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The effects of aerobic interval training on heart rate recovery after cardiac resynchronization therapy

Dissertation presented for Master of Science degree in Exercise and Health

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"*Porque o homem é sempre mais*
do que aquilo que sabe acerca de si…"

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ABSTRACT

Background: Heart failure is characterized by an autonomic nervous system dysfunction which leads to sympathetic overactivation and parasympathetic imbalance, culminating in central and peripheral dysfunction. In advanced HF, cardiac resynchronization therapy (CRT) and exercise training seem to improve these conditions and result in improved functional and clinical parameters. A growing body of evidence supports the benefits of aerobic interval training (AIT) in other several HF populations, but less is known about its influence on autonomic function. Here we assessed the effects of AIT on the heart rate recovery (HRR), an indicator of parasympathetic activity. All participants had HF with a reduced ejection fraction, and six days before the intervention, underwent cardiac surgery. Our objective was to compare if the additive effect of AIT to CRT could indeed result in improved vagal reactivation, measured by the difference between the peak heart rate and the HRR at one minute (HRR_{1diff}). **Methods:** Twenty-nine stable patients (aged 68.96 ± 9.92; LVEF< 27%; and a $\dot{V}O_{2Peak}$= 15 $mL.kg^{-1}.min^{-1}$) who were receiving optimal medical treatment, were randomized either to the control group, or the AIT group. The AIT group exercised twice a week, and began each session with a 10 minute warm-up (50-60% of the peak heart rate), followed by four intervals of 2-minutes (90-95% of the peak heart rate) and a 2-minute recovery (60-70% of the peak heart rate). After the first month, the 2-minute intervals were changed to 4-minute intervals and 3-minutes recovery. After cardiopulmonary exercise testing (CPET) to maximal volitional exertion, using the modified Bruce protocol, patients were seated and the HRR was immediately assessed. **Results:** After the six months of intervention our main effects were significant for $\dot{V}O_{2Peak}$ (*p*= .010) and CPET duration (*p*= .025). Thus, after testing for simple main effects, only the AIT group depicted significant changes in the post-intervention for: $\dot{V}O_{2Peak}$ (*p*= .013), CPET duration (*p*= .020), heart rate reserve (*p*= .035), peak pulse pressure (*p*= .036), and the HRR_{1diff} (*p*= .025). **Conclusions:** After six months of intervention, the simple main effects suggest that AIT could improve vagal reactivation, assessed through HRR_{1diff}, in patients that underwent CRT and were engaged in optimal medical treatment. Our findings also suggest that differences between groups in exercise capacity could be due to peripheral factors. **Keywords:** Heart failure; Heart rate recovery; Vagal reactivation; Aerobic interval training; Cardiac resynchronization therapy.

RESUMO

Contexto: A insuficiência cardíaca (IC) é caraterizada por uma disfunção do sistema nervoso autónomo (SNA) que conduz a uma hiperativação simpática e desiquilíbrio parassimpático, culminando em disfunções centrais e periféricas. Nos casos mais avançados de IC, a terapêutica de ressincronização cardíaca (TRC) e o exercício parecem melhorar estas condições e, outros parâmetros clínicos e funcionais. O emergir de evidência robusta valoriza o treino intervalado aeróbio (TIA) em várias populações com IC, sabendo-se pouco acerca da sua influência sobre o SNA. Nesta análise, avaliámos os efeitos do TIA sobre a frequência cardíaca de recuperação (FCR), um indicador de ativação parasimpática. Todos os participantes possuíam uma fração de ejeção diminuída para ventrículo esquerdo, e colocaram o implante cardíaco seis dias antes do início da intervenção. O nosso objetivo foi o de avaliar se o TIA adicionado à TRC poderia melhorar a reativação vagal, medida pela diferença entre a frequência cardíaca pico e a FCR no primeiro minuto (FCR_{1dif}). **Métodos:** Vinte e nove participantes (idade 68.96 ± 9.92; FEVE< 27%; e o $\dot{V}O_{2Pico}$= 15 $mL.kg^{-1}.min^{-1}$) que estavam a receber tratamento médico otimizado (TMO), foram randomizados diferencialmente para os grupos de TIA e de controlo. O grupo de TIA realizou duas sessões de treino semanais, iniciando as mesmas com 10 minutos de aquecimento (50 a 60% da FC pico), seguido de quatro intervalos de 2 minutos (90 a 95% da FC pico) e 2 minutos de recuperação ativa (60 a 70% da FC pico). Depois de concluído o segundo mês, os intervalos de 2 minutos foram substituídos por intervalos de 4 minutos, enquanto os intervalos de recuperação por outros de 3 minutos. Recorrendo à prova de *stress* cardiopulmonar (PSCP), a qual foi efetuada até a capacidade volitiva máxima usando o protocolo de Bruce modificado, a FCR foi avaliada imediatamente a seguir ao mesmo. **Resultados:** A seguir aos seis meses de intervenção, os efeitos principais foram significativos para $\dot{V}O_{2Pico}$ (p= .010) e a duração da PSCP (p= .025). Contudo, depois de se testarem os *simple main effects*, apenas o grupo de TIA apresentou alterações significativas no período pós-intervenção para: $\dot{V}O_{2Pico}$ (p= .013), duração da PSCP (p= .020), frequência cardíaca de reserva (p= .035), pressão de pulso pico (p= .036), e FCR_{1dif} (p= .025). **Conclusões:** Depois de seis meses de intervenção, os *simple main effects* sugerem-nos que o TIA pode melhorar a reativação vagal, medida pela FCR_{1dif} a seguir ao exercício em pacientes que se encontram em TRC e TMO. Os resultados sugerem-nos ainda que as diferenças encontradas na capacidade funcional devem-se a fatores periféricos. **Palavras chave:** Insuficiência cardíaca; Frequência cardíaca de recuperação; Reativação vagal; Treino intervalado aeróbio; Terapêutica de ressincronização cardíaca.

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Abbreviations

ACCF	American College of Cardiology Foundation
ACE-I	Angiotensin-converting enzyme inhibitors
AHA	American Heart Association
AHF	Acute Heart Failure
AIT	Aerobic interval training
ANS	Autonomic nervous system
AVD	Atrioventricular delay
Ca^{2+}	Calcium
CHF	Chronic HF
CRT	Cardiac resynchronization therapy
ESC	European Society of Cardiology
ExT	Exercise training
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reserved ejection fraction
HR	Heart rate
HRR	Heart rate recovery
HRR_1	HRR at 1-minute
HRR_3	HRR at 3-minute
HRR_6	HRR at 6-minute
HRR_{1diff}	Difference between the peak heart rate and the HRR at 1-minute
HRR_{3diff}	Difference between the peak heart rate and the HRR at 3-minute
HRR_{6dif}	Difference between the peak heart rate and the HRR 6-minute
LBBB	Left bundle branch block
LV	Left ventricle
LVEDV	Left ventricle end-diastolic volume
LVEF	Left ventricle ejection fraction
LVESV	Left ventricle end-systolic volume
NYHA	New York Heart Association
QoL	Quality of life
RCT	Randomized clinical trials
RER	Respiratory exchange ratio
TRIMP	Training impulse method
$\dot{V}O_{2Peak}$	Peak oxygen uptake
$\dot{V}O_{2Max}$	Maximal oxygen uptake

Preamble

An analysis was carried out based on the variables collected from a financially supported investigation project, by the Portuguese Foundation of Science and Technology (i.e., PTDC/DES/120249/2010), and was conducted with the authors' approval. Should the reader feel the need for more detailed information regarding the project or other points of interest, information is available upon request.

With the successful integration of cardiac resynchronization therapy in clinical practice, it is important to explore new paths of unknown knowledge. In this context, the interaction between the autonomic nervous system, exercise and cardiac resynchronization is of extreme importance, as it can improve the patient´s condition.

In this thesis, the **aim** was: To determine the effects of a long-term exercise training program following cardiac resynchronization therapy, while controlling for autonomic function.

The document is organized by chapters, and the reader can follow our rationale throughout each one of them. **Chapter I** is the introduction, were we describe the state of the art of the main topics of our theme, and engage through a brief consideration of our problem. At the end we identify our main hypothesis. **Chapter II,** the literature review, will be dedicated to some of the mechanisms of HF pathophysiology, and how they can benefit from cardiac pacing, exercise or both. The autonomic modulation that seems to occur through pacing will be explored, and detailed attention will be given to the exercise mechanisms responsible for specific central and peripheral adaptations, particularly those related with exercise intensity. The following chapters will then be dedicated to the methodology (**Chapter III**), the results (**Chapter IV**), the discussion and main conclusions (**Chapter V**), and finally, all the references used to elaborate the complete thesis (**Chapter VI**).

CHAPTER I

Introduction

The economic burden of heart failure with reserved ejection fraction (HFrEF) to the western healthcare system has grown and heart transplant inevitability becomes an unsustainable option for every patient (Clarke et al., 2014; Jessup et al., 2011), furthermore, with the increasing ageing population and the growing life expectancy (Beard & Bloom, 2015). Although advances in the treatment and management of heart failure (HF) syndrome can be seen, poor prognosis mirrors an underlying complex pathophysiology (McMurray et al., 2012; Yancy et al., 2013). Indeed, several etiologies, both cardiovascular and non-cardiovascular, have the final common pathway of abnormal cardiac function which results in maladaptive cardiac remodelling. Nevertheless, new methods have been design for accurate diagnosis, prognosis, and risk stratification in clinical practice and experimental field (Brignole et al., 2013; Ponikowski et al., 2016). Considering these epidemiological issues, cardiac resynchronization therapy (CRT) as emerged in a burst of knowledge, technology, and avant-garde approach from distinct areas such as engineering, informatics and medicine (Barold, 2011; Nelson, 1993; Park, Kushwaha, & McGregor, 2012; Zoll, 1973).

The HF syndrome is a continuum and vicious cycle characterized by the hallmarks exercise intolerance and fatigue (Kupper, Bonhof, Westerhuis, Widdershoven, & Denollet, 2015; West, Hernandez, O'Connor, Starling, & Califf, 2010). Concomitantly, form and function become altered, while central and peripheral mechanisms will reflected themselves on several physiological dysfunctions, such as cardiac dyssynchrony (Bank et al., 2015) or muscle myopathies (Piepoli & Crisafulli, 2014). Interestingly, resynchronization seems to improve both of these conditions, as well as challenge the vicious and auto-proliferative cycle of HF. Similarly, exercise training (ExT) has exhibit improvements in clinical and functional parameters in a wide range of HF patients, including those engaged on CRT with optimized therapeutics (Conraads et al., 2007; Haykowsky et al., 2007).

