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EXERCISE INTOLERANCE AND HEART FAILURE: ROLE OF VASCULAR DYNAMICS AND IMPACT OF EXERCISE INTERVENTIONS

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EXERCISE INTOLERANCE AND HEART FAILURE: ROLE OF VASCULAR DYNAMICS AND IMPACT OF EXERCISE INTERVENTIONS

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Summary

Tables and Figures

Abbreviations

HF – heart failure

LVEF - left ventricle ejection fraction

HFpEF – heart failure with preserved ejection fraction

HFrEF – heart failure with reduced ejection fraction

HFmEF - HF with mid-range ejection fraction

NYHA - New York Heart Association

CPET - cardiorespiratory exercise test

6MWT - 6-Minute Walking Test

SPPB - Short Physical Performance Battery

TUG - Time Up and Go

NT-proBNP - N-terminal pro brain natriuretic peptide

RCT – randomized clinical trial

HIIT – high intensity interval training

HTx – heart transplantation

FMD – flow-mediated dilation

AT – aerobic training

RT – resistance training

VO_2 – oxygen consumption

VE – ventilation

VCO_2 – carbon dioxide output

HR – heart rate

SBP – systolic blood pressure

DBP – diastolic blood pressure

RCT – randomized clinical trial

HIIT – high intensity interval training

1RM – one maximal repetition

MCT-AE - moderate continuous training

MD – mean difference

RT – resistance training

RESUMO DA TESE

Esta dissertação de doutorado foi escrita no formato de artigo científico seguindo as normas disponibilizadas pelo Programa de Pós-Graduação em Ciências e Tecnologias em Saúde da Universidade de Brasília e seguindo orientações da *University of Hasselt*. Trata-se de dissertação de doutorado em regime de co-tutela. O tema central da tese é insuficiência cardíaca e intolerância ao exercício. Os três artigos retratados em capítulos no corpo da tese abordaram aspectos relacionados ao tema central de diferentes maneiras. No primeiro artigo, de design transversal e enfoque em fisiologia, a intolerância ao exercício foi retratada pela ótica vascular da extração periférica de oxigênio durante estímulo de força muscular. Neste artigo foi verificado possíveis diferenças entre fenótipos da insuficiência cardíaca e severidade da doença. No segundo artigo, de design ensaio clínico randomizado, a intolerância ao exercício foi retratada como alvo de protocolos de treinamento físico de alta intensidade visando a reabilitação de pacientes, em geral, com menor severidade da doença. Neste artigo, além do desfecho capacidade cardiorrespiratória foram abordados aspectos vasculares pela medida de função endotelial, bem como força muscular e capacidade funcional. No terceiro artigo, de design metanálise, a intolerância ao exercício foi retratada também como alvo de protocolos de treinamento físico e a população incluída foram pacientes previamente com insuficiência cardíaca que passaram por procedimento de transplante cardíaco. Neste artigo, foram comparadas modalidades de exercício físico nos desfechos capacidade cardiorrespiratória e desfechos relacionados a este como função endotelial e força muscular. A conclusão da tese aponta que a extração periférica de oxigênio está mais prejudicada na insuficiência cardíaca de fenótipo fração de ejeção preservada e em pacientes mais severos. Também indica que o treinamento de alta intensidade, independente da modalidade aeróbia ou resistida, reduz a intolerância ao exercício em pacientes com insuficiência cardíaca de severidade menor. Porém o treinamento de alta intensidade aeróbio, em geral, se demonstrou mais benéfico que o treinamento resistido para intolerância ao exercício com a somatória de aspectos relacionados a isso. Por fim, a modalidade de treinamento aeróbio de alta intensidade demonstrou maior redução da intolerância ao exercício em pacientes com insuficiência cardíaca que passaram por transplante cardíaco, verificada pelo maior ganho em capacidade cardiorrespiratória independentemente do tempo pós transplante.

Palavras-chave: intolerância ao exercício, insuficiência cardíaca, treinamento intervalado de alta intensidade, treinamento resistido em circuito, extração periférica de oxigênio, transplante cardíaco

THESIS ABSTRACT

This doctoral dissertation format follows a scientific article template according to the norms of the Graduate Program in Health Sciences and Technologies at the University of Brasília and the norms of the University of Hasselt. This doctoral dissertation is under joint supervision. The central theme of the thesis is heart failure and exercise intolerance. The three articles portrayed in chapters of the thesis body addressed aspects related to the central theme differently. In the first article, with a cross-sectional design and focus on physiology, exercise intolerance was seen from the vascular perspective of peripheral oxygen extraction during muscle strength stimulation. In this article, we explored possible differences between heart failure phenotypes and disease severity. In the second article, a randomized clinical trial design, exercise intolerance was portrayed as the target of high-intensity physical training protocols aimed at the rehabilitation of patients, in general, with less severe disease. In addition to the cardiorespiratory capacity outcome, this article addressed vascular aspects by measuring endothelial function, muscle strength, and functional capacity. In the third article, a meta-analysis design, exercise intolerance was also portrayed as a target of physical training protocols, and the population included were patients with previous heart failure undergoing a heart transplant procedure. In this article, physical exercise modalities were compared in cardiorespiratory capacity and related outcomes, such as endothelial function and muscle strength. The conclusion of the thesis points out that peripheral oxygen extraction is more impaired in heart failure with preserved ejection fraction phenotype and in more severe patients. It also indicates that high-intensity training, regardless of aerobic or resistance training, reduces exercise intolerance in patients with less severe heart failure. However, high-intensity aerobic training, in general, proved to be more beneficial than resistance training for exercise intolerance with the sum of related aspects. Finally, the high-intensity aerobic training modality showed a more significant reduction in exercise intolerance in patients with heart failure undergoing heart transplantation, verified by the more significant gain in cardiorespiratory capacity regardless of the time after the transplant.

Keywords: exercise intolerance, heart failure, high-intensity interval training, circuit-resistance training, peripheral oxygen extraction, heart transplantation

Chapter 1

GENERAL INTRODUCTION

GENERAL INTRODUCTION

Part 1. Heart failure: general overview and exercise intolerance

Heart failure (HF) is a complex syndrome characterized by cardiac dysfunction involving vascular, hemodynamic, neurohumoral, and peripheral disturbances. HF results from ischemic or non-ischemic cardiomyopathy, valvular incompetence, hypertension, or diabetes, occasioning cardiorespiratory and muscular dysfunction(1). First described as an emerging epidemic around 1985 (2) HF incidence keeps rising its prevalence. Evidence suggests that the number of patients with HF may be increasingly struggling with conditions associated with Western-type lifestyle-related health problems such as diabetes and obesity(3).

Considering the syndrome characteristic complexity, talking about prognosis in HF is a big challenge since it is greatly influenced by many factors, mainly etiology, phenotype, and age. Despite that, in age- and risk factor-adjusted models, incident heart failure conferred a fivefold increased risk of death(2). A recent meta-analysis including over 1.5 million all-type heart failure patients estimated the 1, 2, 5, and 10-year survival to be 87%, 73%, 57%, and 35%, respectively(2). A hospitalization is an event with massive prognostic value, and evaluating long-term outcomes among almost 40 000 patients, a very high 5-year mortality rate of 75% was found for HF patients, regardless of left ventricle ejection fraction (LVEF)(2).

It is estimated that 64.3 million people are living with heart failure worldwide. In developed countries, the prevalence of known HF is generally estimated at 1% to 2% of the general adult population. Absolute numbers of HF-related hospital admissions are projected to increase by about 50% over the next 25 years due to a growing and aging population (4).

The diagnose of HF syndrome has been proposed by several clinical criteria, each with its own advantages and disadvantages, as illustrated in Table 1(2).

Definition	Advantages	Disadvantages
Framingham criteria Major and minor signs and symptoms Chest X-ray	Widely used and well-validated High specificity	Poor sensitivity, especially for early heart failure
2016 ESC Criteria Signs and symptoms Natriuretic peptides Echocardiography or other cardiac imaging	Incorporate signs and symptoms with objetictive measures of cardiac dysfunction Natriuretic peptides are easy	Many patient with proven HfpEF have normal natriuretic peptide levels Measurement variability of echocardiographic

	to measure and widely available	parameters may be high
<u>Gotemburg criteria</u> Symptoms and rales Atrial fibrillation on ECG	Easily applicable in primary care	Poor sensitivity
<u>Boston criteria</u> Signs and symptoms Chest X-ray	Predicts adverse outcomes	Heavily relies on dyspnoea, which is often absent in the elderly
<u>2021 ESC Criteria</u> Signs, symptoms, risk factors, abnormal ECG Natriuretic peptides Echocardiography	Incorporate signs and symptoms together with ECG and risk factors screening. Objiective measures of cardiac dysfunction Natriuretic peptides are easy to measure and widely available	Many patient with proven HfpEF have normal natriuretic peptide levels Measurement variability of echocardiographic parameters may be high

Table 1. Heart failure diagnosis criteria

The criteria proposed by ESC is the most recent guideline applied in the field. Patients diagnosed with HF are categorized according to their left ventricular ejection fraction (LVEF) as a useful phenotypic marker indicative of different underlying pathophysiological mechanisms(5,6) and, consequently, exposing other targets to be addressed within a therapy treatment. The various groups or phenotypes based on the LVEF are HF with a reduced ejected fraction (HFrEF), HF with mid-range ejection fraction (HFmEF) and HF with preserved ejection fraction (HFpEF).

Of interest, there are prognostic differences between different HF phenotypes, as illustrated by the Meta-analysis Global Group in Chronic Heart Failure (MAGGIC) study. Integrating data from 31 observational studies and clinical trials, patients with HFpEF were at a 32% lower risk of death than their HFrEF counterparts.(7).

However, independently of HF phenotype, the reduced cardiorespiratory capacity manifested through dyspnoea and fatigue, commonly referred to as exercise intolerance, remains the main clinical repercussion in HF. Such symptoms can be identified during physical activities or even at rest depending on the degree of limitation, which is commonly clinical categorized according to the New York Heart Association (NYHA) Functional Classification(8). This grouping system places patients in one of four categories based on their limited (I, II, III, and IV – the highest, the worst). The detailed description of NYHA classification follows below:

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

Although it is simple to identify exercise intolerance via only two main symptoms, such as dyspnoea and fatigue, it isn't easy to understand where it comes from. There are many systems involved in the pathophysiology of exercise intolerance in HF patients (Figure 1).
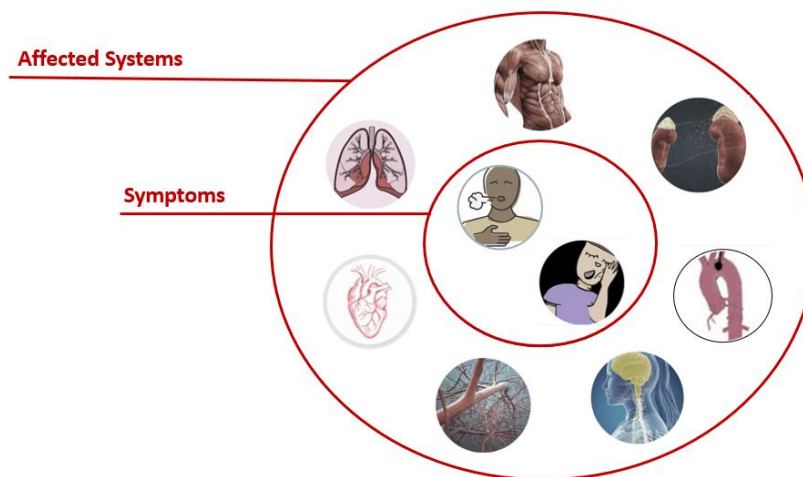
Figure 1. Systems affected on heart failure.

As illustrated in figure 2, we can mainly categorize six systems: pulmonary, cardiac, vascular, central nervous system, peripheral internal reflex, adrenal glands, and muscular. Different system repercussions may coexist, influencing exercise intolerance.

1.1 Exercise tolerance assessment and related variables

Maximal and submaximal tests measure exercise intolerance by collecting information regarding physical performance and perceived exertion can be collected. The gold standard is the cardiorespiratory exercise test (CPET) which can be performed on the treadmill or a bicycle ergometer. CPET precisely defines maximum exercise capacity through the measurement of oxygen uptake. The oxygen uptake measure constitutes the volume of O2 necessary to perform

an exercise and is extracted from the air inspired by pulmonary ventilation in each period: calculated, therefore, as the difference between the volume of inspired and expired O2 (13).

Thus, CPET provides breath-by-breath gas exchange measures. Such measures are prevenient from three main variables: O2 uptake (VO2), carbon dioxide output (VCO2), and ventilation (VE). These three measures derive various gas exchange patterns that reflect organ-specific (mal)adaptive responses from exercising, particularly when CPET is coupled with standard exercise variables such as heart rate, blood pressure, electrocardiography, or cardiac imaging. (9). An adequate CPET duration ranges from 8 to 12 minutes.

The parameter VO_2 peak from CPET is a classic measure routinely considered in clinical practice. Vo_2 peak definition is the higher O_2 rate reached during the exercise test reflects the ability of the cardiovascular system to deliver O_2 to exercising skeletal muscle by extracting O_2 from the blood for the exercising muscle. Unlike the VO_2 peak, when a plateau in VO_2 is established at maximal exertion (VO_2 max) a maximal physiological response is there. However, most patients with HF do not demonstrate a plateau in VO_2 when performing CPET. The peak VO_2 is typically considered as the maximal capacity. Researchers must deal with such limitations in the current studies available in the scientific literature (not assure that the measurement in the upper limit of O_2 transport/utilization as opposed to lack of effort, muscular pain, premature fatigue, or even other limitations incurred before VO_2 max being achieved (10). Subjective perceived exertion assessed via the Borg scale can help in such cases.

The interpretation of peak VO_2 and the determinants of exercise intolerance require assessment of many others CPET parameters, such as respiratory exchange ratio (RER), ventilatory thresholds (VT), hemodynamic and ECG responses to exercise, ventilatory efficiency, and subjective symptomatology. A better understanding of which factors contribute to the inadequate exercise response, often observed in patients, can be obtained by jointly considering these parameters. In the past, the most prevalent causes of exercise intolerance in HF resulted from central hemodynamic derangements. However, it is now clear that significant skeletal, muscular alteration is in this scenareo(1). Peak VO_2 is recognized as an important prognostic marker based on its relationship with ventricular function (change on LVEF), vascular function (e.g. O_2 delivery), and skeletal muscle metabolic capacity (O_2 utilization)(9).

With VE/VCO2 slope (which reflects the increase in ventilation in response to CO2 production, showing the increased ventilatory drive), peak VO2 variables have a pivotal role in the patient selection for advanced HF procedures such as heart transplantation and implantation of ventricular assist devices.(9).

VE/VCO2 slope emphasizes the ventilatory efficiency, reflecting an imbalance between ventilation/perfusion in the lungs, which is related, at least in part, to an impaired cardiac output response to exercise, early lactate accumulation, and abnormalities in respiratory control. The VE/VCO2 slope is a diagnostic and a prognostic marker in patients with HF (1). The rate of increase in the relationship between ventilatory response during exercise (minute volume or VE) and carbon dioxide production (VCO2), expressed in L/min, is analyzed using the V-slope method (VE/VCO2 slope).

 In a general aspect, as illustrated below (Figure 2), the CPET interpretation considers parameters that reflect the joint activity of respiratory, cardiovascular, and peripheral muscle function.
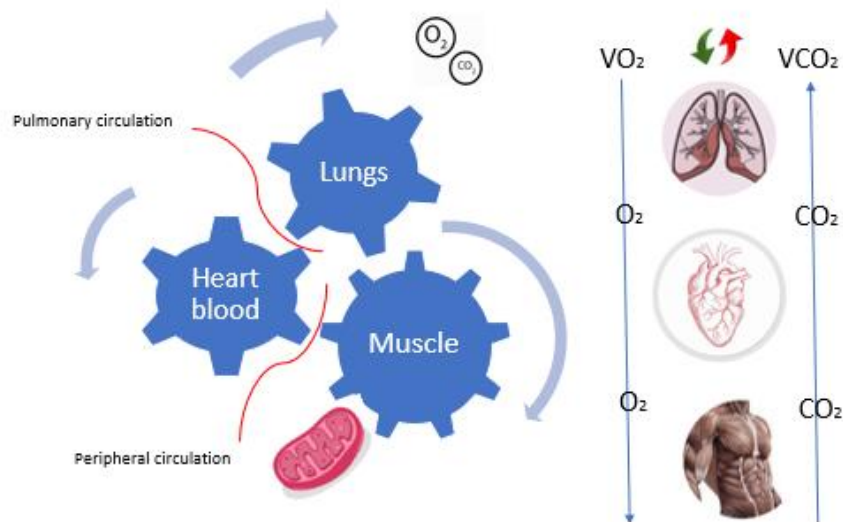
Figure 2. Oxygenation route: from the lungs to the muscle.

Pioneer studies by Weber and Mancini (11,12) proposed the use of CPET in daily practice as a measure for staging disease severity, thereby suggesting using this method to determine optimal treatment timing or follow-up after therapy. Weber et al. proposed a 4-stage classification system based on different categories of physical fitness (defined as peak VO2), which paved the way to many evidence and advancements in the care setting and risk stratification of patients with HF.(13). Weber classification is categorize as described below:

- Class A (VO$_2$ peak>20 ml/min/kg),
- Class B (16-20 ml/min/kg),
- Class C (10-16 ml/min/kg) or,
- Class D (<10 ml/min/kg).

Although other factors contribute to disease status (e.g., BNP levels and LVEF), CPET is important to quantify the degree of exercise tolerance and helps identify when it is appropriate to consider advanced HF treatments (left ventricular assistance devices and heart transplantation). The figure below is based on Malhotra et al (9) summarizes some CPET variables involved on the risk stratification of HF population.
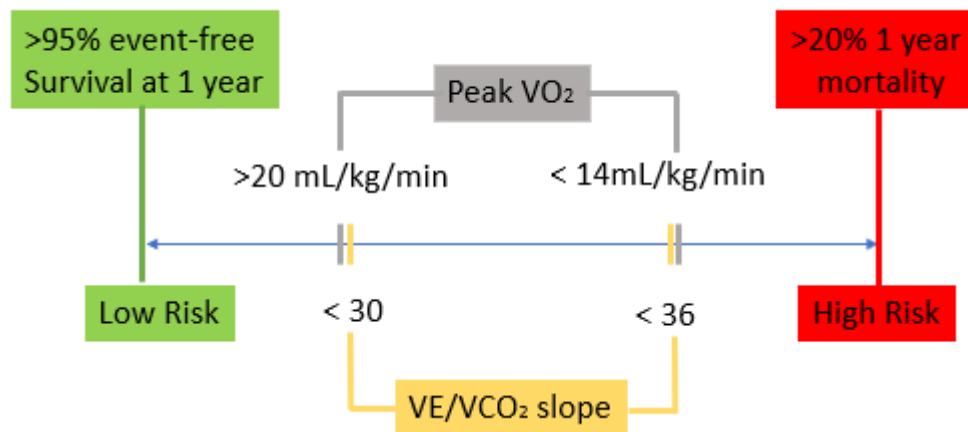
Figure 3. Risk level based on cardiopulmonary exercise test parameters.

The risk stratification is usually applied to surgical prediction as in the case of heart transplantation need.

1.2 Physical and functional performance

As important as exercise intolerance measurement via CPET assessment, the physical functional performance has also been included to measure prognosis in patients with HF. Systematic review and meta-analysis have indicated the 6-Minute Walking Test (6MWT), Short Physical Performance Battery (SPPB), Timed Up and Go (TUG), and Gait Speed test as those more used. (14).

The SPPB and TUG have been used to assess physical or functional frailty in patients with HF, commonly associated with a higher risk of hospitalization and mortality. The utility of the Gait Speed test predicts functional independence loss, cardiovascular disease, hospitalization, and mortality in older adults. HF patients with poor physical functional performance as assessed by the Six Minute Walking Test (6MWT) and the Short Physical Performance Battery (SPPB) showed worse prognosis in terms of more significant risk of hospitalization or mortality than patients with good physical functional performance(14).

Although it is handy as a submaximal test and low cost applicable, when there is the opportunity to apply the CPET test, the 6MWT is normally less used(14). On another side, a previous study has indicated that SPPB can measure cardiovascular health in adults beyond that captured by traditional risk factors. Due to its high test-retest reliability and low administrative burden, the SPPB can easily be a routine part of office-based CVD risk assessment.(15). SPPB focuses on lower extremity function, which has already proved to predict hospitalization burden in outpatients with HF independently. Besides, it is also used as a frailty index in HF. A score below 7 points on the SPPB seems to be the most indicative of a worse prognosis in patients with HF since it was associated with a more significant risk of the combined endpoint of hospitalization and mortality for any cause and a more considerable risk of HF hospitalization(14).

The physical functional performance assessment can complement the exercise intolerance information.

Part 2. Heart Failure and exercise intolerance: where does it originate from?

In patients with HF, the integrated metabolic machinery required to perform exercise is impaired at multiple levels that influence exercise intolerance. Starting with oxygen (O2) uptake, the requisite increase in ventilation is challenged by frequently abnormal mechanics and diffusing capacity. (9). The impaired oxygenation to skeletal muscle is limited by abnormal cardiac output (CO) augmentation arising from chronotropic incompetence, inability to augment, and functional. Shortening of diastole during heart rate (HR) elevation and increased venous return elevate the filling pressures during exercise; impaired vasoreactivity further contributes to dynamic ventriculovascular uncoupling (9). These problems related to pulmonary and cardiac aspects are central mechanisms involved in exercise intolerance.

Besides central, there are peripheral mechanisms such as muscular and vascular that influence exercise intolerance in HF. Muscular and vascular aspects are included in this scenario. When considering the delivery of O2 to the periphery, diffusive O2 conductance and utilization are limited by impaired sympatholysis, reduced capillary density, decreased mitochondrial volume, and selective loss of type 1 muscle fibers having oxidative fatigue-resistant properties. These aspects, together with the exaggerated signaled through intramuscular afferents, called ergoreflex signaling, are peripheral mechanisms related to exercise intolerance present in HF(9).

Didactically, it is possible to summarize the numerous pathophysiological mechanisms related to exercise intolerance in patients with HF in the following main topics (16):

    A. inadequate exchange of O_2 and carbon dioxide (CO_2) through pulmonary ventilation and diffusion across the alveolar-endothelial barrier;

    B. alterations in the cardiovascular system that supplies oxygenated blood at sufficient flow rate to meet the metabolic demands of working muscles;

    C. the inability to carry O2 in the blood and properly distribute blood flow to areas with the greatest need during exercise;

    D. insufficient peripheral muscle strength and endurance in the respiratory muscular system to sustain the increased ventilatory demands with physical exertion and abnormal contraction and,

    E. O_2 diffusion, extraction, and utilization in skeletal muscle

Importantly, distinct causes may coexist and partly contribute to exercise intolerance in patients with HF(16). The figure below extracted from Del buono et al (16) explore the multiple systems involved in the observed reduced functional and exercise capacity in patients with HF.

Reduced Pulmonary Reserve

- Impaired Pulmonary Vasodilation and Vascular Recruitment (exercise-induced PH)

- Ventilation-Perfusion Mismatch
- Reduction on O2 alveolar diffusion
- Abnormal Ventilatory Reserve
- Abnormal Ventilatory Regulation

Other Contributing Factors

- Peripheral Vacular Dysfunction
    - Endothelial dysfunction
    - Slow blood kinetics
    - Reduced capillary red blood cell flux
- Anemia
- Obesity
- Nutritional Factors
- Impaired Autonomic Regulation

Reduced Cardiac Reserve

- Systolic dysfunction
- Functional Mitral Regurgitation
- Ventricular Diastolic Dysfunction
- Left Atrial Dysfunction
- Chronotropic incompetence
- Ventriculo-arterial uncoupling

Skeletal Muscle Dysfunction

- Structural Abnormalities
    - Reduction on capilar density
    - Reduction on intermuscular fat
    - Redction on skeletal muscle mass
    - Fiber type shift
- Functional Abnormalities
    - Mitochondrial dysfunction
    - Biochemical changes
    - Reduction on oxidative capacity
    - Microcirculation abnormalities
- Autonomic Adaptations
    - Increase on metaboreflex

Figure 4. System involved on reduced exercise capacity. Adapted from Delbuono et al(16).

Apart from the different systems involved, we can conclude that most of the potential dysfunctional cardiovascular and non-cardiovascular mechanisms in HF result in problems related to oxygen supply to the demanding tissue, which highlights the exercise intolerance phenomena.

Part 3. HF with preserved and reduced ejection fraction: pathophysiology and relation to exercise intolerance

From the last decades, it has been commonly known that HF is being classified based on the presence or absence of contractile dysfunction of the left ventricle, mainly through evaluating the LV ejection fraction (EF). Based on this functional variable, one can distinguish three phenotypes: reduced ejection fraction (HFrEF), preserved (HFpEF), and moderate (HFmEF), characterized by LVEF <40%, LVEF ≥50%, and LVEF between 40 and 49%, respectively. In addition to these functional classes, other criteria can be considered, such as levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) and echocardiography data (17). The figure below extracted from ESC Guidelines (2021) describes the definition of HFrEF and HFpEF.

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF ≤40%	LVEF 41–49%[b]	LVEF ≥50%
	3	–	–	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides[c]

Figure. 5 Heart Failure diagnose criteria based on ESC Guidelines 2021 (Reprinted with permission from McDonagh et al).

These variables are clinically relevant as a classification system based on LVEF only could lead to oversimplification of a complex syndrome (18). Even though the two most frequent phenotypes amongst patients with HF (HFrEF and HFpEF) have been explored most often in clinical practice. HFpEF and HFrEF are associated with a significant reduction in functional capacity, different comorbidities, and hospitalization rate (19). Patients with HFpEF and HFrEF usually have similar reduced cardiorespiratory capacity. However, the proportion of non-cardiovascular mortality is higher in HFpEF compared to HFrEF (20).

HFpEF affects mostly of the times older people, women, individuals with obesity, and people with a history of hypertension and types two diabetes mellitus. Almost 50% of HFpEF patients have [3]5 significant comorbidities compared to 37% of HFrEF patients(20). Most studies

estimated that over half of all patients with HF in the general population have a preserved LVEF and that this proportion is increasing throughout recent years(4).

Although the challenges in HF classification due to its applicability on clinical practice (HFmEF, for example, is less understandable), this differentiation is vital due to the different aetiologies, demographics, presence of comorbidities, and the response to (non-)pharmacological therapies (17), even even though patients with HF can share many characteristics.

Despite the patients´ specificities and the high prevalence of HF as a disease, the clinical, biological, physiological, and prognostic factors in HFpEF still need to be better understood and treatment strategies for this patient population. Moreover, peripheral mechanisms related to exercise limitation in the HFpEF classification need to be explored (19–21).

Among the peripheral mechanisms in HF, skeletal muscle plays an important role in exercise intolerance (19,22,23).

Molecular alterations occur in the peripheral skeletal muscle of patients with HFrEF and HFpEF (Fig 6). As indicated, aspects related to muscle mass, fiber type, capillarization, oxidative capacity, mitochondrial function, and inflammation influence exercise intolerance, coexisting and differing phenotypes. These skeletal muscle-related changes result in reduced muscle mass and subsequently reduction of exercise capacity and quality of life.
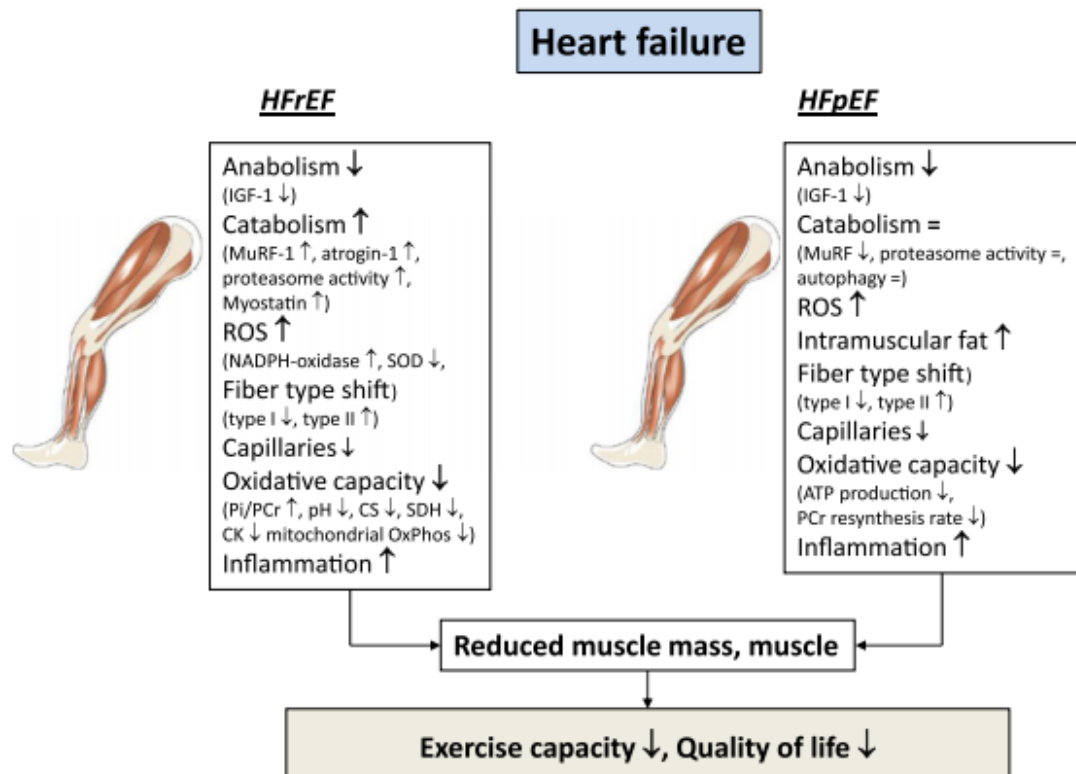
Figure 6. Muscular alterations in heart failure. Reprinted with permission from Adams et al, 2017 (24). ROS reactive oxygen species, CS citrate synthase, SDH succinate dehydrogenase, CK creatine kinase, PCr phosphocreatine, IGF-1 insulin like growth factor 1, MuRF-1 muscle ring finger protein 1.

In animal models, a substantial portion of the capillary bed does not support red blood cell flux in HFrEF. This is responsible, at least in part, for the O2 diffusion reduction and impaired blood-myocyte O2 change. It is not known whether this occurs in HFpEF. However, HFpEF patients seem to display far lower fractional O2 extractions at maximal exercise than seen in HFrEF. Compared with HFrEF, skeletal muscle atrophy and dysfunction may not be present. These observations suggest a very different peripheral microvascular pathophysiology among HF phenotypes and quite possibly a contrasting differentiation phenotype during exercise(10).

Although evidence about muscular aspects in HFpEF is less numerous, there is extensive evidence for HFrEF-inducing a shift in skeletal muscle fiber type distribution towards more fast-twitch type II/IIb. Also, reduction in oxidative capacity, mitochondrial volume and density, further enzymes alterations consequently influence either muscle atrophy or myopathy, or both (10).

Part 4. Specific peripheral systems contribution to exercise intolerance in Heart Failure

4.1 Endothelial Function

Endothelial disfunction is notorious in HF individuals (25), being related to an increase in cardiovascular risk (26) and cardiovascular events (10), progressively worsening the disease severity (27). Occurring in part by an increase on oxidative stress (25,26,28) and reduction nitric oxide (NO) production (25), these contribute to the vessel wall thickness, vasodilation reduction, shear stress increase and vascular damage.

This sum of factors (Fig 7) promotes an increase in peripheral vascular resistance with a reduction in blood supply to the skeletal muscle and lungs, thereby impairing adequate oxygenation resulting in symptoms of dyspnoea, exercise intolerance, and reduced prognosis (29). Such exercise intolerance may occur even during daily life activities, mainly present in more severe HF individuals. Tripokiadis (18) expresses the biochemical cascade involved in

the endothelial dysfunction in heart failure, which is not only related to nitric oxide (Fig 7).
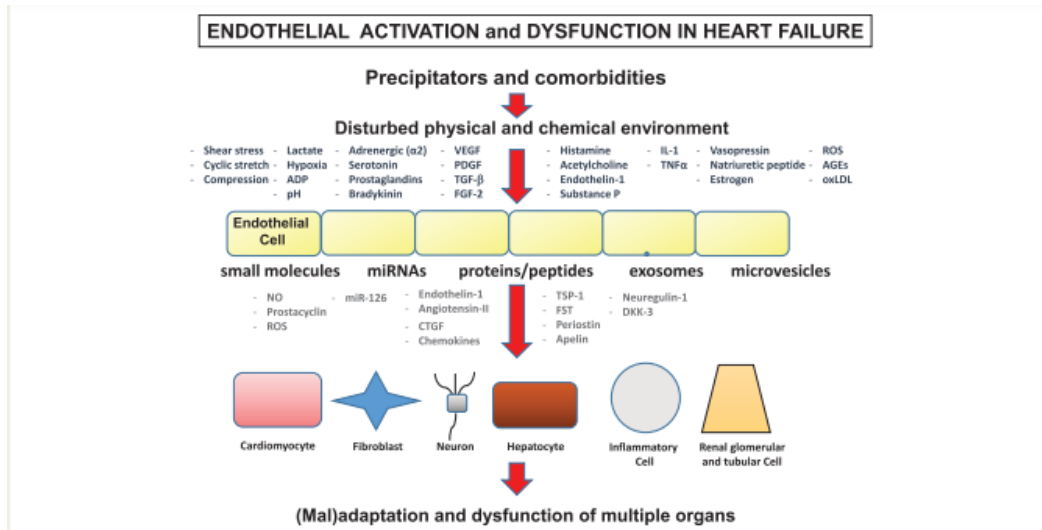
Figure 7. Endothelial dysfunction in Heart Failure. Reprinted with permission from Tripokiadis 2019 (18).

The importance of endothelial function in HF is even more remarkable when considering the multiple pathological and physiological processes performed by the endothelium, such as the regulation of smooth muscle tone, control of thrombosis, inhibition of leukocyte and platelet cell adhesion, and promotion of intra-arterial permeability (30–32). Furthermore, endothelial dysfunction is proposed as the primary etiology of atherosclerosis (33) and is related to morbidity and mortality in patients with HF.

