recent years, less physical effort is required to perform daily tasks. Moreover, the lifestyle has become more sedentary, with an increasing amount of time spent using digital gadgets, such as computers, televisions and mobile phones. However, Westerterp & Speakman[1] did not find a decrease in physical activity energy expenditure during the last 30 years preceding their study, despite an increase in the prevalence of obesity.[1] Other studies have also reported that the total energy expenditure of rural populations was similar to that of populations living in developed countries, despite the clear difference in behavioral patterns, particularly in relation to daily physical activities.[2-4] This study aimed at presenting the "compensatory effect" as a possible explanation for these findings. When there is an increase in physical activity at a given time, behavioral and metabolic changes take place to maintain an energy setpoint, as presented below.

Physical exercise has been recommended as an important component for the prevention and treatment of obesity. For substantial adults' health benefits, at least 150 minutes of moderate-intensity aerobic exercise, or 75 minutes of vigorous-intensity aerobic exercise; in addition, 2-3 times per week of resistance training is recommended.[5] However, for a clinically significant reduction in body weight, Donnelly et al.,[6] recommended that individuals should gradually increase the amount of physical activity and achieve a weekly volume of moderate physical exercise of over 250 minutes.[6] The authors also reported a dose-response effect between physical activity and weight loss.

It is believed that the greater amount of physical exercise (duration and intensity), the higher the total energy expenditure, and consequently, greater loss of body weight. However, energy expenditure through exercise does not explain the variation in body weight observed in the long term. Several studies have shown a weight loss below the expected levels,[7,8] even in controlled studies with a high rate of patient compliance.[9,10] These results do not support the classic additive relationship between physical exercise and energy expenditure, thereby raising questions about the real impact of this strategy on weight control.[8,11]

Some theories have tried to explain the reason for lower-than-expected weight loss and the difficulty in maintaining it over time with increased physical activity. In 1998, Rowland proposed the "activitystat" theory and defined it as a homeostatic mechanism, wherein a biological control center would be responsible for controlling the physical activity (or energy expenditure), similarly to other biologically controlled variables such as body temperature.[12] Whenever an imbalance occurs, the regulatory mechanisms are activated to restore a particular setpoint. According to this theory, an increase

Keywords

Energy Metabolism; Exercise; Weight loss Programs; Overweight; Sedentary behavior; Lifestyle.

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in the amount of physical activity at one time would be compensated with less physical activity at another time, to reestablish the balance of the system. This compensatory effect on subsequent spontaneous physical activities has been observed in several studies in children, elderly individuals, and young adults;[13-15] however, other studies do not corroborate these findings .[16]

Aligned with this theory and in contrast to the classic "additive model," Pontzer et al. (2016) proposed the "restricted model" to explain the relationship between energy expenditure and physical activity.[17] According to this model, an individual's metabolism adapts in response to the increased physical activity, and above a specific "critical point," the increase in physical activity volume does not cause a concomitant increase in energy expenditure. According to the authors, this compensatory effect can be explained by behavioral (longer periods of sitting than standing or less fidgeting throughout the day compared to a period with no exercise) or metabolic changes (decreased resting metabolic rate, increased muscle efficiency for the same activity demand, or even hormonal changes, such as a decrease in estrogen and testosterone production, and a decrease in the activities of the immune system).[17]

This compensatory phenomenon in relation to physical activity is also observed in some species of birds and mammals. The "energy budget" of these animals is also limited, and any increase in energy expenditure to maintain the basal metabolism would leave a less amount of energy available for other functions, such as flying, fighting, or hunting.[18]

The effect of physical exercise in reducing body weight is further impaired due to compensatory responses on the other side of the energy balance. Martin et al. [16] observed that overweight individuals submitted to high volumes of physical exercise (1760 Kcal/week) for a period greater than six months showed increased appetite and caloric intake compared to the moderate exercise group (700 Kcal/week) and the group without exercise. These results were corroborated by Myers et al.,[19] who also observed increased hunger and food intake after 12 weeks of daily physical training (5 x 500 Kcal/week).[19]

Although these compensatory responses are frequently reported in clinical and epidemiological studies, there is significant interindividual variability in weight loss .[20] In a study conducted by McNeil et al. (2017) to evaluate the compensatory effect of exercise in 530 postmenopausal women, the authors observed that 9% of women lost more weight than expected after 12 months of moderate exercise (150, 225, or 300 minutes per week); 20% compensated between 0 and 50%, indicating weight loss lower than expected; around 44% compensated between 50% and 100%, and 27% of women presented compensations above 100%, gaining weight at the end of the intervention. [21] The mechanisms by which individuals respond in such a diverse way to the same stimulus are still a matter of debate; moreover, this compensatory effect seems to be asymmetric, with more intense forces resisting weight loss compared to those acting in response to weight gain.

Therefore, a linear relationship between the prescribed energy deficit and the achieved weight loss should not be assumed. The regulation of the energy balance seems to be a complex and dynamic process, wherein a disturbance in one component can trigger changes in one or more components of energy expenditure and/or food intake. The relationship between individual characteristics (age, sex and nutritional status) and the variables of physical exercise (type of exercise, frequency, intensity and duration) with the compensatory mechanisms requires investigation, as well as the physiological mechanisms responsible for these changes.

The discussion needs to go beyond "eat less and exercise more." Rather, the focus should be on understanding the causal factors and mediating mechanisms for the relationship between physical exercise (and/or diet) and weight loss. Identifying factors that resist weight loss maintenance in some individuals, thereby "disrupting" the entire (or partial) effort, is necessary. Based on the compensatory effects discussed here, the expectation of reducing obesity with programs based exclusively on physical activity should be reduced.[8] However, regardless of the achieved weight loss response, the health benefits associated with regular physical activity are quite significant, as reported in the literature, and the adoption of an active lifestyle with a decrease in sedentary behaviors should be categorically encouraged.

Long-term clinical trials are still necessary for a better understanding of the effect of physical exercise on energy expenditure, food intake, and body weight, and to identify factors (physiological and behavioral) related to the different responses presented by the individuals. The key question is no longer "if" the compensatory effect occurs, but rather "when," "how," and "what" are the individual characteristics that increase the susceptibility to this phenomenon.