According to Florea & Cohn (2014) the HF syndrome progression is a reflex of the autonomic nervous system (ANS) imbalance. The syndrome seems to be mediated by neurohumoral activation, which has a clinical manifestation of sympathetic overactivation and parasympathetic withdrawal (Levy, 1971; Lymperopoulos, Rengo, & Koch, 2013). In recent years, the heart rate recovery (HRR) has been used as a non-invasive and easy way to assess this interdependent relationship. As suggested by Myers et al. (2007), the HRR has a prognostic value and represents an important clinical index of functional capacity and hemodynamics in HF. There is few information regarding autonomic function and CRT, particularly when assessed through the HRR. Could CRT improve autonomic modulation and improve the HRR? If adrenergic and cholinergic receptors are intimately related and a coordinate sympathetic and vagal control is essential for hemodynamics homeostasis (Levy,

1984), as well as for neurohumoral modulation (Arena et al., 2010), could this relationship, altered by HF, be improved by exercise, particularly in the form of aerobic interval training (AIT), and alongside with CRT? Additionally, there are several muscarinic receptors subtypes (Wang et al., 2001) that can actually modulate, and be modulated, in their responsiveness sensibility and specificity to particular amines (e.g., norepinephrine). More, Okutucu et al. (2011) conducted a randomized controlled trial with CRT patients, and suggested that the HRR at 1-minute (HRR_1) could reflect vagal reactivation while the HRR at 3-minute (HRR_3) could be mediated, predominantly, by sympathetic withdrawal. In this particular, several trials conducted with HF populations and adopting AIT protocol depicted improvement in functional parameters (Guiraud et al., 2013; Johnsen, Hoydal, Rosbjorgen, Stolen, & Wisloff, 2013), vagal tone (Guiraud et al., 2013), and QoL as well (Nilsson, Westheim, & Risberg, 2008). However, the effects of AIT in CRT patients assessed through the HRR are not clearly elucidated yet. Moreover, to our knowledge there is only one trial that addressed CRT and the HRR (Okutucu et al., 2011). Furthermore, to our knowledge, the effect of the AIT on improving vagal reactivation in CRT-patients has never been studied. Therefore, the present analysis will focus on finding evidence that clarifies some of the uncertainty regarding these issues.

Chapter II

Literature Review

2.1 Heart failure

EPIDEMIOLOGY AND CLINICAL CRITERIA

The incidence and prevalence of heart failure (HF) in modern society is a growing and serious epidemiological issue (Bleumink et al., 2004; Brouwers et al., 2013; Curtis et al., 2008; Guha & McDonagh, 2013; Levy et al., 2002). HF is estimated to affect more than 23 million people worldwide and be accounted for more than 1 million hospitalizations each year (Roger, 2013), and although its prognostic value is dependent upon several variables, 50% of the patients die within 5 years of the initial diagnosis (Bui, Hornich & Fonarow, 2011). Additionally, the prevalence of HF with preserved ejection fraction (HFpEF) is over 50% within symptomatic HF (Edelmann et al., 2011; Frohling, et al., 2011), having superseded other forms of HF such as HF reduced ejection fraction (HFrEF) (Guha & McDonagh, 2013; Kitzman et al., 2014). Furthermore, HFpEF morbidity, mortality, and functional decline are escalating and almost near HFrEF levels (Edelmann et al., 2011; Kitzman, Brubaker, Morgan, Stewart, & Little, 2010). In response to these facts, the HF syndrome implies more knowledge and epidemiological evidence to respond efficiently to the previous progressive and harmful scenario. Nevertheless, some authors (Guha & McDonagh, 2013) prefer to focus on the unclear definition of HF and inclusion criteria in trials, which may question some gushing fears and trends.

HF is a complex clinical syndrome with signs and symptoms that result in congestion, and/or tissues hypoperfusion (McMurray et al., 2012; Saxon & Marco, 2001). As a multifactorial syndrome it has different etiologies that impair both structure and function, with a direct impact over central (Zile et al., 2013) and peripheral (Amann et al., 2014) homeostasis. It seems difficult to formulate a specific definition for HF considering how complex this syndrome is. However, we can observe its natural history, possible etiology and pathophysiology, and proceed to HF stratification by classification (i.e., New York heart association functional class) (Dolgin, 1994) or HF stages as depicted in Table 1 (Hunt et al., 2009).

According to expert consensus from both the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA), and also the European Society of Cardiology (ESC), the New York Heart Association (NYHA) functional class is more than standard policy and refers to an important step both in clinical (i.e., preventive, prognostic, management of HF) and research field (i.e., trials randomization) (McMurray et al., 2012; Yancy et al., 2013). However, some confusion may arise from asymptomatic cardiac

dysfunction, although pathology is present (e.g., systolic dysfunction, diastolic dysfunction). Whereas NYHA functional class refers to HF syndrome symptoms and exercise capacity, which may change rapidly, the stages of HF (Table 1) focus on the development and progression of the underlying disease and objective criteria described elsewhere (Dolgin, 1994; Hunt et al., 2009). Interestingly, these two characteristics are complementary to one another and their intrinsic relation is illustrated in Table 2.

Table 1. American Heart Association/American College of Cardiology guidelines – stages of heart failure.

Stage	Description
A	Patients at high risk of developing HF because of conditions strongly associated with the development of HF. Such patients have no identified structural or functional abnormalities of the pericardium, myocardium, or cardiac valves and have never shown signs or symptoms of HF.
B	Patients who have developed structural heart disease that is strongly associated with the development of HF but who have never shown signs or symptoms of HF.
C	Patients who have current or prior symptoms of HF associated with underlying structural heart disease.
D	Patients with advanced structural heart disease and marked symptoms of HF at rest despite maximal medical therapy and who require specialized interventions.

HF-Heart failure.
Adapted from Hunt et al. (2009)

According to the ACCF/AHA (Yancy, 2013) and corroborated by others (McMurray et al., 2012), HF is defined as "*a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill or eject blood*". However, to an understanding of HF syndrome, a distinction should be made between acute heart failure (AHF) and chronic HF (CHF). AHF describes patients with tissues hypoperfusion and reduced functional capacity or pulmonary edema that limits active daily living, while CHF describes stable patients with a cardiac dysfunction who may experience decompensation episodes (Pani et al., 2015).

Patients with CHF have received more attention in trials and experimental studies than acute HF patients. In part, this could be due to the difficulty in defining and classifying AHF, although according to ESC guidelines (McMurray et al., 2012) a straightforward interpretation is proposed, namely as: *"a rapid onset of, or change in, symptoms and signs of heart failure"*.

Table 2. Comparison of the American Heart Association/American College of Cardiology - Stages of heart failure and New York Heart Association functional classification.

ACCF/AHA Stages of HF		NYHA Functional Classification	
A	At high risk for HF but without structural heart disease or symptoms of HF	None	
B	Structural heart disease but without signs or symptoms of HF	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF
C	Structural heart disease with prior or current symptoms of HF	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF
		II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF
		III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF
D	Refractory HF requiring specialized interventions	IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest

ACCF/AHA=American heart association/American college of cardiology; NYHA=New York heart association; HF=Heart failure.
Adapted from (Yancy, 2013)

Regrettably, cardiac dysfunction is progressive and leans toward the progression of CHF, with episodic manifestations through AHF (Gaasch & Zile, 2011). Ponikowski et al. (2016), refers that miscellaneous etiologies can be observed in different parts of the world- differing from cardiovascular and non-cardiovascular- that cooperate to HF. Regardless of the aetiology, myocardial injury seems to be the beginning process, followed by cardiac dysfunction and finally HF syndrome (Levy, Larson, Vasan, Kannel, & Ho, 1996; Mosterd & Hoes, 2007; Vasan, Larson, Leip, Kannel, & Levy, 2001). Although improvements in the treatment and the diagnosis of clinical or even preclinical HF conditions have been gradually effective, poor outcomes continue to be challenging for clinicians (Ponikowski et al., 2016).

HF is a multi-systemic syndrome, and most of HFrEF patients present multiple comorbidities and geriatric syndromes (e.g., Frailty, Sarcopenia, Cachexia), alongside with a highly depressed ventricular function (Cruz-Jentoft et al., 2010; Goldwater & Pinney, 2015; Jermyn & Patel, 2014; Jha et al., 2015; Murad & Kitzman, 2012). These patients can exhibit peak oxygen uptake ($\dot{V}O_{2Peak}$)≤ 14 $mL.kg^{-1}.min^{-1}$, which is associated with poor prognosis (Arena, Myers, Abella, Pinkstaff, et al., 2010), increased mortality (Mancini et al., 1991), and can be a landmark for a differential therapeutic approach such as cardiac resynchronization therapy (CRT). CRT can have a direct impact over central function, but remarkably it also seems to be accountable for indirect improvements on peripheral mechanisms such as skeletal myopathies (Piepoli & Crisafulli, 2014) or even several chronic diseases (Booth, Roberts, & Laye, 2012; Kujala, 2006; Pedersen, 2011). Both of this changes induced by CRT can express themselves as exercise improvement (Jaussaud, Blanc, Bordachar, Roudaut, & Douard, 2011) and decrease baseline sympathetic activation (Hamdan et al., 2002; Middlekauff, 2005).

Interestingly, we have been following a line of thought were we interpreted HF as being solely a unique entity and complex syndrome, and our approach, merely theoretically, must be seen in a whole wide spectrum, as a continuum (Levy et al., 1996; McMurray et al., 2012; Vasan et al., 2001). Actually, in CHF, less physical activity and muscle disuse can be seen. The decreased functional capacity is a result of several factors, and not only cardiomyopathies themselves (Dalal, Doherty, & Taylor, 2015). This concomitant and auto-proliferative effect is meaningful over the natural history of HF syndrome, and a burden that must be taken into account when approaching cardiac rehabilitation.

TYPES OF HEART FAILURE

If we delve into cellular mechanisms or sub-cellular levels, proinflammatory biomarkers also seem to have a role in pathogenesis of HF (Dixon, Griggs, Bersten, & Pasquale, 2011; Fink et al., 2012). Cytokines, chemokines and cell adhesion molecules result in cardiac maladaptive remodelling, which is more than simple heart dysfunction, and involves complex signalling pathways (Briasoulis, Androulakis, Christophides, & Tousoulis, 2016). Evidence supports that CHF exhibit activation of neurohormones (e.g., atrial natriuretic peptide, brain natriuretic peptide, and norepinephrine) and proinflammatory cytokines (e.g., IL-6, TNF-α, IL1-β) (Cheng et al., 2013; Ferrari, 2002; Guggilam et al., 2011; Kinugawa et al., 2003). These proinflammatory agents regulate the immune response that will alter cellular metabolism, induce stress and result in morphological and mechanical impairments (Torre-Amione, 2005). These processes seem to be dependent upon innate and adaptive immunity from an evolutionary perspective (Kasturi et al., 2011; Padovan & Martin, 2015; Parham, 2003), and represent a normal physiological response of the immune

system, but if these environment persists, it may become toxic and reflect a chronic detrimental adaptation (Despres & Lemieux, 2006; Hotamisligil, 2006; Libert, 2003). Ultimately, this chronic detrimental adaptation can lead to increased cardiometabolic risk and differential clinical manifestations for risk stratification (Walsh, Fang & Fuster 2013).