Endothelial function can be accessed by the flow-mediated dilation technique. Flow-mediated dilation (FMD) is a non-invasive technique (30) and has been considered an important prognostic variable for patients with HF (34). Also, it is well known that brachial endothelial dysfunction is associated with carotid thickness (35). FMD technique provide information about blood flow and artery compliance. Although when thinking about blood flow we can associate to oxygenation supply, study in healthy young and individuals at risk for cardiovascular disease showed that FMD response did not correlate with the magnitude of muscle O_2 desaturation. However, it seems to be partially associated with the O_2 resaturation rate(36). It seems that the oxygen supply is not linearly related to the blood flow when talking about muscle dynamic and both aspects can separately be involved to exercise intolerance in heart failure individuals.

The lower muscle performance may result from a reduced peripheral blood flow and endothelial dysfunction when associated with muscle myopathy, contributing to exercise intolerance (37). The endothelial dysfunction alone may impair the blood flow to the muscle.

4.2 Muscular aspects and Peripheral Oxygen Extraction in Heart Failure

Another necessary condition contributing to exercise intolerance in HF is the loss of muscle mass (sarcopenia) characterized by atrophy of skeletal muscle, resulting in muscle strength reduction. A muscular performance impairment occurs when jointly considering the muscle mass/strength reduction, the fiber type shift (from type 1 to type 2), the increase on anaerobic metabolism bioenergetic, the decline in high energy phosphates, the reduced skeletal muscle blood flow, and peripheral inflammation (cytokines) (38). Sarcopenia and muscle strength reduction in HF imply lowered oxidative capacity and perfusion(5,39,40) affecting transport and oxygen utilization during exercise and the elimination of metabolic remnants (29,41), essential tasks from the microvascular muscle function. Consequently, it reduces functional and exercise capacity (42–44), revealing signs and symptoms of exercise intolerance.

The muscle microvascular dysfunction in HF may result from vascular rarefactions, skeletal muscle abnormalities (myopathy) and adipose distribution (10). When isolated, microvascular dysfunction already impairs cardiorespiratory capacity (VO2peak), resulting in exercise intolerance(10), regardless of other muscle impairments.

In general aspect, skeletal myopathy contributes to the impaired exercise capacity in both phenotypes HFpEF and HFrEF (45). There is emerging evidence that HFpEF patients display far lower fractional O2 extractions at maximal exercise than HFrEF (46) and that, compared with HFrEF, skeletal muscle atrophy and dysfunction may not be present. These observations suggest a very different microvascular pathology in HFpEF and possibly contrasting damage of the muscle profile during exercise(10). Hirai et al. already focused on analyzing oxygen extraction in HF patients. Still, this study was carried out during aerobic stimulus, demanding the oxidative metabolism (22) revealing that HFpEF presented lower oxygen extractions when compared to HFrEF phenotype.

There is no evidence in the literature regarding the behavior of oxygen extraction in patients with HF during muscle strength stimulus. This is particularly important to prove the behavior of this variable during glycolytic metabolism, allowing a better understanding of the oxygen dynamics scenario. Thus, peripheral theory related to exercise intolerance can be better

understood. The portable infrared spectroscopy equipment can indirectly measure the microvascular dysfunction by analyzing the peripheral oxygen extraction obtained through portable infrared spectroscopy (47).

Peripheral musculature presents more remarkable plasticity and potential for adaptation than central aspects. Because of it, skeletal muscle function and oxidative capacity can be directly addressed, improving cardiopulmonary variables (23). Among the forms of muscle strength assessment, isokinetic assessment is the gold standard to stratify the HF prognosis further (48).

Central, vascular and muscular aspects jointly affect exercise intolerance in heart failure, potentially impairing all physical efforts from the individual.

Part 5. Strategies to treat exercise intolerance in heart failure

HF is a syndrome across a spectrum of phenotypes and each patient follows a unique trajectory based on the initial trigger(s), the genetic, clinical, and sociodemographic background, and available treatment options (18). Nevertheless, there are many treatments approach validated to this population with a high degree of recommendation according to international guidelines (49).

The sections below scrutinize the pharmacological, surgical and exercise intervention treatment in this population.

5.1 Overview of pharmacological approach and specificities in reduced and preserved ejection fraction

The treatment goals in patients with HF are to improve their clinical status, functional capacity, and quality of life, prevent hospital admission, and reduce mortality. There are some differences between pharmacological treatment in HFrEF and HRpEF. The table below shows the treatment strategy for drugs in patients with HFrEF according to ESC Guideline (50).

Table 2. Treatment strategy for the use of drugs in patients with Heart Failure with Reduced Ejection Fraction

Treatments recommended in all symptomatic patients with heart failure with reduced ejection fraction

Recommendations	Class and level	Description	Drugs
Angiotensin-converting enzyme inhibitor (ACEI)	IA	An ACE-Id is recommended, in addition to a beta-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death.	Captopril, Enalapril, Lisinopril, Ramipril, Trandolapril
Beta-blocker	IA	A beta-blocker is recommended, in addition an ACE-Id, for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death.	Bisoprolol Carvedilol Metoprolol succinate (CR/XL) Nebivololc
Mineralocorticoid receptor antagonist (MRA)	IA	An MRA is recommended for patients with HFrEF, who remain symptomatic despite treatment with an ACE-Id and a beta-blocker, to reduce the risk of HF hospitalization and death.	Eplerenone Spironolactone
Other treatments recommended in selected symptomatic patients with heart failure with reduced ejection fraction			
Recommendations	Class and level	Description	Drugs
Diuretics	*IB **IIaB	*to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion **to reduce the risk of HF hospitalization in patients with signs and/or symptoms of congestion	Loop diuretics Furosemide Bumetanide Torasemide Thiazides Hydrochlorothiazide Metolazone lndapamidec Potassium-sparing diuretics +ACE-I/ ARB - ACE-I/ ARB +ACE-I/ ARB - ACE-I/ ARB Spironolactone/

			eplerenone Amiloride Triamterene
Angiotensin receptor neprilysin inhibitor	IB	It is recommended as a replacement for an ACE-I to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE-I, a beta-blocker and an MRAd	Combination of valsartan and sacubitril (neprilysin inhibitor) in a single substance. ACEI (enalapril) - (neprilysin inhibitor)
I_f-channel inhibitor	*IIaB **IIaC	*Ivabradine should be considered to reduce the risk of HF hospitalization or cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm despite treatment with an evidence-based dose of betablocker (or maximum tolerated dose below that), ACE-I (or ARB), and an MRA (or ARB) ** Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm who are unable to tolerate or have contra-indications for a beta-blocker. Patients should also	Ivabradine

		receive an ACE-I (or ARB) and an MRA (or ARB)	
Angiotensin II type I receptor blockers	*IB

**IIbC | *An ARB is recommended to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients unable to tolerate an ACE-I (patients should also receive a beta-blocker and an MRA

**An ARB may be considered to reduce the risk of HF hospitalization and death in patients who are symptomatic despite treatment with a beta-blocker who are unable to tolerate an MRA | Candesartan Valsartan The combination of ACEI/ARB (under strict supervision) |
| Combination of hydralazine and isosorbide dinitrate | *IIaB

**IIbB | No clear evidence to suggest the use of this fixed-dose combination therapy in all patients with HFrEF | hydralazine and isosorbide dinitrate |
Other treatments with less certain benefits in symptomatic patients with heart failure with reduced ejection fraction			
Recommendations	**Class and level**	**Description**	**Drugs**
Digoxin and other digitalis glycosides	IIbB	Digoxin may be considered in symptomatic patients in sinus rhythm despite treatment with an ACE-I (or ARB), a beta-blocker and an MRA, to reduce the risk of hospitalization (both all-cause and HF-hospitalizations).	Digoxin and other digitalis glycosides
n-3 polyunsaturated fatty acids	IIbB	An n-3 PUFAe preparation may be considered in symptomatic HF patients to reduce the	Only preparations with eicosapentaenoic acid (EPA) and docosahexaenoic

		risk of cardiovascular hospitalization and cardiovascular death.	acid (DHA) as ethyl esters of at least 85% (850 mg/g) have shown an effect on the cumulative endpoint of cardiovascular death and hospitalization.

The treatment strategy for the use of drugs in patients with HFpEF according to ESC Guideline (50) is less consistent, but the main direction is described below.

The use of diuretics will usually improve congestion, thereby improving symptoms and signs of HF similarly across the full spectrum of LVEF phenotypes. In contrast, clear evidence that beta-blockers and MRAs improve symptoms in these patients is currently lacking. There is inconsistent evidence for an improvement in symptoms in those treated with ARBs and ACEIs. For patients in sinus rhythm, nebivolol, digoxin, spironolactone, and candesartan might reduce HF hospitalizations. Beta-blockers do not appear to be effective for patients in AF, and digoxin has not yet been studied. The evidence in support of either ARBs or ACEIs is inconclusive(50).

Trials about using ACEIs, ARBs, beta-blockers and MRAs in older patients with HFpEF, such as nebivolol, indicated reduction in the combined endpoint of death or cardiovascular hospitalization, with no significant interaction between treatment effect and baseline LVEF. Patients in arterial fibrillation should receive an anticoagulant to reduce the risk of thromboembolic events.(50)

One of the most important distinctions of HFpEF patients are that traditional pharmacological therapies used to treat HFrEF such as neurohumoral inhibition have not improved patient quality of life or survival (50).

Also, one of the biggest trials involving pharmacological treatment in HF (TOPCAT trial) revealed that the treatment with spironolactone, usually recommended on HFrEF, did not significantly reduce the incidence of death from cardiovascular causes, aborted cardiac arrest, or hospitalization in HFpEF(51).

In addition, sacubitril–valsartan did not result in a significantly lower rate of total hospitalizations for heart failure and death from cardiovascular causes among patients with heart failure and an ejection fraction of at least 45%. This result was expressed by the PARAGON trial (52).

5.2 Heart assistant devices

Many of the deaths in HF occurs due to electrical disturbances, including ventricular arrhythmias, bradycardia, and asystole, although some are due to other acute vascular events. Treatments that improve or delay the progression of the disease reduce the rate of sudden death. Implantable cardioverter-defibrillator is effective at correcting potentially lethal ventricular arrhythmias, and it is indicated to those who have recovered from a ventricular arrhythmia causing hemodynamic instability, and who are expected to survive for >1 year with good functional status, in the absence of reversible causes or unless the ventricular arrhythmia has occurred <48 h after a myocardial infarction(49).

Another treatment resource for HF patients is cardiac resynchronization therapy (CRT) implantation. Inappropriately selected individuals, CRT reduces morbidity and mortality. Furthermore, CRT improves cardiac function and enhances the quality of life. CRT is recommended for symptomatic patients with HF with a QRS duration >150 ms an and with LVEF <_35% to improve symptoms and reduce morbidity and mortality. A CRT rather than right ventricular pacing is recommended for patients with HFrEF regardless of NYHA class or QRS width, which have an indication for ventricular pacing due to severe atrioventricular block to reduce morbidity. This includes patients with atrial fibrillation(49).

5.3 Heart transplantation

Despite the improvements in pharmaceutical, resynchronization treatments and the advent of left-ventricular assist devices (53), heart transplantation (HTx) remains a notable treatment option in (54–57)for end-stage chronic HF (50). In end stage HF, the body can no longer compensate for the lack of blood the heart pumps and the individual experience symptoms all the time such as dyspnoea, fatigue, abdominal pain, unexplained weight loss and irregular heartbeat. Also, end stage heart failure patients may experience kidney or liver conditions. End stage heart failure patients normally need regular hospitalization, and their condition may not respond well to treatment, worsening the HF disease process.

The increasing number of patients with HF and the declining willingness for organ donation resulted in expanded waiting lists and prolonged waiting times for patients listed for

heart transplantation, with more than 60% of patients being transplanted under high-urgency status. (50).

5.4 Heart transplantation and exercise intolerance

There is a consensus that heart transplantation significantly increases survival, quality of life, and return to work rates while it improves exercise tolerance compared with conventional treatment (50). Also, in addition to increased life expectancy, heart transplant recipients report a remarkable improvement of symptoms related to functional capacity. However, exercise capacity following heart transplantation remains impaired (although to a lesser extent than in the pre-operative state), even with no exertional symptoms(58,59).

The maximal symptom-limited oxygen uptake (VO_2max) and the anaerobic threshold are in the range of 50 to 70% of predicted in heart transplant recipients (60), which is comparable to those severe HF patients in stable condition (LVEF lower than 20%).(61) Although the cause of exercise intolerance in heart transplant recipients is not entirely clear, there is increasing evidence that it is multifactorial and involves complex interactions among cardiac, neurohormonal, vascular, skeletal muscle, and pulmonary abnormalities (59,62). The denervated heart has a reduced heart rate (HR) reserve due to the elevated resting HR and its blunted response to exercise. A left ventricular diastolic dysfunction also contributes to this scenario, resulting from a reduced heart compliance. Last but not least, persistent peripheral abnormalities such as abnormal neurohormonal responses to exercise (63) deconditioning,(64) and peripheral circulatory dysfunction impair the exercise performance and tolerance in these patients (65).

Many factors are influencing the decreased exercise capacity (peak VO2) and reduced cardiac output in individuals with heart transplants, such as cardiac allograft denervation, diastolic dysfunction of the transplanted left ventricle, reduced peak exercise end-diastolic and stroke volume by 20%, increased pulmonary capillary wedge pressure/end-diastolic volume index ratio during upright maximal ergometry, myocardial ischemia due to cardiac allograft vasculopathy, impaired peripheral vascular endothelial function, increased systemic vascular resistance by 50%, decreased skeletal muscle oxidative fibers, mitochondrial volume, enzyme activity and capillary density, reduced arteriovenous oxygen difference by 25%, elevated sympathetic activation (66) and the mandatory immunosuppressive treatment post-heart

transplantation used to lower their bodies' immune response which influence not only VO2 peak reduction but also muscle deconditioning (67,68).

5.5 Exercise training intervention in heart failure and heart transplantation

Cardiac rehabilitation through exercise intervention is strongly recommended (IA indication, which defines it as valuable and practical) for patients after a cardiovascular event, including heart failure patients (46,49,69–71). By improving exercise tolerance in patients with HF (72), cardiac rehabilitation reduces cardiac dysfunction related to left ventricular performance during exercise(73), improves vascular flow to the skeletal and to the cardiac musculature (74,75) and improves functional capacity and quality of life in HF patients regardless the phenotype spectrum (10).

Cardiac rehabilitation through exercise training is also recommended for individuals after HTx. Exercise reduces CV risk induced by post-transplantation immunosuppressive medical therapy and increases physical performance. HTx recipients reveal reduced hospital readmissions and higher long-term survival when following cardiac transplantation (76). Importantly, even considering that cardiac allograft neural reinnervation already contributes to improved functional capacity in the first year after transplantation, exercise rehabilitation is strongly recommended(49).

Unfortunately, the potential reward of cardiac rehabilitation is still underutilized around the globe, in part, due to its cost, lack of availability and high dropout rates(77).

Current guidelines recommend aerobic moderate-intensity exercise training for HF patients, 3 to 5 days/week, with a duration from 30 minutes ranging up to 60 minutes and considering 40 to 80% of peak VO_2 (78), depending on the clinical status of HF patients. In patients included on NYHA functional class III, exercise intensity should be maintained at a lower intensity (<40% of VO2peak), according to perceived symptoms and clinical status at least the first 12 weeks. A gradual increase in intensity to 50-70% VO2peak, and if tolerated, up to 85% VO2peak may be considered(78). Also, resistance exercise training recommendations for HF patients indicate intensities lower than 15 (out of 20) on the perceived exertion Borg scale, with a load ranging from 40 to 60% of one-repetition maximum test (1RM). A combination of endurance and resistance exercise is preferred(78).

High-fatigability HF patients with exercise intolerance manifest even earlier reduced oxidative capacity compared with age-matched individuals or low-fatigability HF patients (79).

By considering low-fatigability HF patients, we can rationalize that not all HF patients are immersing into the same clinical repercussion (there are possible groups of low and high fatigable patients and NYHA classification can clinically help this screening) and that is why the clinical approach/prescription needs to consider each patient characteristic. Anyway, the exercise prescription indicated by guidelines includes range of variation enough to allow an assertive individualization of therapy on clinical practice.

The recommendations for HTx follow the same combination of endurance and resistance modalities. The aerobic training in HTx should start at a moderate intensity (60% VO2peak), which can later be increased to 80% of VO2peak. In uncomplicated cases these intensities can be increased to maximum levels. Exercise duration and frequency have ranged from 30 min to 90 min for 2 to 5 times per week, and it is recommended that HTx individuals perform up to five bouts of 30 min of exercise per week(78). Both endurance and resistance training are included, and resistance exercise should focus on large muscle. Upper body resistance exercise should start at least 3 months after surgery, and intensity should gradually increase from low to moderate but can also be performed up to submaximal intensities, in case of uncomplicated disease.

A major limitation of endurance exercise is the reduced chronotropic response to exercise because of allograft denervation. Apart from chronotropic incompetence, other pathophysiological changes present after HTx should also be considered as exercise-induced ischaemia, from cardiac allograft vasculopathy, particularly should be considered when performing higher-intensity exercise.

For heart failure patients in pre-transplantation time, regular exercise through cardiac rehabilitation, combining moderate-intensity aerobic and resistance training, is recommended to revert pathophysiology, reduce cardiovascular risk induced by post-transplantation medical treatment, and improve clinical outcome (IB indication).

Concerning the training intensities, high-intensity training modalities have been under intense debate since the previous decade. This training modality gained prominence in the rehabilitation of individuals with heart failure in 2007 when the researcher Wisloff and collaborators (80) published significant results regarding this intervention. The study showed a substantial increase in the aerobic capacity of patients with heart failure after 36 physical training sessions. This result showed the impact of the HIIT intervention on cardiac rehabilitation for the first time in the history of the scientific literature. Compared to continuous aerobic training (AT) of moderate-intensity, it was demonstrated a percentage difference of 20.8% vs. 12.8%, HIIT and AT, respectively..

Although it depends on the patient's profile, mainly recommended for low-risk heart failure patients, this finding corroborates with the information that intensity seems to be an essential predictor of the effectiveness of cardiac rehabilitation programs Many studies have explored the HIIT intervention in patients with HF, which resulted in HIIT inclusion as a guideline recommendation (76).

Among resistance training modalities, high-intensity protocols are less utilized and scientifically reported. An example of resistance training design is the circuit-resistance training characterized by different exercise machines in which the patient alternates exercise stations after each exercise attempt (CRT) (81). CRT is also considered an interventional methodology with promising results in HF.

Although aerobic high intensity is officially recommended for low-risk HF patients, new studies are warranted for patients with different HF phenotypes and risks level. For heart transplant receipts, an official high-intensity recommendation is far from the reality due to the little evidence in the field regardless of short or long-time post-heart transplant.

The high aerobic intensity was recently included in guidelines for low-risk HF patients (78). For patients after heart transplantation, the use of HIIT is still under study. Concerning resistance training modality, there is a huge need for studies to cave a decision about its recommendation in HF and HTx.

Part 6. Issues on the field and manuscripts written

Based on the abovementioned points, essential issues are seeking scientific answers in heart failure and heart transplantation patients. We wrote three papers to fill such scientific gaps:

- Paper 1

This first paper focused on the mechanisms leading to exercise intolerance. This paper was designed to understand the local oxygen extraction differences among different HF phenotypes and disease severities during muscle strength exercise. This paper also aimed to analyze possible associations between exercise-induced microcirculation responses and ultrasound-derived variables with a) isokinetic muscle strength test, b) cardiorespiratory fitness, and c) peak power output.

Hypothesis: HFpEF patients present a worse microcirculatory dynamic than HFrEF based on previous studies that signalized such behavior during endurance exercise.

- Paper 2

Although high aerobic intensities were recently integrated into the European guideline to treat the heart failure population, the resistance training prescription through high is still under debate. The second paper was made concerning this aspect, providing a clinical view of different systems' repercussions post-high-intensity training and modalities. By exploring the outcomes of exercise intolerance via cardiorespiratory capacity, endothelial health, muscular strength, and functionality, this paper demonstrated essential insights into the clinical approach in HF.

Hypothesis: There is no difference between aerobic or resistance training modalities when applied high-intensity loads in heart failure patients.

- Paper 3

There is bolding evidence regarding exercise program's effects (82) post-HTx; however, the pivotal understanding about the preferred exercise prescription for exercise capacity (modality and intensity) remains unexplored. This review evaluates and compares the isolated and combined effect of the aerobic training (AT) and resistance training (RT) on cardiorespiratory components (V′O2 peak and VE/V′CO2 slope), cardiovascular components (HR peak, SBP peak, and DBP peak), and peripheral components (FMD and muscle strength) post-HTx. We hypothesized that aerobic training with moderate intensity is more favorable post-HTx.

Hypothesis: Aerobic continuous training though the moderate intensity is the best training prescription for HTx patients, regardless of post-transplantation.

The figure below expresses the papers included in this thesis and the quality according to the pyramid of scientific evidence.
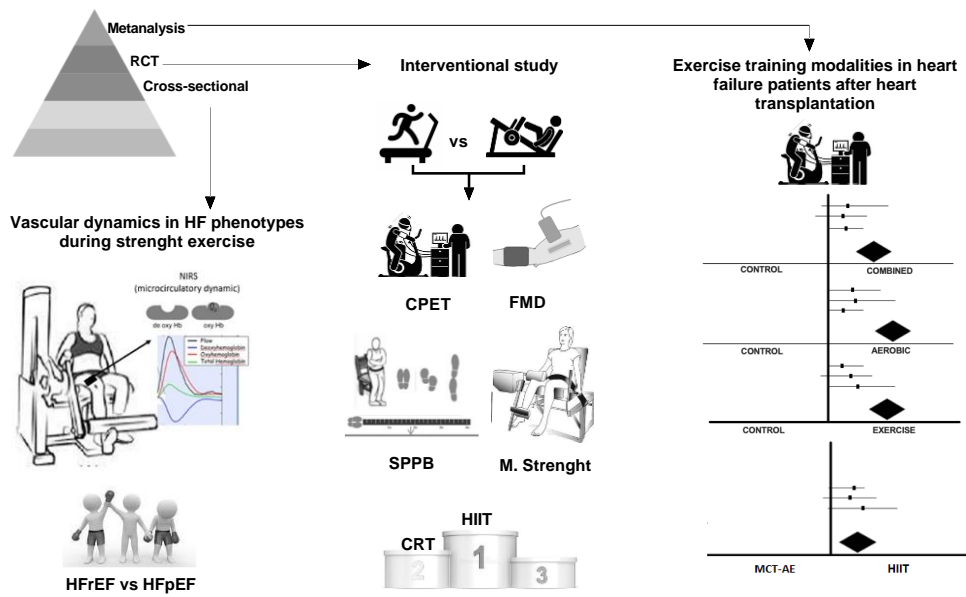
Fig 8. Overview of the papers included on this thesis.

Chapter 2

Peripheral muscle microcirculation dynamics during strength exercise in heart failure patients

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ABSTRACT

Abstract: Background and Objectives: To analyze the effects of aerobic, resistance, and combined training on peripheral and central components related to cardiorespiratory capacity after HTx. Materials and Methods: No time restriction was applied for study inclusion. MEDLINE/PubMed; EMBASE, CENTRAL, and PEDro databases were investigated. Studies reporting heart transplanted patients older than 19 years following aerobic, resistance, and combined training according. The outcomes included: V0O2 peak, VE/V'CO2 slope, heart rate (HR peak), systolic and diastolic blood pressure (SBP and DBP peak), maximum repetition test(1RM), sit-to-stand test, and flow-mediated, dilation (FMD). The studies were selected by consensus. Four hundred ninety-two studies initially met the selection criteria. Cochrane handbook was used for abstracting data and assessing data quality and validity. Independent extraction by two observers was applied. Results: Isolated aerobic training leads to a greater increase in V0O2 peak than combined training compared to the control group ($p < 0.001$, $I2 = 0\%$). However, no significant differences were found in the subgroup comparison ($p = 0.19$, $I2 = 42.1\%$). HR peak increased similarly after aerobic and combined training. High-intensity interval training (HIIT) was better than moderate continuous intensity to increase the V0O2 after long term in HTx. Still, there is scarce evidence of HIIT on muscle strength and FMD. No change on VE/V'CO2 slope, FMD, and SBP, DBP peak. 1RM and the sit-to-stand test increased after resistance training ($p < 0.001$, $I2 = 70\%$) and CT ($p < 0.001$, $I2 = 0\%$) when compared to control. Conclusions: Aerobic and combined training effectively improve VO2 peak and muscle strength, respectively. HIIT seems the better choice for cardiorespiratory capacity improvements. More studies are needed to examine the impact of training modalities on VE/V'CO2 slope and FMD.

Introduction

Cardiovascular disease (CVD) is the most important cause of premature mortality, leading to over 17 million deaths yearly around the globe [1–3]. Heart failure (HF) is a clinical syndrome characterized by ranks as the second most prevalent CVD [4], exhibiting typical clinical symptoms (i.e., breathlessness, fatigue, ankle swelling) or signs (i.e., pulmonary crackles, peripheral edema, elevated jugular venous pressure) in association with key structural and functional cardiac abnormalities, resulting in a reduced cardiac output and elevated intracardiac pressures at rest or during exercise [5]. Left ventricular ejection fraction (LVEF) assessment using transthoracic echography has been utilized to distinguish patients with preserved or reduced ejection fraction phenotype (HFpEF and HFrEF, respectively). This differentiation is required due to different etiologies, demographics, comorbidities, and therapeutic responses [5]. HFpEF and HFrEF patients typically present similar cardiorespiratory fitness reductions and worse morbidity, hospitalization, and five-year mortality rates compared to healthy individuals [6,7]. Although HFrEF has been widely explored, approximately one-half of all patients exhibit preserved ejection fraction 50%, thus reinforcing the need for a better understanding of exercise intolerance in HFpEF patients [8]. Although peripheral mechanisms have been related to exercise tolerance in HF patients [9–11], its etiology remains poorly understood in HFpEF [7,12]. As the muscular component has become a key factor in these peripheral mechanisms, it may differ according to the HF phenotype [5,13,14]. The muscular microcirculatory contributions to exercise tolerance amongst different HF phenotypes are poorly understood, particularly when submitted to muscular stress. A better understanding of muscular microcirculatory dynamics is pivotal in unraveling the integrative pathophysiology of exercise intolerance in these patients. Skeletal muscle dysfunction is widespread in HF patients. A possible kind of musculoskeletal abnormality that could result in impaired peripheral microcirculation is the loss of muscle mass (sarcopenia) characterized by the atrophy of skeletal muscle, resulting in muscle strength reduction [15,16]. Sarcopenia and muscle strength reduction in HF imply lowered oxidative capacity and perfusion, which affect transport and oxygen utilization during exercise, an essential task of the microvascular muscle function [17–19]. Besides that, skeletal muscle microcirculatory abnormalities have also been associated with exercise intolerance in heart failure patients who also present skeletal muscle myopathy [20,21]. Considering the skeletal muscle plasticity and the potential for peripheral adaptation when following exercise-based interventions, changes related to muscle function (such as mass, strength, quality, or microvascular function) may be more noticeable when compared to

changes in cardiopulmonary variables [22,23]. Previous research demonstrated that peripheral skeletal muscle dysfunction majorly affects the exercise tolerance in HFrEF patients [10,22,24–26]. Poole et al. 2018 [12] demonstrated that there is an important deficit in muscle function in both phenotypes (HFrEF and HFpEF). However, in HFrEF patients, exercise intolerance is related to impaired vascular function, capillary rarefaction, and the absence of red blood cells flux in a considerable proportion of capillaries at rest and during contractions, decreased nitric oxide bioavailability, reduced microvascular oxygen pressures, and elevated muscle deoxygenation. While in HFpEF patients, muscle microvascular dysfunction and oxygenation seem to be more pronounced [24,27] due to expected HF-related peripheral adaptations, such as vascular rarefactions, skeletal muscle abnormalities [28], and higher regional adipose distribution [29]. Of interest, skeletal muscle perfusion reduction in HFpEF patients may worsen oxidative capacity and inflammatory stress, which have been strongly associated with diseaserelated muscle loss [30,31]. In this sense, assessing the muscle quality [32] and local microcirculatory response differences among HFpEF and HFrEF patients and the association with muscle strength and cardiorespiratory fitness is clinically relevant [33], paving new secondary prevention and rehabilitation treatment alternatives [34]. A recent study described higher quadriceps echo intensity, muscle thickness (cm), and muscle mass (Kg) values in HF patients compared to a control group and its association with poor exercise capacity in HF [35]. The EI of the quadriceps femoris correlated physical performance in sedentary older adults and was the strongest predictor of this functional test, with 30% of the variance explained by the EI [36–38]. This study primarily aims to explore the mechanisms leading to exercise intolerance by comparing the local oxygen extraction response during muscle strength exercise and ultrasound-derived parameters among different HF phenotypes with different disease severities. Secondarily, it intends to analyze possible associations between exercise-induced tissue saturation index response and ultrasound-derived variables with (a) an isokinetic muscle strength test and (b) cardiorespiratory fitness. The outcome measures will be explored according to HF phenotypes and disease severities. We hypothesized that peripheral dysfunctions are more pronounced in patients with HFpEF compared to HFrEF because of a lower oxygen extraction capacity and poor muscle quality [24,27].

Methods

Materials and Methods

Study Design and Participants

This is a cross-sectional observational study that followed the STROBE recommendations

[39]. The advisors were blinded for the different subgroups only for sample characterization variables. The study was performed in accordance with the Declaration of Helsinki (2013) (approved by the ethical committee of the University of Brasília,CAAE 81309417.7.0000.8093). After a careful explanation of the nature and risks of the experimental procedures, all participating patients provided informed consent before starting the measurements. The study was realized between June 2018 and September 2019 at the University of Brasília. Male and female individuals from a convenient sample, diagnosed with HFpEF or HFrEF, stable and under optimal medical treatment, were recruited and allocated by phenotype. The inclusion criteria were: (1) minimal age of 35 years; (2) at least six months of HFrEF or HFpEF diagnosis [5]; (3) HF with ischemic, hypertensive, or idiopathic etiology; (4) clinically stable for at least three months; and (5) a sedentary lifestyle (in the last six months). The exclusion criteria were: (1) clinically diagnosed pulmonary, inflammatory, musculoskeletal, or orthopedic diseases precluding exercise performance; and (2) functional New York Heart Association (NYHA) [40] class IV. All participants were assessed during four experimental visits. The first visit was directed to clinical assessment, body composition, and pulmonary function; the second to echocardiogram assessment; and the third for muscle ultrasound and cardiopulmonary exercise testing. Finally, a fourth visit was planned to assess the isokinetic muscle strength and local oxygen with near-infrared spectroscopy (NIRS).

Baseline Clinical Characteristics

Patients were evaluated by a cardiologist who collected detailed information about the clinical history, diagnosis, and current symptoms. The NYHA [40] and Weber [41] functional classification was included to provide complementary clinical information regarding HF severity. The whole-body composition was assessed using dual-energy X-ray absorptiometry (DXA), cardiac function using echocardiography, pulmonary function via spirometry, and cardiorespiratory fitness via cardiopulmonary exercise test (CPX).

Dual-Energy X-ray Absorptiometry (DXA)

The whole-body composition was estimated by using DXA (Lunar Prodigy Bone Densitometers, GE Healthcare, Chicago (Illinois), United States), with a full-body examination. Fat and lean mass were expressed in absolute values (kg), and percentage values (%) described by the DXA scan manufactured. The participants were not instructed on food intake or nutritional prescription.

Echocardiography

The echocardiographic measurements were performed according to the recommendations of the American Society of Echocardiography [42]. Classic parameters representing cardiac structure (left atrial enlargement and/or left ventricular hypertrophy) and function (ejection fraction calculation followed Simpson method) were evaluated [5]. All patients were evaluated by the same cardiologist using an ultrasound (Vivid S60, GE Healthcare, Tirat Carmel (Haifa), Israel) and probe (matricial 4V; setorial 3Sc) with both GE 3Sc-RS Probe (Sector) and the GE 4V-D Probe (collector). Resting supine position included the following measurements: left ventricular ejection fraction (LVEF, %), left atrial volume index (LAVI, mL/m2); left ventricular mass index (LVMI, g/m2); pulsed wave tissue Doppler imaging was used for early diastolic velocity (e') at the septal annulus. The E/e ratio was measured as an indicator for LV filling pressures.

Spirometry

Lung volumes and capacities were assessed by forced spirometry, using s calibrated spirometer (MicroLab CareFusion® MK8 ML 3500; CareFusion, Yorba Linda, United States) through a proper Spirometry PC Software, version 2.2 (Williams Medical Supplies Ltd., Rhymney (South Wales), UK). The spirometry evaluations followed the American Thoracic Society/European Respiratory Society's recommendations, 2005 [43]. The predictions were calculated according to the equations for the Brazilian population according to Pereira et al., 2007 [44]. Variables considered were forced expiratory volume in the first second (FVE1, L/s), forced vital capacity (FVC, L/s), ratio FVE1 by FVC (FVE1/FVC, L/s), and all predicted value (%).

Cardiopulmonary Exercise Test

Functional exercise capacity was assessed utilizing a maximal incremental cardiopulmonary exercise test (CPX) of an electromagnetic bicycle (Corival, LODE BV Medical Technology, Groningen, The Netherlands) under cardiologist supervision. The gas analyzer (CPET, Cosmed, Rome, Italy) followed the breath-by-breath method, evaluating the variables determined by both V-slope and ventilatory equivalents method [45], thereby assessing peak oxygen uptake capacity (peak VO2) and peak power using a 1-minute work stage protocol (starting workload of 20W and incremental workload of 10 to 15 W). Oxygen uptake and heart rate (12-lead electrocardiogram) measurements were performed continuously. All patients cycled until volitional exhaustion, when patients were no longer able to maintain a cycling frequency of 55 rpm higher. Peak exercise effort was confirmed when respiratory gas exchange

ratio (RER) was _1.10, with dyspnea or leg or general fatigue. The exercise test occurred at least 2–3 h following the last meal, and the patients could not exercise 24 h before the test. Primarily, patients adopted a rest period on the ergometer of at least 5 min, until a steady-state respiratory had been established. At the end of the exercise, the state of recovery was observed for 2 min. All individuals performed the exercise test on a symptom-limited ramp by increasing the standard ramp's work rate. After a warm-up period of 2 min at 20 W, an increase in the work rate at a slope of 10–15 W/min was stated (recommendation for HF patients) [46]. Individuals were asked about their perception of ventilatory effort and muscular fatigue every 2 min, according to the Borg scale (6 to 20) [47]. The VE/VCO2 was expressed as a slope value, calculated by the linear regression (y = mx + b, b = slope) of the exercise curve from the beginning to the peak of the effort according to Arena, R. et al. 2004 [48]. The determination of RER above 1.1 is defined as a test quality criterion, confirming that the individual has reached the maximum effort. The predicted VO2 max was determined by the equation of Jones and Campbell, 1982 [49,50], as follows for males: predicted VO2 max = [60.0 □ (0.55 _ age)] _ 1.11; and for females: predicted VO2 max = [48.0 □ (0.37 _ age)] _ 1.11.

