Imaging predictive factors and exercise training in patients submitted to cardiac resynchronization

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Abstract

Cardiac resynchronization therapy (CRT) is an established treatment for patients with moderate-to-severe chronic heart failure (CHF) and intraventricular conduction delay, which is identified by a QRS interval of 120 msec or more on a 12-lead electrocardiogram (ECG). CRT improves functional capacity, reduced hospitalizations for worsening CHF and increased survival, however, about 30-40% of patients who undergo CRT are non-responders with no clinical or echocardiographic improvement. Imaging parameters for prediction of CRT response have been reviewed. Cardiac magnetic resonance (CMR), recognized as the gold standard to assess viability, has shown to obtain good results regarding quantification of scar burden. CMR-derived measures of mechanical dyssynchrony appear to predict the outcome of CRT, however these have not been externally validated. Nuclear imaging techniques, namely single-photon emission cardiac tomography (SPECT) provide data on scar burden and location, left ventricular (LV) function, LV contraction and mechanical dyssynchrony from a single scan. The presence, location and burden of myocardial scar have been shown to affect response to CRT. However, compared to CMR, the low spatial resolution of scintigraphy might overestimate the scar extent. This problem can be overcome by positron emission tomography (PET). SPECT has also been used to quantify dyssynchrony, using phase analysis. Imaging investigation is ongoing, trying to better identify CRT non-responders. The combination of ExT in CRT has not been well investigated, however some data show that different aerobic exercise modes and intensities can further improve CRT benefits. Data available on the effects of ExT in patients with CRT have been reviewed.

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Introduction

Cardiac resynchronization therapy (CRT) is an established treatment for patients with moderate-to-severe chronic heart failure (CHF) and intraventricular conduction delay, which is identified by a QRS interval of 120 msec or more on a 12-lead electrocardiogram (ECG) [1]. It occurs in up to a third of patients with severe systolic CHF [2] and is associated with dyssynchronous contraction of the LV, leading to impaired emptying and, in some patients, to mitral regurgitation [3]. Abnormal atrioventricular coupling (identified by prolonged PR interval) and interventricular dyssynchrony, identified on echocardiogram, may also occur. CRT with atrial-synchronized biventricular pacing often improves cardiac performance immediately, by increasing stroke volume (SV) and reducing mitral regurgitation [3,4]. Randomized trials involving patients with severe CHF have shown that CRT results in clinical and prognostic benefit, reporting symptoms reduction, functional capacity (FC) improvement, number of hospitalizations for worsening CHF reduction and survival increase [4-7]. Despite clinical response, several studies demonstrated, as well, left ventricular reverse remodeling benefit, with left ventricular ejection fraction increase and systolic left ventricular volume decrease [8,9]. It has been reported that 3-months after the cardiac implant, responders have significant left ventricular end-systolic volume (LVESV) decrease and LV ejection fraction (LVEF) increase, endothelial function increase, 6-min walk test (6MWT), NYHA class and quality of life (QOL) improvement [11-13], compared to non-responders. Major trials have shown that 30-40% of patients who undergo CRT are non-responders with no clinical or echocardiographic improvement [10].

Effects of exercise training

It is well known that CRT implant is an invasive and costly procedure, which is not exempt of complications [14]. The significant costs associated with unnecessary CRT implantation are even more important in the current situation of global economic concerns. The rationale to cost savings, by identifying adjunctive therapeutics that will help patients to increase the rate of responders, is an attractive notion that we believe is worthy of further exploration.

It is currently not completely established if adding an exercise training (ExT) program, following CRT, provides better clinical outcomes than CRT alone. Prior studies on CRT and ExT have been preliminary in nature, but suggest improvement in QOL and peak oxygen consumption (VO_{2peak}) [15]. However, the ExT was not initiated simultaneously with CRT, lasted only 3-months and no information on autonomic nervous system (ANS) or potential mechanisms were provided. In recent years, there has been a growing consensus that ExT has beneficial effects in CHF patients [16]. ExT in CHF produce meaningful change in VO_{2peak} with an expected average improvement of 17% [17].

