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# Cardiovascular SCIENCES



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## SUMARY

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EDITORIAL

# How Diversity, Equity and Inclusion are Changing Clinical Research

Claudio Tinoco Mesquita[1,2]

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*"Medical journals will force clinical trial designs to be more inclusive.*

*Trials need to include more women and minorities.*

*Clinical research needs to be more patient-centered."*

***Renato D. Lopes***

Clinical research must be translated into changes in clinical practice. One of the difficulties faced by physicians is how to apply results of randomized clinical trials to patients with different profiles from those enrolled in the studies. So, one common question is: Is it appropriate to use clinical trial results in my patient? It is not easy to make clinical decisions based on results from clinical research that does not consider racial identity, ethnicity, age, or gender of patients. One important initiative in science is to promote diversity, equity and inclusion in clinical research in order to produce more reliable data.[1]

Women are historically underrepresented in cardiovascular disease trials, despite sex-determined differences that lead to different forms of clinical presentation and therapeutic management. In cardiology, clinical presentation, risk stratification, prevention, treatment, and outcome parameters are gender sensitive, and this should be taken into account when designing clinical trials.[2] Recently, the American College of Cardiology's Cardiovascular Disease in Women Committee Leadership Council pointed out the low rates of women enrollment in cardiovascular research: the rates of women across coronary artery disease, acute coronary syndrome, and heart failure trials were 27.3%, 26.9% and 28,6%, respectively.[3] Sex-specific data concerning therapy is essential because women may respond differently than men and may even have adverse effects from some drugs at the same dosage that are beneficial to men.[3] To being with, part of this small participation of women in cardiovascular (CV) clinical trials can be attributed to the limited diversity in the leadership of these studies: only 10% of members in leadership committees of CV clinical trials are women. A similar number of 10% of CV trials published have a woman on the first or last author position.[4] Women need to be included, respected, empowered, and adequately represented in clinical research to guarantee the applicability of the results to their gender. Recently, the International Journal of Cardiovascular Sciences endorsed SAGER guidelines to improve the reporting of sex and gender in research while creating an environment able to integrate equity of sex and gender into manuscripts as an integral part of the editorial process.[5,6] As women, minorities also have been underrepresented in CV clinical studies. Some minority populations have shown disproportionately higher rates of certain diseases such as hypertension, heart failure and cerebrovascular disease.[7]

Poverty, marginalization, and inequity, that are very common among minorities are added risk factors for morbidity and mortality from many diseases, including CV diseases.[8] The COVID-19 pandemic is one example of this situation. The COVID-19 pandemic has had a great economic impact, especially in Latin America where the number of poor people has increased substantially. Despite markedly higher rates of COVID-19 infection, hospitalization and deaths in racial and ethnic minority groups, these groups were significantly underrepresented in COVID-19 clinical

## Keywords

Ageism; Cardiovascular Diseases/therapy; Clinical Trials as Topic; Gender Diversity; Equity; Women, Inclusion.

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trials.[9] In the United States of America some measures have been taken to fill this gap like a federal law (Public Health Service Act sec. 492B, 42 U.S.C. sec. 289a-2) and policies such as the National Institutes of Health (NIH) policy NOT-OD-18-014 that mandates the inclusion of minorities in NIH-funded research.

To fight against the lack of diversity in clinical trials it is crucial to understand and address the needs of minority communities, including the costs for participating in a clinical trial. In Brazil, the patient has the right to be reimbursed for the expenses (eg. food and transportation costs) related to the participation in the trial. Other important barriers that must be tackled to promote more inclusive trials are poor health literacy, lack of information, disinformation, science negation, language barriers, lack of diversity of principal investigators, limited accessibility, and biases against minorities.[9] Another possible way to increase inclusion is to promote patient and public involvement (PPI) in trial decisions. For example, PPI is very useful in designing clinical questions and primary objectives that address their needs, developing the clinical protocol, interpreting results; and disseminating results for communities.[10]

How can a medical journal foster diversity, equity and inclusion in clinical research? This question is key in our times. Figure 1 includes some actions that can be taken by the editors. The first step is to understand and to measure the lack of diversity in CV trials. Secondly, to adopt policies focused on diversity, equity and inclusion that can be easily translated into actions such as endorsing guidelines promoting equity such as SAGER, including minorities in editorial and reviewer boards, and promoting diversity publicly (webinars and symposia).[6,11] Finally, some high impact journals are promoting an increase in transparency of data concerning minorities. Since January 1, 2022, the New England Journal of Medicine has demanded that authors prepare a supplementary table that provides background information on the disease, problem, or condition and the representativeness of the study group, to be posted with the article.[1] Demanding clarity and transparency in trials design, patient selection and representativeness of study participants is another step to promote more inclusive clinical research. These actions can contribute to a healthier future, reducing inequalities and promoting equity.

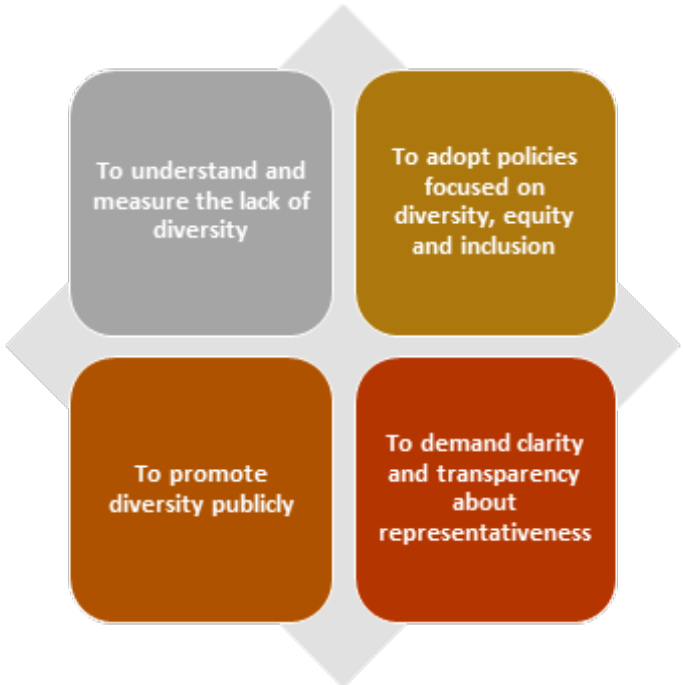


**Figure 1 – Medical journals actions to promote diversity, equity and inclusion in clinical research.**

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ORIGINAL ARTICLE

# School Health Education Program "Happy Life, Healthy Heart": A Randomized Clinical Trial

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## Abstract

**Background:** School interventions based on playful activities have been shown to be good strategies for increasing children's knowledge about health, which may impact healthy habits.

**Objective:** To evaluate whether the school health education program entitled "Happy Life, Healthy Heart" increases health knowledge and causes a change in teachers' and students' lifestyles.

**Method:** Cluster randomized clinical trial including elementary school students and teachers from public schools in the city of Frederico Westphalen, Brazil. The intervention consisted of the training of teachers on topics of health, followed by classes on topics related to cardiovascular health given by these teachers to the students. The students were evaluated for nutritional status and health knowledge using the CARDIOKIDS and DAFA questionnaires, and teachers were assessed for physical activity. The Student's t-test, the chi-square test and the two-way ANOVA test were used for comparisons between groups, and McNemar-Bowker for intra-group comparisons. P values of <0.05 were considered statistically significant.

**Results:** A total of 473 children were included, 211 (44.6%) in the control group (CG) and 262 (55.4%) in the intervention group (IG), and 32 teachers (control = 14, intervention =18). There was no difference in health knowledge of the students after the intervention (CG 10.53 ± 0.11 vs. 11.19 ± 0.09 $p$ = 0.061, IG 10.20 ± 0.12 vs. 11.09 ± 0, 09 $p$ = 0.416), although 57.7% of the children of the IG reported having stopped eating pizza and drinking soft drinks (p <0.001), following the Brazilian Food Guide recommendations. Among teachers of the IG, an increase of 27.9% in physical activity level was observed.

**Conclusions:** The "Happy life, healthy heart" program was able to change students' eating habits and increase physical activity in teachers.

**Keywords:** Health, Knowledge, Atitudes, Practice; Health Personnel; Children; Teachers; School Health Education.

## Introduction

The school is the place where children spend most of their time and recognized as an environment of health promotion and prevention of chronic non-communicable diseases. It can engage students, families, educators, and community members, and create a unique, sustainable environment, that strengthens this objective.[1]

Health-related knowledge is characterized by familiarization with cardiovascular risk factors and psychological and behavioral aspects that directly influence quality of life and the development of obesity.[2] Interventions based on practical, playful and recreational activities have been shown to be good strategies to increase knowledge, including about dietary practices.[1,3] For Duncan et al.,[4] the importance of practical and not only theoretical interventions is in the fact that they offer necessary tools for children to influence and bring benefits to the family environment. In addition, school age is critical for the development of long-lasting habits that will continue into adult life.

An observational study showed that teaching contents related to food, when done by teachers, promotes greater receptivity among students than when it is done by health professionals.[5] However, teachers demonstrate limited knowledge of health-related content and require training[6]

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and thus, most health intervention programs in Brazil have focused on actions promoted by health professionals or academic students rather than by teachers.[7,8]

Considering these aspects, the present study aimed to verify whether the school health education program "Happy Life, Healthy Heart," consisting of classroom interventions performed by qualified teachers and aimed at preventing cardiovascular health, increases health knowledge and causes behavioral changes in the lifestyle of teachers and students. This article was conducted according to the guidelines of the CONSORT Statement.[9]

## Methods

### Study Design

The study entitled "Happy Life, Healthy Heart" consisted of a (parallel) cluster randomized clinical trial (RCT), with two arms (control group [CG] and intervention group [IG]) and blind evaluation of outcomes. The study was conducted in the city of Frederico Westphalen, Rio Grande do Sul, Brazil, from March to December 2017. The randomization units were the schools, to avoid contamination of the results, and the observation units were the students.

### Participants

Public schools located in the rural area of Frederico Westphalen were excluded because of cultural and dietary differences. Of the remaining 11 schools, one did not agree to participate, leaving ten schools for randomization. This was carried out by a health professional not involved in the study through the www.randomization.com website (retrieved in October 2016). Teachers of the first years of elementary school (1st to 5th) of participating schools were included, and those working in more than one school were excluded. We included children from six to 11 years of age, with the consent of parents or guardians, and children over nine years of age who were illiterate or had cognitive, neurological, or hearing and visual impairment, were excluded.

### Ethical aspects

All children consented to participate, and their parents or guardians signed a term of consent. The study was approved by the ethics committee of the Institute of Cardiology, University Foundation of Cardiology, Porto Alegre, Brazil (approval number 5235/16) following the CNS 510/16 resolution, and registered and approved by the Brazilian Registry of Clinical Trials (REBEC): RBR-9sp5HX.

### Intervention

The intervention consisted of two phases: 1) teacher training program and 2) theoretical-practical activities with students in the classroom. The training program took place between April and July 2017 and was held in four face-to-face and remote monthly meetings, totaling 32 class hours of theoretical-practical activities. A handout was specially developed for the program, containing seven topics divided into chapters with theoretical basis and suggestions for activities to be carried out in the classroom: 1) risk factors of cardiovascular diseases in childhood; 2) selection of healthy foods; 3) food labeling; 4) sodium, sugars and fats; 5) emotional health and quality of life; 6) physical activity (PA); and 7) healthy practices and changes in habits. The activities were created based on the themes to be worked on, age of children and intended goals. The CG did not participate in the training course and followed the school's political-pedagogical plan. At the end of the study, teacher of the CG were invited to participate in a seminar with lectures on the topics involved in the study, and they were also given a training program handout.

The intervention program with the students started after the teachers' training program. The program was first planned to be carried out in seven uninterrupted weeks (one theme per week). However, due to the occurrence of a teachers strike in state schools, the program was forced to be interrupted for 45 days at the end of its 5th week. After the strike ended, the teachers resumed the program from the point where they stopped.

Teachers of the GI were instructed to carry out at least one activity per week, and they had the liberty to add activities to the school curriculum or suggest them as a separate project. The activities were monitored by the number of activities performed per week/theme, registered by photos and videos sent to the researcher via message application. Guidance and assistance were offered by the researcher whenever needed.

### Data collection

At baseline, sociodemographic data of the students by collected using a structured questionnaire that was administered to the parents. The children's level

of knowledge on health was assessed quantitatively, using the CARDIOKIDS questionnaire,[10] which divides knowledge into two factors: healthy habits (F1) and risk factors for cardiovascular disease (F2). The instrument consists of 12 questions, with three possible answers: "good for the heart", "bad for the heart" and "I don't know". Eating habits and PA were assessed by the DAFA-Typical Day of Physical Activity and Food[11]. This instrument includes measurement of PA level and 24-hour food recall, where the child reports the foods they had for breakfast and morning snacks, lunch, afternoon snacks and dinner.

For assessment of nutritional status of the children, height and weight measurements were obtained, and used to calculate body mass index (BMI) (body mass divided by height squared) and Z score using the Anthro Plus program.[12] After the intervention period, students from both groups were reevaluated. Data collection was performed by a previously trained team (academics and professionals in nutrition, psychology, pharmacy, physical education and nursing) and the evaluators were blinded to the school allocation group. The evaluation of teachers (baseline and after the training program) was done through a questionnaire with sociodemographic data, nutritional status (reported weight and height), PA and leisure. Outcomes were assessed by a blind examiner.

### Sample size

Sample size calculation resulted in a total of 466 children, 233 in each group (IG and CG). A power of 95% and a significance level of 5% were assumed. An average health knowledge of 5.2 was expected at baseline, with an increase of 0.39 after the intervention.[7] Around 600 children were recruited, considering a 20% loss after the baseline assessment.

### Statistical methods

Data analysis and processing were performed using the Statistical Package for the Social Sciences[13] for Windows version 20.0, and a significance level of 5% was adopted as statistical decision criterion.

To verify the normality of the variables, the Kolmogorov-Smirnov test with Lilliefors correction was used, indicating that all continuous variables had normal distribution. Continuous variables were expressed as mean and standard deviation. Categorical variables were presented as absolute and relative frequencies. Pearson's chi-square test was used to evaluate the association between categorical variables among the groups. In the comparison of continuous variables, the Student's t-test was used for independent samples, considering that all variables had a normal distribution. For comparison of continuous and categorical variables between pre- and post-intervention, the paired Student's t-test and the McNemar-Bowker test were used respectively.

In the study of evaluation of the instruments during follow-up (pre and post), two-way analysis of variance for repeated measures, with post-hoc Bonferroni test, was used. In within-group analysis, the impact of the intervention on the instruments was calculated by Cohen's d effect size estimate. To identify possible influencing factors in the differences between the pre- and post-intervention regarding the instruments' results, the generalized estimation equations were used, a technique that makes it possible to identify the influence of covariables on the behavior pattern identified in the pre-evaluations and post intervention in the total sample. All variations observed in the instruments administered to the children were analyzed by sex and education factors, which in the comparison between the groups, showed potential to discriminate the two groups.

## Results

Ten schools were randomized into two independent groups, as shown in Figure 1. The results refer to a sample of 473 children, 262 (55.4%) in the IG and 211 (44.6%) in the CG, 32 teachers (14 [43.8%] in the CG (CGt) and 56.3% [n = 18] in the IG [IGp]). A loss to follow-up of 7.6% (n=20) in the IG and 10.9% (n=23) in the CG was observed, due to the transfer of students to other schools (n=17) or absence of the student on the day on which the second assessment was carried out (n=26).

Table 1 shows the sociodemographic characteristics of the students at the baseline assessment, showing that the groups were homogeneous in terms of gender, age and family income. Regarding children's schooling, there was a significative difference between the groups, with a greater concentration of 1$^{st}$-grade children in the IG and 4$^{th}$-grade children in the CG.

Teachers' sociodemographic data showed that the average age in the CGt was 39.2 ± 7.7 years and in the IGt 43.4 ± 9.6 years. Regarding marital status, most of teachers in both groups reported living in a common-law marriage (CGp 78.6% and IGp 77.8%). The background of 64.3% of the teachers of the CGt and 77.8% of the IGp was

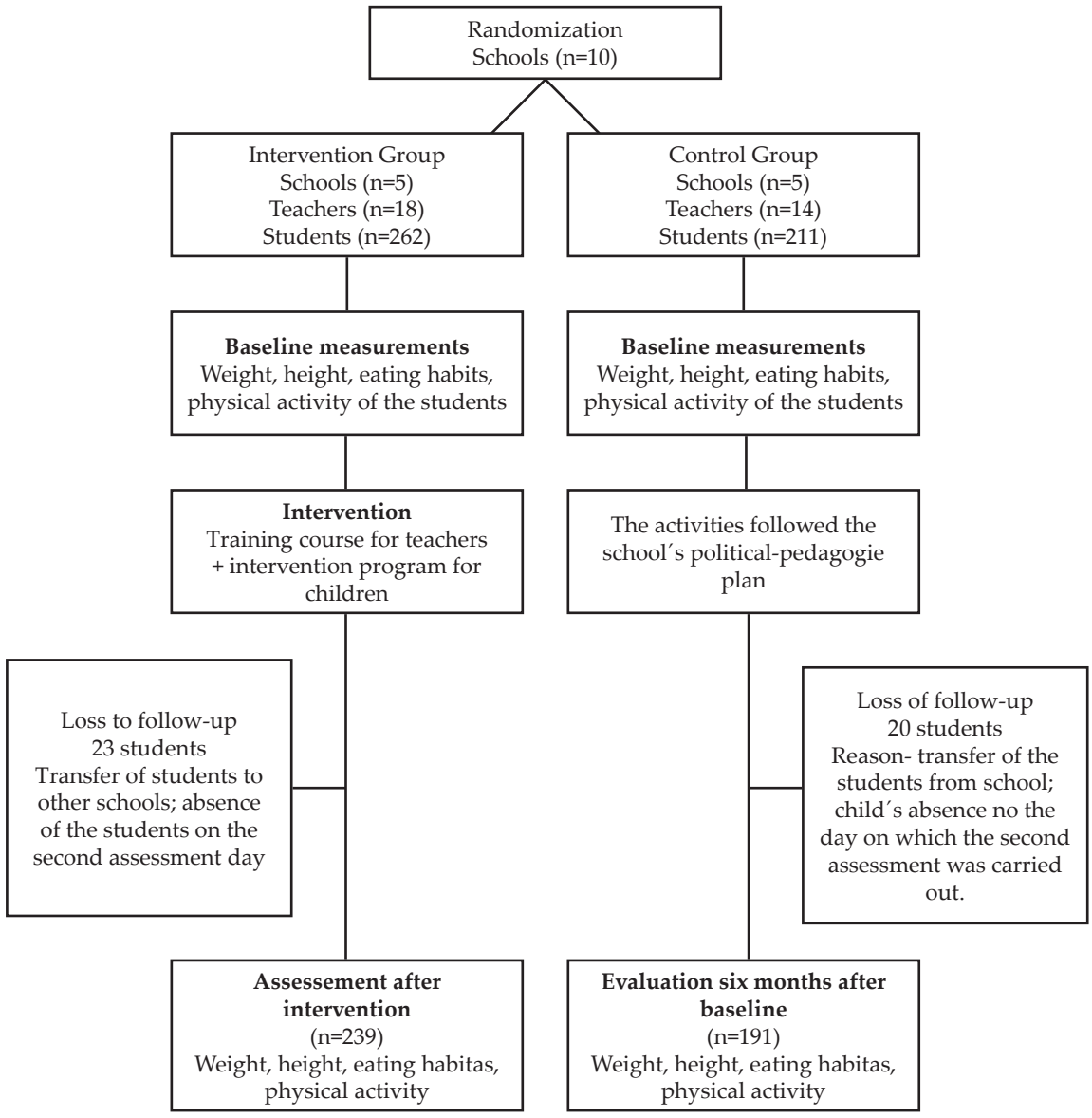


**Figure 1 – Flowchart of the study.**

pedagogy, and most had a specialization degree (CGp 78.6% and IGp 50%). The working day was generally 40 hours per week (CGt 71.4% and IGt 94.4%).

Results on students' health knowledge obtained through the CARDIOKIDS instrument (Table 2), considering the effect of time x group interaction (Size of achievement = 2.293; p = 0.131) showed that there was no difference between the two groups at the two evaluation times. The same behavior was repeated when considering each factor of the scale, with factor 1 (F1) evaluating "healthy habits" (F[1; 421] = 0.229; p=0.866) and Factor 2 (F2) evaluating "risk factors" (F[1, 421]; effect size = 0.456; p=0.473). The within-group analyses showed that there were statistically significant differences in both groups comparing baseline and post-intervention (CG [Pre: 10.53±0.11 vs. Post: 11.19±0.09; p<0.001] and IG [Pre: 10.20±0.12 vs. Post: 11.09±0.09 p<0.001]), i.e., there was evidence of a time effect, with an increase in CARDIOKIDS score in 6.27% of children in CG and 8.73% of children in IG. Regarding the knowledge factors (F1 and F2), the difference was maintained. Regarding the analysis of covariates, gender did not have a significant influence in the comparisons between groups, but a

**Table 1 – Sociodemographic data of children of intervention and control groups at baseline**

| Variables | Groups* | | | | P |
|---|---|---|---|---|---|
| | Control (CG) (n = 211) | | Intervention (IG) (n = 262) | | |
| | N | % | n | % | |
| **Gender** | | | | | 0.066§ |
| Male | 90 | 42.7 | 134 | 51.1 | |
| Female | 121 | 57.3 | 128 | 48.9 | |
| Age (years) | | | | | € 0.097 |
| Average ±DP | 8.8 ± 1.5 | | 8.5 ± 1.6 | | |
| **Schooling** | | | | | <0.001§ |
| 1st grade | 30 | 14.2 | 68 | 26.0 | |
| 2nd grade | 35 | 16.6 | 37 | 14.1 | |
| 3rd grade | 38 | 18.0 | 47 | 18 | |
| 4th grade | 74 | 35.1 | 53 | 20.2 | |
| 5th grade | 34 | 16.1 | 57 | 21.8 | |
| **Parents' marital status** | | | | | 0.932§ |
| Married or living together | 160 | 76.9 | 197 | 75.8 | |
| Divorced | 45 | 21.6 | 57 | 21.9 | |
| Widow | 3 | 1.4 | 6 | 2.3 | |
| **Family Income** | | | | | 0.670§ |
| Up to 2 minimum wages | 79 | 38 | 101 | 39 | |
| From 3 to 5 minimum wages | 87 | 41.8 | 114 | 44 | |
| From 6 to 10 minimum wages | 29 | 13.9 | 34 | 13.1 | |
| 11 or more minimum wages | 13 | 6.2 | 10 | 3.9 | |

*Note: * Percentages obtained based on the total of each group; § Pearson's chi-square; €: Student's t-test for independent groups assuming heterogeneity of variances.*

significant effect of schooling on F2 [$F_{(1; 87)}$ = 12,941; p = 0.001; power = 0.876] was found. Thus, in the IG in the 1st, 2nd and 3rd grades, the average score in the post-intervention was significantly higher compared to the baseline. This result did not occur in the CG, or in the other school years investigated in this study (data not presented).

Anthropometric data are presented in Table 3. Mean z-score was not different between IG and CG, and a significant reduction of the mean was observed after the intervention in both CG and IG. However, this variation did not promote a change in the category and therefore, all children were classified as normal weight based on z-score.

Data of food consumption, evaluated by the DAFA instrument, are presented in Figure 2. A statistically significant difference was detected in the percentage of children who reported avoiding pizza/hamburger/French fries in the IG (p <0.001 ), following the Brazilian Food Guide recommendations.[14] In addition, there was an increase in the frequency of children who followed this recommendation after intervention, when compared to the baseline [57.7% (n=138) vs. 42.5% (n=111)]. A similar result was seen regarding the consumption of soft drinks (p < 0.001), with a significant increase in the percentage of children who stopped consuming sugary drinks in comparison to baseline [57.7% (n = 138) vs.

**Table 2 – Comparison of the students' level of knowledge about health, according to CARDIOKIDS, at baseline and after intervention, in the intervention and control groups**

| Knowledge Level CARDIOKIDS | Bivariate | | | | | Multivariate - Effects | | |
|---|---|---|---|---|---|---|---|---|
| | Groups | | | | p between group | Time£ | Group¥ | Interaction£ |
| | Control (CG) | | Intervention (IG) | | | | | |
| | Mean | SD | Mean | SD | | | | |
| **Total** | | | | | | | | |
| Pre | 10.53 | 0.11 | 10.20 | 0.12 | 0.061 ₸ | <0.001 | 0.107 | 0.131 |
| Post | 11.19 | 0.09 | 11.09 | 0.09 | 0.416 ŧ | | | |
| *p intra- group** | <0.001 | | <0.001 | | | | | |
| **F1** | | | | | | | | |
| Pre | 4.12 | 0.06 | 3.99 | 0.06 | 0.147 ₸ | <0.001 | 0.101 | 0.866 |
| Post | 4.48 | 0.05 | 4.36 | 0.05 | 0.150 ŧ | | | |
| *p intra-group** | <0.001 | | <0.001 | | | | | |
| **F2** | | | | | | | | |
| Pre | 6.41 | 0.07 | 6.22 | 0.07 | 0.078 ₸ | <0.001 | 0.189 | 0.076 |
| Post | 6.71 | 0.05 | 6.73 | 0.04 | 0.871 ŧ | | | |
| *p intra-group** | <0.001 | | <0.001 | | | | | |

*Note: Estimates obtained by analysis of variance for repeated measures (Two way); F1: Factor 1 = Healthy Habits; F2 = Factor 2 = Risk factors; £: Pre-post time effect (considering the sample as a whole); ¥: Group effect; £: Time X Group interaction effect.*

37.9% (n = 99)]. Regarding the other food groups assessed (beans, cereals, meats, dairy products, fruits and sweets), there were no statistically significant differences between the groups.

Regarding the level of PA, also evaluated by the DAFA instrument, after the intervention, most children in the IG (n=87, 36.4%) were classified in the "Most Active" level, while in CG, most children (n=69, 36.1%) were classified as intermediate level of physical activity. However, it is noteworthy that mean PA level in the IG was already higher at baseline than the CG (IG:41.75±9.51 vs. CG: 37.49±17.96, p=0.014), which explains the lack of considerable difference between the groups (IG 35.82±16.18 vs. CG 33.41±14.51; p=0.105) after the intervention. The analysis of the covariates schooling and gender showed no significant difference.

Regarding the practice of PA of teachers, more teachers began to practice PA after the intervention, with an increase of 27.9% in the level of PA [IGp Pre 10 (55.6%) vs. Post 15 (83.5), CGp 7 (50%) vs. 5 (50%), p=0.014]. In addition, there was no difference between the groups regarding the number of times per week that teachers practiced PA. In the IGt, only four (22.2%) of the teachers practiced PA three times a week at baseline and after the intervention this number increased to nine (50%). On the other hand, in the CGt, 50% of the teachers did not practice any PA at baseline and remained so on the second evaluation (p= 0.007).

## Discussion

This study examined the effect of the "Happy Life, Healthy Heart Program" that involved theoretical and playful activities conducted by teachers with students in the classrooms. The results showed that both intervention and control groups had an increase in health knowledge, however only the IG showed changes related to eating habits. The effects on teachers were demonstrated with the increase in the number of teachers who started to practice PA, which was observed in the IG only.

**Table 3 – Anthropometric data of students at baseline and after intervention, in intervention and control groups**

| Anthropometry | Groups | | | | |
|---|---|---|---|---|---|
| | Control (n=211) | | Intervention (n=262) | | P |
| | Mean | SD | Mean | Sd | |
| **Z-score** | | | | | |
| Pre-intervention | 0.762 | 1.433 | 0.765 | 1.316 | 0.982* |
| Post-intervention | 0.732 | 1.375 | 0.597 | 1.371 | 0.316* |
| p | <0.001† | | <0.001† | | |
| Difference | -0.006 ± 0.391 | | -0.155 ± 0.611 | | 0.001* |
| **Z-score - Classification – n (%)** | | | | | |
| Pre-intervention | | | | | 0.300¶ |
| Obesity (z > 2) | 44 (20.8) | | 47 (17.9) | | |
| Overweight (z ≤ 2) | 38 (18.0) | | 60 (22.9) | | |
| Normal weight (z < 1) | 129 (61.1) | | 155 (59.2) | | |
| Post-intervention | | | | | 0.372¶ |
| Obesity (z > 2) | 44 (20.9) | | 47 (17.9) | | |
| Overweight (z ≤ 2) | 37 (17.5) | | 53 (20.2) | | |
| Normal weight (z ≤ 1) | 130 (61.6) | | 162 (61.8) | | |
| p‡ | 0.930 | | 0.371 | | |

**: Student's t-test for independent groups; †: Student t-test for paired data; ‡: McNemar Browker test; ¶: Pearson's Chi-square test; data expressed as mean and standard deviation (SD).*

The fact that the two groups had an increase in average knowledge can be explained by the improvement of existing skills or by learning by inference. When asked "if eating fatty foods is bad", the child activates pre-existing knowledge and skills and seeks to link new information to the existing ones.[15] Also, it is possible that the quality of the classes planned by the CG teachers was as high as that of the intervention program, suggesting that, in this community, the teachers have good knowledge and didactics about health when encouraged. Other studies[16,17] have shown similar results regarding a change in behavior not only in the IG but also in controls.

The impact of schooling, in which students from the 1st to the 3rd grades had higher knowledge scores, can be understood by the fact that these students are in the age group between six and nine years old, at the highest point of the literacy process, considering the whole study group. This phase is considered a sensitive period in child development, since, according to Piaget,[18] children are in a transition period from the pre-operative to the concrete-operative phase. Another factor to be considered is that the CARDIOKIDS instrument proved to be more suitable for measuring the knowledge of younger children, considering its format and language, being less suitable for children aged over 10 years.

In relation to food consumption, the results showed that activities focused on health education can generate behavioral changes, reducing the intake of foods corresponding to an unhealthy diet. Many interventional studies conducted at schools[3,19,20] have shown that changes in eating habits produce positive effects on children's health, which reinforces the importance of developing health programs in these environments.[21] However, even with the increase

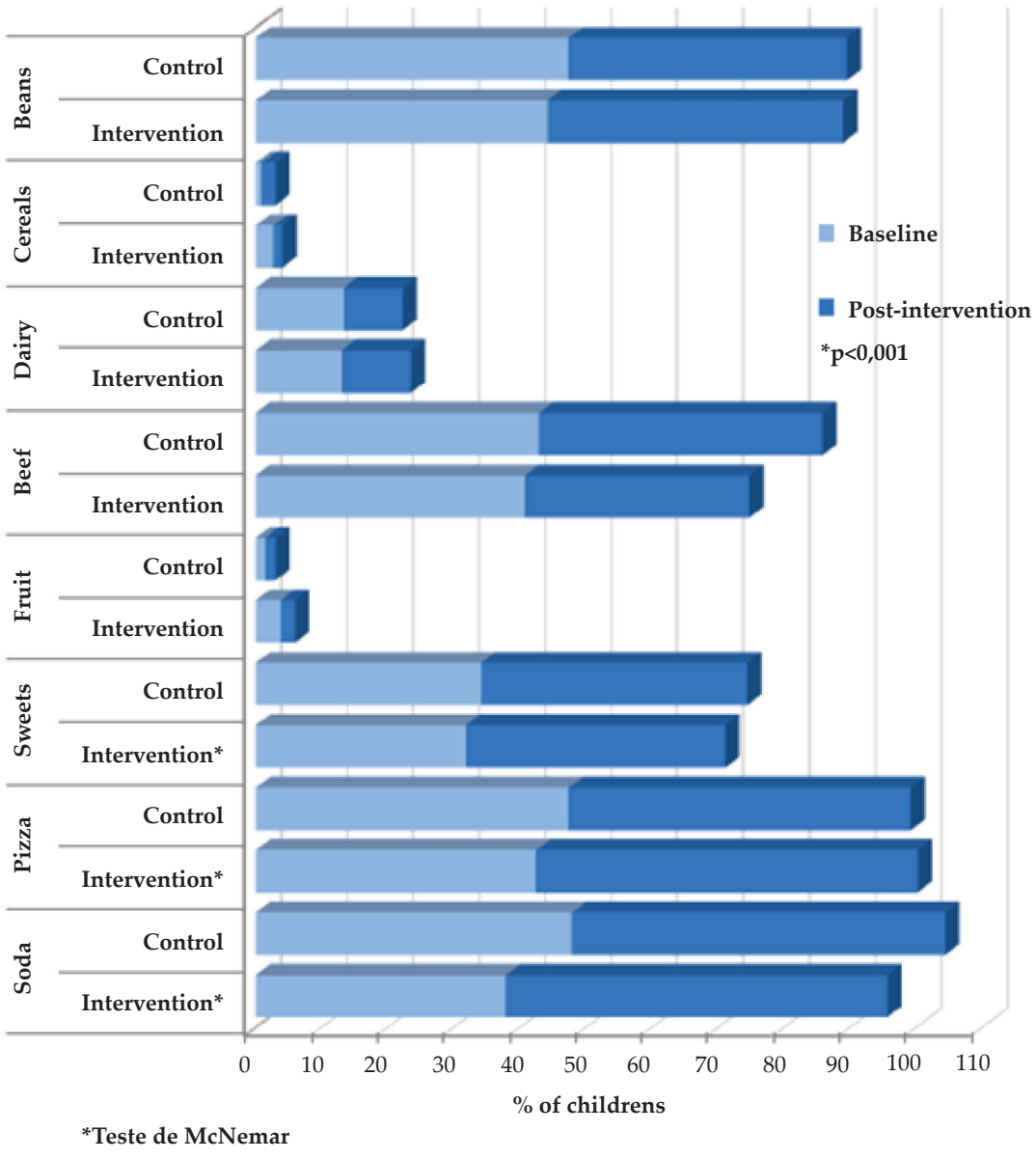


**Figure 2 – Percentage of children who followed the Brazilian food guide recommendations in intervention and control and groups, before and after intervention**

in the number of children in the IG following the recommendations of the Brazilian food guide, the consumption of pizza, French fries and soft drinks was significant, representing 42.3% of the children. These numbers are in line with the 2009 National School Health Survey,[22] which showed that 39% of adolescents reported drinking soft drinks at least five days a week. In this sense, over the last few years, public policies have been developed to change this reality and curb the consumption of ultra-processed foods.[23]

The significant reduction in the level of PA of children both in the CG and IG may be explained by two distinct situations, one related to the seasonal difference in assessments (baseline carried out in the end of summer, and post-intervention in spring, after winter) and the teachers' strike for 45 days between the 5$^{th}$ and 6$^{th}$ weeks of the intervention program, when the topics on PA and physical exercise were being worked on. The influence of seasons on the practice of PA in children was also reported in a similar study carried out in the capital of

Rio Grande do Sul state.[7] In addition, children who are at school participate in at least two periods per week of Physical Education classes, in addition to the school break that has been proven in many studies to facilitate and encourage the practice of PA.[24,25] Thus, it is believed that children who were not attending school due to the strike or in the winter months tended to take on more sedentary behaviors.

On the other hand, evaluation of PA of the teachers showed a different result, indicating a change in habits in the IGt. The practice of PA by teachers can be understood as a protective factor for physical and mental health[25,26] and an important target for different policies to promote healthy living.[27] According to the National Survey of School Health,[28] considering that teachers are models of good practices, the school can be a reference point of support and dissemination. The improvement in PA among teachers and the drop in PA level among children suggests that the latter group are more susceptible to factors such as strikes and seasonal effect.

### Strengths and Limitations of the Study

As strengths of the present study, it is possible to mention its originality with respect to the objective of training teachers for health education. For this, the study proposed an intervention program using materials and resources developed specifically for the project. In addition, in Brazil, few studies have presented the teacher as the protagonist of transmission of health knowledge at school, which has been usually performed by health professionals instead. However, some aspects can be understood as limitations. Considering that the level of the students' knowledge about health at the baseline was high, possibly the knowledge evaluation instrument used may not have been sensitive to capture small differences in such a socially and economically homogeneous population. This does not exclude its use in other communities so that this hypothesis could be confirmed. The fact that the age range of children was wide and included different phases of cognitive development suggests different interpretations of the items of the instrument, especially when it comes to complex themes such as cardiovascular risk factors. In the year in which the study was conducted, there was a work stoppage of state teachers during the intervention period, which may have significantly affected the study, especially in the quantitative results related to the practice of PA, which, in turn, directly affects other data such as anthropometric measurements.

## Conclusions

The "Happy Life, Healthy Heart" program reinforced the results of previous studies showing that an increase in health knowledge in children is not enough to change behaviors and lifestyle habits. Furthermore, the change in the practice of PA observed in the group of teachers corroborates the idea that education programs should be implemented, as they affect not only students, but all involved in the school environment.

## Author contributions

Conception and design of the research: Mari MA, Pellanda LC. Analysis and interpretation of the data: Mari MA, Teixeira PP. Obtaiming financing: Mari MA. Writing of the manuscript: Mari MA, Teixeira PP, Pellanda LC. Data tabulation: Teixeira PP. Critical revision of the manuscript for intellectual content: Mari MA, Pellanda LC.

### 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 Institute of Cardiology, University Foundation of Cardiology, Porto Alegre, under the protocol number 5235/16. 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

# How to Take Care of Your Body: Not an Obvious Insight, but an Essential School Lesson

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***Editorial referring to the article: School Health Education Program "Happy Life, Healthy Heart": A Randomized Clinical Trial***

Over the years, the most traditional institutions provide modern concepts and philosophy, assuming the important role that schools play today. What is relatively new is the comprehension of the student in an active position in the learning process.[1] This change of view has made it evident that, beyond the regular curriculum, there is the need to understand about the basic life skills of others.[2] Bodily functions are one example, as they have a direct impact upon the learning process.[3] Furthermore, the child's capacity as a messenger or influencer is still consolidated as the one who brings knowledge home.[4]

Beyond this scenario, a significant increase in cases of heart disease per year has been observed.[5] Randomized trials demonstrate that a change in lifestyle is the first and foremost step toward preventing the most common incidences of heart diseases, such as myocardial infarction.[6]

Thus, it is clear how essential it is offer schools the knowledge and tools necessary to promote a healthy life. The easy recognition of what is healthy (or not) is important so as to convert the daily choice into a conscious field, which can be a strong weapon against obesity, diabetes, atherosclerosis, and coronary heart disease.[4]

According to Mari et al.,[7] the Happy Life, Healthy Heart program is an effective strategy, through education and the training of teachers and students, to promote the reduction of risk factors for cardiovascular disease within the school environment. However, it should be noted that, despite being a universally recognized technique, the demonstration of these results in the Brazilian population lacks information and recognition of their benefits. In this context, the present results bring relevant information and potential population impact. The present results should serve as a subsidy in the discussions and planning for the development of prevention programs in public and private schools throughout the country, positively impacting cardiovascular health and the quality of life of millions of students and teachers in educational networks.

Clearly, the results over a short period of time are scarce, but over decades, it has the potential to hinder the absurd increase of deaths witnessed throughout this century, strongly correlated to a contemporary habit of eating, working, and exercising, which school lessons can reverse.[8] It is well-known that adults who adhere to a healthy lifestyle show lower rates of cardiovascular morbidity and mortality than those who do not.[9] By contrast, children who have unhealthy habits and who are overweight are at a higher risk to develop risk factors prematurely, in turn producing an increase in cardiovascular mortality during adulthood.[10] Brazilian society's initiatives to prevent CVD, which include teacher training, are crucial in a continental country with a high prevalence of obesity in children and adolescents.

Therefore, now is the time to qualify teachers to improve the quality of health care concerning the prevention of cardiovascular risk factors as a pivotal strategy to preventing cardiovascular mortality within the Brazilian population.

## Keywords

Disease Prevention; Cardiovascular Diseases; Education.

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ORIGINAL ARTICLE

# Treatment of Hepatitis C with Direct-Acting Antivirals does not Induce Significant Arrhythmias

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## Abstract

**Background:** Chronic Hepatitis C (CHC) therapy with direct-acting antivirals (DAAs) has high efficacy and safety, but some cases of bradyarrhythmias have been described.

**Objective:** To evaluate heart rhythm disorders during DAA treatments.

**Methods:** Forty-eight patients with CHC (mean 61 years of age; 56% males; 73% HCV genotype 1) were evaluated before and during treatment with DAAs, analyzed by a resting 12-lead ECG [PR, QRS, and QT corrected (QTc) intervals measured] and a 24-h-Holter system, to evaluate the heart rate (HR) and the occurrence of arrhythmias. The Student's t-test or the Wilcoxon-Mann-Whitney test for continuous, independent variables were performed with a statistically significant p-value < 0.05.

**Results:** The electrocardiographic parameters before and during treatment were: PR interval (147.2 ± 15.6 vs 144.9 ± 15.6 ms; p = 0.21), QTc interval (427 ± 22.3 vs 421.7 ± 25.3 ms; p = 0.24), minimum HR (52.7 ± 8.4 vs 53.2 ± 8.5 bpm; p = 0.49), median HR (74.2 ± 10.4 vs 75.2 ± 9 bpm; p = 0.83), and maximum HR (117.4 ± 16.8 vs 117.9 ± 16.3 bpm; p = 0.25). These parameters proved to be similar among 11 beta-blockers or 22 ribavirin users. During treatment, the 21 cirrhotic patients presented significantly lower median HRs (72.1 ± 9.0 vs 77.9 ± 8.2 bpm; p = 0.02) and maximum HRs (108.9 ± 15.2 vs. 125.1 ± 13.2 bpm, p < 0.0001) through a 24-h-Holter monitoring than the patients without cirrhosis. No clinically relevant arrhythmias were detected.

**Conclusion:** DAAs do not significantly influence heart rate or induce significant cardiac arrhythmias in patients with CHC.

**Keywords:** Sofosbuvir/ therapeutic use; Hepatitis C/treatment; Arrhythmias Cardiacs; Antiviral Agents; Drug Resistance Viral.

## Introduction

Hepatitis C Virus (HCV) infection affects approximately 71 million people, accounting for 400,000 deaths per year worldwide.[1] More than 70% of these patients develop Chronic Hepatitis C (CHC), progressing with different degrees of liver impairment.[2] CHC has been reported as a cause of atherosclerotic heart disease and cardiomyopathies.[3,4] Advanced liver fibrosis may also contribute to the development of structural, hemodynamic, and electrophysiological cardiac changes, which characterize cirrhotic heart disease.[5] Furthermore, antiviral treatment of HCV with interferon or antivirals may be associated with cardiac arrhythmias.[6]

The introduction of direct acting antivirals (DAAs), including sofosbuvir, allowed for patients to be treated with CHC exclusively via the oral route, without

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interferon (IFN-free). These medications have an excellent efficacy and safety profile.[7] However, after the beginning of the use of DAA regimens in 2012,[8] the FDA reported nine cases of severe bradyarrhythmia occurring on the first days of therapy.[9] Another study reported the occurrence of three similar cases in a French reference center, among more than 400 patients treated with DAAs.[10] The nine patients from the FDA report who developed bradyarrhythmia were undergoing amiodarone therapy. In the French report, only one patient was treated with this drug, one patient used a beta-blocker, and the third patient did not use antiarrhythmic drugs. These facts have raised questions about the possible effect of sofosbuvir on patient heart rates (HR).

The objective of this study was to evaluate the HR changes and other clinical and electrocardiographic parameters in patients with CHC during DAA treatment, including sofosbuvir, analyzed by a 12-lead electrocardiography (ECG) and a 24-h ambulatory electrocardiographic monitoring (Holter system),

## Methods

### Subjects

The present study was developed at the Hospital das Clínicas, Universidade Federal de Pernambuco (HC-UFPE), Brazil. We included patients older than 18 years of age with CHC, characterized by serum anti-HCV positivity for more than 6 months and confirmed by the presence of serum HCV-RNA, who met the criteria for treatment with the new DAAs established under the Clinical Protocol and Therapeutic Guidelines for Hepatitis C and Coinfections set forth by the Brazilian Ministry of Health (PCDT-2015).[11] This protocol states that patients should present at least one of the following criteria: hepatic fibrosis (documented METAVIR ≥ F2), clinical signs of liver cirrhosis, HIV coinfection, extrahepatic hepatitis C, hematological malignancies, idiopathic thrombocytopenic purpura, or previous transplant of solid organs.

Patients taking amiodarone were excluded, as were patients with severe heart disease, persistent cardiac arrhythmias [atrial tachycardia, atrial fibrillation or flutter, and second- or third-degree atrioventricular (AV) block], cardiac pacemakers, and chronic renal failure with a glomerular filtration rate ≤ 30 mL/min.

### Methodology

The patients were interviewed and examined at the Hepatology outpatient clinic, in the Gastroenterology Section at HC-UFPE. After study inclusion, 10 mL of venous blood was also collected through the vacutainer system to measure the hematologic, virologic, and liver function tests.

The laboratory tests were performed by automated method at the Central Laboratory of HC-UFPE. HCV RNA and HCV genotype were determined by real-time polymerase chain reaction using COBAS AmpliPrep/ COBAS TaqMan (version 2, Roche, Pleasanton, CA, USA) with a detection limit of 15 IU / ml. Hepatic fibrosis was assessed through the histopathology of a liver biopsy specimen, using the METAVIR classification, point shear wave elastography (pSWE), or Fib4 and APRI serologic scores. The percutaneous liver biopsies were performed using a 16 G x 90 mm Menghini needle in, at most, two punctures. The pSWE was determined by Acoustic Radiation Force Impulse (ARFI) using ACUSON S2000™ ultrasound (Siemens, Muenchen, Germany). The APRI and FiB-4 scores were calculated as described by Wai et al.[12] and Sterling et al.[13] Advanced liver fibrosis was considered when METAVIR F3 or F4, FIB-4 > 3.5, and APRI > 1.5.

Cirrhosis was defined as the presence of clinical and laboratory signs of hepatic impairment, as well as alterations in the hepatic architecture and/or signs of portal hypertension observed in ultrasonography or upper gastrointestinal endoscopy.

The cardiovascular evaluation involved the investigation of specific symptoms, including dyspnea, chest pain, palpitation, and syncope, as well as risk factors, such as systemic arterial hypertension (SAH), diabetes mellitus (DM), previous heart disease, coronary artery disease (CAD), cardiac arrhythmias, and the use of cardiovascular drugs, particularly antiarrhythmic agents.