Most recent ESC guidelines (Ponikowski et al., 2016) enunciate a “new form” of HF, more concretely HF with mid-range EF that ranges between 40 to 49%. Alongside, HFpEF and HFrEF are characterized by reduced physical capacity that can be measured subjectively by exertional dyspnea or objectively by $\dot{V}O_{2Peak}$. Despite research, mechanisms for exercise intolerance and exertional dyspnea in HF patients´ are not completely understood (Kupper et al., 2015; West et al., 2010). Reduced exercise capacity seems to be associated with chronotropic incompetence as a result of impaired heart rate (HR) and cardiac output (Borlaug et al., 2006; Zile et al., 2013). In HFpEF, limitation is firstly due to impaired peripheral function (Haykowsky et al., 2014) and later resulting in the two hallmarks of HF (i.e., exercise intolerance, dyspnea). In one hand, HFrEF expresses peripheral dysfunction coexistence with other multi-systemic impairments, and pulmonary function seems to be the first to limit exercise progression (Kupper, Bonhof, Westerhuis, Widdershoven, & Denollet, 2015; Poon & Tin, 2013). On the other hand, HFpEF expresses diastolic dysfunction, although with left ventricle ejection fraction (LVEF) and left ventricle end-diastolic volume (LVEDV) seems to remain unchanged in most cases (Kitzman et al., 2014). According to these authors, recent attention has being refocusing on peripheral mechanisms as the main source of HF impairments (Kitzman et al., 2014). Concerning HFrEF, there is a systolic dysfunction that affects the rate of myocardium contraction (chronotropy) (Brubaker & Kitzman, 2011), that impairs myocardium contractility (inotropy) and its relaxation (lusiotropy) (Abraham et al., 2015). Moreover, these adverse scenario affects the intrinsic electrical conduction system (dromotropy) (Crocini et al., 2014).

In both of these cases, an elevation of left ventricle (LV) pressure seems to affect right ventricular performance because of secondary pulmonary artery pressure elevation (Solomonica, Burger, & Aronson, 2013). On a different approach, Kaufmann et al. (2013) conducted a multicentre prospective cohort study with subclinical cardiovascular disease as an inclusion criterion, and some of the conclusions were that right ventricular function and morphology seem to be associated with dyspnea, even when adjusted for covariates such as left ventricular function or lung function.

If we´ve been distinguishing HFrEF (systolic dysfunction) from HFpEF (diastolic dysfunction), we must also explain why. In good truth, by separating these two entities we oversimplify a highly complex condition to get deeper into the idiosyncrasies of each type of HF. According to Komamura (2013), HF should be considered as a single and continuous disease, being the two extremes, systolic and diastolic dysfunction phenotypes. The author

emphasizes how distinctive adaptations of the LV occur, more specifically eccentric hypertrophy (systolic HF) and concentric remodelling/hypertrophy (diastolic HF). However, if there are similarities between both conditions, there are also heterogeneous responses, particularly to exercise-induced changes in LV systolic and diastolic properties (Zile et al., 2013).

Interestingly, improvement of exercise capacity is an independent predictor of mortality in HF (Boxer et al., 2010; Tang, Dewland, Wencker, & Katz, 2009), and seems to be associated with those that can be seen with CRT (Takeuchi et al., 2014; Tomczak et al., 2012; Wasserman, Sun, & Hansen, 2007). Primary receivers of CRT are elder and severe HFrEF patients (Schowalter et al., 2013), with pronounced limitations for activities of daily living and whom also experience a higher risk of sudden death, especially when compared with less severe HF patients (Park et al., 2012). When these patients fulfil certain criteria, an implantable cardiac device such as CRT can prevent heart transplant, ameliorate symptoms, improve quality of life (QoL) and improve functional capacity (Cleland, Daubert, & Erdmann, 2005; Marco et al., 2008).

2.2 Cardiac resynchronization therapy

In 2013, the ACCF in collaboration with the Heart Rhythm Society proposed a clinical cardiology practice based on pacing therapy for primary prevention, secondary prevention and even for some comorbidities (Russo et al., 2013). Novel evolutions in HF pharmacotherapy became powerful adjunctive therapeutic to biodevices (e.g., CRT) (Brignole et al., 2013; McMurray et al., 2012; Yancy et al., 2013). The two most common pharmacologic options are angiotensin-converting enzyme inhibitors (ACE-I) and β-blockers, both of which seem to attenuate symptoms, improve QoL, slow progression of HF and contribute to reversal of maladaptive cardiac remodelling (Zile et al., 2013). Added to the widespread use of pacing in a new avangard cardiology era, this scenario is only possible due to epidemiological evidence and on-going burst of knowledge in technology, engineering and medicine.

According to Nelson et al. (1993), in their early days of cardiac pacing, benefits erupted from empirical clinical practice rather than proven by clinical trials. In the 1990´s, the first trials, with relevance for PATH-CHF (Auricchio et al., 1999), approaching of new pacing methodologies were conducted but with little statistical power. Since then, several landmarks have been achieved, and one of the most important is the criteria for device implantation, such as CRT (Poole, 2014).

DYSSYNCHRONY AND RESYNCHRONIZATION

Cardiac dyssynchrony is a complex and multifactorial process (Bank et al., 2015; Sahlen et al., 2010; Verma, Lemler, Zeltser, & Scott, 2010; Yamamoto et al., 1992). We can identify electrical and mechanical dyssynchrony, and each of them occurring at numerous levels. Their manifestation can be seen within the atria, within the atria and the ventricles, and at different levels in the ventricles (i.e. intraventricular, interventricular). In addition, when the normal interplay between intrinsic and extrinsic heart control mechanisms become altered, cardiac remodelling occurs. This remodelling includes both morphological and functional alterations, as a result of structural and electrical adaptations (Arbab-Zadeh et al., 2014; Paulus & Tschope, 2013; Ravassa et al., 2015; Zhang et al., 2015). Inter and intra-ventricular electrical conduction delays reduces cardiac efficiency by reducing stroke volume, systolic pressure, and induce LV wall dyssynchrony and right ventricular/LV wall dyssynchrony, while enhancing myocardial contractility through CRT seems to improve it (Valzania, Gadler, Boriani, & Eriksson, 2011).

CRT has also evidenced, increases in LV filling times and LVEF (Kosmala & Marwick, 2014). This hemodynamic advantage reflects itself in enhanced myocardial metabolic and contractile efficiency, while form and function become more harmonious and problematic LVEDV and left ventricle end-systolic volume (LVESV) improve (Ballo, Mondillo, & Galderisi, 2006). According to Linde et al. (2012), ventricular systolic dysfunction is a hallmark of dilated cardiomyopathy, and beside muscle geometry remodelling, electrical remodelling is also present independently in both ventricles, and may contribute synergistically to the aforementioned (Auricchio & Spinelli, 2000; Leyva, Nisam, & Auricchio, 2014; Paulus & Tschope, 2013).

When atrioventricular delay (AVD) is observed, ventricular systole and ventricular relaxation are delayed as well (Abraham et al., 2002; Young et al., 2003). In normal individuals, atrial and ventricular pressures decrease during relaxation, and increase during contraction. However, if AVD is present, atrial systole will occur under high ventricular pressures (Aktoz et al., 2011), which in turn could lead to mitral regurgitation, decreased preload and depressed LVEF (Nishimura, Hayes, Holmes, & Tajik, 1995).

CRT, dyssynchrony and myocardial oxygen consumption seem to share complex interactions and implications on substrate utilization that may, further, be altered by the underlying HF etiology and pathophysiology (Goliasch et al., 2012; Saxon & Marco, 2001). Nikolaidis et al. (2004) experimental study investigate the effect of adrenergic stimulation in myocardial oxygen consumption and coronary blood flow in HF, and found their deleterious effects on myocardial mechanical efficiency, particularly in the severe CHF arm. These findings were corroborated by Doenst et al. (2013) literature review, which suggested that

myocardial oxygen consumption deficiency seems to alter normal metabolic function in patients with systolic dysfunction.

If dyssynchrony seems to have an independent negative impact on morbidity and mortality, a common way to assess is through the QRS complex (Aleksova et al., 2014). However, QRS complex also reveals the complication of dyssynchrony. On this matter, and according to Brignole et al. (2013), regardless of imaging techniques criteria to evaluate dyssynchrony, CRT trials have typically been based on QRS duration> 120 ms. Contrarily, recent trends seem to emphasize their attention on QRS morphology (Poole, Singh, & Birgersdotter, 2016). QRS morphology may reflect electromechanical dyssynchrony in a more specific and sensitive way (Nagao et al., 2014). Alongside, left bundle branch block (LBBB) is an electrical abnormality and a surrogate for ventricular dyssynchrony that is present in one third of patients with HF (Baldasseroni et al., 2002). Sub-analyses of randomized clinical trials (RCT) and meta-analyses have evidenced LBBB morphology benefits from CRT, and therefore a class I indication and a level A of evidence recommendation to receive this therapeutic (Brignole et al., 2013; Russo et al., 2013).

TRIALS – WHAT DID WE LEARN FROM THEM?

In the birth of CRT era, single centre trials were conducted, whereas limited by their external validity and statistical power, they provided useful information for later use in larger and multicentre trials (Leyva et al., 2014; Linde, Ellenbogen, & McAlister, 2012). According to a meta-analysis of CRT and selected RCT, until 2005 only nine clinical trials had been conducted and terminated (Linde, Ellenbogen & McAlister, 2012). Among these trials, analogous inclusion criteria could be observed. Depicted in Table 3, NYHA functional class (III/IV), depressed systolic LV function, LVEF< 35% and also QRS> 120ms with interventricular conduction disorder were inclusion criteria for these RCT. Importantly, most of the studies also reported improvements in all of these bus parameters. Similar primary end-points were also observed, although secondary end-points tend to vary from a strict range of echocardiographic measurements (e.g., LV systolic function, LVEF, LV reverse remodelling, LV volumes and Mitral regurgitation) (Table 4). Linde et al. (2012) refer that key studies on moderate to severe HF, as others on mild HF patients receiving CRT, were based on LVEF< 35% and QRS wider than 120ms. Jabbour et al. (2015) elaborated a meta-analysis were they pursue either or not some of the reported CRT benefits could be extended for narrow QRS patients? According to these authors, this extrapolation could be deceiving because poor study designs could have induced unwanted bias and conflicting results for CRT benefits in patients with narrow QRS. Conflicting evidence clearly complicates the complexity of synchrony and CRT. In addition, the indications for CRT are not limited to the measurement of LVEF, QRS complex, monitoring data, or even results of

electrophysiological studies, but further expanded to a wide range of cardiovascular signs and symptoms, disease states and physiological assessments (Russo et al., 2013).