2.3. Isokinetic Muscle Strength Test

Isokinetic muscle strength tests were performed using the Biodex system III Isokinetic Dynamometer (Biodex Medical, Inc., Shirley, NY, USA). The dynamometer arm's rotation axis was adjusted to the right knee, and velcro belts were used to secure the thigh, pelvis, and trunk to the chair to prevent compensatory body movement. The lateral femoral epicondyle was used as the bony landmark for matching the knee joint with the axis of rotation of the dynamometer resistance adapter. Gravity correction was obtained by measuring the torque exerted on the dynamometer resistance adapter with the knee in a relaxed state at full extension. Patients were instructed to fully extend and flex the knee and work maximally during each exercise set. Verbal encouragement was given throughout the test session. Isokinetic muscle strength assessment protocol comprised 20 repetitions, requiring maximum concentric effort at an angular velocity of 180_/s. Patients performed six initial submaximal repetitions for familiarization purposes. After three minutes of rest, the isokinetic muscle strength test was performed [18,19,51–54]. Variables analyzed were peak torque (Nm) and adjusted per body weight ratio (Nm.kg), total repetition maximum work (J) and adjusted per body weight ratio (%), total work (J), work fatigue (%), and average power (W).

Near-Infrared Spectroscopy (NIRS)

During isokinetic muscle strength testing, a near-infrared spectroscopy (NIRS) device with a dual-wavelength (760 and 850 nm), continuous-wave system type, containing three pairs of LEDs configured for spatially resolved spectroscopy (SRS) with a source–detector spacing of 30, 35, and 40 mm were utilized to assess local oxygen extraction response (Portamon for OxySoft 3.0.95, Artinis Medical Systems, Amsterdam, The Netherlands). Changes in absorbance were recorded using the oxyhemoglobin (O2Hb, _M) and deoxyhemoglobin (HHb, _M) values to assess the oxygenation status of the muscle [55]. In addition, the tissue saturation index (TSI, %) was calculated from the absorption of coefficients derived from the attenuation of light at different source–detector distances and wavelengths as a relative value (%), which is feasible for comparing and evaluating the achievement of critical limits during exercise. For this, the equipment was positioned on the right leg vastus lateralis (approximately 5 cm from the lateral patellar border) and covered with a dark blue elastic band to avoid interference from ambient light and adhesive tape without pressing the equipment. The data were sampled at 10Hz and stored for offline analysis using the LabChart Pro v8 software (ADInstruments, Sidney, Australia). Data were extracted from the NIRS software in excel (the data were sampled at 10 Hz). Afterward, and according to the timestamps manually performed during the assessment, we extracted the necessary information for data analysis (for example, the data referring to the time used to position the patient or check the signal was excluded). After this process, the data were transferred to the LabChart Pro v8 software (ADInstruments, Sydney, Australia). This software assisted us in graphically revising the extracted NIRS data. We carried out this process because by just looking up values in the spreadsheet, it would not be possible to visualize the continuous waves of the evaluated variables. Thus, we were able to relate the timing during assessment and the behavior of the constant waves. In this way, we determined the stretches of time in each phase of the test that would be considered for the statistical analysis. For the interpretation of NIRS data, it is important to remember the behavior of the variables during exercise. The TSI continuous wave drops during exertion and returns to its baseline condition after exertion. The O2Hb continuous wave behaves similarly to the TSI. The HHb continuous wave is different from the previous ones, as it increases during exertion and falls after exertion, returning to its basal condition or close to it. For statistical analysis and graph signal processing analysis of the NIRS curve, baseline (mean obtained value for the 30s of the resting phase), exercise (lowest obtained value for TSI, %, and O2Hb, _M and highest for the HHb, _M) with a maximum interval variation acceptance of 4 s (20 to 24 s, depending on manual NIRS mark) and recovery (highest obtained value for TSI, % and O2Hb, _M and lowest for the HHb, _M) were considered astime points for comparison [30,56]. An individual visual inspection of the

curves was made to exclude possible failures or noise from the graph signal. Then, eligible individuals were analyzed and presented on graphs that included the individual mean values from each variable (representative cases). Heart rate (HR, bpm), systolic (SBP, mmHg), and diastolic blood pressure (DBP, mmHg) were also monitored before and after the isokinetic muscle strength test to assess hemodynamic parameters.

Ultrasound-Derived Measures: Echo Intensity and Muscle Thickness

The ultrasound images were captured by using an ultrasound device (HD11XE, Phillips, Amsterdam, The Netherlands) with a 7.5 MHz linear matrix transducer. The individuals were evaluated in a supine position with the knee in passive flexion with a 15-centimeter under-knee support and neutral rotation. The images were always acquired on the right leg with the transducer placed transverse and perpendicular to the long axis of the anterior thigh, rectus femoris (RF), and vastus lateralis (VL) muscles (50% of the distance between the iliac spine anterior superior to the superior edge of the patella) to assess muscle thickness, using appropriate transmission gel [57].

The ultrasound was consistent in every examination since the parameter was set at 60 mm of depth, with a preset of gain of 38 Gn, dynamic range of 232 dB, and pulse repetition frequency of 21 Hz. The images were analyzed using the ImageJ software (1.52q version, Bethesda, EUA) [58]. The quadriceps femoris was analyzed between the uppermost part of the femur and the superficial fascia of the rectus femoris (which includes the rectus femoris and vastus intermedius) and the isolated rectus femoris [59,60]. The measurement of echo intensity was determined by a grayscale analysis using ImageJ software. The region of interest was selected for each assessed muscle, including all muscle areas and removing bone or surrounding fascia from the selected area [59]. The mean of grayscale was calculated using an 8-bit resolution measure, resulting in a number between 0 = black and 255 = white. An average of the three measurements per muscle was calculated. In the quadriceps femoris, only the rectus femoris muscle was used for analysis [59,60]. Patients were instructed not to perform any physical activities 24 h before testing.

Statistical Analysis

Data are expressed as mean _ standard deviation (SD), absolute (n), or relative frequencies (%). Shapiro–Wilk test was used to indicate sample data distribution. Parametric or non-parametric tests were applied accordingly. Group differences for continuous outcome variables were compared using unpaired t (mean difference and 95% confidence

interval) or Mann–Whitney U test (Hodges-Lehmann's difference). Categoric variables were compared using Fisher's exact test. We performed a bivariate correlation (Spearman's or Pearson's) analysis to investigate the associations between exercise-induced tissue saturation index response (TSI, %) and ultrasound variables (echo intensity (EI, 0–255) and muscle thickness MT, cm) of rectus femoris (RF), with isokinetic muscle strength (PT, Nm) and cardiorespiratory fitness (peak VO2, mL☐1.min☐1) among HF phenotypes (HFpEF and HFrEF) and severity of functional impairment classification (Weber A + B and Weber C). Association levels were defined according to correlation coefficient (r) (0.00 no association; 0.20 weakly; 0.50 moderately; 0.8 strongly and 1.00 perfectly) [61] or (rho) (0.00 to 0.20 negligible; 021 to 0.40 weak; 0.41 to 0.60 moderate; 0.61 to 0.80 strong and 0.81 to 1.00 very strong) [62]. As a preliminary study, and considering the absence of similar studies involving microcirculatory dynamics within resistance exercise in HF, we included the post hoc analysis to detect the power calculation of the study (effect size) and present in the results. The effect size and power for groups comparisons were estimated using G*Power 3.1. These parameters were chosen because their statistical difference was significant ($p < 0.05$–alpha error). Statistical software GraphPad Prism (8.4.0, San Diego, CA, USA) was used for statistical analyses and figure production. All analyses considered 95% confidence interval (CI), and statistical significance was set at p-value _ 0.05 (two-tailed).

Results

Baseline Clinical Characteristics

Participants' characteristics are shown in Table 1. Both groups were similar by design regarding age and BMI when comparing both phenotypes by Weber class ($p > 0.05$). Fat mass and lean tissue distribution were similar between HF phenotypes groups and severities subgroups ($p > 0.05$) (Table 1). Meanwhile, in HFpEF patients, Weber Class C presented higher fat body mass and fat leg mass than in HFpEF patients with Weber Class A + B ($p < 0.05$) (Table 1). Comparing the total sample between HFpEF and HFrEF, there were no differences ($p > 0.05$) between risk factors and CVDs in the phenotypes (Table 1). However, HFpEF patients used fewer diuretics compared to HFrEF patients ($p = 0.020$) (Table 1). As expected, differences were detected for all echocardiographic parameters between HF phenotypes ($p < 0.05$) (Table 2). Regarding the pulmonary function variables (Table 2), when comparing both phenotypes (HFpEF and HFrEF), Weber Class C presented a lower predicted value of % predicted FEV1 ($p = 0.024$) and FEV1/FVC ratio ($p = 0.020$) for HFpEF than the HFrEF group. In HFpEF

patients, there was a difference in FEV1 (L/s), % predicted FEV1, and FCV (L) parameters, indicating higher values in the Weber Class A + B than Class C group (p < 0.05). Finally, when comparing both HF phenotypes without considering severities, the HFpEF group presented lower values of % predicted FVC and FEV1/FVC ratio (p < 0.05).

Regarding the cardiorespiratory fitness (Table 2), subjects presented similar peak VO2 (mL_kg□1_min□1) and VE/VCO2 slope (p > 0.05), independently of phenotype or disease severity. However, HFpEF presented a higher peak power output (W), predicted peak VO2 (%), and peak VO2 (mL_min□1) than the HFrEF group (p = 0.024; p = 0.046; p = 0.020, respectively). HFpEF withWeber Class A + B patients presented a higher absolute peak power output, peak VO2 (mL_kg□1_min□1), and peak VO2 (mL_min□1) as opposed to HFrEF with Weber Class A + B (p = 0.024; p = 0.060; p = 0.024, respectively). In the HFpEF analysis, there was a difference among exercise (min), peak power output (W), peak VO2 (mL_kg□1_min□1), and peak VO2 (mL_min□1) parameters, indicating higher values in the Weber Class A + B than in the Class C group (p = 0.001; p = 0.0002; p < 0.0001; p < 0.0001, respectively), while in the HFrEF analysis, there were observed differences in exercise (min), peak power output (W), peak VO2 (mL_kg□1_min□1), predicted peak VO2 (mL_Kg□1_min□1), and peak VO2 (mL_min□1) variables, indicating higher values in theWeber Class A + B than in the Class C group (p = 0.048; p = 0.041; p = 0.001; p = 0.048; p = 0.030, respectively).

Results

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than the HFrEF group. In HFpEF patients, there was a difference in FEV1 (L/s), % predicted FEV1, and FCV (L) parameters, indicating higher values in the Weber Class A + B than Class C group (p < 0.05). Finally, when comparing both HF phenotypes without considering

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peak power output, peak VO2 (mL_kg☐1_min☐1), and peak VO2 (mL_min☐1) as opposed to HFrEF with Weber Class A + B ($p = 0.024$; $p = 0.060$; $p = 0.024$, respectively). In the HFpEF analysis, there was a difference among exercise (min), peak power output (W), peak VO2 (mL_kg☐1_min☐1), and peak VO2 (mL_min☐1) parameters, indicating higher values in the Weber Class A + B than in the Class C group ($p = 0.001$; $p = 0.0002$; $p < 0.0001$;
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	HFpEF (n = 16)		HFrEF (n = 12)		HFpEF vs. HFrEF		Weber Class A+B vs. Weber Class C		HFpEF vs. HFrEF
Parameters	**Weber Class A+B (n = 11)** Mean ± SD	**Weber Class C (n = 5)** Mean ± SD	**Weber Class A+B (n = 7)** Mean ± SD	**Weber Class C (n = 5)** Mean ± SD	**p-value (A+B)**	**p-value (C)**	**p-value HFpEF**	**p-value HFrEF**	**p-value**
Male (n, %)	10 (90.9%)	1 (20.0%)	5 (71.4%)	3 (60.0%)	--	--	0.013[c]*	>0.999[c]	>0.999[c]
Age, years	53.7 ± 9.4	59.8 ± 15.7	53.7 ± 7.9	55.4 ± 7.1	0.998[a]	0.590[a]	0.457[a]	0.708[a]	0.737[a]
Body Mass Index, kg/m²	30.0 ± 3.9	30.1 ± 4.8	28.2 ± 5.5	28.3 ± 5.2	0.476[a]	0.588[a]	0.969[a]	0.981[a]	0.335[a]
Drugs									
Beta-blocker (n, %)	10 (90.1%)	5 (100.0%)	7 (100.0%)	5 (100.0%)	--	--	>0.999[c]	>0.999[c]	>0.999[c]
ACEI (n, %)	6 (54.6%)	2 (40.0%)	6 (85.7%)	3 (60.0%)	--	--	>0.999[c]	>0.523[c]	0.253[c]
Angiotensin Receptor Blockers (n, %)	2 (18.2%)	2 (40.0%)	3 (42.9%)	0 (0.0%)	--	--	>0.547[c]	>0.205[c]	>0.999[c]
Diuretics (n, %)	2 (18.2%)	3 (60.0%)	7 (100.0%)	5 (100.0%)	--	--	>0.245[c]	>0.999[c]	0.020[c]*
Statins (n, %)	10 (90.9%)	3 (60.0%)	5 (71.4.0%)	3 (60.0%)	--	--	0.214[c]	>0.999[c]	0.418[c]
Coronary Vasodilators (n, %)	1 (9.1%)	2 (40.0%)	1 (14.3%)	1 (20.0%)	--	--	>0.214[c]	>0.999[c]	>0.999[c]
Antidiabetic (n, %)	2 (18.2%)	1 (20.0%)	1 (14.3%)	1 (20.0%)	--	--	>0.999[c]	>0.999[c]	>0.999[c]
Anticoagulants (n, %)	0 (0.0%)	0 (0.0%)	1 (14.3%)	2 (40.0%)	--	--	>0.999[c]	0.523[c]	0.067[c]
Echocardiogram									
LVEF Simpson (n, %)	58.4 ± 6.3	59.2 ± 6.3	34.4 ± 4.9	28.6 ± 7.4	<0.0001[b]*	0.0001[a]*	0.811[a]	0.407[b]	<0.0001[a]*
Left Atrial Volume Index, mL/m²	25.0 ± 2.9	29.1 ± 10.4	34.4 ± 5.7	39.4 ± 4.8	0.004[a]*	0.094[a]	0.435[a]	0.136[a]	<0.0001[b]*

Left Ventricular Mass Index, g/m^2	83.8 ± 10.8	95.4 ± 38.4	102.6 ± 33.7	141.0 ± 22.9	0.197[a]	0.059[a]	0.543[a]	0.041[a]*	0.002[b]*
E/e', cm/s	6.6 ± 2.1	7.5 ± 0.9	10.9 ± 4.6	11.9 ± 4.7	0.050[a]*	0.099[a]	0.273[a]	0.706[a]	0.006[a]*
Mean e' (septal wall), cm/s	8.0 ± 1.9	6.4 ± 1.7	5.1 ± 1.3	3.8 ± 0.8	0.003[b]*	0.022[a]*	0.127[a]	0.096[a]	<0.0001[a]*
Mean e' (lateral wall), cm/s	12.6 ± 3.7	9.4 ± 3.1	8.3 ± 1.9	5.2 ± 1.8	0.005[a]*	0.040[b]*	0.097[a]	0.032[b]*	0.001[a]*
Cardiopulmonary exercise testing	**(n = 11)**	**(n = 5)**	**(n = 7)**	**(n = 5)**					
Exercise, min	10.8 ± 2.5	6.6 ± 0.9	10.1 ± 2.6	6.9 ± 2.2	0.641[b]	0.782[a]	0.001[b]*	0.048[a]	0.639[b]
Peak RER	1.2 ± 0.1	1.3 ± 0.1	1.2 ± 0.1	1.3 ± 0.1	0.643[b]	>0.999[a]	0.179[b]	0.191[a]	0.859[b]
Peak Power Output, W	140.3 ± 27.0	84.8 ± 15.3	107.3 ± 26.0	74.8 ± 21.7	0.024[a]*	0.426[a]	**0.0002[a]***	0.041[a]*	**0.024[a]***
Peak FC, bpm	141.9 ± 18.0	116.8 ± 28.3	130.6 ± 16.5	125.2 ± 25.6	0.192[a]	0.605[a]	0.113[a]	0.694[a]	0.516[a]
Peak $\dot{V}O_2$, ml.kg^{-1}.min^{-1}	22.1 ± 3.4	14.4 ± 1.2	19.2 ± 2.7	13.7 ± 1.6	0.060[a]	0.434[a]	<0.0001[a]*	0.001[a]*	0.081[a]
% Predicted peak $\dot{V}O_2$, ml.kg^{-1}.min^{-1}	66.0 ± 9.1	54.3 ± 17.1	58.8 ± 10.7	43.4 ± 7.5	0.167[a]	0.151[b]	0.052[b]	0.048[b]*	0.046[a]*
Peak $\dot{V}O_2$, ml.min^{-1}	1884.6 ± 312.7	1180.6 ± 126.2	1469.6 ± 344.0	1034.8 ± 251.5	0.024[a]*	0.291[a]	<0.0001[a]*	0.030[a]*	0.020[a]*
$\dot{V}E/\dot{V}CO_2$ Slope, L/min	27.9 ± 3.7	28.8 ± 8.0	31.1 ± 5.4	30.1 ± 4.0	0.196[a]	0.310[b]	0.510[b]	0.876[b]	0.084[b]

Table 1. Demographic, anthropometric, and clinical characteristics in both heart failure phenotypes.

Legend: Values are expressed as mean ± standard deviation (SD) or absolute and relative frequencies n (%). *Statistics:* [a] Unpaired t-test; [b] Mann-Whitney U test; Fisher's Exact Test. * p≤0.05. *Abbreviations:* HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; kg/m² kilogram per square meter; mL/m², millimeter per square meter; g/m², gram per square meter; ACEI, angiotensin-converting enzyme inhibitors; LVEF, left ventricular ejection fraction; E/e', early mitral inflow velocity and mitral annular early diastolic velocity ratio; cm/s, centimeters per second; min, minute; W, watt; RER, respiratory gas exchange ratio; $\dot{V}O_2$, oxygen uptake; mL.kg^{-1}.min^{-1}, millimeter per minute per kilogram; ml/min, millimeter per minute; VE/VCO₂, minute ventilation/carbon dioxide production slope; L/min, liters per minute.

Peripheral Muscle Microcirculation Dynamics during Isokinetic Muscle Strength Testing

Twenty-eight patients were analyzed in the study. However, 17 patients were considered for peripheral muscle microcirculation dynamics analysis during isokinetic muscle strength testing due to NIRS device and signal analysis limitations. Baseline tissue saturation index (TSI, %), oxyhemoglobin (O2Hb, _M), and deoxyhemoglobin (HHb, _M) were similar between HF phenotypes (HFrEF and HFpEF) and different among severity classifications (Weber Class A + B vs. C) (Table 3; p > 0.05). During the exercise, the TSI values were not different between HFpEF and HFrEF groups (p > 0.05) (Table 3). However, when we consider Weber Class A + B, TSI (%) values tended to be lower in HFrEF patients (44.2 _ 8.2 vs. 36.0 _ 2.4, p = 0.060) (Table 3). A trend of lower TSI was found in the HFrEF group when compared to the HFpEF group (44.8 _ 6.6 vs. 57.6 _ 13.7, p = 0.161). Within HFrEF withWeber Class C patients, there was a trend of higher TSI value than that inWeber Class A + B patients (44.8 _ 6.6 vs. 36.0 _ 2.4, p = 0.071). HFpEF values betweenWeber Class A + B and C were not different (p > 0.05). During the exercise, the O2Hb values were not different between HFpEF and HFrEF groups (p > 0.05) or in between phenotypes with Weber Class A + B (>0.05) (Table 3). Among those withWeber C severity, while HFrEF patients reached lower oxyhemoglobin (O2Hb, _M) (□10.9 _ 3.8 vs. □23.7 _ 5.7, p = 0.029; effect size= 2.6; power = 0.8) during exercise, HFpEF

patients maintained lower O2Hb during the recovery period ($\square$3.0 _ 3.4 vs. 5.9 _ 2.8, p = 0.007; effect size = 2.9; power = 0.9) (Table 3). Altogether, in terms of HFpEF, Weber Class C patients presented (more negative value) a poor capability to reach greater oxygen extraction (oxyhemoglobin, O2Hb, _M) during exercise than Class A + B patients ($\square$10.9 _ 3.8 vs. $\square$27.2 _ 9.2; p = 0.006). HFrEF values between Weber Class A + B and C were not different (p > 0.05). During the exercise, the HHb values were not different between HFpEF and HFrEF groups (p > 0.05) or in Weber Classes A + B and C groups (p > 0.05) (Table 3). Moreover, there was a trend towards a higher value of deoxyhemoglobin (HHb, _M) during the exercise phase in HFpEF withWeber Class A + B patients than those withWeber Class C (14.0 _ 6.4 vs. 3.4 _ 7.6; p = 0.062). HFrEF values between Weber Class A + B and C were not different (p > 0.05).

At the recovery phase, there was no difference found for TSI among phenotypes and subgroups analysis (p > 0.05). At the recovery phase, the only statistical difference was found for the comparison among phenotypes indicating a lower O2Hb value in the HFpEFWeber Class C group than the HFrEF groups ($\square$3.0 _ 3.4 vs. 5.9 _ 2.8; p = 0.007). The HHb values were not different during the recovery phase between HFpEF and HFrEF groups (p > 0.05). When comparing both phenotypes within Weber Class A + B, significant differences for HHb (_M) parameter were observed during the recovery phase. Higher values were observed in the HFrEF group compared to HFpEF group (+18.8 _ 4.8 vs. +8.9 _ 5.6, p = 0.042; effect size = 1.9; power = 0.6). When comparing both phenotypes with Weber Class C (p > 0.05), no difference was found. HFpEF values between Weber Class A + B and C were not different (p > 0.05). Within HFrEF, Weber Class A + B patients presented a higher deoxyhemoglobin (HHb, _M) value during recovery than Weber Class C patients (18.8 _ 4.8 vs. 0.7 _ 1.7; p = 0.016).

The TSI (Figure 1) recovery period was longer for the HFpEF group compared to the HFrEF group in both Weber A + B and Weber C severity subgroups. Similarly, the recovery period for TSI was significantly longer inWeber A + B patients than in C patients with both HFpEF and HFrEF phenotypes (Figure 1).

Table 2. NIRS during isokinetic muscle strength parameters in both heart failure phenotypes and Weber Class.

Parameters	HFpEF (n = 10)		HFrEF (n = 7)		HFpEF vs. HFrEF		Weber Class A+B vs. Weber Class C		HFpEF vs. HFrEF
	Weber Class A+B (n = 6)	Weber Class C (n = 4)	Weber Class A+B (n = 3)	Weber Class C (n = 4)	p-value	p-value	p-value	p-value	p-value
	Mean ± SD (95% CI)	Mean ± SD (95% CI)	Mean ± SD (95% CI)	Mean ± SD (95% CI)	Mean Difference A+B (95% CI)	Mean Difference C (95% CI)	Mean Difference HFpEF (95% CI)	Mean Difference HFrEF (95% CI)	Mean Difference (95% CI)
TSI (%)									
Baseline	73.7 ± 2.2 (71.3 to 76.0)	72.0 ± 5.1 (63.9 to 80.2)	73.4 ± 6.1 (58.3 to 88.6)	70.5 ± 2.0 (67.3 to 73.7)	0.958[a] 0.21(-13.8 to 14.2)	0.616[a] 1.5(-6.2 to 9.2)	0.578[a] -1.7(-9.4 to 6.1)	0.497[a] -2.9(16.7 to 10.9)	0.532[a] 1.2(-2.9 to 5.4)
Exercise	44.2 ± 8.2 (35.7 to 52.8)	57.6 ± 13.7 (35.9 to 79.4)	36.0 ± 2.4 (30.1 to 41.9)	44.8 ± 6.6 (34.3 to 55.3)	0.060[a] 8.2 (-0.5 to 16.9)	0.161[a] 12.9 (-7.6 to 33.3)	0.146[a] 13.4 (-6.9 to 33.7)	0.071[a] 8.8 (-1.2 to 18.8)	0.083[a] 8.6 (-1.3 to 18.4)
Recovery	64.1 ± 8.5 (55.1 to 73.0)	65.1 ± 13.5 (43.6 to 86.5)	58.1 ± 15.3 (20.2 to 96.1)	73.8 ± 3.7 (67.9 to 79.7)	0.583[a] 5.9 (-26.7 to 38.5)	0.290[a] -8.7 (-29.4 to 12.0)	0.899[a] 1.0 (-19.0 to 21.0)	0.214[a] 15.7 (-20.3 to 51.6)	0.475[b] -2.6 (-14.7 to 8.4)
O_2Hb (μM)									
Baseline	0.0 ± 1.2 (-1.3 to 1.3)	0.0 ± 0.6 (-0.9 to 0.9)	-0.2 ± 0.3 (-1.3 to 1.3)	0.7 ± 0.9 (-0.5 to 1.5)	0.712[a] -0.2 (-1.1 to 1.5)	0.245[a] -0.7 (-2.0 to 0.6)	0.990[a] 0.0 (-1.4 to 1.3)	0.132[a] 0.9 (-0.4 to 2.2)	0.475[b] -2.6 (-14.7 to 8.4)
Exercise	-27.2 ± 9.2 (-36.8 to -17.6)	-10.9 ± 3.8 (-17.0 to -4.8)	-30.0 ± 6.7 (-46.5 to -13.4)	-23.7 ± 5.7 (-32.8 to -14.5)	0.626[a] 2.8 (-10.6 to 16.2)	0.029[b*] 13.5 (0.1 to 21.2)	0.006[a*] 16.3 (6.4 to 26.2)	0.400[b] 5.8 (-2.6 to 22.4)	0.204[a] 5.7 (-3.4 to 14.8)
Recovery	-4.1 ± 7.9 (-12.4 to 4.2)	-3.0 ± 3.4 (-8.4 to 2.4)	-4.5 ± 8.3 (-25.1 to 16.2)	5.9 ± 2.8 (1.4 to 10.4)	0.957[a] 0.3 (-15.9 to 16.5)	0.007[*a] -8.9 (-14.4 to -3.5)	0.766[a] 1.1 (-7.4 to 9.7)	0.154[a] 10.4 (-8.3 to 29.1)	0.167[a] -5.2 (-12.8 to 2.5)
HHb (μM)									
Baseline	-0.1 ± 0.3 (-0.4 to 0.2)	-0.2 ± 0.4 (-0.7 to 0.4)	-0.1 ± 0.2 (-0.6 to 0.5)	0.5 ± 0.6 (-0.5 to 1.0)	0.809[a] -0.04 (-0.5 to 0.4)	0.128[a] -0.6 (-1.5 to 0.3)	0.866[a] 0.0 (-0.6 to 0.5)	0.160[a] 0.5 (-0.3 to 1.4)	0.124[a] -0.4 (-0.9 to 0.1)
Exercise	14.0 ± 6.4 (7.4 to 20.7)	3.4 ± 7.6 (-8.7 to 15.5)	11.6 ± 5.2 (-1.2 to 24.5)	8.3 ± 4.3 (1.4 to 15.2)	0.571[a] 2.4 (-7.7 to 12.5)	0.313[a] -4.9 (-16.4 to 6.5)	0.062[a] -10.7 (-22.1 to 0.7)	0.415[a] -3.4 (-13.6 to 6.9)	0.992[a] 0.0 (-6.8 to 6.9)
Recovery	8.9 ± 5.6	4.6 ± 6.1	18.8 ± 4.8	0.7 ± 1.7	0.042[a*]	0.289[a]	0.313[a]	0.016[a*]	0.771[a]

| (3.0 to 14.8) | (-5.0 to 14.4) | (6.9 to 30.8) | (-2.0 to 3.5) | -10.0 (-19.4 to -0.5) | 4.0 (-5.4 to 13.3) | -4.2 (-13.5 to 5.1) | -18.1 (-28.9 to -7.3) | -1.3 (-11.0 to 8.4) |

Legend: Values are expressed as mean ± standard deviation (SD), mean difference (MD), and 95% confidence interval (95% CI) or median difference, number of included patients (n). ***Statistics:*** [a] Unpaired t-test (MD and 95% CI); [b] Mann-Whitney test (Hodge-Lehmann's median difference considered); * $p \leq 0.05$. ***Abbreviations:*** HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

During the isokinetic muscle strength test, a trend of lower TSI (%) for HFpEF was observed, as compared to HFrEF patients among those with Class A+B severity (44.2 ± 8.2 vs. 36.0 ± 2.4, p=0.060) (Table 2). Among those with Weber C severity, while HFrEF patients reached lower oxyhemoglobin (O_2Hb, μM) (-10.9 ± 3.8 vs. -23.7 ± 5.7, p=0.029; effect size= 2.6; power=0.8) during exercise, HFpEF kept lower O_2Hb during the recovery period (-3.0 ± 3.4 vs. 5.9 ± 2.8, p=0.007; effect size= 2.9; power=0.9) (Table 2).

When comparing both phenotypes within Weber Class A+B, significant differences for HHb (μM) parameter were observed during the recovery phase when comparing both phenotypes within Weber Class A+B. Higher values were observed in the HFrEF, compared to HFpEF group (18.8 ± 4.8 vs. 8.9 ± 5.6, p=0.042; effect size=1.9; power=0.6).

Altogether, within HFpEF, Weber Class C patients presented a poor capability to reach a greater oxygen extraction (oxyhemoglobin, O_2Hb, μM) during exercise than Class A+B (-10.9 ± 3.8 vs. -27.2 ± 9.2; p=0.006). Moreover, there was a trend of a higher value for deoxyhemoglobin (HHb, μM) during the exercise phase in HFpEF with Weber Class A+B than Weber Class C (14.0 ± 6.4 vs. 3.4 ± 7.6; p=0.062). In the same way, within HFrEF, Weber Class A+B presented a higher deoxyhemoglobin (HHb, μM) value at recovery than Weber Class C patients (18.8 ± 4.8 vs. 0.7 ± 1.7; p=0.016). Lastly, we did not observe significant differences for HHb (μM) during the exercise phase between both phenotypes and clinical severities (p>0.05) (Table 2).

The TSI (Figure 1) recovery period was longer in the HFpEF compared to the HFrEF group in both Weber A+B and Weber C severity subgroups. Similarly, the recovery period in TSI was significantly longer in Weber A+B than C patients in both HFpEF and HFrEF phenotypes (Figure 1).