The 12-lead ECG was recorded using an EP 12 eletropágina® digital apparatus (Dixtal Biomédica®, São Paulo, Brazil). The ECG traces were evaluated by a single examiner with experience in the method. The measurements of the intervals (in milliseconds) were obtained manually, with extended traces, if necessary, at minimum intervals of approximately 10 ms. For the heart rate (HR) measurement, the RR interval was determined in at least three consecutive QRS complexes and the mean value was used to calculate the final value. The same approach was used to calculate the QT interval. In the

sinus rhythm, normal HR was defined as 60–100 bpm. HR < 60 bpm was considered sinus bradycardia and HR > 100 bpm was considered sinus tachycardia. The normal PR interval was considered to be 120–200 ms. AV block was classified as first degree (PR interval > 200 ms), second degree type I (progressive increase of PR interval before a blocked P wave), type II (P wave blocked without previous PR interval increase), 2:1 (two P waves for each QRS complex), advanced (two or more blocked P waves), and third degree (complete AV block). Intraventricular conduction delays were classified as bundle branch block (right and left) and left fascicular block (anterior and posterior). The QT intervals were corrected using the Bazett formula, defined by the measured QT interval divided by the square root of the RR interval in seconds ($QT/\sqrt{RR}$). Corrected QT (QTc) intervals between 350 and 450 ms in males and 350 and 460 ms in females were considered normal.[14] QTc intervals above 480 ms were considered a significant increase.

The Cardios® system (São Paulo, Brazil) was used for 24-h Holter monitoring. Three simultaneous leads were digitally recorded using Cardiolight® recorders, and the traces were analyzed using the Cardiosmart® software. The analysis was performed by a single examiner experienced in the method. The following parameters were evaluated: minimum, median, and maximum HR; presence of frequent supraventricular arrhythmias (number of supraventricular ectopic beats >30/h), supraventricular tachycardia lasting for >10 s, recurrent ventricular arrhythmias (number of ectopic beats >30/h), non-sustained or sustained ventricular tachycardia, the presence of pauses for >3 s, and impairment in atrioventricular or intraventricular conduction.

The patients included in the study underwent the first cardiac evaluation with ECG and 24-h Holter monitoring. Subsequently, the patients started treatment schemes with DAAs (sofosbuvir combined with either daclatasvir or simeprevir ± ribavirin) for 12–24 weeks. Reassessment during therapy was scheduled 10–40 days after the first dose of the antivirals and included an additional medical consultation, ECG, and 24-h Holter monitoring. Patients were informed about the onset of warning symptoms, including palpitation, shortness of breath, chest pain, dizziness, and syncope. In these cases, they should seek immediate medical care to detect clinical changes outside the evaluation periods. All patients underwent cardiovascular monitoring until 30 days after the end of therapy.

### Statistical analysis

The statistical analysis was performed using the package SPSS Statistics®, version 21 (IBM®). The descriptive analysis included clinical and laboratory variables. Continuous data were presented as mean ± standard deviation (SD) or median and interquartile range (IQR) in the case of the presence or not of normal distribution, respectively. The ECG parameters (HR, PR interval, QRS duration, and QTc interval) and Holter monitoring parameters (minimum, median, and maximum HR) were compared before and during HCV treatment. Inferential analysis of quantitative variables was conducted using homogeneity and normal distribution tests (Kolmogorov-Smirnov and Shapiro-Wilk tests) to determine the use of parametric tests (Student's t-test) or non-parametric tests (Wilcoxon and Mann–Whitney tests). The chi-square test and Fisher's exact test were used for the categorical variables. P-values < 0.05 were considered statistically significant.

### Ethical approvals and consent to participate

The study was approved by the Ethics and Research Committee on Human Beings, UFPE Health Sciences Center (approval no: 1.566.240), and the patients who agreed to participate in the study were asked to sign an informed consent form.

## Results

From December 2015 to August 2017, 53 patients were evaluated. Two patients were excluded from the study because of the presence of chronic arrhythmias (atrial fibrillation and flutter, respectively) and three patients were excluded because they failed to attend the subsequent evaluations. Of the three patients who did not undergo reevaluation, two finished the therapy without complications. The third patient discontinued antiviral therapy without medical advice; however, no complications were found to justify the discontinuation of the treatment. Therefore, 48 patients comprised the final study sample and underwent cardiovascular monitoring.

The following drug combinations were used: sofosbuvir, daclatasvir, plus ribavirin - 21 patients (43.8%); sofosbuvir plus simeprevir - 15 patients (31.2%); sofosbuvir plus daclatasvir - 11 patients (22.9%); and sofosbuvir, simeprevir plus ribavirin - 1 patient (2.1%).

The mean age of the patients was 61 ± 9.8 years (range 37–81), and most patients (56.3%) were males.

Two patients (4.3%) had a positive serology for HIV. The evaluation of liver fibrosis stages was obtained by liver biopsy in 34 patients, by hepatic elastography in one patient, and by APRI and FIB 4 scores in 13 patients. Thirty-three patients (68.8%) presented advanced liver fibrosis, while 21 patients (43.8%) had a clinical diagnosis of liver cirrhosis. The HCV genotype 1 was present in 73% of the sample. Eleven patients (22.9%) were using beta-blockers. Clinical and laboratory data on liver disease are summarized in Table 1.

Specific symptoms were present in 25% of the patients in the initial cardiovascular evaluation. Dyspnea was the most common symptom, alone or combined with other complaints, and was reported by nine patients (18.8%), although none of these cases included cardiac or respiratory changes. With respect to the history of cardiovascular problems, SAH and DM were observed in 56.3% and 39.6% of the sample, respectively. Only one patient had a diagnosis of CAD with previous myocardial revascularization surgery.

Four patients (8.3%) reported symptoms in the reassessment performed after an average of 18.7 ± 9.4 days of treatment initiation. Three (6.2%) of these patients reported palpitations, and one reported dyspnea, which had no association with diagnosed cardiac changes. The systolic blood pressure (131.6 ± 20.8 vs. 128.2 ± 15.8, p = 0.3) and diastolic blood pressure (76.8 ± 10.3 vs. 78 ± 10.5, p = 0.4) before and during treatment were not significantly different.

The baseline ECG data showed changes in 14 patients (29.2%). Sinus bradycardia was the most common finding, found in six patients (12.5%), with HR values ranging from 50 to 60 bpm. First-degree AV block was observed in two patients (4.2%), intraventricular conduction delays in six (12.5%) patients, and increased QTc interval in four patients; however, none of these patients had QTc values > 480 ms. The second ECG recording performed during therapy was considered abnormal in 14 patients (29.2%), particularly in four patients (8.3%) with a long QTc interval, two of whom did not present this alteration at baseline. However, the increase in the QT interval was considered mild in three of the four patients (from 461 to 471 ms) and significant in only one patient (464 ms in the first examination and 494 ms in the second examination). Furthermore, this increase was not correlated with significant changes in the T-wave morphology or the presence of polymorphic ventricular arrhythmias analyzed by 24-h Holter monitoring, and treatment interruption was not necessary. This patient finished therapy without suffering cardiac complications.

The 24-h Holter monitoring did not indicate a significant difference in the minimum, medium, and maximum HR values and the presence of recurrent supraventricular or ventricular arrhythmias when comparing the periods before and during treatment (Table 2). Two patients without ventricular arrhythmias at baseline had a high frequency of ventricular extrasystoles during therapy, corresponding to 13.3% and 3.4% of the total heart beats, respectively. The increase in the number of ventricular ectopic beats in these patients was not associated with the presence of symptoms or other cardiovascular alterations, and interruption of treatment was not indicated. No cases of supra-ventricular or ventricular tachycardia or significant bradycardia with pauses exceeding 3 s were observed. None of the patients using DAAs had cardiovascular complications that required the discontinuation of treatment.

Subgroup analysis was performed to assess the effect of beta-blockers or advanced liver disease on ECG and 24-h Holter monitoring parameters. Eleven patients were on beta-blockers, with propranolol being used by six of them. The use of beta-blockers did not affect the ECG and HR parameters evaluated by 24-h Holter monitoring before and after therapy (Table 3). Moreover, the use of ribavirin by 22 patients did not affect the ECG and HR parameters evaluated by 24-h Holter monitoring before and after therapy. No differences were found before and during treatment: minimum HR (52.48 ± 7.34 vs 54.76 ± 9.15 bpm, p = 0.06), median HR (73.67 ± 10.48 vs 74.48 ± 10.13 bpm, p = 0.58), and maximum HR (114.71 ± 14.24 vs 112.33 ± 16.45 bpm, p = 0.36), respectively. Similarly, there were no significant differences in these parameters when comparing the periods before and during antiviral therapy in the 21 patients with cirrhosis.

However, during the treatment with DAAs, the 21 patients with cirrhosis presented significantly lower median HR and maximum HR values analyzed by 24-h Holter monitoring than did the patients without cirrhosis (Table 4). This difference was possibly due to a slight decrease in maximum HR during treatment in cirrhotic patients and the slight increase in median HR and maximum HR in non-cirrhotic patients (Table 4).

## Discussion

Our findings did not demonstrate the presence of significant changes in the ECG parameters and HR evaluated by dynamic ECG (24-h Holter monitoring) during treatment with DAAs. To date, no studies

have been found in the literature that evaluate 24-h Holter monitoring during treatment with DAAs for CHC patients.

At the beginning of the CHC treatment with these new antivirals, some reported cases of severe bradyarrhythmia that were associated with prior use of amiodarone, and the clinical complication was explained by the interaction between this drug and DAAs, particularly sofosbuvir.[15] Therefore, some studies have investigated the cardio-vascular safety profile of DAAs. In effect, Caldeira et al. performed a meta-analysis that included six large studies and 1,625 patients with CHC on antiviral therapy and found no significant differences in the rate of occurrence of cardiac arrhythmias between patients receiving sofosbuvir and those receiving other treatment regimens without this drug. The presence of arrhythmias was defined by the ECG records or compatible symptoms, including palpitations, pre-syncope, or syncope, and was reported in only three of these studies, with an overall risk of approximately 2% in patients using sofosbuvir.[16]

In effect, Durante-Mangoni et al. found that 26 patients on sofosbuvir regimens did not present changes in HR on serial ECG, including patients using beta-blockers, which suggested that this drug does not increase the risk of developing bradyarrhythmia during treatment with DAAs. These authors reported that the QTc interval increased in the first week after beginning therapy and returned to baseline levels during treatment.[17] Nonetheless, changes in HR were not found in the 11 patients from our study who were using beta-blockers, analyzed by 24-h Holter monitoring.

Additionally, there were four cases of increased QTc interval during treatment among our patients, although the interruption of antiviral therapy was not necessary, since this increase was either mild or moderate (QTc below 480 ms) in three patients and significant in only one case, which was not associated with ventricular arrhythmias or changes in T-wave morphology analyzed by 24-h Holter monitoring. Hagiwara et al.,[18] found cardio-vascular changes related to antiviral therapy in three cases (3.3%) among 91 patients using sofosbuvir plus ledipasvir. According to these authors, one of the patients presented bradycardia and increased QT interval, another patient developed atrial fibrillation, and the third patient presented a prolonged QT interval associated with previous heart failure. The three patients presented clinical improvement after discontinuing the treatment.[18] In contrast, Biomy et al.[19] evaluated patients using sofosbuvir plus simeprevir and found no cardiovascular events or changes in clinical, electrocardiographic, and echocardiographic parameters within 6 months after treatment.[19]

In the present study, two of the non-cirrhotic patients who did not present ventricular arrhythmia before therapy did show a high rate of monomorphic ventricular arrhythmia when analyzed by 24-h Holter monitoring during treatment. The occurrence of ventricular arrhythmia was also reported by Nirei et al. in two cirrhotic patients with spontaneous resolution.[20] The asymptomatic monomorphic ventricular tachycardia occurred at the beginning of therapy with sofosbuvir plus ledipasvir, leading to the interruption of treatment. These authors did not investigate the mechanisms involved in the onset of the arrhythmias but recommended caution in the use of these drugs in patients with advanced liver disease.[20]

In the present study, HR was evaluated in patients with cirrhosis, and in this subgroup, the use of DAAs did not induce the development of significant bradyarrhythmia. The median and maximum HR values evaluated by 24-h Holter monitoring were lower in patients with liver cirrhosis than in non-cirrhotic patients, particularly during treatment, with a decrease in HR values compared with baseline values. Moreover, the use of DAAs appears to increase the median and maximum HR in non-cirrhotic patients. It is noteworthy that these findings were not associated with the use of beta-blockers, which is prescribed for portal hypertension in cirrhotic patients. Likewise, no differences were found in HR during ribavirin use, although this drug may induce hemolytic anemia, which can increase the HR.[21]

The degree of hepatic dysfunction may affect cardiac and autonomic function, causing chronotropic incompetence and an increase in the QT interval.[22] Other authors have reported a lower HR in response to physical or pharmacological stress in cirrhotic patients, as evidenced by maximum HR values in provocation tests, such as physical effort in cycle ergometry[23] or the use of dobutamine.[24] Two mechanisms that lead to this alteration are decreased sensitivity of cardiac beta-adrenergic receptors as a consequence of the chronic hyperadrenergic state observed in cirrhotic cardiomyopathy (down-regulation) and the impairment of other factors involved in sympathetic signal transduction, including the receptor and the activity of G protein and adenyl cyclase, resulting in a decrease in cAMP levels.[25] These changes in HR have not yet been described when using 24-h Holter monitoring

in patients with CHC during treatment with DAAs. The mechanism by which DAAs sensitize chronotropic incompetence in patients with cirrhosis or even increase the HR in non-cirrhotic individuals remains unclear.

The results of this study reinforce the cardiovascular safety profile of the treatment of CHC with DAAs. The widespread use of this therapy in several countries and the low number of complications in the medical literature strongly suggest that the reported complications are due to other factors, including the concomitant use of antiarrhythmics, as well as existing cardiac problems or other cardiovascular risk factors. The strength of this study was the use of 24-h Holter monitoring to evaluate the dynamic characteristics of HR, which allowed for the detection of cardiac arrhythmias, even in the absence of symptoms. In addition, strict parameters were used to define ECG changes, including abnormal QTc intervals > 450 ms instead of values starting from 440 ms, which is the cut-off used in most studies.

One limitation of this study was the low number of patients in the sample due to the high cost of treatment with DAAs, which restricted the access to therapy offered by the Brazilian public health system to patients with more advanced liver disease or comorbidities. This public policy has been reviewed in recent years when treatment became available to all CHC patients.

Another limitation of this study may have been the completion of the evaluation by ECG and 24-h Holter parameters between 10 and 14 days after the start of antiviral therapy, which may have caused some changes in HR that have not been diagnosed. For that reason, long-term continuous ECG monitoring, immediately after beginning treatment, could be more effective in detecting cardiac arrhythmias.

## Conclusion

Our results demonstrate that HCV treatment with DAAs, including sofosbuvir, was not associated with significant clinical and ECG changes, and did not affect the main ECG or 24-h Holter parameters, even in patients using beta-blockers and ribavirin. Long QT interval and ventricular arrhythmia occurred in isolation and did not require the discontinuation of therapy. However, the use of DAAs appears to decrease the median and maximum HR in patients with cirrhosis analyzed by 24-h Holter monitoring. Further studies with larger sample sizes are necessary to confirm our findings.

## Author contributions

Conception and design of the research: Lopes E, Markman-Filho B, Filgueira N, Rezende A. Acquisition of data: Rezende A, Costa W, Felix P. Analysis and interpretation of the data: Rezende A, Lopes E, Batista A, Markman-Filho B. Statistical analysis: Rezende A, Lopes E. Writing of the manuscript: Rezende A. Critical revision of the manuscript for intellectual content: Lopes E, Batista A, Markman-Filho B.

### Potential Conflict of Interest

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

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There were no external funding sources for this study.

### Study Association

This article is part of the thesis of master submitted by André Gustavo da Silva Rezende, from *Universidade Federal de Pernambuco*.

### Ethics approval and consent to participate

This study was approved by the Ethics Committee of the CCS/UFPE under the protocol number 1.566.240. 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.

### Erratum

In Original Article "Treatment of Hepatitis C with Direct-Acting Antivirals does not Induce Significant Arrhythmias", with DOI number: https://doi.org/10.36660/ijcs.20200220, published in ahead of print in the journal International Journal of Cardiovascular Sciences, 2021; [online].ahead print, pp. 0-0, tables 1, 2, 3 and 4 can be found in the supplementary material link: http://ijcscardiol.org/supplementary-material/2022/3505/2020-0220-suplementar-tables.pdf

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ORIGINAL ARTICLE

# Association between Cardiovascular Risk in Adolescents and Daily Consumption of Soft Drinks: a Brazilian National Study

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## Abstract

**Background:** Cardiovascular risk in adolescence is a public health problem that has grown along with the increase in soft drink consumption.

**Objective:** To investigate the association between cardiovascular risk factors and daily consumption of soft drinks in Brazilian adolescents.

**Methods:** We conducted a cross-sectional, national, school-based study of 36,956 Brazilian adolescents aged 12 to 17 years. Daily soft drink consumption was estimated using a 24-hour dietary recall. Cardiovascular risk was categorized as overweight, obesity, hypertension, hyperglycemia, and dyslipidemia. The survey command of Stata 14.0® was used to analyze data from a complex sample. The chi-square test was used to assess differences in soft drink consumption and other variables in the descriptive analysis. The odds ratio of cardiovascular risk factors and their respective 95% confidence intervals were estimated, considering sociodemographic and behavioral variables in the Mantel-Haenszel model. Statistical significance was set at $p < 0.05$.

**Results:** Daily consumption of soft drinks was common among adolescents. A daily serving ≥ 450 mL was significantly associated with overweight and hypertension. Results associated with the consumption of regular soft drinks show the possibility of reverse causality. Consumption of diet soft drinks in adolescence should be considered a cardiovascular risk factor.

**Conclusion:** Daily consumption of soft drinks can be understood as a relevant risk factor in the epidemiological scenario. Improper eating habits are multifactorial in nature and need to be better understood in the context of adolescent health and further explored in national surveys.

**Keywords:** Adolescent; Dietary Sugars, Food and Beverages; Cardiovascular Diseases; Risk Factors; Control and Sanitary Supervision of Foods and Beverages; Healthy Surveys.

## Introduction

Cardiovascular disease (CVD) is a leading cause of death in Brazil, accounting for approximately 20% of all deaths in individuals over 30 years of age.[1] Unhealthy diets and physical inactivity are the main contributors to overweight and obesity, identified as major risk factors for chronic noncommunicable diseases (NCDs).[2]

Surveillance and monitoring of risk factors are effective actions to tackle NCDs. Dietary habits influence the growth and development of individuals, and they seem to vary with sex, age, culture, ethnicity, and socioeconomic status. Unhealthy eating habits and high consumption of soft drinks are common during adolescence, but food choices vary among adolescents.[3]

Both the frequency and amount of soft drink consumption have increased worldwide. In Brazil, the Household Budget Survey found variations of up to 400% in the consumption of soft drinks from 1975 to 2003.[4] When analyzing high-risk behaviors for CVD during adolescence, data from the Brazilian National School Health Survey showed that 27.2% (95% confidence

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interval [CI], 26.1%-28.4%) of the adolescents surveyed consume soft drinks 5 or more days per week.[5]

Limiting soft drink consumption can contribute to reducing weight gain and associated chronic diseases, such as cardiometabolic diseases. Public policies have been adopted to promote health and to reduce soft drink consumption especially in childhood and adolescence, but compensation mechanisms have limited the benefits of these actions.[6-8]

Early interventions have been successful in reducing CVD with the potential to change the current epidemiological scenario.[9] Adolescent exposure to unhealthy habits, such as high consumption of soft drinks, is associated with increased cardiovascular risk and greater lifetime accumulation of exposure. Cardiovascular risk factors include overweight and obesity, dyslipidemia, hypertension, insulin resistance, sedentary lifestyle, and atherogenic diet.[10]

Great human potentialities are developed during adolescence and may have repercussions in adulthood. A better understanding of risk factors common to this age group can strengthen public policies and guide more effective health actions for changes in the epidemiological profile. Therefore, this study aimed to investigate the association between cardiovascular risk factors and daily consumption of soft drinks in Brazilian adolescents.

## Methods

This study analyzed data from the Brazilian Study of Cardiovascular Risks in Adolescents (ERICA), whose methodological approach was based on conglomerate sampling, minutely described in preliminary studies.[11,12]

We conducted a cross-sectional, multicenter, national, school-based study that covers the population of adolescents aged 12 to 17 years enrolled in public or private schools in Brazilian municipalities with more than 100,000 inhabitants.

The data were collected between March 2013 and December 2014. A total of 1251 schools in 124 Brazilian municipalities were selected, for a total sample of 36,956 adolescents with complete data from a self-report questionnaire, 24-hour dietary recall (24-HDR), and physical and biochemical examinations. The sample is representative of the population of Brazilian adolescents at the national and regional levels, for the capital cities and the Federal District.

Food consumption was estimated based on 24-HDR data, collected using ERICA-REC24h, a computer-based direct data collection platform. The software was developed from a database consisting of 1626 food items, including preparation methods and units of predefined serving sizes. The database was developed by the Brazilian Institute of Geography and Statistics and used in the 2008-2009 National Diet Survey.[13,14] Reported foods that were not included in ERICA-REC24h were incorporated by the researchers.

Beverages reported by the adolescents in 24-HDRs were divided into 6 groups: flavored dairy drinks, soy-based beverages, juices and fruit drinks, regular soft drinks, diet soft drinks, and other (beverages that did not fit any of the previous groups).[15]

Participants' sex, age group, and Brazilian region were treated as sociodemographic variables. Eating habits (calories consumed daily and the percentage of sugar in the diet) and sedentary lifestyle (screen time > 2 hours/day) were treated as behavioral variables.

Cardiovascular risks were investigated by anthropometric assessment, blood pressure measurement, and biochemical blood tests using fasting blood samples.[16-18] Cardiovascular risk factors in adolescence were defined as follows: overweight and obesity, classified according to body mass index; hypertension, when systolic or diastolic blood pressure corresponded to the 95th percentile or higher; hyperglycemia, defined as fasting blood glucose ≥ 126 mg/dL; and dyslipidemia, defined as total cholesterol ≥ 170 mg/dL, LDL-cholesterol ≥ 130 mg/dL, HDL-cholesterol < 45 mg/dL, and/or triglycerides ≥ 130 mg/dL. Sex, age, geographic region, and screen time (> 2 hours/day) were used as adjustment variables.

### Statistical analysis

Data were analyzed in Stata 14.0®, and the effect of sample design and expansion based on sample weight were considered by using the *survey* command. A 95% CI was adopted, and the level of statistical significance was set at $p < 0.05$.

The chi-square test was used to assess the association between variables in the descriptive analysis. For inferential analyses, soft drink consumption was categorized by using the median daily consumption of regular soft drinks (450 mL) as a cutoff point. The odds ratio of cardiovascular risk was calculated by associating soft drink consumption with

sociodemographic and behavioral adjustment variables in the Mantel-Haenszel model.

The study met the ethical requirements of the Declaration of Helsinki and was approved by the Research Ethics Committee of the Institute for Studies in Collective Health at the Federal University of Rio de Janeiro (Process 45/2008). Only adolescents who agreed in writing and whose guardians signed the informed consent form participated in the study. The confidentiality and anonymity of the participants were preserved in this study.

## Results

The consumption of sugar-sweetened beverages was high among adolescents attending schools in Brazilian cities with more than 100,000 inhabitants. The mean age of the participants was 14.7 years (range, 12 to 17 years), and 60% were female. Geographic region was a determinant of soft drink consumption (p = 0.000).

As shown in Table 1, beverages in the groups 'juices and fruit drinks,' 'regular soft drinks,' and 'flavored dairy drinks' were the most frequently reported in the 24-HDR by Brazilian adolescents. As measured by the median, the highest daily servings were found in the groups 'regular soft drinks' (450 mL) and 'juices and fruit drinks' (300 mL). Flavored dairy drinks, soy-based beverages, and diet soft drinks had values of 240 mL/day.

The ratio of the amount of added sugar to the total daily energy value, in calories, was checked for the different groups. The groups 'regular soft drinks' and 'juices and fruit drinks' had a ratio of 8.06% and 6.78%, respectively. Diet soft drinks do not contain sugar, which is why the ratio was zero. Daily servings of sugar-sweetened beverages were high and often positively correlated with daily energy (calorie) increase in adolescents, probably because of the added sugar from these drinks (Table 1).

Table 2 presents the distribution of sociodemographic, behavioral, and cardiometabolic characteristics of adolescents in the ERICA study according to the consumption of regular and diet soft drinks. Only 1.06% (n = 391) of the sample reported consuming diet soft drinks in the 24-HDR. In contrast, 45.21% (n = 16,708) reported consuming regular soft drinks. The consumption of soft drinks varied according to the different independent variables (Table 2).

Soft drink consumption was significantly associated with overweight, obesity, and hypertension (p < 0.05), as shown in Tables 3 and 4. Adolescents who consumed more regular soft drinks had a lower odds ratio for overweight, obesity, and hypertension (Table 3). The odds ratio for overweight, obesity, and hypertension increased with increasing servings of diet soft drinks (Table 4). The distribution of associations remained constant after adjustments.

## Discussion

Data from the 2017-2018 Brazilian Household Budget Survey show that soft drinks are the beverages with the highest average daily per capita consumption in Brazil (67.1 g/day). The average daily per capita soft drink consumption in the South is twice as high as in the North and Northeast.[19]

Considered a marker of an unhealthy dietary pattern, soft drink is a beverage made from carbonated water

**Table 1 – Description, median (mL) and ratio (%) between added sugar and the total energy value of beverages reported in the 24-HDR[1] by Brazilian adolescents. ERICA[a], Brazil, 2013-2014**

| Beverage group | Description | N | %[b] | Median (mL) | Ratioc (%) |
|---|---|---|---|---|---|
| Flavored dairy drinks | Dairy drinks sweetened with artificial or natural flavors, and fermented milk | 7,341 | 9.38 | 240 | 2.75 |
| Soy-based beverages | Soy milk and soy-based beverages | 124 | 0.19 | 240 | 2.75 |
| Juices and fruit drinks | Natural and processed fruit juices | 20,462 | 24.12 | 300 | 6.78 |
| Regular soft drinks | Sugar-sweetened soft drinks | 16,708 | 20.72 | 450 | 8.06 |
| Diet soft drinks | Diet and light soft drinks | 391 | 0.46 | 240 | 0.00 |
| Other | Other beverages consumed by adolescents reported in the 24-HDR | 36,953 | 45.14 | 1005 | 9.40 |

*[1] 24-HDR: 24-hour dietary recall. [a] Data extracted from the database of the 2013-2014 Brazilian Study of Cardiovascular Risks in Adolescents; [b] Sample effect considered in the analysis; [c] Ratio (%) = added sugar from the beverage group (kcal/day)/total energy value (kcal/day).*

**Table 2 – Association between daily soft drink consumption and independent variables in Brazilian adolescents. ERICA[a], Brazil, 2013-2014**

| Variable | Regular soft drinks | | Diet soft drinks | |
|---|---|---|---|---|
| | n (%) | p-value[b] | n (%) | p-value[b] |
| **Do not consume** | 20,248 (54.79) | | 36,565 (98.94) | |
| **Consume** | 16,708 (45.21) | | 391 (1.06) | |
| **Sex** | | | | |
| *Female* | 9,882 (26.74) | 0.00 | 227 (0.61) | 0.43 |
| *Male* | 6,826 (18.47) | | 164 (0.44) | |
| **Age group** | | | | |
| *12-14 years* | 7,823 (21.17) | 0.00 | 185 (0.50) | 0.54 |
| *15-17 years* | 8,885 (24.04) | | 206 (0.56) | |
| **Brazilian macro-regions** | | | | |
| *North* | 2,937 (7.95) | 0.00 | 52 (0.14) | 0.00 |
| *Northeast* | 5,047 (13.66) | | 92 (0.25) | |
| *Southeast* | 3,956 (10.70) | | 131 (0.35) | |
| *South* | 2,282 (6.17) | | 59 (0.16) | |
| *Central West* | 2,486 (6.73) | | 57 (0.15) | |
| **Screen time** | | | | |
| *≤ 2 hours/day* | 6,155 (16.65) | 0.00 | 130 (0.35) | 0.03 |
| *> 2 hours/day* | 9,204 (52.42) | | 230 (0.62) | |
| *Do not know* | 1,349 (3.65) | | 31 (0.08) | |
| **Total energy in 24-HDR[1]** | | | | |
| *≤ 2000 kcal/day* | 6,483 (17.54) | 0.00 | 185 (0.50) | 0.27 |
| *2000-3000 kcal/day* | 5,957 (16.12) | | 137 (0.37) | |
| *≥ 3000 kcal/day* | 4,268 (11.55) | | 69 (0.19) | |
| **Added sugar[c]** | | | | |
| *≤ 5% total energy/day* | 8,151 (22.06) | 0.00 | 274 (0.74) | 0.00 |
| *> 5% total energy/day* | 8,557 (23.15) | | 117 (0.32) | |
| **Cardiovascular risk** | | | | |
| Overweight | | | | |
| *Yes* | 4,078 (11.03) | 0.00 | 133 (0.36) | 0.00 |
| *No* | 12,630 (34.18) | | 258 (0.70) | |
| Obesity | | | | |
| *Yes* | 1,287 (3.48) | 0.00 | 47 (0.13) | 0.00 |
| *No* | 15,421 (41.73) | | 344 (0.93) | |
| Hypertension | | | | |
| *Yes* | 1,464 (3.96) | 0.04 | 47 (0.13) | 0.04 |
| *No* | 15,244 (41.25) | | 344 (0.93) | |
| Hyperglycemia | | | | |
| *Yes* | 516 (1.40) | 0.37 | 18 (0.05) | 0.06 |
| *No* | 16,192 (43.81) | | 373 (1.01) | |
| Dyslipidemia | | | | |
| *Yes* | 13,022 (35.24) | 0.30 | 314 (0.85) | 0.30 |
| *No* | 3,686 (9.97) | | 77 (0.21) | |

*[1] 24-HDR: 24-hour dietary recall. [a] Data extracted from the database of the 2013-2014 Brazilian Study of Cardiovascular Risks in Adolescents; [b] Chi-square test; [c] The World Health Organization (2015) states that greater health benefits can be achieved if the daily consumption of sugar is reduced to 5% of the calories ingested*

**Table 3 – Association between cardiovascular risk and daily consumption[a] of regular soft drinks in Brazilian adolescents. ERICA[b], Brazil, 2013-2014.**

| Cardiovascular risk | OR[1] (95% CI) | p-value | OR[2] (95% CI) | p-value | OR[3] (95% CI) | p-value |
|---|---|---|---|---|---|---|
| Overweight | 0.93 (0.90-0.96) | 0.00 | 0.93 (0.90-0.95) | 0.00 | 0.93 (0.90-0.95) | 0.00 |
| Obesity | 0.94 (0.89-0.98) | 0.00 | 0.93 (0.89-0.98) | 0.00 | 0.93 (0.89-0.97) | 0.00 |
| Hypertension | 0.95 (0.91-0.99) | 0.04 | 0.95 (0.91-0.99) | 0.03 | 0.95 (0.91-0.99) | 0.03 |
| Hyperglycemia | 1.01 (0.94-1.09) | 0.66 | 1.01 (0.94-1.09) | 0.69 | 1.01 (0.94-1.09) | 0.73 |
| Dyslipidemia | 0.99 (0.96-1.02) | 0.67 | 0.99 (0.96-1.02) | 0.93 | 0.99 (0.96-1.02) | 0.75 |

*OR: odds ratio (p>0.05); 95% CI: 95% confidence interval.*
*[a] Serving ≥ 450 mL; bData extracted from the database of the 2013-2014 Brazilian Study of Cardiovascular Risks in Adolescents; [1] Analysis adjusted for sex and age group (12-14 years and 15-17 years); [2] Analysis adjusted for Brazilian macro-region; [3] Analysis adjusted for screen time > 2 hours/day.*

**Table 4 – Association between cardiovascular risk and daily consumption[a] of diet soft drinks in Brazilian adolescents. ERICA[b], Brazil, 2013-2014.**

| Cardiovascular risk | OR[1] (95% CI) | p-value | OR[2] (95% CI) | p-value | OR[3] (95% CI) | p-value |
|---|---|---|---|---|---|---|
| Overweight | 1.27 (1.11-1.44) | 0.00 | 1.25 (1.09-1.42) | 0.00 | 1.26 (1.10-1.43) | 0.00 |
| Obesity | 1.37 (1.11-1.68) | 0.00 | 1.34 (1.09-1.65) | 0.00 | 1.35 (1.10-1.66) | 0.00 |
| Hypertension | 1.26 (1.03-1.53) | 0.02 | 1.24 (1.02-1.52) | 0.02 | 1.22 (1.01-1.49) | 0.03 |
| Hyperglycemia | 1.21 (0.87-1.70) | 0.24 | 1.20 (0.86-1.66) | 0.27 | 1.20 (0.86-1.67) | 0.27 |
| Dyslipidemia | 1.10 (0.96-1.26) | 0.14 | 1.12 (0.98-1.29) | 0.08 | 1.13 (0.98-1.29) | 0.07 |

*OR: odds ratio (p>0.05); 95% CI: 95% confidence interval.*
*[a] Serving ≥ 450 mL; bData extracted from the database of the 2013-2014 Brazilian Study of Cardiovascular Risks in Adolescents; [1] Analysis adjusted for sex and age group (12-14 years and 15-17 years); [2] Analysis adjusted for Brazilian macro-region; [3] Analysis adjusted for screen time > 2 hours/day.*

that typically contains substances such as sodium, carbohydrates, and especially sugar.[20] Most Brazilian adolescents consume this beverage daily, and factors such as sex, age, and sedentary lifestyle are pointed out as determinants of unhealthy dietary behavior, varying according to geographic region.[21,15]

Liquid calories do not produce the same level of satiety as solid calories, and the consumption of soft drinks is often associated with excessive calorie intake and increased risk of obesity.[6,22] The World Health Organization recommends that sugar consumption should be reduced to 5% of the calories ingested daily, but consuming diet soft drinks, as a substitute for regular soft drinks, has also been associated with cardiovascular risk and should be considered in the development of public health policies.[23,24]

The association between sugar-sweetened beverages and chronic diseases is complex and can be confused by several factors.[25] Ambrosini *et al.*,[26] identified that the daily serving size of soft drinks influenced the increase in cardiometabolic risk, overweight, and obesity in girls. Among boys, there was a reduction in HDL-cholesterol levels, regardless of weight gain. All adolescents, both female and male, who increased their intake to more than 325 mL/day showed increased triglyceride levels.

In our study, soft drink consumption was negatively associated with overweight and hypertension in adolescents. A possible explanation for these results is the reverse causality effect, considering the cross-sectional design of the study, as restrictions on the consumption of sugar-sweetened beverages have been incorporated into recommendations for dietary changes to prevent cardiovascular risk.[22,23]

Replacing sugar-sweetened beverages by diet/light soft drinks has been pointed out as an alternative

to reduce sugar in the diet. Diet soft drinks are low-calorie beverages, but the artificial sweeteners in their composition can increase the storage of calories from other foods consumed. An increased consumption of diet soft drinks has been associated with increased risk of type 2 diabetes, CVD, and metabolic syndrome.[27] Also, diet soft drinks have more sodium than regular soft drinks, and the increased amount of sodium in the diet may be associated with higher blood pressure in adolescents who consume diet soft drinks than in those who consume regular soft drinks. This possibility should be considered by people on a recommended low-sodium diet.[28] Hypertension is strongly associated with adverse cardiovascular events, including heart failure, ischemic heart disease, and cerebrovascular diseases.[29]

It is important to highlight that the health-disease process is not associated simply with the presence or absence of a certain food in the diet, but rather with the set of foods consumed, their quantity and servings. Therefore, other independent pathways should be considered in the investigation of cardiovascular risk factors in adolescence.[25] For example, high screen time favors physical inactivity and greater consumption of obesogenic foods, in addition to causing distractions that interfere with the physiological signals of hunger and satiety. The media can negatively influence eating behaviors in adolescents, and high screen time contributes to both a sedentary lifestyle and excessive soft drink consumption.[30]

Regional specificities should be considered in the development of public policies aimed at promoting health and reducing cardiovascular risk in adolescents. It is known that the current epidemiological scenario is multifactorial and that social, demographic, and behavioral variables are associated with the development of cardiovascular risk factors in this population. Therefore, in-depth scientific studies on sociodemographic, behavioral, and epidemiological factors associated with soft drink consumption are essential, since the daily consumption of these beverages is high in adolescence. Associations between dietary habits and epidemiological risk factors need to be carefully observed.

One of the limitations of this study is the inability to establish a cause-and-effect relationship between soft drink consumption and cardiovascular risk, as the cross-sectional design makes it impossible to determine the time interval between the variables. However, there are few Brazilian population-based studies of adolescents on this topic with the amount of information provided in this study. The sample size and the standardization of methods and instruments used in data collection reinforce the reliability of the data reported in this study.

## Conclusions

Population-based studies investigating the consumption of sugar-sweetened beverages using a 24-HDR are still incipient, and the association of regular and diet soft drinks with cardiovascular risk factors in adolescents was a relevant finding in the present study.

Brazilian adolescents who are overweight and have hypertension may be realizing the importance of reducing the consumption of regular soft drinks, resulting in lower intake or greater underreporting of soft drink consumption in this group. In contrast, adolescents consuming larger servings of diet soft drinks were at greater risk of being overweight, obese, and hypertensive.

These data highlight the need to expand scientific research and strengthen health actions focused on soft drink consumption among adolescents, considering the susceptibilities and specific characteristics of this population. Adolescents' consumption of sugar-sweetened beverages needs to be explored as an important cardiovascular risk factor for the Brazilian epidemiological scenario and should not be ignored in the development of public policies within the environments in which adolescents live.

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### Author contributions

Conception and design of the research: Neves AFG, Vianna RPT. Acquisition of data: Neves AFG, Vianna RPT. Analysis and interpretation of the data: Neves AFG, Vianna RPT, Lopes MT. Statistical analysis: Neves AFG, Vianna RPT, Lopes MT. Writing of the manuscript: Neves AFG, Vianna RPT, Lopes MT. Critical revision of the manuscript for intellectual content: Neves AFG, Vianna RPT, Lopes MT.

### Potential Conflict of Interest

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

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### Study Association

This article is part of the thesis of Doctoral submitted by Ana Flávia Gomes de Britto Neves, from Universidade Federal da Paraíba.

### Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Institute for Studies in Coletive Health (UFRJ) under the protocol number 45-2008, report number 01/2009. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consente was obtained from all participants included in the study.

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EDITORIAL

# Daily Consumption of Soft Drinks and Cardiovascular Risk in Adolescents

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***Editorial referring to the article: Association between Cardiovascular Risk in Adolescents and Daily Consumption of Soft Drinks: a Brazilian National Study***

Cardiovascular disease (CVD) includes a group of diseases that affect the heart. These are considered a major public health problem and remain one of the main diseases of the 21st century due to their high morbidity and mortality. CVDs have also been appearing themselves more often even in childhood and adolescence.[1]

Among the factors associated with the increase in the prevalence of CVD are the increase in physical inactivity and reduced physical activity, as well as inadequate eating habits, such as a high intake of ultraprocessed foods, long intervals between meals, and a low consumption of fruits and vegetables, common especially among adolescents.[2] The short and long-term effects of such behaviors are worrisome, as they contribute to fat mass gain, risk factors for Chronic Noncommunicable Diseases (NCDs), responsible for 70% of annual deaths, representing an important cause of morbidity during adolescence.[3]

One of the most common unhealthy practices among teenagers is the regular consumption of sugar-sweetened beverages (SSB), including soft drinks. Data from a representative sample of the Brazilian population based on the National School Health Survey (PeNSE, 2016), showed that regular consumption (greater than 5 days a week) of soft drinks among adolescents was 19.1%, with the highest prevalence in the Midwest region with 21.7%. The consumption of SSB has been considered a factor that promotes obesity, and reducing its consumption has been identified as an important measure in the control of weight gain in children and adolescents. Moreover, a diet rich in fruits and vegetables, and with a minimal amount of SSB, shows a cardioprotective effect in adolescents.[4]

Neves and colleagues,[5] in their article published in the current issue, investigate the association between cardiovascular risk factors and the daily consumption of soft drinks in Brazilian adolescents. It was demonstrated that the daily consumption of soft drinks was common among adolescents; the median consumption was 450 ml for soft drinks, 300 ml for industrialized juices and fruit juices, and 240 ml for flavored dairy drinks, soy-based drinks, and diet sodas. A daily serving ≥450 mL was significantly associated with overweight, obesity, and hypertension ($p < 0.05$). In this sense, the consumption of diet soft drinks in adolescence should be considered a cardiovascular risk factor.

Chan et al.,[6] aiming to examine the gender-specific association of SSB with metabolic syndrome (MS) and its components among adolescents in Taiwan, carried out a cross-sectional study of 2,727 adolescents, aged 12 to 17 years. Demographic, dietary, physical, anthropometric, and blood parameters were evaluated. The presence of MS was determined according to the recommendations of the International Diabetes Federation (IDF). A higher intake of SSB was associated with greater waist circumference in both sexes and systolic blood pressure in boys ($p \leq 0.043$). Boys who consumed >500 mL/day of sugary drinks had a 10.3-fold (95% CI: 1.2-90.2) and 5.1-fold (95% CI: 1.01-25.5) risk of developing MS, as compared to an insignificant result in girls. Therefore, the results of this study show that sugary beverage intake is associated with MS in adolescence among boys, but not among girls in Taiwan.

## Keywords

Adolescent; Sugar-Sweetened Beverages; Heart Disease Risk Factors; Cardiovascular Diseases.

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Similar results were found by Hur et al.,[7] in their study carried out in Korea with the aim of identifying associations between total sugar intake and sugar intake from SSB, together with adiposity and ongoing metabolic syndrome (cMetS) scores among Korean children and adolescents, using cohort data with 770 participants. cMetS was calculated based on waist circumference, serum triglycerides, serum high-density lipoprotein (HDL) cholesterol, fasting glucose (blood sugar), and blood pressure. The results showed that there was a significant positive relationship between the consumption of SSB and cMetS at baseline ($\beta = 0.04$, $p = 0.02$), showing that this consumption may play an important role in the risk of adiposity and metabolic disease in children and adolescents.

Herran et al.[8] developed a representative study of the Colombian population, which involved the participation of 50,670 families with children (3,842) and adolescents (6,345), aged 5 to 17 years. To assess the consumption of SSB, a food frequency questionnaire (FFQ) was used, which evaluated the frequency of consumption of 30 foods or food groups in the 30 days prior to the survey. Anthropometric measurements and socioeconomic information were also obtained from the studied population.

It was observed that the prevalence of consumption of SSB in adolescents (aged 11 and 17 years) was 87.4%, and their average frequency of consumption was 0.77 times/day (95% CI, 0.74 to 0.80), with the highest consumption occurring among 16-year-old adolescents, with a prevalence of 90.4% and an average frequency of 0.83 times/day. All variables representing socioeconomic status were differently associated with consumption; however, being overweight was not associated with the consumption of SSB ($p>0.05$). Adolescents consume sugary drinks regardless of gender, but with a higher prevalence among older adults and people who live in urban areas. Furthermore, this study also observed that food security, family education, and the financial condition index were directly linked to the consumption of sugary drinks.[8]

Data from a meta-analysis performed by Farhangi et al. in 2020,[9] aimed at evaluating the effects of SSB intake on blood pressure in children and adolescents, revealed that a high consumption of SSB was associated with an increase of 1.67 mmHg in SSB in children and adolescents (WMD: 1.67; $p<0.001$). Children and adolescents who consumed high doses (above the recommendation) of these beverages were 1.36 times more likely to develop hypertension, when compared to those who consumed small amounts (OR: 1.365; $p=0.001$), which leads us to believe that a high consumption of sugary drinks increases SSB and hypertension in children and adolescents.

The results of the studies show a high prevalence of the consumption of SSB, including soft drinks, by adolescents, which is highly associated with being overweight, metabolic syndrome, diabetes, dyslipidemia, and hypertension. The results of a meta-analysis that evaluated the effectiveness of 16 behavioral nutritional interventions show that it as an effective strategy to reduce the consumption of SSB by adolescents.[10] In this sense, it is necessary to implement educational programs in order to raise awareness among students, parents, and families, in addition to improving the school environment, concerning the need to reduce the consumption of this type of food.

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ORIGINAL ARTICLE

# Interdisciplinary Group Intervention on Nutritional Profile, Quality of Life, and Stress During Cardiopulmonary Rehabilitation: A Randomized Clinical Trial

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## Abstract

**Background**: Participating in therapeutic operative groups with nutritional and psychological interventions might influence the recovery of patients in cardiopulmonary rehabilitation programs.

**Objective:** To evaluate the effectiveness of group interventions on the nutritional profile, stress, and quality of life of patients in cardiopulmonary rehabilitation.

**Methods**: In this randomized clinical trial, adult patients of the Cardiopulmonary and Metabolic Rehabilitation (CPMR) unit were randomized into control group (CG), receiving standard follow-up assessment by the CPMR unit, and intervention group (IG), which additionally participated in 6 meetings of an interdisciplinary group with a nutritionist and a psychologist. Anthropometric data and results from a food frequency questionnaire (FFQ), Lipp's Inventory of Stress Symptoms for Adults (ISSL), and the 12-Item Short Form Health Survey (SF-12) were analyzed. Student's t-tests, Generalized Estimation Equations (GEE), Mann-Whitney tests, and Bonferroni tests were used for statistical analyses, with a significance level of 5%.

**Results**: The sample consisted of 76 patients: 31 in the IG (64±9.2 years old) and 45 in the CG (61.4±11.8 years old). There was a significant reduction ($p<0.001$) in weight, body mass index, and waist circumference, and an increase ($p=0.010$) in the consumption of healthy food only in the IG. The consumption of unhealthy food was reduced in both groups ($p<0.001$), the physical aspect of quality of life improved ($p=0.018$), and women presented better physical ($p=0.011$) and mental results ($p=0.008$).

**Conclusions:** This group intervention was effective regarding the nutritional status of patients in cardiopulmonary rehabilitation. The physical aspect of quality of life showed improvements in both groups.