Table 3. Inclusion criteria in selected randomized controlled studies

Study	n	NYHA class	LVEF (%)	LVEDD (mm)	SR/AF	QRS (ms)	ICD
MUSTIC-SR	58	III	< 35%	>60	SR	>150	No
MIRACLE	453	III, IV	< 35%	>55	SR	>130	
MUSTIC-AF	43	III	< 35%	>60	SR	>200	
PATH-CHF	41	III, IV	< 35%	NA	SR	>120	
MIRACLE-ICD	369	III, IV	< 35%	>55	SR	>130	Yes
CONTAK-CD	227	II, IV	< 35%	NA	SR	>120	
MIRACLE-ICD II	186	II	< 35%	>55	SR	>130	
PATH–CHF II	89	III, IV	< 35%	NA	SR	>120	Yes/No
COMPANION	1520	III, IV	< 35%	NA	SR	>120	
CARE-HF	814	III, IV	< 35%	>30 IH	SR	>120	No
CARE-HF EXTENSION 2006	813	III, IV	< 35%	>30 IH	SR	>120	
REVERSE 2008	610	I, II	< 40%	>55	SR	>120	Yes/No
MADIF-CRT	1800	I, II	< 30%	NA	SR	>130	Yes

AF=atrial fibrillation; CARE-HF=Cardiac Resynchronization-Heart Failure; COMPANION=Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure; CONTAK-CD=CONTAK-Cardiac Defibrillator; CRT-D=cardiac resynchronization therapy with defibrillator; CRT-P=cardiac resynchronization therapy pacemaker; HF=heart failure; ICD=Implantable cardioverter-defibrillator; IH=indexed to the height; LVEDD=left ventricular end-diastolic diameter; LVEF=left ventricular ejection fraction; MADIT-CRT=Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy; MIRACLE=Multicenter InSync Randomized Clinical Evaluation; MR=mitral regurgitation; MUSTIC=Multisite Stimulation in Cardiomyopathies; NA=Non-applicable; n=Number of patients; NYHA=New York Heart Association; PATH-CHF=Pacing Therapies in Congestive Heart Failure trial; REsynchronization reVErses Remodelling in Systolic left vEntricular dysfunction SR=sinus rhythm. *patients in atrial fibrillation
Adapted from Brignole et al.(2013)

Recent and main recommendations for CRT, from some of the most relevant American medical societies (e.g., ACCF, Heart Rhythm Society, AHA, Heart Failure Society

of America) and ESC, accomplishes a standardized approach that reflects the majority of clinical scenarios and permits individual expertize and technical appreciations of each individual case (Brignole et al., 2013; McMurray et al., 2012; Yancy et al., 2013).

Table 4. Endpoints, and main findings of some randomized clinical trials evaluating CRT in sinus rhythm

Study	Primary endpoints	Secondary endpoints	Main findings
MUSTIC-SR	6MWD	NYHA class, QoL, $\dot{V}O_{2Peak}$, LV volumes, MR hospitalizations, mortality	CRT-P improved 6MWD, NYHA class, QoL, $\dot{V}O_{2Peak}$, reduced LV volumes and MR and reduced hospitalizations
MIRACLE	NYHA class, 6MWD, QoL	$\dot{V}O_{2Peak}$, LVEDD, LVEF, MR clinical composite response	CRT-P improved NYHA class, QoL and 6MWD and reduced LVEDD, MR and increased LVEF
PATH-CHF	$\dot{V}O_{2Peak}$, 6MWD	NYHA class, QoL hospitalizations	CRT-P improved NYHA class, QoL and 6MWD and reduced hospitalizations
COMPANION	ACM or Hospitalization	ACM, cardiac mortality	CRT-P and CRT-D reduced ACM or hospitalization
REVERSE	% worsened by clinical composite endpoint	LVESV index, heart failure hospitalizations and ACM	CRT-P/CRT-D did not change the primary endpoint and did not reduce all-cause mortality but reduced LVESV index and heart failure hospitalizations.
MADIF-CRT	ACM or heart failure hospitalizations	ACM and LVESV	CRT-D reduced the endpoint heart failure hospitalizations or all-cause mortality and LVESV.
RAFT	ACM or heart failure hospitalizations	ACM and cardiovascular death	CRT-D reduced the endpoint ACM or heart failure hospitalizations. In NYHA III, CRT-D only reduced significantly ACM

ACM-All cause of mortality; CARE-HF=Cardiac Resynchronization-Heart Failure; COMPANION=Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure; CRT-D=cardiac resynchronization therapy with defibrillator; CRT-P=cardiac resynchronization therapy pacemaker; LV= left ventricular; LVEDD=left ventricular enddiastolic dimension; LVEF=left ventricular ejection fraction; LVESV=left ventricular endsystolic volume; MADIT-CRT=Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy; MIRACLE=Multicenter InSync Randomized Clinical Evaluation; MR=mitral regurgitation; MUSTIC=Multisite Stimulation in Cardiomyopathies; NYHA=New York Heart Association; PATH-CHF=Pacing Therapies in Congestive Heart Failure trial; QoL=quality-of-life score; RAFT= Resynchronization-Defibrillation for Ambulatory Heart Failure Trial; 6MWD=6-min walk distance.
Adapted from Brignole et al. (2013)

It is not the scope of this project to analyse in depth the specific criteria for CRT implementation or the major differences approaching HF definition from medical societies, but instead we intent to identify the main points that lead to this significant clinical decision. Another significant issue is related with, the CRT patients eligibility for clinical trials may not be representative of those from the “real world” (Finegold, Raphael, Levy, Whinnett, & Francis, 2013). Caution should also be taken into account because the assessment of patient clinical status relies upon individual clinical judgment. So, having this in consideration, we narrow the main criteria for CRT implementation to symptomatic HF and depressed LVEF, which can be objectively evaluated as: i) LVEF≤ 35%; ii) QRS duration≥ 120ms and morphology (i.e., LBBB); and finally, iii) NYHA functional class (Brignole et al., 2013; Poole, 2014; Russo et al., 2013; Vardas et al., 2007).

Importantly, CRT treatment is recommend in moderate to severe HF but more information is needed over its application in patients who differ from the aforesaid, specifically those with mild-to-moderate HF (i.e., class I-II), narrow QRS (i.e.,<120ms) and with right bundle branch block (Linde et al., 2012).

2.3 Autonomic function and resynchronization

In recent years, the autonomic nervous system (ANS) has gain attention because its importance in the natural history of HF. New non-invasive and valid ways to assess ANS have arisen through the study of heart rate variables (Piotrowicz, Baranowski, Piotrowska, & Zielinski 2009). The heart rate variability can be used as an index for parasympathetic reactivation post-exercise (Goldberger et al., 2006), while the heart rate recovery (HRR) is a prognostic variable and a good indicator of autonomic function (Arena, Myers, Abella, Peberdy, et al., 2010; Piotrowicz et al., 2009). The HRR has a prognostic and preventive value, and should be considered both in clinical and experimental fields (Arena, Guazzi, Myers, & Peberdy, 2006; Cahalin et al., 2013; Lipinski, Vetrovec, Gorelik, & Froelicher, 2005; Wu, 2014; Liu et al., 2014; Tang et al., 2009). In the scope of this document we will only focus on HRR.

AUTONOMIC NERVOUS SYSTEM MODULATION

The parasympathetic and the sympathetic independent structures, namely the nerve endings of both divisions, modulate the function of one another through complex interactions, varying HR accordingly distinctive adrenergic receptors selectivity stimulation. The HR is intimately dependent on the acetylcholine release in the synaptic cleft and the degree of interaction with muscarinic receptors in the heart (Mizuno et al., 2007).

Chakir et al. (2009) revealed CRT benefits beyond the restoration of electromechanical synchrony, and pointed out that calcium (Ca^{2+}) transient improvement and depressed contractile function seem associated with cholinergic signalling receptors remodelling. The muscarinic receptors subtypes, can actually modulate, and be modulated, in their responsiveness, sensibility and specificity to particular amines. Coordinate sympathovagal control is essential for a normal hemodynamic function (Levy, 1984). Similar findings were achieved when vagus nerve stimulation and β-Blockers were used, which in turn seem to cause more norepinephrine release and reduced renin-angiotensin-aldosterone system effect (Zhang et al., 2009). Both of these adaptations improved autonomic control. In an analogous study, Kannenkeril et al. (2002) assessed parasympathetic effects on cardiac electrophysiology during moderate exercise and recovery, observing reduced sinus cycle length during recovery ($p< .003$), augmented ventricular effective refractory period ($p< .005$) and reduced Q-T interval ($p< .02$), all of these seemed to be associated with parasympathetic reactivation, sympathetic withdrawal or both. However, other findings suggest that discrepancy on sympathovagal tone could be observed in different levels of oxygen consumption (Saito & Nakamura, 1995), what could lead us to accept that exercise intensity could certainly be influencing these autonomic changes (Buchheit, Papelier, Laursen, & Ahmaidi, 2007).

EXERCISE AND AUTONOMIC FUNCTION

After finishing an exercise bout, parasympathetic reactivation occurs and sympathetic function decreases (Buchheit, Laursen, & Ahmaidi, 2007). Athletes tend to have higher vagal tone and more precise and accurate sympathetic modulation, an indicator and predictor of mortality (Prakash, 2012). The HRR at 1-minute (HRR_1) reflects vagal reactivation, while the HRR at 3-minute (HRR_3) seems to be mediated by sympathetic withdrawal (Okutucu et al., 2011). The autonomic balance and their major contributors interplay change continuously since the termination of an exercise bout and during the following recovery phases (Goldberger et al., 2006).

Still, controversial findings (Buchheit, Papelier, et al., 2007) question the initial fall in the post-exercise HR has a result, solely, of vagal reactivation, and argue that sympathetic withdrawal occurring immediately after exercise should also be taken into account. In accordance with these findings, others concluded the same for maximal and supramaximal exercise testing, which is similar to what was observed in the previous study, thereby, reinforcing a unknown role of the anaerobic metabolism influence (Oliveira, Mattos, Silva, Rezende, & Lima, 2013).

If these findings are important to understand the HRR dynamics, could we extrapolate this knowledge to a HF population? Or, vagal reactivation role on HR fall post-

exercise is reduced on low to moderate exercise intensity? It seems that in high intensity exercise, sympathetic and parasympathetic loops could also regulate the HRR (Yaylali et al., 2015). Also of note, and subject to scrutiny, are the different exercise intensities *per se*, or even the exercise mode, which could cause distinct central and peripheral fatigue (O'Leary, Morris, Collett, & Howells, 2015; Sahlin, Tonkonogi, & Soderlund, 1998), therefore contributing to different autonomic modulation.

The broad interpretation of the HRR, such as the difference between the HR at peak exercise and HR post-exercise, could to some extent be variable or even deceiving accordingly to individual scientific background or exercise approaches. For instances, Kubrychtova et al. (2009) used the HRR_1 into the active recovery phase of the exercise test, while Lipinsky et al. (2005) used the HRR measured at 1, 2, 3, and 5-minute time points after treadmill testing. Although the HRR has been discussed mainly in the context of the ANS modulation and exercise, in good truth there is a far more complex domain to learn and explore. The ways adrenergic-cholinergic cross talk can exert their action and are influenced by other mechanisms, such as immune regulatory processes, clearly depicts the ANS capability in promoting or attenuating a response via similar paths (Chobanyan-Jurgens & Jordan, 2015; Levy, 1971; Mizuno, Tajima, Watanabe, & Kuratsune, 2014; Ogoh et al., 2005; Straburzynska, Wallace, & Potter, 1999). Other findings, associate autonomic imbalances and fetal genes activation with profound changes in cardiac structure and function (Paulus & Tschope, 2013). Others suggested that metaboreceptors, neurohumoral activation and baroreflex desensibilization may lead to sympathetic overactivation, resulting in HF vicious cycle of detrimental exercise capacity (Corra et al., 2014).