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This is particularly important since the benefit in functional capacity (FC) is related to the improvement in neuro-hormonal activation, peripheral abnormalities and ventilatory function. Submaximal exercise capacity (SubMaxExC) is also increased, as assessed by a significant change in the ventilatory anaerobic threshold (VAT) and in the 6-MWT result. The improvement in SubMaxExC of CHF patients (NYHA II-III) is probably due to peripheral training adaptations in skeletal muscle mass (SMM). Theoretically, by improving SMM strength, a lower % of maximal contraction would be used to do a similar amount of work following training. A lower relative muscle contraction would be expected to produce less blood lactate, thereby decreasing the need for CO_2 elimination, thus increasing the VAT. The improvement in VAT is important, as it would allow patients to exercise longer and harder, without negative alterations in ventricular dynamics associated with VAT and possibly delaying the onset of the ischemic threshold. To severe CHF patients, the true meaning of SubMaxExC improvement as ExT effect is related to QOL since the engagement in daily activities does not demand VO_{2peak}. All the previous studies were done with low to moderate risk patients but high-risk patients probably have a greater need in order to lead a normal, independent life. Results from previous studies with CHF showed that ExT reduces NE levels at rest and during exercise [18] and decreases central sympathetic nerve outflow as measured by microneurography. ExT also enhances vagal control with a shift away from sympathetic activity, and improves heart rate variability (HRV) and heart rate recovery (HRR) with return to a better sympathetic-vagal balance [19]. Moreover, ExT produces significant reduction in the local expression of cytokines such as IL-6 and inducible nitric oxide synthase (iNOS) in the SMM of CHF patients [20] and has a beneficial effect on peripheral inflammatory markers reflecting monocyte/macrophage-endothelial cell interaction [21]. These local anti-inflammatory effects of ExT may attenuate the catabolic wasting process associated with the progression of CHF. This can be an important issue since inflammatory responses play a pathogenic role in the development and progression of CHF. Probably the impaired availability of nitric oxide (NO) is responsible for the impaired endothelium-dependent relaxation of peripheral resistance and conduit arteries and may contribute to the reduced FC in CHF and to other severe symptoms. Also endothelium-independent vasodilatation abnormalities may relate to a combination of impaired smooth muscle responsiveness to NO, impaired NO diffusion to the smooth muscle and structural alterations in arterial compliance associated with CHF [22]. The combination of ExT in CRT has not been well investigated, however some data show different aerobic exercise modes and intensities can further improve CRT benefits, including improvements in cardiac function, functional hemodynamic and exercise capacity, although data on skeletal muscle function are scarce [15,23-26]. Patwala *et al*. [15] found in-group improvements in peak skeletal muscle function, but no differences between the ExT group and the control group. They reported also improvements in QOL and VO_{2peak} through improved skeletal muscle mass performance with the addition of a 3-month ExT program, beginning 3-month after CRT implant. Limitations in sample size, mode, volume, frequency and intensity of ExT could all have biased the results.

Our previous experience with coronary artery disease patients [27,28], and most recently data in patients with CHF [29], show that an ExT program that combines aerobic exercise (AE) and resistance exercise (RE) training is more effective than an AE program alone, and that the aerobic interval training (AIT) showed better improvements than continuous endurance training. Another important issue is the fact that most of the studies of ExT in CHF patients have been conducted in CHF patients with less severe impairment. Very little or no information is available on patients NYHA class III-IV. It is unknown how CHF with more severe functional limitation respond to ExT and, more important, what is the explanation of the physiological mechanisms that can explain the improvements as a consequence of ExT. This lack of scientific information needs urgently to be responded, since this is the group of patients which is usually targeted for CRT. In 2011, we began our ExT project with CRT patients (PTDC/DES/120249/2010). It was a stratified randomized longitudinal study to determine the additional effects of a 6-month ExT (with AIT), in addition to CRT in NYHA stage III-IV HF patients. The aims of the study were: i) to determine whether a long-term ExT program following the CRT provides better clinical outcomes than CRT alone and ii) to identify the mechanisms of the hypothesized improvement. The primary end points for aim 1 were NYHA class, all-cause mortality, cardiac hospitalization rate, cardiac function and maximal and submaximal FC.