**Keywords:** Patient Care Team; Nutritional Status; Quality of Life; Stress; Psychological; Cardiac Rehabilitation.

## Introduction

Patients tend to face significant changes in their lives due to cardiovascular diseases (CVD). Considering that excess weight, obesity, and diseases such as diabetes, hypertension, and hypercholesterolemia are related to CVD, nutrition plays a fundamental role in the cardiac rehabilitation process.[1,2] From a psychological perspective, symptoms related to stress, anxiety, and depression are linked, for example, to increased vulnerability and the risk of a new cardiac event.[1-3] Therefore, psychological and nutritional aspects are important intervention tools in cardiopulmonary and metabolic rehabilitation (CPMR) programs.[4]

The South American Guidelines for Cardiovascular Disease Prevention and Rehabilitation define CPMR as the set of actions necessary to ensure that people with CVD have favorable biopsychosocial conditions that enable them to assume their roles in society.[4] Physical exercise acts as the main strategy for the effectiveness of a CPMR program, together with multi-professional interventions.[5]

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According to the INTERHEART study, the most prevalent cardiovascular risk factor is abdominal obesity, with a prevalence of 48.6% in Latin America compared to 31.2% in other participating countries.[6] A high calorie intake, rich in simple carbohydrates and saturated fats, associated to a sedentary lifestyle and psychosocial factors such as stress and depression, are responsible for this worldwide epidemic.[4]

Moreover, a Brazilian study with patients subjected to coronary angioplasty showed that 74% of the participants who received pre-intervention psychological assistance by the hospital did not present emotional stress signs. In the other group (without psychological assistance), 94% of the participants showed stress signs.[7]

Group work is essentially important to trigger awareness and reflection on participants. The main purpose of therapeutic operative groups is to improve an organic or mental condition, or both at the same time, favoring the interaction among participants who are experiencing similar situations and developing healthy coping strategies.[8,9]

The understanding of aspects related to the nutritional profile, stress, and quality of life of these patients is also fundamental to support effective interventions that are allied to cardiopulmonary rehabilitation (CPR) objectives. We were not able to identify, in the literature, studies that address these variables in a group context with patients in CPR programs. We also believe that the participation of patients in groups with professionals trained to guide them and clarify doubts and common feelings about falling ill and their rehabilitation might positively influence their general health status. Consequently, the aim of this study was to evaluate the effectiveness of an interdisciplinary group intervention on the nutritional profile, stress, and quality of life of patients in CPMR.

## Methods

The present study is a randomized clinical trial using variables such as nutritional status, stress, and the quality of life of adult patients with heart disease at the CPMR unit of a cardiology referral hospital. Randomization was performed using the www.randomization.com website, with a 1:1 ratio, including all patients treated at the CPMR unit who agreed to participate in this research. The study occurred from April to December 2017.

Using the study by Oliveira et al.,[10] (where 75% of the patients treated at a cardiac rehabilitation center were under stress) as parameter and aiming at a 25% reduction in the number of patients with this problem after this intervention, using an 80% power and a 5% significance level, a sample of 116 patients was calculated. Considering up to 20% of losses during the study, 140 patients were randomized (70 in each group). The randomization diagram is presented in Figure 1. Cardiac patients treated at the CPR unit, aged 18 years or older, who signed the informed consent form were included in the study. Patients who were unable to answer the questionnaires and/or did not attend appointments or the therapeutic operative group (intervention group) were excluded from the study. Patients who missed more than 2 meetings were excluded from the group.

All participants were evaluated at the beginning of the CPR program (maximum 2 weeks after the beginning of rehabilitation) and after a 3-month follow-up assessment (at the end of the program), where all instruments and multidisciplinary evaluations were reapplied. At the first individual appointment, trained professionals collected social demographic data, the reason for applying for the physical activity program, cardiovascular risk factors, family history, and anthropometry (weight, height, body mass index [BMI], and abdominal circumference), and applied a food frequency questionnaire (FFQ), Lipp's Inventory of Stress Symptoms for Adults (ISSL), and the 12-Item Short Form Health Survey (SF-12). Data collection was conducted by a team trained by the authors of this study.

The FFQ used in this study, adapted from Ribeiro,[11] is a semi-quantitative questionnaire that was validated for nutritional analysis and adult food consumption surveys in the Federal District of Brazil. Each group item (food) was evaluated as to its frequency of consumption by patients. Foods were divided into "healthy" and "unhealthy": healthy foods included milk, yogurt, chicken, fish, vegetables, and fruits; unhealthy foods included sausages, viscera, bacon, butter, mayonnaise, margarine, grease, fried food, fast-food, canned and frozen food, sweets, soft drinks, sugar, and industrialized food seasonings. The weight and height of the patients were obtained using an anthropometric Filizola® scale coupled with a stadiometer, with a capacity of 150 kg. Abdominal circumference was measured at the level of the umbilicus using a measuring tape, according to Willis.[12]

ISSL is used to identify the symptoms of stress and its current phase (alert, resistance, near-exhaustion, and exhaustion) in adults. Since stress is associated with risk factors for CVD, its identification and control become

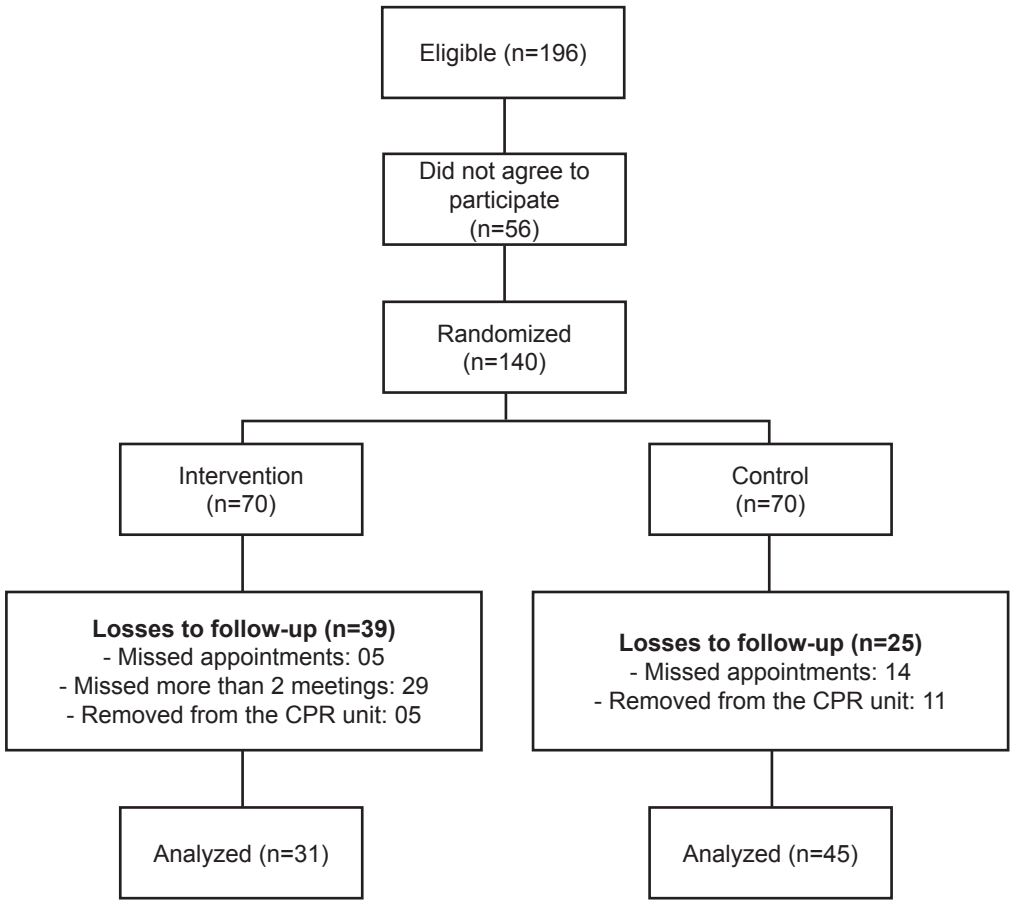


**Figure 1 – Randomization diagram.**

important . ISSL includes 37 somatic symptoms and 19 psychological symptoms. In some cases, the symptoms are recurrent and vary only in intensity. Patients are questioned about the occurrence of these symptoms in periods of 24 h, 1 week, or 1 month.[13]

The SF-12 is an adaptation of the SF-36 for faster instrument application. It includes 12 questions that application, it includes 12 questions that evaluate the previous 4 weeks of the participant's life. The scale is Likert-type, and 8 dimensions are evaluated: physical function, physical aspect, pain, general health, vitality, social function, emotional aspect, and mental health. In the In the inicial and final assessment, physical and mental scores are measured.[14]

At the first appointment, psychological and nutritional (eating habits, individualized nutritional guidance) counseling/guidance was performed. After 1 month, patients had an additional nutritional monitoring appointment. After 3 months of the first appointment, all patients were reevaluated by a psychologist and a nutritionist.

Patients were randomized into CG and IG. The CG received a standard follow-up assessment by the CPR unit: 3 months of physical therapy follow-up, 3 appointments with a nutritionist (guidance on healthy eating related to one's underlying disease and application of the FFQ), and 2 appointments with a psychologist. The CPMR program comprised 34 physical therapy sessions, divided as follows: initial evaluation, 10 aerobic training sessions (33 minutes) with a target training zone of 50–60% of the heart rate reserve (Phase 1); reassessment, 10 aerobic training sessions (33 minutes) with a target training zone of 60–70% of the heart rate reserve (Phase 2); reassessment, 10 aerobic training sessions (33 minutes) with a target training zone of 70–80% of the heart rate reserve (Phase 3); final evaluation. In addition to the standard follow-up offered to both groups, patients allocated to the IG also participated in

an interdisciplinary therapeutic operative group with a mean number of 8 participants per meeting.

The groups held 6 weekly 1-h meetings, comprising 2 general meetings with the psychologist and the nutritionist (discussion of cardiovascular risk factors and related diseases, importance of changing habits, among other aspects demanded by patients), 2 meetings coordinated by the psychologist (acceptance of the disease, rehabilitation and health care, and coping strategies for dealing with stress and improving quality of life), and 2 meetings coordinated by the nutritionist (nutritional education and its relationship with CVD).

## Data analysis

Data were collected and stored in a Microsoft Excel spreadsheet and were then analyzed using SPSS, version 25.0. Quantitative variables were described as means and standard deviations (or standard errors, when indicated). Qualitative variables were described as absolute and relative frequencies. To verify differences in demographic and clinical characteristics, chi-squared and Student's t-tests were applied to independent samples. The nutritional profile and quality of life between and within groups were analyzed using the Generalized Estimating Equations (GEE) model due to the losses that occurred during the study, with multiple comparisons adjusted by Bonferroni when necessary. At each assessment, the comparison of stress levels between groups was made through a Mann-Whitney nonparametric test. The Kolmogorov-Smirnov test was used to analyze the normality of the data. A significance level of 5% was considered.

The study was approved by the ethics and research committee of the Institute of Cardiology of Rio Grande do Sul (No. 31221016.3.0000.5333) and was approved by ClinicalTrials.gov with registration number NCT03082443.

## Results

Out of the 140 patients included in the study, 64 (39 in the IG and 25 in the CG) were excluded because they did not attend the consultations or at least 4 group meetings (IG) or decided to leave the study. For this reason, the total sample consisted of 76 patients, 31 in the IG and 45 in the CG. The mean ages of the participants were 61.4 ± 11.8 years (IG) and 64 ± 9.2 years (CG). In both groups, most of the participants were men (64.5% in the IG and 68.4% in the CG). Considering the IG, 43.3% of the participants had completed elementary school, whereas 40% of participants in the CG had not completed higher education. Most of the population had a partner in both groups. The ischemic etiology was the most prevalent throughout the study population. Table 1 describes the sociodemographic data and similarities between groups.

Regarding the anthropometric measures shown in Table 2, a significant reduction ($p < 0.001$) in weight, BMI, and waist circumference was observed only in the IG when comparing the final and initial appointments. There was no significant difference between groups at any time.

Table 3 shows the FFQ results, where a significant increase ($p = 0.010$) in the consumption of healthy food was observed in the IG but not in the CG. However, no difference was observed between groups, as shown in Figure 2. Both groups had a significant reduction in the consumption of unhealthy food during the CPR period ($p < 0.001$). However, when analyzing variations between groups, a trend towards reduction was seen in the second appointment when adjusting for the IG baseline values, being superior to the CG ($p = 0.091$ ).

When analyzing delta values, these showed significant improvements in the IG, except for the unhealthy foods variable. These data are shown in Tables 2 and 3.

Both the physical and mental aspects of quality of life assessed by SF-12 did not differ significantly between the initial and final appointments or between groups. Nevertheless, the results showed a trend towards an improvement of physical appearance in both groups, as demonstrated by Table 4, and considering the entire population, an improvement was seen in the physical aspect ($p = 0.018$). In addition, female participants presented better results of physical ($p = 0.011$) and mental ($p = 0.008$) quality of life in relation to male participants regardless of the group.

Table 5 shows the results regarding the stages of stress evaluated by the ISSL in the CG and IG at the initial and final appointments. None of the groups had a significant reduction in stress levels when analyzing the variation between visits (IG with $p = 0.902$ and CG with $p = 0.072$).

## Discussion

This study showed that CPMR interfered in the reduction of risk factors, favoring habit changes that may contribute to reducing the risk of a new cardiac event. It is

**Table 1 – General characteristics of the studied population. Data presented as n(%) or means ± standard errors**

| | Intervention (n=31) | Control (n=45) | p |
|---|---|---|---|
| Age | 61.4±11.8 | 64±9.2 | 0.299 |
| Sex | | | 0.880 |
| Male | 20(64.5) | 31(68.9) | |
| Years of schooling | 10.6±5.0 | 11.1±5.6 | 0.667 |
| Education | | | 0.712 |
| Illiterate | - | 1(2.2) | |
| CES | 13(43.3) | 15(33.3) | |
| IHE | 10(33.3) | 18(40) | |
| Higher education or more | 7(23.3) | 11(24.4) | |
| Marital status | | | > 0.999 |
| Married | 23(74.2) | 33(73.3) | |
| Etiology# | | | |
| CHF | 6(19.4) | 10(22.2) | 0.988 |
| Ischemic | 24(77.4) | 33(75) | 0.809 |
| Valvar | 4(12.9) | 5(11.1) | > 0.999 |
| High risk of CVD | 3(9.7) | 6(13.3) | 0.902 |
| Cardiovascular risk factors | | | |
| Sedentary behavior | 17(54.8) | 20(44.4) | 0.511 |
| Dyslipidemia | 11(35.5) | 11(24.4) | 0.432 |
| Diabetes | 6(19.4) | 14(31.1) | 0.380 |
| SAH | 19(61.3) | 26(57.8) | 0.945 |
| Depression | 7(22.6) | 7(15.6) | 0.635 |
| Stress | 15(48.4) | 18(40) | 0.624 |
| Smoking habits | 6(19.4) | 7(15.6) | 0.903 |
| Family history | 18(58.1) | 27(60) | > 0.999 |

*Data reported by the patient; #Data collected from the patient's electronical records. CES: completed elementary school; CHF: congestive heart failure; IHE: incomplete higher education; SAH: systemic arterial hypertension; CVD: cardiovascular disease. Quantitative variables were analyzed by a Student's t-test, and qualitative variables were analyzed by a chi-squared test.*

common for patients to feel insecure during rehabilitation from a cardiac event, and the work of a multi-professional team has been considered a protective factor.[4,15] Even though the CPR unit where the study was conducted is located in a hospital environment, it is still a motivating and welcoming space, which also favors the patient's connection with the multi-professional team. This is in accordance with the Brazilian Rehabilitation Guideline[4], which highlights the importance of this type of program requiring multidisciplinary strategies to facilitate the patient's access to and adherence to rehabilitation.

The study participants were mostly men with ischemic heart disease. The literature shows that this population shows greater difficulty in recognizing their health needs and seeking preventive action.[16] This reinforces importance of CPR programs, since adherence to the program is perceived after the occurrence of a first cardiac event.

**Table 2 – Anthropometric measurements. Data presented as means ± standard errors**

| | Appointment 1 | Appointment 2 | p# | Delta |
|---|---|---|---|---|
| Weight | | | | |
| Intervention | 79.8±17.6 | 78.4±16.3 | <0.001*** | -1.44±2.02 |
| Control | 76.7±2.0 | 76.7±13.5 | 0.978 | 0.15±2.90 |
| p | 0.406 | 0.618 | | 0.009* |
| BMI | | | | |
| Intervention | 28.7±5.7 | 28.2±5.2 | <0.001*** | -1.45±2.02 |
| Control | 27.8±4.5 | 27.8±4.3 | 1.000 | 0.15±2.9 |
| p | 0.436 | 0.718 | | 0.009* |
| AC | | | | |
| Intervention | 100.3±12.9 | 99.9±10.6 | <0.001*** | -1.83±2.84 |
| Control | 98.3±12.1 | 100.2±10.3 | 0.445 | 0.39±2.90 |
| p | 0.902 | 0.470 | | 0.001* |

*AC: abdominal circumference; BMI: body mass index. # Generalized estimating equations. ** p ≤ 0.05; *** p ≤ 0.01*

**Table 3 – Food Frequency Questionnaire. Data presented as means ± standard errors**

| | Appointment 1 | Appointment 2 | p# | Delta |
|---|---|---|---|---|
| Healthy food | | | | |
| Intervention | 4.35±1.782 | 4..84±1.11 | 0.010** | 0.39±0.86 |
| Control | 4.74±1.95 | 4.81±1.48 | 0.786 | -0.03±0.71 |
| p | 0.195 | 0.786 | | 0.024* |
| Unhealthy food | | | | |
| Intervention | 1.50±0.84 | 0.87±0.67 | <0.001*** | -0.55±0.72 |
| Control | 1.25±0.74 | 0.90±0.74 | <0.001*** | -0.32±0.56 |
| p | 0.185 | 0.812 | | 0.120 |

*# Generalized Estimating Equations. ** p ≤ 0.05; *** p ≤ 0.01.*

In this randomized clinical trial, despite limitations concerning a smaller sample number than initially calculated and a short intervention time, the interdisciplinary group intervention was effective in the IG patients regarding the nutritional status of participants, both in relation to anthropometric measures and food quality (figure 2 and 3).

Our results are in agreement with previous studies that demonstrated greater weight loss through nutritional education in group therapy when compared to individual treatment, as well as improvements in different cardiovascular risk factors.[17,18] Also, weight loss may reduce mortality and other risk factors in patients with CVD.[19]

The better quality diet observed in this study was also demonstrated in similar group therapies found in the literature.[20,21] Still, the CG also presented improvements in this study, which reaffirms the effectiveness of individual care and demonstrates that the CPR process by itself interferes in this aspect.

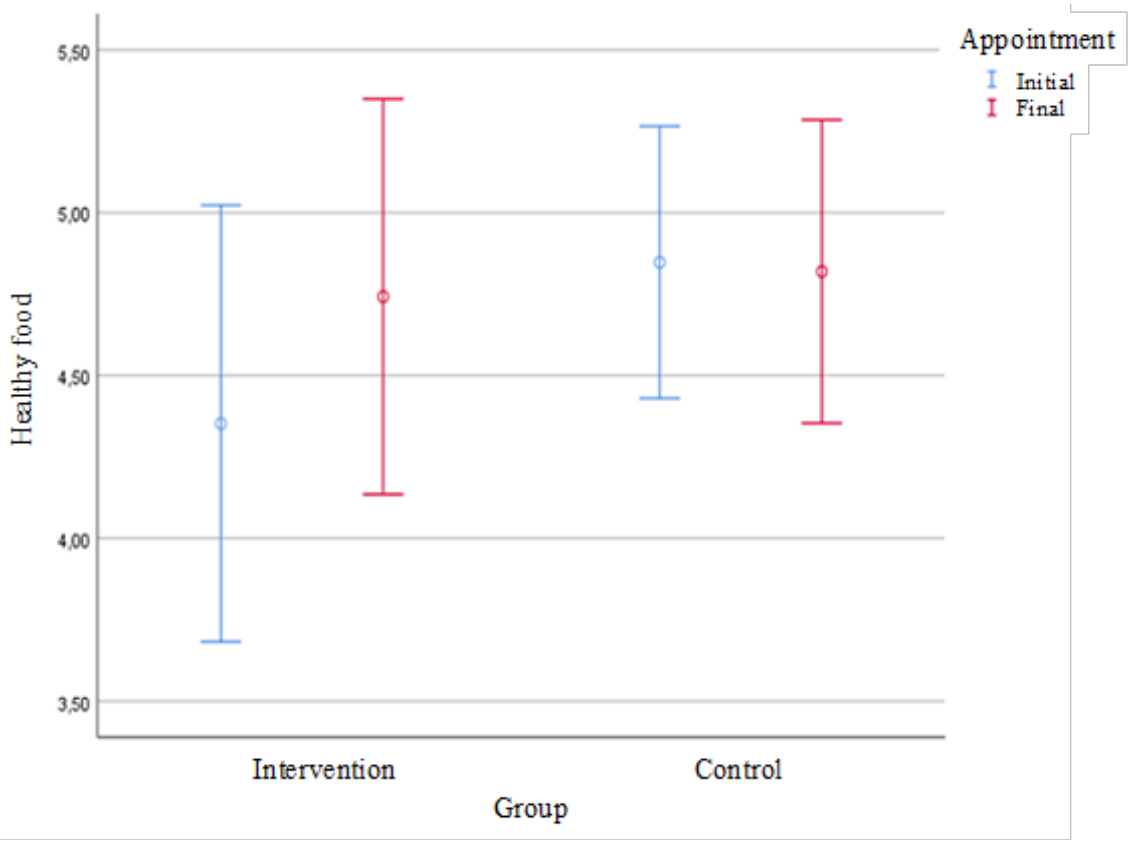


**Figure 2 – Difference between the consumption of healthy food (frequency per week) at the initial and final cardiopulmonary rehabilitation (CPR) appointments.**

**Table 4 – Quality of life (SF-12). Data presented as means ± standard errors**

| | Appointment 1 | Appointment 2 | p# |
|---|---|---|---|
| Physical | | | |
| Intervention | 37.7±0.9 | 39.3±1.0 | 0.090 |
| Control | 38.5±1.0 | 40.2±0.7 | 0.097 |
| p | 0.539 | 0.461 | |
| Mental | | | |
| Intervention | 44.3±1.0 | 43.8±0.9 | 0.629 |
| Control | 43.0±0.9 | 41.6±0.8 | 0.189 |
| p | 0.378 | 0.092 | |

*# Generalized Estimating Equations.*

**Table 5 – Stress (Lipp's Inventory of Stress Symptoms for Adults [ISSL]). Data presented as n(%)**

| | No stress | Alert | Resistance | Near-exhaustion | Exhaustion | p |
|---|---|---|---|---|---|---|
| Initial appointment | | | | | | 0.633 |
| Intervention | 17(54.8) | 1(3.2) | 12(38.7) | 1(3.2) | - | |
| Control | 24(53.3) | - | 17(37.8) | 3(6.7) | 1(2.2) | |
| Final appointment | | | | | | 0.633 |
| Intervention | 19(61.3) | - | 10(32.3) | 1(3.2) | 1(3.2) | |
| Control | 28(62.2) | - | 16(35.6) | 1(2.2) | - | |

*Analysis by a Mann-Whitney test.*

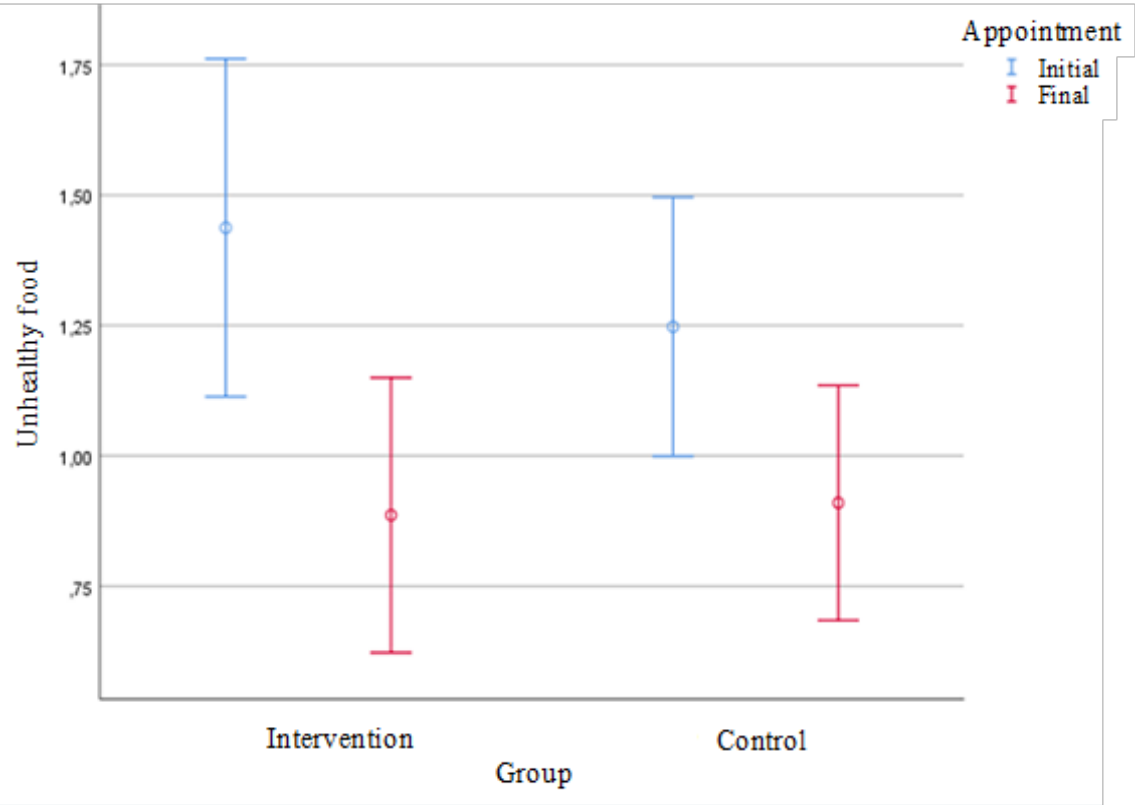


**Figure 3 – Differences between the consumption of unhealthy food (in number of meals per week) at the initial and final CPR appointments.**

Nevertheless, when the variation between groups was analyzed separately and adjusted for baseline values, a greater reduction in the consumption of unhealthy food was observed in the IG.

These results reaffirm the idea that the use of different techniques for changing dietary behavior tends to provide better results. The systematic review and meta-analysis by Cradock[22] showed that employing different behavior change techniques tended to reduce glycated hemoglobin and weight even further.

This study did not result in a significant reduction in stress, but previous studies have shown that a group approach might be effective in this direction and even lead to effects on nutritional status.[23,24] One limitation of this study might have been the short follow-up period at the CPR unit. It is possible that, with a longer time, these patients could have achieved a greater understanding of their disease and physical and emotional health care, thus achieving greater tranquility. Stress levels would consequently fall and the perception of quality of life would improve.

Reinforcing this idea, a retrospective longitudinal cohort study conducted in Australia with cardiac rehabilitation patients draws attention to the fact that, when monitoring patients' depression and anxiety, one can positively interfere with treatment adherence and identify the need for emotional support.[25]

Since it was necessary to include at least 8 patients per therapeutic operative group, only 6 weeks of follow-up were defined for each group, making it possible to generate the sample. Comparing the initial and final evaluations, we observed a decrease in stress levels, although the result was not significant. The relationship between dietary intake and stress is known through other studies[26,27], but it was not observed in the data analyzed for these specific patients.

In addition to a short follow-up time, this study presents other limitations, such as the impossibility of conducting a double-blind randomized clinical trial because depending on the intervention, it would not be possible to blind both the team and the patients. During follow-up, many patients were excluded from the study, mainly due to low attendance at group meetings and/or appointments, which reduced sample size. Losses to follow-up were also observed in other studies, and the low adherence of patients with cardiovascular risk factors is already known[28] and might have played a part in the absence of significant results.

We suggest the conduction of new studies with interdisciplinary group therapy in this population to study whether significant differences occur in relation to stress when patients are followed up in groups, for a longer period, or with a greater number of meetings. Our results allowed the establishment of the hypothesis that further studies in this direction may reinforce the importance of investments in interdisciplinary group therapy associated with CPMR.

## Conclusion

According to this study, a group intervention with cardiac patients in CPMR was effective regarding nutritional status.

The individual care of these patients also affects diet quality, but it shows better results when associated to the therapeutic operative group. Regarding the perception of quality of life, the physical aspect improved in both groups, demonstrating that CPMR benefits patients. It was not possible to establish a significant difference between the control and intervention groups and between the evaluation moments (appointments) considering stress and the mental aspect of quality of life. At the end of the study, there were no significant correlations between nutritional status, stress, and quality of life.

We suggest the conduction of new studies with interdisciplinary group therapy in this population in order to study whether significant differences occur in relation to stress when patients are followed in groups, for a longer period, or with a greater number of meetings. Our results allowed the creation of the hypothesis that further studies in this direction may reinforce the importance of investments in interdisciplinary group therapy associated with CPMR.

Therefore, investments in multidisciplinary teams at any level of care are considered of paramount importance since the etiology of CVD is multicausal. Current efforts in this direction recommend the work of several disciplines interacting with cardiology, and new studies in this area of knowledge are fundamental to advance CPR.

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## Author contributions

Conception and design of the research: Coronel C, Seelig C, Vieira DR, Rodrigues GF, Ruschel PP, Barbiero SM. Acquisition of data: Seelig C, Vieira DR, Rodrigues GF. Analysis and interpretation of the data: Vieira DR, Rodrigues GF, Ruschel PP, Barbiero SM. Statistical analysis: Vieira DR, Rodrigues GF, Ruschel PP, Barbiero SM. Writing of the manuscript: Vieira DR, Rodrigues GF, Barbiero SM. Critical revision of the manuscript for intellectual content: Coronel C, Ruschel PP.

### 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 IC/FUC under the protocol number 612 21016 3 00005333. 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

# A New Look at the Importance of Multidisciplinary Group Interventions in Cardiac Rehabilitation

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***Editorial referring to the article: Interdisciplinary Group Intervention on Nutritional Profile, Quality of Life, and Stress During Cardiopulmonary Rehabilitation: A Randomized Clinical Trial***

Chronic non-communicable diseases (NCDs) are the main cause of death worldwide, being responsible for premature deaths, loss of quality of life, with great socioeconomic impact. More than 17 million (around 45%) of NCD deaths in the world are caused by cardiovascular (CV) diseases. Similar findings are found in Brazil, where 72% of all deaths are attributed to NCDs, 30% due to CV disease.[1]

There is increasing evidence that staying physically active contributes to preserve and recover physical and emotional health, and that a sedentary lifestyle is strongly related to CV disease and early mortality. In this context, the benefits of CV rehabilitation, with emphasis on physical exercise, have emerged in the literature, and correlated with a reduction in CV morbidity and mortality, significant improvement of quality of life and longer life expectancy.[2]

In addition, scientific studies have been conclusive regarding the benefits of cardiovascular, pulmonary and metabolic rehabilitation (CPMR) for individuals with CV disease, obesity, diabetes and high risk for pulmonary and metabolic diseases.[3] Akinyelure et al.[4] reported the fact of not having a healthcare visit in the past year was associated with a higher likelihood of uncontrolled blood pressure (BP) among subjects with hypertension. Understanding that several risk factors can be simultaneously modified through policies, either the complete elimination or reduction to best achieved levels in states of hypercholesterolemia, diabetes, hypertension, obesity, and smoking could prevent 0% to 7% of CV deaths.[4]

According to the South American Guidelines for CV Disease Prevention and Rehabilitation, CV diseases have a close relationship with lifestyle, as well as with modifiable physiological and biochemical factors, and have accompanied the increased prevalence of risk factors in recent decades. Thus, the changes in risk factors stimulated by CV rehabilitation, result in the reduction of morbidity and mortality from CV disease, especially in individuals classified as high risk, with favorable reductions in physical incapacity, disability, and health expenses.[5]

Several cardiac rehabilitation programs are mentioned in the literature, involving actions developed by nurses, nutritionists, physical educators, psychologists and social workers, aiming to contribute to the reduction of risk factors responsible for much of the national burden of CV disease mortality.[5]

According to the INTERHEART study, the most prevalent CV risk factor is abdominal obesity, with a 48.6% prevalence in Latin America. A high-calorie diet, rich in simple carbohydrates and saturated fats, associated with a sedentary lifestyle are responsible for this worldwide epidemic.[6] The prevalence and the incidence of overweight and obesity have increased throughout the planet at alarming levels; obesity is considered a worldwide epidemic, affecting almost a third of the world's population. Therefore, it is necessary to guide the population towards dietary education, aiming at reducing weight and abdominal fat, by decreasing energy intake, consumption of poor-quality fats (saturated and trans) and simple carbohydrates, in addition to increasing complex carbohydrates,

## Keywords

Multidisciplinary patient care team; Cardiac rehabilitation; Quality of life; Healthy nutrition.

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fruits, vegetables, whole grains, and mono- and polyunsaturated fats.[7]

Appropriate food choices, associated with nutritionally balanced, hypocaloric diets, provides moderate amounts of fat, helping to reduce low-density lipoprotein (LDL), normalize serum triglyceride levels and reduce BP. For example, the DASH (Dietary Approach to Stop Hypertension) is a dietary pattern developed to reduce hypertension in individuals with moderate to high BP, encouraging the consumption of fruits, vegetables, whole grains, nuts, legumes, seeds, low-fat dairy and lean meats, and limited salt, caffeinated and alcoholic beverages, that has been associated with weight loss and BP lowering.[8]

Stress is currently considered a CV risk factor as important as hypertension, smoking or dyslipidemia and is clearly associated with Acute Myocardial Infarction (AMI). Stress is defined as the "situation of an individual or any of their organs or systems, which, by demanding a higher-than-normal performance, puts them at risk of becoming ill". It is a response or reaction of the organism that forces adaptations not always well tolerated or accepted and may be acute or chronic. All these changes may lead to anxiety, emotional exhaustion, depersonalization, emotional insecurity, fear of failure, chronic work stress, personality factors, character and social isolation, and ultimately depression.[5]

Unfortunately, there is not enough data on the prevalence of high stress, depression and other psychosocial problems in Latin America. Data from the INTERHEART study estimate the prevalence of chronic stress and depression of 6.8% and 36.7%, respectively, in Latin America. The study highlights the importance of establishing the degree of stress and depression suffered by patients who seek a CV rehabilitation program. The recommendations point to the identification of these groups of patients to intervene prematurely, through psychotherapy support and lifestyle changes, not only aimed at the individual, but also at family members. Measures may include group therapy, specific medication, physical activity and social engagement, all in charge of specialized healthcare professionals.[9]

The original article by Rodrigues et al.,[10] addresses the effectiveness of group interventions on the nutritional profile, stress and quality of life of patients undergoing cardiopulmonary and metabolic rehabilitation, showing a superiority of the intervention group in relation to nutritional status as compared with patients receiving standard follow-up assessment (control group). They also observed improvements in the physical aspect of quality of life in both groups studied. These findings reflect that educational interventions and adequate training is an important action in the Brazilian context, considering its impact on the reduction of CV events in this population. This study showed that CPMR contributed to the reduction of risk factors, favoring changes in habits that can contribute to preventing new cardiac events.

The objective of the intervention is to improve patient's health by preventing complications, reducing morbidity, mortality and other risk factors, and improving quality of life. Thus, the development of multidisciplinary care in CV rehabilitation is of great value to the prioritization and evaluation of investments in preventive health policies.

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ORIGINAL ARTICLE

# Acceptance of Low-Sodium Hospital Diet by Cardiac Patients: A Randomized Controlled Crossover Trial

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## Abstract

**Background:** Cardiovascular diseases are the major cause of hospitalization. Dietary salt restriction is indicated as part of clinical treatment, however, it is not always well accepted by the patients, resulting in low food intake and malnutrition.

**Objective:** To compare acceptance of a low-sodium diet cooked with salt with a standard low-sodium diet in cardiac inpatients. Methods: A randomized controlled crossover trial in patients with low-sodium diet prescriptions (Clinical Trials NCT03481322). Patients were given a control standard low sodium diet (cooked without salt; salt [2g per meal] added by the patient at the time of consumption) on one day and on the next day patients were given the intervention diet – a low sodium diet cooked with salt (2 grams of salt, divided between preparations). Dietary acceptance was evaluated by weighing leftover food and calculating intake. A questionnaire was used to verify reasons that influenced acceptance. For data analysis, parametric data are presented as mean and standard deviation, Student's t test was used to compare means, with significance defined as $p<0.05$.

**Results:** Sixty-four patients were evaluated, with a mean age of 66 ± 11.3 years; 64% were male. There were no differences in percentage acceptance between the standard low-sodium diet and the low-sodium diet cooked with salt at lunch ($p= 0.876$) or at dinner ($p= 0.255$). Around 80% of what was offered at each meal was consumed by the patients, with no significant difference between groups.

**Conclusions:** The low-sodium diet cooked with salt was well accepted, but there was no difference when compared with the standard low-sodium diet, which also had adequate acceptance.

**Keywords:** Sodium Chloride; Diet, Sodium-Restricted; Cooking; Heart Diseases.

## Introduction

Cardiovascular diseases are the major cause of hospitalization in the public sector, affecting 29% of the elderly population.[1] In 2015, 17.7 million people died from cardiovascular diseases worldwide.[2] One of the risk factors for cardiovascular diseases is systemic arterial hypertension (SAH), the treatment for which includes a low-sodium diet. Hospital diets with nutritional restrictions are 50% less likely to be accepted and this should be of greatest concern with relation to low-sodium diets.[3-4] Severe sodium reduction (by 2 g of salt/day) is associated with a lower food intake,[5] which can result in weight loss during hospitalization. Low food intake is the main independent risk factor for hospital mortality[6] and can lead to malnutrition.

Hospital malnutrition affects almost half (48.1%) of inpatients in Brazilian public hospitals.[7] In Latin America, the prevalence rate has ranged from 40 to 60% over the past 20 years. It is known that malnutrition affects the response to clinical treatment, resulting in longer hospital stays and greater risk of complications, and also has a great impact on health system costs, since expenditure on malnourished patients is on average 61% higher.[8-10]

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High rates of nutritional impairment can be prevented if nutritional care is appropriate during hospitalization, with early diagnosis of nutritional risk and malnutrition and adjustment of food intake, thus reducing hospital mortality.[10]

Brazilians consume very large amounts of salt, around 12 g/day, which possibly undermines their acceptance of low-salt diets.[11] The World Health Organization (WHO) recommends a maximum intake of 2,000 mg of sodium/day, which corresponds to 5 g of salt.[12] Many people who consume far more sodium than is recommended are not aware of the risks involved,[11] and changing to a low-salt diet and following it for a long period is quite difficult.[5,13] Moreover, a hospital diet is considered tasteless,[14] as is the case of a salt-free diet, since salt adds flavor to the natural seasonings used in foods. To date, there have been no literature studies that assess food acceptance by hospitalized cardiac patients, comparing low-sodium meals cooked with salt with those to which salt is added after cooking.

Dietary salt restriction is indicated as part of clinical treatment, but it is not always well accepted by patients, resulting in low food intake and, as a likely consequence, in malnutrition, which is highly prevalent in hospital settings. It is therefore necessary to formulate strategies to improve these patients' dietary intake. The goal of this study was to compare acceptance by cardiac inpatients at a tertiary hospital in Porto Alegre, Brazil, of a low sodium diet cooked with salt with acceptance of a standard low-sodium diet to which salt is only added after cooking.

## Methods

A randomized controlled crossover trial was conducted between September 2017 and June 2018 with adult male and female patients aged ≥ 18 years prescribed a low-sodium diet, a low-sodium diet for diabetes, or a low-sodium diet for dyslipidemia, within the first four days after hospital admission. The following patients were excluded from the study: those prescribed any other type of diet or with other dietary restrictions and/or changes to food consistency; those who chose to eat soup and/or chicken soup for lunch or dinner; those who did not receive their meal with proper standardization (e.g., without beans); and those unable to answer the questionnaire and unaccompanied by a caregiver.

### Study Implementation

The salt-restricted diets offered at the hospital consist of four preparations: one portion of carbohydrate (cereals or type C vegetables), one portion of legumes, one portion of meat, and one portion of garnish (type A or B vegetables in the low-sodium diet for diabetes or dyslipidemia, or a portion of type A or B vegetables or another portion of carbohydrate in the low-sodium diet). The amount and weight of foods is the same for all three diets. The characteristics of macronutrients were maintained, differing only in terms of salt, depending on the randomization group.

All patients received both of the diets tested. Each diet was offered at lunch and at dinner on one day, differing only in the order in which they were offered, depending on the randomization group.

Control diet: standard low sodium. Foods cooked without salt, with addition of salt (2 g per meal) by the patient only at the time of consumption.

Intervention diet: low sodium cooked with salt. In this case, each meal was cooked with 2 g of salt per patient divided between the preparations, following standardized recipes.

### Randomization and Blinding

The patients were randomized into two groups using a randomization software program.[15] Following signature of the consent form, the randomization order of each patient was disclosed by a blinded researcher. As a complement to the study, a questionnaire was administered by another researcher, who was blinded to the diet (control or intervention) the patient would receive.

The patients from group 1 received the standard low sodium diet on the first day and the low sodium diet cooked with salt on the second day. The patients from group 2 received the same diets, but in reverse order; thus, on the first day, they received the low sodium diet cooked with salt, and on the second day, the standard low sodium diet.

### Acceptance of the Diets

The amount of foods ingested by the patients was evaluated by weighing leftover food and calculating intake. The weight of the leftovers was deducted from the initial weight and the resulting food intake was later converted to percentage acceptance. The foods given to

each patient were weighed previously when divided into portions. After the meals, the leftovers were stored in plastic vessels and properly labeled for weighing. Weight was measured on an electronic scale (Toledo®), with 3 kg capacity and specificity of 1 g, and the leftovers were immediately disposed of appropriately.

### Questionnaire

The questionnaire contained questions on the reasons for non-acceptance of the diet and on previous control of salt intake, adapted from a study by Santos et al.[16] The questionnaire was administered to each patient twice, i.e., at the end of each diet (standard low-sodium diet and low-sodium diet cooked with salt). Diagnoses of underlying diseases were obtained from patient records and transcribed according to the International Classification of Diseases (ICD-10).

### Ethical Aspects

The study followed the CONSORT statement for randomized controlled studies[17] and was approved by the Research Ethics Committee at the Institute of Cardiology after submission to the Plataforma Brasil (UP 5364/14) and Controlled Trials (NCT03481322). The participants' data were kept confidential. All patients were given a copy of their signed consent form. The data collected were only used for this research and will be stored for five years and destroyed after that, in accordance with Resolution 466/12.

### Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS), version 23.0. Nominal values were presented in absolute and relative frequencies. Parametric data are presented as mean and standard deviation. The Shapiro-Wilk test was used to verify normality of the data. Student's *t* test was used for independent samples. Categorical variables were evaluated with Pearson's chi-square test. Statistical significance was defined as $p<0.05$.

### Sample Size Calculation

The sample size was calculated with PEPI version 4.0, taking into account data from a study by Santos et al.,[16] considering that the mean diet acceptance rate in that study was 66%, with a standard deviation of 29%, and also that the level of acceptance of hospital diet considered appropriate is at least 80%, according to Sousa et al.[18] For a power of 80% and a level of significance of 5% (95% confidence interval), adding 20% for possible losses to follow-up and refusals to participate, it would be necessary to include 68 patients in the study.

## Results

Sixty-four patients were evaluated and 41 completed the study, receiving two meals from each diet. Figure 1 shows the sample losses according to the CONSORT flowchart. The sample of adult male and female patients is described in Table 1.

Table 2 presents the percentage acceptance of the diets. Around 80% of what was offered in each meal was eaten by the patients, without significant difference between diets (standard low-sodium diet or low-sodium diet cooked with salt) or between meals (lunch or dinner). When analyzed according to the percentage considered adequate, that is, consumption of at least 80% of what was offered, the diet cooked with salt achieved a higher rate of adequacy when compared with the standard low-sodium diet, but the difference was not significant (Table 2).

Men consumed greater amounts at lunch (87.0 ± 19.9% of the standard low sodium diet and 85.1 ± 23.3% of the low sodium diet cooked with salt) when compared with women (63 ± 24.3% of the standard low sodium and 69.5 ± 22.7% of the low sodium diet cooked with salt), ($p=0.000$ standard low sodium diet; $p=0.017$ low sodium diet cooked with salt). Regarding previous control of salt intake at home, checked through simple questions, most patients reported controlling salt intake at home. On the other hand, daily or sporadic use of industrialized seasonings was reported by most patients (65%), contradicting their self-reported salt intake control. It was also observed that most of these patients are used to cooking with salt (Table 3).

After eating their diets (standard low-sodium on one of the days and low-sodium diet cooked with salt on the other day, according to their randomization group), the patients were asked about their acceptance of the diets. Most patients (72%) reported not missing salt in the hospital food, and this percentage was the same for both diets ($p=1.0$). As for the preference among diets, 51% of the patients reported preferring the low-sodium diet cooked with salt. Even among the patients who claimed they controlled salt at home, 23% missed salt in the low sodium diet cooked with salt and 24% missed salt in the standard low sodium diet, with no difference between groups ($p=1.0$).