> Although the decrease in O2Hb during exercise was similar in both phenotypes when considering the severity A + B, the return to baseline was faster in HFrEF patients than in HFpEF patients (Figure 2). This faster return to baseline starting in HFrEF patients also occurred when comparing both phenotypes with Weber C severity. In addition, when comparing the severities A + B versus C in HFpEF patients, a greater reduction occurred in Weber Class A + B, although a poor recovery was identified in Class C severity. Among those withWeber Class A + B, HFpEF patients required a longer HHb recovery period after exercise than those with HFrEF (Figure 3). Similarly, in the first seconds of recovery for severity C, HFpEF patients maintained more HHb, while HFrEF patients reduced their values faster. Lastly, HFpEF patients had a worse recovery compared to those with HFrEF, regardless of severity.
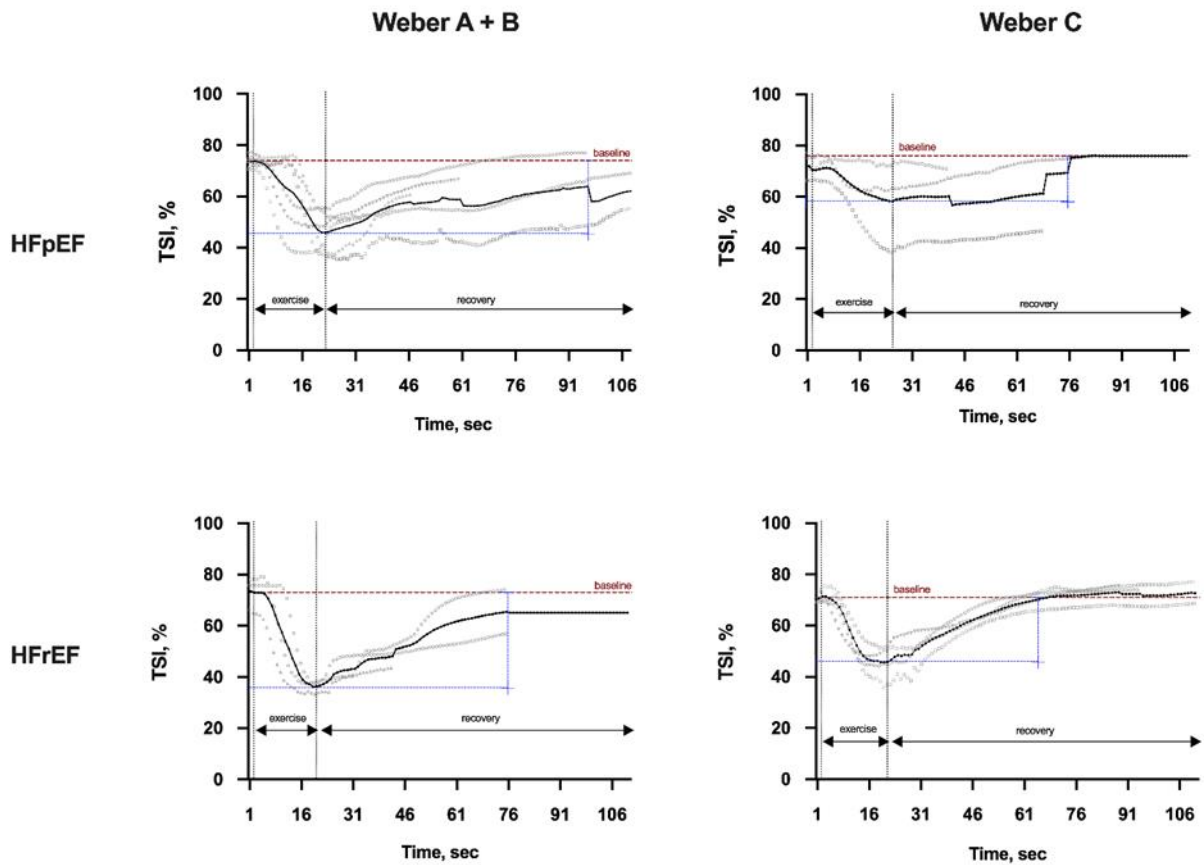
Figure 1. Representative cases of local oxygen extraction (tissue saturation index - TSI, %) during isokinetic muscle strength evaluation by the Weber Class in both heart failure phenotypes. Legend: Average and individual behavior of local oxygen extraction (tissue saturation index) during isokinetic muscle strength maneuver by the Weber Class A+B or C in between heart failure patients' groups. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; TSI, tissue saturation index; sec, seconds.
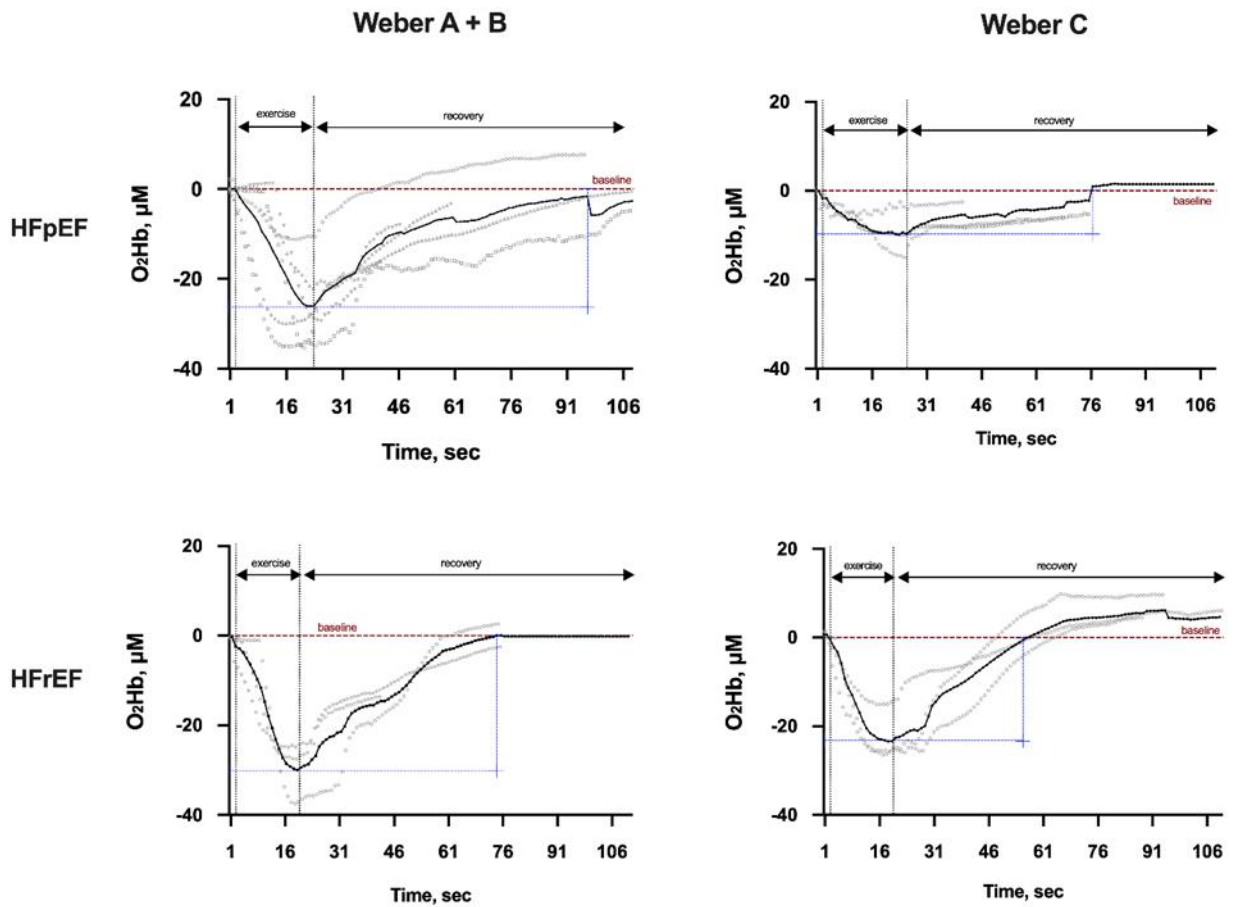
Figure 2. Representative cases of local oxygen extraction (oxygenation - O2Hb, μM) during iso-kinetic muscle strength evaluation by the Weber Class in both heart failure phenotypes. Legend: Average and individual behavior of local oxygen extraction (oxygenation) during isokinetic muscle strength maneuver by the Weber Class A+B or C in between heart failure patients' groups. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; O2Hb, oxyhemoglobin; sec, seconds; μM, micrometer.

This faster return to baseline starting in HFrEF also occurred when comparing both phenotypes with Weber C severity. In addition, when comparing the severities A+B versus C in HFpEF, a greater reduction occurred at Weber Class A+B, although a poor recovery was identified in Class C severity. Among those with Weber Class A+B, HFpEF required a longer HHb recovery period after exercise than HFrEF (Figure 3).
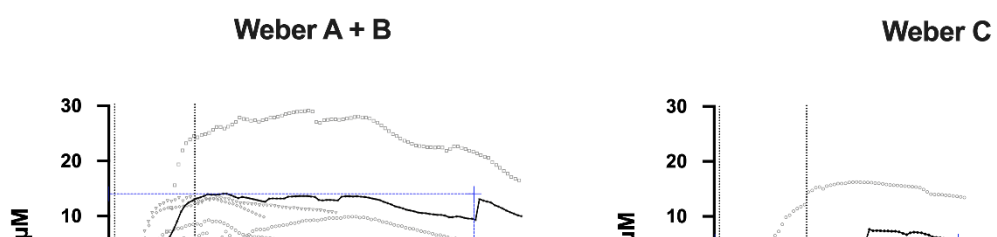
Figure 3. Representative cases of local oxygen extraction (deoxygenation - HHb, μM) during isokinetic muscle strength evaluation by the Weber Class in both heart failure phenotypes. Legend: Average and individual behavior of local oxygen extraction (deoxygenation) during isokinetic muscle strength maneuver by the Weber Class A+B or C in between heart failure pa-tients' groups. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HHb, deoxyhemoglobin; sec, seconds; μM, micrometer.

Similarly, in the first seconds of recovery for severity C, HFpEF maintained more HHb, while HFrEF reduced their values faster. Lastly, HFpEF had a worse recovery com-pared to HFrEF, regardless of severity.

Isokinetic muscle strength parameters

No isokinetic muscle strength parameters (peak torque, peak torque/body mass, maximal repetition total work, work/body weight, total work, work fatigue, and average power) were different among HF phenotypes, nor between disease severity states ($p > 0.05$) (Table 3). However, within HFpEF, peak torque ($p = 0.019$), peak torque/body mass ($p = 0.005$), maximal repetition total work ($p = 0.003$), work/body weight ($p = 0.007$), total work ($p = 0.004$) and average

power (p=0.019) presented a higher values parameters in Weber Class A+B than Weber Class C.

Table 3. Isokinetic muscle strength parameters in both heart failure phenotypes and Weber Class.

Parameters	HFpEF (n = 10)		HFrEF (n = 7)		HFpEF vs. HFrEF		Weber Class A+B vs. Weber Class C		HFpEF vs. HFrEF
	Weber Class A+B (n = 6)	Weber Class C (n = 4)	Weber Class A+B (n = 3)	Weber Class C (n = 4)	p-value / Mean Difference A+B (95% CI)	p-value / Mean Difference C (95% CI)	p-value / Mean Difference HFpEF (95% CI)	p-value / Mean Difference HFrEF (95% CI)	p-value / Mean Difference (95% CI)
	Mean ± SD (95% CI)	Mean ± SD (95% CI)	Mean ± SD (95% CI)	Mean ± SD (95% CI)					
PT, Nm	125.5 ± 25.7 (98.6 to 152.4)	68.2 ± 10.8 (51.1 to 85.3)	136.8 ± 47.5 (18.7 to 254.8)	83.4 ± 38.8 (21.6 to 145.1)	>0.999[b] / -2.0 (-74.4 to 47.6)	0.500[a] / -15.2 (-74.7 to 44.4)	0.019*[b] / 64.8 (11.4 to 83.6)	0.190[a] / 53.4 (-41.3 to 148.1)	0.887[b] / 10.4 (-49.8 to 37.2)
PT/Body Mass, Nm.kg	139.2 ± 28.9 (108.9 to 169.6)	82.4 ± 1.9 (79.4 to 85.3)	159.7 ± 32.6 (78.6 to 240.7)	105.2 ± 37.9 (45.0 to 165.5)	0.414[a] / -20.5 (-84.6 to 43.7)	0.314[a] / -22.9 (-83.0 to 37.3)	0.005*[a] / 56.8 (26.5 to 87.2)	0.099[a] / 54.4 (-15.1 to 123.9)	0.561[a] / -12.1 (-56.3 to 32.1)
Maximal Repetition Total Work, J	143.5 ± 32.2 (109.7 to 177.3)	79.5 ± 15.7 (54.4 to 104.5)	151.5 ± 43.9 (42.6 to 260.5)	99.4 ± 45.2 (27.5 to 171.4)	0.796[a] / -8.0 (-96.7 to 80.7)	0.454[a] / -20.0 (-88.5 to 48.6)	0.003*[a] / 64.1 (28.4 to 99.7)	0.191[a] / 52.1 (-37.9 to 142.1)	0.869[a] / -3.9 (-53.9 to 46.2)
Work/Body Weight, %	159.2 ± 36.6 (120.8 to 197.7)	95.9 ± 10.5 (79.1 to 112.6)	177.9 ± 26.3 (112.5 to 243.3)	125.1 ± 40.9 (60.0 to 190.1)	0.417[a] / -18.7 (-71.7 to 34.3)	0.251[a] / -29.2 (-92.1 to 33.8)	0.007*[a] / 63.4 (24.8 to 101.9)	0.093*[a] / 52.9 (-12.8 to 118.5)	0.527[a] / -13.8 (-59.7 to 32.1)
Total Work, J	2253.5 ± 523.0 (1704.6 to 2802.3)	1245.4 ± 193.5 (937.5 to 1553.2)	2351.1 ± 674.5 (675.7 to 4026.6)	1398.2 ± 593.7 (453.5 to 2342.9)	0.839[a] / -98.7 (-1448.2 to 1252.8)	0.653[a] / -152.9 (-1055.7 to 749.9)	0.004*[a] / 1008.1 (450.3 to 1565.9)	0.122[a] / 952.9 (-396.0 to 2301.8)	0.905[a] / 43.6 (-736.2 to 823.4)
Work Fatigue, %	36.5 ± 11.0 (24.9 to 48.0)	32.8 ± 19.2 (2.2 to 63.4)	40.0 ± 9.3 (17.0 to 63.0)	48.1 ± 2.0 (44.9 to 51.3)	0.634[a] / -3.6 (-21.7 to 14.6)	0.209[a] / -15.3 (-45.7 to 15.1)	0.747[a] / 3.7 (-24.9 to 32.2)	0.267[a] / -8.1 (-30.1 to 13.9)	0.133[b] / -8.3 (-15.1 to 1.7)
Average Power, W	189.4 ± 47.1 (140.0 to 238.8)	103.0 ± 22.7 (66.9 to 139.1)	206.4 ± 78.1 (12.4 to 400.3)	114.4 ± 54.6 (27.6 to 201.2)	0.753[a] / -17.0 (-181.1 to 147.1)	0.719[a] / -11.4 (-93.4 to 70.6)	0.005*[a] / 86.4 (34.4 to 138.4)	0.168[a] / 92.0 (-64.6 to 248.4)	0.978[a] / 1.0 (-75.2 to 77.2)

Legend: Values are expressed as mean ± standard deviation (SD), mean difference (MD) and 95% confidence interval (95% CI) or median difference, number of included patients (n). ***Statistics:*** [a] Unpaired t-test (MD and 95% CI); [b] Mann-Whitney test (Hodge-Lehmann's median difference considered); * p ≤0.05. ***Abbreviations:*** HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; PT, peak torque to Nm, newton-meter; J, Joules; W, Watt.

Ultrasound-derived parameters (echo intensity and muscle thickness)

There was no difference in echo intensity of the rectus femoris between HF pheno-types (p>0.05) (Table 4) despite the greater echo intensity on the HFpEF on Weber C com-pared to the HFpEF group (29.7 ± 8.4 vs. 15.1 ± 6.8, p=0.017). Moreover, within HFpEF, there was a higher echo intensity value in Weber Class C than Weber Class A+B (14.1 ± 8.7 vs. 29.7 ± 8.4, p=0.009).

Table 4. Ultrasound-derived parameters (echo intensity and muscle thickness) in both heart failure phenotypes and Weber Class.

Parameters	HFpEF (n = 16)		HFrEF (n = 12)		HFpEF vs. HFrEF		Weber Class A+B vs. Weber Class C		HFpEF vs. HFrEF
	Weber Class A+B (n = 11)	Weber Class C (n = 5)	Weber Class A+B (n = 7)	Weber Class C (n = 5)	p-value	p-value	p-value	p-value	p-value
					Mean Difference A+B (95% CI)	Mean Difference C (95% CI)	Mean Difference HFpEF (95% CI)	Mean Difference HFrEF (95% CI)	Mean Difference (95% CI)
	Mean ± SD (95% CI)	Mean ± SD (95% CI)	Mean ± SD (95% CI)	Mean ± SD (95% CI)					
Echo intensity, 0-255									
m. rectus femoris	14.1 ± 8.7 (8.2 to 19.9)	29.7 ± 8.4 (19.3 to 40.2)	13.1 ± 5.5 (8.0 to 18.2)	15.1 ± 6.8 (6.8 to 23.5)	0.786[a] 0.9 (-6.2 to 8.1)	0.017[a*] 14.6 (3.4 to 25.9)	0.009[a*] -15.7 (-26.2 to -5.2)	0.606[a] -2.0 (-10.6 to 6.6)	0.140[a] 5.0 (-1.8 to 11.8)
Muscle thickness, cm									
m. rectus femoris	2.1 ± 0.5 (1.7 to 2.4)	1.7 ± 0.3 (1.3 to 2.1)	1.9 ± 0.4 (1.5 to 2.3)	1.5 ± 0.5 (0.9 to 2.1)	0.435[b] 0.2 (-0.3 to 0.9)	0.397[a] 0.2 (-0.4 to 0.8)	0.134[a] 0.4 (-0.1 to 0.8)	0.145[b] 0.3 (-0.2 to 1.0)	0.196[a] 0.2 (-0.1 to 0.6)
	(n = 10)	**(n = 4)**	**(n = 7)**	**(n = 5)**					
m. quadriceps femoris	3.8 ± 0.7 (3.3 to 4.3)	3.0 ± 0.4 (2.3 to 3.6)	3.6 ± 0.8 (2.8 to 4.3)	2.8 ± 1.0 (1.6 to 4.0)	0.570[a] 0.2 (-0.6 to 1.1)	0.734[a] 0.2 (-1.1 to 1.4)	0.023[a*] 0.8 (0.1 to 1.5)	0.203[a] 0.8 (-1.5 to 2.0)	0.364[a] 0.4 (-0.6 to 1.3)

Legend: Values are expressed as mean ± standard deviation (SD), mean difference (MD), and 95% confidence interval (95% CI) or median difference, number of included patients (n). *Statistics:* [a] Unpaired t-test (MD and 95% CI); [b] Mann-Whitney test (Hodge-Lehmann's median difference considered); * p ≤0.05. *Abbreviations*: HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; echo intensity, 0=black, and 255=white; m, muscle; cm, centimeters.

Muscle thickness (MT, cm) (Table 4) did not exhibit significant differences between HFpEF and HFrEF groups independent of severities for rectus femoris analysis (p>0.05). In addition, a smaller rectus femoris MT was observed in HFpEF patients with Weber Class C than Weber Class A+B (p=0.023).

Associations

Regarding the association between exercise-induced tissue saturation index response (NIRS) during strength isokinetic testing (TSI, %) and isokinetic muscle strength parame-ters (PT), there was no correlation for HFrEF (Table 5), while a moderate negative correla-tion was found in the HFpEF group (r=-0.697; p=0.031). Conversely, TSI was correlated with peak $\dot{V}O2$ (mL.min-1) in HFrEF with Weber Class A+B (r=0.999; p=0.010).

The associations between ultrasound-derived measures of RF (echo intensity, EI, 0-255; muscle thickness, MT, cm) with isokinetic muscle strength (PT) and cardiorespira-tory fitness (peak $\dot{V}O2$, mL.min-1) was presented in Table 5.

Table 5. Associations between exercise oxygenation response (TSI, O_2Hb e HHb, μM) via near-infrared spectroscopy (NIRS) and echo intensity (RF_EI) with isokinetic muscle strength parameter (PT, Nm), cardiorespiratory fitness (peak $\dot{V}O_2$, mL.Kg^{-1}.min^{-1}) and peak power output in both HF phenotypes (HFpEF and HFrEF) according to disease severity (Weber A+B and Weber C).

Groups		TSI x PT	O_2Hb x PT	HHb x PT	TSI x peak $\dot{V}O_2$	O_2Hb x peak $\dot{V}O_2$	HHb x peak $\dot{V}O_2$	TSI x peak power output	O_2Hb x peak power output	HHb x peak power output
HFpEF (Weber A+B)	r	-0.429[b]	-0.429[b]	0.600[b]	0.118[a]	0.084[a]	0.152[a]	-0.366[a]	-0.074[a]	0.378[a]
	p	0.419	0.419	0.242	0.824	0.874	0.773	0.476	0.889	0.461
HFrEF (Weber A+B)	r	0.601[a]	-0.042[a]	0.009[a]	0.619[a]	-0.955[a]	-0.969[a]	0.830[a]	-0.369[a]	-0.312[a]
	p	0.590	0.973	0.994	0.575	0.191	0.158	0.376	0.760	0.793
HFpEF (Weber C)	r	-0.414[a]	-0.419[a]	0.170[a]	-0.621[a]	-0.915[a]	0.321[a]	0.527[a]	-0.815[a]	0.127[a]
	p	0.586	0.581	0.823	0.380	0.085	0.679	0.474	0.185	0.873
HFrEF (Weber C)	r	0.339[a]	0.800[b]	0.244[a]	-0.196[a]	0.600[b]	0.726[a]	0.616[a]	0.800[b]	-0.078[a]
	p	0.661	0.333	0.756	0.804	0.417	0.274	0.384	0.333	0.922

Groups		RF_EI x PT	RF_EI x peak $\dot{V}O_2$	RF_EI x peak power output	MT_RF x PT	MT_RF x peak $\dot{V}O_2$	MT_RF x peak power output
HFpEF (Weber A+B)	r	-0.331[b]	-0.068[a]	0.031[a]	0.082[b]	0.599[a]	0.575[a]
	p	0.320	0.842	0.929	0.811	0.052	0.068
HFrEF (Weber A+B)	r	-0.036[b]	0.018[b]	0.179[b]	0.593[b]	0.187[b]	0.297[b]
	p	0.964	0.988	0.713	0.174	0.701	0.529
HFpEF (Weber C)	r	0.121[a]	-0.910[a]	-0.081[a]	0.405[a]	0.468[a]	0.108[a]
	p	0.847	0.032[a]*	0.897	0.499	0.426	0.093
HFrEF (Weber C)	r	-0.228[a]	-0.430[a]	-0.125[a]	0.880[a]	0.613[a]	0.900[a]
	p	0.713	0.470	0.842	0.049*	0.271	0.083

Legend: Values are expressed as absolute values. ***Statistics:*** [a] Person's correlation test (r correlation coefficient with 0.00 no association; 0.20 weakly; 0.50 moderately; 0.8 strongly and 1.00 perfectly) and [b] Spearman's correlation test (rho correlation coefficient with 0.00 to 0.20 negligible; 021 to 0.40 weak; 0.41 to 0.60 moderate; 0.61 to 0.80 strong and 0.81 to 1.00 very strong); * $p \leq 0.05$, correlation coefficient of 0.40-0.59 were

considered moderate. ***Abbreviations*****:** TSI, tissue saturation index; PT, peak torque; $\dot{V}O_2$, oxygen uptake; O_2Hb, oxyhemoglobin; HHb, deoxyhemoglobin; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; RF, rectus femoris muscle; EI, echo intensity.

RF_EI was moderately negatively associated with PT (r=-0.570; p=0.021) and peak $\dot{V}O2$ (r=-0.581; p=0.015) in HFpEF, but not in HFrEF phenotype (p>0.005). Associations among RF_EI and isokinetic PT or peak $\dot{V}O2$ were not found in HF subgroups according to Weber Class (p>0.05).

A moderate association between RF_MT and isokinetic PT was observed in HFrEF phenotype (r=0.778; p=0.03) and Weber Class C subgroup (r=-0.880; p=0.049). Lastly, a moderate association was found between the RF_MT and the peak $\dot{V}O2$ in both pheno-types considering the entire group (HFpEF: r=0.672; p=0.004; HFrEF: r=0.751; p=0.005), which was also observed in the severities subgroups (Weber Class A+B and C), among those with HFpEF (Weber Class A+B: r=0.687; p=0.020; Weber Class C: r=0.937; p=0.019).

Discussion

Our study found poor peripheral muscle microcirculation dynamics, particularly in HFpEF patients during isokinetic muscle strength testing, which was more pronounced in Weber C patients. Also, HFrEF with Weber Class A+B presented a worse recovery than HFpEF following the rationale that HFrEF presents better O2 extraction during strength exercise than HFpEF, which seems to justify why HFrEF recovery worsens than HFpEF for the HHb parameter. Moreover, although lower limb muscle strength and ultra-sound-derived thickness were not different between subgroups, echo intensity revealed worse muscle quality in HFpEF patients. Additionally, was echo intensity negatively as-sociated with cardiorespiratory fitness in the same phenotype. Hence, our preliminary findings suggest that peripheral muscle microcirculation dynamics can affect a strength-type exercise similar to an aerobic-type exercise in HFpEF.

A similar local oxygen response decrease in HFpEF was also observed during the cardiopulmonary exercise test (CPX), highlighting the significant role of impaired arterio-venous O2 difference augmentation in contributing to exercise intolerance in the HFpEF population [19]. Moreover, the arteriovenous O2 difference is also reduced in HFpEF when performing a hand dynamometer test [52]. Another study evaluated the oxygen response during plantar flexion exercise by magnetic resonance with spectroscopy in HFpEF pa-tients and healthy individuals, reveling a poor performance in HFpEF patients, indicated by a faster decrease in phosphocreatine and consequent impairment in the ATP flow [53,54], possibly causing microvascular damage [55]. Among those with HFpEF, we also confirmed that Weber Class C patients presented a reduced capability to reach a greater oxygen extraction during an isokinetic muscle strength test compared to Classes A and B. Moreover, a longer recovery period was found in HFpEF in both severity classes. A previ-ous study comparing HFpEF and healthy controls identified that the major mechanism underlying the functional impairment in such group appears to be related to deranged peripheral hemodynamics, including a reduced leg blood flow and vascular conductance [56]. Moreover, higher deoxyhemoglobin values were observed during the recovery phase when comparing both phenotypes within Weber Class A+B. Considering that both strength and HHb (μM) during exercise were similar, the HHb increase on HFrEF pheno-type during the recovery phase may be related to a worse peripheral response.

The current study thus adds to previous research that HFpEF patients experience significant skeletal muscle oxygen extraction abnormalities during strength-type exercis-es, contributing to exercise intolerance, particularly when greater (skeletal muscle) exercise intensities are elicited.

Higher echo intensity values have been related to an increased intramuscular adi-pose and connective tissue distribution [57-59]. Previous studies have shown that HFpEF presents 30% higher fat tissue and intramuscular fat tissue than the healthy population [60, 23, 61]. Our study arouses new findings regarding muscular quality differences be-tween HFpEF and HFrEF. We found an increasing trend of the RF echo intensity in the HFpEF phenotype with Weber Class C, and most interestingly, its higher echo intensity was associated with a lower peak $\dot{V}O2$ in HFpEF participants. These findings could demonstrate different mechanisms related to exercise intolerance in HFpEF, suggesting a closer association between muscle quality, disease severity, and exercise intolerance. Fur-thermore, Nakano et al. [56] described a positive correlation between quadriceps femoris echo intensity and NYHA class and age. A negative correlation between quadriceps femo-ris echo intensity and peak $\dot{V}O2$ was also described in HF and healthy subjects [62].

A greater quantity of type II muscle fiber in HF and the lower capillarity ratio per fiber were already related to greater exercise intolerance in previous studies [14,23]. Similarly, a lower amount of type I fiber has been shown to cause a lower peak $\dot{V}O2$ [14,23]. Further-more, the reduced oxidative and diffusive capacity combined with a low exercise tolerance on HF patients compared to healthy volunteers suggests that skeletal muscle metabolism is a potentially important target for future HF treatment strategies [54,63,64], providing more assertive and individualized treatment strategies. In this way, oxidative and struc-tural muscle impairment is a possible underlying exercise intolerance mechanism, which appears able to impact strength modality in HFpEF.

This study contains limitations that might be addressed. First, a limited study popu-lation may reduce the results' external validity, and the results should be interpreted with caution. However, this study presents microvascular dynamics during strength exercise for the first time, helping to understand exercise intolerance in HF. Also, despite consid-ering clinical signs, symptoms, and echocardiographic data to justify the clinical diagno-sis, not all patients had their BNP tested; however, the patients were evaluated and diag-nosed by cardiologists. Finally, considering this is the first study evaluating local oxygen extraction during isokinetic

muscle strength and echo intensity at rest in HFrEF vs. HFpEF, these findings add new insights. Future observations studies with a larger sample size are needed to understand better the effects of the peripheral muscle microcirculation dynamics during strength exercise testing in HF patients.

Conclusions

Despite similar isokinetic muscle strength and peripheral muscle microcirculatory dynamics parameters during isokinetic muscle strength testing between HF phenotypes, by considering the HF severity, our study reveals a pronounced microcirculatory impair-ment and slower peripheral recovery following an isokinetic muscle strength testing in HFpEF with Class C, coupled with ultrasound-detectable musculoskeletal abnormalities at rest and which was associated with cardiorespiratory capacity.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of University of Brasília (protocol code: CAAE 81309417.7.0000.8093 and date of approval: 21th march 2018).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data available on request due to restrictions eg privacy or ethical. The data presented in this study are available on request from the corresponding author. The data are not publicly available due to reasons of sensitivity eg human data, patient localization and etc.

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Conflicts of Interest: The authors declare no conflict of interest.

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Chapter 3

High-intensity interval training versus progressive high-intensity circuit resistance training on endothelial function and cardiorespiratory fitness in heart failure: a preliminary randomized controlled trial

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Abstract

Introduction: Exercise training is strongly recommended as a therapeutic approach to treat individuals with heart failure. High-intensity exercise training modalities still controversial in this population. The study aims to premilinary assess the consequences of high-intensity exercise training modalities, aerobic interval training (HIIT) and progressive high circuit-resistance training (CRT), on primarily endothelial function and cardiorespiratory fitness, and secondly on muscle strength and physical performance in heart failure patients. **Methods:** This preliminary multicentric randomized controlled trial comprised 23 heart failure patients, aged 56 ± 10 years old, mainly New York Heart Association classification I and II (%), hemodynamically stable, who compromise at least 36 exercise sessions of a randomly assigned intervention (HIIT, CRT or control group). Endothelial function, cardiopulmonary exercise testing, muscle strength and physical performance were completed at baseline and post-intervention. **Results**: Although no effects on endothelial function; both HIIT and CRT modalities were able to produce a positive effect on $\dot{V}O_2$ peak (HIIT = +2.1±6.5, CRT=+3.0±4.2 and control group=-0.1± 5.3 mL/kg/min, time*group p-value<0,05) and METs (HIIT=+0.6±1.8, CRT=+0.9±1.2 and control group=0±1.6, time*group p-value<0,05). Only HIIT increased isokinetic torque peak (HIIT =+8.8±55.8, CRT=0.0±60.7 and control group=1.6±57.6 Nm) matched p-value<0,05. Regarding the physical performance, the CRT modality reduced chair stand test completion time (HIIT= -0.7±3.1, CRT =-3.3±3.2 and control group = -0.3±2.5 s, matched p-value<0,05 and HIIT improved global physical performance(time*group p<0,05). **Conclusion:** This preliminary study trends to indicate for the first time that high-intensity interval training promotes a jointly superior effect compared to progressive high intensity circuit-resistance training by improving cardiorespiratory fitness, muscular strength, and physical performance. Further research with larger cohort is necessary.

Keywords: heart failure, exercise, high-intensity interval training, circuit resistance training, exercise tolerance.

Introduction

Cardiovascular disease is the most essential cause of premature mortality, causing over 17 million deaths worldwide (83)]. More importantly, heart failure (HF) leads to significant reductions in quality of life and disease-free life years, and hence to elevations in healthcare expenditure (e.g., hospitalizations and medication) (84)]. These reductions in quality of life can, at least in part, be explained by the exercise intolerance development (85). Numerous pathophysiological mechanisms can lead to exercise intolerance, including skeletal muscle dysfunction and endothelial dysfunction (86).

Endothelial dysfunction also related to increased cardiovascular risk and the higher incidence of cardiovascular events in HF individuals(26). Several mechanisms are involved in this endothelial dysfunction, including reduced production of nitric oxide (87), altered vessel thickness (27), and increased oxidative stress (5,74,88). The vascular supply to skeletal muscles and alveoli is significantly reduced (75) and, thereby lowering the exercise capacity. Furthermore, peripheral adaptations such as sarcopenia, inflammation (42), and muscle strength reduction, alongside oxidative capacity reductions and decreased perfusion, are muscular modifications awaited in HF (1,89), contributing to exercise intolerance (90).

Exercise intervention has been used as a clinically effective and safe treatment for HF (moderate GRADE quality of evidence for hospitalizations reduction and low for quality of life improvement) (91) to counteract endothelial and skeletal muscle dysfunction, (46,92,93). Also, improvements in exercise capacity (32), cardiac function (73), and vascular flow (74,75), induced by exercise training, are often observed.

Current guidelines recommend moderate-intensity exercise training for heart failure patients, 3 to 5 days/week, with a duration ranging up to 60 minutes (76). However, some patients cannot sustain continuous aerobic exercise training at adequate intensity for prolonged duration, eliciting leg discomfort and/or dyspnea (94). As a result, alternative and feasible exercise modalities should be explored. The aerobic interval training modality, for example, allows higher-intense bouts of shorter duration (95,96) without losing patient adherence and good clinical effectiveness (97). Moreover, resistance exercise recommendations for HF patients indicate intensities lower than 15 (out of 20) on the perceived exertion Borg scale, with a load ranging from 40 to 60% of one-repetition maximum test (1RM); however, the effect of progressive resistance training reaching higher loads in such population it is still necessary to

explore since remains under intense debate (98). In this sense, circuit-resistance training (CRT) might be considered an engaging alternative training modality.

Recent literature attributes to high-intensity interval training (HIIT), and CRT modalities positive effects in patients with HF (81,96), as evidenced by a favourable effect on exercise capacity (96,99,100). HIIT also improves peripheral O_2 extraction in HF (1), while CRT improves skeletal muscle strength and energetic metabolism capacity through an increase in mitochondrial adenosine triphosphate (ATP) production (100). However, what remains to be studied is the direct comparison of HIIT vs. CRT in HF patients on vascular function and exercise capacity which is this study objective. Considering that HIIT and CRT are training modalities characterized by shorter exercise bouts of greater intensity, with a specific focus/impact on skeletal muscle physiology, we hypothesized with this preliminary report that both exercise modalities promote improvement on vascular function and exercise capacity to a similar extend. If so, additional study could be initiate with large cohort with heart failure patients.

Material and methods

Trial design

This preliminary randomized controlled trial is designed as a longitudinal, parallel, and quantitative study, following CONSORT recommendations (Consolidated Standards for Reporting) (101). Patients were randomized into three groups: High-Intensity Interval Training (HIIT), Circuit-Resistance Training (CRT), and control (CG) with allocation ratio 1:1:1. Assessments occurred in two periods: at baseline and after 36 training sessions of intervention (reassessment) or 12 weeks of follow-up in the control group. One patient on the HIIT group did not complete all expect sessions due to ocular problem as indicated on CONSORT flow chart (Fig 1). Fig 2 shows the study design. CONSORT checklist can be found in the Supporting Information (S1_File).

Figure1. Consort flow chart
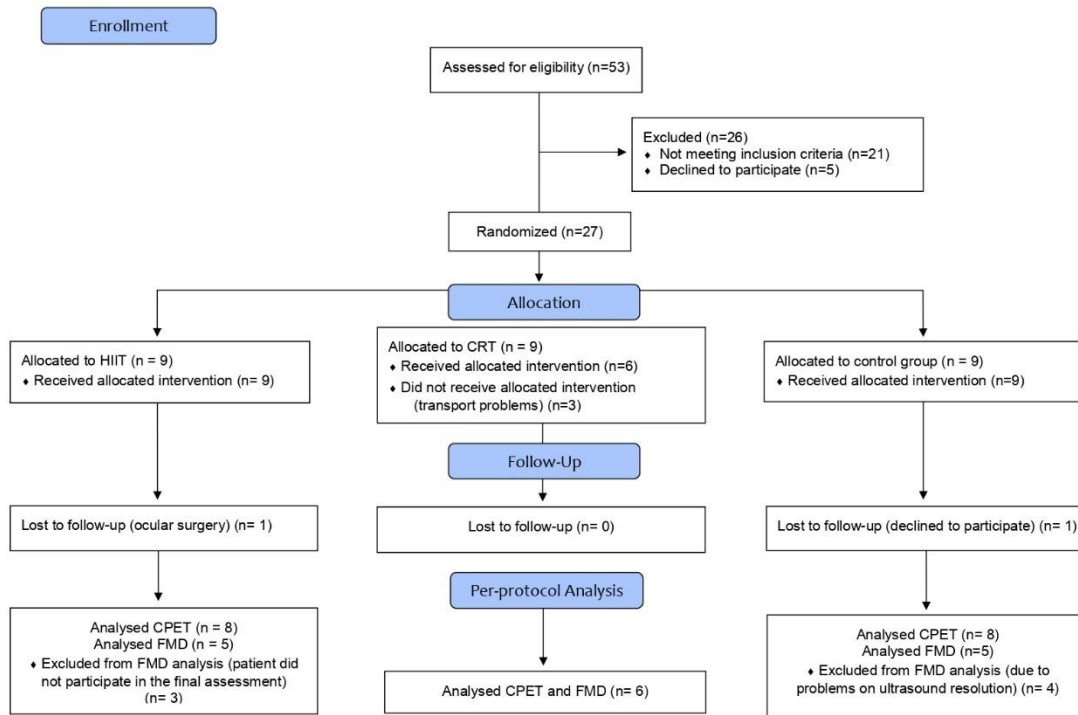
Legend: HIIT, high-intensity interval training; CRT, circuit-resistance training; CPET, cardiopulmonary exercise testing; FMD, flow-mediated dilatation.