The exercise sessions were hospital-based, twice a week, 60 min each, for 6 months. We selected the aerobic interval training (AIT) method for the development of cardiopulmonary system with the inclusion of resistance and sensoriomotor exercises. The AIT design was done based on Wisløff protocol [29]. Due to the clinical status of our patients and longer intervention duration, a different (slower) exercise prescription progression has been employed. We have begun with shorter aerobic intervals and only at the end of the 2nd month we were able to apply the same protocol as Wisløff *et al*. [29]. Compared with continuous exercise training methods, this method allows patients with CHF to complete short periods of exercise at high intensity (which stress the heart's ability), but without deleterious effects of undue stress and fatigue. Another difference in the ExT program is the incorporation of resistive and sensoriomotor exercises. These types of exercises improve the lack of SMM of the CHF patients producing positive consequences in activities of daily life and QOL, and will enhance muscle performance of muscles, which are not involved in the aerobic mode of exercise.

The AIT comprised 4 interval training periods (high intensity) and 3 active pauses (moderate intensity) between interval training periods. The warm-up and aerobic training were conducted using treadmill walking. Patients warmed-up for 10 min at 50% to 60% of CRT-HR_{peak}, before walking to four 2-min intervals at 90 to 95% of CRT-HR_{peak}. Each interval, including the last one, was separated by 2 min active pauses, walking at 60% to 70% of CRT-HR_{peak}. After the first month, every week, each interval training and active pause were increased by 30 s, until we arrived to the 4-min work with 3 min active rest at the end of the second month. Total aerobic exercise time at this moment was 28 min and was maintained to the end of ExT intervention period. The speed and inclination of the treadmill was adjusted continuously to ensure that, in each interval training, the target heart rate (THR) was respected throughout the aerobic training period. Muscle resistance training used Thera-Band® equipment, free weight, dumbbells, and exercises using body weight. It consisted of 1-2 sets of 8-12 repetitions for each of the 6 exercises. Sensoriomotor training was also performed with Thera-Band® equipment, specially stability trainer and flex-bar in 1 to 2 exercises lasting 40 s each, 3 repetitions, with 20 s rest between sets. The resistance and sensoriomotor period had 15-17 min duration. The patients were instructed about correct exercise techniques and avoidance the Valsalva manoeuvre. Every session ended with a 5-7 min cool-down consisting on stretching exercises and relaxation. All patients were monitored using 12-lead ECG during all the exercise session to control both exercise intensity and safety during the high intensity workout, and during the execution of other exercises. Blood pressure was measured and the Borg 6-to-20 scale was used to assess the rate of perceived exertion during and after each training session. The exercise schedule was set according the patient possibility and was maintained during the 6-month intervention. No more than 2 patients were scheduled to the same daytime.

Our ongoing project (PTDC/DES/120249/2010) represents an important contribution to a better understanding of the implications of a combined therapy in CHF patients. Our project will be the first to provide how, in patients with severe CHF, imaging for sympathetic and parasympathetic autonomic nervous system in the heart may be modified over 6-month of AIT, after CRT. This may be of great value for stabilization or regression of the disease with direct impact in patient's daily life. The combination of MIBG scintigraphy, heart rate variability, heart rate recovery, echocardiographic measures and flow-mediated dilation will allow an overview of the expected adaptations and the underlying mechanisms. Four years are past, and this project remains innovative in addressing, with precision and valid methodology, the benefits of a 6-month aerobic high intensity interval ExT program on moderate-to-severe CHF patients after CRT. The preliminary findings and experience from this project have been presented over the last 3 years in National and International Scientific meetings.

Up to now, 58 CRT patients have been randomized to ExT (n=34) or control group (n=24) and 17 patients in the ET group have already completed all evaluation moments. The rate of functional responders in the ExT group was 9% higher (80%) than in the control group. In addition, we found higher exercise capacity and reverse cardiac remodeling and improved hemodynamic response in those patients engaged in the combined therapeutics. Both CRT and CRT + ExT groups increased peak oxygen capacity, LV ejection fraction and decreased the severity of symptoms, LV end-systolic volume and the load on the heart as assessed by B-type natriuretic peptide concentrations, providing evidence to soothe concerns harbored by cardiologists and other medical practitioners that habitual ExT may cause worsening of CHF. These and future findings on the central autonomic pathophysiologic basis of exercise intolerance in CRT patients and ExT induced changes will be published after all patients have completed the ExT.

Imaging predictive factors

It is well known that even selecting CHF patients according to CRT guidelines [30], a significant percentage do not respond to this therapy [3,31]. In order to achieve a better selection, the existence of factors, which could predict the response to CRT has been extensively investigated [32-35]. Factors, like female gender [36-38] and non-ischemic etiology [38,39] are related to a positive response to CRT and, on the contrary, some comorbidities, like end-stage renal failure and pulmonary hypertension appear to diminish the response to CRT [38]. Also, QRS duration and LBBB correlate positively with CRT response [40-42]. Additionally to clinical factors, imaging parameters have been evaluated for prediction of CRT response.

