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Cardiac resynchronization therapy adjustment during the cardiopulmonary testing: study protocol

Kelly Christine Stutz*; Paulo de Tarso Jorge Medeiros, Hugo Bellotti Lopes, Marcos Vinicius de Oliveira Montesi, Carlos Alberto Cordeiro Hossri, Renata Mirelli de Melo Viana, Marilia Amorim Souza Leão.

Instituto Dante Pazzanese de Cardiologia – São Paulo – SP

ABSTRACT

Background: Cardiac resynchronization therapy is known to promote symptom improvement, increased survival, and decreased hospitalizations for heart failure. However, one third of patients on cardiac resynchronization therapy may not achieve any clinical improvement. One of the factors for the lack of improvement is an inadequate adjustment of the cardiac device programming, because such adjustments are commonly made at rest. Cardiac resynchronization therapy optimization can be done by adjusting the cardiac resynchronizer during cardiopulmonary exercise testing, this allow the program to align with the functional class of the patient, thus maintaining atrioventricular synchronism and biventricular pacing according to the chronotropic response to effort. However, there is a lack of protocols that propose device adjustment through cardiopulmonary exercise testing and that evaluate the response to its readjustment. **Objective:** To develop a cardiac resynchronizer readjustment protocol using cardiopulmonary exercise testing. **Methods:** This was a randomized controlled clinical trial to evaluate the effectiveness of device readjustment during maximal exercise. The variables used to measure the degree of response to readjustment will be: Functional capacity by the six-minute walk test, life quality by means of the Minessota questionnaire and sleep quality by means of the pittsburg. Participants will be divided into two groups (control and intervention group), then, the six-minute walk test will be applied, followed by life quality and sleep evaluation. The cardiopulmonary test will be the last proposed activity and will not be performed on the same day as the other evaluations. After three months, they will be submitted again to the same testes mentioned previously. During the initial evaluation by cardiopulmonary testing, the components of the intervention group will undergo cardiac resynchronization readjustment by means of a protocol. **Results:** We hope that the intervention designed by the protocol can contribute to the improvement of functional capacity, quality of life and sleep.

Keywords: Cardiac resynchronization; Biventricular pacing; Dyssynchrony; Cardiopulmonary exercise testing; Heart failure.

BACKGROUND

Cardiac resynchronization therapy (CRT) is a therapeutic strategy for heart failure (HF) patients with reduced left ventricular ejection fraction (LVEF) and refractory cardiac dyssynchrony[1,2]. CRT improves symptoms, reduces HF hospitalizations, and increases survival rates in these patients[1, 3].

Approximately one-third of patients may not achieve any improvement in their clinical status even after initiation of treatment. Many factors may generate an inappropriate response to CRT, among them an inadequate adjustment of the cardiac device programming, because these adjustments are usually made at rest [1,3].

The optimization of CRT can be done by adjusting the cardiac resynchronizer (CR) during effort[1,4]. The cardiopulmonary exercise test (CPET) is a maximum test that allows assessing the capture of biventricular pacing during effort, maintaining atrioventricular synchronism, maintaining biventricular pacing according to the patient's chronotropic response to effort, through the maximum heart rate (HRmax) and the pacemaker atrial refractory period (APR)[1,3]. These adjustments allow the CR programming to be aligned with the patient's functional class (FC) and, therefore, with the patient's daily activities to maintain quality of life[4].

It is known that individuals with HF suffer changes in functional capacity, quality of life and quality of sleep, even after starting CRT[4, 5]. The six-minute walk test (6MWT) is a submaximal exercise test that accurately reflects the ADL limitations[6]. Quality of life can be assessed by the Minnesota Living with Heart Failure Questionnaire (MLHFQ), which is the most widely used and validated questionnaire to assess life quality specifically in HF[7]. Sleep disorders are closely related to depression, anxiety, psychological disorders and poorer physical function, and are frequently found in these individuals. The Pittsburgh Sleep Quality Index (PSQI) is a questionnaire that assesses sleep quality and is often used in individuals with HF[8].