Figure 2. Study design
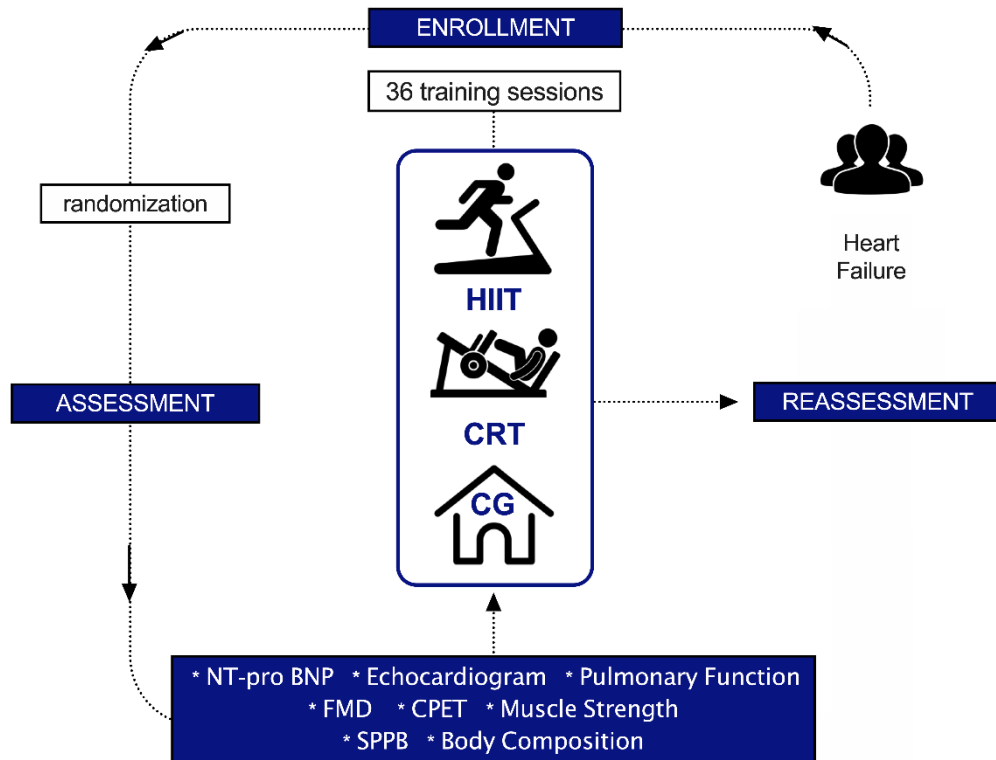
Subjects and randomization

A total of 53 HF stable patients on optimal medical therapy were recruited for this randomized trial at University of Brasilia (Brazil). After exclusions, 27 patients were randomized and 23 completed the training protocol as indicated on CONSORT Flowchart (Fig 1). HF patients were included based upon HF diagnosis with reduced (HFrEF) and preserved ejection fraction (HFpEF) following 2016 ESC Guidelines (17), all referred by a cardiologist. Male and female individuals older than 35 years, not involved in an exercise training program within six months prior to the study, and without Chagas etiology diagnosis were included. Exclusion criteria were: smokers, active bacterial and viral infections, orthopedic symptoms/diseases that could limit exercise performance, and difficulties in reaching the exercise center three times per week. An independent researcher prepared the allocation of a

random sequence (AVL), by sealed envelopes, to either HIIT, CRT, or CG groups. Blocks of 3 patients were always considered for randomization. The allocation concealment was maintained until starting intervention once it occurred after finishing all assessments, at least two weeks before starting the protocol. An independent researcher assigned participants to interventions (NTS). The study was performed in accordance with the standards set by the latest revision (2013) of the Declaration of Helsinki and approved by the local ethical committee (University of Brasilia, Brasilia, Brazil). All participating patients gave written informed consent after careful explanation about the nature and risks of the study's experimental procedures (registration number RBR-668c8v).

Clinical measures

Patient's characteristics

Based on the medical anamnesis and clinical examination, the prevalence of positive cardiovascular risk factors, surgery procedures, and medication prescription were collected. The NYHA (New York Heart Association) and Weber clinical assessment (50), body weight, height, and BMI were obtained. A venous blood sample at a fed state was kept at heparinized (sodium) tubes [a] (Vacuette®) at room temperature and analyzed within 5 hours. The manufacturer's control limits of acceptability were followed. N-terminal pro-brain natriuretic peptide (NT-proBNP) was measured by using test strips (CARDIAC proBNP+) containing monoclonal and polyclonal antibodies against epitopes of the NT-proBNP molecule on a point-of-care device Cobas h232 [b] (Roche Diagnostics). Moreover, the left ventricle ejection fraction (LVEF) was measured by ultrasound for echocardiography [c] (Philips ATL) in semi-lateral decubitus position (by Simpson method, LVEF, %) by using a 4-2 MHz transducer equipped with a second harmonic image through digital Imaging and communication in medicine format and followed recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging [30,31]. Pulmonary Function parameters [maximum inspiratory pressure (MIP, cmH_2O); forced volume expiratory in 1 second (FVE_1, L/s); forced vital capacity (FVC, L); and FVE_1/FVC ratio, % were assessed by a spirometry [d]

test (MicroLab) following standard recommendations of the European Respiratory Society (ERS) (102).

Deviations from the initial study protocol

Changes were made in the initial protocol in order to adapt the trial to a multicentric one. More informations about the study protocol can be found on Supporting Information (S2_File and S3_File). The outcomes initially cited on Brazilian Ethical Committe "quality of life" and "oxygen extraction" were not included on Belgic ethical Commite due to technical limitations. In addition, the outcomes "autonomic modulation", "muscle ultrasound", "pulmonar function" and "oxygen extraction" were not included on this paper, but they were obtained and will be presented in a future paper.

Treatment outcomes

All outcomes were evaluated before and after finishing the protocol period.

Primary Outcomes

Endothelial Function

Prior to evaluating endothelial function (30), subjects received prior instructions, which included a light meal within two hours before testing and abstain from caffeine, alcohol, and exercise for 24 h prior to testing. Tests were performed in the same period of the day to avoid any circadian effect, and the temperature was set at 24° C. Subjects preparation followed standard recommendations (31). A cuff was attached to the subjects' right arm, who remained at rest supine position for 5 min. The diameter was measured for two minutes using high-resolution Doppler duplex ultrasound [e] equipment in Brazil (Phillips) according to Thijssen et al. 2011 (103). For this purpose, a 9 MHz linear matrix transducer was positioned over the brachial artery discretely proximal to the cubital fossa. Signals were obtained in duplex mode

at a pulse frequency of 5 MHz and corrected by an insonation angle of 60°. Sample volumes were adjusted to encompass the entire vessel's lumen without extending beyond the walls, and the slider adjusted in the middle of the vessel. The brachial artery's flow-mediated dilation (FMD) was evaluated by a single examiner on the right arm in the supine position, as previously described (104,105). After resting period evaluation, the cuff was inflated to a pressure of 220 mmHg and held for 5 minutes. The measurements were recorded continuously for 3 min after rapid cuff deflation. All vascular variables were obtained by using specialized edge-detection software [f] (Cardiovascular Suite). Percentage variation of FMD was normalized (106). Baseline arterial diameter (mm), peak arterial diameter (mm), FMD (%) – formula (peak diameter - baseline diameter) / (baseline diameter) * 100 - and delta variations were considered for analysis (31,107). Images with inadequate resolution were excluded from the analysis. The physician who made the data acquisition was blinded to allocation for pre measurements, but not for post measurements.

Cardiorespiratory fitness

Cardiorespiratory fitness was obtained by a maximal cardiopulmonary exercise testing (CPET) on a cycle ergometer [g] (Corival) through an incremental symptom-limited test on a 0-watt electro-magnetic under the supervision of a cardiologist blinded to allocation. Room temperature was controlled (24° C). A ramp protocol started with an initial workload (warm up) of 0 W (free wheel) follow by an individual incremental protocol with a workload ranging from 10 to 20 Watt per minute according to clinical assessment based on NYHA class (108). Pre and post tests were performed by using the same workload. The subjects were instructed to wear comfortable clothes without movement restriction, and the same prior instructions from the endothelial procedure. A breath-by-breath gas analyzer [h] was used to measure oxygen uptake, carbon dioxide production, and ventilation (CPET, Cosmed, Rome, Italy), while the heart rate and electrocardiogram [i] (Quark 3T12x, Cosmed, Rome, Italy) were measured continuously. All patients cycled until volitional exhaustion within a fatigue-limited exercise duration of 8 to 12 minutes(109). Verbal encouragement was given to the patients on each minute and when approaching to the end of the test in order to maintain the requested RPM ≥55. The test was ended when patients were no longer able to maintain a cycling frequency of

≥55 rpm. Peak exercise effort was confirmed when the respiratory gas exchange ratio (RER) was ≥1.10, in combination with exertional dyspnoea, leg, and/or general fatigue. The first and second ventilatory thresholds (VT1 and VT2, respectively) from CPET were considered for exercise prescription. Outcome measures also included exercise duration (s), cycling power output (watt), peak respiratory exchange ratio (RER peak), heart rate at the first ventilatory threshold (HR VT1, bpm), heart rate at the second ventilatory threshold (HR VT2, bpm), peak heart rate (HR peak, bpm), oxygen uptake at the first ventilatory threshold ($\dot{V}O_2$ VT1, mL/kg/min), oxygen consumption and at the second ventilatory threshold ($\dot{V}O_2$ VT2, mL/kg/min), peak oxygen uptake ($\dot{V}O_2$ peak, mL/kg/min and mL/min) (30 s average (108), maximal metabolic equivalent (METs max) (110) .

The first ventilatory threshold (VT1) was determined using the V-slope method, and this threshold was double-checked by establishing the nadir of the VE/VO$_2$ versus work rate relationship. The VT1 marks the limit between the light-to-moderate and the moderate-to-high intensity effort domains. Next, the second ventilatory threshold (VT2) was determined, using the VE vs. VCO$_2$ plot, on the point where VE increases out of proportion to VCO$_2$, and this threshold was double-checked by establishing the nadir of the VE/VCO$_2$ versus W relationship. The VT2 is related to the critical power, which is the upper intensity limit for prolonged aerobic exercise.

Secondary Outcomes

Muscle Strength

Muscle strength was obtained by isokinetic test on an isokinetic dynamometer [j] (Biodex System 3 PRO, Medical Inc., New York, EUA). Patients adopted a seated position (90° hip) in a good posture. Belts were used to stabilize the thigh, pelvis, and trunk. Legs alignment was verified.

All patient measures and dynamometer position (as chair height, chair base, seat backrest, dynamometer distance, arms distance) were standardized at baseline and follow-up evaluation. Patients started isokinetic familiarization by performing six submaximal repetitions as fast as possible. After 3 minutes of recovery, the endurance protocol started, which consisted of 20 maximal repetitions at 180°/s, once (111). Peak torque (N-M); peak torque and body weight ratio (%); total repetition maximum work (J); total work (J); work fatigue (%) and average power (W) were obtained.

Physical Performance

The physical performance was assessed through the Short Physical Performance Battery (SPPB) test. SPPB execution followed previous recommendations (112)] to test the balance, lower limb strength, and walking velocity. The total score of SPPB results from the sum of balance, walking speed, and lower limb strength, totalizing 12 points. Scores from 0 to 3 points were considered incapacity or very poor; 4 to 6 low capacity; 7 to 9 moderate and 10 to 12 good performance.

Body Composition

The whole-body composition was estimated by dual x-ray absorptiometry scan [k] (GE Healthcare) (113,114). Total body fat mass and total body lean mass were expressed in absolute values and percentages.

Intervention

Exercise Training Protocols

The exercise sessions occurred 3 times per week along 36 sessions with a matched session duration (approximately 50 minutes). Training familiarization for both modalities was established for the patient's adaptation (6 to 10 sessions) according to the patients performance to be able to reach HIIT prescription. HR monitorization was continuously registered by Polar® [1] (RS800) during training sessions for clinic monitorization control. The exercise training protocol design is illustrated on Fig 3.

Figure 3. Exercise training protocol design
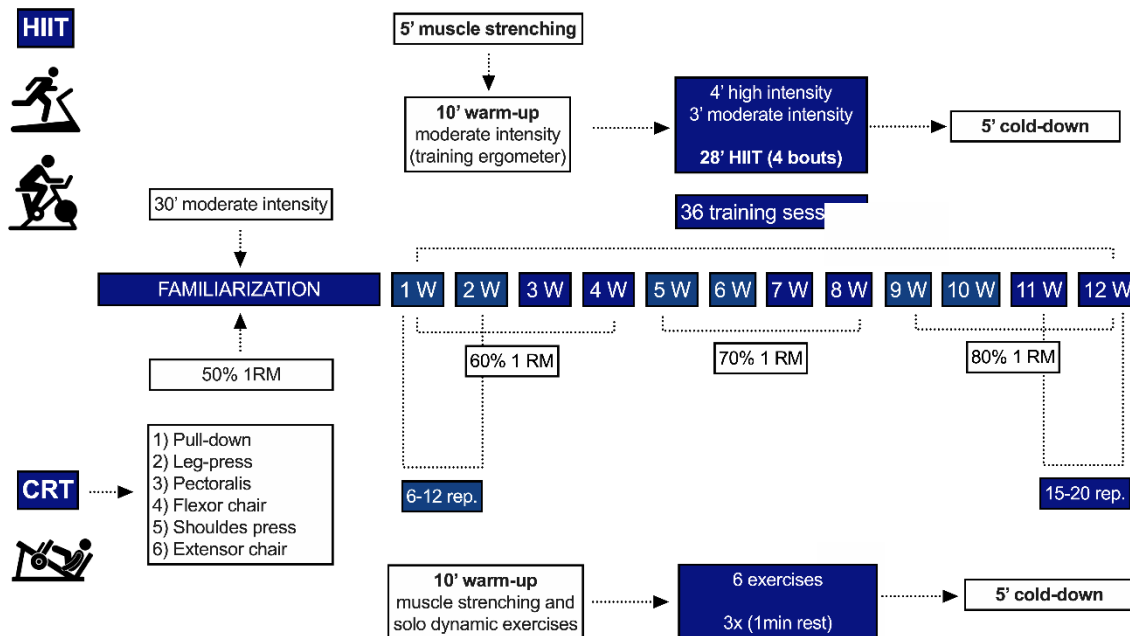
Safety, tolerability and adherence

Trained physiotherapists undertook both training protocols with the supervision of a cardiologist who was available in case of health concerns. Before and after finishing the training sessions, blood pressure, heart rate, and perceived exertion rate were assessed. Also, clinical

signs, such as excessive tiredness, intense sweating, paleness, palpitations, and chest pain, were always investigated. There were no medical complications during the training sessions. In each session the physiotherapists recorded whether or not the patients from the HIIT group reached the expected heart rate according to the training zones. Information about patient adherence was always registered in each session.

Circuit-Resistance Training (CRT)

CRT exercises were executed to target large muscle groups, including: 1) pull-down, 2) leg press, 3) pectoralis, 4) flexor chair, 5) shoulder press, and 6) extensor chair machines. Strength measurements were estimated by a one-repetition maximum test (1RM) (115). The CRT session was preceded by a 10-minute warm-up session led by a physiotherapist, consisting 5 minutes of muscle stretching and 5 minutes of dynamic movements. CRT was performed in resistive stations [m] (EN-Dynamic). The order of the exercise sequence was based on the exercise machines availability at the gymnasium, which were numbered as 1) pull-down, 2) leg press, 3) pectoralis, 4) flexor chair, 5) shoulder press, and 6) extensor chair machines. Patients always alternated between upper and lower extremity exercises. Patients who started the first session on 1) pull down would start the second session on 2) leg press following the chronological order (1,2,3,4,5,6). Patients who started the first session on 2) leg press would start the second session on 3) pectoralis following the chronological order (2,3,4,5,6,1). The starting exercise of the first session varied because there was only one type of each exercise machine and normally more than 3 patient per hour. During the 6 sessions of familiarization on CRT, the training load started at 50% of 1RM, including 3 circuit series of 12 repetitions. After finishing the familiarization, the workloads were set at 60% 1RM for the 1st month, 70% 1RM for the 2nd month, and 80% 1RM for the 3rd month [57]. Repetitions varied from 6 to 12 in the first two weeks of each month and from 15 to 20 in the last two weeks. 3 circuit series of each exercise with 1 min of rest between exercises were executed. Exercise cadence ratio was 1:2. Exercise training protocol design is demonstrated on Fig 3.

High-Intensity Interval Training (HIIT)

HIIT was performed on a treadmill [n] (Biodex Medical Systems) and ergometric bicycle [o] (Biodex Medical Systems) alternately at each session. During the familiarization period, patients performed moderate-intensity continuous aerobic training for 30 minutes. HIIT was gradually incorporated during familiarization in such a way as to guarantee adequate HR response during the research protocol. In each HIIT session, individuals initially performed 10 minutes of continuous aerobic training at moderate intensity which was established according to previous CPET by considering a heart rate range 5% below (lower limit of target heart rate) and 5% above (upper limit of target heart rate) of the first ventilatory threshold (VT1), followed by a 28 minutes of HIIT, now at light- and high-intensity loads (i.e., light intensity – defined as a heart rate range between the moderate-intensity lower limit of target heart rate and 10% below; and high intensity - defined as a heart rate range between moderate-intensity upper limit of target heart rate and 10% above); as recommended by the joint position statement of the European Association for Cardiovascular Prevention and Rehabilitation, the American Association of Cardiovascular and Pulmonary Rehabilitation and the Canadian Association of Cardiac Rehabilitation and by the latest position statement from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology which is in press (116,117) HIIT protocol periods was characterized by 3 minutes of exercise at high intensity followed by 4 minutes of exercise at moderate intensity, totalizing 4 cycles of 7 minutes, resulting in 28 minutes of HIIT (80).

The loads adjustment for HIIT started always by following increments on velocity, however when patient could not tolerate higher speed the load was adjusted by increments on inclination. Regardless the type of increment, patient should always reach the desirable heart rate according to the expected intensity.

Exercise training protocol design is demonstrated on Fig 3.

Control Group

Patients from the control group were instructed to keep their routine without changing habits during the research period.

Statistical Analysis

Descriptive analyses were used for sample characterization of the primary and secondary outcomes. Shapiro-Wilk test was applied to check data normality, and parametric or non-parametric tests were applied accordingly. A mixed ANOVA with post-hoc Tukey was used for parametric distribution for all outcomes considering factors group (between) and time (within) to compare HIIT, CRT, and control group. The Friedman two-way test for non-parametric distribution following within non-parametric comparisons for the outcome SPPB. Delta comparisons were performed by following one-way ANOVA (parametric distribution) or Kruskal-Wallis (non-parametric distribution) for the outcome FMD. Comparison between pre and post moments at the same group was made by following the paired student T-test (parametric distribution) or Wilcoxon test (non-parametric distribution) for all outcomes. Sample size calculation was made by using the G*Power Software 3 [p] (Heinrich Heine Universität Düsseldorf), selecting an F test with the statistical test ANOVA (fixed effects, special, main effects and interactions), following a priori test. The total sample size was based on a pilot study (three patients in each group), calculated from the partial eta square (mixed ANOVA, between groups) for the primary outcomes $\dot{V}O_2$ peak, mL/kg/min (eta partial squared 0.19; effect size 0.48; total sample size 45 – 15 patients per group) and FMD, % (eta partial squared 0.23; effect size 0.55; total sample size 36 – 12 patients per group). The alpha error considered was 0.05 and power 1-beta was 0.80. Considering this is a stop early trial due to covid outbreak, the total sample size was not reached, but the preliminary findings are expressed. Statistical software SPSS version 22.0 [q] and GraphPad Prism (8.4.0 version) [r] were used for statistical analysis and figure production. P-value followed a 5% significance level.

Results

Recruitment and follow up occurred from 2018 and 2019. Patients' characteristics are presented in Table 1. The trial was stopped early due to covid outbreak. At baseline, patients in all groups were similar in terms of sex, age, body mass index, functional classification (NYHA and Weber classifications), heart failure classification (reduced, mid-range, or preserved ejection fraction), cardiorespiratory fitness (as represented by $\dot{V}O_2$ peak, mL/kg/min and mL/min, and cycling peak power output, Watt), left ventricular ejection fraction (%) and pulmonary function ($p > 0.05$).

Table 1. Sample characterization.

	HIIT (n = 8)	CRT (n = 6)	CG (n = 8)	p value
	Baseline	**Baseline**	**Baseline**	
Male (n, %)	5 (62.5)	4 (66.7)	7 (87.5)	0.590[a]
Age (years)	60.9 ± 9.7	55.0 ± 10.9	56.0 ± 9.7	0.497[b]
BMI (kg/m²)	29.4 ± 5.2	32.9 ± 6.5	28.6 ± 4.5	0.706[b]
Classification				
NYHA I/II (n, %)	3 (37.5) / 3 (37.5)	2 (33.3) / 3 (50.0)	5 (62.5) / 2 (25.0)	0.831[a]
NYHA III (n, %)	2 (25.0)	1 (16.7)	1 (12.5)	
Weber Class I/II (n, %)	3 (37.5) / 1 (12.5)	1 (16.7) / 3 (50.0)	5 (50.0) / 3 (37.5)	0.421[a]
Weber Class III (n, %)	4 (50.0)	2 (33.3)	1 (12.5)	
HFrEF (n, %)	3 (37.5)	3 (50.0)	2 (25.0)	
HFmEF (n, %)	0 (0.0)	2 (33.3)	3 (37.5)	0.273[a]
HFpEF (n, %)	5 (62.5)	1 (16.7)	3 (33.3)	
Cardiorespiratory fitness				
$\dot{V}O_2$ peak (mL/kg/min)	17.5 ± 4.2	16.9 ± 2.5	20.2 ± 3.3	0.186[b]
$\dot{V}O_2$ peak (mL/min)	1437.3 ± 411.3	1565.7 ± 365.6	1605.0 ± 458.4	0.712[b]
Cycling peak power output (Watt)	96.8 ± 26.3	104.2 ± 27.7	123.3 ± 35.2	0.225[b]
Echocardiogram				
LVEF *Simpson* (%)	50.4 ± 17.0	42.2 ± 13.5	46.8 ± 14.4	0.614[b]
Pulmonary Function				
MIP (cmH₂O)	83.8 ± 38.5	83.0 ± 34.5	103.5 ± 28.5	0.511[b]
FVE₁ (L/s)	2.3 ± 0.7	2.3 ± 0.9	2.5 ± 0.8	0.888[b]
FVC (L)	3.2 ± 0.9	3.0 ± 1.1	3.2 ± 0.8	0.904[b]
FVE₁/FVC (%)	70.4 ± 8.2	74.5 ± 7.6	76.0 ± 11.4	0.522[c]
Etiology for HF				
Ischaemic (n, %)	5 (62.5)	4 (66.7)	7 (87.5)	0.566[a]

Hypertension (n, %)	1 (12.5)	1 (16.7)	0 (0.0)	
Idiophatic (n, %)	2 (25.0)	1 (16.7)	1 (12.5)	
Coronary Artery Disease (n, %)	4 (50.0)	4 (66.7)	7 (87.5)	0.279[a]
Risk Factors				
Arterial Hypertension (n, %)	4 (50.0)	4 (66.7)	4 (50.0)	0.758[a]
Diabetes Mellitus (n, %)	3 (37.5)	3 (50.0)	2 (25.0)	0.853[a]
Dyslipidaemia (n, %)	5 (62.5)	5 (83.3)	6 (75.0)	0.842[a]
Obesity (n, %)	4 (50.0)	4 (66.7)	3 (37.5)	0.520[a]
Drugs				
Beta-blocker (n, %)	7 (87.5)	5 (83.3)	8 (100.0)	0.723[a]
ACE-inhibitors (n, %)	4 (50.0)	4 (66.7)	7 (87.5)	0.279[a]
Angiotensin Receptor Blockers (n, %)	1 (12.5)	1 (16.7)	2 (25.0)	1.000[a]
Loop Diuretics (n, %)	6 (75.0)	5 (83.3)	4 (50.0)	0.522[a]
Antiplatelet (n, %)	3 (37.5)	5 (83.3)	3 (37.5)	0.216[a]
Statins (n, %)	4 (50.0)	5 (83.3)	7 (87.5)	0.290[a]
Coronary Vasodilators (n, %)	2 (25.0)	0 (0.0)	1 (12.5)	0.751[a]
Antacids (n, %)	0 (0.0)	1 (16.7)	2 (25.0)	0.460[a]
Antiarrhythmic (n, %)	1 (12.5)	0 (0.0)	2 (25.0)	0.751[a]
Antidiabetic (n, %)	2 (25.0)	2 (33.3)	2 (25.0)	1.000[a]
Anticoagulants (n, %)	1 (12.5)	0 (0.0)	2 (25.0)	0.751[a]

Values are expressed as mean ± standard deviation (SD) and frequencies (%). HIIT, high-intensity interval training; CRT, circuit-resistance training; CG, control group; BMI, Body Mass Index; kg, kilogram; m², squared meter; NYHA, New York Heart Association Functional Classification); HFrEF, heart failure reduced ejection fraction; HFmEF, heart failure mid-range ejection fraction; HFpEF, heart failure preserved ejection fraction; $\dot{V}O_2$ peak, oxygen consumption uptake; mL, mililiter; min, minute; LVEF, left ventricular ejection fraction; MIP, maximum inspiratory pressure; cmH_2O, centimeters of water; FVE_1, forced expiratory volume in first second; L/s, liters per second; FVC, forced vital capacity; L, liters; FVE_1/FVC, ratio between forced expiratory volume in first second and forced vital capacity; ICD, implantable cardioverter-defibrillator; CP, cardiac pacemaker; ACE, angiotensin-converting enzyme.

[a] Fisher's Exact Test;

[b] One-way ANOVA;

[c] Kruskal-Wallis H Test. *p ≤0.05.

Safety, tolerability and adherence

For safety and exercise prescription reasons, heart rate were always clinically monitored by using wearable heart rate monitors in both training groups. Also, blood pressure was measured before and after an exercise session . Throughout the intervention period of CRT

occurred the following events: one patient presented hypotension, one diabetic patient presented three peaks of hyperglycemia on different days, one patient presented hypoglycemia at one session, and one patient referred higher dyspnea during the first three sessions of intervention. All events were controlled. For HIIT modality, the following events occurred: one patient did not reach the anaerobic threshold at two different sessions, and another patient-reported angina at the end of session thirty-two. The patient who reported angina was followed to the medical doctor, who did not detect any problem that could affect exercise training. Borg scores indicated good tolerability, not reaching mean values higher than 15 (Borg scale 6-20) in any intervention group, indicating good tolerability. In both HIIT and CRT, adherence to the exercise sessions was high (93.51% and 97.22% of sessions performed, respectively). Fig 4 demonstrates the clinical measurements of the parameters assessed before starting and at the end of the training sessions number 1, 12, 24 and 36.

Figure 4. Clinical measurements at the training sessions

HIIT
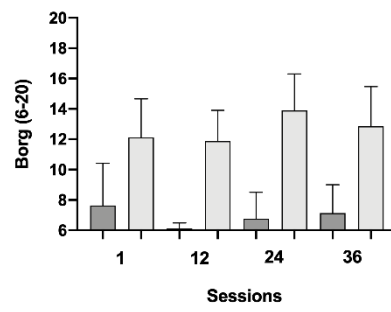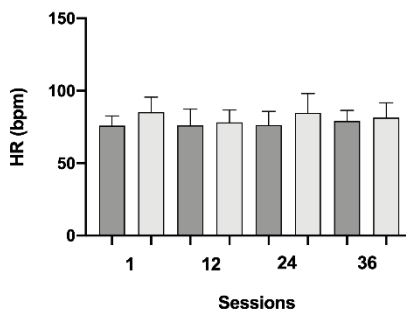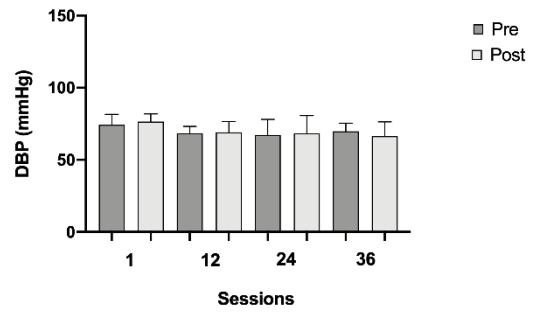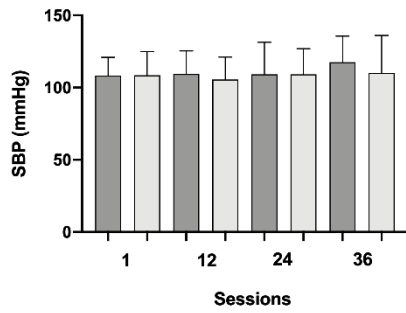
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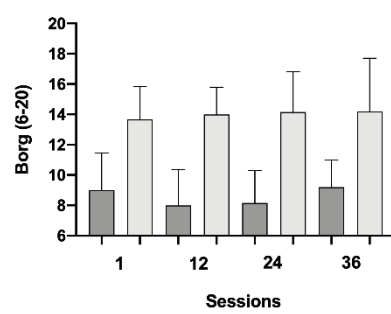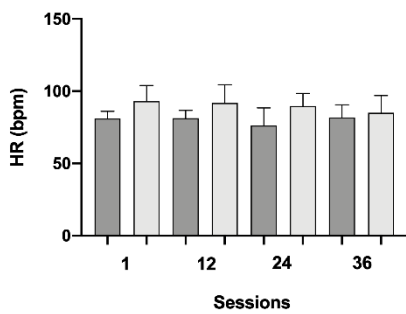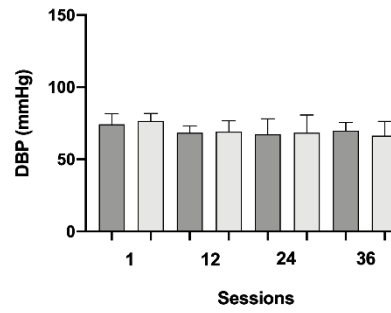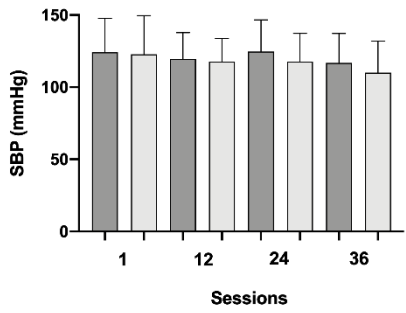
Endothelial Function

Table 2 illustrates the endothelial function before and after training and in the control group. Patients were equally distributed at baseline, meaning there was no differences between groups at the baseline moment (p>0,05). No changes over time or between groups were found (p>0.05). To conclude, HIIT nor CRT was potent to improve vascular function.

Table 2. Impact of interventions on endothelial function in heart failure.

FMD	HIIT Mean ± SD (95% CI)		CRT Mean ± SD (95% CI)		CG Mean ± SD (95% CI)		Within-group difference (post minus pre) MD (95% CI)			Between-group difference MD (95% CI)		
	pre (n=5)	post (n=5)	pre (n=6)	post (n=6)	pre (n=4)	post (n=4)	Δ HIIT	Δ CRT	Δ CG	HIIT vs. CRT	HIIT vs. CG	CRT vs. CG
Rest diameter (mm)	4.54 ± 1.09 (3.19 to 5.88)	4.54 ± 0.92 (3.39 to 5.68)	4.38 ± 0.58 (3.77 to 4.98)	4.52 ± 0.61 (3.88 to 5.17)	4.36 ± 1.17 (2.94 to 6.23)	4.35 ± 0.51 (3.55 to 5.16)	0.00 (-0.67 to 0.67)	0.15 (-0.47 to 0.76)	-0.01 (-0.76 to 0.74)	0.09 (-1.24 to 1.41)	0.18 (-1.29 to 1.65)	0.09 (-1.32 to 1.50)
Peak diameter (mm)	4.77 ± 1.10 (3.41 to 6.13)	4.75 ± 0.88 (3.66 to 5.84)	4.57 ± 0.59 (3.95 to 5.19)	4.74 ± 0.57 (4.14 to 5.33)	4.54 ± 1.12 (2.77 to 6.31)	4.58 ± 0.39 (3.96 to 5.21)	-0.02 (-0.72 to 0.68)	0.17 (-0.47 to 0.80)	0.04 (-0.74 to 0.82)	0.10 (-1.16 to 1.37)	0.19 (-1.21 to 1.60)	0.09 (-1.26 to 1.44)
FMD (%)	5.37 ± 2.59 (2.16 to 8.59)	5.01 ± 3.93 (0.13 to 9.90)	4.54 ± 2.65 (1.76 to 7.32)	4.96 ± 4.54 (0.19 to 9.72)	4.62 ± 2.60 (0.48 to 8.76)	5.51 ± 3.61 (-0.22 to 11.25)	-0.36 (-5.05 to 4.33)	0.42 (-3.86 to 4.70)	0.90 (-4.35 to 6.14)	0.45 (-4.42 to 5.31)	0.13 (-5.27 to 5.52)	-0.32 (-5.51 to 4.87)

Legend: Values are expressed as mean ± standard deviation (SD), mean difference (MD) and 95% CI (confidence interval). Comparisons between groups were analyzed by the mixed ANOVA with Bonferroni post-test (within and between) for all parameters. *p ≤0.05. HIIT, high-intensity interval training; CRT, circuit-resistance training; CG, control group; FMD, flow-mediated dilatation; mm, millimeter; Δ, post - pre values.

As supporting information, S1_Fig illustrates the individual dynamic of flow-mediated dilation per group.

Cardiorespiratory Fitness

Table 3 illustrates the effects of the interventions on cardiorespiratory fitness. Patients were equally distributed in relation to all CPET parameters at baseline (p>0,05). Differences were found among groups for $\dot{V}O_2$ peak (mL/.kg/min) and METs max in which patients from HIIT experienced significant improvements (p<0.05), next to improvements in cycling power output (p = 0.019). As a result of CRT, improvements also occurred for $\dot{V}O_2$ peak (mL/kg/min) (p = 0.026) and METs max (p-values of 0.025).

Table 3. Impact of interventions on exercise capacity in heart failure patients.