Besides evaluation of LV ejection fraction and LV end-systolic ventricular volume, standard echocardiographic parameters of LV mechanical dyssynchrony have been extensively studied in experienced centers [43-48], showing to predict CRT response. However, these data were not consistently replicated in multicentre studies [49,50]. In PROSPECT, a CRT randomized trial with long QRS patients [49], 12 different echocardiographic dyssynchrony parameters failed to relate to improved outcome after CRT. Even after validation by blinded core laboratories, no echocardiographic measure of dyssynchrony could reliably predict the response to CRT. Negative evidence also comes from the recent Echo-CRT study, which failed to show benefit from CRT-D in patients with QRS duration <130 ms and dyssynchrony assessed echocardiographically [50]. Accordingly, all clinical guidelines have abandoned echocardiographic measures of dyssynchrony for patient selection.

For a while, right ventricular function was forgotten, once CRT was developed to improve left ventricular systolic function. However, we know that right ventricular function had previously been related to exercise tolerance and prognosis [44-48]. Interestingly, right ventricular dysfunction, evaluated mostly by TAPSE, but also by DTI of tricuspid ring, was one of the features associated to nonresponse and in some cases to prognosis [9, 51-54].

Our group analyzed several variables, clinical, functional, echocardiographic and scintigraphic, as possible predictive factors for response to CRT, in the first 79 patients studied (68% male, mean age 68.1±10.2 years, 24% ischemic) [55]. At 6 months, 62% were considered as echocardiographic *responders*. Only TAPSE showed association with echocardiographic response (OR=1.13; 95%CI:1.02-1.26; p=0.020), with higher baseline TAPSE values predicting the responders. In our study, TAPSE <17, which is the defined cut-point between normal and abnormal right ventricular function, was not associated with echocardiographic left ventricular CRT response. However, decreasing cut-point to 15, lower TAPSE values, meaning moderate and severe RV dysfunction, associated to CRT nonresponse. We concluded that TAPSE was the only parameter in multivariate analysis associated to being a CRT responder, pointing out the importance of right ventricular function for CRT response in CHF patients [55].

It is very important to understand how much the presence of baseline RV dysfunction can affect LV reverse remodeling after CRT.

A few studies looked at the relation of previous RV dysfunction with CRT effect on LV and RV remodeling [9,51,56], showing that a low baseline TAPSE could predict a bad response to CRT.

Others, demonstrated the relation of RV dysfunction (low TAPSE values) to adverse prognosis [51] and the independent prediction of preserved RV function, evaluated by echo (including speckle-tracking strain imaging) for long-term event-free survival after CRT [52].

Although, the large study, CARE-HF [41], showed a smaller response of CRT in patients with severely reduced TAPSE (<14 mm), this association was not strong enough to consider TAPSE as an independent predictor of response to CRT [54].

On the other hand, Kjaergaard *et al*. [53], in the sub-analysis of the REVERSE study in which only class I-II CHF patients were included, demonstrated that TAPSE is an important predictor of outcome in CHF patients. Although changes of LV reverse remodeling were greater at 12 months follow-up in patients with TAPSE>14 mm, the additional effect of CRT did not reach statistical significance.

The differences in these studies might result from different populations and methodologies.

The existence of several limitations for echocardiography leads to the hypothesis that non-echocardiographic imaging techniques may optimize decision prior to CRT.

Computed tomography (CT) has been used for the assessment of scar burden after acute and chronic myocardial infarction [57,58]. Though no large published studies evaluated the impact of CT on CRT response, a small study, with 38 patients, evaluated dyssinchrony by CT, revealing a good correlation of global dyssinchrony parameters, much better than regional, with CRT response[59].

Cardiac magnetic resonance (CMR), recognized as the gold standard to assess viability [60], has shown to obtain good results regarding quantification of scar burden [61,62]. A linear relationship between total scar and LV remodeling or response to CRT has been described [63-65]. Furthermore, CMR derived measures of mechanical dyssynchrony appear to predict the outcome of CRT [66], however they have not been externally validated.