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Author Contributions

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VIEWPOINT

A Probable Relationship between Physical Exercise and COVID-19 Mediated by the Renin-Angiotensin-Aldosterone System

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At the end of 2019, a novel human virus (SARS-CoV-2) causing severe acute respiratory syndrome (SARS) expanded globally from China. In February 2020, the World Health Organization (WHO) officially named this infectious disease coronavirus disease 2019 (COVID-19), and in March 2020, WHO announced COVID-19 a global pandemic. In June 2020, according to an interactive web-based dashboard to track COVID-19 in real time developed by the Johns Hopkins University Center for Systems Science and Engineering (https://www.eficiens.com/coronavirus-statistics/), more than 7 million people infected with the new coronavirus and more than 400,000 deaths were confirmed around the world.[1] China and European countries have found solutions to manage and reduce the number of daily infections. However, new COVID-19 cases have risen at alarming rates in many other countries, and today Brazil is the third country in number of cases.[2]

Recently, angiotensin-converting enzyme 2 (ACE2) was identified as an entry receptor for SARS-CoV-2. The binding of the novel coronavirus to ACE2 can reduce (downregulation) the number of ACE2 receptors, causing severe damage to alveolar cells that triggers a series of pulmonary and respiratory reactions that can lead to death.[3,4]

ACE2 is part of a complex and integrated metabolic pathway known as the renin-angiotensin-aldosterone system (RAAS), which has been the target of several studies that describe physiological adaptations induced by physical exercise. Thus, given the potential role of ACE2 in the pathophysiology of coronavirus infection, this scientific letter sought to establish a probable relationship between physical exercise and COVID-19 through the RAAS and thereby add a contribution to studies on the management and prevention of COVID-19.

Keywords

COVID-19; Betacoronavirus; SARS-CoV2; Severe Acute Respiratory Syndrome; Pandemics; Renin-Angiotensin System; Exercise/prevention and control.

The Pathways of the RAAS

The classical pathway of the RAAS is initiated by the release of angiotensinogen by the liver, which, combined with renin secreted by the kidneys, produces angiotensin I (Angio I). Angio I is converted to angiotensin II (Angio II) by the action of the angiotensin-converting enzyme (ACE) in the lungs. The physiological effects of Angio II are mediated primarily through membrane receptors, especially of the Angio II type 1 (AT1) receptor. These receptors, when stimulated, promote vasoconstriction, hypertrophy and hyperplasia of vascular cells, sodium retention, generation of reactive oxygen species (ROS), and inflammatory, thrombotic and fibrotic processes, which can cause tissue damage.[5]

A counter-regulatory pathway of the RAAS involves the conversion of Angio II to angiotensin 1–7 (Angio-1–7) and membrane receptors (MAS) through the enzymatic activity of angiotensin-converting enzyme 2 (ACE2), which promotes a vasodilatory, anti-inflammatory, anti-fibrotic, and anti-proliferative effect on the tissues.[6] Under appropriate physiological conditions, there is a balance between these two RAAS pathways (Figure 1).

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Physical Exercise and the RAAS

Previous studies, especially experimental studies, have shown that physical exercise can reduce the activation of the classic RAS pathway and increase the activation of the components of the counter-regulatory pathway (ACE2/Angio-1–7/MAS) (Figure 2).[7-13]

However, the literature is still scarce about the effects of physical exercise on the ACE2/Angio-1–7/MAS pathway, mainly on ACE2 (the primary receptor site of SARS-CoV-2). In short, it was shown in rodents that physical exercise increased the expression of MAS receptors in aortas, thereby improving the vasodilatory effect of Angio-1–7.[9] Deficiency of ACE2 has been shown to be related to impaired physical performance and adaptations of the cardiac and skeletal muscles.[10] In addition, swimming improved oxidative capacity[11] and sensitivity to insulin in muscle tissue,[12] and in all these studies, a role of the ACE2/Angio-1–7/MAS pathway has been suggested to be involved in the adaptive process. In humans, it was shown that aerobic physical exercise acutely increased the activity of the ACE2/Angio-1–7/MAS pathway, leading to increased plasma and urinary levels of ACE2, especially with a continuous moderate exercise protocol.[13]

In addition, evidence from genetic studies have shown the relationship between physical exercise and RAAS modulation. Among the main findings, it has been highlighted that physical exercise affects the cardiovascular system, by lowering blood pressure, inhibiting the interactions between ACE, Angio II, and AT1 receptors activated by the classical RAAS pathway, and increasing the expression of ACE2.[14,15]

COVID-19 and Physical Exercise

The lethality of COVID-19 has been associated with a decrease in the number of ACE2 receptors, impairing the activation of this important lung-protective protection pathway.[3,4] With less ACE2 available to convert Angio II to Angio-1–7, preventing the anti-inflammatory and anti-fibrotic effects of the ACE2/ Ang-(1-7)/Mas pathway, more angiotensin is produced via the ACE/Ang-I/AT1 pathway, leading to a heightened inflammatory milieu and lung damage.[16]

With respect to therapeutic research on COVID-19, at least three clinical approaches targeting ACE2 receptors have been described: vaccines, Angio II receptor blockers, and by increasing the levels of the soluble form of ACE2.[4]

