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Optimizing patient selection for Cardiac Resynchronization Therapy: The role of cardiopulmonary exercise testing

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List of abbreviations

ACC: American College of Cardiology

AHA: American Heart Association

AV: atrial ventricular

BMI: body mass index

Bpm: beats per minute

CARE-HF: cardiac resynchronization-heart failure

CHF: chronic heart failure

COMPANION: comparison of medical therapy pacing and defibrillation in heart failure

CPET: cardiopulmonary exercise testing

CRT: cardiac resynchronization therapy

CRT-P: cardiac resynchronization therapy pacemaker

DHF: diastolic heart failure

HF: heart failure

HR: heart rate

ICD: implantable cardioverter defibrillator

LBBB: left bundle branch block

LV: left ventricular

LVEF: left ventricular ejection fraction

LVESV: left ventricular end systolic volume

MIRACLE: multicenter insync randomized clinical evaluation

MUSTIC: multisite simulation in cardiomyopathies

NASPE: North American Society for Pacing and Electrophysiology

NYHA class: New York Heart Association class

RER: respiratory exchange ratio

SBP: systolic blood pressure

SCD: sudden cardiac death

SHF: systolic heart failure

VAT: ventilator anaerobic threshold

VE/VCO_2: volume of expired gas to carbon dioxide production

VO_2: oxygen consumption

VO_{2peak}: peak oxygen consumption

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1. ABSTRACT

Background: Cardiac resynchronization therapy (CRT) is an established treatment modality for moderate to severe heart failure (HF) but 30–40% of patients treated with CRT do not experience clinical improvement. **Purpose:** the aim of this study was to identify predictors of response to CRT, in two different definitions of responders, by using the cardiopulmonary exercise testing (CPET) before CRT implantation. In definition A, responders were defined as ≥15% improvement in left ventricular ejection fraction (LVEF); in definition B combined parameters were defined as ≥5% improvement in LVEF and ≤1 level NYHA classification. **Methods:** this is a prospective observational study of 15 HF patients undergoing CRT. Clinical CPET and echocardiography assessment using standard methods were performed at baseline and 5 months. **Results:** the number of patients classified as responders in definition A was 9 (60%) and 6 (40%) as non-responders; the number of responders in definition B was 11 (73.3%) and 4 (26.7%) as non-responders at 5 months after CRT. The responders according to definition A did not present any statistically significant difference. According to definition B, the heart rate (HR) response during CPET was higher in non-responders: HR peak (157±13bpm *vs*. 118±18bpm, $p<0.05$) and HR recovery at minute 3 (54±13bpm *vs.* 31 ± 14bpm, $p<0.05$). Overall, the responders were older (68±9years *vs*. 55±9years, $p<0.05$). **Conclusions:** baseline measurements of CPET may be utilized to identify patients that benefit from CRT. The use of combined criteria is a better predictor than LVEF alone.

KEY WORDS: HEART FAILURE, CARDIAC RESYNCHRONIZATION THERAPY, RESPONDERS, PROGNOSIS, CARDIOPULMONARY EXERCISE TESTING, EXERCISE CAPACITY, OXYGEN UPTAKE, HEART RATE RESPONSE, VENTILATORY THRESHOLD, SLOPE OF THE VENTILATORY RESPONSE

2. THEME'S PRESENTATION

2.1 INTRODUCTION

Approximately 1–2% of the adult population in the western world has heart failure (HF), with the prevalence increasing sharply from 1% in 40-year-old individuals to 10% above the age of 75 years[1]. There are many causes of HF, and these vary in different parts of the world. The overall prevalence of HF in Portugal was slightly higher than other European studies[2]. The HF prevalence increases markedly with age in both sexes and tends to be slightly higher in men up to the age of 70. In women, it continues to increase with age and becomes greater than the prevalence for men in the age group of 70–79 years old[3].

HF is the leading cause of death and hospitalization in most Western countries in patients over 65 years of age[4]. In recent years, cardiac pacemakers have been modified in an effort to correct ventricular dyssynchrony. This treatment is referred to as cardiac resynchronization therapy (CRT).

CRT has been used extensively over the last years in the therapeutic management of patients with end-stage HF[5]. The CRT, delivered via atrial-synchronous biventricular pacing, has emerged as an effective treatment for moderate-to-severe HF patients with ventricular dyssynchrony. At present, the selection criteria include moderate to severe HF (New York Heart Association functional class III or IV), left ventricular ejection fraction ≤ 35%, and wide QRS complex (>120 ms)[5]. However, current guidelines do not adequately identify responders to CRT; approximately 30% to 40% of patients treated with CRT do not respond or improve with treatment[6]. The identification of non responders to CRT may be also of clinical interest. This therapy requires high costs and has potential related complications that may be avoided in patients who will not, for an instance, have clinical benefit[7].

Predicting whether a patient will benefit, or respond, to CRT has been the focus of more than 500 publications during the last 5 years. However, the definition of responder to CRT varies widely between studies, and numerous criteria to define a positive response to CRT exist in the literature[6, 8].

Improvement in clinical end points (symptoms, exercise and functional capacities, quality of life) and echocardiography end points (systolic function, left ventricular size, mitral regurgitation) have been reported after CRT, with a reduction in hospitalizations for decompensated HF and an improvement in survival[5, 7, 9-16]. However, detailed analysis of improvement in functional capacity after CRT is still lacking[12].

Cardiopulmonary exercise testing (CPET) with respiratory gas analyses is a standardized approach for objectively documenting functional capacity[17] that provides noninvasive objective measures for cardiopulmonary reserve and is thus suitable for evaluation, risk stratification and control of treatment effects[18].

Peak oxygen consumption (VO_{2peak}) measured during maximal exercise testing provides an objective assessment of functional capacity in patients with HF and an indirect assessment of cardiovascular reserve. Previous studies have suggested that this measurement is a good short-term predictor of mortality[19].

Mancini *et al.*[19], Stelken *et al.*[20] and others observational studies[21, 22] have demonstrated that the short-term prognosis of patients with a $VO_{2peak} \leq 14$ kg/ml/min is markedly impaired compared with heart transplant patients followed up for a similar duration.

Patients with a baseline $VO_{2peak} < 14$ ml/kg/min regularly benefit from CRT during the first year of treatment[23]. These findings have not yet been included in the current Guidelines for the Implantation of Permanent Pacemakers by the ACC/AHA/ NASPE[24], while the German “Statement on cardiac resynchronization”[25] already recommends a baseline $VO_{2peak} < 14$ ml/kg/min as one criterion to indicate CRT.

2.2 OBJECTIVES’ OF THE STUDY

The aim of this study was to identify predictors of response to CRT, in two different definitions of responders, by using the CPET before CRT implantation.

The secondary aim of this study was to evaluate VO_{2peak}, VE/VCO_2 slope, HR response, anaerobic threshold, NYHA class symptom and LVEF, immediately before and 5 months after CRT implantation, to study the

ventilatory and haemodynamic response evolution and to assess improvement in functional and echocardiography variables.

In this study, the criteria used to define responders to CRT will be considered according to 2 different ways found in the literature review. The first way of defining responders is based on echocardiography, through the increase of LVEF ≥ 15%[26, 27]. The second way combines echocardiography and clinical setting, through the increase of LVEF ≥ 5% and decrease of NYHA ≥ 1, respectively[28].

The relevance of this study is to have reproducible inclusion criteria parameters that are crucial for a reliable evaluation of the CRT response. Considering the high costs and non responder rates of about one-third of the patients, a careful selection of patients prior to CRT is crucial.

This document is composed by five chapters; each chapter will have a short introduction that explains the theme in question. The theme's presentation (2) is a brief description of the state of knowledge of the main theme. The emerging of some questionable issues justifies the purpose and objectives of the present study and also the study's limitation. The literature review (3) comes to specify the theoretical background followed by the methodology section (4) that describes all the steps of this study, from the sample selection and the instruments used to collect data to the statistical analysis. The results and discussion are considered together for better critical analysis and evaluation of the different variables. In the same chapter, it will be presented the future research perspectives. The last chapter (6), contains the conclusions of this study.

2.3 LIMITATIONS

The following limitations were considered:

1. Small study sample size, limited power to detect significant differences in the studied parameters.
2. Peak SBP measurements during exercise are also influenced by technique and sampling frequency. Vasodilator drug therapy may also limit exercise SBP response. In the present study, not all

antihypertensive drug therapy data was collected at the time of exercise testing.