Although CRT optimization is proposed during effort, there is still a gap in literature about protocols that perform readjustment of the device through the treadmill CPET. Thus, the aim of this study is to create a protocol that evaluates the improvement of the cardiac device after its readjustment during CPET, through functional capacity, quality of life and quality of sleep.

***Corresponding author:** Kelly Christine Stutz**; Email:** kelly.stutz@dantepazzanese.org.br

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METHODS

This is a randomized, controlled, single blind study. This is a randomized controlled clinical trial protocol with patients on CRT for at least three months. It will be conducted with volunteers being followed-up in the pacemaker clinic of the Instituto Dante Pazzanese de Cardiologia.

Inclusion Criteria

Volunteers of both genders, aged 18 years or older, diagnosed with HF in CRT for at least three months, and with a device working at full capacity will be included in the study. Volunteers must be clinically stable and agree to the informed consent form.

Exclusion criteria

Clinically unstable individuals, those in atrial fibrillation (AF) rhythm, those with any osteo-neuro-muscular comorbidity that may interfere with the performance of the proposed activities, the ones diagnosed severe lung disease, those performing regular physical activity, those with malnutrition, evidenced by a body mass index (BMI) < 20 kg/m2, or who do not understand the proposed interventions and assessments will be excluded from the study.

Variables and components evaluation

Characterization of the sample: Initially, participants identification data will be collected, such as full name, age, height, gender, etiology of HF, LVEF, CRT time, FC, baseline heart rhythm, types of cardiac devices, presence or absence of sinus node disease, percentage of previous ventricular pacing and previous diseases.

Cardiopulmonary test: The CPET will be performed indoors, with good lighting, adequate temperature and relative humidity. Individuals will undergo maximal effort on a treadmill using the ramp protocol[9, 10]. The CPET will be performed under a ramp protocol, individualized according to the age, gender, clinical evaluation, and objective answers of each participant's walking ability. During the evaluation, electrocardiographic records will be collected from each individual[9]. Volunteers will be instructed to take their usual medication, fast for two hours, avoid food and drinks containing caffeine, cigarettes, and exercise on the test day. The exercise stress test will be preceded by two minutes of rest with the subject standing on an ergometric treadmill (Inbramed Master ATL). To collect ventilatory and metabolic data during the TCPE, patients will wear a Neoprene or Hans-Hudolph orofacial mask. Then, a three-minute warm-up will be performed, succeeded by the incremental period with the proposed protocol[9, 10]. The sensation of the degree of effort will be quantified using the Borg scale for the perception of fatigue and dyspnea, and HR and peripheral oxygen saturation (SpO2) will be recorded continuously and blood pressure every two minutes during the test, at the end of the test (peak), and at the 1st, 2nd, 4th, and 6th minutes of the recovery phase. The interruption of the CPET will be for limiting signs and symptoms according to the III Brazilian Guideline on Exercise Tests. All evaluations will be performed under the supervision of cardiologists trained in ergometry and advanced life support[9].

The variables analyzed in the CPET will be Maximal oxygen consumption (VO2 max or peak), percentage of predicted VO2 max, percentage of VO2 at anaerobic threshold, ventilatory power, (SBP x VE/VCO2 slope), circulatory power (SBP x VO2max), optimal respiratory compensation point (POC, lowest VE/VO2), oxygen pulse (VO2/FC), OUES (Oxygen Uptake Efficency Slope) and the presence of periodic ventilation[11].

Six-minute walk test: It will be performed following the Guidelines of the American Thoracic Society in a 30-meter runner[12]. At the beginning of the course blood pressure (BP) will be measured with a sphygmomanometer (Tycos®), HR and SpO2 with Nonin® oximeter and grading of perceived exertion using the modified Borg scale[12,13]. At the end of the test, the distance walked will be measured, repeating the cardiac monitoring, pulse oximetry and Borg scale. The test will be performed under the guidance and control of the same physical therapist[12, 13].