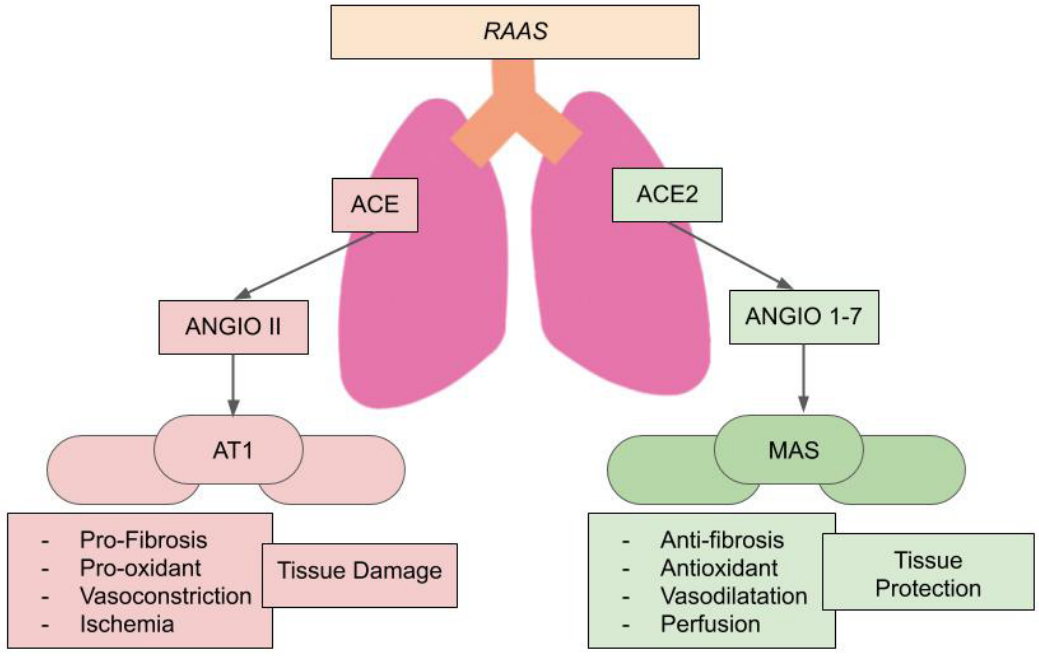

Figure 1 – Balance between the two pathways of the renin-angiotensin-aldosterone system (RAAS) and their general effects. Classical pathway: ACE: Angiotensin-converting enzyme; ANGIO II: Angiotensin II; AT1: Membrane receptors for Angio II; Counter-regulatory pathway: ACE2: Angiotensin-converting enzyme 2; ANGIO 1-7: Angiotensin 1-7; MAS: Membrane receptors for Angio 1-7.

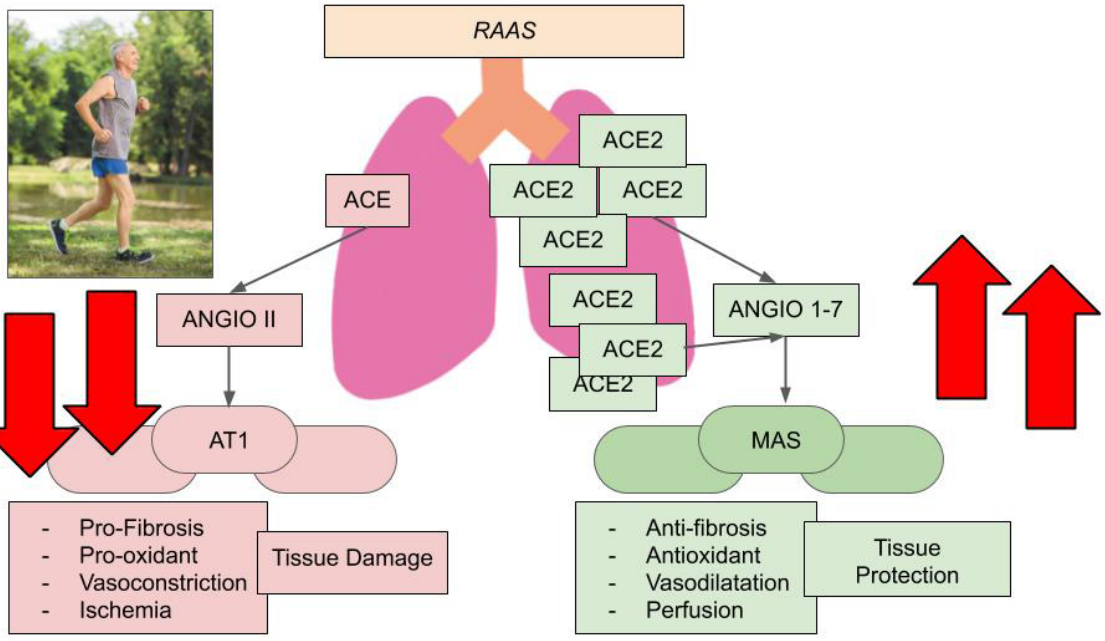

Figure 2 – Possible effect of physical exercise on the two pathways of the renin-angiotensin-aldosterone system (RAAS); classical pathway: ACE: Angiotensin-converting enzyme; ANGIO II: Angiotensin II; AT1: Membrane receptors for Angio II; Counter-regulatory pathway: ACE2: Angiotensin-converting enzyme 2; ANGIO 1-7: Angiotensin 1-7; MAS: Membrane receptors for Angio 1-7. Down arrows indicate downregulation and decreased activation. Up arrows indicate upregulation and increased activation.

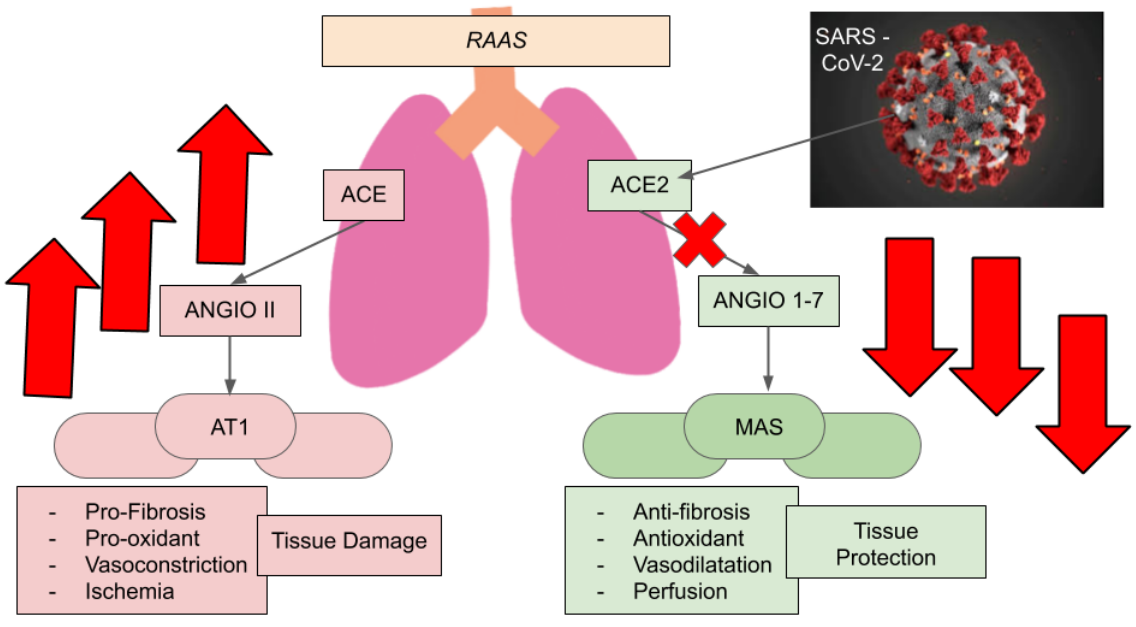

Figure 3 – Effect of coronavirus disease-2019 (COVID-19) on the two pathways of the renin-angiotensin-aldosterone system (RAAS); classical pathway: ACE: Angiotensin-converting enzyme; ANGIO II: Angiotensin II; AT1: Membrane receptors for Angio II; Counter-regulatory pathway: ACE2: Angiotensin-converting enzyme 2 (receptor site for the new coronavirus); ANGIO 1-7: Angiotensin 1-7; MAS: Membrane receptors for Angio 1-7. Down arrows indicate downregulation and decreased activation; up arrows indicate upregulation and increased activation.