3. The fact that these patients have skeletal muscle pathology as a major contributor to exercise intolerance, fatigue, and exertional dyspnea in chronic heart failure, restricts the clinical value of the variables of the CPET, like VAT and VO_2/VCO_2 slope.
4. In most patients only one baseline exercise test was performed, and an improvement in exercise time and VO_2 may occur with familiarization of the technique[29]. Other potential limitations of VO_{2peak} also must be considered.
5. There are many different methods to define a positive response to CRT in the literature and poor agreement was found amongst them. Nevertheless, in this study two criteria to assess different types of responders were considered. For the reasons previously mentioned, a question can be formulated for continuing the research work to find an answer: which method should be used in the future to determine whether a patient could benefit or not from CRT?

3 LITERATURE REVIEW

3.1 HEART FAILURE

Chronic heart failure (CHF) is a clinical syndrome resulting from a structural or functional cardiac disorder and it could be defined by systolic dysfunction, diastolic dysfunction, or both which usually involves an assessment of the patient's ejection fraction[30]. It usually begins after an initial event that produces a decline in pumping capacity of the ventricle. This syndrome manifests primarily as dyspnea, fatigue, fluid retention, such as pulmonary congestion or ankle swelling, and decreased exercise tolerance[31].

Systolic dysfunction and diastolic dysfunction, both describe an abnormal mechanical property, while systolic heart failure (SHF) and diastolic heart failure (DHF) describe a clinical syndrome[30].

The SHF reflects a fundamental weakness of the pump and thus the inability to deliver sufficient cardiac output at an adequate mean arterial pressure. The failing heart often exhibits both major decrements in resting systolic function and also limitations of systolic reserve required for individuals to perform normal activities of daily living and exercise. The systolic dysfunction refers to impaired ventricular contractions due to the loss of myocardium secondary to myocardial infarction or loss of contractility, and the underlying mechanisms are numerous. Patients with HF and a low left ventricular ejection fraction (LVEF), usually < 40–45%, are classified as having systolic dysfunction[15, 30].

In contrast, in patients with DHF, the dysfunction occurs when the ventricular chamber is unable to accept an adequate volume of blood during diastole and the sufficient volumes to maintain an appropriate stroke volume at rest and during exercise. The functional abnormalities leading to DHF includes abnormal ventricular relaxation and filling, decreased LV suction, and/or an increase in ventricular stiffness. Diastolic dysfunction refers to a condition in which abnormalities in mechanical function are present during diastole. It is characterized by an increased resistance to the filling of one or both ventricles, elevated diastolic pressure in the ventricles, and reduced ventricular compliance. Patients with symptoms and exam findings consistent with HF, but with a preserved ejection fraction are often said to have diastolic dysfunction[4,32].

The demographic characteristics present in patients with DHF differ significantly from those with SHF. Patients with DHF are older, often female, have hypertensive heart disease, and are less likely to have ischemic heart disease compared to patients with SHF. Diastolic dysfunction is estimated to be the principal etiology in 40% or more of the estimated 500.000 new cases of HF each year[30].

HF is a final common pathway of all diseases of the heart and is a major cause of morbidity and mortality. It is a complex syndrome with numerous risk factors and determinants of outcomes. Approximately 4.9 million Americans carry the diagnosis of HF[33] and about 550.000 new cases occur each year in the USA[34]. Reports from several countries suggest that approximately 1–2% of the total healthcare budget is spent on the management of HF[35].

In Portugal the overall prevalence of HF was markedly higher than other European studies and increases sharply with age[2]. HF with LV systolic dysfunction is more frequent in males below the age of 80 years and with preserved LV systolic function affects mainly older females[3].

HF remains a large medical and epidemiological problem[31], and the number of HF hospitalizations has risen more than a million per year over the past decade, accounting for at least 20% of all admissions for persons older than 65 years[16].

At the cellular level, is caused by changes in the biology of the cardiac myocyte together with a progressive loss of cardiac myocytes. The loss of myocytes may be focal (e.g., myocardial infarction), or diffuse (e.g., viral infection, hemodynamic overload, genetic abnormalities).

Thus HF is the common clinical syndrome caused by any of a diverse group of injurious stimuli sufficient to produce myocardial insufficiency[36]. Abnormal impulse generation and propagation is frequently observed in these patients. Both functional and structural alterations (cardiac remodeling) are responsible for such abnormalities[32].

Cardiac remodeling commonly refers to persistent changes in the properties of myocardium in response to abnormal external stresses. Although most notably cardiac remodeling occurs in the setting of structural heart diseases such as myocardial infarction, hypertrophy, and HF, it may also occur in the absence of anatomic dysfunction, as is the case during abrupt changes in heart

rate and/or activation sequence. Indeed, remodeling is a prominent feature of atrial fibrillation and flutter, ventricular pacing or intrinsic conduction delays and sustained tachycardia[32].

Left bundle branch block (LBBB) results from block or conduction delays in any of several sites of the left-sided intraventricular conduction system, including the main left bundle branch or its subdivisions or, less commonly, within the fibers of the distal His bundle. The result is an abnormal and slow pattern of electrical activation within the LV due to conduction through the working myocardium.

LBBB usually appears in patients with underlying heart diseases, typically in patients with dilated cardiomyopathy of any etiology[32].

It has long been recognized that discoordinate cardiac contraction itself reduces the systolic performance of the chamber, and recent developments in therapies to resynchronize contractions have shown this to be a valuable target for HF treatment. Conduction disease at or above the atrial ventricular (AV) node affects chronotropic competence and effective preload (and left atrial pressure). Both short and excessively long AV delays the reducing of net LV filling. LBBB induces discoordinate contraction. Cardiac discoordination induced by LBBB or right ventricular pacing depresses systolic function, increasing the end-systolic volumes at a given pressure, prolongs isovolumic relaxation, and has been coupled to the widening of the QRS complex.

Significant progress has been made to identify the major risk factors and the population patterns of HF and associated trends. However the prognosis remains poor, with mortality data comparable with data from the worst forms of malignant disease. Therefore, it deserves adequate planning for investigation, education, prevention and treatment.

3.2 CARDIAC RESYNCHRONIZATION THERAPY

CRT improves HF outcomes[37] and has been used extensively over the last years in the therapeutic management of patients with end-stage HF[5].

Approximately 40 years ago, the first descriptions of the short-term haemodynamic effects of left or of simultaneous right and left ventricular stimulation were published[38-40]. Cardiac pacing as an adjunct therapy for HF

began to be the subject of scientific research at the start of the 1990's. The CRT began in 1994, when Cazeau *et al.*[41], in France, and Bakker *et al.*[42], in Netherlands, described the first cases of atrio-biventricular pacemakers implanted in patients with severe CHF and no conventional indication for cardiac pacing.

CRT is an effective treatment for patients with moderate to severe HF and LV systolic dysfunction if they have a prolonged QRS interval on the surface electrocardiogram suggesting cardiac dyssynchrony[43, 44]. It aims providing hemodynamic benefit by correcting an electrical disturbance.

Both atrioventricular and intraventricular conduction delays further aggravate LV dysfunction in patients with underlying cardiomyopathies. Notably, as mentioned previously, LBBB alters the sequence of LV contraction, causing wall segments to contract early or late, with redistribution of myocardial blood flow, non-uniform regional myocardial metabolism, and changes in regional molecular processes[45].

Intraventricular dyssynchrony seems to represent a pathophysiological process that directly depresses ventricular function, causes LV remodeling and CHF. Consequently, it causes a higher risk of morbidity and mortality. Such dyssynchrony is apparent on the electrocardiogram as a QRS interval lasting more than 120 miliseconds. Some studies have proposed that this intraventricular conduction delay may further impair the ability of the failing heart to eject blood (shortening of LV filling) and may thus enhance the severity of regurgitant flow through the mitral valve[11, 46].

The clinical effects of long-term CRT have been evaluated in a large number of randomized multi-centre trials with crossover or parallel treatment assignment [47-53] using CRT pacemakers (CRT-P) or CRT in combination with implantable cardioverter defibrillator (ICD) therapy (CRT-D). However, there are some unresolved issues for this device selection, namely whether CRT-D is better to reduce risk of death than CRT alone.

CRT-P is a therapy that differs from the classical cardiac pacing, as: 1) all CRT patients have advanced HF; 2) the rationale of atrio-biventricular pacing is electromechanical resynchronization and not correction of bradycardia (most of the patients do not have conventional pacing indications); 3) the devices are

more sophisticated, with an additional lead; and 4) a significant number of the patients have an ICD indication[46].