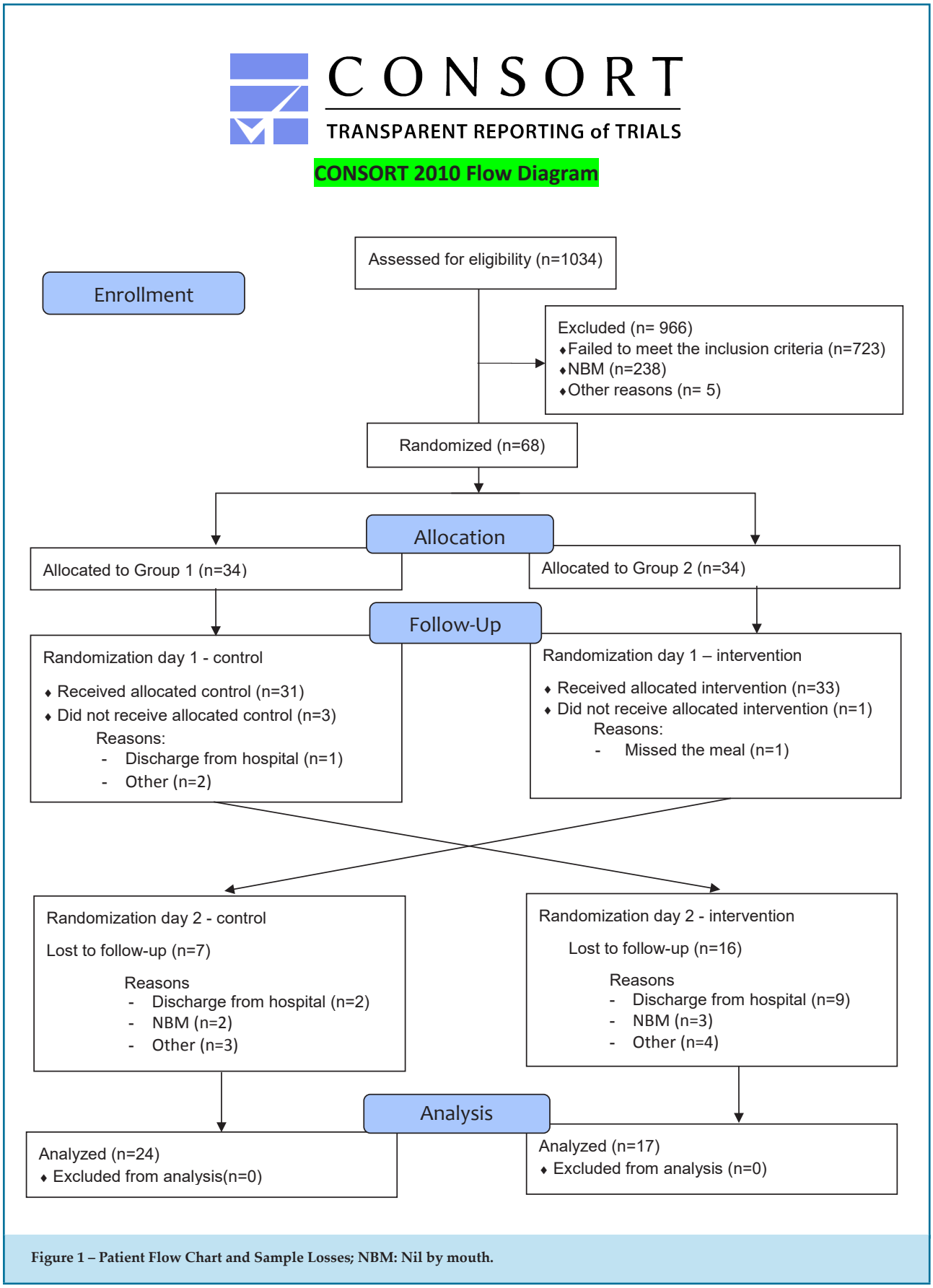


**Figure 1 – Patient Flow Chart and Sample Losses; NBM: Nil by mouth.**

**Table 1 – Sample characteristics**

| Characteristics | Results n=64 (100%) |
|---|---|
| **Age** | 66 ± 11.3 |
| > 60 years | 41 (64%) |
| **Sex** | |
| Male | 41 (64%) |
| **Pathologies** | |
| CHF | 17 (26.6%) |
| Angina | 12 (18.8%) |
| CAD and IC | 10 (15.6%) |
| Flutter and Fibrillation | 5 (7.8%) |
| **Diet prescription** | |
| Low sodium | 32 (50%) |
| Low sodium for Diabetes | 18 (28.1%) |
| Low sodium for Dyslipidemia | 14 (21.8%) |

*CHF: Congestive Heart Failure; CAD: Coronary Artery Disease; IC: Ischemic cardiomyopathy.*

The findings related to reasons that may have interfered with acceptance of the diets were similar for both diets (Table 4), but lack of salt was the most prevalent reason for both diets, followed by lack of seasonings, inappropriate mealtime, and excessive quantity of food.

## Discussion

The present study identified an adequate percentage acceptance of the diets, meaning that patients consumed around 80% of what was offered to them. There was no difference in acceptance between the two diets offered. No studies in the literature have tested a low-sodium diet cooked with a controlled amount of salt in hospitalized cardiac patients. However, accounts of acceptance of salt-restricted diets in the literature are usually below the recommended levels, which is at odds with the findings of the present study, in which the patients consumed 80% of what was offered in each meal, with no significant difference between the diets. It was also observed that men consumed greater amounts at lunch than did women, with acceptance of 85.06 ± 23.3% for the diet cooked with salt.

**Table 2 – Percentage acceptance of diets**

| | Standard low sodium | Low sodium cooked with salt | p |
|---|---|---|---|
| **Acceptance per meal** | | | |
| Lunch (n=51) | 79.8 ± 24.1 | 80.2 ± 22.7 | 0.876 |
| Dinner (n=42) | 75.6 ± 23.9 | 79.2 ± 22.1 | 0.255 |
| **Appropriate acceptance (>80% of the meal)** | | | |
| Yes (n=119) | 54 (51%) | 65 (59%) | 0.292 |
| No (n=97) | 51 (49%) | 46 (41%) | |

**Table 3 – Previous salt control**

| | Yes | No | Sometimes |
|---|---|---|---|
| Controls salt at home | 37 (61%) | 19 (31%) | 5 (8%) |
| Cooks with salt | 50 (82%) | 9 (15%) | 2 (3%) |
| Adds salt to food already cooked with salt and salad | 6 (10%) | 46 (75%) | 9 (15%) |
| Uses industrialized seasonings | 19 (31%) | 21 (34%) | 21 (34%) |

**Table 4 – Reasons that interfered with the acceptance**

| | Standard low sodium | Low sodium cooked with salt |
|---|---|---|
| Lack of salt | 15 (29.4%) | 15 (27.3%) |
| Lack of seasonings | 14 (27.5%) | 13(23.6%) |
| Inappropriate mealtime | 13 (25.5%) | 9 (16.4) |
| Excessive amount | 9 (17.6%) | 10 (18.2%) |
| Lack of appetite | 3 (6%) | 8 (14.5%) |
| Unpleasant flavor | 4 (7.8%) | 5 (9.1%) |
| Inappropriate temperature | 3 (5.9%) | 1 (2%) |
| Difficulty chewing/swallowing | 1 (2%) | 1 (2%) |
| Gastrointestinal disorders | 1 (2%) | 3 (5.5%) |
| Does not like the food | 2 (3.9%) | 0 |
| Unpleasant odor | 2 (3.9%) | 0 |
| Unpleasant appearance | 1 (2%) | 1 (2%) |

Souza et al. (2011) evaluated acceptance of hospital diets and found that the salt-restricted diet presented a greater leftover-intake percentage (33.84%).[18] Santos et al.[16] found a leftover-intake percentage of 27% for salt-restricted diets. Casado et al.[19] evaluated acceptance of low-sodium diets, finding good acceptance, as most individuals said the diet offered had adequate flavor and temperature. However, in this study, most patients (51% at lunch and 60.6% at dinner) ate less than half of the meal offered to them. An appropriate leftover-intake percentage for the sick population should not exceed 20%.[18]

In the present study, acceptance of both low-sodium diets was above average, this aspect may not have influenced improved acceptance of the low-sodium diet cooked with salt. In this study, 4 g of salt/day was used for each patient for both diets, unlike the standard diet used in Brazilian hospitals, which is 2 g of salt/day.[16,20] An intake of only 2 g of salt/day is considered severe and impacts on acceptance of the diet and on inpatients' nutritional status. Studies suggest that a strict reduction of sodium to 2 g of salt/day in patients with heart failure (HF) is associated with reduced food intake and can worsen prognosis and influence the progression of cardiac cachexia[5]. In the present study, salt restriction was not so severe, in accordance with what has been advocated in the literature. The Brazilian Guidelines on Heart Failure recommend a less severe salt reduction, not exceeding 7 g of salt/day for patients with chronic HF, and not exceeding 5 g of salt/day for those with seriously symptomatic or advanced HF.[21]

It is known that acceptance of low-sodium diets is historically low and modifications are not always well accepted, nor do they improve acceptance by patients. In a crossover study, Filipini et al. (2014) evaluated acceptance of low-sodium diets using light salt – potassium chloride-based salt, with sodium reduced by 60%. The meals were prepared using 2.5 g of light salt, divided between the preparations. However, the modification was not well accepted by the patients and acceptance was considered unsatisfactory, and the percentage of leftover-intake ranged from 29 to 40% of the meals. Use of spices was the characteristic most widely mentioned by the patients as a factor that negatively impacted on acceptance of this diet and even the potassium salt may have interfered with the patients' perceptions, since it has a characteristic flavor and is not part of this population's eating habits.[22] In the present study, the proposed intervention – a diet cooked with a controlled amount of salt – did not improve the patients' food intake. This may have been influenced by an inappropriate previous control over salt restriction. As shown in this study, although 61% of the patients claimed that they restrict salt at home, lack of salt was the main reason that influenced

acceptance, reported by approximately 30% of the patients for both diets.

According to the patients, lack of salt was the factor that most influenced acceptance of both diets, followed by lack of seasonings, inappropriate mealtimes, and excessive quantities – which can explain the inpatients' lack of appetite. Lack of salt and seasonings is usually reported as the factor that most interferes with acceptance of salt-restricted diets. Yabuta et al. (2003) evaluated the acceptance of a low-sodium diet in hospitalized patients and found that factors negatively affecting acceptance were lack of salt (21.1%) and the flavor of the meal (11.5%).[23] In a similar population, even among those patients who claimed to fully accept the meal offered, 82% missed salt in their meals and 52% missed spices.[16]

The amount of salt offered in these diets is very close to the amount considered by the Brazilian Ministry of Health as normal, i.e., 5g/day.[12] On the other hand, in this study, 82% of the patients said they cook with salt at home. Thus, it can be inferred that this salt control may not be adequate for the reduction needed and that the patients' eating habits are too far from what would be appropriate, which is the biggest challenge for these patients to overcome. Therefore, the low-sodium diet cooked with salt is an option for nutritional education of patients at hospital admission, since most of them are in the habit of cooking with salt. Thus, the proposed modification could adjust their taste perception to cooking with an appropriate amount of salt from hospital admission.

In the present study, temperature did not influence acceptance of the diets, which was not observed in other studies. Ribas et al. (2013) observed that temperature was the factor with the greatest negative impact on acceptance of the diet.[20] Both meal delivery carts without a temperature control system and food vessels may have contributed to inappropriate temperature of the food. In the study by Souza et al. (2011), temperature was also a key factor, mentioned by 43% of the patients.[24] Even though the hospital where the research was carried out did not have heated and chilled meal delivery carts, appropriate routines helped maintain the temperature of the meals until the time of delivery. Maintenance of the temperature may have contributed to adequate levels of acceptance in this study.

One of the limitations of this study is that a considerable number of patients did not complete the study and did not receive both meals from each diet. As the study was conducted in the usual hospital admission setting, interruption of feeding as preparation for medical examinations and hospital discharge earlier than planned is possible and sometimes prevented the patients from completing the study. Another important factor is that the standard low-sodium diet was well accepted by inpatients, which is not usually observed and may have influenced the lack of difference in acceptance between the two diets. Unlike at most Brazilian hospitals, the standard low-sodium diet at this hospital included 4 g/day of additional salt, which may have led to greater acceptance of the diets. The fact that all foods were weighed before and after being given to the patient attests to the reliability of intake measurements, with no variations caused by differences in the division of food into portions or by evaluators' visual perceptions.

## Conclusions

In conclusion, the low sodium diet cooked with salt was well accepted; however, there was no difference when compared with the standard low sodium diet, which also had adequate acceptance. Lack of salt and seasonings were the main reasons for poor acceptance of the diets, demonstrating that these factors still have to be addressed to improve acceptance and other strategies need to be tested in future studies. Low sodium diets cooked with salt are suggested as an alternative option for hospital meals. Although the proposal of this study did not show better acceptance than that the standard low-sodium diet, it was able to maintain food intake at an amount considered to be appropriate. Therefore, we consider using it to promote nutritional education on salt control, because this diet stimulates the patient's taste perception of the adequate amount of salt soon after hospital admission, considering that patients are in the habit of cooking with salt at home.

## Author contributions

Conception and design of the research: Santos BF, Corrêa IVS, Antunes ALG, Martins CM, Eibel B; Acquisition of data: Santos BF, Martins CM, Giustina RD, Duarte MB; Analysis and interpretation of the data: Santos BF, Corrêa IVS, Antunes ALG, Eibel B; Statistical analysis: Santos BF, Corrêa IVS, Eibel B; Writing of the manuscript: Santos BF, Corrêa IVS, Antunes ALG, Martins CM, Giustina RD, Duarte

MB, Eibel B; Critical revision of the manuscript for intellectual content: Santos BF, Corrêa IVS, Antunes ALG, Eibel B.

### Potential Conflict of Interest

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

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### Study Association

This article is part of the thesis of master submitted by Bruna Fraga dos Santos, from Instituto de Cardiologia de Porto Alegre.

### Ethics approval and consent to participate

This study was approved by the Ethics Committee of the CEP do Instituto de Cardiologia under the protocol number 5364/14. 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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ORIGINAL ARTICLE

# Cardiovascular Risk Factors in Children and Adolescents with Fontan Circulation

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## Abstract

**Background:** Long-term outcomes of patients with Fontan circulation are uncertain regarding the prevalence and role of risk factors (RFs) such as increased body mass index (BMI), arterial hypertension, and hypercholesterolemia.

**Objectives:** To describe the prevalence of RFs in patients with univentricular heart, with variable follow-up times.

**Methods:** This mixed cohort study was performed with 66 patients, who underwent blood count, fasting blood glucose, C-reactive protein (CRP), and lipid profile tests; systolic/diastolic blood pressure (SBP/DBP) measurements; and anthropometric and sociodemographic data collection. Cardiovascular RFs among first-degree relatives and physical activity habits were also assessed. Prevalence was described using proportions, with a 95% confidence interval. Continuous variables (height, weight, age, SBP, DBP) were described as means and standard deviations (m±SD). Associations between RFs were assessed using chi-squared or Fisher's exact tests. Spearman's correlation was used for analyzing CRP and the presence of 2 or more RFs. The Shapiro-Wilk test was used to check for data normality. Statistical significance considered $p<0.05$.

**Results:** In our population, 19.7% were overweight, mean SBP was 89.44±37.4, and mean DBP was 60.0±26.08. The most prevalent diseases in the interviewees' families were systemic arterial hypertension (30.3%), obesity (16.7%), and 2 or more cardiovascular RFs among first-degree relatives (13.8%). We observed a trend towards significance between the presence of 2 familial RFs and overweight, as well as a risk profile for cardiovascular disease. There was an association between the BMI percentile, the presence of 2 or more RFs ($p<0.05$), and CRP ($p<0.01$).

**Conclusions:** Overweight is common in patients with univentricular heart, being related to more than 2 cardiovascular RFs among first-degree relatives; physical inactivity and changes in lipid profiles are also frequent.

**Keywords:** Child, Adolescent; Fontan Procedure/methods; Cardiovascular Diseases; Heart Defects,Congenital/surgery; Risk Factors;Obesity; Physical Inactivity.

## Introduction

Univentricular heart, also known as functionally single ventricle, is a complex group of heterogenous congenital heart defects, comprising multiple pathological subtypes. This may occur either with ventricular hypoplasia, double-inlet atrioventricular connections, or mitral or tricuspid valve atresia. Surgical correction is represented by the Fontan procedure, which is used to bypass the ventricular mass. When unsuccessful, cardiac transplant is an alternative.[1]

Previous studies have shown that obesity is associated with symptomatic heart failure and mortality in patients with Fontan palliation.[2] The prevalence of overweight and obesity increases with the age of patients undergoing Fontan conversion, with

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36% being overweight and 14% being obese after the age of 30 years.[3]

Nevertheless, the available data on the prevalence and role of risk factors (RFs) such as increased body mass index (BMI), arterial hypertension, and hypercholesterolemia with regard to long-term outcomes are insufficient. Additional studies are needed to determine factors causing geographic and racial differences in outcomes.

Therefore, the aim of this report is to describe the prevalence of major RFs in patients with univentricular heart.

## Methods

Four hundred and forty-one patients with congenital heart disease were recruited to participate in this mixed cohort study that occurred between September 2010 and March 2016. They were aged between 2 and 18 years and had been attending the Pediatric Cardiology Unit of a reference center in southern Brazil.

This group of patients attended regular follow-up visits based on the severity of each patient's illness. The follow-ups were conducted by the unit's pediatric cardiologist. All the information obtained with the applied questionnaires was further recorded in a database.

Out of this group, 66 patients with univentricular heart who attended the follow-ups consistently were selected to participate in this study. Exclusion criteria consisted of genetic syndromes, conditions that precluded the patients from providing an anthropometric measurement (such as patients in wheelchairs or with underdeveloped limbs), and unwillingness to participate.

The unit's schedule was revised weekly to select patients who met the criteria and had appointments with the doctor on that specific week. The patient and their legal guardian were then contacted by telephone and were invited to take part on the study on the day the appointment had been set. Those who agreed to participate were required to fast for at least 12 hours before the appointment for laboratory tests. If telephone contact failed, patients were still offered to participate right before the doctor's appointment and the laboratory exams were postponed.

Written informed consent was obtained from all participants and legal guardians after they had been explained the process. A fasting venous blood sample was then drawn for laboratory testing, which included blood count, glucose, lipid profile, and C-reactive protein (CRP) tests. In addition, anthropometric measurements, blood pressure (BP), sociodemographic factors, physical activity habits, family history, and the presence of RFs among first-degree relatives (diabetes, systemic arterial hypertension [SAH], obesity, and dyslipidemia) were investigated.

The nutritional state of patients was evaluated through the BMI, which was calculated and classified using the World Health Organization (WHO) Anthro and Anthro Plus software. The WHO 2006/2007 BMI cut-off criteria were: overweight (> 85$^{th}$ percentile and < 97$^{th}$ percentile) and obesity (> 97$^{th}$ percentile).[4]

BP was measured with properly calibrated aneroid sphygmomanometers that could measure up to 300mmHg. These values were analyzed according to the Report of the Second Task Force on Blood Pressure Control in Children.[5]

The patient's level of physical activity was assessed through the International Physical Activity Questionnaire (IPAC) in its short version, which had been previously validated and culturally adapted to the Brazilian reality. The self-administered questionnaire was filled in during the doctor's appointment. IPAC scores were then calculated, and individuals were classified as: very active, active, irregularly active, and sedentary.[6]

Blood samples were collected through a peripheral venous puncture after 12 hours of fasting. Blood serum was separated after the blood was centrifuged. Serum total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides were analyzed by enzymatic methods in an automatic analyzer (Selectra E, Vital Scientific, USA). The reagent kits and protocols used for the enzymatic methods were in accordance with the operating instructions manual. Serum CRP levels were determined by nephelometry using a Behring Nephelometer 100 Analyzer (Dade Behring, USA). Blood samples collected with ethylenediaminetetraacetic acid (EDTA) were used for determining hematocrit and hemoglobin levels using an automatic analyzer (Coulter Act, Coulter, USA).

Reference ranges for the laboratory tests were in accordance with Brazilian (2005) and American (2011) guidelines for the reduction of cardiovascular risk in children: total cholesterol > 170mg/dl; LDL cholesterol > 110mg/dl; HDL cholesterol < 45mg/dl; triglycerides > 75mg/dl (2 to 9 years old) or > 90mg/dl (10 to 18 years old); fasting plasma glucose > 100mg/dl; CRP > 0.3mg/dl; hematocrit (HCT) < 35%; hemoglobin (HGB) < 11g/dl;

systolic blood pressure (SBP) and diastolic blood pressure (DBP) > 90th percentile.[7]

All data in this study were collected by professionals who had been trained to properly fill in the study questionnaires on at least 2 different days.

### Statistical analysis

Prevalences were described as proportions, with an appropriate 95% confidence interval. Continuous variables (height, weight, age, SBP, DBP) were described as means and standard deviations (m ± SD). The chi-squared or Fisher's exact tests were used with categorical variables (dyslipidemia, hypertension, sex, blood glucose, BMI percentile, and sedentary lifestyle) and for verifying the association between RFs. Spearman's correlation was used for CRP values and the presence of two or more RFs; the Shapiro-Wilk test was used to verify the normality of the data. The "CRP" and "RFs family" variables were not normally distributed and were described using medians and interquartile ranges. Statistical significance considered $p \leq 0.05$. All data were analyzed and stored using SPSS, version 17.0. Patients with altered results were promptly referred to a deeper investigation by a specialized unit . This study was approved by the Ethics Committee of the Institute of Cardiology, number 4470/2010.

## Results

The study comprised 66 children and adolescents, mostly male (65.2%), White (83.9%), with a mean age of 10.18 ± 4.6 years. According to the interviews, 19.7% of them were overweight and more than 20% had increased BP, with a mean SBP of 89.44 ± 37.4 and a mean DBP of 60.0 ± 26.08. Most of the patients had had corrective surgery early in life (93.4%) and of these, 36.1% presented an extracorporeal circulation time greater than 80min. Regarding their birth, 78.5% had been born at term. The characteristics of the study cohort are shown in Table 1.

Table 2 shows the cohort's laboratory profile: 34.8% of the patients presented low HDL levels and 30.3% presented increased triglycerides. Moreover, 6.1% of the patients presented low hematocrit levels.

Reports of hypertension (30.3%), obesity (16.7%), and 2 or more RFs among first-degree relatives (13.8%) were the most prevalent diseases in the families of the interviewed patients (Table 3). By associating nutritional state with risk profile, we identified a greater prevalence of elevated cholesterol (23%), low HDL (46%), high LDL (23%), elevated triglycerides (46%), elevated CRP (23%), and the presence of 2 or more cardiovascular RFs (33%) in overweight patients when compared to eutrophic patients. However, statistical significance has not been found for these associations.

When associating overweight patients and cardiovascular risk profile, none of the variables showed significance, except for the "presence of 2 or more RFs" variable, which showed a trend towards statistical significance ($p = 0.05$).

The non-parametric correlation (Spearman's test) between the BMI percentile and the presence of 2 or more RFs resulted in a coefficient of 0.30 ($p < 0.05$) (Chart 1). When using the same test to correlate the BMI percentile with CRP values, we found a coefficient of 0.35 ($p < 0.01$).

## Discussion

The current study describes a pediatric population with univentricular heart; most of them underwent the Fontan procedure to correct this congenital heart disease in the past. The analysis of data collected from the cohort has shown a 19.7% prevalence of overweight (> 97th BMI percentile) and the presence of at least 2 RFs among first-degree relatives.

This single ventricle population represents 15% of all children and adolescents with congenital heart disease examined between 2010 and 2016 in a medium-sized hospital in southern Brazil. This percentage is much higher than those found in Germany (9.4%) and in the United States (3.7%).[8,9] We believe that Brazilian policies prohibiting the interruption of pregnancy when this heart disease is detected early may have an impact on the prevalence of this disease in our country.

Previous studies have shown prevalence rates of 15.9% and 13.4% for overweight and obesity, respectively, in children and adolescents who underwent a palliative Fontan procedure; this is in line with our results.[10,11] Patients with congenital heart disease who underwent cardiac surgery in the past have an increased risk of developing cardiovascular disease when overweight and obesity are associated. Fogel et al.,[12] analyzed the cardiovascular effects of obesity in ventricular function and mass in patients who underwent a Fallot procedure, showing that obese patients had increased heart rates and decreased systolic and diastolic volumes in both ventricles when compared to normal-weight patients.[12] Therefore, weight control and overweight prevention are

**Table 1 – Characteristics of the population (n = 66)**

| Variables | n (%) |
|---|---|
| Sex | |
| Male | 43 (65.2) |
| Female | 23 (34.8) |
| White ethnicity | 52 (83.9) |
| Weight (kg) (m±SD) | 35.64 ± 17.55 |
| Height (cm) (m±SD) | 137 ± 24.32 |
| Age (m±SD) | 10.18 ± 4.6 |
| BMI | |
| Eutrophic | 47 (71.2) |
| Overweight | 13 (19.7) |
| Obesity | 6 (9.1) |
| SBP (m±SD) | 89.44 ± 37.4 |
| DBP (m±SD) | 60.0 ± 26.08 |
| Born at term | 51 (78.5) |
| Birth weight (m±SD) | 2.97 ± 0.64 |
| Birth length (m±SD) | 48.07 ± 4.25 |
| Gestational hypertension | 11 (18.3) |
| Gestational diabetes | 5 (8.3) |

*m: mean; SD: standard deviation; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; n (%): absolute and relative numbers, respectively.*

**Table 2 – Laboratory profile of the cohort (n = 66)**

| Variables | n (%) |
|---|---|
| Low HDL | 23 (34.8) |
| Elevated triglycerides | 20 (30.3) |
| Elevated total cholesterol | 13 (19.7) |
| Elevated CRP | 8 (12.1) |
| Elevated LDL | 8 (12.1) |
| Hyperglycemia | 7 (10.6) |
| Low hematocrit | 4 (6.1) |
| CRP (median IQR) | 0.09 (0.04-0.18) |
| RFs family (median IQR) | 0 (0-1) |

*n (%): absolute and relative numbers, respectively; CRP: C-reactive protein; RFs family: risk factors in the family.*

**Table 3 – Cardiovascular risk factors among first-degree relatives.**

| Variables | n (%) |
|---|---|
| Hypertension | 20 (30.3) |
| Obesity | 11 (16.7) |
| Dyslipidemia | 6 (9.2) |
| Diabetes | 4 (6.2) |
| Presence of 2 or more RFs | 9 (13.8) |

*n (%): absolute and relative numbers, respectively; RFs: risk factors among first-degree relatives.*

very important for these patients because they may avoid surgical and non-surgical interventions in the long term.

Stefen et al.,[13] reported an 8-year follow-up of 110 children with congenital heart disease, in which the BMI was carefully analyzed throughout the years. There was an increase in BMI of 10 points in the cohort at the eighth year, whereas an increase of 21.6 points was observed in the group of children with exercise intolerance, and an increase of 27.3 points was seen in the group of children with physical activity restrictions.[13] It is important to note that physical activity restrictions are one of the main causes of overweight in children with congenital heart disease, whilst it is also an important RF for cardiovascular diseases and other complications of the underlying disease. A study with overweight children who had undergone Fontan's showed the fragility of this population, mostly because they are susceptible to impairments of the pulmonary artery and endothelial function, as well as to increased pulmonary arterial resistance in the long term, all of which are aggravated by excess weight.[10]

Fuenmayor et al.,[14] analyzed the prevalence of dyslipidemia in a pediatric population of 52 patients with congenital heart disease and verified that 13.4% of them presented elevated LDL levels, which was similar to our findings (12.1%).[14] However, when analyzing a population of 476 children free of congenital heart disease, 13.27% of them presented elevated LDL levels. These findings, which are in line with our results, thus suggest that the presence of congenital heart disease is not a RF for elevated LDL. Nonetheless, it is long known that elevated LDL levels are a RF for the development of atherosclerosis and long-term cardiovascular events.

The presence of HTN and/or more than 2 cardiovascular RFs among first-degree relatives were prevalent in this sample. A study by Borges et al.,[15] investigated cardiovascular RFs in 155 parents/caregivers of children with heart disease and observed that obesity and hypertension were among the most prevalent RFs, which was similar to our results.[15] Farias et al.,[16] by identifying the predetermining factors in the prevention of cardiovascular disease in adolescents, showed that the occurrence of HTN and diabetes mellitus among the interviewees' relatives was high.[16] Importantly, both studies suggest that interventions are highly recommended, in view of the great impact the family has on shaping the long-term habits and lifestyle of children and adolescents.

## Conclusion

This study suggests that overweight is frequent in patients with univentricular heart and can be related to the presence of more than 2 cardiovascular RFs among first-degree relatives. Furthermore, physical activity habits and alterations of the lipid profile are also important characteristics of the studied population. We recommend that future studies assess the prevalence of cardiovascular RFs in patients with a single ventricle who have had a Fontan procedure, as well as the nutritional profile and energetic metabolism of these patients.

## Author contributions

Conception and design of the research: Barbiero SM, Pellanda LC. Acquisition of data: Barbiero SM, Carloto RB, Schwantes GC, Guimarães MM, Goulart MR, Schuh DS. Analysis and interpretation of the data: Barbiero SM, Carloto RB, Pereira DS, Goulart MR, Schuh DS, Pellanda LC. Obtaining financing: Barbiero SM, Pellanda LC. Writing of the manuscript: Barbiero SM, Carloto RB,

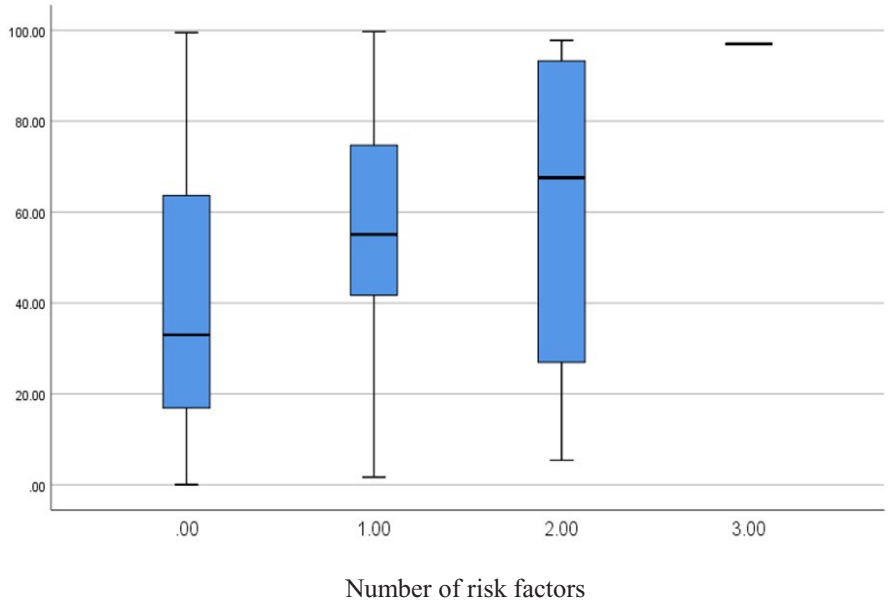


**Chart 1 – Data distribution between the number of risk factors and body mass index. percentiles.**

Pereira DS, Schwantes GC, Guimarães MM, Pellanda LC. Critical revision of the manuscript for intellectual content: Pellanda LC. Project coordination: Pellanda LC.

### 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 de Cardiologia (RS) under the protocol number 4470. 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

# Analysis of the Influence of Abdominal Obesity on Systemic Arterial Hypertension and on the Lipid Profile on Cardiometabolic Risk Stratification in Adult Women

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## Abstract

**Background:** Obesity is a public health problem and has been associated with the development of metabolic disorders that have a strong relationship with the onset of cardiovascular diseases (CVD).

**Objective:** The objective was to analyze the influence of abdominal obesity (AO) on systemic arterial hypertension (SAH) and on the lipid profile in cardiovascular risk stratification in adult women.

**Methods:** Altogether, 91 women participated in the research. Lifestyle information was collected, in addition to the analysis of clinical measures of cardiovascular risk and biochemical parameters. Unpaired Student's t-test, logistic regression, and Pearson's correlation were performed for data analysis, with a value of $p < 0.05$ considered significant.

**Results:** The prevalence of AO was 62.6%. Logistic regression showed that AO increased the chance of developing SAH by 2.9-fold. The same behavior was observed in the TG/HDL-c lipid ratio ($3.93 \pm 0.3$ vs. $2.16 \pm 0.2$), representing an 82% increase in obese women. The present study also demonstrated that the best anthropometric parameter to analyze cardiovascular risk in the studied population was the waist/height ratio (AUC = 0.707).

**Conclusions:** It can therefore be concluded that AO plays a significant role in the development of SAH and changes in lipid values that predict increased cardiovascular risk, configuring a strong influence factor for CVD.

**Keywords:** Obesity, Abdominal; Cardiovascular Diseases; Hypertension; Metabolic Syndrome; Risk Stratification; Adult; Women; Lipidic Metabolism; Hyperlipidemias.

## Introduction

In Brazil, the prevalence of overweight individuals reaches values close to 60% of the total population. This is due to changes in the economic policies of the state that have been responsible for socioeconomic transformations in recent years, leading the country to a situation called epidemiological transition.[1]

This transition promoted changes in the morbidity and mortality profile of the population, thus replacing a profile where the main causes of death were due to infectious communicable diseases, for a new reality in which chronic non-communicable diseases (NCDs) are the main causes of morbidity and mortality in the country.[2-4]

This fact can be attributed to a better socioeconomic situation, associated with a greater consumption of refined, energy-dense, and lower-cost foods, favoring a significant increase in overweight and obesity, especially in developing countries.[4-6] Thus, obesity should be understood as an NCD that is characterized by excess body fat resulting from the imbalance between the individual's dietary intake and energy expenditure.[7,8]

Thus, obesity has become a major public health problem, since it has been associated with metabolic and

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hemodynamic risk factors that strongly contribute to the development of metabolic syndrome parameters, such as systemic arterial hypertension (SAH), dyslipidemias, insulin resistance (IR), and glucose intolerance.[9-11]

In the Northeast region, obesity has taken on alarming proportions and is associated with the increase in the incidence of SAH, especially in the female population, which has a significant prevalence of morbidities associated with the metabolic syndrome.[12] Thus, this study aimed to verify the influence of abdominal obesity on hypertension and lipid profile, as well as to evaluate the best anthropometric method to help stratify cardiometabolic risk in adult women.

## Methods

### Study type and location

This was an observational, quantitative, descriptive, cross-sectional study, developed between October 2016 and July 2017, through the collection and analysis of sociodemographic, biochemical, anthropometric data, and lifestyle habits in a convenience sample of 91 women over the age of 18 years living in the city of Petrolina, Pernambuco. These volunteers were recruited through an invitation made through social networks, and their participation in the research was manifested through their own request.

### Ethical considerations

The present work respected the standards for research with human beings, established by the Declaration of Helsinki, and meets all ethical requirements according to Resolution 466/2012 of the National Health Council. The work meets the requirements of the Ethics and Deontology in Studies and Research Committee (CEDEP) of the Federal University of Vale do São Francisco, logged under protocol number CAAE 62537316.3.0000.5196.

All participants volunteered to participate by signing the Informed Consent Form (ICF), where they were instructed on the procedure to be performed and on the possible risks and benefits.

### Data Collection Instrument

Data collection was performed in two stages. In the first stage, the volunteers answered a structured questionnaire containing sociodemographic and health questions, habits, lifestyle, and medication use. In the second stage, the participants were referred to perform a peripheral venipuncture to collect blood samples.

### Obtaining and analyzing blood samples

Prior to blood sampling, all volunteers were instructed to fast for 12 to 14 hours and not to drink alcoholic beverages in the previous 72 hours. The samples were then stored in test tubes without anticoagulant to obtain serum and transported in thermal boxes to avoid alterations until the processing site, which took place on the same day of collection.

Fasting blood glucose, total cholesterol, HDL-cholesterol, and triglycerides were determined by specific colorimetric enzymatic methods (LABTEST, BR). The quantification of low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) was estimated by the Friedewald equation (FRIEDEWALD, 1972). From the lipid profile determinations, the lipid ratios indicating cardiovascular risk were determined: Total cholesterol/HDL-cholesterol (TC/HDL-c), LDL-cholesterol/HDL-cholesterol (LDL-c/HDL-c), and Triglycerides/HDL-cholesterol (TG/HDL-c).

### Anthropometric measurements

Height, and abdominal and hip circumference measurements were obtained with an inextensible measuring tape. Weight was taken from a portable scale calibrated by the National Institute of Metrology, Standardization, and Industrial Quality (INMETRO).

To take the abdominal circumferences, the volunteers remained standing with arms extended along the body and feet together. For waist circumference measurement, the tape was positioned on the smallest curvature located between the last costal arch and the iliac crest, based on the techniques of Callaway and collaborators (1988).[13]

### Blood pressure (BP) measurement

The measurement of systolic blood pressure (SBP) and diastolic blood pressure (DBP) was obtained by means of a portable pulse device, duly calibrated and validated by INMETRO. The volunteers remained seated with legs uncrossed, feet flat on the floor, and backs resting on the chair. The blood pressure levels were measured in two moments, the first after five minutes of rest in a calm environment (the patient was instructed not to talk during the measurement) and the second, 20 minutes after the first measurement. The arithmetic mean of the two measurements was used.

### Diagnosis of abdominal obesity and hypertension

To diagnose an individual with SAH according to the VII Brazilian Guideline of Hypertension, 2016, the individuals had to present SBP and DBP with values equal to or greater than 140 mmHg and 90 mmHg, respectively, measured using a sphygmomanometer (SBC, 2016).[14]

According to the National Cholesterol Education Program's Adult Treatment Panel III - NCEP ATP III, to be diagnosed as abdominal obesity, a woman must have an abdominal circumference of 88 cm or more.[15,16]

## Statistical Analysis

The database was built in Microsoft Excel program and exported to STATVIEW (version 5.0, 1998) and GraphPad Prism 5.01 programs. The population profile was evaluated by calculating percentage frequencies, where the respective distributions of abdominal obesity and hypertension frequencies were built, together with the lipid ratios of cardiovascular risk in the population in question. Previously, sample distribution normality was verified using the Kolmogorov-Smirnov Test.

The unpaired Student's t-test was performed to compare parameters of SAH and cardiovascular risk lipid ratios in women with and without abdominal obesity. Thus, continuous variables were described by mean ± standard deviation (SD). Pearson's coefficient descriptive statistics were used to verify the correlation between the increase in abdominal circumference and lipid ratios, and to correlate abdominal circumference with SBP and DBP in relation to SAH. In cases where the relationship was significant, odds ratios were calculated through logistic regression, used to measure the chance that obese people have of developing hypertension when compared to participants who are not obese. All conclusions were obtained considering the significance level of 5% and the 95% Confidence Interval (CI) ($p<0.05$), with all statistical analyses adjusted for age.

To identify the respective cut-off points, along with the sensitivity and specificity of the anthropometric methods, the Receiver Operating Characteristic (ROC) curve technique was performed using the MedCalc software (version 17.9) to discriminate the best relationship between abdominal obesity and cardiovascular risk among the anthropometric indicators.

## Results

Abdominal obesity prevalence was 62.6%. From this, analyses of clinical and laboratory parameters were performed in two distinct groups – one with the presence and the other with the absence of abdominal obesity – in order to study its effect on such parameters.

When the presence or absence of abdominal obesity was assessed in relation to blood pressure levels, searching for a relationship between abdominal obesity and hypertension, it was observed that SBP and DBP values were altered when compared to non-obese women, as shown in Figure 1 (a) and (b), respectively. Nevertheless, no significant difference was observed between the ages of the two groups in this study: non-obese (44.3 ± 9.1) vs. obese (45.3 ± 8.7).

The correlation between the positivity of abdominal obesity and pressure parameters (SBP and DBP) was significant. Moreover, obesity was significantly associated with BP levels in women who had mean SBP and DBP values of higher than those of non-obese women.

To establish the odds ratio of a woman with abdominal obesity developing SAH, a logistic regression analysis was performed. Table 1 shows that abdominal obesity was associated with increased odds of an obese woman developing SAH.

It was found that the lipid ratios TC/HDL-c and LDL-c/HDL-c had a direct relationship with increasing obesity. Likewise, TG/HDL-c, which has a correlation with insulin resistance (IR), obtained the highest statistical difference with an odds ratio of approximately 82% higher in obese women compared to non-obese women, as presented in Figure 2. It was also observed that obese women had significantly higher values of lipid parameters compared to non-obese women. By contrast, a significant decrease in HDL-c values was observed in the group of obese women when compared to non-obese women, as presented in Table 2.

To evaluate whether waist-to-height ratio (WHtR) would be an ideal anthropometric parameter to analyze the correlation between abdominal obesity and cardiovascular risk, ROC curve analysis was performed. The best cutoff point for the anthropometric parameters was verified; thus, it was also possible to assess the parameter with the highest correlation in the identification of SAH in women, as shown in table 3.

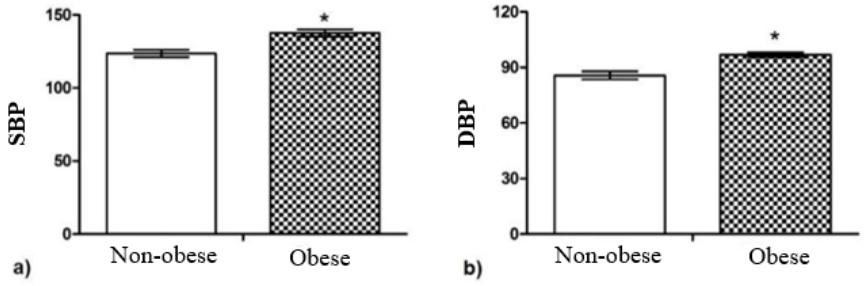


**Figure 1 – Difference between blood pressure levels of women with and without abdominal obesity**
*SBP - Systolic Blood Pressure; DPB - Diastolic Blood Pressure.*
*Source: the author*

**Table 1 – Odds ratio of a woman with abdominal obesity developing SAH**

| Parameters | Odds Ratio | CI | P-value |
|---|---|---|---|
| SAH | 2.9 | 1.1 – 4.2 | 0.0086* |

**p<0.05. CI: confidence interval; p: significance level; SAH: systemic arterial hypertension.*
*Source: the author*

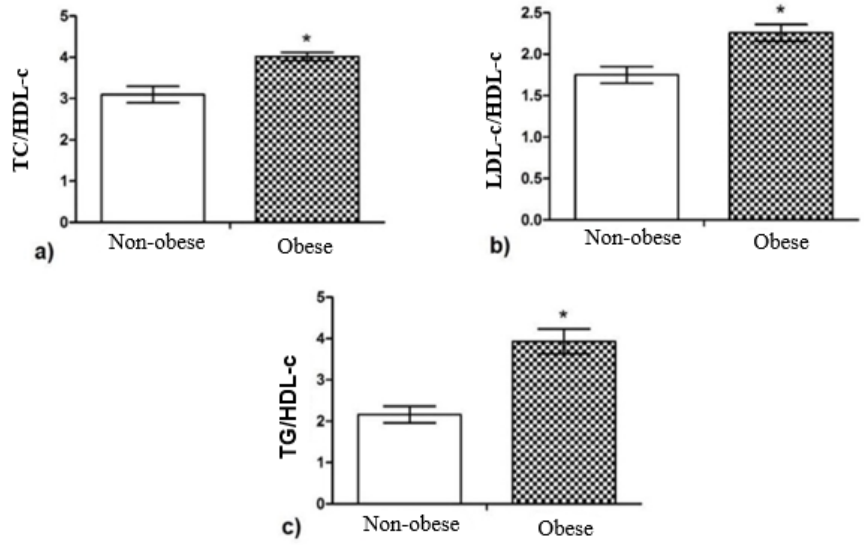


**Figure 2 – Lipid ratios in womwn with presence and obsence of abdominal obesity.**
*All analyses were adjusted for the variable sex. TC (total cholesterol). TG (triglycerides). LDL-c (low density lipoprotein cholesterol). HDL-c (high-density lipoprotein cholesterol).*
*Source: the author*

**Table 2 – Clinical and laboratory parameters obtained with the group of obese and non-obese women**

| | PARAMETERS | STANDARD DEVIATION (±) | P-value |
|---|---|---|---|
| **SBP** | | | |
| Obese | 137.5 mmHg | 2.5 mmHg | <0.0001* |
| Non-obese | 123.6 mmHg | 2.5 mmHg | |
| **DBP** | | | |
| Obese | 96.8 mmHg | 2.5 mmHg | 0.0459* |
| Non-obese | 85.7 mmHg | 85.7 mmHg | |
| **Lipid Ratio TC/HDL-c** | | | |
| Obese | 4.02 | 1.4 | 0.0005* |
| Non-obese | 3.10 | 0.6 | |
| **Lipid Ratio LDL/HDL-c** | | | |
| Obese | 2.26 | 1.0 | 0.0084* |
| Non-obese | 1.75 | 0.6 | |
| **Lipid Ratio TG/HDL-c** | | | |
| Obese | 3.93 | 0.7 | <0.0001* |
| Non-obese | 2.16 | 0.5 | |
| **Total Cholesterol** | | | |
| Obese | 155.01 | 12.7 | <0.0001* |
| Non-obese | 143.5 | 13.8 | |
| **LDL-c** | | | |
| Obese | 87.7 | 12.9 | 0.0056* |
| Non-obese | 81.0 | 6.1 | |
| **Triglycerides (TG)** | | | |
| Obese | 152.4 | 21.1 | <0.0001* |
| Non-obese | 100.0 | 11.1 | |
| **HDL** | | | |
| Obese | 38.5 | 9.0 | <0.0001* |
| Non-obese | 46.3 | 7.7 | |

**p<0,05. Comparisons performed using unpaired Student's t-test. p: significance level; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; HDL-c: high-density lipoprotein; LDL: low-density lipoprotein; SAH: systemic arterial hypertension.*
*Source: the author*

The ROC curve showed that the best anthropometric parameter, having the best ratio between sensitivity and specificity to identify SAH in this population, was the waist-to-height ratio (WHtR) (Figure 3) with a cut-off point equal to 59, corresponding to the ratio between the waist circumference (WC) and the height of the individual, as shown in Table 3.

The correlation between the WHtR and the BP parameters as well as the lipid parameters, TC, TG, LDL-c, and HDL-c was performed. It was verified that the correlation between WHtR and SBP and DBP was positive and significant p<0.0001. Among the lipid parameters, the correlation was also positive and significant. However, the only variable that did not correlate positively was HDL-c in Table 4.