This last strategy has been suggested based on the fact that soluble ACE2 could prevent the binding of the coronavirus to the full-length ACE2, and thereby not only neutralize the virus but also rescue ACE2 cellular activity, counter-regulating RAAS and protecting pulmonary tissue.[17]

Thus, based on the above, the potential link between physical exercise and COVID-19 is the following: while the new coronavirus is capable of compromising the ACE2/Angio-1–7/MAS pathway (Figure 3), physical exercise would be able to stimulate it, and hence prevent the RAAS imbalance and associated lung injury.[18]

In addition, considering that (I) chronic diseases, such as diabetes, obesity, dyslipidemia and hypertension, are important risk factors that increase the lethality of COVID-19, (ii) the elderly population is the group with the highest COVID-19 mortality rates,[3] (iii) the aging process reduces the expression of ACE2, and the classical pathway of RAAS is involved in the pathophysiology of many chronic diseases , and that (iv) there is scientific evidence supporting the benefits of regular physical exercise for the elderly population and people with chronic non-transmissible diseases,[19,20] a protective effect of physical exercise against the effects of COVID-19 may be suggested.

However, until now, there has been no scientific study evaluating the preventive effects of exercise on COVID-19 or studies with patients with COVID-19 submitted to physical exercise. In fact, the American College of Sports Medicine (ACSM) recently published a brief position recommending that people exercise during the COVID-19 pandemic.[21]

Given the scientific basis presented here, it seems reasonable to consider a protective effect of physical exercise in relation to COVID-19, by restoring or maintaining an appropriate balance between the classical and counter-regulatory pathways of the RAAS. Future studies are needed to clarify the relationship between physical exercise and COVID-19. For now, in addition to the widespread use of preventive measures, such as the correct hand washing, use of gel alcohol and face masks, and social isolation/distancing, physical exercise should also be considered for COVID-19 prevention.

Author Contributions

Conception and design of the research: Souza RA, Nakamura PM, Teixeira IP, Souza MT, Passoni WH. Analysis and interpretation of the data: Souza RA, Nakamura PM, Teixeira IP, Souza MT, Passoni WH. Writing of the manuscript: Souza RA, Nakamura PM, Teixeira IP, Souza MT, Passoni WH. Critical revision of the manuscript for intellectual content: Souza RA, Nakamura PM, Teixeira IP, Souza MT, Passoni WH.

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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Study Association

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CASE REPORT

Aborted Sudden Death Due to Severe Ventricular Arrhythmia in Timothy Syndrome

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Abstract

Timothy Syndrome is a rare autosomal dominant multisystem genetic condition. The CACNA1C gene, codifier of the CaV1.2 calcium channel, is affected, resulting in the loss of voltage-dependent calcium channel inactivation. Relevant clinical characteristics: (1) corrected QT interval greater than 480ms; (2) syndactyly. Death often occurs during childhood, and results from ventricular tachyarrhythmias. This study presents the case of a female newborn who suffered a cardiorespiratory arrest, secondary to ventricular arrhythmia. A prolonged QT interval, combined with 2:1 AV block, was also identified, requiring a definitive cardiac pacemaker implant that, during inpatient care, developed pulmonary sepsis, followed by death.

Introduction

Timothy Syndrome (TS) or LQTS8, is a very rare multisystem genetic condition (incidence: $1.5/10^{8}$)[1], first reported in 1992.[2] The inheritance pattern is autosomal dominant,[3] and it is caused by a de novo missense mutation in exon 8A.[4] TS type 2 stems from a missense mutation on an alternatively spliced exon 8, with different phenotypical expression, which will not be addressed in this work. TS is easily identifiable, as the typical phenotype permits a very high degree of clinical suspicion long before the results of confirmatory genetic testing are available.

Characterized by high mortality, and an average age of death at 2.5 years, TS represents a diagnostic challenge.[5] Mortality in TS is considered multifactorial and sudden cardiac death is the main cause of death.[6] The most reliable clinical evidence available on the subject is level 4,[7] i. e. case series.

The pathogenic variant of the CACNA1C (p.Gly406Arg) can be identified through molecular testing.[8] It encodes the calcium channel Cav1.2, a voltage-dependent L-type channel, capable of increasing the cytosolic ion concentration and of triggering cell excitation. This fact justifies the sustained calcium depolarization currents during the plateau phase and the prolonged QT interval. Thus, arrhythmogenesis in TS derives from the lack of Cav1.2 inactivation.[9]

With the prolonged depolarization of the ventricular myocytes, early afterdepolarizations surge. Initially, they manifest as ventricular extrasystole and later as ventricular tachycardia (VT).[10] Once converted into a functional reentry circuit, this electrical activity can degenerate into a polymorphic ventricular tachycardia, culminating in sudden death.[11]

Knowledge, expertise, and solid academic grounding on clinical manifestations of TS contribute to early diagnosis, as well as to the prevention of negative outcomes. TS patients also demand specialized care during anesthetic induction, due to a specifically increased risk of malignant arrhythmias in this group.[12] The aim of this work is to report a case of a newborn that presented VT, associated with the prolongation of the QT interval and phenotypic manifestations of TS.

Keywords

Long QT Syndrome; Syndactyly/genetics; Arrhythmias Cardiac/complications; Death Sudden; Child.

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Case Report

This study examined a female child, born at term, with a birth weight of 3020g, 40 weeks old, presenting syndactyly in hands and feet and posteriorly identified long QT interval (Figure 1).