The typical CRT patient is a high-risk patient with an increased risk for sudden cardiac death (SCD) that is significantly reduced[54] but probably not optimally prevented by CRT alone. Three randomized, prospective, controlled trials have shown the efficacy of the stand-alone ICD in the primary prevention of SCD in patients with a history of previous myocardial infarction and depressed ejection fraction[55-57]. Two relevant randomized, controlled trials have demonstrated that HF patients with LV dysfunction treated with an ICD have a reduced risk of death, regardless of the aetiology[52, 58].

There has been a substantial increase in implantation rates for CRT across Europe, although with marked differences amongst countries[59-61]. Meta-analyses were also published[9, 10, 62, 63], suggesting that the most efficacious option in patients with HF and LVEF would be a CRT-D.

Therefore, it is strongly recommended that the choice of the most appropriate device (whether CRT-P or CRT-D) for a patient be based upon careful evaluation of the following two considerations: first, the patient's expectation of survival, which, when considering an ICD, should exceed 1 year; and the second point, relates to health care logistical constraints and cost considerations.

Pacing in HF may be achieved by means of two different pacing modalities, biventricular pacing or LV pacing alone. Biventricular pacing has been extensively studied and most widely used but LV pacing may be acceptable in certain patients. Although indications for LV pacing must still be clearly defined, there is more evidence suggesting that applying LV pacing is comparable with the biventricular mode in selected HF patients presenting LBBB or echocardiographic evidence of significant mechanical delay at the level of the LV lateral wall[64-69]. In selected cases who present LBBB, conventional CRT indication, advanced age, and/or important comorbidities, without a bradycardiac indication for a pacemaker, in whom an improvement in quality of life is sought, it may be reasonable to consider LV pacing alone.

The development of devices that make use of atrial-synchronized biventricular pacing to coordinate right and left ventricular contraction have suggested, in recent studies, that short and long term CRT can improve cardiac

function, exercise capacity, functional class, VO_{2peak}, hemodynamic measures, and quality of life score[5, 7, 11-15]. It also reduces hospital readmissions and decreases mortality[10,13,14,37]. These benefits primarily occur due to an improvement in the central cardiovascular function of the heart.

A recent study, called CARE-HF (Cardiac Resynchronization-Heart Failure), has focused on the effect of CRT on morbidity and mortality in HF patients[53]. The conclusion was that CRT improves symptoms, the quality of life and reduces complications and the risk of death. It subsequently demonstrated a clear survival benefit after the CRT compared to optimized medical therapy.

A reduction in hospitalizations was observed in the Multisite Simulation in Cardiomyopathies (MUSTIC) and Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trials[47, 70].

The Comparison of Medical Therapy Pacing and Defibrillation in Heart Failure (COMPANION) trial demonstrated a reduction in the composite end point of all-cause mortality or hospitalization during the 16 months of follow-up[52].

Current guidelines do not adequately identify responders to CRT; approximately 30% to 40% of patients treated with CRT do not respond to treatment or improve subsequently. The definition of response to CRT varies widely between studies, and numerous criteria to define a positive response to CRT exist in the literature[6].

The response to CRT can be measured in terms of symptomatic response or clinical outcome, or both[71]. The symptomatic response is typically assessed by quantifying the change in left ventricular ejection fraction[26, 27, 72, 73] or left ventricular end systolic volume (LVESV)[73-75] 3 to 6 months after CRT implantation. The clinical response is assessed with the increase in the distance walked in 6 minutes[13] or improvement in New York Heart Association functional class (NYHA)[73, 76] 3 to 6 months after CRT implantation (table 1). Some studies have defined response to CRT as a combination of several clinical measures[72, 77, 78] or as a combination of both clinical and echocardiographic (symptomatic) measures[28].

Table 1: NYHA functional classification (Severity based on symptoms and physical activity)[31]

Class I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnea.
Class II	Slight limitation of physical activity. Confortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III	Marked limitation of physical activity. Confortable at rest, but less than ordinary activity results in fatigue, palpitation, or dyspnea.
Class IV	Unable to carry on any physical activity without discomfort. Symptoms at rest. If any physical activity is undertaken, discomfort is increased.

The lack of improvement with CRT can be due to many factors including the placement of the LV pacing lead in an inappropriate location, the absence of electrical conduction delay or mechanical dyssynchrony despite wide QRS complexes, and possibly failure to optimize the CRT settings after device implantation[79].

The reverse left ventricular remodeling or cardiac remodeling, as explained previously, has been demonstrated with drugs that are known to benefit patients with HF, such as angiotensin converting enzyme inhibitors and beta-blockers. Reductions in LVESV appears to be the most useful measure of reverse remodelling[80].

Reverse LV remodeling is a promising surrogate outcome measure for the CRT. Yu *et al.*[81] explored the value of reverse LV remodeling in discriminating prognostic responders and non responders to CRT in a study of 141 patients, in which a reduction in LVESV ≥ 9.5% 3 to 6 months post-implantation was identified as a predictor of all-cause (p = 0.0003) and cardiovascular (p < 0.0001) mortality.

This study has a specificity of 69%, which means that 31% of patients, that do not benefit prognostically, are wrongly classified as responders. Furthermore, in this study they found no relationship between reduction in LVESV and changes in NYHA class, 6 minute walk distance or quality of life score after CRT.

Likewise, Ypenburg *et al*.[82] found similar improvement in NYHA class, quality of life score, and 6 min walk distance in patients exhibiting ≥ 15%

reduction in LVESV compared with those exhibiting a reduction in LVESV of < 14%.

In a review, Foley *et al.* group numerous studies that have shown significant reduction in LVESV after CRT[71]. Such reductions are evident as early as 1 month post-implantation[83], and are sustained at 29 months[53].

Table 2: Seventeen Different Response Criteria Identified From the Fornwalt (2010) review[6]

Response Criteria	**Response Rate, %**
Echocardiographic	Echocardiographic
1. ↑ LVEF ≥ 5%[72, 73]	51
2. ↑ LVEF ≥ 15%[26, 27]	54
3. ↓LVESV ≥ 10% and did not die of progressive HF within 6 months [78, 84]	62
4. ↓LVESV > 15%[73-75, 85]	56
5. LVESV < 115% of baseline[86]	91
6. ↓ LVESVI > 15%[87]	
7. ↓LVEDV > 15%[73]	49
8. ↑Stroke volume ≥ 15%[27, 88, 89]	34
Clinical	Clinical
9. ↓NYHA ≥ 1 [73, 76, 90, 91]	71
10. ↓NYHA ≥ 1 and did not die of progressive HF within 6 months[92]	70
11. ↓NYHA ≥ 1 and ↑ 6MWD ≥25%[72]	33
12. ↓NYHA ≥ 1 and ↑ 6MWD ≥25% and did not die of progressive HF within 6 months[77, 78]	
13. ↑ 6MWD > 10% no heart transplant, did not die of progressive HF within 6 months[13]	32
14. (↓NYHA ≥ 1 or ↑VO_2max > 10% or ↑6MWD >10%) and alive, no hospitalization for decompensated HF[93]	61
15. Two of 3:[74]	
a. ↓NYHA ≥ 1	
b. ↑6 MWD ≥ 50m	63
c. ↓QOL ≥ 15	
16. Clinical composite score improved[75]	69
Combined	Combined
17. (↑LVEF ≥ 5% or ↑6MWD ≥ 30m) and (↓NYHA ≥1 or↓ QOL ≥ 10)[28]	71

↑ indicates increase; LVEF, left ventricular ejection fraction; ↓, decrease; HF, heart failure; LVESV, left ventricular end-systolic volume: LVESVI, LVESV indexed by body surface area; LVEDV, left ventricular end-diastolic volume; NYHA, New York Heart Association functional class; 6MWD, 6-minute walk distance; VO_2max, oxygen consumption at peak exercise, and QOL, quality-of-life score.

If the authors did not specify whether death was considered a nonresponse, then it was assumed that deaths were excluded.

Fornwalt *et al.*[6] collected seventeen different primary response criteria in the 26 most-cited publications on predicting response to CRT (table 2). Eight of these seventeen response criteria were based on echocardiography, eight were based on clinical measures, and one criterion was based on a combination of both echocardiographic and clinical measures. The percentage of patients defined as having a positive response to CRT ranged from 32% to 91% for the 15 response criteria.

The reasons for a lack of response to CRT are not well known[7, 13, 14, 37]. So far, better characterization of patients who will respond to CRT has been the main focus of ongoing research.

The identification of non responders to CRT may be also of interest. This therapy requires high costs and potential implantation related complications that may be avoided in patients who won't have clinical benefit. Current inclusion criteria may not be accurate enough to differentiate patients who will or will not respond to CRT. Other pathophysiologic factors such as HF etiology, LV dimensions and function, mitral regurgitation, LV dyssynchrony, position of LV pacing lead, and extent/location of myocardial scar have also shown to influence CRT response[7].