Quality of life questionnaire: The MLHFQ questionnaire will be applied, which was translated and validated for the Portuguese language following all the standards required by the expert committee[7]. The MLHFQ is composed of 21 self-administered items, with the overall score based on the physical and emotional dimensions of how HF affects the lives of these individuals. Items are scored individually from zero to five, with a higher score representing more significant impairment in disease-specific quality of life[7]. The MLHFQ questionnaire is widely used and validated to assess quality of life specifically in heart failure[7].

Sleep quality questionnaire: To assess sleep quality the PSQI will be used. This questionnaire is validated in the Portuguese language, reproducible and sensitive[14]. The PSQI consists of 19 self-administered questions and five questions directed to the room attendant, being used only for clinical practice, not contributing to the total score of the index[14,15]. This evaluative instrument is

divided into seven categories (subjective sleep quality, sleep latency, sleep duration, usual sleep efficiency, sleep disturbances, use of sleep medications, and daytime sleep dysfunction), which are scored in scores ranging from 0 to 3 points, with higher scores representing worse sleep quality. The overall PSQI score ranges from 0 to 21 points, considering that the higher the total score value, the worse the sleep quality of the participants[14, 15].

Groups: After randomization, which will be done by software, through the website (https://www.random.org/) to guarantee the secrecy and randomness of the sample, the patients will be allocated to the control or intervention group.

Control group: They will be submitted to functional capacity evaluation using the 6MWT, quality of life using the MLHFQ and quality of sleep using the PSQI questionnaire. The evaluation of maximal effort will be done by the TCPE. After three months they will be submitted again to functional capacity evaluation, quality of life, quality of sleep and the TCPE. The TCPE will not be performed on the same day as the other proposed activities, to avoid fatigue of the individuals.

Intervention group: They will be submitted to functional capacity evaluation using the 6MWT, quality of life using the MLHFQ and quality of sleep using the PSQI questionnaire. The evaluation of maximal effort will be done by the TCPE. After three months they will be submitted again to functional capacity evaluation, quality of life, quality of sleep and the TCPE. The TCPE will not be performed on the same day as the other proposed activities, to avoid fatigue During the initial evaluation by the CPET, patients will undergo CR adjustments by means of a protocol.

Cardiac resynchronizer adjustment protocol: Evaluation of atrial ventricular (AV) interval and biventricular capture during rest, exertion and recovery phase of the TCPE through electrocardiogram and telemetry of the device. After this assessment, the CR will be programmed with the goal of ensuring biventricular capture in all phases of exercise, with progressive reduction of the AV interval with increasing sinus rate and optimization of the intraventricular (IV) interval, aiming to reduce the QRS complex as needed. As with the TCPE the RC adjustment will be performed by the medical electrophysiology specialist team.

Ethical Aspects

The research project will be sent to the Ethics Committee on Research involving Human Beings of the Dante Pazzanese Institute of Cardiology according to resolution 196/96 of the National Health Council (CNS) and all patients must consent and sign the Informed Consent Form (ICF) for participation in the study.

Data Analysis

Data normality will be assessed by the Shapiro-Wilk test and data will be expressed as mean and standard deviation when they present a Gaussian distribution, or median and interquartile range when they do not present an asymmetric distribution.

The comparison between the tests, when in pairs, will be performed by paired Student's t test or Mann-Whitney test, depending on their distribution.

The correlation between the CR values and the other variables will be performed by the Pearson or Spearman correlation test, depending on the distribution of the data.

SPSS® version 22 software will be used to perform the statistical analyses with a significance level of $p < 0.05$.

Sample Calculation

The calculation to define the sample size was performed using the program G*Power 3.1.9.4, adopting as alpha error = 0.05 and beta error = 0.80. The outcome variable used for calculation was VO2 (ml/kg/min) at peak exercise. To answer the clinical question of the study the necessary sample will consist of 30 patients, 15 for each group[16].

DISCUSSION

This paper provides a detailed description of a randomized and controled clinical trial to determine the impact of the cardiac resynchronization adjustment during the cardiopulmonary testing protocol on functional capacity, quality of life and sleep.

Trial status: Patients are being recruited at the time of submission.

Competing interests: Nothing to declare.

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