2.4 Exercise and resynchronization

Epidemiological evidence depicts physical activity and structured exercise importance for treatment and management of several chronic diseases (Bamman et al., 2014; Fleg et al., 2015; Kujala, 2006; Rosenthal & Dorsey, 2013). Exercise represents an independent protective role for the growing sociocultural problem of cardiometabolic diseases (Bamman et al., 2014; Powers, Smuder, Kavazis, & Quindry, 2014).

Conraads et al. (2007) compare the additive effect of exercise to the implantation of CRT, and verified that endurance training enhanced exercise tolerance in the intervention group versus the control for the $\dot{V}O_{2Peak}$ (+40% versus +16%, p= .005), WattMax (+43% versus + 13%, p= .0005), and circulatory power (+74% versus + 32%, p= .01). Similarly, the HF-ACTION trial (Zeitler et al., 2015) enrolled a heterogeneous population of device patients, including CRT (n= 435), and allocation to usual care and exercise training. The three major findings were: first, the safety of the exercise; second, the improvement of

exercise capacity and QoL; lastlty, clinical events may be attenuated in patients with devices. According to Mayer et al. (2013) CRT falls under the category of ventricular assisted devices, which seems to benefit from exercise, but still lacks from a standardized exercise training programme. Independently of the specific programing of the pacemaker, some precautions should be made, namely: 1) the upper limit of the device which should be 20 beats per minute below the device intervention; 2) Graded exercise testing (GXT) is mandatory; 3) heart rate training zone and rate of perceived exertion should be measured at all times (Maeyer, Beckers, Vrints & Conraads, 2013).

If exercise training (ExT) in cardiac rehabilitation setting has class I indication for safety and effectiveness on HF functional status improvement, and class IIa recommendation for improvement of functional capacity, exercise duration, QoL and mortality, it is imperative to know the best form of exercise for this patients (Yancy, 2013). As new frontiers are reached new insides and discoveries happen. It´s obvious that old and new questions addressed to aerobic interval training (AIT) safety, efficacy, and physiological mechanisms should be made to an understanding of the functional improvement and survival rates it promotes, as well as to further bolster its clinical implementation. However, it seems clear its undeniable value, and therefore, more randomized controlled trials, with more statistical power should be conducted in order to clarify some of the concerns AIT may raise.

PHYSIOLOGICAL ADAPTATIONS TO EXERCISE PROTOCOLS

In recent years, novel approaches to exercise training and CRT have been done, either in the experimental or clinical field. AIT has been shown superior results over moderate continuous training (MCT) (Wisloff et al., 2007), and if there is biological plausibility for this superiority, it must be analysed, and also understand from which population, and which methodological approach this findings come from. Furthermore, it is of great relevance to differentiate myocardium adaptations arising from volume overload, from those arising from pressure overload, although this may be controversial and, further, raise new questions (Conraads & Beckers, 2010; Piepoli et al., 2011).

Myocardial architectural remodelling leads to alterations on the force-length curve relationship, and we can differentiate between eccentric and concentric remodelling, which in turn could lead, as already discussed in the HF continuum, to systolic or diastolic dysfunction respectively (Paulus & Tschope, 2013). Aerobic training can enhance exercise performance due to increased LV function (Haykowsky et al., 2013), cellular maladaptive hypertrophy regression (Gaasch & Zile, 2011), improved metabolic status (Bassett & Howley, 2000), mitochondrial adaptations (Hawley, Hargreaves, Joyner, & Zierath, 2014), improved cardiomyocyte contractility and also Ca^{2+} handling (Johnsen et al., 2013; Kemi et al., 2012).

Aerobic training also improves myocardium efficiency, leading to higher cardiac output and augmented peripheral oxygen consumption (Kemi & Wisloff, 2010). However, oxygen consumption and oxygen supply can´t be dissociated one from another. Oxygen consumption relies on the ability of the heart to contract efficiently, the ability to reach and maintain a high HR, and the relative wall tension, whereas oxygen supply depends on the arteriovenous difference and coronary blood flow. In CRT patients, ExT seems to improve energy metabolism (Hafstad et al., 2011), while pharmacological medicamentation could improve patient clinical status (Patwala et al., 2009).

As previously supported, we can assume that exercise intensity plays the key role in cardiac rehabilitation setting. The individual differences induced to individual cardiac myocytes are pivotal to the exercise induced cardioprotection (Powers et al., 2014). Exercise intensity relates with specific cellular metabolic pathways that are the foundation of either positive or adverse outcomes, through specific acute and chronic adaptations (Egan & Zierath, 2013). But another question emerges! How can we be precise and assume valid data while selecting exercise intensity? Intensity can be determined indirectly (i.e., formulas) and directly (i.e., HR, $\dot{V}O_2$). Other related variables are duration and exercise protocols. Aerobic training implies the presence of oxygen or more specifically oxidative mechanisms predominance for energy production (Egan & Zierath, 2013). Of note, aerobic interval training main energy system is oxidative, although the rate of oxygen utilization and therefore energy production is much higher than could be observed through, the also aerobically, continuous mode.

In a highly cited, and already considered a classic study from Trondheim team, Wisloff et al. (2007) AIT protocol was applied in patients undergoing optimal treatment for HF after myocardial infarction. In this controlled and randomized trial, the authors seek to understand differences between MCT and AIT in several parameters, ranging from reverse remodelling, exercise capacity and QoL. They conclude that AIT was superior to MCT in several parameters, including the $\dot{V}O_{2Peak}$ (46% versus 14%, $p< .001$). CHF is clearly a disease of the elderly, and in this study, the included population had 88% of the patients with more than 65 years old, and 49% of the patients with more than 80 years old. The exercise protocol was maintained during the 12 weeks of the trial, in which it was revealed that, even in the elderly exercise is still able to induce adaptations.

Another study from Wisloff et al. (2001), and corroborated elsewhere (Kemi, Loennechen, Wisloff, & Ellingsen, 2002), concluded that exercising at 85/90% of the maximal oxygen uptake ($\dot{V}O_{2Max}$) induces architectural and conformational transformations in cardiomyocytes, specifically inducing wider and long myocytes proteins, also termed as physiological hypertrophy. Exercise also seems to induce changes in Ca^{2+} transients, namely, faster systolic rise and diastolic decay. The magnitudes of these changes have a

direct and positive correlation with exercise intensity (Kemi et al., 2005). Kemi et al. (2005) observed a Ca^{2+} transient improvement of 40% on 85/90% of the $\dot{V}O_{2Max}$ group, versus 20% for the moderate intensity. The same pattern was observed in mice and rats, as well as in humans, although some methodological and controversial issues could be raised (Helgerud et al., 2007).

Regarding the mode, most studies used treadmill walking (Fu et al., 2013; Iellamo et al., 2013; Wisloff et al., 2007), while others preferred concurrent training (Santa-Clara, Fernhall, Mendes, & Sardinha, 2002). However, dynamic exercise tends to put a volume overload in the myocardium (Erhman, 2010), while static exercise seems to depend more on neurogenic effect (Folland & Williams, 2007). The first mechanism is the basis for cardiac adaptation to aerobic exercise, while the second seems to focus mainly on peripheral mechanisms.

IN THE URGE OF A NEW EXERCISE METHODOLOGY

Several guidelines for exercise prescription in various populations, with specific intensities that promote optimal stimuli for expected adaptations are described elsewhere (Pescatello, 2013). These guidelines were born from robust scientific evidence supporting its value, but their practical application is often difficult and some pitfalls may be pointed out. Several training protocols (e.g., AIT, CMT), different modes (e.g., walking, cycling), different weekly frequency, different volume and intensity are proposed in literature (Erhman, 2010) as well as in several clinical trials (Fu et al., 2013; Rognmo et al., 2012; Wisloff et al., 2007). However, intensity is probably the most important variable, and apart from being independently manipulated, it also depends in the above-mentioned.

Nevertheless, some intriguing issues regarding exercise intensity can be raised, even more in the clinical domain. Specifically, we must question: **i)** the homogeneity of metabolic reactions among patients, which according to Arena et al. (2013) are heterogeneous among patients; **ii)** the methods accuracy and validity for evaluating metabolic reactions through gas analyses, which seems to be altered by several factors such as physiological and technical equipment variability (Bensimhon, 2008); **iii)** is the peak value (e.g., $\dot{V}O_2$, peak HR) the "true" maximal value for the tested variable? If not, can we measure the difference between them? **iv)** and most of all, is it possible to guarantee **fixed** and **specific** exercise intensity in the clinical domain? To address these concerns, we analyse Wisloff et al. (2007) work, in a well-designed and randomized controlled trial, and a reference work to the AIT apology. In this paper, and regarding exercise intensity, the authors write: "*One of the weaknesses of our study is that the usual care programme was not very well defined in means of exercise intensity*". The authors also referred a variation of HR both between and within subjects. However, the use of isocaloric at the same exercise duration intended to control for some

confounding effect over the outcome. Fu et al. (2013) also adopted this strategy, which allows for distinguishing the periods of high intensity from the average periods and its effects over a specific outcome. Iellamo et al. (2012) adopted a training impulse method (TRIMP), alongside with complex algorithms to guarantee maximum control of possible confounders.

Percentages of the $\dot{V}O_{2Max}$ and HR, as the hallmarks to set exercise training intensity, seem to yield heterogeneous metabolic and cardiocirculatory responses in different patients (Hofmann & Tschakert, 2011). Actually the same patient can respond differently upon different stressful and variable hormonal interactions (Hashimoto & Brooks, 2008) or even as a result of ExT chronic adaptation (Blazevich, 2006; Hambrecht et al., 2000). There has been proposed more accurate methods that rely upon submaximal markers, thresholds or turning points (Arena et al., 2012; Straburzynska-Migaj, Gwizdala, Siniawski, Ochotny, & Grajek, 2010). These are particularly important for those engaged on CRT (Conraads & Beckers, 2010). Could this actually be a turning point, or just a shifting to a more individualized and even more specific accurate method?

On a recent review over HF trials (Niederseer, Thaler, & Niebauer, 2013), it was observed a mismatch between the trials and the “real” world patients´. Spall et al. (2007) went further and conducted a review of several RCT in which they seek to understand the nature and extent of exclusion criteria in certain patients´ population. Invariably, when assuming certain scientific methodology premises, we are also limiting the extent of our findings. Maybe one size fits all is not applicable in cardiac rehabilitation, moreover when regarding such a specific syndrome as HF (Hofmann & Tschakert, 2011), and with another complex variable such as CRT.

Chapter III

Methodology

3.1 Introduction

This chapter describes the methodology process of the study. **Firstly**, we identify our variables; **secondly**, our hypothesis; **thirdly**, the conceptual design of the study, where the patient population, as well as the inclusion and exclusion criteria are described; **fourthly**, the equipment and protocols of the assessments are overviewed in detail; and **lastly**, based on our data, we describe how our statistical treatment was conducted.