CRT was associated with increased total costs when compared with standard medical treatment. Over a mean follow-up of 29.6 months in CARE-HF[94], the mean €4316 overcost was mainly attributable to the device itself, with an estimated cost of €5825.

The mean incremental cost-effectiveness ratio per life year gained was €29 400[94] and $28 100[95] with CRT-P and $46 700 with CRT-D[95]. These data suggest that the clinical benefits of CRT are economically viable and can be achieved at a reasonable cost in most European countries.

Long-term treatment with CRT-P appears cost-effective compared with medical therapy alone. From a life-time perspective, assuming a reasonable life expectancy when receiving effective treatment for HF, CRT–D may also be considered cost-effective when compared with CRT-P and medical therapy[96].

The 2007 ESC/EHRA Guidelines for Cardiac Pacing[46], the 2008 ESC Heart Failure Guidelines[31], and the 2008 ACC/AHA/HRS Guidelines for Device Therapy[97] provide class I A recommendation for CRT treatment with or without

an ICD function in patients with QRS width ≥ 120 ms, LVEF ≤ 35% and NYHA functional class III and IV. Those are the current inclusion criteria for CRT.

ECG recording should be taken to know the PR interval, QRS duration and morphology, and underlying rhythm to choose the most appropriate device. There is strong evidence that patients with prolonged QRS duration (≥120/ ≥130 ms) show worse prognosis but the impact of QRS duration to predict response to CRT is still unclear[98].

Another important diagnostic tool is echocardiography evaluation for precise assessment of ventricular dimensions, presence of mitral regurgitation, the estimation of the LVEF (≤ 35%) and diagnosis of ventricular dyssynchrony. Lafitte *et al.*[99] concluded that a multiparametric echocardiographic strategy based on the association of conventional criteria is a better indicator of CRT response than the existing single parametric approaches. Nevertheless, many currently used echocardiographic parameters failed to improve responder identification. There is no consensus about which echocardiographic parameters may best determine baseline dyssynchrony and which of these can predict response to CRT[72, 85, 87, 89, 98, 100-108].

Besides ECG and echocardiographic parameters, cardiopulmonary exercise testing (CPET) is an important criterion for screening patients undergoing CRT[18].

3.3 CARDIOPULMONARY EXERCISE TESTING

CPET and the 6-minute walk are the most common modalities for evaluating the functional capacity of patients with HF.

The 6-minute walk is usually used as an alternative to CPET, as it evaluates low-level or submaximal work and is more compatible with activities of daily living. This test and the NYHA classification may be helpful for assessing patient's physical ability. Many clinical trials have used the 6-minute walk test to classify patients with HF into syndrome severity categories. A significant correlation between distance walked during 6 minutes and survival is noted. A total distance walked of less than about 300 meters in a study carried an annual mortality risk of 11%, in contrast to 4% among patients who could walk more than about 450 meters[109].

CPET is used to evaluate maximal exercise capacity, for prognostic stratification, and for staging for possible cardiac transplantation. There is different exercise testing protocols in which the workload is progressively increased during the test, either on a bicycle or a treadmill. The selection of a particular protocol should be based on the experience of the testing physician, on the physical ability of the patient, and on the availability of the facility where the test is being performed. Exercise testing of patients with HF is supported by the American Heart Association for clinical and research application[36].

The CPET has some advantage compared to the traditional exercise testing. Both of the tests are ECG monitoring however, the CPET used gas exchange analysis, which can provide directly the peak VO_2, a measure of coupling between central pulmonary gas exchange, cardiac output, and peripheral oxygen delivery to and use by skeletal muscle[36].

Even so, this testing has some implications like time-consuming, expensive (it requires specialized equipment for gas exchange, coupled to ECG), and requires great skill in cardiopulmonary physiology.

In spite of these limitations, the measurements of carbon dioxide production and oxygen consumption during this test can provide numerous additional data that have both diagnostic and prognostic information, such as the ratio of volume of expired gas to carbon dioxide production (VE/VCO_2), ventilatory threshold, and respiratory exchange ratio.

HEART RATE RESPONSE

There is yet no consensus about the value of the resting heart rate (HR) relative to measure the risk to develop cardiovascular diseases and mortality.

Some authors defend that HR is not recognized as a factor for cardiovascular risk assessment or risk reduction in U.S. and European guidelines. A review of resting HR in cardiovascular disease, leaves some doubts that HR is a risk factor for cardiovascular mortality, independent of currently accepted risk factors and other potentially confounding demographic and physiological characteristics. It has been difficult to determine whether modulation of HR can beneficially alter risk; currently available interventions that lower HR, such as beta-blockers, certain calcium channel blockers, and

physical conditioning have multiple additional actions. Nonetheless, improved HR is important and potentially beneficial for patient care[110].

More recently, there has been a study with patients with left ventricular dysfunction and a recent myocardium infarction or HF showed that resting HR was independently associated with increased risk of overall mortality over a 10 year follow-up period. The results suggest that the prognostic importance of resting HR is stronger in patients with myocardium infarction compared to patients with HF, especially in the short term[111].

The immediate response of the cardiovascular system to exercise is an increase in HR due to a decrease in vagal tone. This increase is followed by an increase in sympathetic outflow to the heart and systemic blood vessels. During dynamic exercise, HR increases linearly with workload and VO_2. Heart rate will reach a steady state within minutes during low levels of exercise and at a constant work rate. As workload increases, the time necessary for the HR to stabilize will progressively lengthen. The HR response to exercise is influenced by several factors such as age, deconditioning, body position, type of exercise, and various states of health and therapy, including heart transplant[29, 112]. The HR peak is the highest value of the heart rate or pulse rate which can be attained and measured during incremental exercise.

HR recovery refers to the deceleration of the HR in early exercise recovery in association with vagal tone reactivation. It is the difference between HR at peak exercise and after one minute or other time defined of recovery. An abnormal value for the recovery of HR was defined as a reduction of 12 beats per minute (bpm) or less from the HR at peak exercise[113, 114]. The increase in HR that accompanies exercise is due in part to a reduction in vagal tone. HR recovery immediately after exercise is a function of vagal reactivation, a decrease of vagal activity is known to be a risk factor for death[114].

Lipinski *et al.*[115] and Tang *et al.*[116] conclude that HR recovery on the first minute recovery is a significant predictor of mortality and may provide valuable prognostic information for patients with HF or LVSD. HR recovery should be evaluated along with VO_2, age, HR peak, and other variables to predict mortality and may also aid in determining which patients with HF and LVSD will require heart transplantation[113, 115]. Even after adjusting for other exercise derived

predictor variables and previously validated HF survival scores, post-exercise HR recovery remained an independent predictor of adverse clinical events[116].

Moreover, a recent study concludes that CRT favorably alters the cardiac autonomic functions assessed by HR recovery indices[117]. This effect of CRT on cardiac autonomic functions was observed both in responders and in non responders. However, the degree of improvement in HR recovery indices is correlated with left ventricular reverse remodeling. In the Okutucu *et al.*[117] study, the baseline HR recovery indices could not predict response to CRT, considering a responder as a decrease of ≥ 15% in LVESV at the 6-month follow-up was defined as a positive echocardiographic response.

OXYGEN UPTAKE

Maximum oxygen uptake (VO_{2max}) or peak oxygen uptake (VO_{2peak}) is the maximum capacity of an individual's body to transport and use oxygen which can be attained and measured during an incremental exercise protocol for a specific exercise mode. It can, however, be affected by age, gender, muscle mass, aerobic conditioning and medication therapy. It is measured in liters per minute, but is often relativised for body mass (ml/kg/min) to allow better comparison between individuals of different body size.

Functional status and cardiac reserve of patients with CHF can be objectively characterized by determining exercise tolerance. Particularly important is the precise measurement of VO_{2peak} consumption.

VO_{2peak} is one of the most important independent predictors of mortality and hospitalization for patients with HF[19, 118]. This functional variable represents functional effort capacity and is improved significantly by CRT[119, 120], but is influenced by non-cardiac factors (age, motivation, anaemia and obesity). It has become probably the most important test to determine whether ambulatory patients are ill enough to list for cardiac transplantation[36].