Nuclear imaging techniques, namely single-photon emission cardiac tomography (SPECT) provide data on scar burden and location, LV function, LV contraction and mechanical dyssynchrony from a single

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scan [67-70]. The presence, location and burden of myocardial scar have been shown to affect response to CRT [71]. An inverse relationship was described between the extent of fixed perfusion defect and absolute or relative increase in LVEF 6 months post-CRT (r=-0.63 and -0.53, p<0.01). Furthermore, patients who responded to CRT had lower global scar burden and scar density versus non-responders. An advantage of SPECT is the ability to automatically quantify the scar burden with good reproducibility [72]. However, comparing to CMR, the low spatial resolution of cardiac scintigraphy might overestimate the extent of scar. This problem can be overcome in nuclear cardiology, to a certain extent, by positron emission tomography (PET).

SPECT has also been used to quantify dyssynchrony [73], using phase analysis [67].

One of the most interesting nuclear techniques for studying CHF is related to autonomic nervous system function. Cardiac 123I-MIBG scintigraphy is a nuclear imaging technique which allows to image autonomic cardiac innervation.

CRT has been shown before to improve sympatho-vagal balance in patients with advanced heart failure [74-76]. It is not known whether this improvement is due to changes in circulating plasma catecholamines, central sympatho-vagal tone, or to direct cardiac innervation. Specific cardiac sympathetic nerve activity can be assessed by 123I-metaiodobenzylguanidine (123I-MIBG) scintigraphy. 123I-MIBG shares the same presynaptic uptake, storage, and release mechanisms as norepinephrine, but is biologically inactive. Increased MIBG washout, representing increased sympathetic nerve activity, has been associated with increased risk of sudden death and hospital admission for heart failure in patients with systolic heart failure [77,78].

It has been demonstrated that CRT reduces mortality, due to heart failure, as well as to sudden death [7,79]. The reduction in sudden death by CRT is intriguing, and may be due to substrate modification because of reverse remodeling, as well as to changes in sympathetic activity. Burri *et al.* [80] assessed changes in cardiac adrenergic activity by 123I-MIBG scintigraphy with cardiac resynchronization therapy (CRT) and investigated whether these changes were related to improvement in left ventricular ejection fraction (LVEF) in a small group of 16 patients, at baseline and after 6 months of CRT (mean follow-up 9.2+3.2 months). Responders (8 patients), defined as showing 5% absolute increase in LVEF, improvement in 1 NYHA class and absence of heart failure hospitalization, showed lower 123I-MIBG washout at follow-up when compared to non-responders (p=0.002), indicating lower cardiac sympathetic nerve activity. Decrease in 123I-MIBG washout at follow-up compared to baseline was only seen in the responder group (p=0.036). A moderate correlation was present between increase in LVEF and decrease in 123I-MIBG washout (r= 0.52, p=0.04). CRT induced a reduction in cardiac sympathetic nerve activity in responders that paralleled an improvement in LVEF, whereas non-responders did not show any significant changes. This study showed, for the first time, that responders to CRT have a reduction in cardiac sympathetic nerve activity at follow-up, reducing 123I-MIBG washout, whereas non-responders do not show any significant changes. There was a significant (albeit moderate) correlation between improvement in 123I-MIBG washout and improvement in LVEF because of CRT.

To date, the use of MIBG cardiac scintigraphy in our CRT patients has identified more severe autonomic dysfunction and worst prognosis in nonischemic CRT patients **[81]**. In our patients, scintigraphic parameters were associated with echocardiographic response and risk of ventricular sustained events **[82]**. Cardiac autonomic nervous system dysfunction evaluated by MIBG cardiac scintigraphy in CRT patients seem to have a predictive value for the occurrence of sustained ventricular arrhythmic events, therefore contributing to decision-making on CRT device with or without defibrillator capacity.

In our ongoing High Intensity Aerobic Interval Study (BETTER-HF), preliminary comparison of exercise and control groups showed a difference in clinical functional class variation (Δ) (p=0.01), ΔWO (-18.970±29.565 *vs* 13.212±18.274; p=0.012) and HMR (0.045±0.1 *vs* -0.137±0.202; p=0.021), being significantly better in the exercise group (AIT).

Although preliminary, high intensity interval exercise training, in CHF patients submitted to CRT, looks to improve by itself clinical functional class and nervous system autonomic function. The conclusion of BETTER-HF study might confirm this data.

Imaging investigation will continue, trying to better understand those who might not be able to respond to CRT.

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