3.2 Variables in the study

Dependent variables. According to the following equipment and protocols mentioned below, the present analysis considered the main variables of interest: the $\dot{V}O_{2Peak}$, the CPET duration, the resting exchange ratio (RER), the NYHA functional class, the systolic blood pressure and the diastolic blood pressure (rest and peak exercise), the HR (i.e., at rest, at peak exercise), the HR reserve and the HRR (i.e., 1-minute, 3-minute and 6-minute). Other variables were then computed based on the abovementioned.

Independent variables. ExT in the form of AIT was our independent variable.

3.3 Hypothesis

Main hypothesis. In 6 months, there will be differences between the intervention and the control group on autonomic function.

Secondary hypothesis. In 6 months, there will be differences between the intervention and the control group on exercise capacity, hemodynamics and chronotropic capacity.

3.4 Study design

The present analysis uses a longitudinal approach with two assessment time points: the baseline, before the cardiac implant (M1); and on the 6th month (M2), after the experimental therapy (i.e., ExT). Additionally, another moment was considered at the 3rd month (3Mo). All patients meeting inclusion criteria underwent the CPET in all three time points, and the data was collected. The 3Mo was utilized, when necessary, and in accordance with the CPET, to adjust exercise intensity. Aiming for the major outcome (i.e., autonomic function), the

variables HRR_{1diff}, HRR_{3diff}, HRR_{6diff} were acquired in M1 and M2. Written informed consent was obtained from all patients, and an ethics committee approved the study protocol.

Participants. The enrolments of patients began in January 2012 and were concluded before the beginning of this project. Patients meeting the inclusion criteria were recruited from a local hospital (Centro Hospitalar de Lisboa – Santa Marta), and were invited to participate in a study after a clinical screening for CRT. After randomization to ExT or control group, patients were stratified (by age and etiology– ischemic and non-ischemic). This process was conducted by a physician who wasn´t involved in the study, and was merely aware of the results from the screening task. Our analysis is based on a sub-sample (n=121) of the initial screening. Twenty-nine patients were eligible for our analysis based on the full availability of data regarding our main variable of interest (HRR_1).

Inclusion criteria. Patients with CHF, classified in the NYHA functional class III or IV, with a LVEF< 35%, QRS duration≥ 120 ms, and receiving optimal medical therapy for CHF (including an ACE-I or an angiotensin receptor blocker and a β-blocker, unless a contraindication was evident). To conclude, a clinical stable condition for more than one month (no hospitalization for HF, no change in medication, and no change in NYHA functional class). Exceptionally, 6 patients that were included in our sub-sample were part of the NYHA functional class II while presenting a LVEF< 35%.

Exclusion criteria. Patients younger than eighteen years of age, patients who are older than ninety, and patients who are unable to give informed consent. Those who have been treated with an intravenous inotropic agent within the thirty days prior to implantation, presented an unstable angina pectoris, and any kind of orthopaedic or neurological limitations to exercise. During the six month study period, all pharmacological therapy should be maintained and no additional drugs should be introduced. Also, all patients who did not respect the required standardized conditions in the M1, M2 and 3Mo.

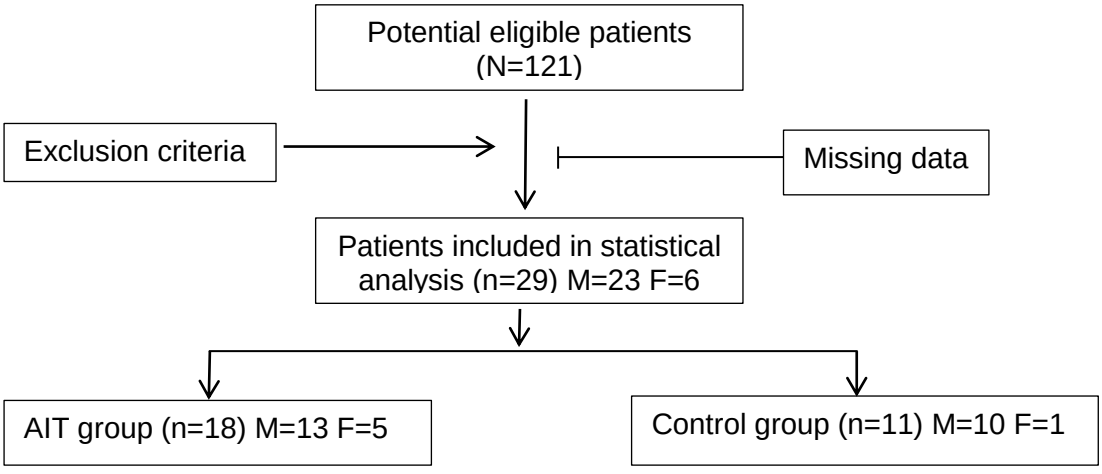

Figure 1. Flow chart of the inclusion/exclusion criteria. M=Male; F=Female

3.5 Equipment and protocols of assessment

Cardiopulmonary exercise testing. This test was conducted with the subjects in a non-fasting condition and under the regular medication. A symptom-limited incremental GXT, the modified Bruce protocol, was performed with breath-by-breath gas exchange measurements with one-line real time calculation of the VCO_2, the VO_2 production and the RER (MedGraphics CPX Ultima), being performed on a treadmill. Before each test, the gas analyser was calibrated with gases of known concentrations (5% CO_2, 35% O_2, and 60% N_2) and the pneumotach calibrated with a known volume (5L syringe). A twelve-lead ECG (MedGraphics CPX Ultima) was continuously monitored. Subjects were encouraged to exercise to exhaustion, as defined by intolerance, leg fatigue or dyspnea, unless clinical criteria for test termination were considered (Balady et al., 2010). Participants were seated on a chair as soon as they stopped walking, while recovery measurements were taken. The VO_{2Peak} was defined as the highest attained $\dot{V}O_2$ during the final 30 seconds of the exercise.

Blood Pressure. Blood pressure was measured by auscultation before, during and after the different stages of the test (i.e., baseline, during the 2nd minute of each stage, at peak exercise and during recovery) using a mercury sphygmomanometer.

Double product. Double product was acquired through standard equation (heart rate x systolic blood pressure).

Resting heart rate. Resting HR was measured at rest, before the CPET, with the participants seated on a chair for five minutes before the measurement.

Peak heart rate. The assumed peak heart rate was the one extracted from the CPET at the maximal point of exertion.

Heart rate recovery. The HRR was obtained during the recovery period of CPET, at 1, 3 and 6-minutes. Patients were seated while data was collected, and the recovery period continued for seven minutes after peak effort, providing the HRR at 1 minute (HRR_1), the HRR at 3-minutes (HRR_3) and the HRR at 6-minutes (HRR_6).

Heart rate recovery difference. The HRR difference (HRR_{diff}), was calculated as the difference between HRR at 1-minute and the peak heart rate (HRR_{1diff}), the HRR 3-minutes and the peak heart rate (HRR_{3diff}), and the HRR 6-minutes and the peak heart rate (HRR_{6diff}).

Heart rate reserve. The HR reserve was acquired by equation (peak heart rate - resting heart rate).

Pulse pressure. Pulse pressure was acquired through standard equation (systolic blood pressure - diastolic blood pressure).

Exercise protocol. The ExT design was hospital-based, twice a week for 60 minutes and on non-consecutive days, and had the duration of six months. The total forecasted numbers of sessions were between 48 and 50, and took into account 24 to 25 weeks of

training. The AIT comprised four interval training periods (high intensity) and three active pauses (moderate intensity), between interval training periods. The warm-up and aerobic training was conducted using treadmill walking. The patient warmed up for 10 minutes at 50% to 60% of the peak heart rate, he then walked four 2-minute intervals at 90% to 95% of the peak heart rate. Each interval, including the last one, was separated by 2-minutes of active pauses at 60% to 70% of the peak heart rate. After the first month, each interval and active pause was increased by 30 seconds every week until it reached up to 4 minutes of work (90 to 95% of the peak heart rate) and 3 minutes of active rest (60% to 70% of the peak heart rate), at the end of the second month. The total aerobic exercise time at this moment was 38 minutes, considering a 3 minute cool down, and was maintained until the end of ExT intervention period. This protocol was based on an AIT which could be found elsewhere (Wisloff et al., 2007). The Borg 6-to-20 scale of perceived exertion was used during and after each training session. The inclination or the speed of the treadmill was continuously adjusted to ensure the pre-defined HR intervals during the training sessions. The HR monitor (Polar, Electro, Kempele, Finland) was used to achieve the assigned exercise intensity. The exercise was scheduled according to patient availability, and was maintained during a 6-month intervention. No more than two patients were scheduled for the same day and time. Training sessions were conducted by a healthcare provider (i.e., exercise physiologist or nurse).

3.6 Statistical treatment

Data was analysed with the Statistical Package for Social Science (SPSS 23.0 for Windows ®, SPSS Inc, Chicago, USA). To summarize baseline clinical and patient reported characteristics of the sample, continuous variables are presented as mean with standard deviations when normally distributed, categorical variables as frequencies with percentages and as medians (25th–75th percentiles) with interquartile ranges (IQRs) in case of non-normal distribution. A mixed-way ANOVA was used to determine changes between groups (AIT, Control) and within groups (M1, M2). Conditions of tests application were assessed through Shapiro-Wilk test of normality, Mauchly´s test of sphericity and Levene´s test for homogeneity of variances. Subsequently, analyses of covariance (ANCOVA) for mixed-way ANOVA was conducted to adjust for potential confounding effects of age, gender and the HR Reserve. Although the mixed-way ANOVA may be robust to violations of its norms of application, in some variables which did not met these specific criteria we conducted non-parametric tests. To test for simple main effects, paired samples T-test or alternatively, in the case of non-parametric data, the Wilcoxon signed rank test were used to assess pre-test versus post-test differences. Association between variables was tested by using Pearson's

correlation coefficient or Spearman´s correlation coefficient in the case of non-parametric data. All tests were 2 tailed, and statistical differences considered significant for p-value< .05.

Chapter IV

Results

Baseline characteristics of the study population according to their group allocation are shown in Table 5. Our main hypothesis was to determine the effects of a long-term (six months) AIT program following CRT implantation on autonomic function, measured by the HRR responses within and between groups. All 29 patients completed the CPET and provided full data for the autonomic function variable HRR_1, and no missing values were reported for this statistical analysis. The measured exercise capacity data, the hemodynamics data, and the chronotropic capacity data, was not fully available in some cases, so the statistical analysis was conducted with these missing values (Table 5 and Table 6).