Mancini *et al.*[19] analyzed if VO_{2peak} can be used to identify ambulatory patients in whom cardiac transplantation can be safely deferred. According to the study protocol, patients with a VO_{2peak} > 14 ml/kg/min were denied transplantation, whereas those with a VO_{2peak} ≤ 14 ml/kg/min were offered transplantation. Thus, in spite of similar LVEF, patients with VO_{2peak} < 14

ml/kg/min have a far worse prognosis than those with VO_{2peak} >14 ml/kg/min. It is important to include in the follow-up of CHF patients the determination of VO_{2peak} to establish more effectively the optimal therapeutic strategy[23]. Recent recommendations for the International Society for Heart and Lung transplantation guidelines for CPET were VO_{2peak} ≤ 12.0 ml/kg/min for patients receiving beta-blockers and VO_{2peak} ≤ 14.0 ml/kg/min for patients not receiving such therapy[121].

An accurate estimation of VO_{2peak} might be underestimated and it is difficult to obtain in patients with severe HF. It is difficult to assess whether a truly maximal test was performed and rarely is reach a true plateau of oxygen consumption with increasing workloads because of some limitations such as peripheral muscle fatigue, motivation or procedural difficulties (selection of an appropriate exercise protocol)[98, 121].

HF patients rarely reach a plateau of VO_2 with increasing workloads, common determinants of a maximal exercise test have been respiratory exchange ratio (RER) > 1.1 and reaching an anaerobic threshold. The RER rises from a resting value of around 0.7 at rest during exercise. Healthy controls achieve a RER at peak exercise of between 1.10 and 1.20 or even higher, indicating that anaerobic metabolism is occurring. Such a RER is used as an indicator of maximal effort[112]. Patients with CHF are typically less able to exercise to a level with such a high RER, and some CHF patients are unable to reach a RER ≥ 1.0. Ingle *et al*.[122] conclude that independent predictors of mortality were different in patients with a RER < 1.0 compared to those with a RER ≥ 1.0. In CHF patients with a RER < 1.0, traditional prognostic markers (VE/VCO_2 slope, VO_{2peak}) were not independently predictive of mortality. However, a review of studies defining the criteria for VO_{2peak} showed that 6 of 14 studies used an RER cutoff of 1.0 or 1.05, so these criteria may be too stringent. Decisions might also need to be made based on a submaximal test[121].

In a study by Auricchio *et al.*[12] patients with peak VO_2 > 16 ml/kg/min did not show significant cardiorespiratory improvements during CRT. In contrast, a study by Piepoli *et al.*[123] showed that patients with a peak VO_2 ≤ 7 ml/kg/min did not benefit from CRT. A difference of approximately 2 ml/kg/min in VO_{2peak} strongly depends on the motivation of the patients.

In a recent study Berger *et al.*[98] analyzed the impact of the cardiorespiratory functional reserve to predict the response to CRT. Submaximal cardiopulmonary treadmill exercise testing prior and 6 months after implantation of a CRT device was made. Responders to CRT, defined by a decrease in LVESV > 15% showed a significant lower cardiorespiratory reserve at baseline (prior CRT) as compared to the non responders. The conclusion of this study was that non responders to CRT showed a more preserved cardiorespiratory functional reserve as compared to responders despite similar NYHA classification.

Some authors have used percentage of predictive VO_{2peak} rather than the absolute value to stratify risk. In multivariate analysis, 50% or 55% of predicted peak oxygen uptake (when the respiratory exchange ratio is greater than 1.10) has generally been selected as the most significant predictor of cardiac death[121]. The proposed cutoff point of 50% has been confirmed by Stelken *et al*.[20], who showed that in a cohort of 181 HF patients those with an oxygen uptake greater than 50% predicted value had a 94% possibility two year survival as compared to only 50% survival in patients with an oxygen uptake of below 50% predicted value.

Therefore, the percentage of predicted value in clinical reports must be interpreted in a patient specific context in view of other comorbidity conditions, for example, adjustments have to be made if the patient is taking a beta-blocker[124].

SLOPE OF THE VENTILATORY RESPONSE

VE/VCO_2 is calculated during a cardiopulmonary exercise test and is the slope of the relationship between minute ventilation (VE) and oxygen uptake (VO_2) during incremental exercise[125]. The ventilatory response evaluation is not influenced by beta-blocker therapy and submaximal exercise. It is well recognized that VE/VCO_2 slope is measurable at any point during exercise and adds significant prognostic value in HF population[126].

In patients with HF an increased ventilator response throughout exercise is observed. A VE/VCO_2 slope value up to 35 was associated with a one-year

mortality rate of 30% in the Corra *et al.* study[127]. Francis *et al.*[128] found a two-year mortality rate of 65% for patients with a value up to 55.

The VE/VCO_2 slope seems to be a better predictor of outcome than VO_{2peak} with regard to submaximal effort[128]. The complementary prognostic value especially with the VO_{2peak} is of great interest. Patients with VO_{2peak} < 11 ml/kg/min and VE/VCO_2 slope ≥ 34 are at particularly high risk for transplantation or death. Thus, patients with well preserved exercise capacity and low VE/VCO_2 slope are at low risk for transplantation or death. This approach allows high-risk patients to be identified noninvasively and could provide guidance for intensified treatment (medical regimen, CRT, exercise training and heart transplantation) and monitoring[129].

This parameter should be a routine component of exercise analysis in HF population. Consideration should be given to revising clinical guidelines to reflect the prognostic importance of the VE/VCO_2 slope in addition to VO_{2peak}[129, 130].

VENTILATORY ANAEROBIC THRESHOLD

In 1991, submaximal exercise parameters such as the ventilatory anaerobic threshold (VAT) were introduced to evaluate the cardiopulmonary functional reserve. In fact, most activities of daily living do not require maximal effort, so submaximal exercise parameters should be used like VAT.

There is a point during progressive exercise in which lactate accumulation caused a nonlinear increase in ventilation. The increase in blood lactate concentration during exercise is thought to cause a nonlinear increase in ventilation as a result of bicarbonate buffering of excess hydrogen ions from lactate in the blood and consequent production of carbon dioxide. The resulting hyperventilatory response has been commonly termed the VAT[131].

VAT is assessed by ventilatory expired gas, defined by the exercise level at which VE begins to increase exponentially relative to the increase in VO_2.

Nevertheless, VAT cannot be obtained in 25% to 30% of patients with HF because of severe deconditioning, early onset of acidosis, and the presence of an irregular breathing pattern[132].

4 METHODOLOGY

4.1 INTRODUCTION

This chapter describes the methodological procedure of the study. In the first part, a description of the experimental concept such as the study design and the characterization of the sample are presented. In the second part, study variables are presented, including the independent and dependent variables and how they were evaluated. The statistical treatment of the data of interest to the present study was the last task of the procedure to be done.

4.2 STUDY DESIGN

The present study is an observational and analytical prospective cohort study. This study design requires a comparative analysis between data collected in CPET before and after the implantation of a CRT considering two types of criteria to define responders as well an echocardiography and clinical consultation to assess the ejection fraction and analyze the NYHA class.

Data were collected before and after the implantation of a CRT, under the same conditions, with the same procedures.

4.3 PARTICIPANTS

The study sample initially included 22 patients from both genders with CHF referred to Santa Marta Hospital, Lisbon. From the 22 patients that initially met the criteria for enrolment in the study, 7 were excluded for data analysis. Therefore, the total sample for this study consisted of 15 patients.

Patients were excluded for several reasons, such as: having traditional exercise testing done after CRT instead of CPET (n=2), missed some variables measured from CPET (n=2), missed CPET after CRT before data were analyzed (n=2) and CRT not working properly (n=1).

The study sample receiving CRT based on the following clinical criteria were considered for this study: patients presenting severe symptomatic heart failure despite optimal pharmacological therapy (NYHA functional Class III or IV),

LVEF < 35% and free of exercise-limiting comorbidities such as cerebrovascular disease, muskuloskeletal impairment, or peripheral vascular disease.

All patients were followed-up prospectively at Santa Marta Hospital. Clinical status (NYHA class) was assessed at baseline and approximately 5 months after CRT. The average time of the echocardiogram performed after CRT was 2 months ± 18 days. The CPET after CRT was 5 months ± 13 days.

RESPONSE CRITERIA

There are two possible criteria used to classify the CRT response according to the literature. The first is defined by an increase of 15% or more of LVEF, measured by conventional echocardiography from baseline to follow-up[26, 27]. The second was a combinination of two criteria, defined by clinical and echocardiography measures with an increase of 5% or more of LVEF and a decrease of 1 or more NYHA class, respectively[28]. These measures were chosen because of their percentage of response rate, the first with 54% and the second with 71% of response rate, as seen in table 2, page 18.

4.4 VARIABLES IN STUDY

4.4.1 DEPENDENT VARIABLES

In this study the following dependent variables were considered: in echocardiography, the ejection fraction; in the clinical category, the NYHA class; and in the CPET the, VO_2 peak, predicted VO_2, HR initial, HR peak, HR recovery at first and third minutes, blood pressure at the start and maximum reached, RER, VAT and VE/VCO_2 slope.