At the age of 5 days, the patient presented cardiorespiratory arrest (CRA), secondary to VT. After electrical cardioversion, a prolonged QT interval was identified, intercalated with 2:1 AV block and hypoglycemic episodes. The transthoracic echocardiogram (TTE) revealed an ejection fraction at 53% and a structurally normal heart. At the age of 21 days, a dual chamber epicardial pacemaker was implanted.

Two days after surgery, the patient developed respiratory discomfort. The X-ray showed a large chylothorax pleural effusion to the right, followed by thoracic drainage. The patient was sedated and put under mechanical ventilation support, propranolol (5.0mg/kg/day), furosemide (infusion at 0.2 mg/kg/h), and antimicrobial prophylactic therapy with cefazolin and vancomycin. No neurological abnormalities were observed.

For presenting tachyarrhythmia in the pre and postoperative periods, the patient was admitted to a quaternary care hospital, where the device was electronically programmed in DDD mode (Figure 2). Beta-blocker therapy was maintained, and clinical follow-up was provided.

At the age of 44 days, the patient presented assisted CRA in asystole. At this point, proper care was provided, and the CRA was reversed. TTE revealed mild right ventricular hypertrophy. During hospitalization, the patient developed pulmonary sepsis and died.

Discussion

The CACNA1C mutated gene is expressed in multiple cell types,[13] and the clinical presentation may vary. However, special attention should be driven to core findings: a QTc interval of greater than 480ms and syndactyly, which can be cutaneous or skeletal, uni or bilateral, of hands or feet.[14] As displayed on Figure 1, the first finger is spared, while only the second and third toes are usually affected.[12]

Many patients express facial dysmorphisms, such as flat nasal bridge, receding upper jaw, low auricular

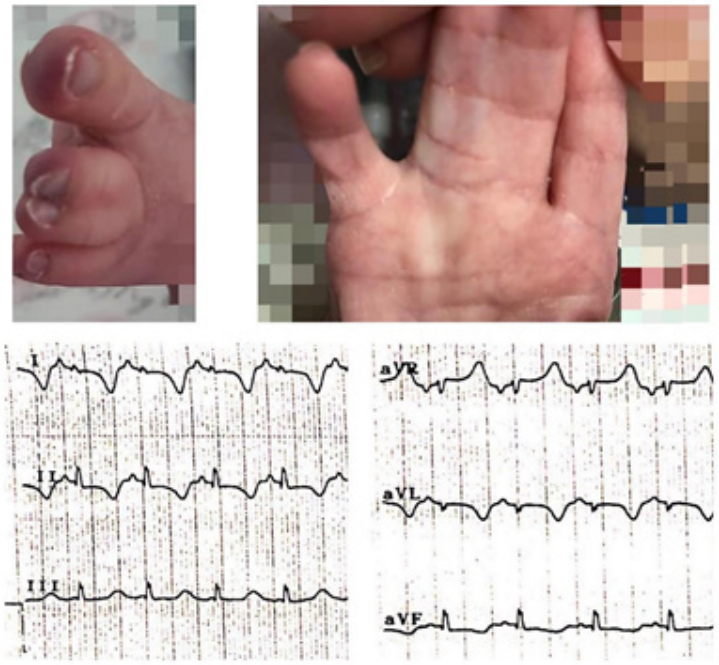

Figure 1 – Superior section: syndactyly of foot and hand, respectively. Inferior section: ECG shows long corrected QT (QTc-interval: 514ms) in peripheral leads.

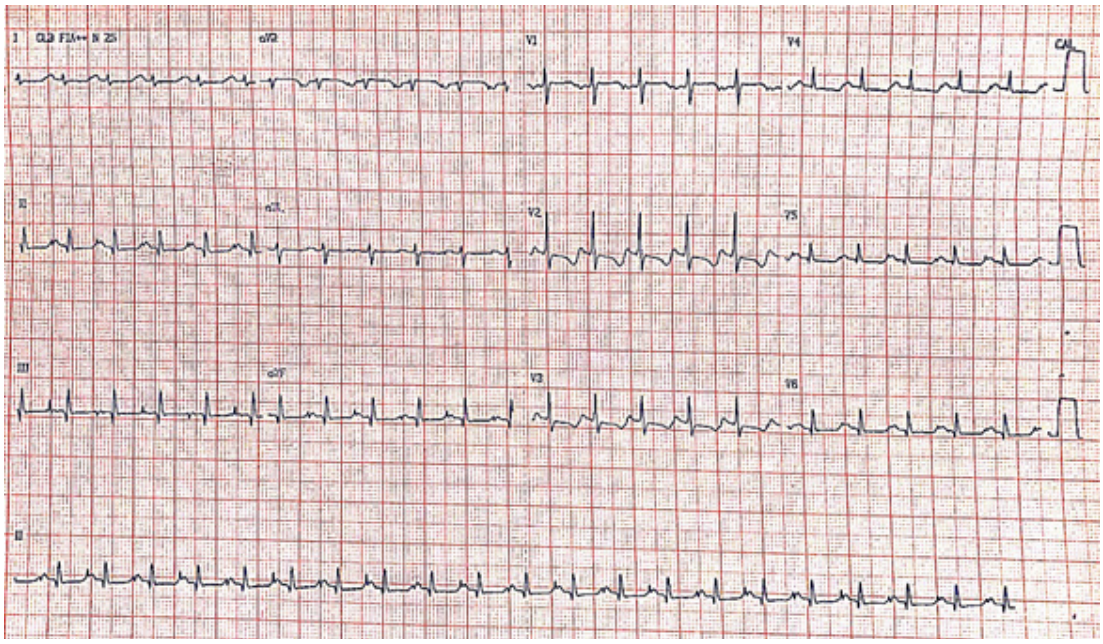

Figure 2 – Electrocardiographic findings in our patient with TS. A standard 12-lead electrocardiogram shows QTc-interval of 365ms, after pacemaker implantation in DDD stimulation mode.

implantation, and round face. Immune deficiency, cognitive abnormalities and autism have also been reported.[3] The patient presented no such feature.

Since cardiac malformations (such as patent foramen ovale, tetralogy of Fallot, or hypertrophic cardiomyopathy) are frequently observed in TS patients, fetal echocardiography stands out as an important screening tool.[11] Although any of these findings, during or after prenatal care, should raise diagnostic suspicion, especially in mosaic parents, current evidence does not support routine ECG testing for children referred for syndactyly release.[15] Electrocardiographic screening in newborns with syndactyly can lead to early clinical suspicion.