**Table 3 – Relation between the anthropometric parameters investigated to obtain a cutoff point that predicts the early identification of SAH**

| Parameters | AUC | CI (±) | Sensitivity | Specificity | P-value |
|---|---|---|---|---|---|
| Waist circumference | 0.695 | 95%: 0.590 to 0.788 | * | * | 0.001 |
| Waist-to-height ratio | 0.707 | 95%: 0.602 to 0.798 | 67.6% (95% CI: 50.2% to 82.0%) | 74.1% (95% CI: 60.3% to 85.0%). | 0.005 |
| Waist-to-hip ratio | 0.664 | 95%: 0.558 to 0.760 | 78.4% (95% CI: 61.8% to 90.2%) | 55.6% (95% CI: 41.4% to 69.1%); | 0.0048 |
| Body Mass Index | 0.667 | 95%: 0.561 to 0.763 | 45.9% (95% CI: 29.5% to 63.1%) | 85.2% (95% CI: 72.9% to 93.4%) | 0.0049 |

*AUC: area under the curve; CI: confidence interval; p: significance level *: measure not applicable.*
*Source: the author*

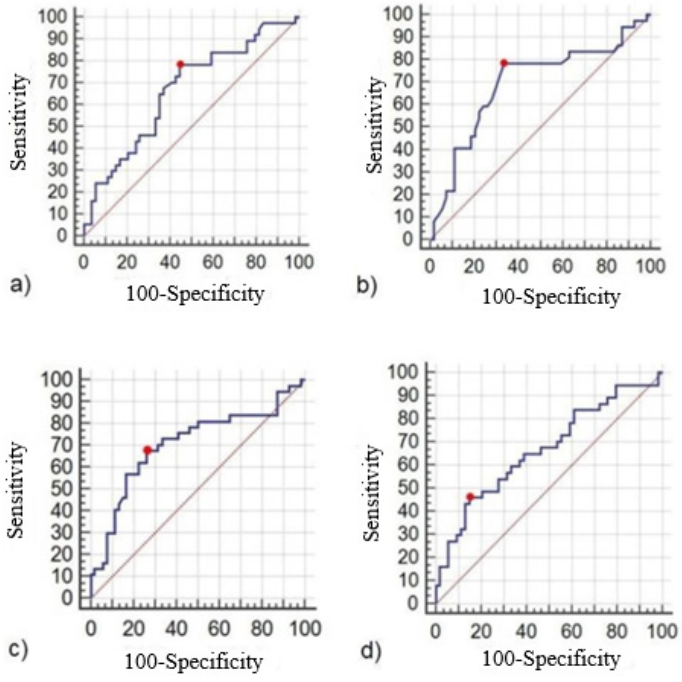


**Figure 3 – ROC curve plots related to the relationship between the anthropometric parameters os SAH.**
*Source: the author*

**Table 4 – Pearson's correlation between WHtR and blood pressure levels, total cholesterol, triglycerides, LDL-c, and HDL-c**

| Parameters x WHtR | Value of r |
|---|---|
| SBP (mmHg) | r = 0.465* (0.287 to 0.614) |
| DBP (mmHg) | r = 0.276* (0.132 to 0.377) |
| TC (mg/dL) | r = 0.330* (0.133 to 0.502) |
| TG (mg/dL) | r = 0.443* (0.261 to 0.595) |
| LDL-c (mg/dL) | r = 0.195* (0.120 to 0.385) |
| HDL-c (mg/dL) | r = -0.133* (-0.330 to 0.075) |

**p<0.05. All analyses were adjusted for the variable of sex. SBP: Systolic Blood Pressure. DBP: Diastolic Blood Pressure. TC: Total Cholesterol. TG: Triglycerides. LDL-c – Low: density lipoprotein cholesterol. HDL-c: High density lipoprotein cholesterol. Source: the author*

## Discussion

Several epidemiological studies provide evidence for the connection between obesity and several comorbidities, and there is a clear correlation between excess weight, especially fat in the visceral region, and the occurrence of CVD. SAH stands out in this group of diseases associated with obesity, since the increase in body fat, especially abdominal fat, is pointed out as a relevant risk factor for hypertensive disease.[17-21]

In Latin America, the prevalence of overweight individuals is around 40%. When dealing specifically with obesity, studies point to a greater variability among Latin American populations, which is between 9.9% and 35%.[17,18]

In Brazil, the scarcity of population studies corroborates the lack of specific data to the reality of each region. This is due to the fact that the country has a great social diversity among its regions, which is reflected in eating habits, lifestyles, and especially in population health.

According to this study, it was noticed that abdominal obesity was quite predominant among women. In line with this research, a study conducted in 2006 with 1,800 individuals residing in the state of Pernambuco showed that 51.9% of adults of both sexes were obese, with a prevalence of 69.9% in women.[22]

Many studies have suggested that not only the amount of fat, but especially the pattern of fat distribution, may be associated with cardiovascular risk. Excess fat located in the abdominal region is considered the main risk factor for the development of other metabolic abnormalities.[19-21]

In obesity, there is an increase in adipocyte volume due to a higher concentration of triglycerides. This is due to the inability of adipocytes to store fatty acids beyond their biological limit, thus leading to a release of free fatty acids (FFA) into the bloodstream, which may culminate in their deposition in organs, such as the liver, as well as in skeletal muscles. This factor is closely linked to an IR profile.[19] Moreover, IR is also directly related to the increase in BP, for in healthy people, it has a vasodilator effect, but the increase in its concentration can increase BP through its action on sodium reabsorption in the renal tubule.[23]

The presence of abdominal obesity is also capable of promoting alterations that are directly related to SAH. The obese women in this study had significantly higher SBP and DBP values than the non-obese women. The pathophysiological mechanisms that favor the development of SAH in obesity are complex and multifactorial.[23]

According to Loskutoff et al.,[24] adipose tissue is associated with the deregulation of circulatory homeostasis through the action of plasminogen activator inhibitor 1 (PAI-1), which is increased in overweight and obese individuals due to the greater expression of its mRNA in adipose tissue, as well as angiotensinogen, which has high serum levels in individuals with abdominal obesity due to its greater synthesis in adipocytes. High levels of angiotensinogen may serve as a substrate for the renin-angiotensin system (RAS), thus generating a high production of angiotensin II and triggering several mechanisms that are linked to the

elevation of BP, either by direct effects on the kidneys or by sympathetic action.[25,26]

Marchi-Alves et al.,[27] in turn stated that high levels of leptin, a peptide hormone secreted mainly by adipocytes, positively modulates systemic blood pressure levels. The concentrations of this hormone are directly proportional to the fat cell volume and increase in proportion to the rise in body fat percentage. Leptin acts, among other ways, by increasing the sympathetic tone in the kidneys, adrenals, and heart, which can trigger BP elevation.

This study identified that women with abdominal obesity are approximately three times more likely (OR=2.9; p=0.0086) to develop SAH than non-obese women. This data confirms that the expansion of adipose tissue in the abdominal region is an important factor in the pathophysiology of SAH.

To strengthen the analysis of cardiometabolic risk, an analysis of lipid ratios allows one to establish some predictive parameters for CVD development.[28] With the likely onset of abdominal obesity-induced IR, the lipid ratios of TC/HDL-c and LDL-c/HDL-c, and Castelli indices I and II, respectively, all predictors of cardiovascular risk, were significantly high in obese women. These data suggest a direct and significant relationship between abdominal obesity and a rise in circulating lipids in plasma. In line with these results, the TG/HDL-c ratio was 82% higher in obese women than in non-obese women.

This fact confirms that the obese group is more likely to develop metabolic diseases, since with a higher concentration of triglycerides, with a reduction in the HDL-c levels, the individual will be more predisposed to being insulin resistant and hypertensive as a direct and indirect consequence.

In recent years, there has been a growing interest in an anthropometric method called waist-to-height ratio (WHtR) as an index to assess adiposity. This method has been proposed as an anthropometric measure to assess central adiposity, as it is strongly associated with cardiometabolic risk factors and because of its relationship with mortality, regardless of body weight.[29] Meta-analysis studies by Savva et al.,[30] and Ashwell et al.,[31] have shown that WHtR has a greater predictive ability for cardiovascular and metabolic risk than the classic anthropometric indicators, BMI, WC, and WHR.

According to the results of the ROC curve analysis, the anthropometric parameter with the highest correlation was WHtR, showing a higher value of area under the curve (AUC 0.707), followed by WC (AUC 0.695), BMI (AUC 0.667), and WHR (AUC 0.664). The WHtR showed a sensitivity value equal to 67.6%, a specificity of 74.1%, and a WHtR cutoff point=0.59.

Thus, a cut-off point of WHtR ≥0.50 has been proposed to predict the risk of CVD as well as diabetes for both sexes. Furthermore, some authors claim that WHtR may be the most useful clinical tool for the global detection of abdominal obesity and for screening cardiometabolic risk in adults and children.[32,33] However, in Latin America, there is a scarcity of major studies assessing the correlation between WHtR and cardiometabolic risk.

Thus, the results of this study corroborate the meta-analyses by Savva and Ashwell,[30,31] indicating WHtR as a better predictor of cardiovascular risk than classical indicators. The definition of cut-off points for anthropometric indicators that stand out for their operational simplicity and good accuracy in detecting at-risk individuals is of great use in health services, since they enable the early identification of health risks in specific population groups, and are also very useful in the use of epidemiological research.[29] However, there is a need to develop more studies with different approaches that can contribute to the construction of scientific knowledge on the problem posed in this study. Furthermore, the development of studies involving a larger number of volunteers (a limitation observed in this study) may contribute significantly to a greater understanding in this area.

## Conclusion

The increase in waist circumference is positively associated with the presence of SAH, as well as with the presence of dysregulated lipid parameters, corroborating the increase in cardiovascular risk. This is a worrisome factor, since obesity was present in 62.6% of the women. In addition, it was possible to establish the waist-to-height ratio as a more specific anthropometric indicator that has a better correlation in predicting cardiometabolic risk than the classic parameters, which can contribute to the early diagnosis of CVDs.

## Author contributions

Conception and design of the research: Cavalcanti, IML, Araújo TFS. Acquisition of data: Cavalcanti, IML,

Araújo TFS. Analysis and interpretation of the data: Cavalcanti, IML, Araújo TFS, Tenório PP, Nascimento CR. Statistical analysis: Cavalcanti, IML, Araújo TFS. Writing of the manuscript: Cavalcanti, IML, Araújo TFS, Tenório PP, Nascimento CR. Critical revision of the manuscript for intellectual content: Cavalcanti IML, Araújo TFS, Tenório PP, Nascimento CR.

### Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade Federal do Vale do São Francisco under the protocol number CAAE 62537316.3.0000.5196. 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.

### 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.

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ORIGINAL ARTICLE

# Effectiveness of Telemedicine in Reducing Hospitalizations in Patients Discharged from the Hospital Due to Heart Failure: A Randomized Clinical Trial Protocol

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## Abstract

**Fundament:** Telemedicine for follow-up in heart failure (HF) patients is effective in reducing hospitalizations, total and cardiovascular mortality. However, few studies were conducted in low and middle income, where lower access to technology and illiteracy could impact the results.

**Objective:** To assess the effectiveness of associating telemedicine strategies, when compared to usual care, in reducing hospitalizations related to HF in patients discharged from the hospital due to HF.

**Methods:** Controlled, randomized, multicenter, parallel-arm clinical trial, with an allocation ratio of 1:1, blinded to outcome evaluation, in which 340 patients who were discharged from public hospitals in Belo Horizonte due to HF will be randomized. Patients will be followed for 6 months and the intervention group will receive, in addition to the usual care, Structured Telephone Support (STS) from a nurse, a doctor, and an educational program. Counseling will be according to a clinical decision tree. The level of significance in the statistical analysis will be 5%.

**Expected results:** Reduction in the number of hospital readmissions and/or in hospitalization time, in addition to developing a software with a clinical decision tree for remote follow-up and patient education about HF adapted to local culture.

**Conclusions:** The intention of this study is to develop a telemedicine strategy and assess whether or not, in addition to the usual care, it is effective in reducing hospitalizations and mortality from HF. If effective, the aforementioned strategy could reduce costs and hospital needs in the Unified Health System (SUS, in Portuguese) for patients with HF. These results will be even more relevant considering the pandemic of COVID-19.Keywords: Heart Failure; Telemedicine; Telemonitoring; Hospitalization; Quality of Life.

## Introduction

Heart Failure (HF) is a disease that affects more than 64.34 million people worldwide.[1] The survival rate after 5 years diagnosed can be of only 35%, higher in individuals of older ages. HF is the main cause of hospital admissions (50%) for the South American population.[2]

In the Brazilian context, in 2018, HF was the main cause of clinical hospitalizations related to the circulatory system, comprising 36% (222.394) of all admissions. Additionally, HF was responsible for 39% (R$348,832,330) of cardiovascular hospitalization costs in the Brazilian Unified Health System (SUS, in Portuguese).[3] It is important to note that at least one third of all HF hospitalized patients are readmitted 90 days after discharge.[4]

The *Brazilian Registry of Acute Heart Failure* (BREATHE) data showed that the main cause of hospital readmission is patient non adherence to prescribed therapy. Moreover, the registry revealed a high in-hospital mortality rate, ranking Brazil amongst countries with the highest rates in Western countries.[2] Other risk factors for decompensation identified by these records were: advanced age; infections;

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nonadherence to nonpharmacological treatment, such as water and salt consumption; and cardiac arrythmias, especially atrial fibrillation.

Although HF treatment represents a challenge to health systems, the advances in technology has been creating alternative opportunities to aid HF patients, reducing their hospitalizations and improving their quality of life through the use of telemedicine strategies. These strategies can improve the self-care of HF patients, identify decompensation signs to provide timely and effective interventions, and optimize treatment recommended by guidelines to reduce hospital admissions.

Based on previous studies of the efficacy of the telemedicine associated telemonitoring showed a reduction in hospitalizations due to all-causes (OR 0.82, 95% CI, 0.73-0.91), hospitalizations due to heart disease (OR 0.83, 95% CI, 0.72-0.95), and a reduction in all-cause mortality (OR 0.75, 95% CI, 0.62-0.90).[5] Mortality by all causes (grouped OR = 0.80, 95% CI, 0.71-0.91, p<0.001), HF related admission rate (grouped OR = 0.63, 95% CI, 0.53-0.76, p<0.001), and length of stay in the hospital related to HF (standardized difference grouped into means = -0.37, 95% CI, -0.72 to -0.02, p = 0.041) were significantly lower in the telemedicine group (remote transmission and telephone support).[6]

The results of another meta-analysis indicated that non-invasive telemonitoring reduced all-cause mortality (RR 0.80, 95% CI, 0.68-0.94) and HF related hospitalizations (RR 0.71, 95% CI, 0.60-0.83). The structured telephone support reduced all-cause mortality (RR 0.87, 95% CI, 0.77-0.98), and HF related hospitalizations (RR 0.85, 95% CI, 0.77-0.93).[7]

Despite the result of meta-analyses, the telemedicine approach was not recommended by guidelines from such organizations as the European Society of Cardiology (ESC) and the American Heart Association, due to the negative result of large trials, mainly in low and middle income countries.[8]

The aim of the present study is to test whether or not adding telemedicine strategies to usual care can in fact further reduce HF-related hospitalizations of patients recently discharged from hospital, when compared to usual care. Through STS, allied with an educational program, we intend to promote self-care, as well as improve the quality of treatment and patient adherence to it, which could generate benefits to patients' quality of life and reduce unfavorable outcomes.

## Methods

This study will be a multicenter, controlled, randomized clinical trial, in two parallel arms with an allocation ratio of 1:1 and blinded for outcome assessments. This study was logged under the Universal Trial Number (UTN): U1111-1263-9802, Brazilian Clinical Trials Registry (ReBEC) RBR-10znr9xn (https://ensaiosclinicos.gov.br/rg/RBR-10znr9xn).

### Participants (trial environment and eligibility)

We will include patients hospitalized for HF (CID10 I50) who are close to being discharged from the public hospitals in Belo Horizonte. Hospital Metropolitano Odilon Behrens (HOB), Santa Casa de Misericórdia de Belo Horizonte, Hospital Risoleta Tolentino Neves (HRTN), Hospital Metropolitano Dr. Célio de Castro (HMDCC), Hospital das Clínicas da UFMG/EBSERH (HC) and Hospital Julia Kubitschek of FHEMIG (HJK) were selected because, together, they were responsible for 72.8% of the HF hospitalizations in SUS in Belo Horizonte, Brazil. in 2018.[3]

The uptake of patients will be carried out by undergraduate students, Scientific Initiation scholarship holders, who have been previously trained and who will invite eligible participants for the study. These activities will be coordinated by the study's management team, made up of two nurses and a doctor.

The inclusion criteria are: patients living in Belo Horizonte and its metropolitan region, older than 30 years of age, using diuretics regularly (Functional Class II/III/IV, according to *The New York Heart Association*), defined as continuous use prior to admission or use upon hospital discharge, and who agreed to participate and signed the Informed Consent Form. The exclusion criteria are patients with diseases that reduce life expectancy to less than six months after their inclusion in this study (patients in palliative care described in medical records); patients in renal replacement therapy; pregnant patients; patients with difficulties or that are unable to complete the interview or to use the telemonitoring devices, defined as patients with dementia or cognitive alterations described in medical records; illiterate patients (those unable to read and/or write) with no responsible caregiver who agrees to help; patients with some condition that could limit the conformity with the study procedures (i.e. known alcohol or other drug abuse); patients that are participating in other HF intervention studies.

## Interventions

Patients included in this study will be randomized and allocated either to the control group (CG), which will receive usual care from the SUS unit where they are referred to, or to the intervention group (IG), for which STS and case management by a nurse, linked to a consultant physician (cardiologist), in parallel with a remote educational program, will be added to the usual care. For both groups, a booklet containing information and counselling about HF itself and about self-care will be offered[9] in addition to an echocardiogram for those patients who have not done this exam in the month prior to their inclusion in this study.

The IG group will receive weekly STS with the same nurse – the case manager. Each call will last around 20 minutes, including the 5 following approaches: i) measuring of daily weight, blood pressure, and heart rate monitoring; ii) investigation of signs and symptoms of decompensation; iii) assessment of pharmacological therapy adherence and barriers to achieve it; iv) educational approach of the disease – signs and symptoms, treatment, and healthy habits; and v) questions & answers.

Weekly, the case manager will meet with the consulting physician to discuss the clinical condition and progress of patients, particularly those who present non-urgent signs and symptoms of early decompensation or that required elective treatment optimization, according to predefined protocols based on the current guidelines. If needed, elective teleconsultations can take place via telephone or videocall. In addition, the case manager will be able to contact an on-call cardiologist (24/7) and, according to predefined protocols, discuss and request an urgent teleconsultation.

Subjects in the intervention group will also receive WhatsApp unidirectional educational messages twice a week, with self-management strategies, counselling about the subject's disease, according to the respective week's topic and to the subject's characteristics (diabetics, non-diabetics, smokers, and/or non-smokers), and reminders about their scheduled medical visits. Table 1 shows examples of messages to be sent to each participant from the intervention group according to each topic.

Participants in the intervention group will have access to a WhatsApp queries channel on office hours and a 24/7 medical on-call service available for guidance in urgent situations (Figure 1).

**Table 1 – Examples of messages sent to the intervention group**

| Main topic of discussion | Message example |
|---|---|
| HF Understanding | Heart failure is the main cause of clinical hospitalization in Brazil. We need to take care of you together so that we can avoid another hospitalization. We're counting on you! |
| Medication | The treatment of heart failure with medication aims to reduce or delay the onset of symptoms, such as tiredness (fatigue), shortness of breath (dyspnea) and swelling (edema). Take your medications every day, as per the prescription. |
| Signs and Symptoms of Decompesation | Do you know when to contact the health team to avoid hospitalization? Please contact us: worsening shortness of breath, worsening swelling and weight gain greater than 2 kilos in 3 days. A simple orientation or adjustment of medications can solve it! |
| Diet | One of the pillars of cardiovascular disease prevention is healthy eating. Try to eat natural foods and avoid processed foods, which in general have a lot of salt and preservatives. |
| Lifestyle changes | One of the best things you can do for the success of your treatment is to have a healthy lifestyle. A balanced diet, regular physical activity, and getting enough sleep and rest are essential. Ask health team professionals for guidance. |
| Caregiver involvement | Ask someone you like to help you remember medication times and to accompany you during appointments. It is always good to have support! |
| Smoking | Quitting smoking is the most important action that a smoker can take to improve his health. Have you thought about it? Ask a professional for help and believe in yourself! |
| Diabetes Mellitus | Test your capillary blood glucose as directed by your healthcare team. Values that are too high (> 200 mg / dl) or too low (<60 mg / dl) are warning signs and should be reported to the healthcare team. |

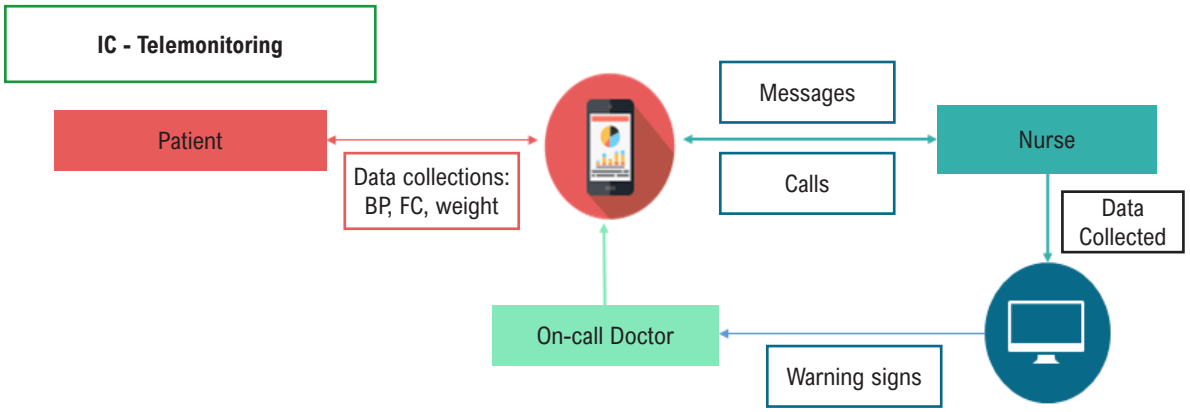


**Figure 1 – Scheme of the technological telemedicine intervention proposed for the Clinical Trial, GI, 2021.**

## Outcomes

The primary outcome will be unplanned HF-related hospitalizations in six months, defined as those with CID-10 I50 or with diseases that may be related to HF decompensation (Ex. arrhythmias, exacerbated chronic kidney disease, dehydration, electrolyte imbalance), evaluated by an adjudication committee consisting of two physicians, based on discharge notes.

The secondary outcomes will be the evaluation of all-cause death; cardiovascular death (CID-10, Chapter IX); readmission by all causes (≥24h length of stay, unplanned); readmission due to HF (CID-10 I50, ≥24h length of stay, unplanned); sought emergency health services, including ambulances (<24h); lost days for unplanned hospitalization or death by all causes in six months; lost days for unplanned hospitalization in six months; change in quality of life of HF patients, assessed through quality of life scores: Minnesota Living with Heart Failure Questionnaire (MLHFQ),[10] HF self-knowledge,[11] and 12-Item Health Survey (SF-12).[12]

The outcome events will be registered for both groups, either through structured telephone calls every 45 days made by trained research team members or through identified mortality and hospital admission data from Belo Horizonte. Data collected through telephone calls will be checked by videocall in 180 days ± 15 after hospital discharge.

## Sample Size

To determine the study's sample size, the following formula will be used:

$$2N = \frac{2\{Z_\alpha\sqrt{\bar{p}(1-\bar{p})} + Z_\beta\sqrt{\overline{p_c}(1-\overline{p_c}) + \overline{p_i}(1-\overline{p_i})}\}^2}{(p_c - p_i)^2}$$

The following parameters were used:

- Outcome: readmission ratio
- Control group ratio (pc)=0.386
- Intervention group ratio (pi)=0.26
- Type II Error ($\beta$) =0.20
- Type I Error ($\alpha$) =0.05

The reference for case and control parameters in hospitalization outcome were taken from "Oscalices MIL, Okuno MFP, Lopes MCBT, Campanharo CRV, Batista REA. Discharge guidance and telephone follow-up on heart failure therapeutic adherence: randomized clinical trial. Rev Lat Am Nursing, 2019".[13] Although in the mentioned study the telemedicine intervention has been less intensive than that proposed herein, we chose to use this study data because the target population is similar and, as the present study intervention is more robust and intensive, we might overestimate the sample.

Considering a loss ratio of 25%, after this correction the study generated a sample of 340 randomized patients randomly assigned to two groups (1:1).[14] The patient who does not follow the intervention or answer the calls will be considered a loss in the sample.

The planned total duration of the study is 10 months, with an inclusion time (4 months) and a follow-up time (6 months).

## Assignment/allocation and blinding

The present study will have a two-form randomization, simple and stratified. The simple randomization ensures total randomness in assigning participants to each group. This will be applied in a complete and random manner to the first patient, and subsequently each patient will be evaluated in order to avoid disbalancing between the two groups at the end of participant inclusion phase. This means that for every randomized patient, the next one will have the probability of being assigned to each recalculated group. To this end, the algorithm below will be used:

```
#nc: number of cases
#ni: number of interventions
loop
n=nc+ni
intervention=ni/n
if
rand= randomization (0 a 1)> intervention returns "CASE" otherwise "INTERVENTION"
    if rand = "CASE" returns nc-1 otherwise nc-1
#End
```

On the other hand, knowing that subject's profile may differ according to the hospital in which one was hospitalized (for example: sociodemographic or severity profile); thus, the randomization will be stratified by hospital. The stratification will be conducted through separated randomization blocks for each hospital. After the assignment of subjects to a hospital pack, the simple randomization is applied inside each pack. The randomization system will be centralized, applied by a software after the inclusion of subject's baseline data, in previously created packs for each hospital. The allocation is confidential, preventing researchers from predicting the distribution order.

This is an open study because of its intervention nature and, as such, the treatment allocation will not be blinded either to researchers or to the participant. The outcomes will be collected by blinded researchers for the participant group and endorsed by a blinded adjudication committee.

## Data collection methods

The data collection will be made using a designed and dedicated software, via tablet, with automatic data transfer to the center, and will be carried out in four steps, according to the flowchart presented in **Figure 2.**

## Data managing and monitoring

Participants will be registered through codes, ensuring confidentiality. Each patient will have an electronic chart where data collected will be registered in eachg step. Access to a data managing system will be authorized via personal and non-transferable password, and the forms will be signed electronically, guaranteeing data confidentiality.

Group data analysis and monitoring team will be responsible for registered data. Data input will happen via WEB: "website" with user management, identification, and password. Systematic verifications of data consistency will be done periodically. The general responsibility for the study will be of the steering committee, along with the responsibility for decisions to improve the study monitoring.

Considering the intervention nature that does not expose participants to additional risks to their health, there are no pre-defined conditions to withdraw the study before the planned period.

## Statistical analysis

The main data analysis will be performed after finishing the inclusion of participants estimated in sample planning. During the participant's' inclusion period, the composition of each sample will be evaluated by descriptive analysis to assure homogeneity.

Four months after the beginning of data collection, the first partial results will be presented, showing the descriptive analysis of the participants' baseline sociodemographic and clinical variables.

The final report will be comprised of a primary analysis, following the "intention to treat" principle. As a sensitivity analysis, we will also analyze data per protocol. Statistical tests will be applied to compare groups and the 95% confidence intervals of group variables will be estimated. Moreover, a secondary analysis will be drafted using logistic regression models to estimate the odds ratio according to the comparison group. Chi-square tests (categorical variables) and the Student t mean comparison tests, paired and unpaired, will be applied, as well as the accepted normality test, will be performed. Otherwise, non-parametric tests will be applied (Mann-Whitney, Wilcoxon, McNemar, Sign-Test, Kruskal-Wallis, among others, if necessary). The level of significance adopted in the statistical analysis will be 5%.

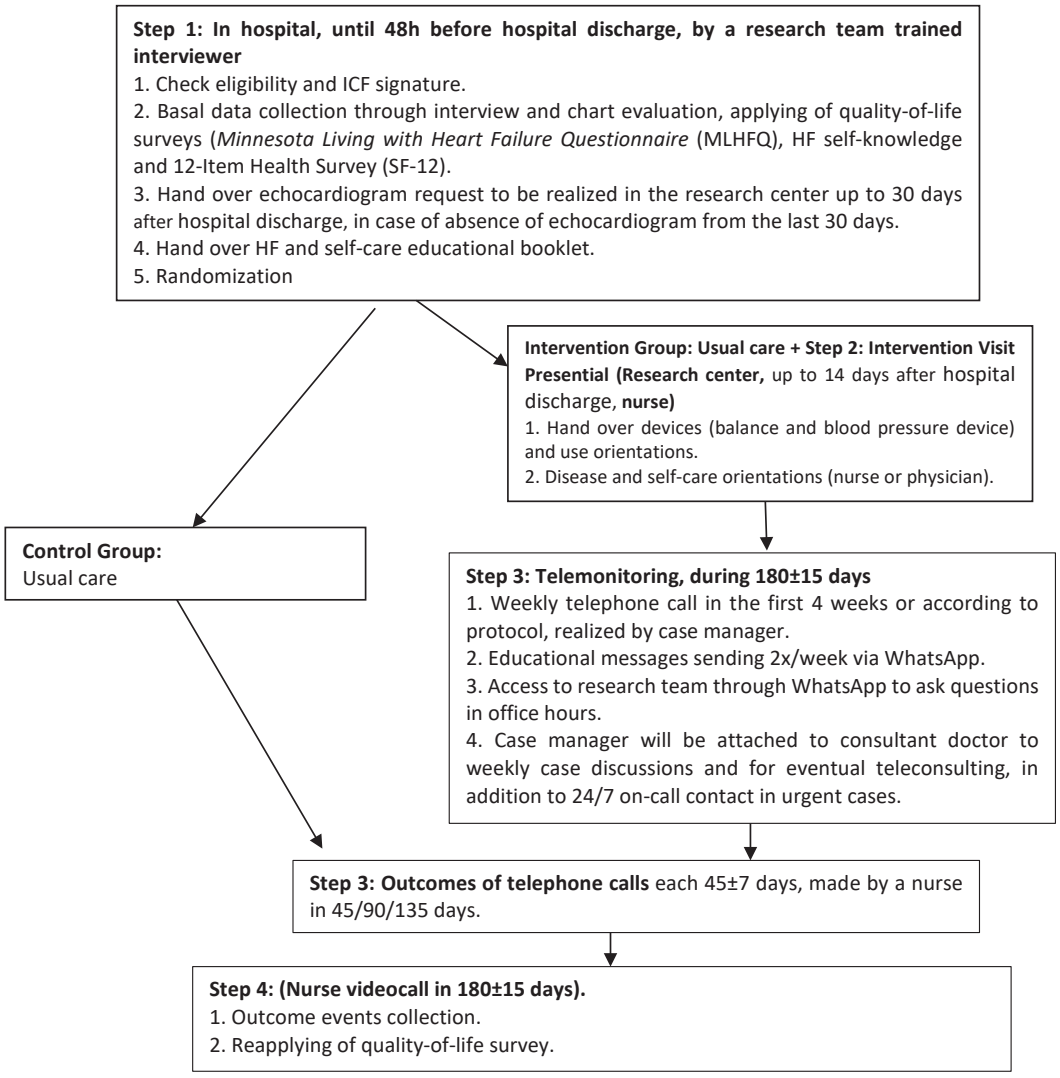


**Figure 2 – Data collection flow chart**

Participants that die during the 180 days of follow-up will be considered in the analysis of days lost by hospitalization until the day of death.

The pre-specified subgroup analysis will include:

- Sex
- Age (stratified at 60 years)
- Literacy (incomplete elementary education vs. others)
- HF cause (ischemic vs. others)
- NYHA II vs. III and IV
- LVEF < 40%, > 50%
- Center

It is important to emphasize that all project planning was defined using information gathered prior to the COVID-19 pandemic. The study planning estimated the mean period of hospitalization so that the project would be developed in the stipulated time. However, different scenarios can be observed and, consequently, adaptations and alterations can be made. For example, the data collection process was elaborated to include the last patient until the end of the 6$^{th}$ month. If the partial analysis shows that this projection is not feasible, the inclusion period could be extended as a way to maintain the study's statistical power for the comparison group regarding outcomes.

## Ethics and promotion

This research was approved by the Research Ethics Committee (REC) of Fluminense Federal University (FFU), CAAE: 38594020.0.1001.5243. It will follow the Regulatory Norms and Guidelines involving Human Beings, established by Resolution 466/12 of the National Health Council and Tripartite Harmonized Manual of Harmonization International Conference (HIC) for Good Clinical Practice (GCP).

This study was registered in the Brazilian Clinical Trials Registry (ReBEC), RBR-10znr9xn, logged under UTN number: U1111-1263-9802 and followed Consolidated Standards of Reporting Trials 2010 (CONSORT 2010) recommendations.

The adverse events that may occur during the study period will be registered and informed to the attending physician or to participants of the Health Center management via e-mail, fax, or telephone calls and forwarded on the partial reports. The following will be registered:

- Nature of events, its beginning and ending dates, its severity;
- The introduction of treatment, if applicable, including adjustment of HF pharmacological therapy or patient counselling conducts, such as recommendations to search for medical assistance, urgently or not;
- Event results and its relation with the allocated study intervention, evaluated by the researcher.

The actions that will follow an adverse event identified by telemonitoring will be defined by pre-defined protocols.

An adverse event is defined as any adverse medical occurrence in a patient or clinical trial subject that does not necessarily have a cause relation with the treatment.[15]

## Expected results

The expected result is to answer if telemedicine by STS follow-up of HF patients will reduce the need for re-hospitalization or the amount of time that they spend in the hospital, in comparison to usual care, in our country.

The secondary outcomes will be cardiovascular death, readmission for HF; search for emergency services, such as Emergency Care Units, Hospital Emergency Service, or SAMU; and days lost due to unplanned hospitalization. It is expected that this study can contribute to improvements in the quality of life and functional class of patients with HF upon hospital discharge. In addition, software is being developed to record patient data and the compilation of results after six months of follow-up. The use of assisted technologies, such as telemedicine, to assist HF patients has the potential to reduce hospital admission and disease mortality rates through improved understanding and self-care; individualized counselling on diets, especially water and salt restrictions; and the practice of physical activity, as well as stimulus for regular medication use, the fast optimization of current guideline based treatments, and the early detection of decompensation signs and symptoms.[7,16,17]

Hospitalizations are associated with the worsening of health-related quality of life and with an increasing risk of death, and are responsible for most health costs in the treatment of individuals living with severe chronic conditions.[7,16,18,19] Considering COVID-19 concomitance, these outcomes could be worsened. In this context, testing new evidence in the field of telemedicine could support health care.

## Conclusion

In conclusion, this study aims to provide information by means of controlled randomized data as to whether or not telemedicine interventions are effective in reducing re-hospitalizations due to HF.

Importantly, the telemedicine and STS apparatus developed for this study, such as software and applications, may be used afterwards, even in patients who live in areas where the access to specialized medical care is scarce. If the expected results of the present study are confirmed, the trial may serve as a reference to the implementation of similar strategies in a wider context in the scope of SUS, reducing HF hospitalization in Brazil.

## Acknowledgments

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## Author contributions

Conception and design of the research: Edmar Geraldo Ribeiro, Luisa Brant, Lilian Cristina Rezende, Renato Azeredo Teixeira, Laura Carvalho Parreiras, Tulio Batista Franco, Antônio Ribeiro, Deborah Carvalho Malta. Statistical analysis: Renato Azeredo Teixeira. Obtaining financing: Tulio Batista Franco. Writing of the manuscript: Edmar Geraldo Ribeiro, Luisa Brant, Lilian Cristina Rezende, Laura Carvalho Parreiras, Deborah Carvalho Malta. Critical revision of the manuscript for intellectual content: Luisa Brant, Deborah Carvalho Malta.

### Potential Conflict of Interest

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

### Sources of Funding

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### Study Association

This article is part of the thesis of Doctoral submitted by Edmar Geraldo Ribeiro, from Federal University of Minas Gerais.

### Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Ethics Committee on Animal Experiments of the Research Ethics Committee (REC) of Fluminense Federal University (FFU) under the protocol number CAAE: 38594020.0.1001.5243. 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

# What is the Future of the Hospital of the Future? The Seven Pillars

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***Editorial referring to the article: Effectiveness of Telemedicine in Reducing Hospitalizations in Patients Discharged from the Hospital Due to Heart Failure: A Randomized Clinical Trial Protocol***

*"Let the future tell the truth, and evaluate each one according to his work and accomplishments. The present is theirs; the future, for which I have really worked, is mine"* – **Nikola Tesla**

In the current edition of the International Journal of Cardiovascular Sciences, Ribeiro et al. presented a controlled, multicenter, randomized, and blinded (regarding the outcome) study with a set of 340 patients. The authors proposed to assess whether a telemedicine strategy could be effective in reducing mortality and the number of hospitalizations in patients with heart failure.[1] Studies like this reiterate the leading role of telemedicine and bring a broader thought: what is the future of the "hospital of the future", and what experiences would be fundamental to make this a reality? Given the complexity of the issue, some elements seem to be indispensable; we listed them in the following paragraphs.

First pillar: the need for truly patient-centered care strategies, allowing patients to actively participate in decisions about their health. Salisbury et al.[2] highlighted that this type of care includes a comprehensive review of patients' problems, considering circumstances of each case, focusing on the quality of life and disease control. To this end, the authors point out the need to develop a personalized therapeutic strategy weighing the risks and benefits of the treatment, aiming to reduce their burdens, promote self-care and build an environment of shared decisions.[2] In addition to patients, we must empower families to participate actively in their health care through collaboration with health professionals and the health system.[3] Therefore, empathy and an effective doctor-patient relationship remain essential.

Second pillar: the future hospital is an environment of continuous innovation and data-driven. In this context, tools such as artificial intelligence, natural language processing, smartphone apps, blockchain, wearables, and virtual/augmented reality are part of a continuum of solutions that must be thought of in an integrated way to generate value.[4] This scenario brings a corollary – the need for interoperability and electronic health records linked to an intelligence infrastructure that couples information quality, security, and high-level processing. Command centers are promising. However, additional headwinds still need to be addressed before digital technologies fully integrate into the clinical workflow from a device and regulatory perspective.

Third pillar: the hospital of the future needs to be sustainable. Thus, it is crucial to be resolute and increase the probability of favorable outcomes. There is also a concern with the relationship between cost and effectiveness. Discussions about remuneration models are also essential here, such as controversies between the fee-for-service model and value-based care (or even a hybrid model). Fourth pillar: the undeniable connection between the hospital and primary care. It is necessary to speak of an enlarged and "without walls" hospital: the concern with health extends to those patients who are not in their traditional physical space. It is, therefore, a multi-professional environment based on a modus operandi of research and knowledge generation in a continuous and real-time manner. In this context, education and literacy are crucial for patients and health professionals.[5]

## Keywords

Hospital; Future; Pillars.

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Fifth pillar: the hospital of the future must expand access. Technology and connectivity are essential to reduce the barriers of costs and improve accessibility to high-quality health system in any country, logically with a look at specific characteristics of each region. It is mandatory to do previous analysis of the entire local and expanded care network, at all levels of care, its physical and digital capacity, and specialties served. We also should assess the real possibility of patient access (whether private, by health insurance companies, or public/government) and the connection to hubs of excellence (when necessary, for highly complex cases). The regulation and management of the beneficiary access should be planned in this context of "Hospital of the Future" to establish means to facilitate access, considering issues such as cost-effectiveness and physical, digital, and service remuneration. Therefore, it is fundamental to use management tools that enable data analysis for proactive management of specialties, appointments, specific needs for clinical and imaging exams, procedures, hospitalizations, and referrals to providers of all types. In this sense, digital health care can benefit health management (promotion and prevention) and disease management (acute and chronic care). Some primary points that should guide patient access are:

(i) Design of services that ensure care in the right measure, whether physical or virtual;

(ii) Understanding the population, access queues (pent-up demand), service designs, and journeys that reflect their clinical condition;

(iii) Strengthening and improving internal controls and regulation rules already in practice (positive) and redesigning others that are not effective.

Sixth pillar: the hospital of the future must deliver value.[6] Finding the right platforms and building a digital journey for the clients is the way to generate value in a sustainable form for the system. Therefore, the technology must collaborate to reduce healthcare costs, real strengthen primary care, improve better care outcomes and services, impact wealth generation and productivity of the health ecosystem, and align with patient expectations.

Seventh pillar: we must replace the war environment with a collaborative one. Developing a comprehensive digital strategy is the key to maximizing efficiencies across organizations and must involve a multi-stakeholder group with no niceties and win/win business models. Integration is central to achieving this goal. Stakeholders, IT, business, the health team, and scientists must form consistent working groups with aligned interests. For this, clinical governance must work hard to build the health team loyalty through meritocracy and performance. We should create an ecosystem[7] focused on high-performing clinics, hospitals, and professionals, but collaboratively and dynamically. When assessing potential partners or targets, companies must ask themselves some critical strategic questions:

(i) "Does this exist, or is it still a concept?";

(ii) "What does this solve for, and what will the impact be?";

(iii) "How will this integrate into my systems and those of any partners?";

(iv) "How easy is this to use?";

(v) "How do we scale this?"

In light of what we have exposed, we cannot determine a single hospital model of the future, much less believe that it will be a static entity. On the contrary, it is a complex, dynamic environment with several challenges and at least seven well-defined pillars. Besides, in light of Nikola Tesla's arguments, it is possible to say that this new hospital is the result of hard work. In this way, the future of the hospital of the future seems to increasingly depend on the construction of an innovative, collaborative ecosystem focused on the sustainable promotion of collective health and well-being.

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ORIGINAL ARTICLE

# Effects of Exercise Training on Left Ventricular Diastolic Function Markers in Patients with Obstructive Sleep Apnea: A Randomized Study

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## Abstract

**Background:** Exercise training (ET) is an adjunctive treatment for obstructive sleep apnea (OSA) and its consequences. However, the effects of exercise on heart remodeling are unknown in the population with OSA.

**Objective:** We investigated the effect of ET on markers of diastolic function, sleep parameters, and functional capacity in patients with OSA.

**Methods:** Sedentary patients with OSA (apnea-hypopnea index, AHI ≥15 events/hr) were randomly assigned to untrained (n=18) and trained (n=20) strategies. Polysomnography, cardiopulmonary exercise test, and echocardiography were evaluated at the beginning and end of the study. ET consisted of 3 weekly sessions of aerobic exercise, resistance exercises, and flexibility training (72 sessions, completed in 11.65±0.86 months). A two-way analysis of variance (ANOVA) was used, followed by Tukey's post-hoc test. The level of statistical significance was set at $p<0.05$ for all analyses.

**Result:** Thirty-eight patients were included (AHI:45±29 events/hr, age:52±7 y, body mass index: 30±4 kg/m$^2$). They had similar baseline parameters. ET caused a significant change in OSA severity (AHI:4.5±18 versus -5.7±13 events/hr; arousal index:1.5±8 versus -6.1±13 events/hr, in untrained and trained groups respectively, $p<0.05$). The trained patients had an increase in functional capacity after intervention. ET improved isovolumetric relaxation time (IVRT, untrained=6.5±17.3 versus trained=-5.1±17.1 msec, $p<0.05$). There was a significant correlation between changes in IVRT and arousal index in the trained group ($r=-0.54$, $p<0.05$). No difference occurred in the other diastolic function parameters evaluated.

**Conclusion:** ET promotes modest but significant improvement in AHI, functional capacity, and cardiac IVRT, a validated parameter of diastolic function.

**Keywords:** Sleep Apnea; Obstructive; Heart Ventricles; Exercise.

## Introduction

Obstructive sleep apnea (OSA) is characterized by episodes of total or partial upper airway obstructions during sleep. These respiratory events result in oxygen ($O_2$) desaturation, arousals, sleep fragmentation, and negative intrathoracic pressure that potentially impair the cardiovascular system.[1,2] The negative intrathoracic pressure in particular leads to increased thorax and consequently an increase in preload. These responses may result in dilation of the right ventricle[3] and left ventricular (LV) septal deviation,[4] which contribute to cardiac diastolic dysfunction. Hypoxia also causes increased inflammatory cytokines, decreased

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bioavailability of nitric oxide, and oxidative stress, all of which contribute to arterial stiffness,[5,6] which in turn increases LV afterload in OSA patients. In the long term, these responses can cause LV remodeling,[7] contributing to diastolic dysfunction in patients with OSA.[8]

It has been reported that diastolic dysfunction markers can be improved with exercise training (ET).[9] ET improves diastolic function in healthy volunteers[10] and patients with heart failure.[11] Active elderly people have better diastolic function (reduced peak A wave, increased E wave) compared with their sedentary peers.[12] Experimental evidence showed that elderly rats with diastolic dysfunction had decreased isovolumetric relaxation time (IVRT), increased E/A ratio,[9] increased E wave, and decreased E wave deceleration time[13] after 10 and 12 weeks of aerobic training, respectively. Also, Baynard et al.[14] found decreased IVRT in obese patients with metabolic syndrome who underwent 10 consecutive days of aerobic training.

ET promotes many benefits in patients with OSA. The benefits include decreased apnea-hypopnea index (AHI) and muscle sympathetic nerve activity,[15,16] and reduced body weight and blood pressure (BP).[15] This information suggests that ET may be a useful nonpharmacological method for improving LV diastolic function markers related to OSA severity. However, no information is available about the effects of ET on LV diastolic function markers in patients with OSA without other major comorbidities. The aim of this study was to investigate the effect of ET on diastolic function markers, sleep parameters, and functional capacity in patients with recently-diagnosed OSA. We hypothesized that ET would improve parameters of diastolic function associated with improvement in OSA severity.

## Materials and Methods

### Subjects

We invited male and female individuals aged 40 to 65 y to undergo a standard nocturnal polysomnography at the Sleep Laboratory at the Heart Institute (InCor), School of Medicine, University of São Paulo. These volunteers were part of a large study investigating the effects of ET on cerebral function in patients with OSA. In the present study, in order to evaluate the effect of ET on diastolic function markers in OSA patients without other major diseases, we opted to exclude major confounders such as patients with body mass index (BMI) >40 kg/m$^2$, smoking or alcohol abuse (2 or more drinks/d), cardiopulmonary disease, chronic renal disease, diabetes mellitus, history of psychiatric disorders, shift workers, hypertension (resting BP >140/90 mmHg on more than one occasion), use of medicines that affect sleep or the vascular system, and any OSA treatment. Of note, some study subjects took part in our previous research dealing with the effects of exercise training on muscle metaboreflex control[16] and cardiac autonomic modulation.[17] The sample size calculation for the present study was based on mean and standard deviation scores reported in a previous study.[18] With 18 participants in this cross-sectional study design, we anticipated a priori that our sample size would be sufficient to detect a 10% difference in diastolic function markers between groups, assuming a power of 0.80 and significance level of 0.05 (2-sided). The Institutional Committee on Human Research (InCor-HCFMUSP) approved the study (0833/10), and all subjects provided written informed consent. Patients were randomly assigned to either the untrained or exercise-trained group on a one to one basis. Full nocturnal polysomnography, maximal exercise capacity, and echocardiographic measurements were performed at baseline and the end of the study.

### Sleep study

All participants underwent overnight polysomnography (Embla N7000, Medcare Flaga, Reykjavik, Iceland) at the Sleep Laboratory of the Heart Institute (InCor), University of São Paulo Medical School. Polysomnography was performed using standardized techniques, with a standard staging system for sleep stages used as previously described.[16] Obstructive hypopneas were defined as a reduction of at least 30% of the airflow amplitude captured by the nasal cannula, lasting at least 10 s, associated with oxyhemoglobin desaturation greater than 3% and/or arousal. The sum of apnea and hypopneas per hours of sleep determined AHI. Considering the consistent evidence suggesting that mild OSA is not associated with increased cardiovascular risk,[19] we used a more conservative AHI cut-off of ≥15 events/hr of sleep.