Table 5. Baseline characteristics of patients

Characteristic	AIT group	Control group	*p*
Anthrometric/clinical	(n=18)	(n=11)	
Age (years)	68 ± 11.05	71 ± 7.34	= .486
Gender (Male)	13	10	= .228
Height (Cm)	1.66 ± 0.10	1.69 ± 0.94	= .451
Weight (Kg)	74 ± 18.25	83 ± 17	= .207
BMI (Kg/m_2)	27 ± 4.77	29 ± 4.67	= .208
NYHA II/III (n)	2 / 14	4 / 7	= .319
Resting heart rate ($beats/min^{-1}$)	78 (23)	74 (17)	= .820
LVEF (%)	28 ± 7	25 ± 8	= .208
Etiology (ISQ/MCD/VAL)	6 / 10 / 1	3 / 8 / 0	= .612
Smokers	8 (44%)	0 (100%)	= .007*
Medication			
Dyslipidemia (n)	13 (72%)	9 (82%)	= .970
Diuretics (n)	17 (94%)	11 (100%)	= .426
Hypertension (n)	13 (72%)	10 (91%)	= .330
Diabetes (n)	8 (44%)	4 (36%)	= .576

Continuous data are presented as mean and standard deviation (M ± SD) and analysed by independent sample t-test. Non-continuous data are presented as median (25th–75th percentiles) analysed by Mann–Whitney U test, and associated with interquartile range. Categorical variables are presented as number and analysed by Chi-square test. *Differences between AIT group and control group statistically significant ($p < .05$). n=number of participants; LVEF=Left ventricle ejection fraction; NYHA=New York heart association; ISQ=Isquemic; MCD=Myocardial coronary disease; NA=Not applicable; VAL=Valve.

4.1 Exercise capacity

The mean $\dot{V}O_{2Peak}$ and the CPET duration displayed a statistical significant main effect of within-subjects effects [F(1,24)= 7.819, *p*= .010, η_{p2}= .246; F(1,25)= 5.712, *p*= .025, η_{p2}= .186]. The interaction effect was non-significant in both variables [F(1,24)= 1.124, *p*= .300, η_{p2}= .45; F(1,25)= 1.848, *p*= .186, η_{p2}= .069]. Regarding the main effects, we intended to see where those differences were and after a pairwise comparison by group, only the AIT group was statistically significant for both variables, namely: the $\dot{V}O_{2Peak}$ [t(15)= -2.835; *p*= .013] and the CPET duration [t(16)= -2.587, *p*= .020). For both variables, the AIT group had a higher mean value for M2 when compared to M1. The RER was similar in both groups and no statistical differences were detected within or between subject groups.

4.2 Hemodynamics

Most hemodynamic variables remained constant throughout the intervention, while peak pulse pressure differed from this result. Although the peak pulse pressure did not report a significant value in the mixed way-ANOVA (*p*< .05), the pairwise comparison conducted next exposed differences only in the AIT group [t(17)= -2.271; *p*= .036]. All the other variables measured in this sub-analysis were non-significant.

4.3 Chronotropic capacity

The main effects were not significant. While testing for simple main effects, the Wilcoxon ranks test indicated that, only in the AIT group the HR reserve increased throughout time (Z= -2.11, *p*= .035). With the intent of clarifying this result, we analysed post-intervention correlations between the HR reserve, the resting HR and the peak heart rate. A strong and positive correlation was seen between the HR reserve and the peak heart rate (AIT: r_s=.778, *p*= .0001; Control: r_s= .834, *p*= .001), but no significant result was obtained for the resting HR. The post-intervention chronotropic capacity and the autonomic function interaction were tested through the HRR_{1diff} and the peak heart rate. A moderately positive correlate for the AIT group (r_s= .519, *p*= .027), and a non-significant correlate for the control group (r_s= .415, *p*= .205) was observed. Similarly, and also at the post-intervention, a positive correlation was observed between the HRR_{1diff} and the HR reserve (AIT: r_s= .738, *p*= .0001; Control: r_s= .664, *p*= .026). Another tested interaction was the one between parasympathetic and sympathetic function, which was accomplished by correlating the HRR_{1diff}, respectively, with the HRR_{3diff} (AIT: r_s= .706, *p*= .001; Control: r_s= .756, *p*= .007) and the HRR_{6diff} (AIT: r_s= .756, *p*= .0001; Control: r_s= .679, *p*= .022). Concerning this last

analysis, all levels revealed a positive correlation, while those with r_s> .700 were also considered as strongly correlated.

4.4 Autonomic function

The main effects were non-significant. Regarding parasympathetic reactivation, simple main effects of the HRR_{1diff} ranks depicted differences within groups for the AIT group (Z= -2.246, *p*= .025), with a higher median value in M2, when compared with M1. The control group was not statistically significant (Z= -1.687, *p*= .092). With regard to a marker of sympathetic withdrawal, neither the HRR_{3diff} nor the HRR_{6diff} were statistically significant, either between or within groups.

Table 6. Selected variables for Aerobic Interval Training and Control group

	Units	AIT						Control					
		M1			M2			M1			M2		
Exercise capacity													
$\dot{V}O_{2Peak}$	$mL.Kg^{-1}.min^{-1}$	14.17	±	5.10	16.99	±	2.33*	16.21	±	6.57	17.43	±	5.71
CPET duration	seconds	380.59	±	237.57	571.65	±	186.08*	404.80	±	261.25	457.30	±	219.26
RER	NA	1.01	±	.13	1.04	±	.05	.99	±	.15	.99	±	.10
Hemodynamics – rest													
Systolic blood pressure	mmHg	112.17	±	16.09	117.67	±	13.38	121.82	±	18.34	120.27	±	18.41
Diastolic blood pressure	mmHg	62.89	±	10.85	65.33	±	8.76	67.73	±	8.17	67.55	±	9.50
Double product	$mmHg.min_{-1}$	8998,28	±	2655.40	8689.73	±	1672.55	9676.36	±	2915.80	9217.18	±	2349.32
Pulse pressure	mmHg	49.28	±	13.59	52.33	±	12.38	54.09	±	12.81	52.73	±	14.89
Hemodynamics - peak exercise													
Systolic blood pressure	mmHg	147.67	±	23.82	149.67	±	23.87	165.91	±	28.53	150.45	±	26.60
Diastolic blood pressure	mmHg	62.89	±	10.85	65.33	±	8.76	73.64	±	11.20	70.91	±	8.31
Double product	$mmHg.min^{-1}$	16530.56	±	4686.07	16563.06	±	4105.78	19443.64	±	4504.20	18823.64	±	6173
Pulse pressure	mmHg	69.72	±	15.76	80.56	±	17.98 *	76.36	±	22.03	79.55	±	22.30
Chronotropic capacity													
HR Reserve	$beats.min^{-1}$	38 (23.25)			46 (27.25)*			44 (19)			46 (35)		
Peak heart rate	$beats.min^{-1}$	110.50 (33)			121 (23)			128 (40)			132 (46)		
Autonomic function													
HRR_{1diff}	$beats.min^{-1}$	11 (13)			17 (15)*			16 (16)			21 (17)		
HRR_{3diff}	$beats.min^{-1}$	29 (16)			41 (35)			34 (23)			45 (35)		
HRR_{6diff}	$beats.min^{-1}$	30 (27)			43 (31)			42 (29)			50 (38)		
$HRR_{1diff} < 12$	$beats.min^{-1}$	10			5			4			2		

AIT=Aerobic interval training; CPET=Cardiopulmonary exercise testing; HR=Heart rate; HRR_{1diff}=Heart rate recovery difference at 1-minute; HRR_{3diff}=Heart rate recovery difference at 3-minute; HRR_{6diff}=Heart rate recovery difference at 6-minute; $HRR_{1diff} < 12$=Heart rate recovery at 1 minute lower than 12 beats per minute; M1=baseline, before the cardiac implant; M2= at the 6^{th} month; NA=Not applicable; RER=Respiratory exchange ratio.

*Different from baseline, $p < .05$.

Chapter V

Discussion

Although evidence presented alongside with our rationale during the literature review may inexorably prone the reader to support our hypothesis, our results unravel some ambiguity on this matter. When evaluating the main effects and available interaction effects, the results did not point us, unequivocally, towards a benefit of the exercise group over the control group. However, testing for simple main effects led us to believe otherwise. In accordance with these suggestions, findings in the literature also point to the ANS being modulated either by CRT (Okutucu et al., 2011), by exercise (Myers et al., 2007), or even both (Piepoli et al., 2011). Interestingly, when considering the simple main effects, the exercise capacity measured by the $\dot{V}O_{2Peak}$ and the CPET duration was improved, which is reinforced by similar findings from other authors (Kosmala & Marwick, 2014; Marco, 2008; Mastenbroek et al., 2016). Regarding our primal variable of interest, the HRR_{1diff}, our results suggested several trends and strong correlations. According to Spearman's rho correlation, the positive correlation between the HRR_{1diff} and the HR reserve was stronger for the AIT group, which may support its significant simple main effects for the HR reserve variable. If the HR reserve (post-intervention) is higher and has a positive correlation with the HRR_{1diff}, then we can assume that the HRR_{1diff} also increases. In contrast, one could argue that the sample was lacking statistical power to detect this effect, which is in fact, something we undertake as a limitation of our analysis. Moreover, we are inclined to conjecture a scenario where exercise, in the form of AIT, appears to have a biological mechanism which increases the HRR_{1diff}, a marker of vagal reactivation. In this perspective, we are compelled to accept some constraints, but also seek to understand some of outcomes that mesmerize us.

After having verified an increased exercise capacity (i.e., $\dot{V}O_{2Peak}$ and CPET duration) solely on the AIT group, the information suggested by several authors (Chicos, Kannankeril, Kadish & Goldberger, 2009; Kannankeril & Golderberger, 2002; Myers et al., 2007), who also observed similar improvements paired with effects on parasympathetic activity, led us to search for a similar pattern on the HRR_{1diff} and the $\dot{V}O_{2Peak}$ (Fig.1). Surprisingly, after clustering our data as the $\dot{V}O_{2Peak}$ responders/non responders (>/< 15% post-intervention) and comparing it to the modifications of the HRR_{1diff} percentages of change (>15% for post-intervention), we did not find statistical differences between groups, [$c^2(1, N=29)= 1.981, p= .159$)]. However, by looking at the individual level, the AIT group seemed to observe more cases with an increase in percentage of the $\dot{V}O_{2Peak}$. Nevertheless, the lower interval of a responder (15% of the $\dot{V}O_{2Peak}$) could be a limitation because we assume the protective effect for those who have already improved above the threshold, but neglect those who are improving, as well as those in which we did not detect an occurring improvement.

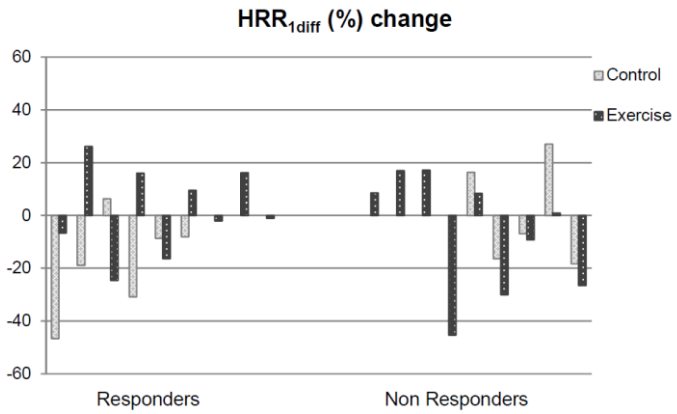

Fig.1. The effects of aerobic interval training in the control group and the exercise group. Individual cases are presented as percentages (%) of the difference between pre and post-intervention of the difference of the heart rate recovery at 1-minute and the peak heart rate [HRR_{1diff} (%) change], according to the $\dot{V}O_{2Peak}$ category responses at pre and post-intervention (i.e., responder > 15% from baseline; and non-responder < 15% from baseline).