EQUIPMENTS AND PROTOCOLS OF ASSESSMENT

Echocardiography: resting cardiac echocardiogram was recorded in a lying position using a commercially available digital ultrasound scanner (Vivid 7, Vivid 3 and Vivid IE9, GE Vingmed Ultrasound, Horten, Norway). In this exam, LVEF

was measured which represents the volumetric fraction of blood pumped out of the left ventricle which ejects via the aortic valve into the systemic circulation. Although this value is one of the inclusion criteria for this study, their difference before and after CRT indicates one of the criteria to response.

NYHA class: the assessment was made according the table 1 on page 17. The classification was made by a cardiologist in the medical consultation before and after the implantation of CRT.

CPET: all subjects underwent maximal symptom-limited treadmill CPET (GE Marquette Series 2000 treadmill and Mortara instrument, Milwaukee, USA), using modified Bruce Protocol. The 12-lead electrocardiogram and HR were recorded continuously during the test and continued for six minutes of the recovery period. Blood pressure was measured at rest, during the last 30 seconds of each stage, at peak exercise and at the first, third and sixth minute of the recovery phase.

In no case did altered blood pressure, arrhythmia, chest pain or electrocardiographic changes lead to interruption of the test, in accordance with international standards[133]. All studies were, accordingly, interrupted by subjective fatigue or dyspnea preventing the patient from continuing the exercise. No medication was discontinued before the test.

Minute ventilation (VE in l/min) and oxygen uptake (VO_2 in l/min/kg) were acquired breath-by-breath, using a gas analyzer. Gas analysis was preceded by calibration of the equipment and began three minutes prior to exercise.

Patients were encouraged to perform exercise until the VCO_2/VO_2 ratio (RER) was ≥ 1.10. But in this type of patients it is complicated achieve that ratio, however, ratios under 1.10 were considered to this study. Besides RER, other derived variables were calculated, including ventilatory equivalent for oxygen (VE/ VO_2).

VO_{2peak} was expressed as the highest VO_2 attained during the final 30 seconds of exercise[134]. Predicted peak VO_2 and the percentages of the predicted values achieved were calculated by the system software. The VAT was determined using the V-slope method, and corrected, when necessary, using the VE/VO_2 versus VE/VCO_2 criterion and/or the end-tidal oxygen and carbon dioxide partial pressures method[135]. The VE/VCO_2 slope was calculated

as the slope of the regression line relating VE to VCO_2 during exercise, with data obtained over the complete duration of exercise.

4.4.2 INDEPENDENT VARIABLES

The implantation of CRT was the independent variable; the most common being the CRT-D. According to the Guidelines for cardiac pacing and CRT[46], implantation of a CRT device is more demanding than implantation of a conventional pacemaker or implantable cardioverter defibrillator. Thus, additional laboratory, operator, and technical support were considered.

In our study and according to the experts advise, patients with CRT should fulfill the following conditions: a) two or more cardiologists qualified for device implantation and management; (b) all physicians should possess knowledge and experience in haemodynamic monitoring and administration of cardiovascular support; (c) trained nurses and technical personnel; (d) pacing system analyzer and programmer of implanted device: electronic patient file is highly encouraged; (e) continuing medical education for physician, nurses, and technicians is mandatory.

Two operators were required, especially during extraction/insertion of guidewires, handling of wires, sheaths, and stylets. Ideally, two nurses were required. One nurse monitors patient status and manages all necessary impellent accesses, including the urine catheter and the intravenous administration of drugs. A second nurse provides implant assistance by monitoring some variables, handling over sterile material; and positioning the ECG screen.

Continuous anaesthesiological support is not obligatory, but quick anaesthesiological assistance must be available if a critical clinical situation develops.

4.5 STATISTICAL ANALYSIS

For statistical analysis it was used the Statistical Package for Social Science (SPSS 19.0 for Windows ®, SPSS Inc, Chicago, USA).

Efficacy of CRT was examined by comparing variables at baseline and after implantation of CRT. Differences between pre and post CRT were tested according to the variables categories, qualitative and quantitative, to evaluate the effect of this treatment.

For the quantitative variables, it was used the Student's t-test for paired samples if the normal distribution is assumed or the Wilcoxon signed-rank test if normal distribution cannot be assumed. Regarding normality and homogeneity of variances data was tested using Shapiro-Wilk and Levene's tests, respectively. Pearson χ^2 test was used for comparisons of qualitative variables. Results were expressed as means ± standard deviation.

The differences in quantitative variables (before CRT) between responders and non responders were analyzed using the Student's t-test for independent samples or, when normality was not observed, the Mann-Whitney U test. Responders were defined by two parameters: an increase of 15% of the LVEF or an increase of 5% of the LVEF and a decrease of one level or more in the NYHA classification.

A p-value <0.05 was considered statistically significant.

5 RESULTS AND DISCUSSION

INTRODUCTION

In this chapter, the results and discussion will be described, respectively, for each dependent variable. Initially, the results will be referred to the baseline, describing their characteristics, and then the comparison will be made between the group of responders and non responders according to the studied variables before CRT. Finally, the comparisons between the studied variables before and after CRT on exercise performance will be described.

PARTICIPANTS CHARACTERISTICS

Table 3: Clinical and demographic characteristics at baseline for the sample in the study (n=15)

Men	11 (73.3%)
Women	4 (26.7%)
Age (years)	64 ± 10 (48; 81)
BMI (kg/m^2)	27.3 ± 5 (19.3; 36.7)
Etiology	
Isquemic	2 (13.3%)
Dilated Cardiomyopathy	9 (60%)
Dilated Valvulopathy	2 (13.3%)
Isquemic Dilated Cardiomyopathy	2 (13.3%)
NYHA class	
III	14 (93.3%)
IV	1 (6.7%)
LVEF (%)	27 ± 8 (11; 38)

Values are expressed as mean ± standard deviation (minimum; maximum)

The clinical and demographic characteristics of the study population are summarized in table 3. Around 75% of the patients were medicated with beta-blockers, 60% with diuretics and 40% with angiotensin-converting enzyme inhibitors or/and angiotensin receptor blockers. A high percentage of patients had a CRT-D implanted (93%).

COMPARISON BETWEEN RESPONDERS AND NON RESPONDERS VARIABLES

According to the different classification criteria to define responders to CRT (either an increase of 15% of the LVEF or an increase of 5% of the LVEF and a decrease of one level or more in the NYHA classification), the demographic characteristics, the patients' medications, echotrocardiographic values and functional characteristics at baseline were listed in tables 4 and 5.

Table 4: Comparisons of baseline demographic, clinical, and functional characteristics in responders *vs.* non responders to CRT considering echocardiographic parameters

	Responders (n=9)	Non Responders (n=6)	P-value
Age (years)	63 ± 9	66 ± 12	0.644
Men/women (n)	5/4	6/0	0.057
Heart failure etiology (n)			
Ischemic	1	1	
Dilated Cardiomyopathy	6	3	0.937
Dilated Valvulopathy	1	1	
Isquemic Dilated Cardiomyopayhy	1	1	
Medications (n)			
Angiotensin	3	3	0.519
Diuretics	6	3	0.519
Beta-Blockers	6	5	0.475
NYHA III/IV	3.11 ± 0.3	3 ± 0	0.435
LVEF (%)	27 ± 8.4	26.7 ± 8.9	0.942
Peak VO_2 ≤ 14 ml/kg/min	4	3	0.833
VO_2(ml/kg/min)			
Peak exercise	14.7 ± 6.2	17.7 ± 4.7	0.348
Percentage of predicted VO_2 (%)	56.4 ± 17.8	64 ± 6.3	0.399
VE/VCO_2 slope (L/min)	30.5 ± 10.1	38.6 ± 4.4	0.200
Anaerobic threshold (n achieve)	4	5	0.132
Systolic blood pressure (mm Hg)			
Initial	112 ± 19	118 ± 18	0.473
Peak	143 ± 20	140 ± 24	0.778
Diastolic blood pressure (mm Hg)			
Initial	60 ± 10	68.33 ± 8	0.115
Peak	72 ± 10	70 ± 9	0.711
Heart rate (bpm)			
Initial	80 ± 12	92 ± 13	0.088
Peak	125 ± 25	132 ± 24	0.628
Heart rate recovery (bpm)			
1^{st} minute	14 ± 7	18 ± 12	0.437
3^{rd} minute	38 ± 17	36 ± 19	0.813
Respiratory Exchange Ratio	0.95 ± 0.17	0.98 ± 0.11	0.935

Positive echocardiographic response to CRT was observed in 9 patients, corresponding to a 60% responder rate, as seen in table 4. No differences were observed between the two groups regarding demographic, clinical and functional characteristics, probably owing to the small study sample size.