Considering, on the one hand, the limitations of existing studies due to the aforementioned aspects and, on the other hand, that the best clinical decision consists of a triad, composed of (a) best available science (b) healthcare professional's clinical experience; and (c) the patient's values,[16] we recommend decision-making regarding complementary exams to be individualized in such cases.

Neurological findings are extremely common in TS, summing up to 80% of the patients.[17] This might be related to the essential role of L-type calcium channels on the developing brain.[17] Anomalous phosphorylation or increased calcium cell inflow leads to the neurotoxicity in TS patients.[18] No atypical neurological findings were observed.

As seen in this case, hypoglycemia is common in TS and is allegedly linked to the activation of LTCs on pancreatic B-cells. The same study suggests that some unsuccessful resuscitations might have been related to hypoglycemia.[1]

Therapy is frequently based on monotherapy with betablockers (BBs). BBs are the treatment of choice for LQTS patients[19] and were adopted in this case. The patient presented a 2:1 AV block, requiring a dual chamber pacemaker, in order to maintain cardiac output and prevent variation of the QT.[20] Therapeutic options include implantable cardiodefibrillators (ICDs),[6] considered in symptomatic LQTS patients not to be responsible for or tolerable to BBs, in order to avoid sudden cardiac death.

Although there is an increasing trend in pediatric ICD implantation, limited evidence on population characteristics, complications, and survival is available,[21] especially among newborns. As there are no specific guidelines concerning pediatric populations, adult indications are applied in a practical sense. Recent studies suggest that non-transvenous ICD (NT-ICD) is safe and effective in infants and young children.[22]

The therapeutic decision-making process must consider anthropometric parameters and lead characteristics.[23,24] Thus, in small body patients, NT-ICDs are often the only option.[22-25] It is possible to use either an abdominal device and subcutaneous shock coil, or a subcardiac device and a pleural shock coil.[25]

Clinical evidence shows that infectious diseases are the second leading cause of death in TS.[11] In the present case report, the patient presented a reversed CRA, and later developed septic lung disease, culminating in death.

Conclusion

Timothy syndrome is a very rare genetic condition, even though it is easily identifiable, as the typical phenotype allows for a very high degree of clinical suspicion long before the results of confirmatory genetic testing are available. The phenotypic findings of syndactyly of hands and feet associated with electrocardiographic records of QT prolongation are frequent. Its high lethality is mainly related to ventricular arrhythmic events, and, in this scenario, the use of beta-blockers and a definitive pacemaker are part of the therapeutic mainstay. Early diagnosis can prevent negative outcomes and should be based on clinical suspicion. Fetal echocardiography stands out as an important screening tool in mosaic parents, but current evidence does not support routine ECG testing for children referred for syndactyly release.

Author Contributions

Conception and design of the research: Nascimento E, Silva CD, Tinoco CF, Cortez FFM, Kaufman R. Acquisition of data: Nascimento E, Silva CD, Tinoco CF, Cortez FFM, Kaufman R. Analysis and interpretation of the data: Nascimento E, Silva CD, Tinoco CF, Cortez FFM, Kaufman R. Writing of the manuscript: Nascimento E, Silva CD, Tinoco CF. Critical revision of the manuscript for intellectual content: Nascimento E, Silva CD, Tinoco CF, Cortez FFM, Kaufman R.

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

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CASE REPORT

Concordance of Congenital Heart Defect in Monozygotic Twins in Brazil

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Abstract

Tetralogy of Fallot (TOF) consists of four cardiac changes: interventricular communication, pulmonary stenosis, aortic dextroposition and right ventricular hypertrophy. The prevalence is 0.1 per 1,000 live births. A primiparous mother with gestational age of 38 weeks came to the emergency. At the time, it was verified in her twin pregnancy that one fetus had TOF, thus a pregnancy interruption was scheduled for the following day. In the neonatal physical examination of both, localized acrocyanosis, regular heart rhythm with the presence of a heart murmur, and good peripheral perfusion were found. The echocardiogram of twin 1 revealed: patent foramen ovale; a wide perimembranous interventricular communication of misalignment, with the aorta riding the septum by 50%; hypertrophied and long infundibulum with pulmonary infundibulo-valvular stenosis, with a maximum systolic gradient of 66 mm Hg; both pulmonary arteries presented dimensions of 0.35 mm; pulmonary valve annulus: 0.56 mm; and patent ductus arteriosus measuring 0.19 mm. The echocardiogram of twin 2 showed: patent foramen ovale; a wide perimembranous interventricular communication of misalignment, with the aorta riding the septum by 50%; hypertrophied infundibulum with stenosis pulmonary infundibulo-valve, with a maximum systolic gradient of 33 mm Hg; reduced confluent pulmonary arteries; right pulmonary artery measuring 0.40 mm and left pulmonary artery measuring 0.55 mm; pulmonary valve annulus measuring 0.72 mm; a closed arterial canal, and mild aortic regurgitation. Tetralogy of Fallot is a multifaceted syndrome with a high prevalence in pediatrics. This case is the first case of congenital heart defect concordance for TOF in monozygotic twins in Brazil.

Keywords

Heart Defects,Congenital, Twins,Monozygotic; Pregnancy Twin; Tetralogy of Fallot/surgery; Heart Septal Ventricular/surgery; Neonatal.

Introduction

Tetralogy of Fallot (TOF) is a common congenital heart malformation, with an incidence of 0.1/1,000 newborns.[1] The disease was first described in 1671 by the Danish anatomist Niels Stens on a fetus with *ectopia cordis*. However, only in 1888, with the French physician Arthur Fallot, is the existence of a single pathological process explaining the disease that he himself called *la maladie bleue* (Blue disease) proposed.[2] Based on autopsies of patients with the so-called "blue disease", Arthur Fallot described four morphological abnormalities in the heart: ventricular septal defect, pulmonary stenosis, biventricular origin of the aorta, and right ventricular hypertrophy.[1]

The TOF diagnosis can be performed on a prenatal fetus by ultrasound and later confirmed with fetal echocardiography. In other situations, the diagnosis is only made after birth due to the child's clinical condition, which can vary depending on the degree of obstruction at the level of the right ventricular outflow tract. Although the prenatal diagnosis has several advantages for the child and family, it still does not match most cases.[2]