### Echocardiogram

Echocardiographic measurements were performed with commercially available ultrasound equipment (Vivid E9, GE Vingmed, Horton, Norway) using a 4 MHz multifrequency transducer, with patients in the left lateral decubitus position. Echocardiographic examination was performed as follows: 1) a comprehensive 2-dimensional echocardiogram, to exclude presence of structural heart

disease; 2) measurements of LV diameters and wall thickness, with resultant ejection fraction (Teichholz) and LV mass[20] and mass index; 3) two-dimensional guided conventional and tissue Doppler echocardiography to evaluate diastolic function and estimate LV filling pressures. For mitral valve inflow tracings, the volume sample was positioned between the free edges of mitral valve leaflets, parallel to the flow obtained from color flow mapping. Three consecutive beats were selected for offline measurements at the end of expiration. Peak E (early) wave, A (late) wave, E wave deceleration time, and isovolumic relaxation time (IVRT) were measured, and the E/A ratio was calculated. IVRT (msec) was measured as the time between closing of the aortic valve and the earliest detection of mitral flow. Tissue Doppler tracings were obtained from the apical 4-chamber view with the sample volume positioned in the basal septal and lateral mitral annulus to assess early septal diastolic myocardial velocity (e') wave and late septal diastolic myocardial velocity (a') wave. The E/e' ratio was calculated for lateral and septal velocities and the average of these measurements was used for analysis. All measurements were performed according to American Society of Echocardiography and the European Association of Cardiovascular Imaging.[20] Echocardiography was performed by a physician blinded to the group to which each participant was assigned. Intraobserver and interobserver variability of IVRT was measured in 10 individuals by 2 independent observers.

### Cardiopulmonary exercise test

Maximal exercise capacity was determined with a maximal progressive cardiopulmonary exercise test (SensorMedics - Vmax Analyzer Assembly, Encore 29S) on an electromagnetically braked cycle ergometer (Via Sprint 150P, Ergoline, Bitz, Germany), with work-rate constant increments (5 to 20 W/min) at 60 to 70 rpm until exhaustion as previously described.[21] Peak oxygen uptake (peak $VO_2$) was defined as the maximum $VO_2$ attained at the end of the exercise period in which the subject could no longer maintain the cycle ergometer velocity at 60 rpm.

### Exercise training protocol

Supervised ET consisted of 3 weekly sessions lasting 50 mins in the first month and 60 mins from the second month onwards. Each session was distributed as follows: 5 mins of stretching; 40 mins (30 mins in the first month) of aerobic exercise (cycle ergometer), with intensity varying between the anaerobic threshold and the point of respiratory compensation (detected from the cardiorespiratory capacity test), which was measured by heart rate; 10 mins of resistance exercises; 5 mins of relaxation. The subjects in the untrained group were asked to control their non-participation in systematic physical activity programs during the control period.

### Statistical analysis

Data are expressed as mean ± standard deviation (SD). The Kolmogorov–Smirnov test was used to assess the normality of the data distribution for each variable studied and Levene's test was used to assess the homogeneity of variance for each variable studied. The categorical variable was expressed as absolute frequency. A $\chi^2$ test was used to compare differences according to sex. Unpaired Student's *t* tests were used to determine differences between groups (baseline and delta changes). Two-way analysis of variance with repeated measures was used to compare within and between group differences before and after intervention. In case of significance, Tukey's post-hoc test was used. Pearson correlation analysis was used to examine the association between changes in echocardiographic parameters and changes in arousal index. $P<0.05$ was considered statistically significant. Statistical analysis were performed using STATISTICA 12 (StatSoft Inc., Tulsa, OK, United States) software. Interobserver and intraobserver variability were calculated as the difference between the 2 observations divided by the means of the observations and are expressed as percentages.

## Results

We initially selected 98 potentially eligible patients who were referred for the following examinations: conventional nocturnal polysomnography, echocardiography, and cardiopulmonary testing. Of these, 46 had no diagnosis of OSA, 2 had asymptomatic LV systolic dysfunction (LV ejection fraction<50%), and 6 had hypertension. Thus, 44 patients diagnosed with OSA were included in the study and were randomly assigned to the untrained group (n = 22) or the exercise-trained group (n = 22) through the recruitment sequence at the ratio of 1:1, in which one subject was selected for the untrained group and the next subject was selected for the exercise-trained group. One additional patient in the untrained group

started continuous positive airway pressure treatment and 3 did not complete the protocol evaluations, including echocardiography; thus 18 patients in this group remained in the study. In the trained group, 2 patients did not complete the ET. Thus, 20 patients remained in this group. Descriptive statistics are presented in Table 1. There was no difference in physical, baseline cardiovascular, functional capacity, sleep, or echocardiographic measurements between untrained and trained groups with OSA. For more details of baseline echocardiographic measurements, see Supplemental Content Table S1.

## Post-intervention measures

In the present study, 100% (72 sessions) of the post-intervention measurements were obtained by 11.65±0.86 months. The untrained group was paired with the exercise-trained group. Table 2 presents the physical, hemodynamic, and functional capacity post intervention measurements in both untrained and trained groups. There were no significant differences in physical characteristics after the intervention period. Regarding the hemodynamic parameters, there were also no significant differences in systolic BP, diastolic BP, or heart rate measurements in either

**Table 1 – Baseline physical, cardiovascular, functional capacity, sleep, and echocardiographic parameters.**

| Parameters | Untrained (n=18) | Trained (n=20) | p Values |
|---|---|---|---|
| Physical | | | |
| Sex, M/F | 12/6 | 8/12 | 0.18 |
| Age, y | 50±6 | 53±7 | 0.20 |
| BMI, kg/m² | 29±4 | 30±4 | 0.62 |
| Cardiovascular | | | |
| SBP, mm Hg | 121±11 | 119±12 | 0.53 |
| DBP, mm Hg | 78±8 | 78±6 | 0.82 |
| HR, beats/min | 65±10 | 68±8 | 0.37 |
| Functional capacity | | | |
| Peak $VO_2$, ml/kg/min | 26±6 | 23±6 | 0.11 |
| Sleep | | | |
| Total sleep time, min | 388±47 | 360±60 | 0.11 |
| AHI, events/hr | 43±26 | 47±31 | 0.71 |
| Arousal index, events/hr | 31±16 | 33±17 | 0.79 |
| $O_2$ desaturation, events | 33±26 | 41±31 | 0.34 |
| Echocardiographic | | | |
| E wave, cm/sec | 74±14 | 72±13 | 0.69 |
| A wave, cm/sec | 66±17 | 68±14 | 0.73 |
| E/A ratio | 1±0.3 | 1±0.2 | 0.30 |
| IVRT, msec | 89±12 | 90±15 | 0.93 |
| DT, msec | 209±55 | 205±34 | 0.76 |
| Septal e', cm/sec | 9±2 | 9±2 | 0.94 |
| Septal a', cm/sec | 9±2 | 10±2 | 0.20 |
| Septal E/e' | 9±2 | 8±2 | 0.55 |
| Lateral e', cm/sec | 11±3 | 10±2 | 0.26 |
| Lateral a', cm/sec | 10±2 | 10±3 | 0.47 |
| Lateral E/e' | 7±2 | 7±2 | 1.00 |
| E/e' average | 8±2 | 8±2 | 0.88 |

*Values are presented as means ± SD. BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; Peak $VO_2$: peak oxygen uptake; AHI: apnea-hypopnea index; $O_2$: oxygen; IVRT: isovolumetric relaxation time; DT: E wave deceleration time. A $\chi^2$ test was used to compare differences according to sex. Differences between groups were analyzed using Unpaired Student's t tests.*

**Table 2 – Physical characteristics, cardiovascular parameters, functional capacity, and sleep parameters before and after the intervention period.**

| Parameters | Pre | Post | Change (Δ) |
|---|---|---|---|
| Physical | | | |
| BMI, kg/m² | | | |
| Untrained | 29±4 | 30±4 | 0.2±0.9 |
| Trained | 30±4 | 30±3 | (-)0.1±1.2 |
| Cardiovascular | | | |
| SBP, mm Hg | | | |
| Untrained | 121±11 | 123±15 | 2.2±13.2 |
| Trained | 119±12 | 114±10 | (-)5.4±15.7 |
| DBP, mm Hg | | | |
| Untrained | 78±8 | 78±8 | (-)0.6±10.8 |
| Trained | 78±6 | 77±6 | (-)0.3±9.1 |
| FC, beats/min | | | |
| Untrained | 65±10 | 66±10 | 0.9±12.7 |
| Trained | 68±8 | 66±7 | (-)2.3±5.5 |
| Functional capacity | | | |
| Peak $VO_2$, ml/kg/min | | | |
| Untrained | 26±6 | 25±7 | (-)1.1±1.9 |
| Trained | 23±6 | 26±7*† | 3.9±2.9†† |
| Sleep Parameters | | | |
| Total sleep time, min | | | |
| Untrained | 388±47 | 392±51 | 3.9±44 |
| Trained | 360±60 | 371±56 | 11±66 |
| AHI, events/hr | | | |
| Untrained | 43±26 | 48±29 | 4.5±19 |
| Trained | 47±31 | 41±25 | (-)5.7±13†† |
| Arousal Index, events/hr | | | |
| Untrained | 31±16 | 33±19 | 1.5±8 |
| Trained | 33±17 | 26±14* | (-)6.1±13†† |
| $O_2$ desaturation, events | | | |
| Untrained | 32±26 | 44±30* | 11±20 |
| Trained | 41±31 | 37±23† | (-)4.3±13†† |

*Values are expressed as means ± SD. BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; Peak $VO_2$: peak oxygen consumption; AHI: apnea-hypopnea index. Pre and post-intervention data were analyzed using two-way ANOVA with repeated measurements followed by Tukey's post-hoc test. Change (Δ) data were analyzed using Unpaired Student t test. *p<0.05 within groups; † p<0.05 between groups after intervention period; ††p<0.05 between groups in mean difference in change.*

group. There was a significant increase in peak $VO_2$ in the trained group (p=0.0001). The comparison between groups showed that the changes in peak $VO_2$ were greater in the trained group than those observed in the untrained group (p=0.0001).

Concerning the sleep parameters, AHI slightly increased in the untrained group and decreased in the trained group. There was a significant increase in $O_2$ desaturation in the untrained group (p=0.03), whereas no change was found in the trained group. Arousal index slightly increased in the untrained group and significantly decreased in the trained group (p<0.05). The comparisons between groups showed that the absolute arousal index value was significantly improved in the trained group in the post-intervention period. The comparisons between groups showed that

there were significant differences between the groups in delta changes in AHI (p=0.03), $O_2$ desaturation (p=0.001), and arousal index (p=0.02).

The echocardiographic measurements (Table 3) were unchanged in untrained and trained groups (see Supplemental Content - Table S2 for more details about echocardiographic measurements before and after the intervention). IVRT slightly increased in the untrained group and decreased in the trained group. The comparison between groups showed that absolute IVRT was significantly lower (p=0.01) in the trained group in the post-intervention period (Figure 1A) with a significant difference between groups in changes after intervention (Figure 1B). Further analysis showed a significant association between the changes in IVRT and changes in arousal index in the trained group (r = -0.54, p<0.05).

Interobserver variability was 2±6% and intraobserver variability was 1±6% for IVRT.

## Discussion

The main novel findings of the current randomized study are the following: 1) ET improves IVRT and ameliorates sleep severity and functional capacity; 2) changes in IVRT are associated with amelioration of sleep severity.

IVRT represents the interval between closure of the aortic valve and opening of the mitral valve[22] and is influenced by intraventricular mitral and aortic pressure gradients. Danica et al[23] reported that in the early stages of diastolic dysfunction, IVRT increases in patients with OSA compared to patients without OSA. Prolonged IVRT has also been used by several authors as an indicator of impaired LV diastolic function in patients with OSA compared to controls.[24-27] A previous study[28] showed that patients with AHI ≥ 40 events/hr had significantly longer IVRT than those with AHI < 40 events/hr (106 ± 19 msec vs. 93 ± 17 msec, respectively; p = 0.005).

**Table 3 – Echocardiographic parameters before and after the intervention period.**

| Parameters | Pre | Post | Mean difference in change (Δ) |
|---|---|---|---|
| Echocardiographic | | | |
| E wave, cm/sec | | | |
| Untrained | 74±14 | 75±15 | 1.1±12.1 |
| Trained | 72±13 | 74±14 | 1.4±10.6 |
| A wave, cm/sec | | | |
| Untrained | 66±17 | 68±17 | 2.2±8.5 |
| Trained | 68±14 | 69±12 | 1.0±9.0 |
| E/A ratio | | | |
| Untrained | 1±0.3 | 1±0.3 | 0±0.3 |
| Trained | 1±0.2 | 1±0.3 | 0±0.2 |
| IVRT, msec | | | |
| Untrained | 89±12 | 96±10 | 6.5±17 |
| Trained | 90±15 | 85±11† | (-)5.1±17†† |
| DT, msec | | | |
| Untrained | 209±55 | 211±41 | 1.7±48.0 |
| Trained | 205±34 | 210±46 | 5.6±39.9 |
| Septal e', cm/sec | | | |
| Untrained | 9±2 | 9±3 | (-)0.1±2.3 |
| Trained | 9±2 | 9±2 | (-)0.1±1.9 |

| | | | |
|---|---|---|---|
| Septal a', cm/sec | | | |
| Untrained | 9±2 | 10±2 | 1.0±2.8 |
| Trained | 10±2 | 10±2 | (-)0.3±2.1 |
| Septal E/e' | | | |
| Untrained | 9±2 | 9±3 | 0.5±2.4 |
| Trained | 8±2 | 9±3 | 0.5±2.1 |
| Lateral e', cm/sec | | | |
| Untrained | 11±3 | 11±3 | 0.2±2.3 |
| Trained | 10±2 | 11±2 | 0.6±2.0 |
| Lateral a', cm/sec | | | |
| Untrained | 10±2 | 10±2 | 0.9±2.6 |
| Trained | 10±3 | 10±3 | (-)0.1±2.1 |
| Lateral E/e' | | | |
| Untrained | 7±2 | 7±2 | 0±1.5 |
| Trained | 7±2 | 7±1 | 0±2.2 |
| E/e' average | | | |
| Untrained | 8±2 | 8±2 | 0.2±1.5 |
| Trained | 8±2 | 8±2 | 0.1±1.3 |

*Values are expressed as means ± SD. IVRT: isovolumetric relaxation time; DT: E wave deceleration time; †p<0.05 between groups after intervention period. Pre and post-intervention data were analyzed using two-way ANOVA with repeated measurements followed by Tukey's post-hoc test. Change (Δ) data were analyzed using Unpaired Student's t tests. ††p<0.05 between groups in mean difference in change.*

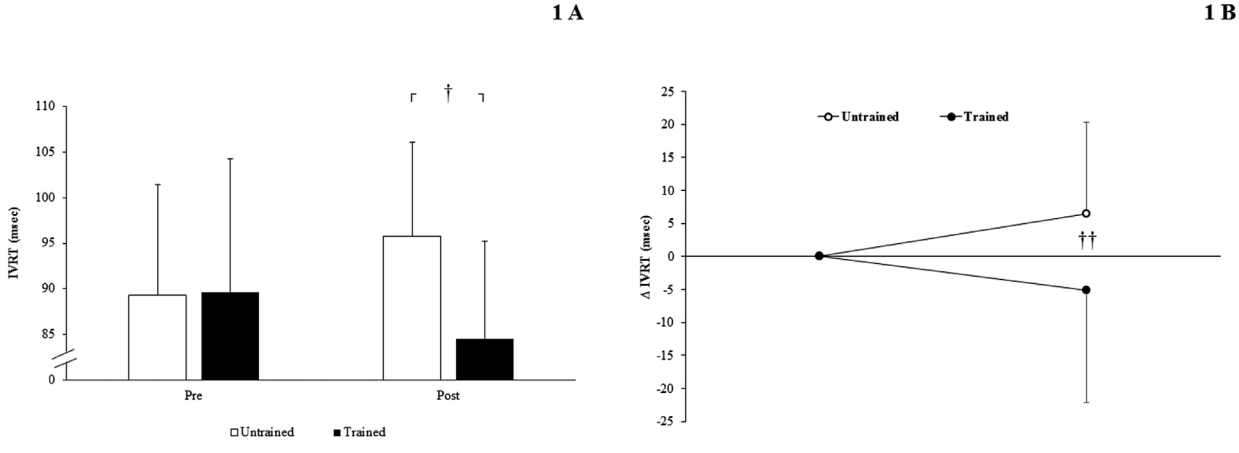


**Figure 1 – 1A, B. Absolute values (A) and delta (Δ) changes (B) in isovolumetric relaxation time in untrained and trained groups. Values are presented as means ± SD. †*P*<0.05 = between groups in the post intervention period; ††*P*<0.05 = between groups in mean difference in change. Data were analyzed using two-way ANOVA with repeated measurements followed by Tukey's post-hoc test.**
*IVRT: isovolumetric relaxation time*

IVRT was longer in metabolic syndrome patients[14] compared with non-metabolic syndrome patients and a 10-day training program resulted in a 17.5% decrease in IVRT. Another interventional study using 12 weeks of effective nasal continuous positive airway pressure induced significant reductions in IVRT ($p<0.05$) in patients with OSA.[18] In the present study, IVRT slightly increased in the untrained group and decreased in the trained group. The comparison between groups showed that absolute IVRT was significantly lower in the trained group in the post-intervention period with significant differences between groups after intervention. Our results concerning the effects of ET on IVRT are in line with the results of these previous studies. Of note, there is a possibility that IVRT will change first because it is an energy-dependent phase and is the first to change in patients with grade I dysfunction.

In the present study, overall training effects were found for changes in sleep severity. The comparisons between groups showed that changes in AHI, $O_2$ desaturation, and arousal index were greater in the trained patients than in the untrained patients. Amelioration of sleep pattern after ET has also been reported in heart failure[21] and metabolic syndrome patients.[15] ET reduces the accumulation of fluid in the neck region in patients with OSA.[29,30] The accumulation of rostral fluid in the neck region in patients with OSA causes collapse of the upper airways by reducing air space.[31] Reduction of fluid in the neck contributes to the decrease in AHI and improves sleep quality in patients with OSA.[30,31]

It has been reported that after each arousal, there is an increase in pulmonary capillary wedge pressure, which can lead to a concomitant reduction in LV compliance in patients with OSA.[32] Arousals and $O_2$ desaturation events in patients with OSA result in increased sympathetic nerve activity, vascular resistance, afterload, and arterial stiffness.[5-7] These factors can contribute to diastolic dysfunction in patients with OSA. On the other hand, in our present study, amelioration in arousal index was significantly associated with changes in IVRT ($r = -0.54$, $p<0.05$). Individuals with greater decreases in arousal index also had greater decreases in IVRT. Other possible mechanisms of ET involved in the amelioration of IVRT are beyond the scope of this study. However, we see some potential explanations for such changes. ET improves endothelial function[33,34] and coronary microvascular perfusion, increasing cardiac blood flow.[9] Likewise, arterial stiffness, measured by brachial-ankle pulse wave velocity and cardio-ankle vascular index decreases in exercise-trained subjects.[35] ET decreases muscle sympathetic activity and increases forearm vascular conductance in patients with OSA.[15] All of these factors can contribute to improving ventricular relaxation and reducing IVRT. Our study also shows that ET provoked a significant increase in peak $VO_2$ in patients with OSA. This response has several implications. Physical capacity is a marker of prognosis. The survival rate is higher in people with greater physical capacity regardless of comorbidities.[36] The increase in peak $VO_2$ provides evidence of the effectiveness of our exercise paradigm.

The reported prevalence of diastolic dysfunction among OSA patients varies from 23% to 56%,[18,28,32,37] depending on the sample size and the method of diastolic dysfunction assessment. However, in numerous studies, LV diastolic dysfunction was observed in OSA patients,[37] together with arterial hypertension,[24,38] LV hypertrophy,[27,39] or older age.[32] Notwithstanding, the influence of these comorbidities in our study is unknown. In the present study, using tissue Doppler echocardiography, diastolic dysfunction was only observed in 2 patients.

In the present study, the groups were similar in several baseline variables that can influence baseline diastolic function parameters, including BMI, level of physical activity (functional capacity), age, gender, and systolic function. In addition, other variables that may influence diastolic function, such as diabetes and cardiovascular disease were not included in this study.

Our study has potential limitations. The present study was planned to carry out 6 months of supervised ET performed 3 times a week, totaling 72 training sessions. However, in contrast with what was planned, the exercise-trained individuals were actually able to participate in the training with a frequency ranging from 1 to 3 times a week, which is something that happens in real life. Thus, we decided to extend the duration of the ET protocol to complete the 72 sessions (11.65±0.86 months). Notwithstanding, in the present study, 72 exercise sessions, regardless of frequency, caused significant improvements in functional capacity and sleep and ameliorated IVRT. These results suggest that LV dysfunction in moderate to severe OSA should be confirmed by large data, excluding confounding factors. On the other hand, as OSA leads to a worsening of prognosis over time, the

prevention of decline in the parameters of diastolic function seems to be beneficial in these patients.

## Conclusion

Supervised ET ameliorates sleep severity, improves functional capacity, and could prevent progression of diastolic abnormalities in the cardiac IVRT parameter, at least in the early stages before major structural changes may have developed. These results confer an important role for this nonpharmacological strategy in the treatment of moderate to severe OSA.

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## Author contributions

Conception and design of the research e Statistical analysis and writing of the manuscript: Durante BG, Ueno-Pardi LM; Acquisition of data: Durante BG, Silva RF, Goya TT, Jordão CP, Lima MF; Analysis and interpretation of the data: Durante BG, Lima MF, Rodrigues ACT, Rodrigues AG; Critical revision of the manuscript for intellectual content: Durante BG, Rodrigues ACT, Drager LF, Lorenzi Filho G, Alves MJNN, Negrão CE, Ueno-Pardi LM.

### Potential Conflict of Interest

No potential conflicts of interest relevant to this article were reported.

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### Study Association

This article is part of a Masters dissertation submitted by Bruno Gonçalves Durante to the Faculdade de Medicina FMUSP.

### Ethics approval and consent to participate

This study was approved by the Research Committee at the Heart Institute (SDC 3536/10/125) and by the Human Subject Protection Committee at the Clinical Hospital of the School of Medicine of the University of São Paulo (0833/10). 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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## *Supplemental Materials

For additional information, please click here.

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ORIGINAL ARTICLE

# Abnormalities of Cardiac Situs and Heart Disease Diagnosed by Echocardiography in Patients with Biliary Atresia

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## Abstract

**Background**: Left isomerism (LI) is a common finding in patients with biliary atresia (BA), and it can be identified by echocardiography. Several comorbidities may be present in patients with LI, including heart disease.

**Objective**: To investigate the prevalence of LI and heart disease in children (< 18 years of age) with BA followed-up at Hospital das Clínicas, UFMG.

**Methods**: This is a cross-sectional study involving patients diagnosed with BA between February 2016 and April 2020 who underwent transthoracic echocardiography and, in case of situs abnormalities, also electrocardiography.

**Results:** Our study recruited 58 patients (mean age: 3.08 years; female/male ratio: 1.5:1). The general prevalence of situs abnormalities was 8.6% (5/58) and the most common one was LI (4/5 or 80%). One patient had situs inversus. Among patients with situs abnormalities, the general prevalence of heart disease was 80% (4/5), apart from anomalies of the inferior vena cava), with pulmonary valve stenosis (PVS) as the only change seen (75% of mild forms and 25% of moderate forms). Among patients with situs abnormalities, the prevalence of rhythm changes was 80% (4/5), and low atrial rhythm was the most common finding (3/4 or 75%).

**Conclusion**: The prevalence of situs abnormalities in our sample was similar to that described in the literature. We observed an exclusive prevalence of PVS and a high prevalence of rhythm changes among patients with LI. Although the diagnosis of isomerism does not initially add much cardiovascular risk to the sample, possible late deterioration should be considered.

**Keywords:** Heterotaxy Syndrome; Heart diseases; Biliary atresia.

## Introduction

Biliary atresia (BA) occurs in 1:8000 to 1:23 000 live births, being responsible for over 50% of liver transplantations in children.[1-3] Among these patients, 7% to 12% have situs abnormalities known as left isomerism (LI) or polysplenia syndrome.[4,5] Similarly, 31% to 50% of all patients with LI have BA.[1,6]

The essential characteristic of LI is the unusual laterality and symmetry of the thoracic and abdominal viscera. In LI, left-sided structures are usually replicated (replacing the corresponding morphologically correct structures).[7-9] Characteristic findings are: double left atrium, double left lung and left main bronchus; descending aorta positioned anterior to the spine (slightly to the right or to the left); stomach usually positioned to the right; transverse liver; polysplenia.[2,3,4]

Regarding situs abnormalities, special interest is given to the identification of the atrial situs, which is a significant factor in the association with several heart diseases. According to the principle of thoracoabdominal compliance, atrial situs may be inferred from an echocardiography assessing the

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abdominal situs and estimated by the relative position of large vessels near the spine.[7,8]

Several comorbidities of varying severity may be present in patients with LI, such as craniofacial, musculoskeletal, tracheoesophageal, cardiac, and genitourinary malformations as well as malformations of the central nervous system and digestive system (intestinal malrotation, BA).[7,8]

In patients with LI, cardiac malformations are usually less significant than those found in cases of right atrial isomerism. Cyanogenic heart diseases are less common, and some cardiac defects may be only partially seen.[7,8] The absence of the right atrium and sinus node (a typical right atrial structure) is also part of the syndrome, resulting in risk of rhythm disorders.

The literature is scarce when it comes to the prevalence of heart disease among patients with BA and LI. Therefore, it is unknown if this population has particular heart conditions when compared to those with left atrial isomerism only.

The objective of this study was to investigate the prevalence of LI and structural heart disease among patients with BA followed-up by the Pediatric Hepatology team at Hospital das Clínicas (HC)/Universidade Federal de Minas Gerais (UFMG), considering that the diagnosis might have been underestimated.

## Methods

### Study design

This was a cross-sectional study involving patients diagnosed with BA at HC/UFMG from February 2016 to April 2020. Once the case was identified and after the written consent form was signed, a transthoracic echocardiography was performed in all patients; in case of situs abnormalities, an electrocardiography was performed at the Department of Cardiology.

### Inclusion criteria

Patients with BA under 18 years of age and followed-up at the Pediatric Hepatology outpatient unit at HC-UFMG during the study period who agreed to take part in the research, regardless of the surgical approach (Kasai procedure or liver transplant), with an acceptable echocardiographic window to determine abdominal situs.

### Exclusion criteria

All patients with BA and followed-up at the same unit who did not agree to take part in the research or without an acceptable echocardiographic window.

### Data collection

Echocardiographic assessment was performed according to the local routine and to national and international guidelines[10,11] using TOSHIBA APLIO 400 equipment (Tustin, CA, USA). Situs was assessed through longitudinal and transverse subcostal scanning using Doppler ultrasound. The connection between the inferior vena cava (IVC) and the right atrium was investigated at the longitudinal scan. The blood vessel distribution around the spine was identified at the transverse scan (Table 1 and Figure 1).

Electrocardiographic assessment was performed according to national and international guidelines,[12,13] using EDAN SE-3 MHE (Shenzhen, P.R. China) or PHILIPS

**Table 1 – Definition of abdominal situs via echocardiography**

| Types of situs | Solitus | Inversus | Ambiguous | |
|---|---|---|---|---|
| Position of the AO | Anterior and to the left | Anterior and to the right | AO‡ and inferior vena cava side by side (to the right or to the left of the spine) | |
| Position of the inferior vena cava* relative to the spine | Anterior and to the right | Anterior and to the left | Anterior vena cava = RI§<br>Posterior vena cava = LI// | |
| Connection between inferior vena cava –RA† | Present | Present | Present = RI; | Absent = LI |

*§ Inferior vena cava: inferior vena cava or equivalent (azygos / hemiazygos); † RA: right atrium; ‡ AO: aorta; § RI: right isomerism; // LI: left isomerism.*

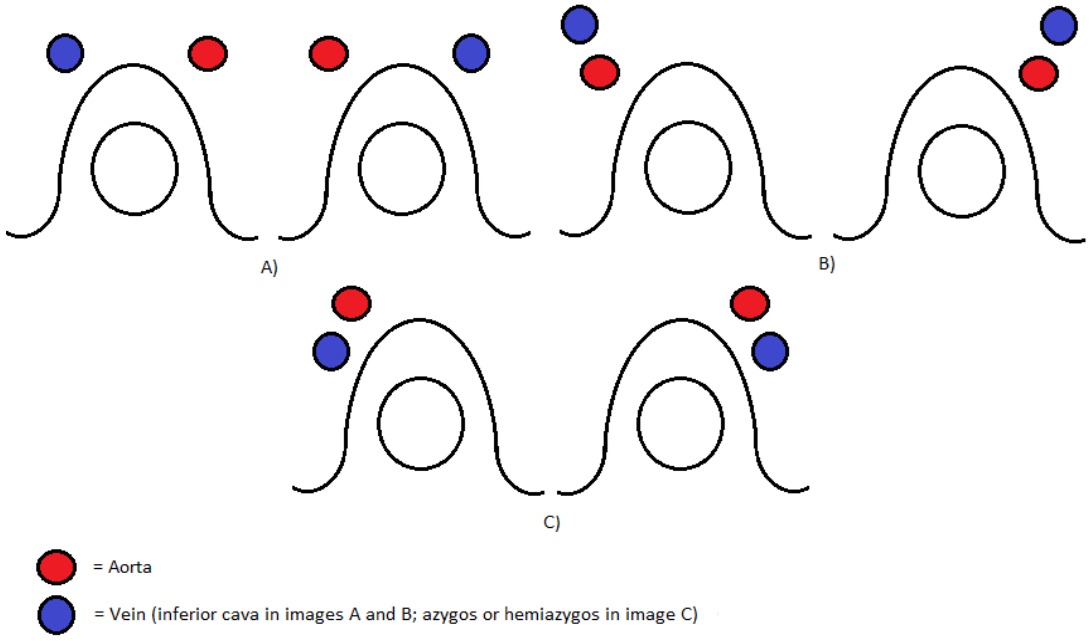


**Figure 1 – Position of blood vessels around the spine.**
*A) Situs solitus (to the left) and inversus (to the right); B) Right isomerism; C) Left isomerism.*

PageWriter Trim III (Andover, MA, USA) equipment.

The following variables were reported and analyzed: identification data, patient situation regarding surgical interventions, which had been considered, situs classification, record of associated structural heart disease, and heart rhythm classification in patients with abnormal situs.

### Statistical analysis

Data were analyzed using SPSS for Windows, version 16.0 (SPSS Inc., Chicago, IL, USA).

Our descriptive analysis used frequencies or median and interquartile range values for categorical and continuous variables, respectively. A Kolmogorov-Smirnov normality test with a cut-off of 0.05 was used to test for normality of distribution.

### Ethical aspects

The present study is in accordance with Resolution 466/2012 of the National Health Council of the Brazilian Ministry of Health, meeting the required ethical standards, including free and informed consent of the participants. The study was approved by the institution's Research Ethics Committee, No. 77 0 203000-09.

## Results

Fifty-eight patients were recruited, 3 of whom had been referred from the hospital admissions unit (young infants recently diagnosed with BA). The remaining patients were referred from the Pediatric Hepatology outpatient unit at the same institution.

All 58 recruited patients met the selection criteria and research protocol requirements. Patient data are shown in Table 2.

Data distribution revealed a non-normal pattern (Kolmogorov-Smirnov normality test with $p = 0.021$).

The patients' median age at the time of echocardiography was 3.08 years (interquartile range: 0.83–9.25 years). There was a predominance of female patients, with a 1.5:1 ratio compared to male patients. The median age of patients with situs abnormalities was 5 months (data not shown in the table).

Forty-two patients (72.4%) were in the postoperative period of a Kasai procedure, 10 (17.2%) were in the postoperative period of a liver transplant, and the remaining 6 (10.3%) were in the preoperative period of a Kasai procedure.

The overall prevalence of situs abnormalities in

**Table 2 – Patients recruited prospectively (n = 58)**

| Characteristics | Scores |
|---|---|
| $M_d$/(IR)* of age (years) at the time of echocardiography | 3.08/(0.83 – 9.25) |
| Sex M/F† (%) | 23 (39.7%)/35 (60.3%) |
| Pre-K/post-K/post-LT‡ (%) | 6 (10.3%)/42 (72.4%)/10 (17.2%) |
| Situs situation: A/N§ (%) | 5 (8.6%)/53 (91.4%) |
| Situs abnormality: LI/RI/SI// (%) | 4 (80%)/0 (0%)/1 (20%) |
| Cardiac condition with abnormal situs: PVS¶/absent (%) | 4 (80%)/1 (20%) |
| Severity of PVS in abnormal situs: light/moderate (%) | 3 (75%)/1 (25%) |
| Rhythm in abnormal situs: LAR#/N§ (%) | 4 (80%)/1 (20%) |
| Cardiac condition with normal situs: present/absent (%) | 1 (1.9%)/52 (98.1%) |
| Interruption of the inferior vena cava in LI (%) | 100% |

** $M_d$/(IR): median/interquartile range; ¶ PVS: pulmonary valve stenosis; † M/F: male/female; # LAR: left atrial rhythm; ‡ Pre-K/post-K/post-LT: pre-Kasai/post-Kasai/post-liver transplant; § A/N: abnormal/normal; // LI/RI/SI: left isomerism/right isomerism/situs inversus.*

the sample was 8.6% (5/58), and the most common abnormality was LI (4/5 or 80%). One patient had situs inversus.

Among patients with situs abnormalities, the overall prevalence of congenital heart disease, apart from anomalies of the IVC, was 80% (4/5). Pulmonary valve stenosis (PVS) was the only abnormality found in these patients, with 3/4 or 75% of mild forms (Doppler peak instantaneous gradient between 10mmHg and 35mmHg) and 1/4 or 25% of moderate forms (Doppler peak instantaneous gradient between 36mmHg and 64mmHg). The 4 patients with LI had interrupted IVC (agenesis of the suprahepatic segment) with no clinical implications.

All patients with a heart condition were on regular cardiology follow-ups.

Among patients with situs abnormalities, the overall prevalence of rhythm changes at electrocardiography was 80% (4/5). The most common change was low atrial rhythm (left atrium) (3/4 or 75%). The P-wave axis was shifted to the right (over 120°) in the patient with situs inversus.

Among patients with situs solitus, the overall prevalence of congenital heart disease was 1.9% (1/53): a case of persistent ductus arteriosus (small canal, with no clinical implications).

## Discussion

Our sample (58 patients) is small. On the one hand, it reflects the small annual inflow of new cases (6 to 9 patients/year). On the other hand, it reflects the losses to follow-up due to death, transfer to other healthcare facilities, or to the Adult Hepatology unit of the same institution (for patients over 18 years old). Nevertheless, the number of cases is noteworthy as these are records from a single healthcare center.

Despite the availability of an echocardiogram database within the institution, the prospective record was chosen focusing on the diagnosis of situs, implying which implied in repeating the echocardiography in some patients. This strategy was aimed at optimizing the accuracy of the echocardiography in the definition of situs.

The definition of atrial situs depends on the correct identification of atrial appendages, which are structures more consistently related to atrial morphology (right or left). However, appendages are not easily accessed by transthoracic echocardiography, making the direct definition of atrial situs challenging. On the other hand, atrial situs is generally consistent with abdominal and thoracic situs. Even though thoracoabdominal situs discordance may be seen exceptionally, the identification of abdominal situs using conventional echocardiography allows the echocardiographer to infer atrial situs. Therefore, in the present study, situs evaluation was performed through the subcostal view of the echocardiogram, a widely available and non-

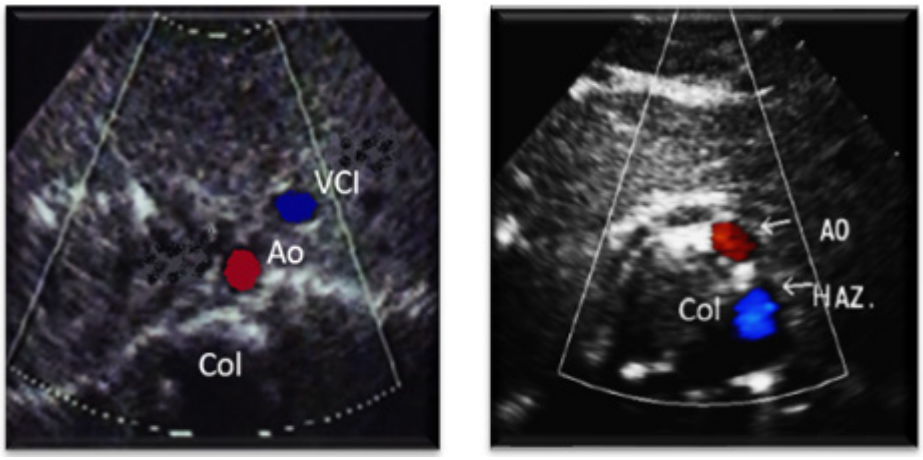


**Figure 2 – Subcostal views of patients with right isomerism (left panel) and left isomerism (right panel).**
*AO: aorta; IVC: inferior vena cava; HAZ: hemiazygos; Col: spinal column.*

invasive technique that is reasonably accurate (Figure 2).

We were not able to determine the actual moment of echocardiographic diagnosis of situs, since not all patients had a previous echocardiography record in the institution's database. The median age of patients with situs abnormalities was significantly lower than that of the total sample (5 months compared to 3.08 years). These data suggest that all situs abnormalities were detected early on and were not seen in patients over one year of age at the time of echocardiography. An explanation for these findings is the poor prognosis of patients with polysplenia syndrome. Other authors have reported a lower survival rate with native liver among patients with BA and LI when compared to those with no LI.[14,15]

A clear predominance of BA was observed in female patients, reflecting similar findings in the literature.[1-2]

The general prevalence of situs abnormalities in the sample (8.6%) was similar to other records (between 7% and 12%),[4,5] with LI being the most common finding (80% of cases); this is in accordance with data in the literature[4-5]. One patient had situs inversus. Other cases of total or abdominal situs inversus in patients with BA have been described.[16-18]

The prevalence of congenital heart disease was 80% among patients with situs abnormalities and 100% among those with left atrial isomerism (no structural heart disease was detected in the patient with situs inversus). The only structural heart disease found in patients with situs abnormalities, except for the absence of the suprahepatic segment of the IVC (present in almost 100% of patients with LI), was PVS. The prevalence of structural heart disease reported in the literature for patients with left atrial isomerism ranges from 91% to 97%.[19-21]

Among the cardiac abnormalities of LI found in the literature, the main ones are dextrocardia/mesocardia (24%–42% and 2% of all cases, respectively), anomalous pulmonary venous return (37%–56%), persistent left superior vena cava (33%–59%), unroofed coronary sinus (26%–42%), absence of the suprahepatic segment of the IVC (86%–100%), hepatic venous drainage into the left atrium (32%–41%), common atrium or interatrial communication (80%), total or partial atrioventricular septal defect (49%–80%), univentricular atrioventricular connection (20%–40%), ventricular septal defect (11%), transposition of the great arteries (5%–21%), double-outlet right ventricle (17%–37%), PVS or pulmonary atresia (28%–61%), and aortic stenosis/atresia or coarctation of the aorta (7%–45%).[19,22-28]

The literature on the prevalence of heart disease among patients with BA and LI is scarce. Using the MEDLINE, LILACS, and SciELO databases and associating the main descriptors in different manners, our search did not retrieve more than a few case series. Nevertheless, a Canadian study reported 25 cases of polysplenia among 328 patients (7.6%) using a national database of children with biliary atresia and including a 17-year period. Congenital cardiac defects were found in 26 patients. These included pulmonary stenosis (n = 12), ventricular septal defect (n = 10), atrial septal defect (n = 7), patent ductus arteriosus (n = 3), total anomalous pulmonary venous return (n = 3), double-outlet right ventricle (n = 3), bicuspid aortic valve (n = 3), dextrocardia (n = 2), atrioventricular canal defect (n = 2), tetralogy of

Fallot (n = 2), partial anomalous pulmonary venous return (n = 1), hypoplastic aortic arch (n = 1), aortic stenosis (n = 1), and mitral stenosis (n = 1).[29] Another report from the United Kingdom, a 28-year single-center retrospective study, described 43 cases of polysplenia among 548 patients (7.8%). Cardiac abnormalities were found in 25 patients, including tetralogy of Fallot (n = 1), aortic arch abnormality and severe left pulmonary hypoplasia (n = 1), aortic coarctation (n = 1), hypoplastic left heart (n = 1), ventricular septal defect (n = 5), atrial septal defect (n = 7), patent ductus arteriosus (n = 7), and pulmonary artery stenosis (n = 1). Nine infants required cardiac surgery.[30]

Considering the list of cardiac conditions described in patients affected by LI with or without heterotaxy, it would be reasonable to assume that other conditions might have been observed in this sample. The small absolute number of patients with situs abnormalities in this study prevents any conclusion regarding the real prevalence of cardiac disorders among these patients. Further studies, with larger sample sizes, are required to elucidate this matter in Brazil.

Other conditions of clinical interest associated with LI are sinus node dysfunction (escape rhythm with chronotropic incompetence), supraventricular arrhythmias — tachyarrhythmias and atrioventricular block (up to 71% of all cases, with 7%–22% of atrioventricular block), and the presence of dysfunctional spleens (increasing the risk of infections and sepsis).[7,8,25,26]

The overall prevalence of rhythm disorders among patients with situs abnormalities in this sample, at electrocardiographic assessment, was 80% (4/5). The most common one was low atrial rhythm (3/4 or 75%). The incidence of arrhythmias in patients with LI may reach 87% in 3 years of follow-up, with sinus node dysfunction (escape rhythm) being the most common one (around 60% of the cases), followed by total atrioventricular block (20% of all cases). The risk of sinus node dysfunction with an indication for pacemaker implantation reaches 19% in some case series, reinforcing the need for a long-term cardiology follow-up of such patients.[21,31] The abnormalities seen in patients in this study do not seem to lead to increased morbidity at the time of echocardiography. However, the escape rhythm in patients with LI may cause chronotropic incompetence during situations of high cardiac demand.

Despite the low complexity of heart diseases observed in this study and considering the cardiac conditions described in patients affected by BA and LI in larger series, it is possible to infer that the associated cardiac abnormalities may be prognostically important and life-threatening even before biliary malformation can be treated.

The main limitation of this study, apart from the ones inherent to our methodology, are the possible losses of patients related to their death or transfer to other healthcare facilities. At all events, the sample included all patients who were being followed-up by the Pediatric Hepatology team at HC/UFMG during the study period.

The identification of LI is important for the medical specialties that manage most of the care of patients with BA. Even though the diagnosis of isomerism does not represent, at the moment of data collection, a high cardiovascular risk for the patients in our sample, it is important to acknowledge the possibility of late illness and the need for regular cardiology follow-ups.

## Conclusion

The prevalence of situs abnormalities in our sample was similar to that described in the literature. As expected, LI was the most common finding.

The prevalence of congenital heart disease in patients with situs abnormalities was high, as anticipated by the analysis of patients with LI only. We found an exclusive prevalence of PVS and a high prevalence of rhythm changes (escape rhythm) in patients with left atrial isomerism. However, due to the small number of affected patients, it is not possible to confirm whether PVS occurs in a preferential association with BA and LI.

Although the diagnosis of isomerism does not increase cardiovascular risk in patients in our sample at first, possible late deterioration should be considered, requiring continued monitoring.

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## Author contributions

Conception and design of the research: Tonelli HAF, Queiroz TCN. Acquisition of data: Tonelli HAF, Queiroz TCN, Meira ZMA, Guimarães AFM, Castilho SRT. Analysis and interpretation of the data: Tonelli HAF, Queiroz TCN. Statistical analysis: Tonelli HAF, Queiroz

TCN. Writing of the manuscript: Tonelli HAF, Queiroz TCN. Critical revision of the manuscript for intellectual content: Tonelli HAF, Queiroz TCN, Ferreira AR.

### Potential Conflict of Interest

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

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### Study Association

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

### Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade Federal de Minas Gerais under the protocol number 77.0.203000-09. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consente was obtained from all participants included in the study.

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REVIEW ARTICLE

# Gene Silencing Therapeutics in Cardiology: A Review Article

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## Abstract

Therapeutics that inhibit enzymes, receptors, ion channels, and cotransporters have long been the mainstay of cardiovascular medicine. Now, oligonucleotide therapeutics offer a modern variation on this paradigm of protein inhibition. Rather than target a protein, however, small interfering ribonucleic acids and antisense oligonucleotides target the messenger RNA (mRNA) from which a protein is translated. Endogenous, cellular mechanisms enable the oligonucleotides to bind a selected sequence on a target mRNA, leading to its degradation. The catalytic nature of the process confers an advantage over the stoichiometric binding of traditional small molecule therapeutics to their respective protein targets. Advances in nucleic acid chemistry and delivery have enabled development of oligonucleotide therapeutics against a wide range of diseases, including hyperlipidemias and hereditary transthyretin-mediated amyloidosis with polyneuropathy. While most of these therapeutics were initially designed for rare diseases, recent clinical trials highlight the potential impact of oligonucleotides on more common forms of cardiovascular disease.

## Introduction

Almost every drug targets a protein, the last step in the flow of genetic information from DNA through transcription and translation. However, as early as 1978, Zamecnik envisioned targeting the prior step and demonstrated that a 13-base oligonucleotide complementary to a sequence in the Rous sarcoma virus inhibited translation of viral messenger RNA (mRNA) and the consequent oncogenic transformation of cells in culture. Furthermore, a chemical modification of the oligonucleotide prolonged its efficacy, presumably by slowing its degradation.[1,2] This latter observation foreshadowed the chemistry that enables the remarkable duration of action of oligonucleotide therapeutics today.

Silencing the expression of a gene by targeting its mRNA via an oligonucleotide expands the therapeutic armamentarium, overcoming major hurdles such as the identification of "druggable" proteins and therapeutics that bind them. Furthermore, target proteins may not have a suitable drug binding site, or binding to off-target proteins may cause undesirable side effects. Oligonucleotides can circumvent these limitations and expedite the drug discovery process. With a target protein and the sequence of its coding gene, an antisense oligonucleotide (ASO) or a small interfering ribonucleic acid (siRNA) can be designed to bind to a complementary sequence on an mRNA with exquisite specificity. Different cellular mechanisms are co-opted to degrade the mRNA: RNase H1 (ASO) or RNA inhibition (RNA interference [RNAi]). The physiologic functions of RNase H1 and RNAi include antiviral defense,[3] and the RNAi pathway is fundamental to controlling gene expression in diverse eukaryotic species.[4,5]

ASOs are single-stranded oligonucleotides of 15-20 bases, designed to be complementary (antisense) to a target site on the mRNA transcript,[6,7] to which they bind via Watson–Crick base pairing. The ASO chemical modification pattern determines whether the target mRNA is degraded or processed. The most widely used mechanism involves an endogenous nuclease, RNase H1, which recognizes chimeric DNA/RNA duplexes formed by the ASO and target mRNA (Figure 1A). Hence the ASO needs to contain at least 8-10 deoxyribonucleotide residues in the center, which can be flanked by other

## Keywords

Cardiovascular Disease; Gene Silencing; RNA Interference, Oligonucleotides; Antisense; Amyloidosis.