As we can see in table 4, the baseline characteristics of the two groups were overall similar, including functional capacity and echocardiographic measurements.

The HR initial was lower in responders than non responders, the difference were 12 bpm, but did not reach statistical significance ($p > 0.05$). No significant differences were observed between patients with $VO_{2peak} \leq 14$ ml/kg/min.

No clear-cut value was found for separating responders and non responders.

Table 5: Comparisons of baseline demographic, clinical, and functional characteristics in responders *vs.* non responders to CRT considering echocardiographic and clinical parameters (Combined)

	Responders (n=11)	Non Responders (n=4)	P-value
Age (years)	68 ± 9	55 ± 9	**0.024**
Men/women (n)	7/4	4/0	0.159
Heart failure etiology (n)			
Ischemic	2	0	
Dilated Cardiomyopathy	5	4	0.304
Dilated Valvulopathy	2	0	
Isquemic Dilated Cardiomyopayhy	2	0	
Medications (n)			
Angiotensin	5	1	0.475
Diuretics	7	2	0.634
Beta-Blockers	7	4	0.159
NYHA III/IV	3.09 ± 0.3	3 ± 0	0.566
LVEF (%)	27 ± 9	26.5 ± 7	0.922
Peak $VO_2 \leq 14$ ml/kg/min (n)	6	1	0.310
VO_2(ml/kg/min)			
Peak exercise	14.3 ± 5	20.4 ± 5.4	0.058
Percentage of predicted VO_2 (%)	56.4 ± 15.2	67.8 ± 7.3	0.186
VE/VCO_2 slope (L/min)	30.6 ± 8.2	28 ± 5.7	0.975
Anaerobic threshold (n achieve)	6	3	0.475
Systolic blood pressure (mm Hg)			
Initial	114 ± 16	116 ± 26	0.847
Peak	140 ± 21	146 ± 25	0.661
Diastolic blood pressure (mm Hg)			

Initial	60 ± 9	70 ± 8	0.108
Peak	70 ± 10	75 ± 6	0.338
Heart rate (bpm)			
Initial	82 ± 10	93 ± 19	0.145
Peak	118 ± 18	157 ±13	**0.002**
Heart rate recovery (bpm)			
1st minute	13 ± 9	21 ± 8	0.149
3rd minute	31 ± 14	54 ± 13	**0.014**
Respiratory Exchange Ratio	0.95 ± 0.15	0.98 ± 0.14	0.732

As we can see in table 5, in the combined parameters, positive responders to CRT corresponding to a 26.7% non responder rate. Overall, the baseline characteristics of the NYHA, LVEF and SBP (both at initial and peak of CPET) of the two groups were similar (table 5).

Among all variables examined, in our study, the only significant differences detected were the age, peak HR and HR recovery after 3 minutes from CPET performance.

The mean age was significantly higher approximately 13 years in responders compared to non responders (p = 0,024). Whether age negatively affects response to CRT is currently unknown; this is an important issue, because most patients with HF are of greater age[136].

The peak HR before CRT was higher 39 bpm in non responders than in responders ($p \leq 0.05$), whereas the minute 3 of HR recovery was lower 23 bpm in responders than in non responders before CRT (p = 0.014). In contrast to a previous finding, baseline HR recovery at minute 1 and 3 could not predict response to CRT, their values between responders and non responders were very similar[117]. In our study, this does not happen, there were different values at baseline. According to the literature, HR recovery immediately after exercise is a function of vagal reactivation, a decrease of vagal activity is known to be a risk factor for death[114]. Thus, the faster the recovery, in this case for non responders, there is an increase of vagal activity.

Responders, compared with non responders, were more likely to have dilated cardiomyopathy heart disease (33.3% *vs*. 26.7%, $p > 0.05$), and more diuretic and beta blocker medications (46.7% *vs.* 13.3% $p > 0.05$ and 46.7% *vs.* 26.7% $p > 0.05$, respectively). However, none of these variables were statistically significant.

The group of non responders had a VO_{2peak} and a percentage of predicted VO_2 higher than the group of responders although not reaching statistical significance (20.4 ± 5.4 ml/kg/min *vs.* 14.3 ± 5 ml/kg/min $p = 0.058$ and 67.8 ± 7.3% *vs*. 56.4 ± 15.2%, $p = 0.186$). In a recent study, Arora *et al.*[137] found a significant value for the VO_{2peak} between responders and non responders. A positive responder was considered if $VO_{2peak} \geq 1$ ml/kg/min. In the non responder group, the value was higher than the group of responders (11.7 ± 2.4 ml/kg/min *vs.* 10.6 ± 2.3 ml/kg/min $p < 0.05$). The percentage of predicted VO_{2peak} was not significantly different between groups but was higher in the non responder's group.

As mentioned previously, patients with a baseline $VO_{2peak} < 14$ ml/kg/min regularly benefit from CRT during the first year of treatment[23]. The German "Statement on cardiac resynchronization"[25] already recommends a baseline $VO_{2peak} < 14$ ml/kg/min as one criterion to indicate CRT. As we can observe in table 5, the value of the VO_{2peak} for the responder's group was almost < 14 ml/kg/min, with a p = 0.058. Probably owing to the small study sample size, it was not possible to obtain statistically significance in the VO_{2peak}, but there is a trend towards a lower VO_{2peak}.

The VE/VCO_2 slope (30.6 ± 8.2 l/min *vs.* 28 ± 5.7 l/min) and the achievement of the VAT (n = 6 *vs.* n = 3) were higher in the group of responders than non responders, but no significant differences were found.

In this study, it was possible to make a relation between the response criteria and their efficacy response rate according the Fornwalt review[6] mentioned previously. In that review, the response rate for the response criteria parameter ≥ 15% improvement of LVEF was 54%; the response criteria for combined parameters was 71%, as we can see in table 2. Similar findings have also been demonstrated in this study, it was on the combined response criteria that were statistical significant values for the variables in study.

EFFECT OF CRT ON EXERCISE PERFORMANCE

Table 6: Patient characteristics before and after CRT

Variable	Before CRT	After CRT	P Value
VO_2(ml/kg/min)			
Peak exercise	15.9 ± 5.6	16.3 ± 5.6	0.691
Percentage of predicted VO_2 (%)	60.8 ± 15	63.4 ± 20	0.438
VE/VCO_2 slope (L/min)	34.6 ± 8.5	29.9 ± 7.5	0.241
Anaerobic threshold (%achieve)	60	73.3	0.132
Systolic blood pressure (mm Hg)			
Initial	115 ± 18	122 ±19	0.343
Peak	142 ± 21.2	158 ± 27.8	**0.032**
Diastolic blood pressure (mm Hg)			
Initial	63.3 ± 9.7	70.3 ± 12	**0.046**
Peak	71 ± 9.3	77 ± 13	0.089
Heart rate (beats/min)			
Initial	85 ± 13	80 ± 12	0.255
Peak	128 ± 24	126 ± 15	**0.033**
Heart rate recovery (beats/min)			
1^{st} minute	15 ± 9	22 ± 11	0.516
3^{rd} minute	37 ± 17	38.4 ± 15	0.118
Respiratory Exchange Ratio	0.96 ± 0.14	1 ± 0.11	0.262
NYHA	3.07 ± 0.26	2.2 ± 0.4	**0.0001**
LVEF (%)	26.9 ± 8.3	41.3 ± 11.5	**0.006**

The average time lapse between the first and second echocardiograms (before and after CRT, respectively) was 2 months ± 18 days.

As observed in table 6, the mean LVEF was significantly increased approximately 14 % ($p < 0.05$). One of the inclusion criteria to CRT is the LVEF ≤ 35%, the value after CRT was higher than 35%, which indicates good improve of this variable. Moreover, HF patients with normal LVEF (> 50% LVEF) have a lower mortality risk than cases with reduced LVEF[138].

In the clinical parameter, five months after the implantation of CRT, the mean NYHA functional class improved significantly, it decreases to a NYHA class 3 to a class 2 ($p < 0.0001$). It is noteworthy that our results are consistent with the findings of some studies[12, 23, 75, 137] which demonstrates a near identical level of improvement on NYHA class after CRT. According to the 2010 focused update of the European Society of Cardiology Guidelines[15] on device therapy in

HF, the impact of CRT, on average, in NYHA function class is the decreased by 0.5–0.8 points. In this study, the decrease was 0.87 points. This indicates that, on average, patients with marked limitation of physical activity (NYHA class 3) improved to slight limitation of physical activity (NYHA class 2) (table 1, page 17).