While there may be variation in specific anatomical variations, the TOF is responsible for between 7% and 10% of all congenital heart diseases in the United States, making it one of the most common congenital lesions, requiring early intervention in life.[3] In Brazil, 973 cases of TOF were registered in 2010, but it is well-known that underreporting is high.[4] TOF can be part of some genetic syndromes, such as Down's syndrome, Klinefelter's, Di George's, Goldenhar's,

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Robinow's, Shprintzen's, conotruncal anomaly, and Pentalogy of Cantrell, and may even be associated with teratogens, such as trimethadione, thalidomide, and phenylketonuria. When it occurs alone, it is rarely Family-based.[5] The incidence of congenital heart defects among children is only 6/1,000 live births, compared to 17.2/1,000 in monozygotic twins, as compared to dizygotic twins, where the incidence is approximately 8/1,000.[6]

Case report

SS, a 24-year-old black woman, of Haitian origin, was admitted to the maternity emergency ward, in labor, at a gestational age of 38 weeks. The mother, primiparous, revealed that the pregnancy had been uneventful, though no prenatal exams had been conducted. The obstetric examination revealed a uterine bottom of 45 cm; a fetal heart rate of 140 bpm and 144 bpm; and fetal movements present. Upon obstetric emergency examination, it was found that in the twin pregnancy, one fetus presented TOF, and was thus admitted for maternity and pregnancy termination by Caesarean section, scheduled for the next day.

Twin 1, female, had Apgar scores of 7 and 8 (first and fifth minutes respectively), a weight of 2,640 g, a length of 46 cm, and a cephalic perimeter of 34 cm. Twin 2, also female, presented an Apgar score of 8 and 8, a weight of 3015 g, a length of 47.5 cm, and a cephalic perimeter of 35 cm. In the neonatal physical examination of both, localized cyanosis, of the acrocyanosis type, was verified, coupled with primitive reflexes, universally audible breath sounds and no adventitious noise, a regular heart beat with the presence of a murmur in all cardiac foci, and good peripheral perfusion. No other changes were found in the exam. It was hypothesized that the other twin had the same diagnosis as her sister.

The echocardiogram demonstrated patent foramen ovale, large interventricular communication, moderate arterial canal patency, aorta dextroposition, anterior deviation of the interventricular septum with the presence of a long and hypertrophied infundibulum, and reduced caliber pulmonary arteries, confirming the diagnosis of TOF in both newborns.

The daily physical examinations showed that both were eupneic, for the neonatal age, breathing in ambient air without difficulties, with a regular heart beat, with the presence of a heart murmur 3+ / 6+ in all cardiac foci, and acrocyanosis on their hands and feet when they cried. The twins did not need ventilatory or hemodynamic support during hospitalization. The conduct was clinical support with routine physical exams and echocardiograms weekly to control the neonatal outcome until they could be referred.

The following week, an echocardiogram was again performed by a pediatric specialist. Twin 1's exam revealed patent foramen ovale; a perimembranous wide interventricular communication of poor alignment, with an aorta dextroposition in 50%; infundibulum with pulmonary infundibular-valvular stenosis, with a maximum systolic gradient of 66 mm Hg; as well as confluent and small pulmonary arteries. The right pulmonary artery measured 0.35 mm and the left pulmonary artery measured 0.35 mm; the pulmonary valve ring measured 0.56 mm and the patent ductus arteriosus measured 0.19 mm.

Twin 2's echocardiogram showed: patent foramen ovale; a perimembranous wide interventricular communication of poor alignment, with an aorta dextroposition in 50%; hypertrophied infundibulum, with pulmonary infundibular-valvular stenosis and with a maximum systolic gradient of 33mm Hg; confluent pulmonary arteries that were reduced size. The right pulmonary artery measured 0.40 mm and the left pulmonary artery measured 0.55 mm; the pulmonary valve ring measured 0.72 mm; closed ductus arteriosus and mild aortic insufficiency were also observed.

The twins have evolved with stable frameworks and were discharged on the fifteenth day of hospitalization for a consultation in a cardiopediatric outpatient clinic. They were then forwarded for monitoring in a referral hospital for follow-up and for future surgical approaches. An informed consent was received from the patient's mother.

Discussion

Congenital heart disease is considered the most common of all congenital defects, corresponding to more than 40% of all identified defects at birth. Congenital heart diseases with conotruncal defects, which are characterized by changes in the outflow tract of the heart, correspond to about 50% of all congenital heart diseases found in newborns. This group consists of TOF, the interrupted aortic arch, truncus arteriosus, a ventricular septal defect with pulmonary atresia, transposition of the great arteries, and double-outlet right ventricle. Together with transposition of the

great arteries, TOF is one of the most common cyanotic entities, and its prevalence is around 11% of live births with congenital heart disease.[1]

From the clinical anatomical perspective, TOF is due to the anterocephalic deviation of the infundibular septum, the abnormality that produces essential pulmonary stenosis, in such a way that the right ventricular infundibulum adopts a path through a wide and narrow cylinder. A thick, hypertrophic trabecula in the ventricular free wall, which is dependent, in part, on the so-called septum-marginal trabeculae, which contributes to the obstruction. The terminal portion of the septum is diverted anteriorly and to the right. This alteration prevents adequate fusion of the interventricular septum, narrows the exit of the right ventricle to the pulmonary artery, and widens the aortic root, with its cavalcade on the septum.[1-2]

The etiology is multifactorial, lying associated with maternal consumption of retinoic acid, poorly controlled diabetes, and maternal phenylketonuria. Some chromosomal abnormalities also associate themselves with the disease, including trisomy 21 (Down's syndrome), 18 (Edwards' syndrome), and 13 (Patau's syndrome). There is a strong correlation between TOF and 22 chromosome microdeletions in the region q1,[2] especially in those children with right aortic arch (17%).[1] According to clinical tests, neither twin presented a phenotype typical of genetic diseases, but, due to a lack of resources, no specific genetic test was requested.

Congenital heart defects are more common in monozygotic compared to dizygotic twins. The incidence of agreement, that is, twins being affected, is about 5% for dizygotic twins, as compared to 25% in monozygotic twins.[7] There are few reports of multiple births associated with TOF, few cases of specific congenital heart defects of agreement for TOF, and rare cases of phenotypic discordance for TOF. Some reports make the association with 22q11 deletion syndrome, while others do not have this information or no association between them.