CPET	HIIT Mean ± SD (95% CI)		CRT Mean ± SD (95% CI)		CG Mean ± SD (95% CI)		Within-group difference (post minus pre) MD (95% CI)			Between-group difference MD (95% CI)		
	pre (n=8)	post (n=8)	pre (n=6)	post (n=6)	pre (n=8)	post (n=8)	Δ HIIT	Δ CRT	Δ CG	HIIT vs. CRT	HIIT vs. CG	CRT vs. CG
Time Exercise (min)	9.2 ± 2.6 (7.0 to 11.4)	10.6 ± 2.4 (8.5 to 12.6)	10.0 ± 2.8 (7.0 to 12.9)	10.8 ± 2.1 (8.6 to 13.0)	10.2 ± 2.6 (8.1 to 12.4)	10.4 ± 2.6 (8.2 to 12.5)	-1.3 (-0.3 to 3.0)	0.8 (-1.1 to 2.7)	0.1 (-1.5 to 1.8)	0.5 (-2.9 to 3.9)	0.4 (-2.7 to 3.5)	-0.1 (-3.5 to 3.3)
Cycling peak power output (watt)	**96.8 ± 26.3** (74.8 to 118.7)	**114.9 ± 34.7** (85.9 to 143.9)	104.2 ± 27.7 (75.1 to 133.3)	112.0 ± 34.1 (76.2 to 147.8)	123.3 ± 35.2 (93.8 to 152.7)	123.6 ± 37.5 (99.3 to 155.0)	**18.1 (4.4 to 31.9)***	7.8 (-8.1 to 23.7)	0.4 (-13.4 to 14.1)	2.3 (-43.4 to 47.9)	17.6 (-24.6 to 59.9)	15.4 (-30.3 to 61.0)
RER peak	1.2 ± 0.1 (1.1 to 1.3)	1.2 ± 0.1 (1.1 to 1.2)	1.2 ± 0.1 (1.0 to 1.3)	1.1 ± 0.1 (1.0 to 1.2)	1.2 ± 0.1 (1.1 to 1.3)	1.2 ± 0.1 (1.2 to 1.3)	-0.1 (-0.2 to 0.1)	-0.1 (-0.2 to 0.1)	0.0 (-0.2 to 0.1)	-0.1 (-0.2 to 0.1)	0.0 (-0.1 to 0.1)	0.1 (-0.1 to 0.2)
HR VT1 (bpm)	100.3 ± 13.0 (89.4 to 111.1)	100.4 ± 11.0 (91.2 to 109.6)	109.2 ± 12.8 (93.4 to 125.0)	107.6 ± 8.5 (97.1 to 118.1)	101.4 ± 20.5 (84.3 to 118.5)	96.3 ± 15.3 (83.5 to 109.0)	0.1 (-13.5 to 13.8)	-1.6 (-18.8 to 15.6)	-5.1 (-18.8 to 8.5)	8.1 (-10.7 to 26.9)	-1.5 (-18.0 to 15.0)	-9.6 (-28.4 to 9.2)
HR VT2 (bpm)	113.1 ± 19.0 (97.3 to 129.0)	122.4 ± 13.2 (110.2 to 134.7)	119.3 ± 16.4 (102.1 to 136.6)	123.2 ± 5.6 (116.1 to 130.1)	122.8 ± 20.8 (105.3 to 140.2)	116.4 ± 12.7 (105.8 to 127.0)	7.6 (-7.8 to 23.0)	2.0 (-16.1 to 20.2)	-6.4 (-21.0 to 8.3)	3.4 (-17.0 to 23.8)	2.6 (-16.0 to 21.3)	-0.8 (-21.0 to 19.4)
HR peak (bpm)	125.0 ± 24.7 (104.3 to 145.7)	129.4 ± 20.5 (112.2 to 146.6)	122.7 ± 16.9 (104.9 to 140.4)	129.2 ± 9.9 (118.8 to 139.5)	142.0 ± 17.9 (127.0 to 157.0)	139.9 ± 14.5 (128.8 to 152.0)	4.4 (-13.4 to 22.1)	6.5 (-14.0 to 27.0)	-2.1 (-19.9 to 15.6)	-1.3 (-23.5 to 21.0)	13.8 (-6.9 to 34.4)	15.0 (-7.3 to 37.3)
V̇O₂ VT1 (mL/kg/min)	11.0 ± 2.2 (9.2 to 12.8)	13.8 ± 1.9 (12.2 to 15.4)	13.8 ± 3.2 (10.4 to 17.2)	15.0 ± 2.9 (12.0 to 18.1)	13.5 ± 6.4 (8.1 to 18.9)	13.1 ± 3.0 (10.6 to 15.6)	2.7 (-1.6 to 7.1)	1.3 (-3.8 to 6.3)	-0.4 (-4.8 to 4.0)	2.0 (-2.0 to 6.0)	0.9 (-2.8 to 4.6)	-1.1 (-5.1 to 2.9)
V̇O₂ VT2 (mL/kg/min)	**15.1 ± 2.5** (13.1 to 17.1)	**18.8 ± 3.4** (15.6 to 21.9)	17.9 ± 5.0 (12.7 to 23.2)	19.2 ± 2.6 (16.5 to 21.9)	17.4 ± 2.0 (15.7 to 19.0)	16.2 ± 2.3 (14.2 to 18.1)	**3.7 (1.0 to 6.3)***	1.3 (-1.6 to 4.2)	-1.2 (-3.7 to 1.3)	1.6 (-2.2 to 5.4)	-0.2 (-3.7 to 3.1)	-1.8 (-5.6 to 2.0)
V̇O₂ peak (mL/kg/min)	**17.5 ± 4.2** (14.0 to 21.0)	**19.6 ± 4.9** (15.6 to 23.7)	**16.9 ± 2.5** (14.3 to 19.5)	**19.9 ± 3.4** (16.4 to 23.5)	20.2 ± 3.3 (17.4 to 23.0)	20.1 ± 4.2 (16.6 to 24.0)	**2.2 (0.2 to 4.1)***	**3.1 (0.8 to 5.3)***	-0.1 (-2.0 to 1.9)	-0.1 (-5.5 to 5.2)	1.6 (-3.4 to 6.5)	1.7 (-3.6 to 7.1)
V̇O₂ peak (mL.min)	1437.3 ± 411.3 (1093.4 to 1781.1)	1563.4 ± 445.7 (1190.7 to 1936.0)	1565.7 ± 365.6 (1182.0 to 1949.3)	1749.0 ± 421.7 (1306.4 to 2191.6)	1605.0 ± 458.4 (1221.8 to 1988.2)	1586.4 ± 474.3 (1189.9 to 1982.9)	126.1 (-37.4 to 289.6)	183.3 (-5.5 to 372.2)	-18.6 (-182.1 to 144.9)	157.0 (-446.3 to 760.4)	95.4 (-463.2 to 654.0)	-61.7 (-665.0 to 541.7)
Slope VE/VCO₂	30.1 ± 5.8 (25.3 to 35.0)	31.9 ± 5.8 (27.1 to 36.7)	27.1 ± 5.0 (21.8 to 32.4)	30.4 ± 7.2 (22.9 to 38.0)	**28.7 ± 7.1** (22.8 to 34.6)	**32.9 ± 6.7** (27.3 to 38.4)	1.8 (-1.6 to 5.1)	3.3 (-0.6 to 7.2)	**4.2 (0.8 to 7.5)***	2.3 (-6.3 to 10.8)	0.2 (-7.7 to 8.2)	-2.0 (-10.6 to 6.6)
METs max	**5.0 ± 1.2** (4.0 to 6.0)	**5.6 ± 1.4** (4.4 to 6.8)	**4.8 ± 0.7** (4.1 to 5.6)	**5.7 ± 1.0** (4.7 to 6.7)	5.8 ± 1.0 (5.0 to 6.6)	5.8 ± 1.2 (4.8 to 6.7)	**0.6 (0.0 to 1.2)***	**0.9 (0.2 to 1.5)***	0.0 (-0.6 to 0.5)	0.0 (-1.6 to 1.5)	0.5 (-1.0 to 1.9)	-0.5 (-1.1 to 2.0)

Legend: Values are expressed as mean ± standard deviation (SD), mean difference (MD) and 95% CI (confidence interval). Comparisons between groups were analyzed by the mixed ANOVA with Bonferroni post-test (within and between) for all parameters. *p ≤0.05. HIIT, high-intensity interval training; CRT, circuit-resistance training; CG, control group; CPET, cardiopulmonary exercise testing; RER, respiratory exchange ratio; HR, heart rate; VT1, first ventilatory threshold; VT2, second ventilatory threshold; V̇O₂, oxygen uptake; mL, millimeter; kg, kilogram; min, minute; METs max, maximal metabolic equivalent.

The individual dynamic of V̇O₂ peak along the groups are demonstrated on Fig 5. In order to complement this, the responders treshold is illustrated on Fig 6 for VO2 peak, i.e., the minimum expected improvement range desirable according to previous literature. This responder threshould was based on previous literature (118) which reported that every 6% increase in VO2 peak in heart failure population, was associated with a 8% lower risk of cardiovascular mortality or heart failure hospitalization and a 7% lower all-cause mortality. The majority of patients responded for improvements on V̇O₂ peak in both intervention groups.

Figure 5. Individual dynamic of cardiorespiratory fitness, isokinetic peak power, and physical performance
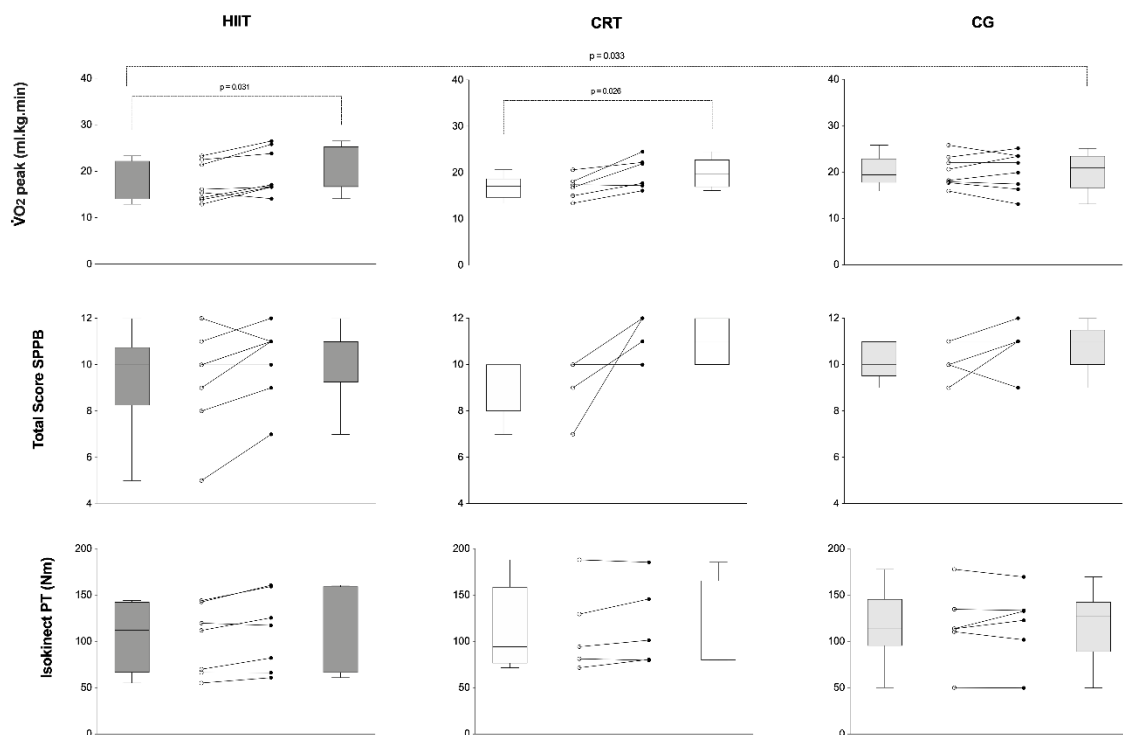
Absence of patients on Muscle Strength and Physical Performance test

Two patients from CG did not have their muscle strength and physical performance assessed due to absence at the evaluation centre. One patient from HIIT group were not able to execute properly both tests. One patient from CRT group referred joint pain in the knee during the post test (due to a small incident at his home). All other patients were normally tested.

Muscle Strength

Table 4 indicates the effects of both training modalities and control period on muscle strength parameters in heart failure individuals. Figs 5 and 6 indicated the individual variations and delta changes for muscle strength, respectively, in all groups. Considering the absence of a prognostic cutoff point in the literature about knee extension muscle strength in heart failure patients, a responder treshould, i.e., the minimum expected improvement range desirable according to previous literature was not indicated for this parameter, but the delta changes are graphically demonstrated on Fig 6. Groups were statistically similar at baseline moment. HIIT led to significant increments in isokinetic torque peak and average power, while in CRT, there was not statistical increase. To conclude, the HIIT group had a superior effect on muscle strength indicators vs. CRT.

Figure 6. Delta changes variations of cardiorespiratory fitness, isokinetic peak power and physical performance.

$\dot{V}O_2$ peak (ml.kg.min)

Isokinect PT (Nm)

Total SPPB Score
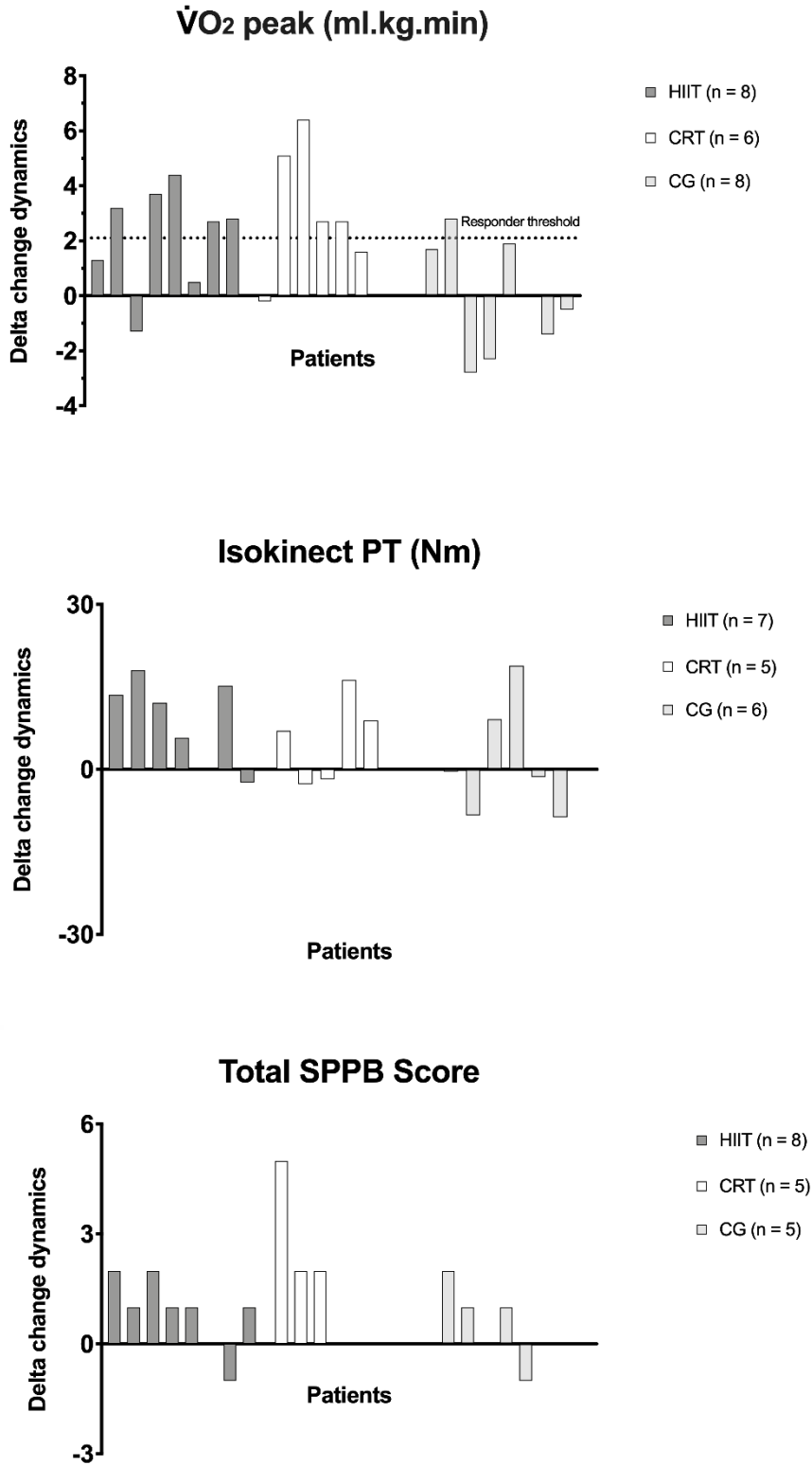
Table 4. Impact of interventions on muscle strength in heart failure patients.

BIODEX	HIIT		CRT		CG		Within-group difference (post minus pre)			Between-group difference		
	Mean ± SD (95% CI)		Mean ± SD (95% CI)		Mean ± SD (95% CI)		MD (95% CI)			MD (95% CI)		
	pre (n=7)	post (n=7)	pre (n=5)	post (n=5)	pre (n=6)	post (n=6)	Δ HIIT	Δ CRT	Δ CG	HIIT vs. CRT	HIIT vs. CG	CRT vs. CG
Isokinetic torque peak (Nm)	101.4 ± 37.2 (66.9 to 135.8)	110.2 ± 41.6 (71.8 to 148.7)	112.9 ± 47.4 (54.1 to 171.8)	118.5 ± 46.1 (61.3 to 175.6)	116.7 ± 41.4 (73.3 to 160.1)	118.3 ± 40.1 (76.1 to 160.4)	8.9 (-0.2 to 18.0)	5.5 (-5.2 to 16.3)	1.5 (-8.3 to 11.4)	9.9 (-55.9 to 75.7)	11.7 (-50.8 to 74.2)	1.8 (-66.2 to 69.8)
Isokinetic torque peak / Body weight (%)	**117.3 ± 28.8 (90.7 to 144.0)**	**129.4 ± 32.3 (99.6 to 159.3)**	122.6 ± 40.5 (72.4 to 172.9)	129.3 ± 37.3 (83.0 to 175.6)	146.0 ± 29.1 (115.4 to 176.6)	151.9 ± 36.7 (113.4 to 190.4)	**12.1 (1.8 to 22.4)***	6.7 (-5.5 to 18.8)	5.9 (-5.2 to 17.0)	2.6 (-50.2 to 55.4)	25.6 (-24.6 to 75.7)	23.0 (-31.6 to 77.5)
Total Work (J)	1742.5 ± 590.5 (1196.3 to 2288.6)	1902.1 ± 610.2 (1337.8 to 2466.5)	2016.3 ± 733.7 (1105.0 to 2927.5)	1981.3 ± 1181.1 (514.8 to 3447.9)	2060.5 ± 664.4 (1363.3 to 2757.7)	2117.9 ± 731.8 (1350.0 to 2885.8)	159.7 (-224.7 to 544.1)	-34.9 (-489.8 to 419.9)	57.4 (-357.8 to 472.6)	273.8 (-1358.7 to 811.1)	-318.1 (-1348.8 to 712.8)	-44.3 (-1166.2 to 1077.7)
Work / Body weight (%)	132.3 ± 32.5 (102.3 to 162.4)	148.5 ± 39.7 (111.8 to 185.2)	139.6 ± 39.1 (91.0 to 188.1)	144.7 ± 38.5 (97.0 to 192.5)	166.8 ± 31.5 (133.7 to 199.9)	176.9 ± 40.0 (134.9 to 218.8)	16.2 (-3.4 to 35.9)	5.2 (-18.1 to 28.4)	10.1 (-11.2 to 31.3)	1.7 (-54.4 to 57.8)	31.4 (-21.9 to 87.7)	29.7 (-28.4 to 87.7)
Total Work Max Repetition (J)	115.1 ± 45.8 (72.4 to 157.9)	124.6 ± 42.1 (85.7 to 163.5)	127.4 ± 45.2 (71.3 to 183.5)	132.7 ± 49.9 (70.6 to 194.6)	132.9 ± 42.6 (88.3 to 177.6)	138.0 ± 45.2 (90.6 to 185.4)	9.5 (-6.8 to 25.9)	5.5 (-14.1 to 24.6)	5.1 (-12.6 to22.7)	10.2 (-59.5 to 80.0)	15.6 (-50.6 to 81.9)	5.4 (-66.7 to 77.5)
Work Fatigue (%)	35.3 ± 14.3 (26.7 to 43.9)	41.3 ± 4.2 (38.8 to 43.7)	39.2 ± 6.8 (34.3 to 44.1)	35.7 ± 11.6 (23.5 to 44.0)	39.2 ± 12.7 (25.8 to 52.5)	43.4 ± 4.9 (38.3 to 48.5)	8.1 (-4.3 to 20.5)	-3.1 (-17.7 to 11.6)	4.2 (-9.2 to 17.6)	-0.1 (-14.2 to 14.0)	4.1 (-9.4 to 17.5)	4.2 (-10.5 to 18.8)
Average power (Watt)	**141.1 ± 50.8 (94.2 to 188.1)**	**161.9 ± 63.2 (103.4 to 220.4)**	175.2 ± 77.4 (79.1 to 271.4)	191.3 ± 75.7 (97.3 to 285.2)	167.6 ± 59.7 (105.0 to 230.2)	169.0 ± 60.5 (105.5 to 232.6)	**20.8 (4.7 to 36.8)***	16.0 (-2.9 to 35.0)	1.4 (-15.9 to 18.7)	31.7 (-68.3 to 131.8)	16.8 (-78.2 to 111.9)	-14.9 (-118.3 to 88.5)

Legend: Values are expressed as mean ± standard deviation (SD), mean difference (MD) and 95% CI (confidence interval). Comparisons between groups were analyzed by the mixed ANOVA with Bonferroni post-test (within and between) for all parameters. *$p \leq 0.05$. HIIT, high-intensity interval training; CRT, circuit-resistance training; CG, control group; Nm, newton-meter; J, Joules; Max, maximum.

Physical Performance

Groups were similar at baseline. Figs 5 and 6 indicated the individual variations and delta changes, respectively, for muscle strength in all groups. Considering the absence of studies indicating an appropriate prognostic cutoff point for physical performance on this population, a responder treshould was not indicated for this parameter, but the delta changes are graphically demonstrated on Fig 6. Differences among groups were seen for the parameters balance test and total SPPB (Table 5). HIIT group demonstrated improvement for the parameter total SPPB score (p = 0.041) which was not statistically indicated for CRT (p = 0.250). CRT reduced the time to complete the chair stand test (p = 0.050), demonstrating an improvement on this parameter. To conclude, CRT was more effective in improving physical performance when compared to HIIT.

Table 5. Impact of interventions on short physical performance battery in heart failure patients.

SPPB	HIIT		CRT		CG		Within-group difference (post minus pre)			Between-group difference		
	pre (n=8)	post (n=8)	pre (n=5)	post (n=5)	pre (n=5)	post (n=5)	Δ HIIT MD (95% CI)	Δ CRT MD (95% CI)	Δ CG MD (95% CI)	HIIT vs. CRT	HIIT vs. CG	CTR vs. CG
Balance test												
Score [Q1-Q3]	4.0 [2.5-4.0]	4.0 [4.0-4.0]	4.0 [3.0-4.0]	4.0 [4.0-4.0]	4.0 [4.0-4.0]	4.0 [4.0-4.0]	-	-	-	**0.046***		
Gait test												
Score [Q1-Q3]	3.5 [3.0-4.0]	3.5 [3.0-4.0]	3.0 [3.0-4.0]	4.0 [3.0-4.0]	3.0 [3.0-4.0]	4.0 [3.0-4.0]	-	-	-	0.739		
Seconds (95% CI)	3.6 ± 0.6 (3.1 to 4.1)	3.7 ± 0.9 (2.9 to 4.4)	3.5 ± 0.6 (2.8 to 4.2)	3.4 ± 0.6 (2.7 to 4.1)	3.6 ± 0.7 (2.7 to 4.5)	3.4 ± 0.7 (2.6 to 4.2)	0.0 (-0.8 to 0.8)	-0.1 (-1.1 to 0.9)	-0.2 (-1.2 to 0.8)	-0.2 (-1.1 to 0.6)	-0.2 (-1.0 to 0.7)	0.0 (-0.9 to 1.0)
Chair stand test												
Score [Q1-Q3]	2.5 [2.0-3.0]	3.0 [2.3-3.8]	2.0 [1.0-3.5]	3.0 [3.0-4.0]	3.0 [2.0-3.3]	3.0 [2.5-4.0]	-	-	-	0.083		
Seconds (95% CI)	13.5 ± 2.0 (11.8 to 15.1)	12.8 ± 2.4 (10.8 to 14.8)	**14.3 ± 2.9 (10.7 to 18.0)**	**11.0 ± 1.4 (9.3 to 12.7)**	12.9 ± 1.6 (11.0 to 14.9)	12.6 ± 2.1 (10.0 to 15.3)	-0.6 (-3.1 to 1.9)	**-3.3 (-6.5 to -0.2)***	-0.3 (-3.4 to 2.9)	-0.5 (-3.1 to 2.1)	-0.4 (-3.0 to 2.2)	0.1 (-2.8 to 3.0)
Total SPPB												
Score [Q1-Q3]	10.0 [8.3;10.8]	11.0 [9.3;11.0]	10.0 [8.0;10.0]	11.0 [10.0;12.0]	10.0 [9.5;11.0]	11.0 [10.0;11.5]	-	-	-	**0.008***		

Legend: SPPB, short physical performance battery; HIIT, high-intensity interval training; CRT, circuit-resistance training; CG, control group. Values are expressed as median and interquatile range (Q1-Q3) for scores and mean ± standard deviation (SD), mean difference (MD) and 95% CI (confidence interval) for seconds. Comparisons between groups were analyzed by mixed ANOVA for parametric distribution, while Friedman two-way test was applied for the difference among groups (HIIT, CRT and CG) which does not allow the comparison between groups pairwise. *p ≤0.05.

All tables were also made in a different format containing the p values, and can be seen in Supporting informations S1_Tables (SS2 –SS5)

Body Composition

No changes were observed for dexa scan parameters. The results obtained from DXA scan are illustrated on Supporting information S1_Tables (Table S1).

Discussion

The novelty of this study is the comparison of high-intensity protocols of aerobic and resistance-training modality in heart failure patients. This preliminary study indicated that aerobic high-intensity interval training promotes similar effects than circuit-resistance training over cardiorespiratory fitness, although only HIIT indicated better responses on muscular strength improvement. Both training impacted physical performance but better global effects were seen on HIIT. Taking together, HIIT trend to demonstrate superior benefits over high intensity circuit-resistance training in heart failure.

HIIT's role as an exercise prescription modality for heart failure patients has increased and started to be recommended for low-risk heart failure patients (76). Although the HIIT has been more explored in HF with reduced ejection fraction (119,120) and needs to be carefully applied in HF patients with NYHA III (121), the present study, which included all ejection fraction classifications for HF, did not indicated risks related to training. Despite the high intensities, HIIT and CRT were well tolerated, which can be related to the absence of severe muscle dysfunction and the mean age of the patients included (general mean age around 57 years old). High intensity training, independent of aerobic or resistance modality, demonstrated to be safe in HF.

Interestingly, similar effects on exercise capacity was evidenced in both training groups, with improvements in $\dot{V}O_2$ peak and METs max. However, only HIIT demonstrated improvements on cycling peak power output and isokinetic peak torque, positively impacting muscular strength and better prognosis (122). Muscular adaptations promoted by HIIT, as similar effects on microvascular and mitochondrial adaptations in type I and type II muscle fibers (123), and less obesity present on this group (mean BMI lower than 30) may have

influenced such greater muscle strength responses (124). Considering HIIT was based on alternately sessions on the treadmill and cycle ergometer, patients from this group were submitted to half of the training period on dynamic contractions of quadriceps and hamstring, which may also have influenced the positive anwers on muscle strength. Also, considering higher aerobic loads were necessary to maintain an adequate heart rate range on HIIT along the training period, higher muscle demands were required reversing skeletal myopathy (125) and impacting muscle strength gains. Improvements on physical performance were seen on both training groups. Taking together, HIIT indicated better global responses than CRT.

Resistance-training intervention as a single intervention have demonstrated to increase aerobic capacity (81), and our results also confirm this increase when adopting a progressive high intensity circuit-resistance training. Also, the best training effects on chair stand component from the functional performance test seen on CRT, corroborate with previous findings that resistance training shows good response on physical disability in HF patients (126) . Some evidence points to high resistance loads as more useful to increase acutely myofibrillar protein synthesis causing neural adaptations, and further muscle strength (127–131), however our fundings did not indicated muscle strength improvements after CRT. Considering the superior prognostic value of the $\dot{V}O_2$ peak and muscle strength (132) in HF by following gold standard measurements (cardiopulmonary exercise testing and isokinetic peak torque), our findings indicate better results for HIIT.

One of the main targets of this study was also to verify the impact of both high intensity traininig on endothelial function of HF patients. Considering that endothelial dysfunction in HF(133) (134) is mainly caused by lower production of nitric oxide, increasing oxidative stress, and vasoconstriction response(134) and has been associated with increased mortality hazard, potential effective approaches to tackle the dysfunction is wanted. The majority of studies evaluating the training effects on endothelial function applied aerobic training modality indicating improvements on this variable (135–137) however, neither HIIT or CRT findings have indicated changes on this parameter. Resistance training combined with aerobic training already demonstrated improvement on FMD (138), but the isolated effect of high-intensity resistance training was not previously demonstrated. Our findings did not indicate the potential to increase endothelial function parameters in HF. Different cardiovascular aetiologies, ejection fractions and the small sample size for this outcome may also have influenced the results.

These preliminary findings' main clinical implications shows that reaching high loads of training can improve exercise capacity in HF, independently of the training modality.

However, HIIT trend to be more attractive to impact the global health status than high intensity circuit resistance training in HF patients by jointly increasing exercise capacity, muscle strength and physical performance. In the era in which refined exercise prescription is under intense debate, this study stresses the clinical practice revealing that although its safety high loads of training needs to be carefully applied in HF after a detailed investigation about the patient needs. Clinical trials with more patients are expected to keep building knowledge on exercise prescription with high-intensity loads in HF, mainly for circuit-resistance training modality.

Study Limitations

Sources of bias was analyzed by Rob2 tool, and we identified bias related to missing outcome data criteria for the outcomes FMD, SPPB and muscle strength due to different reasons as reported on consort flowchart and results session. The main limitation of this study was the covid-19 outbreak, which forced this multicentre in-progress collaboration with Belgium be early terminated and only data from one center could be provided. This made us recognize the imprecision of the findings due to the relatively small sample size which restricts the generalization of our findings to the entire heart failure patient population. Despite those limitations, the current study offers a unique perspective in heart failure population comparing high intensity training protocols also providing head-to-head results on exercise capacity, endothelial function, muscular strength and physical performance. This preliminary study indicated trends that helps building up knoledgement about the therapeutic value of high-intensity protocols on cardiovascular rehabilitation.

Conclusions

This preliminary study indicates that high-intensity interval training seems to promote a superior effect than high-intensity progressive circuit-resistance training by increasing cardiorespiratory fitness, muscular strength, and physical performance in heart failure patients. To a greater extend, no training effects were detected on endothelial function. Further studies with larger cohorts of patients are however needed.

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Supplier's list

[a] Heparinized (sodium) tubes - Vacuette® from Greiner Bio-One, Kremsmünster, Áustria

[b] Cobas h232 - Roche Diagnostics, Basel, Switzerland

[c] Ultrasound for echocardiography - HDI 5000 2-4 MHZ, Philips ATL, Bothell, WA

[d] Spirometry - MicroLab ML3500MK8, CareFusion, EUA

[e] High-resolution Doppler duplex ultrasound - HD11.XZ, Phillips, Barueri, SP, Brazil

[f] Edge-detection software - Cardiovascular Suite, Quipu, Pisa, Italy

[g] Cycle ergometer - Corival, LODE BV Medical Technology Groningen, Netherlands

[h] Breath-by-breath gas analyzer - CPET, Cosmed, Rome, Italy

[i] Electrocardiogram - Quark T12x, Cosmed, Rome, Italy

[j] Isokinetic dynamometer - Biodex System 3 PRO, Medical Inc., New York, EUA

[k] Dual x-ray absorptiometry scan - DXA - Lunar Prodigy Bone Densitometers, GE Healthcare, USA

[l] Polar® - RS800, Polar Pro Trainer, Kempele, Finland

[m] Resistive stations - EN-Dynamic, Enraf-Nonius, Rotterdam, the Netherlands

[n] Treadmill - Gait Trainer, Biodex Medical Systems, Inc., New York, EUA

[o] Ergometric bicycle - BioStep™ Semi-Recumbent Elliptical, Biodex Medical Systems, Inc., New York, EUA

[p] G*Power Software 3 - 3.1.9.6 version, Heinrich Heine Universität Düsseldorf, Germany

[q] Statistical software SPSS version 22.0 - SPSS, Inc. Chicago, IL, USA

[r] GraphPad Prism - 8.4.0 version, California, San Diego

Supporting information

S1 File. Consort checklist

S2 File. Study Protocol

S3 File. Chronological dates of the study steps

S1 Fig. Individual dynamic of flow mediated dilation. Flow-mediated dilation individual

dynamics. HIIT, high-intensity interval training; CRT, circuit-resistance training; CG, control group.

S1 Table. Body composition parameters in heart failure. DXA (dual x-ray absorptiometry); **HIIT** (high-intensity interval training); **CRT** (circuit-resistance training); **CG** (control group). Comparisons between groups were analyzed by the Two-way ANOVA (group*time interaction and group interaction). The baseline and post were analyzed by Kruskall-Wallis Test. The normality was analyzed by Kolmogorov-Smirnov test. Values are expressed as mean ± standard deviation (SD). A statistically significant difference was considered when there was a p value <0.05. **Obs.** Considering some patients made use of pacemakers, only 16 patients made biodex assessment. No differences among baseline parameters were found, neither differences related to the intervention.

Figure 1. Study flowchart. HIIT, high-intensity interval training; CRT, circuit-resistance training; CPET, cardiopulmonary exercise testing; FMD, flow-mediated dilatation.

Figure

CRT, circuit-resistance training; CG, control group; NT-pro BNP, N-terminal pro-brain natriuretic peptide; FMD, flow-mediated dilatation; CPET, cardiopulmonary exercise test; SPPB, Short Physical Performance Battery.

Figure 3. Training protocol. Design of the training protocol. HIIT, high-intensity interval training; CRT, circuit-resistance training; 1RM, one-repetition maximum; W, weeks; rep, repetitions; min, minute.