When comparing the HR profile during exercise, there was a significantly changed after CRT (table 6), beta blockers must be considered because of their HR lowering action[32]. In our study, as mentioned previously in the chapter of limitations, the drug therapy was sometimes collected at the time of exercise testing.

The peak HR was significantly lower about 2 bpm after CRT ($p < 0.05$). Unlike other studies[12, 137], the peak HR showed a decrease instead of an increase in our study. The exact mechanism for the restoration of a more physiologic increase in HR during exercise after CRT remains to be elucidated, but it is probably related to unloading of ventricular sensory receptors or improved ventricular filling capability[139].

The HR assessed at the start of the CPET decreased 5 bpm after CRT, $p > 0.05$. It is not certain whether there is a long-term relation between risk of death associated with increased rest HR and HF. Two studies done on HF patients found that increased HR at baseline[140, 81] was associated with worse outcome. The decreased HR initial may reflect increased vagal tone and decreased sympathetic tone after CRT, which has been associated with more favorable prognosis[141]. Sustained reduction of sympathetic activity during CRT has been recently demonstrated[142].

The HR recovery after the first and third minutes from the performance of CPET was not significantly different. However, the HR measured at minute 1 after CPET increased 7 bpm and at minute 3 increased approximately 1 bpm. According to previous studies, an abnormal value for the HR recovery at minute 1 was defined as a reduction of 12 bpm or less from the HR at peak exercise[114]. As we can see in table 6, the mean of the HR recovery at minute 1 either before or after CRT, were higher than 12 bpm. Some authors[115, 116] conclude that HR recovery on the first minute recovery is a significant predictor of mortality and may provide valuable prognostic information for patients with HF or LVSD. This

indicates that, in this study, there is a tendency to be significant the HR recovery at minute 1 because of the improvement and the high value assessed.

Furthermore, the importance of HR in determining exercise capacity in CRT patients has been investigated in a recent study and it was demonstrated that chronotropic incompetence is an important determinant of peak exercise capacity[143].

The increased peak systolic blood pressure may indicate a higher chronic peak cardiac output or more efficient vasoconstriction of non exercising vascular beds occurring after CRT[12]. In this study, the increased in the peak SBP was statistically significant, going from 142 ± 21.2 to 158 ± 27.8 $p = 0.032$.

In turn, the increase of diastolic blood pressure from 63.3 ± 9.7 to 70.3 ± 12, was also statistically significant. The significance of this finding is unclear, although a slight increase in diastolic pressure may be responsible for a better coronary perfusion, as well as an indicator of improved arterial compliance.

VO_{2peak} consumption, obtained during maximal exercise testing, has been the gold standard to assess exercise performance. Seven patients (46.7%) had a baseline peak $VO_2 \leq 14$ ml/kg/min, one patient (6.6%) had a VO_{2peak} ranging between 14 and 16 ml/kg/min, and 7 patients (46.7%) had a $VO_{2peak} \geq 16$ ml/kg/min. Thus, these seven patients in our study that has $VO_{2peak} < 14$ ml/kg/min at baseline, regularly benefit from CRT during the first year of treatment according to a study[23].

Both VO_{2peak} and percentage predicted VO_{2peak} are similar in providing prognostic information in patients with advanced HF[144]. However, a closer examination of the initial exercise test showed that VO_{2peak} increases with no significant difference (table 6). The percentage of predicted VO_{2peak} was also not significant, it raises from 60.8 ± 15% to 63.4 ± 20% indicating that, according to the literature, these patients have a 94% possibility two year survival compared to patients with a below 50% of predicted VO_{2peak}[20]. In multivariate analysis, of other studies, 50% or 55% of predicted VO_{2peak} has generally been selected as the most significant predictor of cardiac death[121].

The RER rises from almost 0.5 but it wasn't significant. However, this raise might indicate better anaerobic metabolism and an indicator of maximal effort. In a study, independent predictors of mortality were different in patients with a RER < 1.0 compared to those with a RER ≥ 1.0. In CHF patients with a RER <

1.0, traditional prognostic markers (VE/VCO_2 slope, VO_{2peak}) were not independently predictive of mortality, conclude Ingle *et al.*[122]. By our result, it appears that the RER does not reach the value that indicates maximal effort.

One possible reason to do not reach that value was that the modified Bruce protocol on a treadmill may be too challenging for elderly CHF patients with comorbidities, alternative methods of exercise testing such as a more gentle ramping treadmill protocol, or cycle ergometry may yield greater success for this type of population. Rostagno *et al.*[145] estimated that 1 in 3 CHF patients were unable to perform a CPET successfully as defined by RER criteria (RER ≥ 1.10). In this study, as we can see in tables 5, 6 and 7 the average of RER was always ≤ 1.10.

By our result in this study, it appears that there is a tendency to lower the risk for transplantation or death after CRT. The reason for that affirmation was that patients with VO_{2peak} < 11 ml/kg/min and VE/VCO_2 slope ≥ 34 are at particularly high risk for transplantation or death[129]. Thus, in our study, as we can observed in table 6, the value of the VE/VCO_2 slope increased after the CRT to 29.9, lesser than 34.

It was observed that the respiratory efficiency given by the VE/VCO_2 slope decreased after CRT ($p > 0.05$). The same findings were shown in previously studies that describe the decrease of the VE/VCO_2 slope after CRT[98, 137].

Evidence has suggested that the prognostic value of the VE/VCO_2 slope could be greater than VO_{2peak}, particularly for patients undergoing sub-maximal effort, patients treated with beta-blockers and those with LVEF less than 45%[127, 146-148]. In fact, the main limitation is the frequent sub-maximal effort during CPET, with an underestimation of maximal VO_{2peak} leading to the wrong prognostic interpretation.

VAT was not detected in all patients, 60% achieved the threshold before the CRT and 73.3% after the CRT. VAT cannot be obtained in 25% to 30% of patients with HF because of severe deconditioning, early onset of acidosis, and the presence of an irregular breathing pattern[132].

The skeletal musculature in HF patients might be a reason to this severe deconditioning. Patients with HF are limited in their ability to tolerate exercise. Recent research has suggested that this limitation cannot be entirely attributed to cardiac or lung impairment. The peripheral muscles may play an important

role. HF patients have deficiencies in peripheral blood flow and skeletal muscle function, morphology, metabolism and function. Moreover, an exaggerated activity of the receptors sensitive to exercise derived metabolic signals leads to early and profound exercise-induced fatigue and dyspnea. These muscle afferents contribute to the ventilatory, haemodynamic and autonomic responses to exercise both in physiological and pathological conditions, including chronic HF[149, 150].

6 CONCLUSIONS

Considering the purposes defined for the present study and the obtained results, we conclude that:

1. CRT significantly increases ventilatory and haemodynamic responses after 5 months in some variables. Patients with an increased SBP peak, a higher DBP initial, increased LVEF and decreased HR peak and NYHA seem to benefit the most from this therapeutic approach.

2. CPET baseline measurements can potentially be used to identify patients who will respond to this therapy. The comparison between responders and non responders in two separate classification criteria were different.

3. The echocardiography criteria (increase of 15% of the LVEF) did not show any statistically significant result. On the contrary, the so called combined criteria definition (increase of 5% of the LVEF and a decrease of one level or more in the NYHA classification) has shown some significant differences.

4. The variables that were significant were the age, HR peak and HR recovery at minute 3.

Further studies are needed to document and assess these predictive variables to be part of the inclusion criteria in order to direct responder patients to benefit from CRT.

CPET testing in patients with systolic HF provides noninvasive objective measures of cardiopulmonary reserve and is thus suitable for evaluation, risk stratification and control of treatment effects. Echocardiography and CPET parameters may be combined to define CRT inclusion criteria that will decrease the rate of non response.

7 FUTURE RECOMMENDATIONS

In future investigations in this topic, we consider that it will be important to assess how relevant in follow up will be the role of including a monitored physical activity, such as walking and cycling, or other leisure time and occupational activity.

The protective effects of physical training have been described in many recent studies. It would be recommended a cardiac rehabilitation program to bring additional benefits for CRT patients and compare their influence in responders and non responders.

Thus, it is important to have a continuous assessment of these patients at 3, 6 and 12 month post procedure. This may include all the exams that were done before the CRT, such as CPET and Echocardiography, in order to assess the patient's progress before and after CRT in the short and long term.

8 REFERENCES

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