In the literature, one of the first reported cases of multiple births associated with TOF was in 1970, where Haar B.G.[8] in the Netherlands reported a case of monozygotic twin accordance with TOF associated with cleft palate, vesicoureteral reflux and pre-auricular fistulas. In 1974, Adams H.D.[9] reported one of the first cases of identical twins with TOF diagnosed and successfully corrected in Texas (USA). In 1967, also in Texas, Nora et al.,[10] identified a set of twins with TOF when she conducted an analysis of monozygotic twins. She also proposed an association of 25% agreement for cardiac involvement in monozygotic twins after combining the results of nine previous studies. In Ohio (USA) in 1991, Cassidy et al.,[11] identified a case of triplet siblings, all three infants presented TOF, each with a different type and degree of pulmonary stenosis.

In China in 2001, Lu et al.,[12] reported monozygotic twins concordant for 22q11.2 microdeletion, but discordant for standardization. Both twins showed identical intracardiac defects, including TOF with pulmonary atresia. In France, also in 2001, Laugel et al.,[13] discussed a case of monozygotic twins affected by TOF, though the prenatal diagnosis excluded microdeletion 22q11. In 2002, Patel et al.,[14] in India, reported seven-year-old monozygotic twins with TOF. This was one of the first case reports of concordance of heart disease among twins detected in older children. In 2010 in Mexico, Alva et al.,[15] reported 8-year-old monozygotic male twins, with almost identical phenotypes. Both had O+ blood, and the fluorescence in situ hybridization tests of both boys were negative for the microdeletion of chromosome 22q11. In 2016, in India, Govind[7] reported an example of twins born without adverse prenatal factors but with twin-to-twin transfusion syndrome. It was observed that both babies had TOF with pulmonary atresia.

In cases of phenotypic discordance of heart defect associated with monozygotic twinning, some cases in the literature stand out. In 1995, Goodship et al.,[16] discussed the case of monozygotic twins concordant for 22q11.2 deletion, but discordant for the clinical phenotype. Both boys show typical dysmorphic features with short palpebral fissures, square nasal tip, small mouth, and nasal speech, but only one twin presented TOF. In 1998, Yamagishi et al.,[17] reported monozygotic male twins with 22q11.2 deletion and discordant phenotypes. The twins presented a transfusion twin-to-twin syndrome. One twin, had TOF associated with a characteristic facial appearance, swallowing dysfunction, anal atresia, short stature, and mental retardation, while the second twin had a facial characteristic appearance, but no other sign of 22q11 deletion syndrome. In 2005, Kádár.[18] reported the first case published in Hungary, to the best of our knowledge, of two twin children with conotruncal anomalies (one having truncus arteriosus communis and the other having TOF), which have been associated with the deletion of chromosome 22q11. Finally, in 2009, in Cuba, Moreno et al.,[19] reported a case of a baby at the age of 10 months who was born with TOF

and distal arthrogryposis, although his twin brother was born without congenital defects; however, there was no association with SD 22q11.2.

In the case of the twins of the present case, there is great agreement regarding the cardiac defect; however, one twin has a mild aortic insufficiency different from the sister, the pulmonary infundibulum-valvar of both twins have differences in the stenosis diameters, and the pulmonary arteries are of small but distinct sizes. However, they did not have the SD 22q11.2 phenotype. There are no reports in Brazil of this relation of agreement of TOF in twins.

Furthermore, histological studies of the myocardium of patients with TOF showed the presence of hypertrophy, cardiomyocyte disarray, and various degrees and types of fibrosis, edema, infiltration by mononuclear cells and degenerative changes, such as vacuolar degeneration of cardiomyocytes. It was observed that at birth there is no difference between the diameter of cardiomyocytes of TOF and normal patients. After birth, this diameter increases progressively and gradually, and connective tissue proliferation occurs proportionally to hypertrophy and age. These findings support the hypothesis that in fetal life, ventricular septal defect and low left ventricular afterload relieve the pressure overload imposed by the obstruction of the right ventricular outflow tract, decreasing the stimulus for right ventricular remodeling.[20]

After birth the physiological increase in afterload of the left ventricle, which is reflected in the right ventricle through the ventricular septal defect, adds to that imposed by the obstruction of the right ventricular outflow tract, generating great stimulus to right ventricular remodeling. Thus, we can consider that the right ventricular remodeling possibly occurs mainly in the post-natal period.[20] Right ventricular hypertrophy is a secondary response to increased afterload. There are a few additional changes that occur with some frequency in this disease: obstruction at the level of branches of the pulmonary artery, coronary anomalies, right aortic arch, and additional defects in the interventricular septum. Thus, blood ejected by the ventricle has two possible routes: the outflow tract anatomically assigned to it or, in the opposite tract, through the interventricular defect. The relative strength of each of these pathways will determine the direction and intensity of the blood flow.[2-20]

The distortion of cardiac morphology in congenital heart diseases leads to variable hemodynamic consequences that promote myocardial adaptation and may eventually induce ventricular dysfunction.[20] In 1960, Somerville, et al.[21] have observed hemostatic changes in 50 patients with congenital heart disease (40 cyanotic and 10 non-cyanogenic), including TOF, tricuspid atresia, pulmonary stenosis, bypass atrial septum, and transposition of the great arteries. Disorders that they identified were hypofibrinogenemia, thrombocytopenia, and the reduction of thromboplastin synthesis. This last change is proportional to the level of polycythemia in patients with heart disease of the cyanogenic type. These disorders are related to an increased bleeding propensity to trauma and/or surgery in these children. The authors suggested that the bleeding disorders observed in patients with polycythemia could occur as an effect of chronic hypoxemia.

TOF is a multifaceted syndrome, which is underreported and has a high prevalence in pediatrics. According to research carried out in the literature, some cases of TOF concordance have been found to be associated with twinning in the world, though no cases have been reported in Latin America. This fact corroborates the relevance of the present case, which is, to the best of our knowledge, the first case of congenital heart defect concordance for TOF in monozygotic twins in Brazil. Understanding the dimensions and implications of this disease is of great clinical relevance, as pediatric interventions will reflect the adult life of these patients.

Author contributions

Acquisition of data: Liborio-Neto AO. Writing of the manuscript: Liborio-Neto AO. Critical revision of the manuscript for intellectual content: Liborio-Neto AO.

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

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