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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.

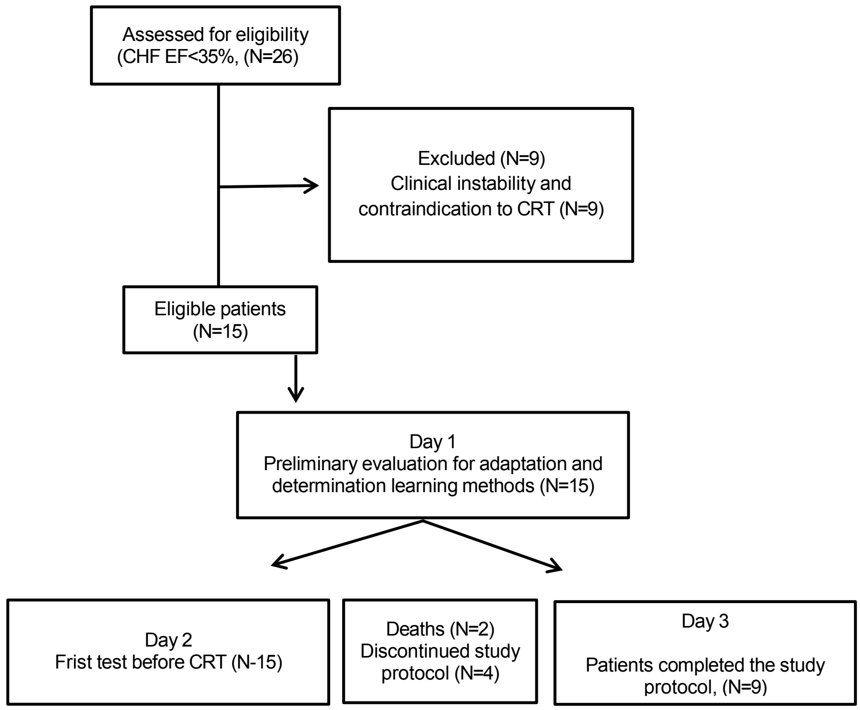

Chart 1 – Patient's demographic characteristics and functional parameters before and after 6 months of C are shown in Table 1. Medication included angiotensin converting enzyme inhibitors (n=8), diuretics (n=8), and β – blockers (n=9).

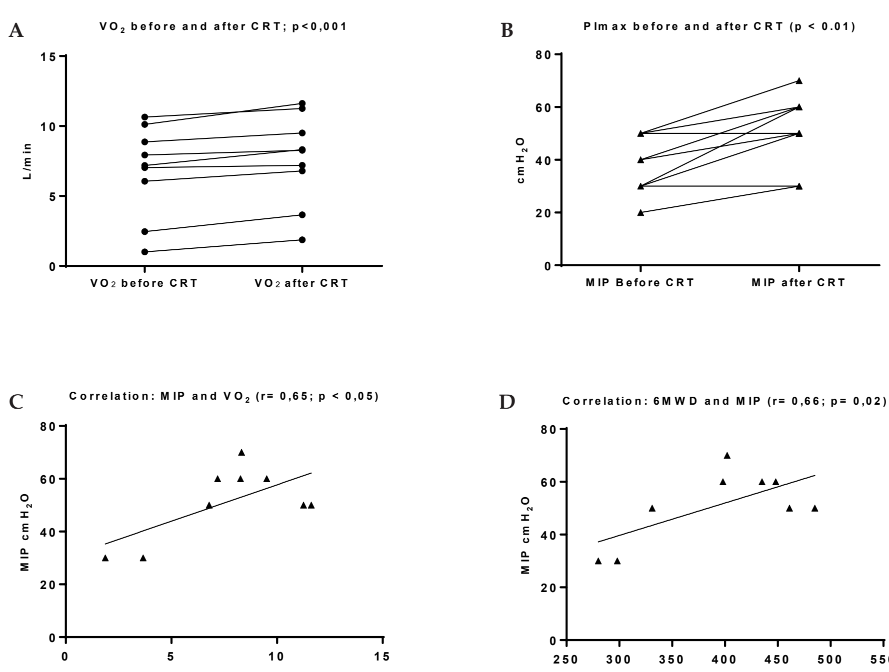

Figure 1 – a: Peak oxygen before and after cardiac resynchronization therapy during; b: MIP before and after CRT; c: Correlation between maximal inspiratory ressure and Peak oxygen after CRT; d: Correlation between maximal inspiratory pressure and six-minute walk distance.

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 cmH_2O, while six months after the CRT implant, the MIP was 51±13 cmH_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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