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chemically modified residues. After recognizing? the ASO/mRNA duplex, RNase H1 cleaves the mRNA, thereby reducing production of the target protein.

siRNAs are double-stranded RNAs, 19-25 base pairs in length, which utilize the highly conserved natural RNAi pathway. The siRNAs are designed to recruit and bind to an enzyme complex called RNA-induced silencing complex (RISC) to mediate degradation of their respective mRNA targets.[4,5] During the loading process into RISC, the 2 strands of the siRNAs are separated (Figure 1B). The sense "passenger" strand is ejected, and the antisense "guide" strand remains loaded and "guides" the RISC to a complementary site on the target mRNA, where it binds through Watson–Crick base pairing.[8] After cleaving the mRNA, the antisense strand remains bound to the enzyme; thus, in the catalytic action of siRNAs, a single molecule serves to cleave a large number of target mRNAs.

In this review, key technical advances in the evolution of oligonucleotide therapeutics, including ASOs and siRNAs approved or in late-stage clinical development for cardiovascular diseases, are discussed.

## Methods

Based on standard review methods, a comprehensive literature search of the PubMed database was conducted to find relevant published articles on gene silencing in cardiology. Search terms were gene+silencing+cardiac (2157 results), RNAi+cardiac (491), and antisense+olig onucleotide+cardiac (1131). Adding "clinical" and/or "phase" refined searches to include only therapeutics in, or previously in, clinical trials, resulting in 78 publications under consideration. Only English language articles were reviewed, no date limits were specified, and searches were undertaken up to July 20, 2020. Relevant publications identified from references of the retrieved articles were also included. Up-to-date information on clinical trials of siRNA and ASO therapeutics in cardiology was sought on the website https://clinicaltrials.gov.

## Oligonucleotide therapeutics: evolution of a novel class of medicines

Oligonucleotide therapeutics, with ASOs and siRNAs representing the most prominent gene silencing technologies, have emerged as a new generation of precision medicines for an increasing number of diseases with high unmet medical needs, including cardiovascular diseases. However, unmodified oligonucleotides lack drug-like properties, and decades were spent optimizing their chemistry and developing advanced drug delivery systems that were required for these molecules to become drugs.

Oligonucleotide therapeutics are rapidly degraded and eliminated without the chemical modifications that

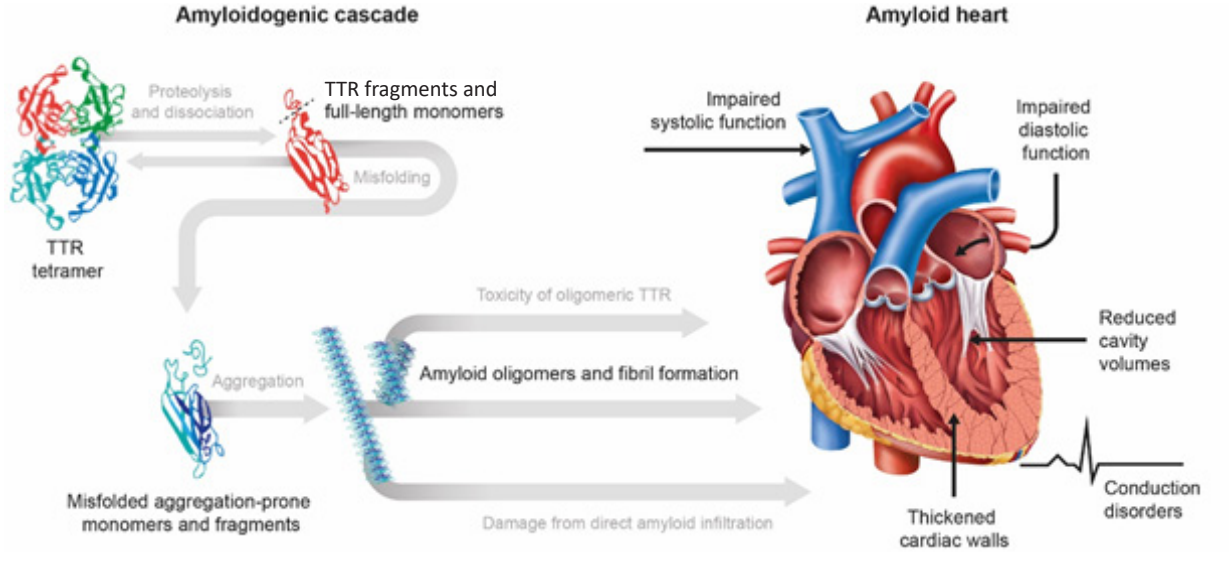


**Figure 1 – ASO and RNAi mechanisms for cleavage of target mRNA.**
*ASO: antisense oligonucleotide; mRNA: messenger RNA; RISC: RNA-induced silencing complex; RNAi: RNA interference; siRNA: short interfering RNA.*

assure stability and mediate delivery to the intended tissue. Ubiquitous nucleases hydrolyze the bond between phosphodiester groups in DNA/RNA and the sugar moiety of each base, thus degrading nucleic acids. A phosphorothioate modification (Figure 2A) protects the phosphodiester bond in ASOs and siRNAs against enzymatic hydrolysis[9] and improves delivery of ASOs by increasing hydrophobicity and improving protein binding. Formation of ASO-protein complexes increases the ASO's half-life in circulation and reduces urinary excretion to facilitate distribution (predominantly) to liver, spleen, and kidney. While a phosphorothioate backbone confers advantages, it also elicits unwanted interactions with proteins, e.g., the platelet-specific glycoprotein receptor VI or complement, which may mediate thrombocytopenia or glomerulonephritis associated with ASOs.[7]

Chemical modifications of sugar moieties in an ASO or siRNA, such as 2′-*O*-methoxyethyl (2′-MOE), 2′-*O*-methyl (2′-O-Me), and 2′-fluoro (2′-F) (Figure 2A), are commonly incorporated to increase stability against nucleases, enhance avidity for the target mRNA, and mitigate any innate immune response.[9] Of note, 2′-F and 2′-O-Me substitutions along the entire length of an siRNA (Figure 2A) can dramatically increase potency and duration of action.[10,11]

Alongside advances in nucleic acid chemistry, highly effective drug delivery platforms were developed. Encapsulation of an siRNA in a lipid nanoparticle (LNP) represented a significant early advance in systemic delivery (Figure 2B). Demonstrating proof-of-concept, an LNP-siRNA formulation reduced hepatic apolipoprotein B (ApoB) mRNA and levels of ApoB and cholesterol in nonhuman primates.[12] Second-generation LNPs showed approximately 100-fold improved potency in mouse models.[13] The improvement was translated to humans, leading to the first siRNA therapeutic, patisiran, for patients with hereditary transthyretin-mediated (hATTR) amyloidosis with polyneuropathy.[14,15]

LNPs effectively deliver siRNAs to the liver, but manufacturing is complicated, and administration is intravenous. A simpler solution targets ASOs and siRNAs to cell surface receptors via a conjugated ligand that triggers endocytosis. A current strategy involves conjugation to an *N*-acetylgalactosamine (GalNAc) ligand (Figure 2B), which binds the asialoglycoprotein receptor (ASGPR). The ASGPR recognizes *N*-acetylgalactosamine residues on glycoproteins and is highly expressed on hepatocytes.[16,17] High-affinity, multivalent GalNAc ligands suitable for subcutaneous administration have been developed for ASOs and siRNAs.[11,18]

Chemically modified nucleic acids and GalNAc ligands have greatly expanded the potential of oligonucleotide therapeutics for diseases that can be treated by suppressing hepatic synthesis of a protein. The combination of stabilized siRNAs with a high-affinity GalNAc ligand, termed enhanced stabilization chemistry (ESC) conjugates, has enabled potent and durable gene silencing in the liver with infrequent administration at low doses.[11] The first GalNAc-siRNA conjugate approved was givosiran for the treatment of acute intermittent porphyria.[19] The safety of the GalNAc-siRNA platform has been established in large clinical trials of inclisiran, discussed below.[20,21] Several other GalNAc-ASO and -siRNA conjugates for cardiovascular indications are currently in clinical trials (Table 1).

## Gene silencing in hyperlipidemias

Loss-of-function variants of proprotein convertase subtilisin/kexin type 9 (*PCSK9*), angiopoietin-like protein-3 (*ANGPTL3*), *APOC3* (ApoC-III), and *LPA* (ApoA) are associated with reduced low-density lipoprotein (LDL), cholesterol (LDL-C), or triglyceride levels and protection from coronary heart disease.[22,23] Human genetics suggested that lowering circulating levels of these proteins could be used to treat hyperlipidemias and reduce cardiovascular risk. Large clinical trials of monoclonal antibodies against PCSK9 have since validated this therapeutic hypothesis.[24-26] Oligonucleotide therapeutics targeting each of the genes above have been developed (Table 1). We discuss below those approved or having phase 3 clinical trial results.

Mipomersen, an ASO that suppresses ApoB synthesis, was the first oligonucleotide therapeutic approved for a cardiovascular indication. The rationale for its development in familial hypercholesterolemia was based in part on the phenotype of individuals with familial hypobetalipoproteinemia. Protein-truncating variants of *APOB* are associated with very low levels of LDL-C and ApoB,[27] and early clinical observations of humans who carried such *APOB* mutations suggested a reduced risk of atherosclerotic disease.[28] In initial clinical studies, mipomersen given weekly to patients with homozygous familial hypercholesterolemia reduced ApoB by 26.8% and LDL-C by 24.7% (from baseline 441 ± 139 mg/dL).[29] In subsequent phase 3 trials, mipomersen reduced LDL-C by 28-37% in patients with heterozygous familial

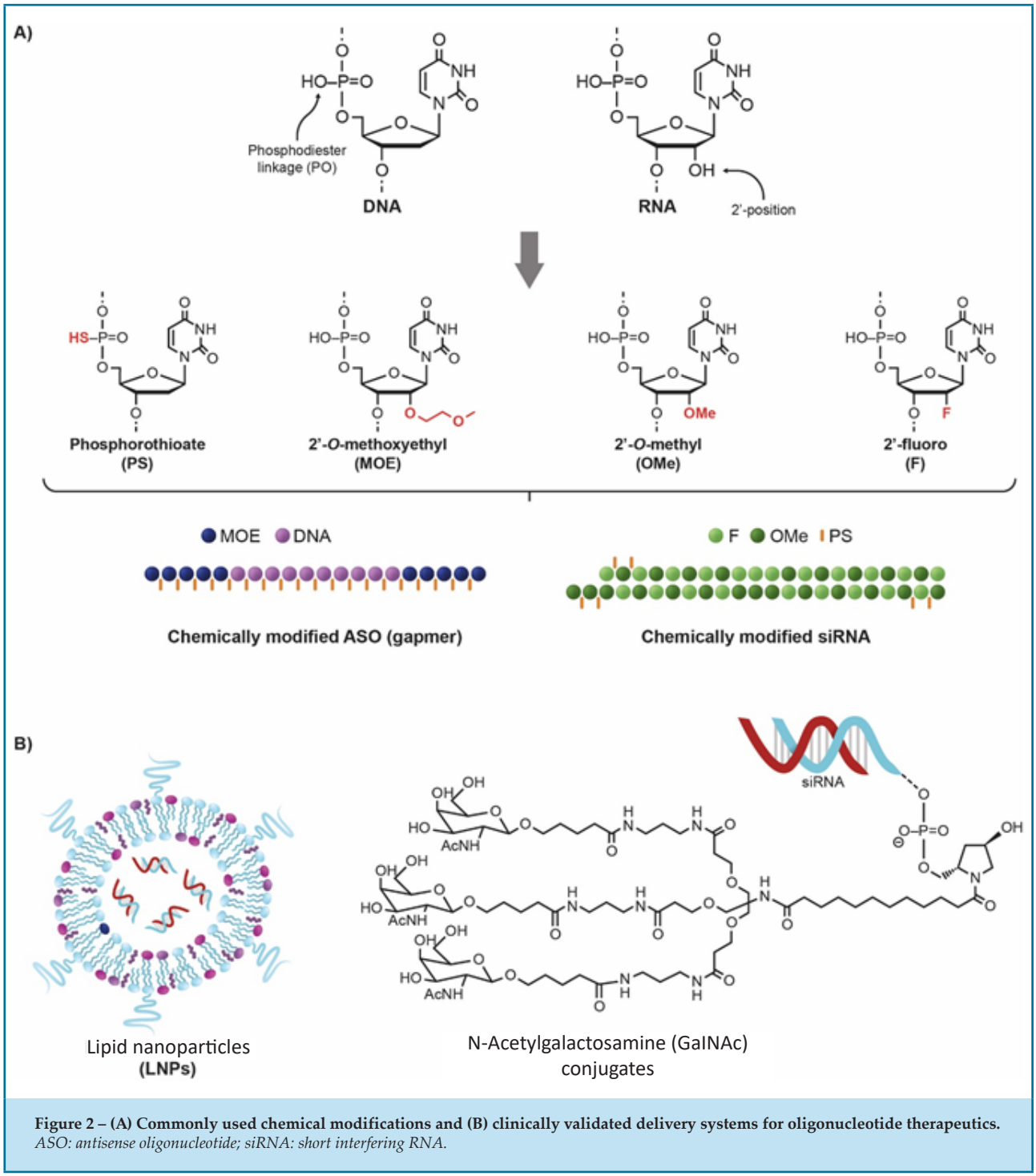


**Figure 2 – (A) Commonly used chemical modifications and (B) clinically validated delivery systems for oligonucleotide therapeutics.**
*ASO: antisense oligonucleotide; siRNA: short interfering RNA.*

hypercholesterolemia or severe hypercholesterolemia, on maximally tolerated lipid-lowering therapeutics.[30-32] In all these trials, some patients developed elevations of hepatic transaminases and hepatic steatosis that resolved following discontinuation of mipomersen.[30-32] Familial hypobetalipoproteinemia is likewise associated with hepatic steatosis because ApoB is necessary for export of triglycerides from the liver.[33] Mipomersen was withdrawn from the market.

Volanesorsen, an ASO that suppresses ApoC3 synthesis, is approved in the European Union (EU) for the treatment of familial chylomicronemia syndrome (FCS).[34] Characterized by hypertriglyceridemia and pancreatitis,

**Table 1. Oligonucleotide therapies in mid- to late-stage development or approved for cardiovascular indications**

| Gene | Therapy | Disease indication | Clinical phase | Links |
|---|---|---|---|---|
| APOB | Mipomersen (ASO) | Familial hypercholesterolemia | Approved, but withdrawn from market | See text |
| APOC3 | Volanesorsen (ASO) | Familial hyperchylomicronemia | Approved in some countries | See text |
| | | Familial partial lipodystrophy | Phase 2 | NCT02527343 |
| | | Hypertriglyceridemia | Phase 3 | NCT02300233 |
| | AKCEA-APOCIII-LRx (GalNAc-ASO) | Hypertriglyceridemia and cardiovascular disease | Phase 3 | NCT03385239 |
| ANGPTL3 | AKCEA-ANGPTL3-LRx (GalNAc-ASO) | Familial chylomicronemia | Phase 2 | NCT03360747 |
| | | Familial partial lipodystrophy | Phase 2 | NCT03514420 |
| | | Hypertriglyceridemia, type 2 diabetes mellitus, and nonalcoholic fatty liver disease | Phase 2 | NCT03371355 |
| *LPA* (ApoA) | TQJ230 (GalNAc-ASO) | Cardiovascular disease with elevated Apolipoprotein A | Phase 3 | NCT04023552 |
| PCSK9 | Inclisiran (GalNAc-siRNA) | Hypercholesterolemia | Phase 3 | See text NCT03705234 |
| TTR | AKCEA-TTR-LRx (GalNAc-ASO) | Transthyretin-mediated cardiac amyloidosis | Phase 3 | See text NCT04136171 |
| | Patisiran (siRNA) | | Phase 3 | See text NCT03997383 |
| | Vutrisiran (GalNAc-siRNA) | | Phase 3 | See text NCT04153149 |

*ANGPTL3: angiopoietin-like protein-3; APO: apolipoprotein; ASO: antisense oligonucleotide; LPA: lipoprotein a ; GalNAc: N-Acetylgalactosamine; PCSK9: proprotein convertase subtilisin/kexin type 9; siRNA: short interfering RNA; TTR: transthyretin*

FCS is caused by a deficiency in the lipoprotein lipase (LPL) enzyme that hydrolyzes triglycerides in chylomicrons and very low-density LDL particles. In contrast to the action of LPL, ApoC3 inhibits the clearance of triglyceride-rich lipoproteins via inhibition of LPL and LPL-independent mechanisms.[35] In a phase 3 study of patients with FCS, volanesorsen decreased ApoC3 levels by 84% from baseline. Notably, total triglyceride fell 77% from mean 2267 ± 1259 mg/dL at baseline to 590 ± 497 mg/dL at 3 months with once-weekly subcutaneous injections.[36] While the decrease in triglycerides was significant, almost 50% of patients developed a fall in platelet counts below 100 000 per microliter, and 2 patients' counts fell below 25 000, leading to treatment discontinuation.[36] In the United States (US), volanesorsen has not been granted Food and Drug Administration approval. A phase 2/3 study of volanesorsen for the treatment of familial partial lipodystrophy and a phase 2 study of a second-generation ApoC3 GalNAc-ASO conjugate for the treatment of hypertriglyceridemia in patients with cardiovascular disease are ongoing (Table 1).

Inclisiran, a GalNAc-siRNA conjugate that suppresses PCSK9 synthesis, significantly reduced LDL-C levels in large, phase 3 trials of patients with familial hypercholesterolemia, atherosclerotic cardiovascular disease (ASCVD), or high risk of ASCVD.[20,21] LDL receptors on the hepatocyte cell surface remove LDL-C from circulation, following which the receptor is recycled back to the cell surface. Secreted by the liver, PCSK9 regulates the number of LDL receptors by binding them and thus diverting them from recycling to degradation. Gain-of-function variants of PCSK9, hence, lower LDL receptor numbers resulting in higher LDL-C and cardiovascular risk.[37] Loss-of-function variants have the opposite effect.[22]

Inclisiran has a sustained duration of action and potency. In ORION-1, a phase 2 study of patients with ASCVD and elevated LDL-C (on maximally tolerated

doses of statins), a single 300-mg subcutaneous dose lowered LDL-C by 38.4% from baseline on day 180. A second dose (day 90) resulted in a 52.6% decrease from baseline on day 180.[38] Data from phase 3 ORION-10 and ORION-11 trials has validated these results.[21] These 2 studies enrolled patients with ASCVD or an ASCVD equivalent (type 2 diabetes, familial hypercholesterolemia, or a 10-year risk of a cardiovascular event of ≥ 20% as assessed by Framingham Risk Score for Cardiovascular Disease or equivalent), who had a baseline LDL-C of ≥ 70 mg/dL (100 mg/dL for ASCVD equivalent) on a maximally tolerated dose of statins.[21] Administered every 6 months, inclisiran reduced LDL-C by 52.3% and 49.9% on day 510 in ORION-10 and ORION-11, respectively.[21] ORION-9 tested the same regimen in patients with heterozygous familial hypercholesterolemia. On day 510, inclisiran reduced LDL-C by 39.7% from a baseline level of 151.4 ± 50.4 mg/dL.[20] Adverse events were similar between the inclisiran and placebo groups in ORION-9, -10, and -11. Injection-site reactions were more common in the inclisiran group and were generally mild. ORION-4, an ongoing trial of 15 000 patients, will assess the impact of inclisiran on cardiovascular outcomes.[39] Together, the results indicate that, if approved, inclisiran has the potential to be a novel, safe, effective approach to treating hypercholesterolemia in high-risk patients. The pharmacodynamic profile supporting infrequent (biannual) administration additionally suggests this approach could minimize patient noncompliance with treatment and allow hypercholesterolemia to be managed with a dosing strategy more akin to routine vaccinations for diseases such as influenza. Approval of inclisiran is under review in the US and Europe.

## Gene silencing in transthyretin-mediated amyloidosis

Transthyretin-mediated (ATTR) amyloidosis is a rare, underdiagnosed, rapidly progressive, debilitating, and fatal disease caused by misfolded transthyretin (TTR) (prealbumin) that accumulates as amyloid deposits in multiple tissues.[40,41] Cardiomyopathy and polyneuropathy are the most prominent features, but systemic manifestations arise from amyloid infiltration of other tissues, including the gastrointestinal (GI) tract.[41,42] Polyneuropathy includes sensory, motor, and autonomic impairment and has an aggressive course leading to deteriorating quality of life (QOL) and loss of function.[41] Cardiac involvement typically presents as heart failure with preserved ejection fraction (HFpEF) or unexplained left ventricular (LV) wall thickening;[43] progressive symptoms of heart failure (HF) and cardiac arrhythmias are experienced, with death typically occurring 2.5-5.5 years after cardiomyopathy diagnosis.[44,45] In 2 studies, 13% of patients with HFpEF and 16% of older patients who underwent transcatheter aortic valve replacement for severe aortic stenosis had evidence of cardiac amyloid involvement.[46,47] While delays in diagnosis are common,[48] recognition of the early signs of ATTR amyloidosis (e.g., connective tissue manifestations such as carpal tunnel syndrome)[43] could be an important opportunity for therapeutic intervention before cardiac (and/or neurologic) symptoms develop.[49]

Pharmacotherapies that target steps in the amyloidogenic pathway are available. TTR is predominantly produced in the liver and normally circulates as a stable tetramer. However, abnormal destabilization of the protein causes dissociation into monomers that misfold, deposit, and accumulate as amyloid in various tissues, including heart (Figure 3), nerves, and GI tract.[50] The disease has 2 types, hereditary and wild-type (hATTR and wtATTR amyloidosis, respectively).[40,41] In hATTR amyloidosis, also known as ATTRv amyloidosis, *TTR* gene variants destabilize the protein.[50] hATTR amyloidosis can have a heterogeneous presentation, differing according to *TTR* variant, age of onset, and geography.[51] Historically, certain variants have been associated with predominant cardiomyopathy or neuropathy; however, a majority of patients develop a mixed phenotype.[52-54] Several geographies are endemic for hATTR amyloidosis, including Brazil, where the most common variant, V30M, was found in 92% of patients.[55] This variant has previously been associated with predominant polyneuropathy, although a Brazilian study reported cardiac symptoms in at least 40% of patients with ATTRV30M amyloidosis.[56] In contrast, patients with wtATTR amyloidosis do not carry a *TTR* variant and disease is associated with aging;[57] patients typically present with predominant cardiomyopathy.[58]

Orthotopic liver transplantation (OLT) was the first available treatment for patients with hATTR amyloidosis with polyneuropathy, and it acts by eliminating the production of variant TTR.[59] In patients with early-stage polyneuropathy and absence of cardiac involvement, certain symptoms can improve or stabilize in the short term following OLT,[59] supporting the therapeutic rationale for silencing the *TTR* gene in this disease. However, disease progression can occur after OLT; death of 38% of patients due to cardiac events post OLT was reported in a retrospective study.[60] End-stage HF and

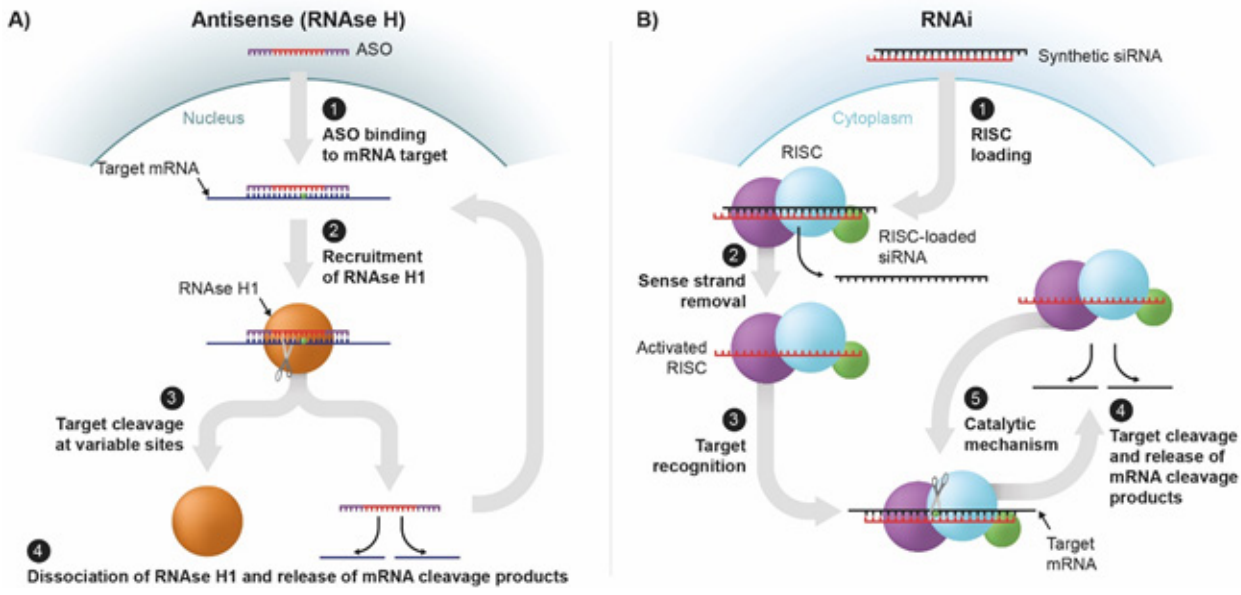


**Figure 3 – Cardiac amyloidosis. The amyloidogenic cascade leads to the production of toxic TTR oligomers and amyloid deposits, which impact cardiac structure and function.**
*TTR: transthyretin.*

sudden death have been observed, due to continued deposition of wild-type (wt) TTR at the site of pre-existing cardiac deposits (e.g., in the myocardium).[59,61]

Thyroid hormone binding to TTR stabilizes the tetramer,[62] motivating the development of small-molecule stabilizers (e.g., diflunisal and tafamidis). Diflunisal, a nonsteroidal anti-inflammatory therapeutic, slows the worsening of neuropathy in patients with hATTR amyloidosis.[63] However, adverse effects on renal and platelet function have limited its use in patients with cardiomyopathy,[64] and diflunisal is not approved in any region for the treatment of ATTR amyloidosis. Tafamidis can delay peripheral neurologic impairment[65] and is available for the treatment of early-stage neuropathy in regions including Latin America (e.g., Brazil, Mexico), EU, and Japan.[66,67] Tafamidis has not been approved in the US as a treatment for hATTR amyloidosis with polyneuropathy. Tafamidis has, however, been recently approved for treatment of ATTR amyloidosis with cardiomyopathy following a study of patients with wtATTR and hATTR amyloidosis with New York Heart Association class 1, 2, or 3 HF.[68] At 30 months, tafamidis was associated with lower all-cause mortality than placebo (hazard ratio [HR], 0.70; 95% confidence interval [CI], 0.51-0.96) and a lower rate of cardiovascular-related hospitalizations (relative risk ratio 0.68 per year; 95% CI, 0.56-0.81). Secondary analyses demonstrated lower rates of decline in 6-minute walk test (6-MWT) distance and in Kansas City Cardiomyopathy Questionnaire overall score compared with placebo.[68]

Phase 3 studies of 2 oligonucleotide therapeutics, inotersen and patisiran, validated *TTR* gene silencing in the liver as an effective therapeutic strategy in hATTR amyloidosis with polyneuropathy[53,54] and offered insights into the potential of this approach in patients with cardiomyopathy. Indeed, patisiran and 2 other oligonucleotide therapeutics are being evaluated in ongoing trials for ATTR amyloidosis with cardiomyopathy (Table 1).

The efficacy of inotersen and patisiran was evaluated via 2 measures in the pivotal studies of patients with hATTR amyloidosis with polyneuropathy: the modified Neuropathy Impairment Score+7 tests (mNIS+7), a composite measure of neuropathy (higher scores indicate more impairment[69]); and the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN) questionnaire, which assesses patients' perception of their QOL (higher scores indicate poorer QOL[70]). Of note, the scoring range of mNIS+7 differed between the trials of inotersen (-22.4-346.3) and patisiran (0-304), reflecting differences in the measurement of sensation, nerve conduction, and autonomic function.[53,54]

Inotersen is an ASO administered weekly via subcutaneous injection. In the phase 3 NEURO-TTR trial, inotersen reduced serum TTR protein levels to a median nadir of 79% from baseline.[54] This resulted in significant improvement compared with placebo in mNIS+7 scores (least-squares mean change from baseline on week 66 of +5.8 points in the inotersen group compared with +25.5 points in the placebo group) and in Norfolk QOL-DN scores (mean change from baseline was +1.0 and +12.7 points for inotersen and placebo groups, respectively).[54]

Among patients in the NEURO-TTR trial, 63% had echocardiographic signs of cardiac amyloid involvement, but no significant changes were observed in echocardiographic variables at the end of the study.[54] A small, uncontrolled study of inotersen for patients with hATTR or wtATTR amyloidosis with cardiomyopathy suggested disease improvement relative to baseline after 1-3 years of treatment, with declines in LV mass, LV wall thickness, and *N*-terminal prohormone of brain-type natriuretic peptide (NT-proBNP), as well as an improvement in global longitudinal strain (GLS).[71] Functional capacity appeared to stabilize or improve relative to baseline over the first 2 years of treatment in patients with hATTR amyloidosis, as quantified by the 6-MWT.[71] In contrast, data from natural history studies show a progressive decline in the 6-MWT over a similar period.[44,45]

Inotersen is approved in several countries, including Brazil, for hATTR amyloidosis with polyneuropathy, but treatment requires regular monitoring for thrombocytopenia and acute glomerulonephritis. Each complication occurred in 3% of patients in NEURO-TTR; 1 death was associated with a case of grade 4 thrombocytopenia.[54] Inotersen is not being developed for cardiomyopathy; however, a GalNAc-ASO conjugate with a similar sequence and design to inotersen is being evaluated in a phase 3 trial of patients with hATTR or wtATTR amyloidosis with cardiomyopathy (Table 1).

Patisiran, an siRNA formulated in an LNP, is administered intravenously every 3 weeks. In the phase 3 APOLLO trial, patisiran reduced TTR protein levels by median 81% from baseline.[53] Patisiran resulted in improvements in mNIS+7 and Norfolk QOL-DN scores relative to both placebo and to the patients' own baseline.[53] In the patisiran and placebo arms, the least-squares mean changes from baseline were -6.0 and +28.0 in mNIS+7 and -6.7 and +14.4 in Norfolk QOL-DN, respectively. Patisiran also improved gait speed in a 10-meter walk test (change relative to baseline was +0.08 and -0.24 meters per second in the patisiran and placebo arms, respectively).[53]

Data from APOLLO suggest that patisiran may also improve measures of cardiac structure and function in patients with cardiomyopathy. Prespecified exploratory analyses assessed patisiran and placebo in a subpopulation with evidence of cardiac amyloid involvement, defined by a baseline LV wall thickness ≥ 13 mm and no history of aortic valve disease or hypertension.[72] Reflecting the multisystem nature of hATTR amyloidosis, the cardiac subpopulation comprised 56% of APOLLO patients who were enrolled on the basis of polyneuropathy. Compared with placebo, patisiran reduced mean LV wall thickness, increased end-diastolic volume, decreased GLS, increased cardiac output, and lowered NT-proBNP. A decrease in GLS in the patisiran arm is notable since an absolute 1% increase has previously been associated with an increased risk of death (HR, 1.1, 95% CI, 1.01-1.19).[73] Patisiran demonstrated a positive benefit:risk profile in both the overall and cardiac subpopulations. In post hoc analyses of safety data, among the entire APOLLO population, the exposure-adjusted rates of cardiac hospitalizations and all-cause death were 18.7 and 10.1 per 100 patient-years in the placebo and patisiran groups, respectively (Andersen–Gill HR, 0.54; 95% CI, 0.28-1.01).[72] While these data suggest that improvement in cardiac parameters following patisiran treatment may lead to improved outcomes, the APOLLO study was not designed to investigate clinical outcomes such as death or cardiovascular hospitalization, and further studies are needed.

Patisiran is approved in > 30 countries globally, including Brazil, for the treatment of hATTR amyloidosis with polyneuropathy (specific indications vary by country/region).[74-78] Except for infusion-related reactions, the overall incidence and types of adverse effects were similar between patisiran and placebo arms of the APOLLO trial. Infusion-related reactions occurred in 19% and 9% of patisiran- and placebo-treated patients, respectively.[53] They were generally mild or moderate, spontaneously resolved, and decreased in frequency with subsequent infusions; risk was reduced by premedicating patisiran-treated patients. An ongoing trial, APOLLO-B, is evaluating the safety and efficacy of patisiran in ATTR amyloidosis with cardiomyopathy (Table 1).

Vutrisiran, a second-generation investigational RNAi therapeutic targeting TTR, uses a GalNAc-siRNA ESC conjugate, similar to that used for inclisiran, with chemical modifications that confer increased potency and

high metabolic stability. Administered subcutaneously once every 3 months in a phase 1 study of healthy volunteers, a single 25-mg dose resulted in a maximum 80% TTR reduction sustained for approximately 90 days.[79] This vutrisiran regimen is predicted to achieve 88-90% TTR reduction, similar to patisiran in the APOLLO trial. Two phase 3 trials are currently ongoing to evaluate vutrisiran for the treatment of hATTR amyloidosis with polyneuropathy (HELIOS-A) and ATTR amyloidosis with cardiomyopathy (HELIOS-B; Table 1).

## Summary

More than 40 years after Zamecnik envisioned targeting RNA as a therapeutic modality, oligonucleotides have emerged as cutting-edge medicines that exploit endogenous mRNA degradation mechanisms. By silencing the expression of disease-causing proteins with genetic precision, siRNAs and ASOs expand the range of biologic targets beyond those that require direct drug-protein binding. Advances in nucleic acid chemistry and oligonucleotide delivery to the liver have yielded novel therapeutic approaches to cardiovascular diseases. They include common conditions like hypercholesterolemia and rarer ones like ATTR amyloidosis, which may be more prevalent than previously thought. GalNAc-siRNA conjugates have demonstrated positive benefit:risk profiles in clinical studies and have potential to be convenient treatments for conditions that are difficult to manage. Their characteristics also raise the possibility that these therapeutics may be useful for both symptomatic and presymptomatic individuals. For example, early diagnosis and quarterly treatment with an siRNA in patients with noncardiac signs of ATTR amyloidosis may prevent the development of congestive HF. Also, semiannual injections of inclisiran for high-risk individuals with hypercholesterolemia may achieve better outcomes than current medications whose compliance is inconsistent. While oligonucleotide-based therapeutics are relatively new, their ability to target the fundamental bases of diseases is already clear, and their impact on medicine is certain to grow.

## Author contributions

Conception and design of the research: Jay PY, Vest J. Acquisition of data: Jay PY, Maier MA. Analysis and interpretation of the data: Jay PY. Writing of the manuscript: Jay PY, Maier MA. Critical revision of the manuscript for intellectual content: all authors.

### Potential Conflict of Interest

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

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### Study Association

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

### Ethics approval and consent to participate

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

### Erratum

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In Review Article "Gene Silencing Therapeutics in Cardiology: A Review Article", with DOI number: https://doi.org/10.36660/ijcs.20200306, published in ahead of print in the journal International Journal of Cardiovascular Sciences, 2021; [online].ahead print, pp. 0-0, swape the position of Figures 1 and 3, and keep the subtitles in the current position. For a better comprehension, please access the following link: http://ijcscardiol.org/supplementary-material/2022/3505/2020-0306_material-suplementar.pdf

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CASE REPORT

# Pacemaker Implantation without Fluoroscopy and Guided by Anatomical Mapping

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## Introduction

Cardiogenic syncope is an uncommon pathology in the context of pregnancy,[1] and an associated transient atrioventricular block is even more rare. The harmful effects of radiation exposure for fetus are already well-known.[2] Thus, alternative guiding techniques are being proposed as an alternative in order to avoid radiation exposure. Previous reports have described the use of intracardiac echocardiography or three-dimensional (3D) electroanatomical mapping.[3] Despite efforts to develop non-fluoroscopic approaches, cardiac device implantation still requires some fluoroscopic imaging. Each hour of fluoroscopic imaging is estimated to increase the lifetime risk of developing a fatal malignancy by up to 1%, as well as being an increased risk of a genetic defect in up to 20 in every 1 million births.[4,5]

With technological advancement, the use of less invasive techniques, together with short procedure times and less radiation exposure is essential. Therefore, repurposing technologies, which were originally developed for other applications, but that have been proven to be safe, should be encouraged. In this light, the present study advocates the use of the CARTO system technology (Biosense Webster, INC., Diamond Bar, CA) to delineate right atrium and right ventricle geometry so as to allow the pacemaker lead to be identified as a catheter to navigate the cardiac cavity without fluoroscopic exposure.

## Keywords

Artificial Pacemaker; Fluoroscopy; Pregnancy.

## Case report

A 35-year-old female, in the 28th week of pregnancy, was admitted for the second time to the emergency department due to syncope. This condition is characterized by a rapid onset, short duration, and spontaneous complete recovery associated with light-headedness. The baseline electrocardiogram showed a sinus rhythm at 65 beats per minute and a first-degree atrioventricular (AV) block. During her initial admission, the symptoms were associated with reflex (neural-mediated) syncope. During her second admission, the patient was referred for an external loop recorder, which was installed, and the patient was discharged. Three days later, the patient returned to the emergency department with the same complaint of syncope. An analysis of the loop recorder revealed a transient high-degree atrioventricular block (Figure 1) coinciding with the syncopal episode. The patient has no other known comorbidities and no significant family history. A transthoracic echocardiogram revealed a normal left ventricular ejection fraction (68%), normal heart valves, and normal right ventricular size and function. The electrolytes and thyroid function were normal. In addition, an exercise electrocardiographic stress test was normal. She was therefore referred for a pacemaker implantation, and given her ongoing pregnancy, an alternative technique was applied.

The patient was brought to the electrophysiology laboratory, and prior to commencing the procedure, a fetal heartbeat monitor was installed, and the entire procedure was followed by an obstetrician. The patient was sedated, using propofol, and both the right groin as well as the left pectoral region were ??? and draped using alcoholic chlorhexidine. Under local anesthesia, with 2% lidocaine 10cc, the right femoral vein was

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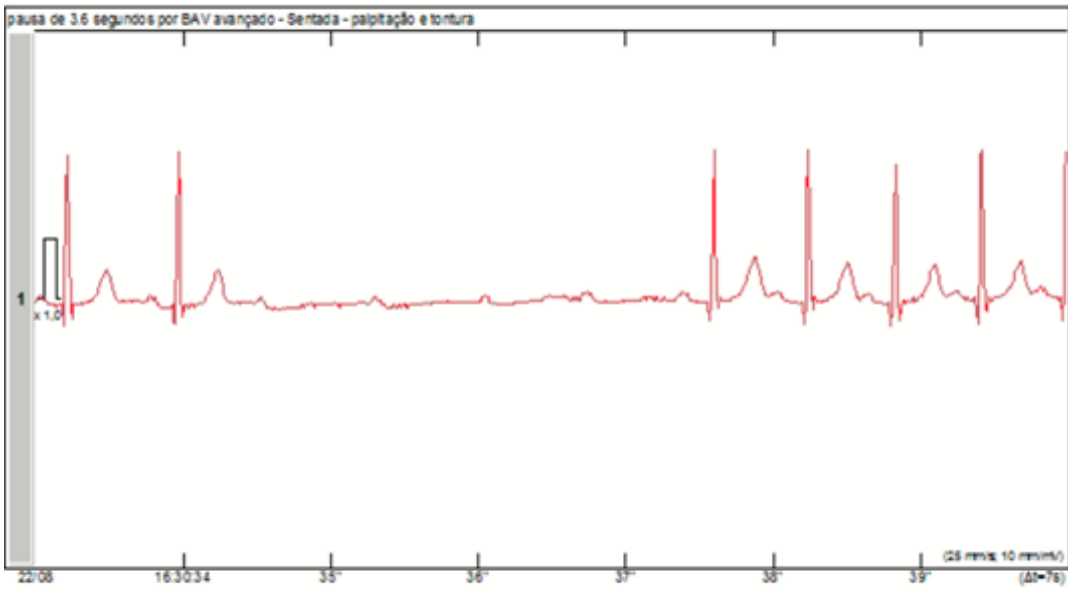


**Figure 1 – Looper recorded showing an intermittent high-degree AV block with 3.6 seconds related with Syncope episode.**

accessed using an 8F sheath. A deflectable mapping catheter – 4mm-tip quadripolar steerable (Biosense Webster, Inc., Diamond Bar, CA) – was then advanced and used to create 3D electroanatomic mappings of the right atrium and right ventricle using only the navigation system and bipolar electrogram tracings, usingthe CARTO system (Biosense-Webster). Set points were captured and marked by points to delineate areas of interest such as the His bundle position, superior vena cava, inferior vena cava, right ventricle outflow tract, the entire tricuspid ring, and the right ventricle. The geometry mapping of the His showed a prolonged HV interval (HV=80ms) (Figure 2). After the right atrium and ventricle geometry was completed, the ablation catheter was pulled back to the inferior vena cava.

After local anesthesia injection, 2% lidocaine 10cc, by left subclavian venous access, was obtained, using anatomical landmarks and ultrasound without the aid of fluoroscopic guidance. A 7-F sheath was advanced into the left subclavian vein using the modified Seldinger technique. The intracavitary lead (Capsure- Fix model 4076, Medtronic, Inc., Minneapolis, MN) was connected by means of alligator clips to the CARTO-3 system as a bipolar connection that allowed one to view the lead tip on the electroanatomic map. The lead tip was advanced into the right ventricle following the 3D mapping. A curved stylet was used to lead the electrode to the right ventricular outflow tract. This was relatively simple with the help of the navigation system, which allows the operator to continuously confirm if the electrode is inside the ventricle or not. From the right ventricular outflow tract, the electrode was slowly pulled back, now with a straight stylet, until the electrodes dropped to the low septum following the 3D mapping. The intracavitary signal was followed until an acceptable R wave amplitude was obtained, associated with an R-wave injury pattern before engaging the screw. After placing the screw with 10 loops, impedance, sensing, and threshold tests were performed (Figure 3). The following results were obtained: impedance of 644 ohms, R-wave amplitude at 11.2mV, and pacing threshold at 0.75ms at 0.4V. Lead slack was estimated using the created map and measuring the distance from the access point to the final lead position, and then comparing to the lead marker. The lead was then connected to a permanent VVI pacemaker (Medtronic Attesta SR MRI ATSR), which was lodged in a subcutaneous pocket with the wound securely sutured. The catheter from the right femoral vein was removed with the sheath and a compressive dressing was placed for 4 hours after the procedure. Upon follow-up after delivery, the patient is doing very well and all pacemaker parameters are the same. The patient is using less than 2% of pacing due to sinus rhythm at baseline with only intermittent high-degree AV block. Therefore, there has

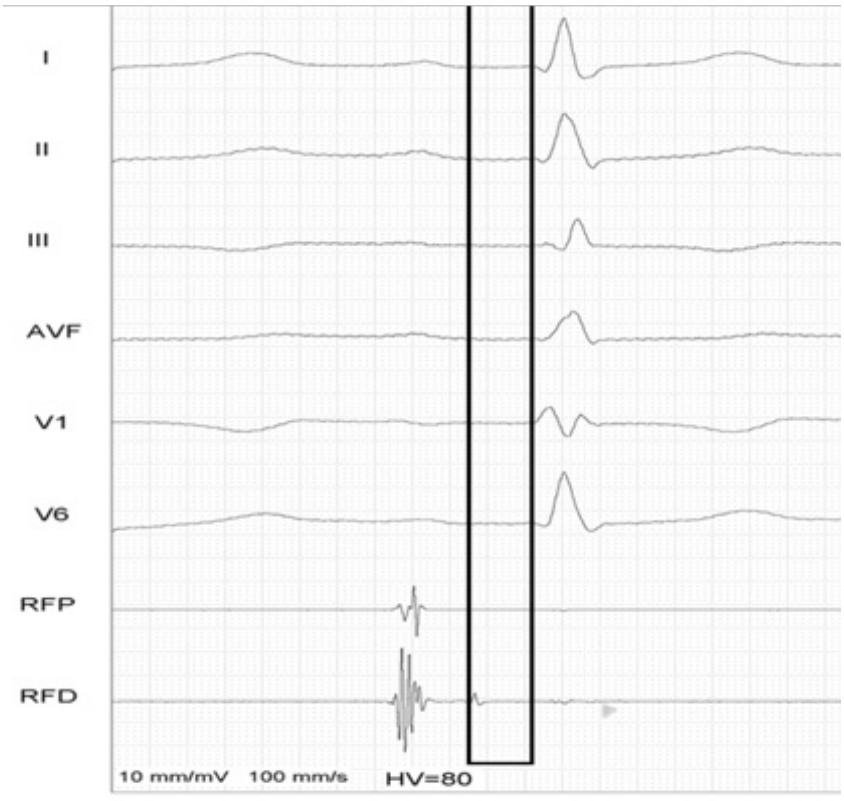


**Figure 2 – Intracavitary measurements revealed a prolonged HV interval.**

been no need to upgrade to a dual chamber pacemaker. A chest X-ray was performed after pregnancy and the lead slack is quite satisfactory.

## Discussion

The present case report describes a patient who required a permanent pacemaker implantation during pregnancy due to a transient atrioventricular block and syncope. A single chamber pacemaker was implanted at that time as the best strategy for a rapid procedure with minimal complications. The patient will be reassessed after the pregnancy to assess the need for an upgrade, if necessary.

The CARTO system works by using ultralow intensity magnetic fields emitted from coils in a locator pad beneath the laboratory table. The magnetic field strength from each coil is different and is detected by a location sensor embedded proximal to the tip of the specialized mapping catheter. The locator pad interacts with a magnetic field generator locator pad (placed beneath the operating table), an external reference patch (fixed on the patient's back), a deflectable 7 Fr quadripolar mapping-ablation catheter with a 4- or 8-mm tip and proximal 2-mm ring electrodes, location sensors inside the mapping-ablation catheter tip (the three location sensors are located orthogonally to each other and lie just proximal to the tip electrode, fully embedded within the catheter), a reference catheter, a data processing unit, and a graphic display unit to generate the electroanatomic model of the chamber being mapped.[6]

The CARTO system can create an imaginary catheter using the electrode measurements and tip; connecting the electrode to the patient interface unit helps it to recognize the lead as a catheter. This configuration in a bipolar setting allowed it to be enabled when connected to the patient interface unit (connection between the patient and CARTO) and the location pad positioned under the table. The tip of the lead was connected using the usual alligator clips with the red color in the proximal position and black portion at the distal electrode connections.