Figure 4. Clinical measurements at training sessions. HIIT, high-intensity interval training; CRT, circuit-resistance training; CG, control group; SBP, systolic blood pressure; mmHg, milimeters of mercury; DBP, diastolic blood pressure; HR, heart rate; bpm, beats per minute; Borg (6-20), perceived of exertion.

Figure 5. Individuals dynamics per groups. HIIT, high-intensity interval training; CRT, circuit-resistance training; CG, control group; $\dot{V}O2$, oxygen uptake; mL/kg/min, millimeter per kilogram per minute; SPPB, short physic performance battery; PT, peak torque; Nm, newton-meter; p, statistical significance.

Figure 6. Delta change variation. Responder threshold for $\dot{V}O2$ (minimum 6% increase mL/kg/min). HIIT, high-intensity interval training; CRT, circuit-resistance training; CG, control group; $\dot{V}O2$, oxygen uptake; mL/kg/min, millimeter per kilogram per minute; W, watt; SPPB, short physic performance battery.

Chapter 4

IMPACT OF EXERCISE MODALITIES ON PERIPHERAL AND CENTRAL COMPONENTS OF CARDIORESPIRATORY CAPACITY IN HEART TRANSPLANTATION PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CLINICAL TRIALS

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Abstract

Background: Exercise training is recommended after Heart Transplantation(HTx), however the pivotal understanding about training prescription is not addressed. An overview of training modalities and intensities for improving cardiorespiratory health is HTx is needed as it relates to a better prognosis. **Objectives**: To analyse the effects of aerobic, resistance, and combined training on peripheral and central components related to cardiorespiratory capacity after HTx. **Methods**: PRISMA guidelines was applied, and Studies ranged from 1998 to 2019. Inclusion criteria: studies with participants post HTx$\geq$19 years old, reporting aerobic training(AT), resistance training(RT), or the combination of both(CT) and comparing them with a control group, or comparisons between modalities or training intensities. Studies reporting aquatic exercises were excluded. Outcomes analysed: $V'O_2$ peak, $VE/V'CO_2$ slope, heart rate(HR peak), systolic and diastolic blood pressure(SBP and DBP peak), maximum repetition test(1RM), sit-to-stand test and flow-mediated dilation(FMD). **Results** Isolated aerobic training leads to a greater increase in VO_2 peak than combined training when compared to the control group ($p<0.001$, $I^2=0\%$), although no significant differences were found in the subgroup comparison ($p=0.19, I^2=42.1\%$). HR peak increased similarly after aerobic and CT. High-intensity interval training(HIIT) was better than moderate continuous intensity to increase the VO_2 after long term in HTx, but there is scarce evidence of HIIT on muscle strength and FMD. No change on $VE/V'CO_2$ slope, FMD, and SBP, DBP peak. 1RM and the sit-to-stand test increased after resistance training ($p<0.001, I^2=70\%$) and CT($p<0,001, I^2=0\%$) when compared to control. **Conclusions**:Aerobic and combined training are effective in improving VO_2 peak and muscle strength post HTx, respectively. Aerobic training modality promotes more benefits on prognosis in which HIIT superiority is detected for cardiorespiratory capacity improvements. More studies are needed.

Keywords: exercise; heart transplantation; prognosis, exercise tolerance

List of abbreviations

HTx – heart transplantation

FMD – flow-mediated dilation

AT – aerobic training

RT – resistance training

VO2 – oxygen consumption

VE – ventilation

VCO2 – carbon dioxide output

HR – heart rate

SBP – systolic blood pressure

DBP – diastolic blood pressure

RCT – randomized clinical trial

HIIT – high intensity interval training

1RM – one maximal repetition

MCT-AE - moderate continuous training

MD – mean difference

RT – resistance training

1. Introduction

Despite the improvements in pharmaceutical and resynchronization treatments and even considering the advent of the left-ventricular assist device(53), heart transplantation(HTx) remains a notable treatment for advanced heart failure(54–57). HTx gives a new life opportunity for such patients improving peak oxygen uptake (V′O$_2$ peak) (139,140), though it is still reduced in comparison to healthy age-matched individuals(82,141). Nonetheless, to reach a better prognosis after HTx, a V′O$_2$ peak increase is wanted(82).

Reduced exercise capacity is associated with cardiac, vascular and muscular limitations post HTx(67). Cardiovascular limitation involve chronotropic incompetence with higher resting heart rate and reduced peak heart rate(67,142). Peripheral limitations involve vascular endothelial dysfunction by flow-mediated dilation (FMD) reductions(67,143–148) and losses in lean mass affecting muscle strength and exercise intolerance post HTx(67). The immunosuppressive treatment also promotes muscle and V′O$_2$ peak reduction(67,68), and peak systolic and diastolic blood pressure increase due to its vasoconstrictor effect(19). Peak heart rate and systolic blood pressure are also affected by the sympathetic reduction due to the removal of the sinus node(19).

Clinical practice guidelines recommend exercise training for HTx to increase exercise capacity(149). Regarding exercise training modalities, aerobic training (AT) increase V′O$_2$ peak, reduce both systolic and diastolic blood pressure and perceive exertion in HTx patients(150). Resistance training(RT) added to aerobic training improve muscle strength and V′O$_2$peak in HTx(151). Reductions in blood pressure and increments in muscle strength can significantly influence the increase on exercise capacity. VE/V'CO$_2$ slope can stratify the survival rate being an important parameter post-HTx.

There is bolding evidence regarding exercise program's effects (82)post-HTx(82); however, the pivotal understanding about the preferred exercise prescription for exercise capacity (modality and intensity) remain unexplored. This review evaluates and compare the isolated and combined effect of the aerobic training (AT) and resistance training (RT) on cardiorespiratory components (V′O$_2$ peak and VE/V'CO$_2$ slope), cardiovascular components (HR peak, SBP peak and DBP peak) and peripheral components (FMD and muscle strength)

post HTx. We hypothesized that aerobic training with moderate intensity is more favourable post-HTx.

2. Methods

2.1 Searches

We followed the recommendations described in the preferred reporting items for systematic reviews and meta-analyses (PRISMA) and Cochrane Handbook(152). The protocol was registered in the PROSPERO database (www.crd.york.ac.uk/prospero/) under number: CRD42017059911.

The systematic review was performed in MEDLINE/PubMed; EMBASE, CENTRAL and PEDro. The search strategy can be checked on Electronic Supplemental Material.

2.2 Study inclusion and exclusion criteria

Eligibility criteria: (1) Randomized Clinical Trials (RCTs) with or without a cross-over strategy, (2)participants ≥ 19 years old, who received HTx, (3)studies that described the aerobic training (AT), resistance training (RT), or the combination of both, at any intensity; and (4)studies that compared physical training through exercise with a control group without exercise or comparisons between modalities or training intensities. Language inclusion: English, French, Dutch, and Portuguese. We excluded studies without comparison group and with aquatic exercise.

2.3 Types of interventions and outcomes

We considered isolated AT, RT or CT performed at a hospital, outpatient, or home-based setting. We considered exercise interventions post-HTx with the following characteristics: (1)Frequency: at least two days per week; (2)Duration: at least eight weeks and (3)Intensity: at least 50% of maximum heart rate (HRmax) or 50% of $V'O_2$ peak for aerobic exercise and 40% of one maximum repetition (1RM) for resistance exercise. The clinical outcomes of the studies should have included at least one of the following measures: peak oxygen uptake ($V'O_2$ peak mL/kg/min), VE/$V'CO_2$ slope, peak systolic and diastolic blood

pressure (SBP peak and DBP peak, mmHg), peak heart rate (HR peak, bpm), muscle strength (1RM and sitting to stand test) and flow-mediated dilation (FMD, %).

2.4 Data extraction, synthesis, and presentation

Type of study, population, interventions (including the type of exercise, intensity, frequency, duration, and modality), comparison and outcomes, risk of bias, and results were extracted. A single researcher performed the data extraction procedure, and a second researcher scrutinized it. All recommendation for systematic review with metanalysis was followed according to Cochrane Handbook version 6.0(152). All analyses were conducted using Review Manager Version 5.0.

Relative changes were reported as differences between arithmetic means of continuous data before and after interventions according to the adequate correlation coefficient calculated per outcome. When it was not possible to calculate the correlation coefficient for a given study (lack of information), the value was based on data from the same outcome obtained in other studies included in the meta-analysis. When it was not possible to calculate the correlation, the coefficient based on any study for a given outcome, a literature search was made to enable data extraction from other similar studies, or only post values were reported to avoid possible statistical errors according to the Cochrane Handbook (152) recommendation. If the correlation value was smaller than 0,5, it was little benefit in using change from baseline. Pre- and post-intervention or control group values of $V'O_2$ peak, VE/ $V'CO_2$ slope, HR peak, SBP peak, DBP peak, FMD (mean and standard deviation), and the total number of analyzed subjects were extracted accordingly in excel sheets. Pooled-effect estimates were obtained by comparing the least-squares mean percentage change from baseline to the end of the study for each group and expressed as the mean difference (MD). For the overall comparisons, the effect was calculated utilizing a random-effects model when the heterogeneity was high (> 50%) due to the high risk of false-positive results. However, when heterogeneity was low (< 50%), the effect was based on a fixed model. An α value < 0.05 (2-tailed) was considered statistically significant. Subgroup analysis was made for different training modalities. Publication bias was assessed using a contour-enhanced funnel plot of each trial's effect size against the standard error. Begg and Egger's tests evaluated funnel plot asymmetry. Statistical heterogeneity of the treatment effect among studies was assessed using the Cochran Q test, a threshold p-value < 0.05 (2-tailed) was considered statistically significant, and the inconsistency I^2 test in which values greater than

50% were considered indicative of high heterogeneity. All calculations were based on Cochrane Handbook version 6.0 (152).

2.5 Quality of the trials, Risk of bias and Summary of Findings Table and Quality of Evidence

Quality assessment was performed by two independent reviewers (WCCR and JSF) (and a third reviewer (GCJ) in case of disparities). PEDro scale was used. On this scale, 11 questions were answered as 'yes' (score 1) or 'no' (score 0) to obtain more information about the internal and external validity of the study and interpretability of the statistical results (Pedro). According to Pedro guidelines, item 1 from the Pedro scale was not used to calculate the score, which resulted in a total score maximum of 10. The risk of bias was checked by Rob 2 assessment. The risk of bias was assessed by Rob 2 tool. Pedro and Rob2 tool information complement each other information, thus the readers can better identify the trials' methodological details. The GRADEpro tool was applied to generate the summary of findings table indicating the quality of evidence. Two independent review authors (NTS, GCJ) applied the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to evaluate the outcomes and used the GRADE pro-GDT 2015 online platform to import the data from Review Manager software, creating the summary of findings table. The following outcomes generated the table: $V'O_2$ peak, VE/ $V'CO_2$ slope, SBP peak, DBP peak, HR peak, and FMD. Even considering few studies for some of the outcomes, the authors decided to include all of them in the summary of findings table in order to provide certainty of evidence (study design, risk of bias, inconsistency, indirectness, imprecision, and other considerations) overview per outcome. The authors strictly followed the methods and recommendations described in Section 8.5 and Chapter 12 of the Cochrane Handbook for Systematic Reviews of Interventions using GRADE pro GDT software and further detailed information expressed on GRADE guidelines. All quality decisions were justified using footnotes, as recommended.

3. Results

3.1 Selection, evaluation of studies and quality assessment

The initial search identified 2712 studies and present systematic review included 20 studies based on eligibility in which 15 were included in the qualitative synthesis and 13 studies considered for quantitative synthesis (metanalysis). The reasons for exclusion are in Figure 1.

Nine studies involving AT(153–161), three studies involving CT(162–164) and two involving RT(165,166) were included. Only two studies compared exercise intensities(160,161) and one study compared home-based versus hospital-based intervention (167). All the other studies included an intervention group compared to a non-exercise control group.

Figure 1. Prisma Flow chart

PRISMA flow diagram:

Identification

Records identified through database searching
MEDLINE − 878
EMBASE − 2712
CENTRAL − 205
PEDro − 24

Additional records identified through other sources
(n = 0)

Screening

Records after title duplicates removed
(n = 492)

Records screened on abstract

Records excluded based on abstract
(n = 475)

Eligibility

Full-text articles assessed for eligibility
(n = 20)

Full-text articles excluded
(n = 2)
- 1 paper without control group
- 3 papers with duplicated result
- 1 paper with long term follow up from a randomized trial

Included

Studies included in qualitative synthesis (n = 15)

Full-text articles excluded from metanalysis
(n = 2)
- 1 paper hospital vs home-based
- 1 paper with only graphic data

Studies included in quantitative synthesis (meta-analysis)
(n = 13)

3.2 Studies included in the systematic review.

The publication period of the included studies ranged from 1998 to 2019, involving a total of 453 patients undergoing HTx with 407 (72%) males, with a mean age of 51 years in the intervention group and 47 years in the control group. Two studies reported only the RT protocol and three studies, included combined training (resistance + aerobic training). Surprisingly, only one of those CT studies reported a detailed prescription of the RT (30). Also, only two studies presented a comparison between aerobic intensities, high-intensity interval training (HIIT) vs.

moderate continuous training (MCT-AE) (161,168), and one study compared hospital-based versus home-based exercise following the same training prescription.

Regarding the AE, the average frequency was 3 days per week, with a duration of 35 ± 5 minutes per session and a protocol duration of 18 ± 11 weeks. Among the AE modalities, with MCT-AE, the intensity ranged from 60-80% of V′O$_2$ peak(154,158,169), 10% below the anaerobic threshold (153), or Borg RPE between 11-14(155,159).

One study utilized the higher patient's tolerance sustained for 30 min (163). Four studies applied HIIT (156,157,160,161) and one applied HIIT alternating with continuous training (169). HIIT intensities ranged from 80-90% of the V′O$_2$peak, 80-95% of the HR peak or 90-100%(39,40) of the baseline peak power output. Interval duration varied from 30 seconds to 4 minutes, alternated by low-intensity phases with an intensity ranging from 11 to 13 (157) according to the BORG scale or a recovery rest phase(156,162,170). Recovery duration varied from 30 seconds to 3 minutes, while some studies adopted passive rest recovery (Table 1).

Heterogeneity was low for V′O$_2$peak, slope VE/V'CO$_2$, and sit-to-stand test ($I^2<50\%$). SBP, DBP and HR peak, FMD and 1RM indicated high heterogeneity($I^2 >50\%$). No study reported adverse effects. The agreement level between the reviewers, by Kappa coefficient was 0.95(95% CI: 0.75 to 1.0

Table 1. Description of studies included in the systematic review

Study[ref], year, type	Time after HTx and local	Sample Size (n)		Age (yrs) (mean±SD)	Outcomes	Intervention description	Frequency (d/wk)	Session duration (min)	Program duration (wk)	PEDro score
					AEROBIC TRAINING VS. CONTROL					
Tegtbur [23] RCT	2003 5 years	AT CG	20 12	55.0 ± 7.0 54.0 ± 8.0	$VO2_{peak}$	**Outpatient – home-based - controlled remotely** **AT:** bicycle ergometer (10% below the Anaerobic threshold); **CG**: usual medical care	3	28	48	4
Bernardi et al. [24] RCT	2007 6 months	AT CG	13 11	34.9 ± 4.0 33.9 ± 4.3	$VO2_{peak}$	**Outpatient – home-based – non-supervised** **AT**: bicycle ergometer (50 rpm for 30 min at 60–70% of $VO2_{peak.}$ New training load calculated after 3 months by a new exercise test to exhaustion); **CG**: avoid exercise above their regular pre-study routine and specifically to avoid exercise that would lead to feelings of dyspnoea or exhaustion.	5	30	24	4
Pierce et al. [29] RCT	2008 8 weeks	AT CG	08 06	53.6 ± 13.6 54.2 ± 6.4	$VO2_{peak}$, HR_{peak}	**Outpatient – clinic - supervised.** **AT**: Training protocol started with 30 min of continuous exercise and progressed to 34 to 40 min as tolerated after the initial 4 weeks. Continuous treadmill walking (Borg RPE between11–13, or 'moderate' to 'somewhat hard' range, following ACSM guidelines. Progression to an RPE in the 12–14 Borg scale range 'as tolerated' by each participant) **CG**: standard medical care and encouragement to engage in regular walking, but did not participate in a supervised exercise.	-	Initial: 30 After 4 wk: 40	12	4
Braith et al. [25] RCT	2008 8 weeks	AT CG	09 07	54.3 ± 9.5 54.4 ± 13.1	$VO2_{peak}$, FMD	**Hospital - supervised** **AT**: initial 4 weeks: 5 min warm-up + 30 min continuous treadmill walking + 5 min cool-down. Exercise progressed to 35 to 40 min thereafter. The intensity in a range from Borg RPE between11–13, or 'moderate' to 'somewhat hard' range	3	Initial: 30 After: 35 to 40 as tolerated	12	5

and progressing to RPE in the 12–14 Borg scale range 'as tolerated' following ACSM guidelines. **CG**: standard medical care and encouragement to engage in regular walking but did not participate in a supervised exercise.

Study	Year	Duration	Group	N	Age	Outcomes	Intervention				
Hermann et al. [26] RCT	2011	1 year	AT	14	53.0 ± 11.0	VO2$_{peak}$, FMD	**Outpatient – clinic - supervised.** **AT**: warm-up (above 50% VO2 peak) + HIIT on bicycle (interval blocks of 4 min/2 min/30 s according to 80%, 85%, and 90% of VO$_{2\ peak}$ and 30s recovery periods) + staircase running (80% of peak VO$_{2\ peak}$); **CG:** Patient education (4 h of teaching to the patients about the benefits of exercise training together with information on nutrition)	3	42	8	7
			CG	13	47.0 ± 18.0						
Nytrøen et al [27] RCT	2012	1–8 years	AT	24	48.0 ± 17.0	VO2$_{peak}$, HR$_{peak}$, SBP$_{peak}$ DBP$_{peak}$, VE/VCO$_2$ slope, Muscle strength	**Outpatient – clinic - supervised.** **AT**: HIIT on a treadmill (10 min warm-up + 4 min exercise bouts at 85–95% of HR$_{peak}$, separated by 3 min active pauses at Borg scale 11–13, 6-20 RPE). Additionally, the patients were encouraged to continue any physical activity on their own. **CG**: No intervention was given to the control group other than basic.	3	35	24	5
			CG	24	53.0 ± 14.0						
Pascoalino et al. [28] RCT	2015	≥ 1 year	AT	31	45.0 ± 3.0	VO2$_{peak}$, VE/VCO$_2$ slope, HR$_{peak}$, SBP$_{peak}$, DBP$_{peak}$	**Outpatient – clinic - supervised.** **AT**: Supervised: 5 min warm-up + 40 min walking/jogging on a treadmill (80% HR of the RCP - 69.0% $\pm$ 1.9 % of VO$_2$ max. Endurance Exercise Intensity was continually adjusted) + 5 min cool down. Non-supervised: Same exercise protocol following exercise intensity of 11-13 on the rate of Borg scale (range: 16-20); **CG**: maintain their daily activities without AE during the 12-week period.	3	40	12	6
			CG	09	45.0 ± 6.0						

				COMBINED TRAINING VS. CONTROL GROUP							
Kobachigawa et al[33] RCT	1999	2 weeks	CT	14	55.0 ± 8.0	VO2$_{peak}$, HR$_{peak}$, SBP$_{peak}$, Muscle strength	**Outpatient – clinic - supervised.** **RT**: closed-chain resistive activities + abdominal exercises; **AT**: Treadmill or bicycle ergometer (a goal of at least 30 min of continuous exercise at a moderate intensity according to patient's tolerance) **CG**: Written guidelines (exercises at home)	1-3	AT: ≥30	24	5
			CG	13	50.0 ± 12.0						
Wu et al. [34] RCT	2008	1 year	CT	12	60.6 ± 6.2	VO2$_{peak}$, HR$_{peak}$, Muscle strength	**Outpatient – home-based – supervised every 1–2 weeks.** **RT**: 5 min warm-up + upper and lower extremity light-weight; **AT**: 15 – 20 min walking at a prescribed intensity	3	40	8	5
				19	51.6 ± 12.8						

			Group	N	Age	Outcomes	Intervention	Freq	Min	Weeks	
			CG				with 60–70% VO_2 peak + stepping exercise with a stool + 5 min cool down. **CG:** control group was asked to keep their usual activity lifestyle during the study period.				
Haykowsky et al. [32] RCT	2009	≥0.5 year	CT	22	57.0 ± 11.0	$VO2_{peak}$, HR_{peak}, SBP_{peak}, DBP_{peak}, FMD	**Outpatient – hospital - supervised.** **AT**: treadmill and bicycle (HR: 60–80% $VO_{2\ peak}$) for 30–45 min. After 4 weeks, continuous aerobic training 3 days/week (HR=80% $VO_{2\ peak}$) + Interval training 2 days/week (10 to 25 rep – gradually increase - of 30s exercise at 90-100% baseline peak power output followed by 60 s rest); **RT:** upper (chest press, latissimus dorsi pulldown, arms curls) and lower extremity (leg press) strength training 10 rep, gradually increased until 25 rep at 50% of maximal strength (1 rep = 30 s exercise and 60 s rest); **CG**: continued with their usual activities of daily living.	AT: 5 RT: 2	30-45 45	12	4
			CG	21	57.0 ± 11.0						

RESISTANCE TRAINING VS. CONTROL GROUP

			Group	N	Age	Outcomes	Intervention	Freq	Min	Weeks	
Braith et al [35] RCT	1998	2 months	RT	7	54 ± 3	Muscle strength	**Outpatient – clinic – supervised.** **RT:** 5 min of warm-up walking on a treadmill + lumbar extensor training 1 day/week and upper and lower body resistance training 2 days/week. A single set of 10-15 repetitions was completed for each exercise: lumbar extension, duo-decline chest press, knee extension, pullover, knee flexion, triceps extension, biceps flexion, shoulder press, and the abdominal machine. The initial training weight represented 50% of the one-repetition maximum (1-RM) test. The transplant recipients were not permitted to exceed 15 repetitions. Rather, when 15 repetitions were successfully achieved, the weight was increased by 5-10% at the next training session. **CG:** No resistance training intervention	3	Not described	12 24	4
			CG	7	51 ± 8						
Braith et al. [36] RCT	2005	2 months			52 ± 2	Muscle strength	**Outpatient - home-based - supervised** **RT**: standard care home-based walking program (not supervised) associated with resistance training. 5 minutes warming-up + a single set from 10 to 15 repetitions were completed for each exercise: chest press, knee extension, pulldown, seated leg curl, shoulder press, seated triceps dip, biceps curl, and lumbar extension at 50% of 1 RM. The resistance was increased by 5% to 10% at the next training	2	Not described	24	6
			RT	8							
			CG	7	53 ± 2						

							session when 15 repetitions were successfully achieved. Upper body exercises were alternated with lower body exercises. **CG**: standard care home-based walking program (not supervised)				
HIIT VS. MCT											
Dall [31] RCT	2014	≥1 year	HIIT MCT	16	51.9 (33–70) Cross-over	$VO2_{peak}$, HR_{peak}	**Outpatient – clinic - supervised.** **AT – HIIT:** Each HIIT session consisted of 16 min interval training with intervals of 4-, 2-and1-min duration at>80%ofVO2peak, separated by a 2-min active rest period (approx. 60% of VO2peak) **AT – MCT-AE:** The CON sessions consisted of biking for 45 min with an intensity corresponding to 60–70% of VO2peak. All sessions began with a 10min warm-up and ended with a 10-min cooldown.	3	16 45	12	7
Nytrøen [30] RCT	2019	11 weeks	HIIT MCT	37 41	50 ± 12 48 ± 14	$VO2_{peak}$, HR_{peak}, VE/VCO2 slope, Muscle strength, FMD	**Outpatient – clinic - supervised.** **AT; HIIT:** 2- to 4-minute intervals at 85% to 95% of peak effort (85%–95% of peak HR or ≈81%–93% of Vo2peak - 16 to 18 on Borg scale). 3–6 months after HTx, training consisted of 1 HIT session, 1 resistance training session (core musculature and large muscle groups), and 1 combined session per week. From 6–9 months after HTx, 2 HIT sessions and 1 resistance training session per week. The last 2 to 3 months of the intervention consisted of 3 HIT sessions per week **AT; MCT-AE:** 60% to 80% of peak effort, regular core strengthening exercises, and exercises for large muscle groups	2-3	40	48	7
HOSPITAL VS. HOME-BASED											
Karapolat [38] RCT	2007	15 months	CT Hosp	15	45.27 ± 13.10	$VO2_{peak}$	**CT – Hospital - supervised**: Exercise sessions included flexibility exercises, aerobic exercises, strengthening exercises, breathing exercises, and relaxation exercises. 30 min of aerobic exercises on either a treadmill or a stationary bicycle at 60% to 70% of the maximal VO_2 and at a level of 13 to 15 on the Borg scale. After 2 weeks, strengthening exercises were added:	3	90	8	3

CT Home	13	35.61 ± 12.91	abdominal, upper limb, and lower limb muscle groups, using progressively heavier "light-weights", ranging from 250 to 500 g. In the end, all patients performed relaxation exercises according to the Jacobson technique of progressive muscle relaxation
			CT – Home-based – non-supervised: All exercises taught to group CT - Hosp patients were the same ones as those performed by the patients in CT – Home-based group. In addition, a walking program was performed.

Legends: HTx: Heart Transplantation; **AT**: Aerobic Training; **RT**: Resistance Training; **CT**: Combined Training; **CG**: Control Group; $VO_{2\ peak}$: peak oxygen uptake; HR_{peak}: peak heart rate; SBP_{peak}: peak systolic blood pressure; **VE/VCO₂ slope**: exercise ventilatory efficiency slope; **FMD:** Flow-mediated dilation; **HIIT**: High-intensity interval training**; MCT-AE:** moderate continuous training **HRmax**: Maximum Heart Rate; **RMT**: Respiratory Muscle Training; **RPC**: Respiratory Point Compensation; **RPE:** Rating of perceived exertion scale; **ACSM**: American college of sports medicine.

3.3 Exercise effects on peak oxygen consumption

Exercise training significantly improve $V'O_2$ peak considering all pooled data (9 studies, n=294 patients) with a mean difference [MD]=2.84, 95% CI: 2.10 to 3.58, ml·kg-1·min-1, $I^2 = 0\%$. However, greater $V'O_2$peak were found for isolated AE(6 studies, n=187 patients) MD=3.36, 95% CI: 2.29 to 4.44 ml·kg-1·min-1, I^2=0% than combined intervention (CT) (3 studies, n=107 patients) MD=2.37, 95% CI: 1.36 to 3.39 ml·kg·min-1, I^2=27% (Figure 2A) when compared to control group.

A greater $V'O_2$ peak increase were found for HIIT-AE (2 studies, n=75 patients), MD=4.43, 95% CI: 0.54 to 8.31 ml·kg·min-1, I^2=0%) than MCT-AE (4 studies, n=112 patients), MD=3.23, 95% CI: 1.94 to 4.52 ml·kg·min-1, I^2=0%, (Figure 2B) when both were compared to a control group. The HIIT superiority over MCT-AE was directly demonstrated when compared one versus another (2 studies, n=110 patients) with a mean difference MD=1,96, 95% CI: 0.99 to 2.93 ml.kg-1.min-1, I^2=0% (Figure 2C).

Figure 2 - Impact of exercise training on $V'O_2$ peak (mL/kg/min) in HTx (**A**) exercise versus the control group (**B**) moderate continuous training and high-intensity training versus the control group (**C**) moderate continuous training versus high-intensity interval training
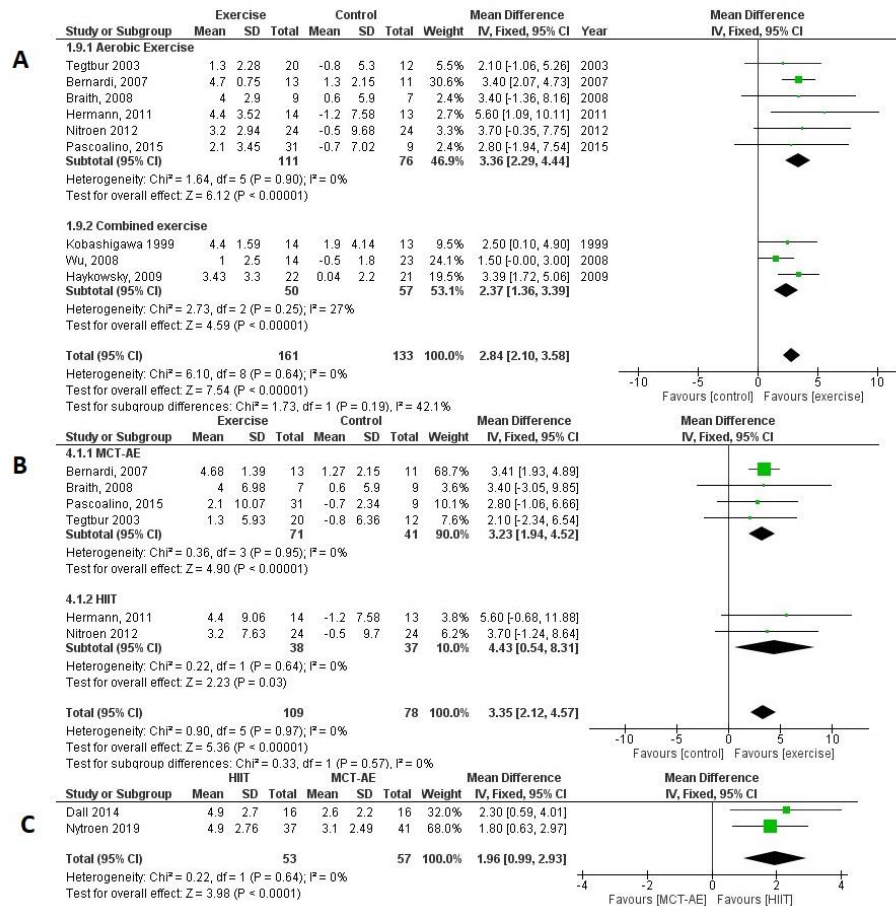
3.4 Exercise effects on peak heart rate

The analysis of peak heart rate was separated according to time post HTx: de novo and long therm. Comparing the pooled effect analysis of aerobic and combined training versus control group after long term post HTx ($\geq$ 1 year), jointly both training induced a slightly favourable effect in HR peak (4 studies, n=164 patients), MD=8.10, 95% CI: 1.98 to 14.22 bpm, I^2=87%, p=0,009, with no subgroup differences (p=0,12) -Figure 3.

Two studies have explored exercise versus control in de novo HTx (< 1 year) and both aerobic (159) and combined training (163) did not indicated improvement on HR peak. Two studies compared HIIT versus moderate continuous training in de novo (160) and long term (161) post HTx and the delta comparison indicated better results for HIIT only in long term post HTx (p=0,027) (161).

Figure 3 - Impact of exercise training on Heart Rate peak (bpm) in HTx (**A**) exercise versus the control group (**B**) moderate continuous training and high-intensity training versus the control group (**C**) moderate continuous training versus high-intensity interval training
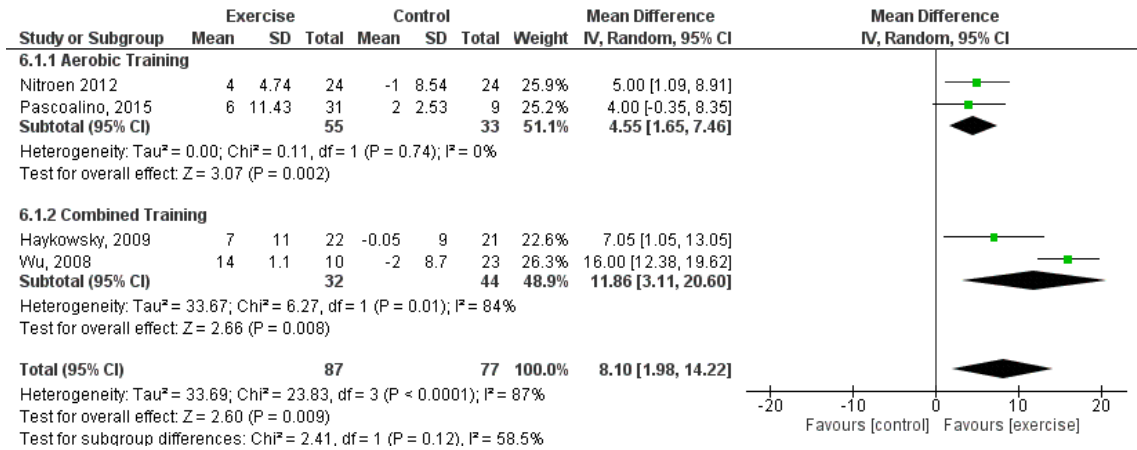
3.5 Exercise effects on peak systolic and diastolic blood pressure

Aerobic and combined exercise modalities comparison did not demonstrate changes in SBP peak post-HTx (4 studies, n=158 patients), MD=7.87, 95% CI: -18.64 to 34.39, mmHg, I^2=87% (Figure 4A) and DBP peak (3 studies, n=131), MD=-6,90, 95% CI: -14.81 to 1,02, mmHg, I^2=72%(Figure 4B) although the separated analysis demonstrated a superior effect on DBP peak reduction from the aerobic exercise compared with a control (2 studies, n=135), MD=-11.0, 95% CI: -16.03 to -5.97 mmHg, I^2=0% -Figure 4B.