Keteyian et al. (2008) findings show that 1 $mL.Kg^{-1}.min^{-1}$ increase in the $\dot{V}O_{2Peak}$ is associated with a decrease in risk of death. Thus, although not statistically significant, we must account for the abovementioned trends because they impact the clinical status and daily living of every patient. Of equal importance is the length of the intervention (i.e., 6 months), which seems to be sufficient to induce changes in the cardiorespiratory system, and can in fact be sufficient to induce improvements at the autonomic function level. The intricate relation between ANS and cardiovascular system complexity in normal physiology is a reality, and we can expect an even higher one when systemic dysfunctions are present, such as in HF.

To the best of our knowledge, quantifying parasympathetic effect is not an easy task, because vagal independence from sympathetic withdrawal in the initial fall of peak heart rate cannot be completely guaranteed (Dupuy et al., 2012; Golderberger et al. 2006; Oliveira et al., 2013). Several studies (Kannankeril & Golderberger, 2002; DeMazumder, Kass, Rourque & Tomasselli, 2015) include selective autonomic blockage (mostly atropine), which is unfeasible in clinical practice. Still, on the basis of our data, and without this crystal clear evidence, we must question if the parasympathetic reactivation in the recovery period of our exercise could happen later in time. The lack of papers regarding the HRR and CRT population may be hiding underlying mechanisms that could explain a probable cause for this eventual late effect. Interestingly, Yaylali et al. (2015) conducted a RCT with HF patients where the HRR_1 did not change, but the HRR_2 results did. These revealing results happen only for the interval training arm, contrarily to the continuous moderate training or the nonexercise group. Similarly, Myers et al. (2007) also reported as main results a faster HRR_2 and HRR_6 for the exercise group. The resemblance with both of these exercise interventions seem to suggest that the patients from our analysis could actually follow this pattern of late

vagal reactivation. However, the methodology used to assess the various HRR was not the same, as well as the exercise intervention, both of which should be taken into account as possible bias.

Patwala et al. (2009) conducted a study where their design did the randomization to exercise group or control group after 3-months of the beginning of the study. Interestingly, after this period, they detected an increase in: the exercise capacity parameters (i.e., $\dot{V}O_{2Peak}$, NYHA functional class, RER), a hemodynamic variable defined by cardiac power output, and also for peak skeletal muscle function. As already stated during the literature review, CRT seems to improve both central and peripheral function through several mechanisms. Considering Patwala et al. (2009) findings and our own analysis, could our variables related with central function (e.g., the HRR_{3diff}, the HRR_{6diff}, the peak heart rate), which improved similarly between groups, be the result of CRT independently, and an indication that peripheral mechanisms could be accounted for the detected simple main effects on other variables (e.g., HRR_{1diff})? In CHF, the "muscle hypothesis" is supported by mounting evidence, which identifies muscle afferents as a primal responsible for exercise intolerance, and exercise training as a way to improve it (Piepoli & Crisafulli, 2014). Actually, this shift in our attention, from central to peripheral mechanisms, as the pivotal booster of exercise capacity and the HRR_{1diff} trends of our data is compelling with other CRT findings in the literature (Jaussaud et al., 2011). Therefore, our data seems to suggest us that, CRT in addition to AIT could improve exercise capacity and sympathovagal balance, not only, but also through peripheral mechanisms.

Groundbreaking knowledge from highly statistical powered trials leads to new paradigms and new practices. One of the major findings of the HF-ACTION trial was ExT beneficial effects over clinical events, which may be reduced in patients with implanted devices (Zeitler et al., 2015). The authors suggest a future concern for investigation regarding this matter, and argue that potential interactions between cardiac implanted devices, ventricular pacing and exercise intolerance may explain these findings. In harmony with these outcomes, could our results have suffered a contracted effect because of these unknown interactions on the HRR, CRT and between them? And if so, could these interactions co-exist with the lack of intensity itself? Even with low level of exercise adherence? In order to answer these intriguing questions, and shed some light over our results, we will address possible confounding issues regarding exercise intensity and exercise adherence. Regarding **intensity**, we see it from three different angles: **i)** could these deconditioning patients, who will receive a cardiac implant within 6 days, have been able to provide a maximal effort in the CPET?; **ii)** what about the real accuracy of this supposed maximal effort, that is, can we assume a match between the percentages of an external load in accordance to a liable maximal internal load; and, **iii)** the differential

physiological outcomes according to the respective intrinsic characteristics of the CPET itself.

Concerning this 1st viewpoint, we must consider that these participants have a recent history of exercise intolerance, and may be reluctant to reach their "maximal" capacity before surgery for cardiac implant. Following surgery, they may as well present the same constraints for the exercise intervention.

With respect to the 2nd viewpoint, peak values acquired through CPET are not the "true" maximal physiological values (Balady et al., 2010; Edvardsen, Hem & Anderssen, 2014). For instance, the gap between peak and "true" maximal oxygen uptake is a huge limitation for exercise intensity prescription, and so for the expected adaptations (Hofmann & Tschakert, 2011). The same happens for the peak heart rate although the use of the HR reserve could reduce this degree of error. More, as others have reported, theoretical pre-determined bout duration at a given exercise intensity may not be flawless (Wisloff et al., 2007). Typically, in patients with cardiometabolic diseases, the peak heart rate and the $\dot{V}O_{2Peak}$ is underestimated (Pescatello, 2013). This suggests that the patients from our analysis may indeed be exercising at lower intensities, considering what was expected of them.

Regarding the 3rd viewpoint, different physiological responses are expected from different exercise intensities (Hafstad et al., 2011; Wisloff et al., 2007), particularly for sympathovagal balance (Golderberger et al., 2006; Meyers et al., 2007). Parasympathetic reactivation following exercise seems to respond proportionally to exercise intensity (Cunha et al., 2007). In our sample, participants did not reach their true physiological limit, which can be ascertained by a RER< 1.10 (Balady et al., 2010). Keteyian et al. (2010) alerts for technical variability in certain conditions, and the need to repeat testing if the RER< 1.05, once it has a larger coefficient of variation. Therefore, the parasympathetic benefits acquired through ExT could have been reduced, not reproduced by the mode of testing or even both. Arena et al. (2013), also refers recovery and high intensity bouts, and emphasizes the heterogeneous physiological response among patients, particularly in those portraying extreme deconditioning $\dot{V}O_{2Peak}$, such as the one participants from our analysis depicted, respectively, a mean of 15 $mL.kg^{-1}.min^{-1}$ ± 5,18. This similarity, could explain why we only detected significant differences for the simple main effects instead of the main effects themselves. Also of note, is the fact that these patients were being medicated with β-blockers, which block the effects of norepinephrine, which in turn lowers peak heart rate and diminishes exercise capacity.

Exercise adherence in cardiac rehabilitation context is a multidimensional phenomenon relating patients and health care providers in an interplay of clinical, social, economic and cultural factors (Piepoli et al., 2011). Regarding our analysis, exercise

adherence was not fully accomplished, with long periods of exercise absence which could be detrimental for our outcomes. Could these characteristics, alongside with the "muscle hypothesis" likelihood, be the explanation for the apparent reduced effect of CRT plus AIT over ANS? Exercise adherence in our sample was low, and we verify that: only four participants completed more than forty sessions; only three perform more than twenty but less than thirty sessions; and, only three participants performed more than thirty and less than forty sessions. In these conditions we can question if basic exercise training principles were present in a manner that could induce exercise adaptation and consequent supercompensation, both at central and peripheral level.

If the abovementioned perspectives seem to shed some light on the results regarding our variables of interest, they may also represent important information for further trials and clinical practice. Several authors stressed the need for new and effective strategies to promote exercise adherence in the context of cardiac rehabilitation, mostly to guarantee the beneficial effects of ExT (Conraads et al., 2012; Conraads & Beckers, 2010; Maeyer et al., 2013; Piepoli et al., 2011). These questions intend to clarify our hypothesis and facilitate the interpretation of results, while simultaneously lead us to the strengths and weaknesses of this analysis. Some **strengths** regarding this design must be reported, more specifically: **i)** no missing data for our main variable of interest (HRR_{1diff}) was reported during our statistical analysis; **ii)** the design, methods and instruments used to assess our variables of interest were robust and precise, which conferred a high internal and external validity; **iii)** the expertise of health care providers who conducted and analyzed the measurements and the training sessions. In contrast, a few study **limitations** should be acknowledged, namely: **i)** the mild reduced number of patients (n=29) when compared with other similar trials, and therefore limited statistical power; **ii)** the patients included in the study were recruited from the same hospital, which may limit, in one hand the findings, and on the other hand the generalization of the data (external validity); **iii)** the statistical differences found for baseline smokers between the intervention group and the control group (p= .007); **iv)** the high number of patients that didn´t complete the initial schedule training sessions; **v)** the difficulty to guarantee the protocoled exercise intensities; **vi)** the lack of a standard definition of the HRR_1 which makes it difficult to compare to the results from other trials; and finally, **vii)** missing data in some variables.

The impact of the clinical syndrome of HF justifies that some findings of this analysis should be taken into account, and **future recommendations** be made. **Firstly,** a more harmonious definition of the HRR and the gold-standard methods for its assessment should be stated, published, and adopted by the scientific community in the field of cardiology/exercise science. In turn, robust and reliable knowledge could easily emerge. **Secondly,** the characteristics of the exercise recovery itself is also a vital element that may

confound the HRR (Cahalin, Arena, & Guazzi, 2012). As this matter is concerned, once again, to our knowledge, there are no standardized methods, and most trials use active or passive workload to measure HRR. This is also true for the chosen minutes of the HRR assessment, while another relevant issue is data normalization. **Thirdly,** if hemodynamic variables are more closely related to endothelial dysfunction and HRR is associated with autonomic function, what is the relation between them, if any? In the context of AIT, our data suggested interesting trends for the HRR_{1diff} and pulse pressure. There are several pathways of unknown knowledge to explore at this point, could they be the explanation for relevant autonomic mechanisms (sympathetic and parasympathetic)? **Fourthly**, valid and precise methods for assessing and prescribing exercise intensity should be scrutinized, as well as their relation with autonomic function, in a way it could guarantee accurate exercise intensity and subsequent expected adaptations. **Fifthly,** with the intent of portioning the benefits from CRT, from those arising from the exercise intervention, it could be highly valuable another control group that do not follow the CRT. **Lastly,** these methodological issues should all be taken into account for internal and external validity, and more importantly from a practical point of view, for critical appraisal purposes.

Conclusion

To summarize, after six months of intervention, the simple main effects suggested that AIT could improve vagal reactivation, assessed through the HRR_{1diff}, in patients that underwent CRT and were engaged in optimal medical treatment. Regarding the HRR_{3diff} and the HRR_{6diff}, no significant differences were observed in the post-intervention which could indicate that differences between groups are at the peripheral level. Our findings also suggested, reduced sample size, lack of intensity and poor ExT adherence as possible confounders over the outcomes. Future RCT, with a more robust control of intensity, and a higher adherence to ExT are needed to better understand the exact influence of CRT plus AIT on the HRR.

Chapter VI

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