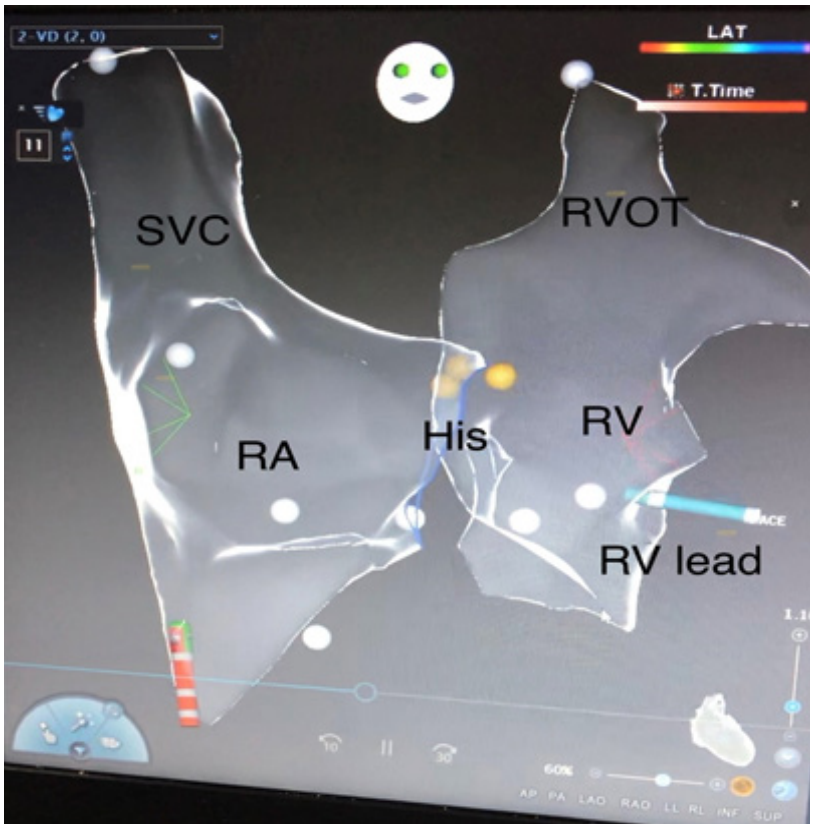


**Figure 3 – Electroanatomic mapping showing the right atrium and right ventricle. Blue catheter showing the RV pacemaker lead. Red catheter showing the mapping catheter.**

A similar case was performed by Payne et al.,[7] which used the St. Jude NavX mapping system, with a minimal fluoroscopy time to confirm the lead position.

The radiation risks throughout pregnancy are related to the stage of pregnancy and the absorbed dose.[5] These risks are more significant during organogenesis and in the early fetal period, somewhat less in the second trimester, and least in the third trimester. Malformations, typically associated with central nervous system disorders have a threshold of 100 to 200 mGy or higher, which can be reached through a fluoroscopy guided pacemaker implantation.[8]

The possible effects on pregnancy on a congenital complete heart block have been previously postulated.[9] These patients have a high stroke volume and bradycardia due to the hypervolemia related to pregnancy, as well as vagal stimulation related to a gravid uterus. Vagal mediated bradycardia is also common. However, our patient was in the 3rd trimester of pregnancy, and this was an unlikely mechanism. Furthermore, during right atrial mapping, the HV intervals revealed a prolonged HV related to the intermittent intraventricular block. Moreover, there has been a higher rate of Stokes-Adams attacks documented during pregnancy in these patients.[10] This approach can be considered the first option in pregnant patients in order to avoid fluoroscopy exposure, since the procedure appears safe and with a similar procedural duration, 20 minutes longer than the usual pacemaker implantation, though this would likely decrease with experience. The use of 3D anatomic mapping has proven to significantly reduce fluoroscopy time and fluoroscopy dose during routine device implantation,[11] as well as being a safe and effective approach.[12]

Some limitations of this approach should be mentioned. With this technique, final lead position and lead slack, which is important in young patients, could not be easily determined. Therefore, this technique should only be used in selected patients who would derive the greatest benefit, such as pregnant patients.

## Conclusion

This study presented a case report on a totally non-fluoroscopic transvenous pacemaker implantation in a pregnant patient with syncope related to high-degree atrioventricular block. This technique enabled the use of the CARTO system to demarcate the right atrium and ventricle geometry, as well as the visualization of the pacemaker lead in order to ensure the proper location in the right atrium and ventricle as a guide to find the best position to place a right ventricular lead endocardial fixation. The clinical benefit of this approach requires further investigation and validation.

## Author contributions

Conception and design of the research: Montemezzo M. Acquisition of data: Montemezzo M, Jakolinski M. Analysis and interpretation of the data: Montemezzo M. Writing of the manuscript: Montemezzo M, AlTurki A. Critical revision of the manuscript for intellectual content: Montemezzo M, AlTurki A, Jorge JCM.

### Potential Conflict of Interest

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

### Sources of Funding

There were no external funding sources for this study.

### Study Association

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

### Ethics approval and consent to participate

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

**Erratum**

Int J Cardiovasc Sci. 2022 Issue vol 35(5), pages 676-680.

In Case Report "Pacemaker Implantation without Fluoroscopy and Guided by Anatomical Mapping", with DOI number: https://doi.org/10.36660/ijcs.20210005, published in International Journal of Cardiovascular Science, 35(5) in page 676-680. Correct, in the 4th paragraph, the phrase: "The patient was sedated, using propofol, and both the right groin as well as the left pectoral region were ??? and draped using alcoholic chlorhexidine." to "The patient was sedated, using propofol, and both the right groin as well as the left pectoral region were draped using alcoholic chlorhexidine."

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CASE REPORT

# Danon Disease in an Asymptomatic Woman: A Five-Year Follow Up

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## Introduction

Danon disease (DD)[1] is a rare, dominant X-linked disease caused by mutation of the LAMP2 gene, which encodes a lysosome-associated membrane glycoprotein, thereby affecting lysosomal deposition. DD is characterized by a classic triad of cardiomyopathy (featured by hypertrophic cardiomyopathy [HC]), skeletal myopathy, and cognitive changes. While female patients tend to have milder phenotypic manifestations, an isolated cardiac involvement, in addition to a later onset of symptoms, without the need for heart transplantation before the fourth decade of life, male patients commonly have the presentation of the classic triad of disease.[2]

The clues of the involvement of HC with pre-excitation and persistent increased troponin I in these individuals are related to the process of autophagy that contributes to cardiac remodeling.[3] However, there is still no specific treatment for DD. The approach to cardiac manifestations includes implantable cardioverter defibrillator (ICD) and ablation to improve symptoms and decrease the risk of sudden death. In cases of advanced heart failure (HF), heart transplantation is an effective and safe measure. Studies for gene therapy are currently in progress.[4,5]

## Keywords

Glycogen Storage Disease Type II/genetics; Cardiomyopathy Hypertrophic; Phenotype; Lysosomal-Assoiated Membrane Protein 2/genetics (DD Danon Disease).

Considering the small number of cases described in the literature about DD and the gap in knowledge for an earlier approach, we aimed to describe the case of a patient with incidental diagnosis of DD, presenting a mutation not previously described in the literature and its five-year follow-up.

## Case description

A female 23-year-old Caucasian patient, only daughter of a no consaguineous couple, was incidentally diagnosed with HC at 18 years of age during the preoperative period of an orthopedic surgery and confirmed by cardiac resonance. The parents were asymptomatic, with normal echocardiogram.

At the age of 20, she was admitted to the emergency department with atypical chest pain, and no other findings at physical examination, and laboratory tests showed an increase in troponin I (6ng/dL). She underwent a new cardiac magnetic resonance imaging confirming the diagnosis of CH with delayed gadolinium enhancement (Figure 1). At the time, she was diagnosed with acute myocarditis.

Patient was referred to a specialized HF center, where a Doppler echocardiography was performed, confirming the findings of HC (Figure 2), and revealing slight obstruction of the outflow pathway, and a Wolff-Parkinson-White (WPW) preexcitation pattern. The patient had elevated and stable levels of troponin I (7.74ng/dL), and natriuretic peptide (BNP) levels of 401 pg/mL six months after admission for chest pain. The patient underwent genetic testing; a new mutation *NP_002285.1:p.Asn242Thrfs*41* compatible with DD was identified, and referred as accessory pathway (VA) ablation due to the WPW-type preexcitation.

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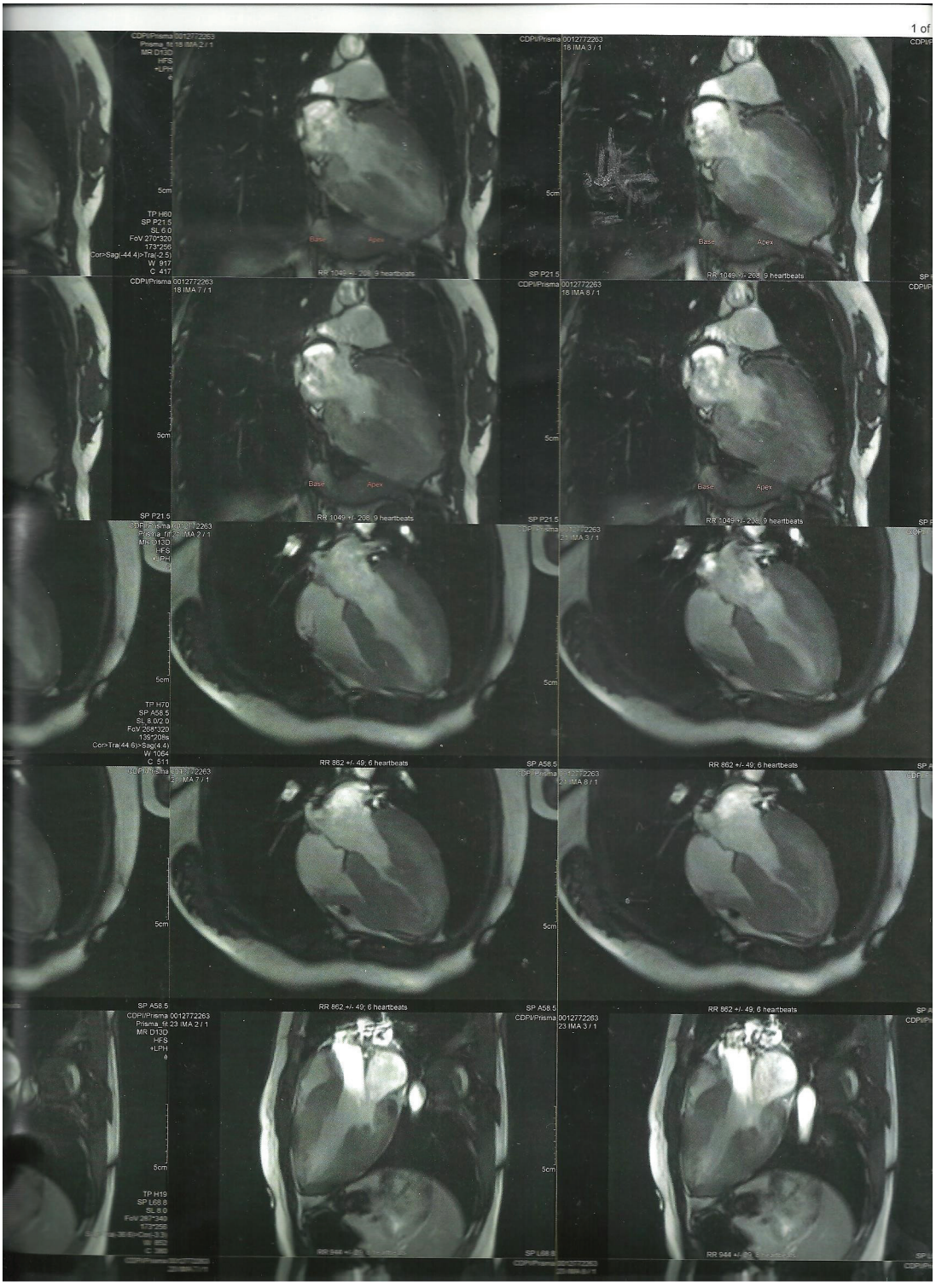

**Figure 1 – Gadolinium-enhanced cardiac magnetic resonance imaging showing left ventricular hypertrophy with involvement of apical segments and mid-basal portion of the anterior and lateral walls and left ventricular diastolic dysfunction, suggestive of myocardial fibrosis observed in cases of hypertrophic cardiomyopathy. Left ventricular ejection fraction: 78%. Maximum end diastolic thickness of septum IV = 2.1 cm; lateral wall = 2.0 cm.**

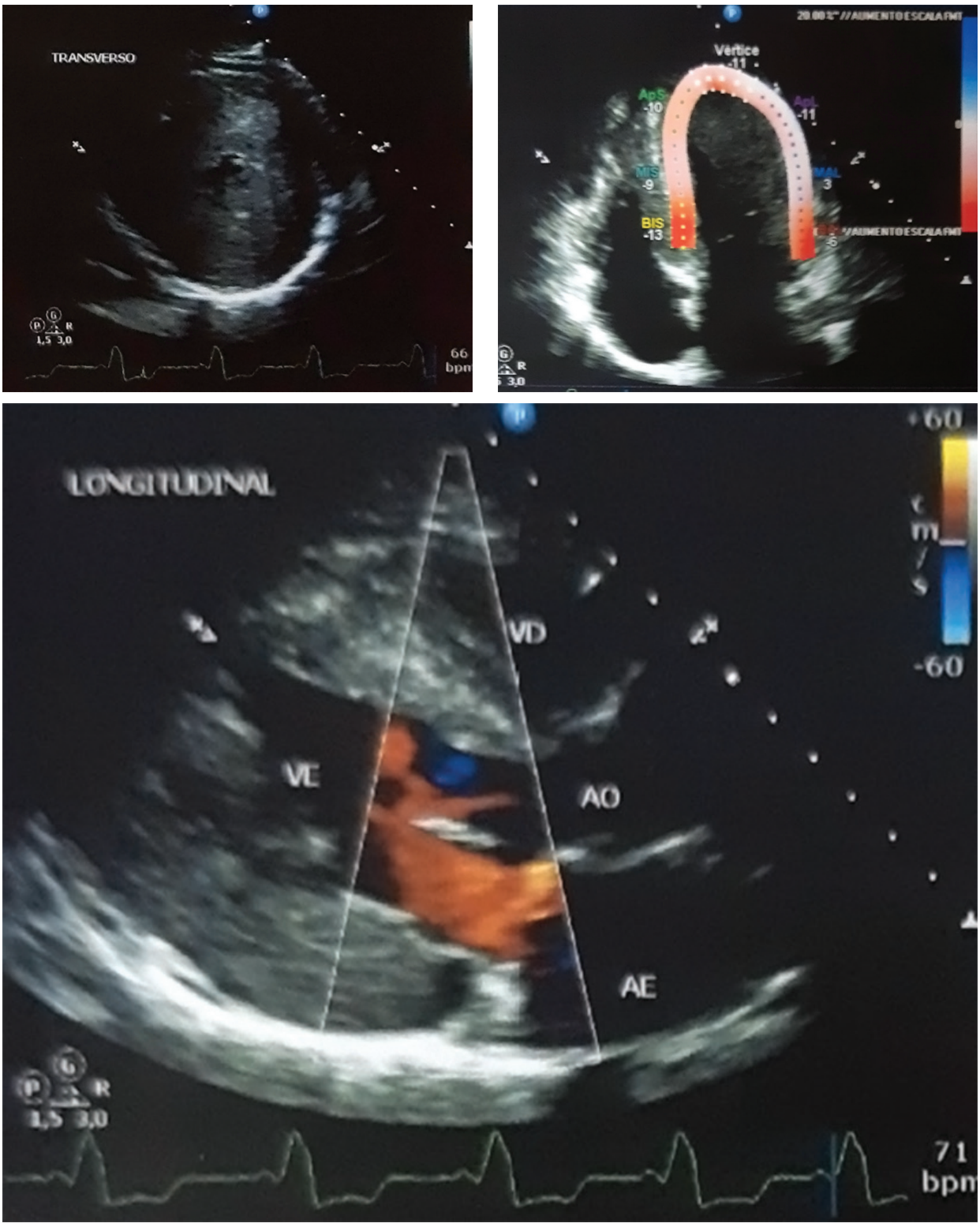


**Figure 2 – Doppler echocardiogram showing alteration of left ventricular diastolic function and hypertrophic cardiomyopathy**

After three months, the patient presented with a new WPW-compatible pre-excitation episode involving the same VA, and referred for another ablation. A follow-up Holter revealed an asymptomatic, non-sustained ventricular tachycardia (VT) (Figure 3), and an implantable cardioverter defibrillator (ICD) was indicated, based on the cardiac resonance imaging findings also.

Since then, the patient has been asymptomatic, undergoing cardiac rehabilitation and treatment with beta-blockers. There has been no ICD firing since its implantation, in addition to normal renal, hepatic, ophthalmic and neurological functional tests. The patient has been followed by the departments of clinical genetics, cardiology, and arrhythmology, and received psychological support for anxiety disorder. In the last months she has been in isolation due to the COVID-19 pandemic and routinely performed physical activities and in telemedicine consultation. The temporal progression of the events were described in Tablet 1.

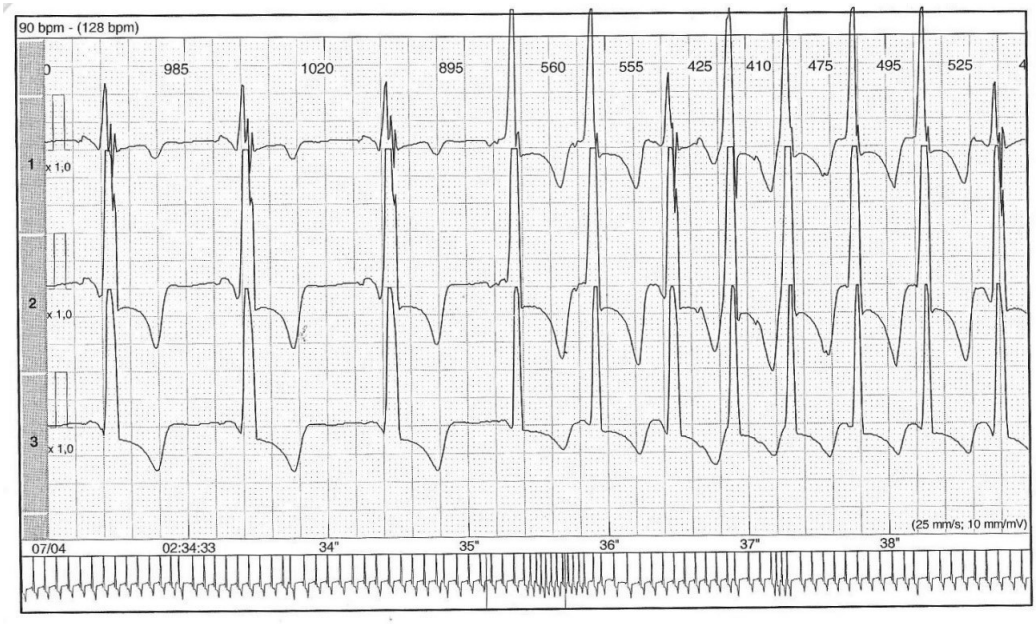


**Figure 3 – Electrocardiogram showing non-sustained ventricular tachycardia.**

**Table 1 – Table describing the temporal progression of events**

| Temporal Evolution | Events |
|---|---|
| **2014**<br>18 years old | Diagnosis of hypertrophic cardiomyopathy during the preoperative evaluation for orthopedic surgery. |
| **2016**<br>20 years old | Patient admitted for atypical chest pain. The patient was referred to a specialized cardiac failure service that identified in 12-lead ECG the presence of Wolff-Parkinson-White preexcitation pattern. |
| **2017**<br>21 years old | Patient seeks the emergency for the second time with complaint of palpitation; she was diagnosed with Wolff-Parkinson-White pre-excitation and referred to first ablation. |
| **2018**<br>22 years old | After the insertion of the Holter track, several episodes of non-sustained ventricular tachycardia (VT) were observed. The patient was referred for implantable cardioverter defibrillator placement. |
| **2019**<br>23 years old | The patient remains asymptomatic, undergoing multidisciplinary follow-up and cardiac rehabilitation three times a week. In the last months she has been in isolation due to the COVID-19 pandemic and routinely performing physical activities and in telemedicine consultation. |

## Discussion

The present study reports the case of late diagnosis of DD as the cause of HC, with a new genetic variant in heterozygosis NP_002285.1:p.Asn242Thrfs*41 in the LAMP2 protein encoding the protein *Lysosome-associated membrane glycoprotein* 2. This variant of the truncating frameshift mutation has not been previously published, or even identified in controls. No truncating variant of this gene is listed in the database *Exome Aggregated Consortium* (ExAC). The consequence of this mutation is the creation of a stop codon that causes a premature interruption in the coding of the LAMP2B protein.[3,6]

Biological diagnosis of DD involves demonstration of normal or high acid maltase activity in combination with muscle biopsies showing large vacuoles filled with glycogen, cytoplasmic degradation products and partial or total absence of LAMP-2 protein in immunohistochemical analysis.[1,8] Thus, the diagnosis can be confirmed by molecular analysis of the LAMP2 gene and evaluation of the three isoforms: LAMP 2A, LAMP 2B and LAMP 2C. The LAMP 2B isoform is responsible for metabolic defects, impairing autophagosome-lysosome fusion, leading to heart disease in DD.[7]

The Wolff-Parkinson-White syndrome is an important diagnosis, especially in women.[9]. This finding culminated in the indication of the first ablation of the anomalous pathway. In a recent systematic review evaluating 146 patients with DD, while female patients had a predominant pattern of cardiomyopathy alone, as presented in our case report, men more commonly presented the clinical triad of HC, skeletal myopathy and mental illnesses.[9]

In addition, the reported case had chest pain accompanied by elevated troponin I levels, which raised the suspicion of acute myocarditis. Later, the persistence of elevated troponin levels over the months indicated a false diagnosis of myocarditis. Cardiac resonance has allowed a more accurate evaluation of the site of myocardial hypertrophy, presence of intracavitary thrombi, and recently, presence of fibrosis, which is an important prognostic marker in this group of patients. Myocardial injury and increased troponin may cause myocardial remodeling and explain the progression to a dilated form of myocardiopathy. High levels of troponin I in DD has prognostic value in the clinical decision-making process.[10]

A recent clinical trial[5] studied gene therapy in male patients with DD. This therapy involves a recombinant adeno-associated virus containing the transgene isoform LAMP2B (RP-A501), which will contribute to a better management and understanding of the disease.[5]

## Danon Disease

Danon disease is an uncommon condition, and rarely recognized as a red flag for CH phenocopying. Because there was no specific treatment during the follow-up of the patient reported in this study, several interventions and hospitalizations were necessary over the five years of follow-up. This shows the importance of cardiac surveillance and multidisciplinary approach of this group of patients. Also, telemedicine support allows the maintenance of care despite the COVID-19 pandemic. Finally, genetic testing should be incorporated into clinical practice for congenital heart disease.

### Potential Conflict of Interest

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

### Sources of Funding

There were no external funding sources for this study.

### Study Association

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

### Ethics approval and consent to participate

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

## Author contributions

Conception and design of the research: Matos RC, Soares AC, Silva RTB, Mesquita ET. Acquisition of data: Matos RC, Soares AC, Silva RTB, Mesquita ET. Analysis and interpretation of the data: Matos RC, Soares AC, Silva RTB, Mesquita ET. Writing of the manuscript: Matos RC, Soares AC, Mesquita ET. Critical revision of the manuscript for intellectual content: Mesquita ET.

**Erratum**

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In Case Report "Danon Disease in an Asymptomatic Woman: A Five-Year Follow Up", with DOI number: https://doi.org/10.36660/ijcs.20210038, published in ahead of print in the journal International Journal of Cardiovascular Sciences, 2022; [online].ahead print, pp. 0-0, correct the author's name "Ricardo Cardoso Cardoso de Matos" to "Ricardo Cardoso de Matos".

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VIEWPOINT

# Quality of Highly Complex Care in Cardiology

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Factors like the high costs of currently available technologies, the work overload of health professionals, and population aging and consequent increase of chronic diseases have highlighted the need for special attention to the quality of health care provided, especially in high-complexity cardiovascular care.[1]

Although there are several definitions of health-related quality, the present analysis is grounded in the concept that aspects like efficiency, or effectiveness, are associated with the safety of care provided, which in turn is closely related to patient centrality and protection of their rights.

When the concept of quality is discussed, structural or physical factors, including material, financial and human resources, assessment tools, education and research activities, clinical protocols, and process approaches should be addressed. Process approach is a method to plan activities and processes performed by health providers who are directly involved in patient care, that can lead to (desirable or undesirable) changes in individual or population health.[2]

The exhaustive search for reliable processes in health care has yielded remarkable achievements such as elimination of waste, undesirable waiting, unnecessary pain, and preventable death. One example is the "Enhanced Recovery After Surgery" (ERAS), a multimodal perioperative care pathway, already validated in cardiac surgeries.[3] The ERAS refers to a multidisciplinary, patient-centered, evidence-based approach aimed to optimize patients' physiologic function in the preoperative period, leading to improved patient outcomes and satisfaction, and reduced hospital stay, postoperative complications, and hospital costs.

In the Brazilian public health system, "highly complex" procedures are those involving technology and high costs, aiming at providing access to high-quality services that should be integrated to other levels of complexity (low and moderate complexity). The National Policy of Cardiovascular Care, launched in 2014 and updated in 2018, regulates the criteria for the habilitation of health care units and referral centers involved in the highly complex care of cardiovascular diseases.[4,5] These health care units should provide technical conditions, physical facilities, equipment, and human resources and promote a close interaction and integration with the local and regional system. Procedures performed in these centers include adult and pediatric cardiovascular surgeries, interventional procedures, vascular, endovascular and extracardiac surgeries, and electrophysiological analyses. These units should also offer outpatient cardiovascular care, emergency care, preoperative and postoperative follow-up, laboratory tests and cardiovascular prevention measures.

The concern about the quality of care provided by institutions where cardiac surgery is performed has to do with the fact that surgical mortality rates were shown to vary across them.[6]

Indeed, the continuous analysis of mortality is crucial in the search for excellence. Mortality committee and surgical mortality meetings may help in this regard. The number and frequency of deaths, patient gender, action plans for potential failures of the processes, and the level of complexity of the cases should be analyzed. Many publications have reported the need for adjusting the risk to mortality found in cardiac intensive care units and during the postoperative period in children

## Keywords

Cardiovascular Diseases: Hospitals,Special; Hospitals,Chronic Diseases/trends; Quality of Health Care/trends; Staff Committee

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and adults post-cardiac surgery.[7-9] In addition, the length of stay in the hospital and intensive care unit of patients undergoing highly complex procedures should be continuously analyzed.

The Health Technology Assessment (HTA) aims to produce knowledge about the basis for health care, potentiate the synthesis of evidence, and test suggested or required knowledge for health system planning, to ultimately improve all dimensions of quality in care, including disease prevention. A greater participation of the HTA in the implementation and use of technologies in health would reduce inequity in health care, optimize resource allocation, and improve effectiveness and quality of services and financial sustainability of the system.[10] Considering the high costs of cardiac procedures, the benefits of HTA are unquestionable.

However, it is worth to mention that measuring is essential, but not sufficient. After data are collected, they should be analyzed and an action plan for their improvement and implementation should be developed. In this regard, predictive models with computerized solutions, aimed at making improvements in patient care, are currently available.[11]

National databases are usually difficult to be generated in most countries, but there are exceptions, notably Denmark, in which analysis of specific diseases has been successfully performed through nationwide databases. Consolidated in the country for more than 40 years, the Danish Breast Cancer Group (DBCG) was the first to create a clinical database with the purpose of research. The Danish Lung Cancer Registry (DLCR) was the first database primarily focused on the quality of care. The Danish Heart Registry (DHR) is a national database for collecting medical and administrative data on patients referred for invasive cardiovascular procedures and cardiac surgeries and is used for analytical and planning purposes in health care quality and reimbursement of institutions.[12,13]

The Society of Thoracic Surgeons Adult Cardiac Surgery Database (STS ACSD) is another example of nationwide registry that has an important impact on cardiovascular care. The STS ACSD also allowed the development of a score that has been widely used and continuously updated, for the assessment of mortality among patients undergoing cardiac surgery.[14]

In Brazil, despite the dissemination of private and public centers where highly complex cardiac procedures are performed, there is an evident lack of large databases of data related to these procedures. Besides, some of the available data are clearly underused, including the authorization for hospital admission that can provide valuable information on the diagnosis of cardiovascular diseases.[15] There is also an undervaluation of data obtained from currently available registries.

In this brief analysis of highly complex care in cardiology, we conclude that:

- High-quality care not only gives the patient the best opportunity to achieve the results they seek, but also avoid inefficiency and waste;
- Improvement of quality and safety of care is challenging and has long term results, requiring the involvement of all members of the organization;
- Assessment is essential but not sufficient. Solving the problems detected requires action;
- An effective interaction between research, care, and management translates into better quality;
- Adequate registries of data are still scarce;
- Implementation of HTA is essential not only for the evaluation but also for the achievement of better results.

## Author contributions

Conception and design of the research: Aurora Felice Castro Issa. Acquisition of data: Aurora Felice Castro Issa. Analysis and interpretation of the data: Aurora Felice Castro Issa. Writing of the manuscript: Aurora Felice Castro Issa. Critical revision of the manuscript for intellectual content: Aurora Felice Castro Issa.

### Potential Conflict of Interest

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

### Sources of Funding

There were no external funding sources for this study.

### Study Association

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

### Ethics approval and consent to participate

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

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BRIEF COMMUNICATION

# Effects of Cardiac Resynchronization Therapy on a Six-minute Walk Test, Maximal Inspiratory Pressure and Peak Expiratory Flow in Patients with Heart Failure: A Longitudinal Study

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## Abstract

**Background:** Cardiac resynchronization therapy (CRT) is an effective treatment for patients with heart failure.

**Objective:** To evaluate the response of CRT in maximal inspiratory pressure (MIP), peak expiratory flow (PEF), and exercise tolerance as determined by the six-minute walk test (6MWT) in patients with HF.

**Methods:** This study used the 6MWT and Manovacuometer to assess functional capacity in relation to activities of daily living, in which fatigue and dyspnea are common.

**Results:** After six months of CRT, this study identified improvements in the 6MWT, $p<0.05$; MIP, $p=0.01$; and PEF, $p=0.03$.

**Conclusion:** After CRT, this study showed a significant improvement in MIP, PEF, and exercise tolerance. However, further studies are warranted to demonstrate the relevance of these findings.

**Keywords:** Heart Failure; Cardiac Resynchronization Therapy; Walk Test; Maximal Inspiratory Pressures.

## Introduction

Patients with advanced heart failure (HF) have limited functional capacity, reducing their ability to engage in the physical tasks of daily living and determining a decrease in one's quality of life. Cardiac resynchronization therapy (CRT) is an adjuvant therapy option for selected HF patients. It improves the heart pumping efficiency by restoring synchronous contraction of the atria and ventricles.[1] This therapy is associated with decreased mortality, reduced hospitalization, reversed remodeling, and improvement in one's quality of life and exercise tolerance.[2]

HF is not merely an organ disease, but rather a multifaceted syndrome, which can result in musculoskeletal and pulmonary, endocrine, endothelial, renal, and hepatic impairment.[3] A reduction in skeletal muscle performance measured by handgrip strength is common in HF.[4]

Clinical trials have shown that CRT improves functional capacity. Melo et al., (Journal Cardiac Arrhythmias, 2013) observed that CRT produces consistent improvements in one's quality of life (QOL), functional class, and exercise capacity, in addition to reducing hospitalizations and mortality rates. The peak oxygen is reached through $VO_2$ consumption and has a significant response in the six-minute walk test (6MWT). In addition to CRT improving the capacity of exercise tolerance, it also promotes improvements in the NYHA functional class (New York Heart Association).[5]

Patients with HF often appear with a lack of strength and endurance in the inspiratory muscles. These factors are associated with a limited exercise response and QOL, as well as with a poor prognosis. Inspiratory muscle weakness (IMW) is prevalent in patients with reduced ejection fraction and contributes to reduced exercise capacity and dyspnea during daily activities. $VO_2$ is a predictive sign of mortality in HF,

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and recent data indicate that maximal inspiratory pressure (MIP) accompanies this marker and may contribute independently to worse prognoses. In addition, MIP is an independent predictive factor mortality in HF.[6]

The reduction in skeletal muscle performance measured by handgrip strength is common in HF and was measured in a previous study in patients undergoing CRT, although the MIP had not yet been performed. Inspiratory muscle training improves the functional capacity of patients with HF, but the mechanisms of this effect on CRT are unknown.[4] The objective of this study was to evaluate the response of CRT in MIP, peak expiratory flow (PEF), and exercise tolerance as determined by 6MWT through improvements in the six-minute walk distance (6MWD) in patients with HF.

## Methods

Patients with HF and left ventricular dyssynchrony from the HF clinic of ***Hospital Universitário Antônio Pedro*** and ***Instituto Estadual de Cardiologia*** **Aloysio de Castro** were enrolled according to the following inclusion criteria: 18 years of age or older; stable NYHA functional class HF II and III at least three months before enrollment in the study, guideline-directed HF therapy including beta blockers and ACE inhibitors, a left ventricular ejection fraction of less than 35%, an intrinsic QRS duration of greater than 120ms with left bundle branch block morphology and sinus rhythm, **and patients with implanted cardioverter defibrillator implantation for primary prevention or cardiac death syndrome**. Patients with atrial fibrillation or atrial flutter; patients with a serious disease at risk of non-survival; patients with a right bundle branch block and pregnancy, or those who were breast-feeding were excluded from this study.

The present study contains national data which are a part of the international multicenter International Atomic Energy Agency's sponsored project VISION CRT and was submitted to the Research Ethics Committee of Hospital Universitario Antônio Pedro through the Brazil platform, being approved under number 884,844, on November 25, 2014.

This study follows an observational and prospective protocol. The patients who participated in the study took the protocol exams before CRT and six months after the CRT. The assessments were were performed by means of an Analogue Manovacuometer (WIKA CL 1.8). A maximal respiratory pressure and the 6MWT were performed according with ATS protocol. Briefly, the test was performed on a 30-m-long level hallway surface with 1-m distance marks. Patients were asked to walk as far as possible and allowed to set the pace of ambulation with rest and stops as needed. Exercise tolerance was determined as distance in meters, along a 30-m-long level hallway surface. A subjective sense of effort was evaluated every two minutes of exertion, using the BORG scale separately for overall effort and for leg discomfort. All tests were performed by the same researcher.

The PEF measurements were performed though a portable peak flow meter. The measurements were performed before and after the CRT.

### Statistical analysis

All results of this present study, are expressed as means ± standard deviation. Chronotropic response to the 6MWT was calculated as the difference between the peak heart rate during exercise and the resting heart rate. All data were evaluated by the Kolmogorov-Smirnov statistical test to determine whether these followed normal distributions. The distance walked in the 6MWT, MIP, maximal expiratory pressure (MEP) and estimated $VO_2$ (before and after CRT) was compared by applying the paired Student's test. The adequate number of participants to be studied was calculated on the basis of previous publications, showing that interventions, such as exercise tests and CRT, cause changes of 30 ± 20 m in the 6MWT distance. For this size effect, and fixing the statistical power at 0.8 and ± error at 0.5, the minimum sample size should be at least 8 participants. The results found in the study were statistically significant, showing $p < 0.5$.

## Results

Nine patients achieved the endpoint of the study. This process is presented in Chart 1.

### Six- minute walk test

Figure 1 subtracts the difference in walking distance before and 6 months after CRT. A significant improvement in 6MWD after CRT ($p < 0.05$) was observed.

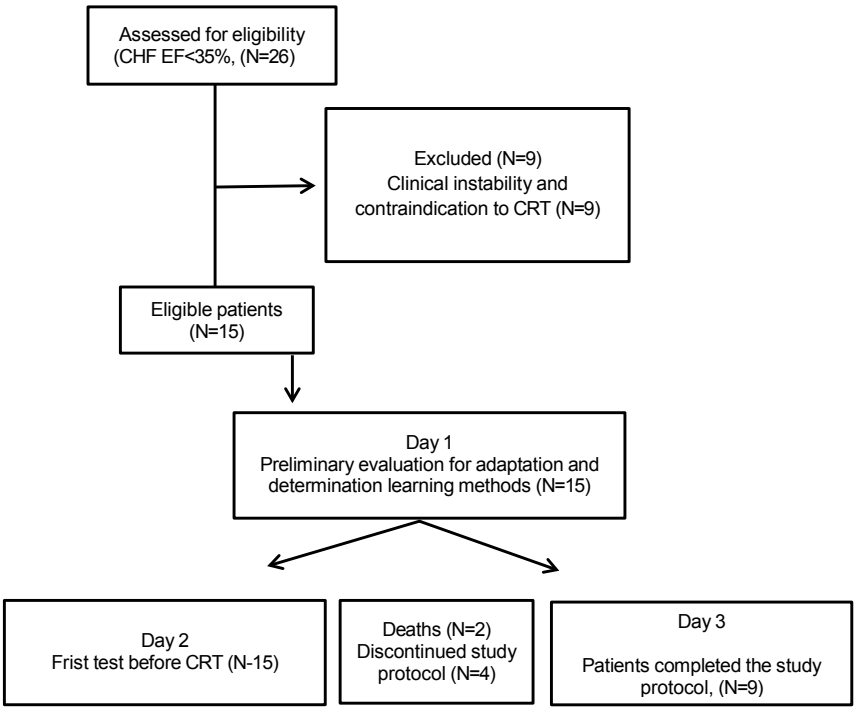


**Chart 1 – Patient's demographic characteristics and functional parameters before and after 6 months of C are shown in Table 1. Medication included angiotensin converting enzyme inhibitors (n=8), diuretics (n=8), and β – blockers (n=9).**

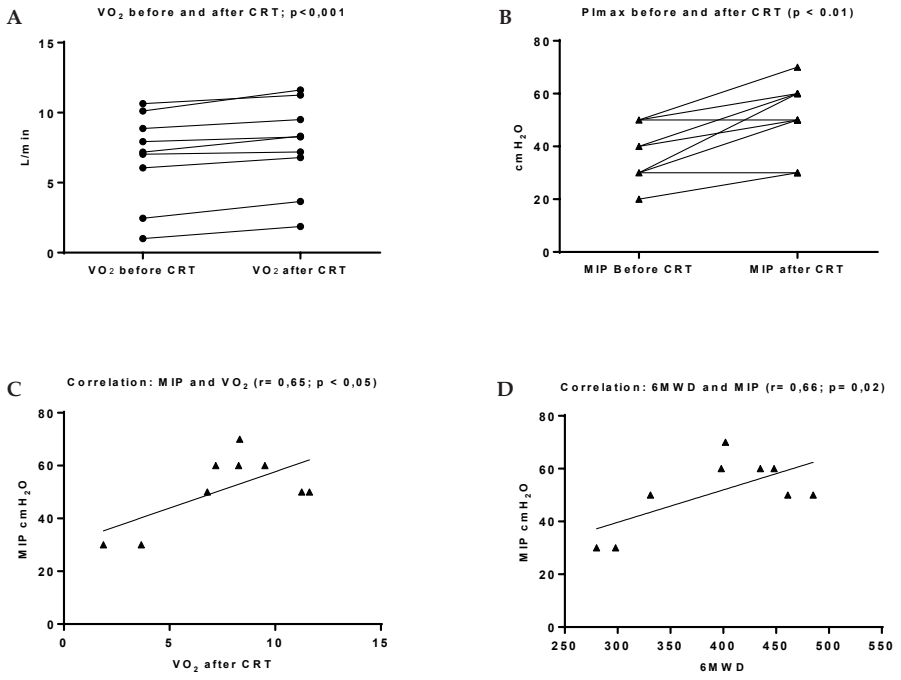


**Figure 1 – a: Peak oxygen before and after cardiac resynchronization therapy during; b: MIP before and after CRT; c: Correlation between maximal inspiratory ressure and Peak oxygen after CRT; d: Correlation between maximal inspiratory pressure and six-minute walk distance.**

**Table 1 – Demographics, clinical data, and functional parameters before and after 6 Months of CRT**

| **Demographic and clinical data n-9 subjects** | | |
|---|---|---|
| Male / Female | 3 M / **6** F | _ |
| Age (years) | 64 ± 8 | _ |
| Weight (Kg) | 74 ± 21 | _ |
| Height (cm) | 163 ± 10 | _ |
| Body Mass Index $m^2$/kg | 26.7 ± 1.45 | _ |
| Ethnicity (CAU. / AFD) | (2/6) | _ |
| NYHA III | 9 | _ |
| **Baseline and 6 Months before and After CRT** | | ***p* value** |
| LVEF (%) | 28±3 / 34±4.7 | < 0.001 |
| VSF (ml) | 206±76 /158±96 | = 0.04 |
| VDF (ml) | 293±107/ 231±112 | = 0.02 |
| 6MWD | 349±81 / 393±70 | < 0.001 |
| MIP (cm/$H_2O$) | 40±15 / 51 ± 13 | < 0.01 |
| MEP (cm/$H_2O$) | 47±21 / 63 ± 20 | < 0.05 |
| PEF (L/min) | 282±98 /384±101 | < 0.03 |
| $VO_2$ (estimated) | 6.8±3.2 / 7.7±3 | < 0.001 |

**M: male; F: female; Kg: kilogram; cm: centimeter; m: meters; 6MWT: six-minute walk test; MIP: maximal inspiratory pressure; cm/H2O: centimeters of water; EPF: peak expiratory flow; L/min: liters per minute; CAU: caucasian; AFD: afro-descendants; LVEF: left ventricular ejection fraction; 6MWD: six-minute walk distance graph.**

### Maximal inspiratory pressure

Figure 1: Significant improvement was observed in the values. Before CRT, the MIP was 40±15 cm$H_2O$, while six months after the CRT implant, the MIP was 51±13 cm$H_2O$, ($p < 0.01$).

### Peak expiratory flow

Figure 1: six months after CRT implant, there was an improvement in the EPF, before CRT was 282±98 L/min and after CRT was 384±101 L/min , ($p < 0.03$).

## Discussion

This original study tested a hypothesis that CRT could determine an improvement in exercise tolerance in patients with HF, undergoing the six-minute walk test, in the strength of the respiratory muscles and PEF. Our results showed an increase in exercise tolerance through the six-minute walk test, MIP, and PEF. After the CRT, an improvement was found in the strength of the patients' respiratory muscles, which can be assessed through exercise tolerance. Significant improvement after CRT in respiratory efforts could be determine by exercise tolerance due an increase in respiratory muscle strength. According to our results, CRT provides clinical benefits to HF patients because of peripheral and respiratory muscle improvement, determining a significant increase of 24% from the MIP. This is the first study to show these CRT benefits in cardiorespiratory physiology or function.

The reduction of MIP is associated with a reduction in exercise tolerance, increased cardiovascular activity , and overall mortality[10]. Some authors suggest that respiratory muscle training improves MIP, provides better exercise tolerance, and reduces hospital admissions.[7] Our results showed that inspiratory muscle strength can also be improved by CRT. This improvement may well be associated with increased cardiac output associated with CRT. Another possible explanation is a better distribution of cardiac output, as is observed after muscle training, in

patients with CHF and inspiratory muscle weakness, inspiratory muscle loading results in a marked reduction of blood flow to resting and exercising limbs. Inspiratory muscle training improves limb blood flow under inspiratory loading in these patients.[8] This fact could explain the improvement in 6MWT and the inspiratory muscle force due to the improvement of the cardiac output by CRT[4].

Few studies mention a significant improvement in MEP, such as the study by Forgiarini et al. In our study, as in the case of Forgiarini, there was also a significant increase in MEP, most likely due to an improvement in cardiac output distribution as a consequence of improvement in the central hemodynamic response.[9]

Dyspnea is a common subjective outcome variable measured in several clinical trials. The present study shows that PEF improvement in the subsequent 24h in acute HF.[10] Our study, showed a significant increase in PEF values after 6 months of CRT therapy, showing a relevant chronic effect. We founded that have a significant moderate correlation with respiratory muscle strength in this group suggesting an association of MIP with both DP6M and VO2 calculated by DP6M.

Limitation: Our sample is still small, but the results are very consistent with the +clinical improvement observed after CRT implantation. More patients are being recruited in order to expand these observations and to analyze different factors that could influence these results.

## Conclusion

The present study found a statistically significant improvement after CRT in maximal inspiratory pressure, peak expiratory flow, and exercise tolerance. The new findings of improved cardiovascular function after CRT could be associated with a better cardiac output determined by reverse remodeling. More studies are warranted to demonstrate the magnitude of these findings.

## Author contributions

Conception and design of the research: Alves CR, Chermont SSMC, Reis CW, Nascimento EA, Mesquita ET, Mesquita CT. Acquisition of data: Alves CR, Chermont SSMC, Reis CW, Nascimento EA, Ribeiro ML, Ribeiro F, Mesquita ET, Mesquita CT. Analysis and interpretation of the data: Alves CR, Chermont SSMC, Reis CW, Nascimento EA, Ribeiro ML, Ribeiro F, Mesquita ET, Mesquita CT. Statistical analysis: Chermont SSMC. Writing of the manuscript: Alves CR. Critical revision of the manuscript for intellectual content: Chermont SSMC, Mesquita CT.

### 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 Universitário Antonio Pedro under the protocol number 884.844. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consente was obtained from all participants included in the study.

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# ERRATUM

## Int J Cardiovasc Sci. 2022 Issue vol 33(2), pages 175-184.

In Original Article “Predictors of Post-Discharge 30-Day Hospital Readmission in Decompensated Heart Failure Patients”, with DOI number: https://doi.org/10.36660/ijcs.20180088, published in International Journal of Cardiovascular Science, 33(2) in page 175-84. Correct the author’s name “Wayner Viera de Souza” to “Wayner Vieira de Souza”.

## Int J Cardiovasc Sci. 2022 Issue vol 35(5), pages 676-680.

In Case Report “Pacemaker Implantation without Fluoroscopy and Guided by Anatomical Mapping”, with DOI number: https://doi.org/10.36660/ijcs.20210005, published in International Journal of Cardiovascular Science, 35(5) in page 676-680. Correct, in the 4th paragraph, the phrase: "The patient was sedated, using propofol, and both the right groin as well as the left pectoral region were ??? and draped using alcoholic chlorhexidine." to "The patient was sedated, using propofol, and both the right groin as well as the left pectoral region were draped using alcoholic chlorhexidine."

DOI: https://doi.org/10.36660/ijcs.20220133