Figure 4 - Impact of exercise training on blood pressure (mmHg) in HTx (**A**) exercise versus control group for systolic blood pressure (**B**) exercise versus control group for diastolic blood pressure
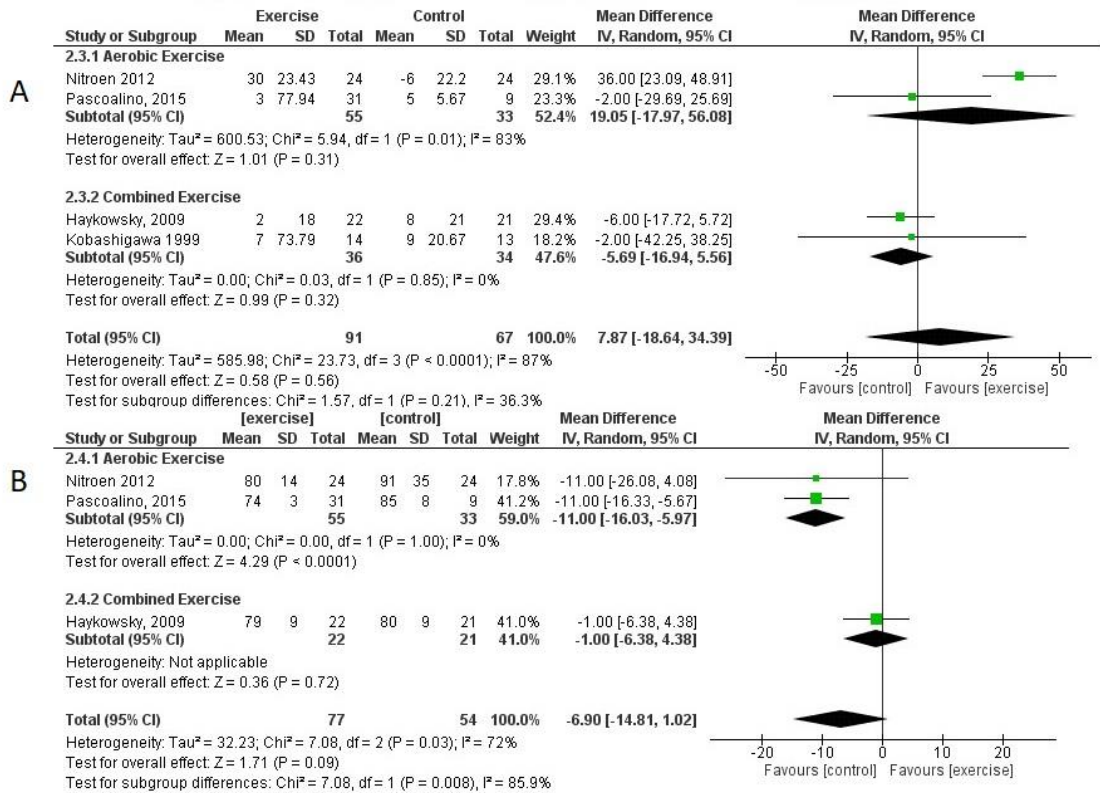
3.6 Exercise effects on VE/ V'CO$_2$ Slope

Only two studies had reported this outcome comparing exercise versus control group in HTx patients, both involving aerobic training(157,158). The exercise treatment did not demonstrate any difference on VE/V'CO$_2$ slope (2 studies, n=88 patients), MD=0.77, 95% CI: -0.18 to 1.72, $I^2 = 18\%$, p=0.11 -Figure 5. One study explored the comparison between HIIT vs moderate continuous training, not indicating any differences between them (n=78), MD=-1.6 (-5.2 to 2.0), p=0,375(160).

Figure 5 - Impact of exercise training on VE/V'CO$_2$ slope in HTx
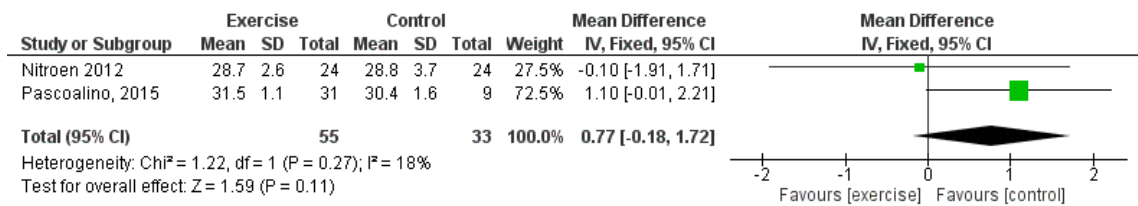
3.7 Exercise effects on flow-mediated dilation

Three studies compared the exercise treatment with control in HTx patients. Exercise training did not demonstrate positive effect on FMD (3 studies, n=86 patients), MD=3.48%, 95% CI: -0.29 to 7.25%, p=0.07). However, the studies presented a high heterogeneity (I^2=80%)-Fig 6. From those included studies, one study applied MCT-AE(155), one study applied CT(169), and one HIIT(156). Only HIIT(28) presented an expressive improvement in FMD. However, a subgroup analysis was not possible due to the small number of studies in each exercise modality. Nytroen 2019 compared HIIT vs moderate continuous training and did not indicated differences for this parameter between modalities (n=78), MD=-1.5 (-4 to 0.9), p=0.208(160).

Figure 6 - Impact of exercise training on flow-mediated dilation in HTx
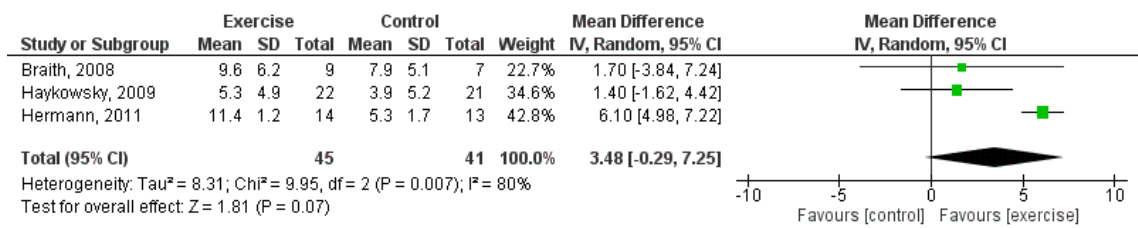
3.8. Exercise effects on muscle strength

Six studies analysed the exercise impact on muscle strength, but two were not included in the metanalysis forest plots due to different muscle strength assessments (Isokinetic and isotonic evaluations). Two studies evaluated the maximum repetition test (1RM) and two the sit-to-stand test. Isolated resistance training (RT) was associated with a significant improvement in the 1RM for both chest press and leg extension movements, MD =35.50Kg, 95% CI: 19.42 to 51.59, I^2=70, p<0.0001) (Figure 7A) while the other two studies involving combined training showed increases on the sit-to-stand test, MD: 5.54, 95% CI 3.07 to 8.01; I^2=0% (Figure 7B). Isokinetic and isotonic evaluations not included in the metanalysis forest plots, also suggested an increase in muscle strength after CT and AT, respectively(157,164).

Figure 7 - Impact of resistance training on muscle strength in HTx (**A**) 1 maximum repetition test (**B**) sit-to-stand

test
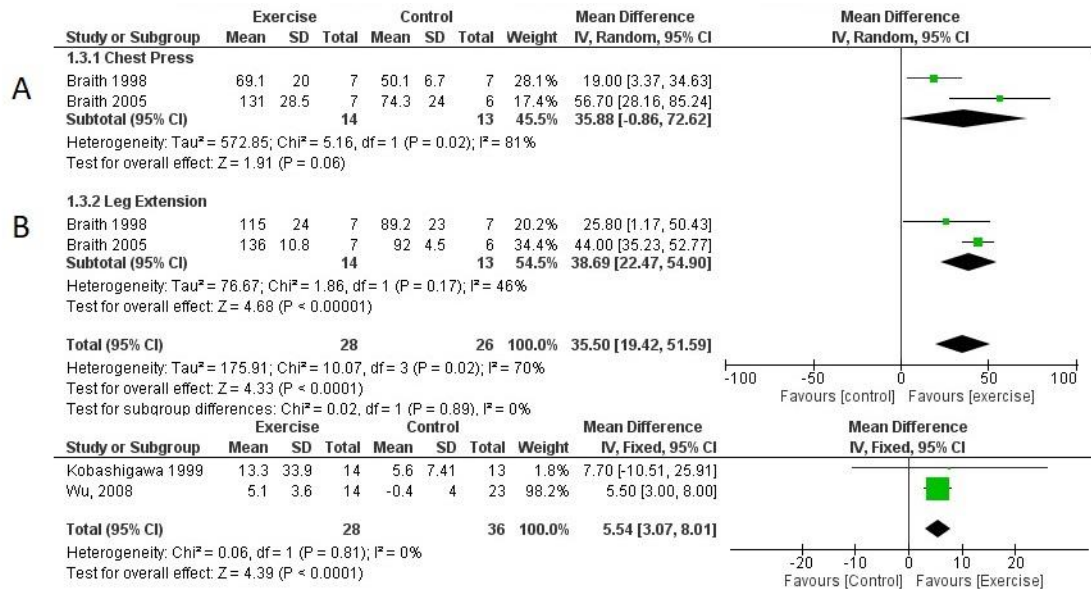
3.9. Quality of the trials, Risk of bias assessment and Summary of Findings Table with quality of evidence.

In general, the risk of bias was lower for the domains *missing outcome data* and *selecting the reported result* as illustrated on Fig 8. The correspondent frame can be seen in the Electronic Supplementary Material 2.

The quality of the trials assessed by Pedro and the risk of bias verified by the Rob2 tool jointly gave detailed information on the studies' truthfulness and internal validity in which the highest scores indicated by Pedro scale did not coincide with the lowest risk of bias identified via the Rob2 tool on this manuscript.

igure 8 - Risk of bias of the included studies

Study	Experimental	Comparator	Outcome	D1	D2	D3	D4	D5	Overall
THE PER-PROTOCOL EFFECT									
Bernardi 2007	MCT-AE	Control Group	VO2 peak	+	?	+	+	?	!
Rustad 2014	HIIT	Control Group	VO2 peak	+	+	+	?	+	−
Rustad 2014	HIIT	Control Group	HR peak	+	?	+	?	+	!
Nitroen 2012	HIIT	Control Group	VO2 peak	+	+	+	?	+	!
Nitroen 2012	HIIT	Control group	HR peak	+	+	+	?	+	!
Nitroen 2012	HIIT	Control Group	Peak SBP	?	+	+	−	+	−
Nitroen 2012	HIIT	Control Group	Peak DBP	?	+	+	+	?	!
Nitroen 2012	HIIT	Control Group	VE/VCO2 slope	?	+	+	+	+	!
Monk-Hansen 2015	HIIT	Control Group	VO2 peak	+	−	+	?	+	−
Monk-Hansen 2015	HIIT	Control Group	HR peak	+	−	+	?	+	−
Pascoalino 2015	MCT-AE	Control Group	VO2 peak	?	?	+	?	+	!
Pascoalino 2015	MCT-AE	Control Group	VE/VCO2 slope	?	?	+	?	+	!
Pascoalino 2015	MCT-AE	Control Group	SBP max	?	?	+	?	+	!
Pascoalino 2015	MCT-AE	Control Group	DBP max	?	?	+	?	+	!
Pascoalino 2015	MCT-AE	Control Group	HR peak	?	?	+	+	+	!
Hermann 2011	HIIT	Control Group	VO2 peak	+	?	+	?	+	!
Hermann 2011	HIIT	Control Group	FMD	?	+	+	+	+	!
Haykowsky 2009	Combined Training	Control group	VO2 peak	?	+	+	?	+	!
Haykowsky 2009	Combined Training	Control Group	HR peak	+	+	+	?	+	!
Haykowsky 2009	Combined Training	Control Group	Peak SBP	?	+	+	+	+	!
Haykowsky 2009	Combined Training	Control Group	Peak DBP	?	+	+	+	+	!
Haykowsky 2009	Combined Training	Control Group	FMD	?	?	+	+	+	!
Braith 2008	MCT-AE	Control Group	peak VO2	?	+	+	?	+	!
Braith 2008	MCT-AE	Control Group	FMD	?	+	+	+	+	!
Kobashigawa 1999	Combined Training	Control group	VO2 peak	−	+	+	?	+	−
Kobashigawa 1999	Combined Training	Control group	VE/VCO2 slope	−	+	+	?	+	−
Kobashigawa 1999	Combined Training	Control group	HR peak	−	+	+	?	+	−
Kobashigawa 1999	Combined Training	Control group	sit-to-stand	−	+	+	?	+	−
Kobashigawa 1999	Exercise Training	Control group	Peak SBP	−	+	+	?	+	−
Braith 1998	Resistance Training	Control	1RM	+	+	+	+	+	!
Braith 2005	Resistance Training	Control	1RM	?	+	+	+	?	!
Dall 2014	HIIT	MCT-AE	VO2 peak	+	+	+	+	?	!
Dall 2014	HIIT	MCT-AE	HR peak	+	+	+	+	?	!
Nytroen 2019	HIIT	MCT-AE	VO2 peak	?	+	+	?	?	!
Nytroen 2019	HIIT	MCT-AE	HR peak	?	+	+	?	?	!

Study ID	Experimental	Comparator	Outcome	D1	D2	D3	D4	D5	Overall
THE INTENTION-TO-TREAT EFFECT									
Wu 2008	Combined Training	Control Group	VO2 peak	?	+	+	+	?	!
Wu 2008	Combined Training	Control Group	HR peak	?	+	+	+	?	!
Wu 2008	Combined Training	Control Group	sit-to-stand	?	+	+	+	?	!

Legend:
- + Low risk
- ? Some concerns
- − High risk

- D1 Randomisation process
- D2 Deviations from the intended interventions
- D3 Missing outcome data
- D4 Measurement of the outcome
- D5 Selection of the reported result

3.10 Summary of Findings Table with quality of evidence

The summary of the quality check from the included studies is described in Figure 9 for exercise interventions versus control group. In Figure 10 it is described the comparison between HIIT and MCT-AE.

The certainty of the evidence differed across the outcomes ranging from very low to high. We noticed that 50% of the outcomes for exercise interventions versus the control group presented very low certainty of the evidence (FMD, VE/ V'CO2 slope, peak SBP, peak DBP, and peak HR), 20% low (1 RM and sit-to-stand test), 20% moderate (V′O2 peak for all training modalities jointly and V′O2 peak for isolated aerobic training modality) and 10% high certainty

of evidence (VʹO2 peak only for combined training modality). The two studies demonstrated in the comparison between HIIT versus MCT-AE, VʹO2 peak, and peak HR presented moderate certainty.

Figure 9 - Summary of findings and certainty of the evidence for exercise versus no intervention control group in HTx

Author(s):
Question:
Setting: Exercise training compared to Control after Heart Transplantation
Bibliography: Turri Silva et al, 2020

Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Exercise	Control	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
FMD (%)												
3	randomised trials	not serious	very serious ᵃ	serious ᵇ	serious ᶜ	none	38	36	-	MD 3.48 higher (0.29 lower to 7.25 higher)	⊕◯◯◯ VERY LOW	
Ventilatory Equivalent slope (VE/VCO2)												
3	randomised trials	serious ᵈ	serious ᵉ	serious ᶠ	very serious ᵍ	none	55	33	-	MD 0.77 higher (0.18 lower to 1.72 higher)	⊕◯◯◯ VERY LOW	
Oxygen Uptake (VO2 peak)												
11	randomised trials	serious ʰ	not serious	not serious ⁱ	not serious ʲ	none	204	161	-	MD 2.88 higher (2.15 higher to 3.61 higher)	⊕⊕⊕◯ MODERATE	
Oxygen Uptake (VO2 peak) - Aerobic Exercise												
8	randomised trials	serious ʰ	not serious	not serious	not serious ʲ	none	148	112	-	MD 3.44 higher (2.39 higher to 4.49 higher)	⊕⊕⊕◯ MODERATE	
Oxygen Uptake (VO2 peak) - Combined exercise												
3	randomised trials	not serious	not serious	not serious	not serious ʲ	none	58	49	-	MD 2.36 higher (1.35 higher to 3.37 higher)	⊕⊕⊕⊕ HIGH	
Peak Systolic Blood Pressure (mmHg)												
4	randomised trials	not serious	very serious ᵃ	serious ᵏ	very serious ˡ	none	91	67	-	MD 7.87 higher (18.64 lower to 34.39 higher)	⊕◯◯◯ VERY LOW	
Peak Heart Rate												
8	randomised trials	serious ᵐ	very serious ᵃ	not serious	serious ⁿ	none	141	120	-	MD 5.41 higher (0.19 higher to 10.63 higher)	⊕◯◯◯ VERY LOW	
Maximum Repetition (1 RM)												
2	randomised trials	not serious	serious ᵒ	not serious	serious ᵖ	none	28	26	-	MD 35.5 higher (19.42 higher to 51.59 higher)	⊕⊕◯◯ LOW	
Sit-to-stand Test												
2	randomised trials	not serious	serious ᵒ	not serious	serious ᵖ	none	28	36	-	MD 5.54 higher (3.07 higher to 8.01 higher)	⊕⊕◯◯ LOW	
Peak Diastolic Blood Pressure (mmHg)												
3	randomised trials	not serious	very serious ᵃ	not serious	serious ᶠ	none	79	56	-	MD 6.9 lower (14.81 lower to 1.02 higher)	⊕◯◯◯ VERY LOW	

CI: Confidence interval; MD: Mean difference

Explanations

a. All criteria for inconsistency were violated. The authors believe it can be influenced by different exercise prescriptions (modalities and training intensities).
b. Indirectness can be related to differences in intervention, population or outcomes measurements. Along those 3 included stuies, Braith 2007 applied aerobic training with moderate intensity, Haykowsky 2009 applied combined training (AER+RES) and Hermann 2011 applied HIIT modality. However, there were no relevant variations regarding the assessments and matched population that could have influenced the external validity.
c. Considering not dicotomic outcomes, all data from imprecision were based on confidence interval and sample size. Braith, 2008 and Haykowsky, 2009 presented both positive and negative results (crossed neutral line). Furthermore, considering the small general sample size the authors rate down for imprecision.
d. Uncial randomization and allocation concealed procedure for Bernardi, 2007. Also, although a detailed description of randomization procedure in Pascoalino, 2014, there is a big difference in relation to sample size in between intervention group and control group. Considering these limitations the authors believe there is a serious limitation for VE/VCO2 evidence.
e. Although low heterogeneity, points estimates varied widely across the 2 included studies and showed minimal overlap.
f. Indirectness can be related to differences in intervention. Just 2 studies were included for this outcome and they varied regarding the intervention duration, Nitroen 2012 did the double time of intervention than Pascoalino 2014 (24 vs 12 weeks, respectively). Also, Nitroen 2012 applied HIIT intervention, while Pascoalino 2014 used aerobic moderate intensity.
g. Considering not dicotomic outcomes, all data from imprecision were based on confidence interval and sample size. Considering just 2 studies included the outcome VE/VCO2 slope presenting wide variation on their confidence interval with positive and negative results, the authors rate down for imprecision
h. There are 3 studies considering with serious risk of bias and 1 study with very serious risk of bias. All them without a clear randomization procedure and allocation concealed (Pierce, 2007; Pascoalino, 2014; Braith, 2007; Bernardi, 2007; Tegtbur, 2003). However, Pierce, 2007 and Braith, 2007 presented a big loss of follow up (> or equal 20%). There was no bliding, even for statistic analysis in all papers included. The other included studies presented nor serious risk of bias (Haykowsky, 2009, Kobashigawa, 1999, Monk-Hansen, 2013, Rustad, 2014, Nytroen, 2012, Hermann, 2011).
i. Indirectness can be related to differences in intervention, in outcomes or population. Even considering differences in training modalities, (both aerobic and combined training included), training intensities (HIIT and moderate intensity) and some differences in regards the cardiopulmonary exercise testing methodology, the authors believe there is no reason to rate down for indirectness. This is because none of those criteria were able to affect the overall comparison for VO2 peak.
j. Considering not dicotomic outcomes, all data from imprecision were based on confidence intervals and sample size. Even considering the variations on confidence intervals for some studies, the authors did not consider it important for the main result.
k. Indirectness can be related to differences in intervention. Among the 4 included studies, 2 applied aerobic intervention (Nitroen 2012, Pascoalino 2015), while 2 applied combined intervention, resistance and aerobic exercises (Haykowsky, 2009 and Kobashigawa, 1999), however, since it is already included as subgroup analysis the authors decided not rate down for variation, but considering the differences in aerobic interventions (HIIT and moderate continuous training, Nitroen, 2012 and Pascoalino, 2015, respectively), the authors rate down for indirectness.
l. Considering not dicotomic outcomes, all data from imprecision were based on confidence intervals. Excepting Nitroen, 2012, all studies included included negative values in their confidence interval.
m. There was 1 study included with high risk of bias due to unclear randomization and allocation concealed procedure further 30% of loss to followup (Pierce, 2007). Also, Wu, 2008 and Pascoalino,2014 scored as serious risk of bias also due to unclear randomization and allocation concealed procedure. No blinding were considered for data analysis in any study. The authors judged Kobashigawa, 1999, Haykowsky, 2009, Monk-Hansen, 2013, Nytroen, 2012 and Rustad, 2014 as no serious risk of bias.
n. All data from imprecision were based on confidence interval and sample size. Considering 4 of the included studies crossed the neutral line and 3 did not crossed it, the authors decided to classify imprecision as serious.
o. Although points estimates did not vary widely across studies and has showed overlap, the authors rated down for inconsistency due to high heterogeneity.
p. All data from imprecision were based on confidence interval and sample size. The main concern for this outcome is the general low sample size. Also, although Wu, 2008 indicated no problems regarding confidence interval, Kobashigawa 1999 presented results in both directions of the forest plot.
q. Considering only two studies were included for this outcome and the poin estimates vary widely across them, the authors rated down for inconsistency.
r. All studies presented positive and negative values in theis minimum and maximum confidence interval.

Figure 10 - Summary of findings and certainty of the evidence for high-intensity interval training versus moderate continuous training in HTx

The summary findings table demonstrated a high level of certainty of the evidence was achieved for the outcome V′O2 peak compared to combined training (aerobic + resistance training) versus no intervention control group. However, the reduced sample (slightly higher than 100 patients) from only 3 randomized trials showed few differences between them. Therefore, a mean increase of 2,37 mL.kg.min after combined training can be considered reliable for patients after HTx above 19 years old.

A moderate level of evidence was reached by considering the outcome V′O2 peak for joint aerobic training and combined training or isolated aerobic training versus the control group. The same occurred for the comparison between HIIT versus MCT-AE for V′O2 peak and peak HR. All of them had in common the presence of only one factor of certainty assessment. By comparing all exercise modalities or isolated aerobic training versus control group, the certainty assessment risk of bias was rated down due to failures on randomization and allocation concealment, while the indirectness aspect was the only one severely affected in the comparison between HIIT and MCT-AE, mainly due to different training prescriptions on HIIT.

All outcomes that reached a very low level of certainty of evidence (FMD, VE/ V'CO2 slope, peak SBP, peak DBP, and peak HR) had usually presented a serious or very serious inconsistency and imprecision. Inconsistency was related to a wide variation among numerical values from outcome results and high heterogeneity. Simultaneously, imprecision was based on confidence interval (differences in the upper versus the lower boundary of the CI and if CI was around the absolute effect) and optimal information size criteria which revealed limitations as described in the footnote of Figures 9 and 10.

4.   Discussion

The novelty of this meta-analysis is the analysis of different exercise modalities and intensities in clinical outcomes related to cardiorespiratory capacity after HTx, strengthening the pivotal understanding about exercise training prescription as a treatment approach in the clinical practice. A superior effect of aerobic training to improve $V'O_2$ peak in HTx patients was demonstrated with moderate level of certainty of evidence. Interesting, high-intensity interval training(HIIT) demonstrated higher effect on the $V'O_2$ peak than moderate continuous training(MCT-AE) with no adverse effect(160,161).

The certainty assessment revealed that indirectness influenced the level of evidence in the comparison between HIIT and MCT-AE, which is justified by different training prescription among aerobic modalities. We recognize the challenge of having the same prescription in between paper protocols. However, a promissory future would be to verify possible differences between HIIT prescriptions in HTx. Additionally, larger randomized controlled trials comparing HIIT versus MCT-AE are recommended, mainly for the outcomes $V'O2$ peak and peak HR.

In relation to the outcome muscle strength, although the low level of certainty of evidence, resistance exercise training (RT) indicated improvements on this. The skeletal muscle weakness, vasodilatory capacity impairment, and muscle capillary density reduction are the main peripheral factors related to exercise capacity reductions after HTx and partially explain the $V'O_2$ peak impairment(171). Nytrøen et al. pointed the association between muscular deconditioning and $V'O_2$peak reduction(157), recognizing the peripheral limitations in HTx patients. Peripheral adaptation such as mitochondrial volume density, oxidative enzyme capacity, and the percentage of type 1 muscle fibers distribution increase, are associated with the cardiorespiratory capacity increase(67,166,172). These results indicate RT, isolated, or in combination with AT, increase muscle strength and attenuate $V'O_2$ peak impairment post-HTx.

There was no evidence that exercise affect DBP and SBP peak in HTx(157,158,163) and like HR peak, all indicated very low level of certainty of evidence. HR peak increased after all training modalities, especially after AE. Compared to MCT-AE, a higher increase in HR peak occurred after HIIT with a moderate level of certainty of evidence. However, the magnitude seems not equivalent to the exercise capacity improvement (140,173,174), possibly due to the chronotropic incompetence(154,175). Autonomic nervous system improvement may explains it (154,174,175). The average increase of SBP peak should be 50% of the resting value

and an insufficient increase has been associated with left ventricular systolic dysfunction(176). Nevertheless, the relationship between SBP response and $V'O_2$ peak is still unclear.

Absence of improvements after CT(163), HIIT(157,177), or MCT-AE(178) on LV end-diastolic or end-systolic volume, stroke volume, or ejection fraction after HTx (67) contributes to the rational that the improvements in peak $V'O_2$ seem not only related to central (cardiac) adaptations (67).

A healthy endothelium function positively impacts exercise-induced vasodilation capacity, an essential part of the maintenance of adequate $V'O_2$ during exercise. FMD increase positively influence $V'O_2$ peak in healthy individuals (179–181), coronary heart disease, hypertension, and heart failure(182–185). Inversely, endothelial dysfunction is associated with plaque progression and a lower peak $V'O_2$ post-HTx(186,187).

Exercise training was not associated with FMD benefits (156,169,188) (very low level of certainty of the evidence), but an expressive improvement was when HIIT was compared to a control group (156). More studies are needed, but recognizing that endothelial dysfunction predicts cardiac allograft vasculopathy(145), HIIT seems a promising approach post-HTx. The unique study that compared HIIT vs moderate continuous training did not indicated differences between those modalities, although statistical difference was seen only within HIIT group. Although an endothelial function recovery occurs post HTx (189), peripheral endothelial dysfunction remains after 1 to 13 years(190). The primary mechanism of the endothelial dysfunction post-HTx relates to cyclosporin therapy (67,189). Exercise training can counteract it by enhancing nitric oxide (NO) production (179,180).

According to the two included studies and with a very low level of the evidence, there is no effect on VE/V'CO$_2$ slope after exercise training post-HTx when compared to a control group. Nytroen, 2019 when compared HIIT vs moderate continuous training also did not revealed any difference between modalities(160). VE/V'CO$_2$ slope is a strong independent predictor of mortality in HF patients(191) more accurate than the current listing criteria based on the $V'O_2$ peak for HTx. Positive association between VE/V'CO$_2$ slope reduction and functional capacity improvement was identified in 40% of the patients post-HTx, even five years later(192). VE/V'CO$_2$ slope increase has been associated with peripheral factors, such as muscle deconditioning, peripheral oxygen transport problems and type IIb-muscle-fiber increased, leading to a primary lactic acidosis during exercise demanding high ventilatory

re(192)sponse(192). In our meta-analysis, only aerobic training (157)(158) explored VE/V'CO$_2$ slope post-HTx.

Future trials in this field should consider improving study quality and reducing the risk of bias to provide accurate information about this underrepresented population. Also, randomized trials involving more than 100 HTx can contribute to improve discrepancies among studies and increase reliability.

Study Limitations

The small number of studies available and the low level of certainty of evidence from many outcomes is the major limitation of this systematic review with meta-analysis. Additionally, the lack of studies reporting comparison between modalities has limited the results of exercise training post HTx. More research is required, mainly for the outcomes VE/V'CO$_2$ slope and FMD. However, this review is important to demonstrate the state of the art on training prescription in HTx, revealing the need for new clinical trials with higher quality.

5.   Conclusions

This metanalysis revealed that scientific literature is seeking for high quality studies on exercise prescription field in HTx. From the 13 studies included on this metanalysis, aerobic training modality is current the best to be applied after HTx. From this modality, high-intensity interval training showed the biggest effect on peak oxygen consumption. In another side, isolated resistance training or combined training can improve muscle strength. The clinical meaning from this study indicated that although both training modalities can improve health status in patients post HTx, aerobic modality promotes more benefits on prognosis. More studies are needed, specially reporting resistance training modality and intensities comparison. Also, studies examining the impact of training modalities on VE/V'CO2 slope and FMD are required.

Declarations

Consent for publication

The authors declare consent for publication.

Availability of data and material data transparency

The authors confirm that the data supporting the findings were truly extracted from the included studies. The datasets analysed during the current study are available from the corresponding author on reasonable request.

Author's contribution

WCCR, JSF, NTS, and GCJ contributed substantially to the conception and design of the study; NTS, FVS, WCCR, and JSF contributed substantially to the acquisition of data; NTS, FVS, and GCJ contributed substantially to the analysis and interpretation; KV and GCJ provided a double-check analysis for Rob2 and Grade score; NTS, FVS, KV, LCC, JLQD, DH, and GCJ drafted or provided critical revision of the article; GCJ and DH provided final approval of the version of the review.

Disclosure Section

All authors from this manuscript have no conflicts of interest or financial ties to disclose.

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Captions

Figure 1 PRISMA Flowchart of the procedures for the selection of articles inserted in the final analysis

Table 1 Description of studies included in the systematic review

Figure 2 - Impact of exercise training on $V'O_2$ peak (mL/kg/min) in HTx (**A**) exercise versus the control group (**B**) moderate continuous training and high-intensity training versus the control group (**C**) moderate continuous training versus high-intensity interval training

Figure 3 - Impact of exercise training on Heart Rate peak (bpm) in HTx (**A**) exercise versus the control group (**B**) moderate continuous training and high-intensity training versus the control group (**C**) moderate continuous training versus high-intensity interval training

Figure 4 - Impact of exercise training on blood pressure (mmHg) in HTx (**A**) exercise versus control group for systolic blood pressure (**B**) exercise versus control group for diastolic blood pressure

Figure 5 - Impact of exercise training on VE/V'CO$_2$ slope in HTx

Figure 6 - Impact of exercise training on flow-mediated dilation in HTx

Chapter 5

General discussion and conclusions

Taken together all the paper's information, it was explored the link between heart failure and heart transplantation population with exercise intolerance, revealing novel understanding and insights in this field. The vascular aspects, scientifically under-explored on this population, mainly when considering the exercise stimulus scenario (acute or after exercise training), were the main protagonists in the transversal study (chapter 2). However, in the two others (chapters 3 and 4), the results on this aspect were not as promissory as expected.

The novelty of the acute study (chapter 2) reinforced the pivotal role of the muscular system in the exercise intolerance of patients with heart failure, revealing the vascular oxygenation contribution as a mechanism involved to exercise intolerance in HF phenotypes. The paper showed a worst peripheral muscle microcirculatory dynamic in HFpEF patients in Weber class C than Weber A+B, i.e., in those patients more severely affected. The same situation occurred in HFrEF. Patients classified as Weber C also presented the worst muscle microcirculatory dynamic than Weber A+B, indicating the take-home message: "worst HF severity, worst microcirculatory dynamic." Intriguing, when comparing HFrEF and HFpEF, independently of severity, there was no difference in microcirculatory dynamic.

Why did such microcirculatory dynamic differences not appear when only focusing on HF phenotypes? Maybe the younger age of the patients included in this study contributed since, in general aspects, patients with HFpEF are used to being older than 60 years old, even considering that in South America, there are more young HFpEF patients(193)(Figure 9).
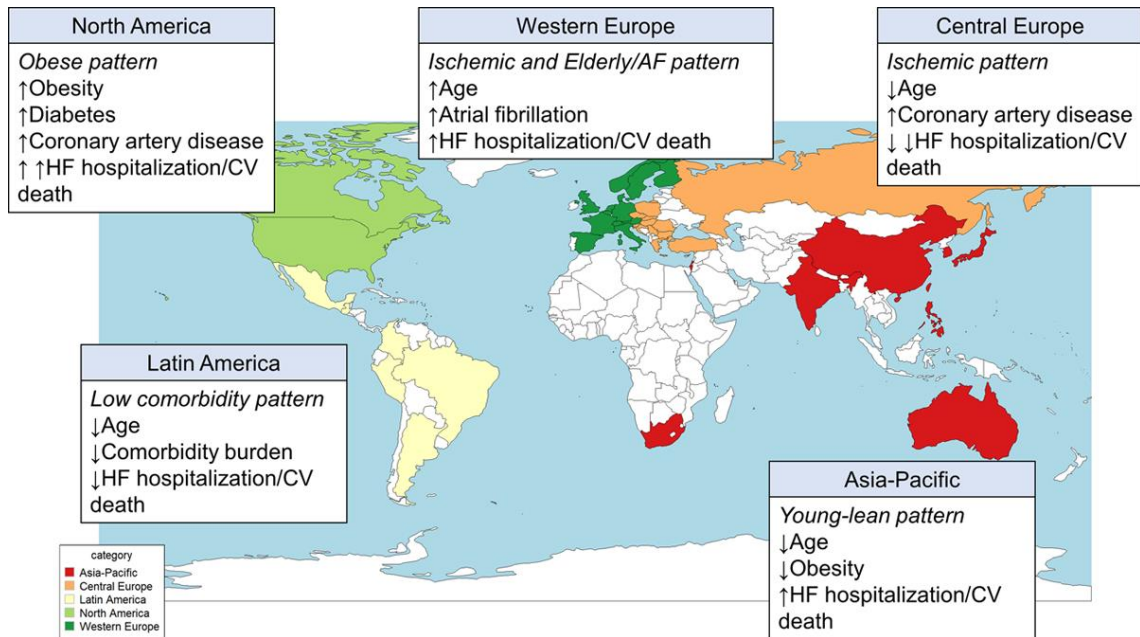
Fig 9. Global Differences in Heart Failure With Preserved Ejection Fraction. Reprinted with permission from the Paragon trial(193).

Another important point from the acute study was the absence of muscular strength difference between phenotypes when comparing isokinetic muscle strength. However, when comparing endurance muscle strength, as indicated by the parameter peak power output from CPET, HFpEF showed higher values than HFrEF. Interestingly, although the different peak power output, a similar VO2 peak was verified between phenotypes, revealing a similar cardiorespiratory performance.

Extra information not contained in this paper (chapter 2) but that can contribute to the interpretation of the findings is the association between muscle strength and cardiorespiratory capacity. By analyzing correlations of muscle strength (regardless of the type, i.e., muscular endurance or power) with VO2 peak, both phenotypes indicated a linear association between these variables (Figure 10). As muscular power (isokinetic torque peak, more type II fiber requested) as muscular endurance (cycling peak power output, more type I fiber requested) demonstrated importance when considering the gold standard parameter for HF prognosis (VO2 peak). It means that, although the known muscle type shift in HF, from type I to type II in both phenotypes (less oxidative metabolism present), it does not seem to be always the only decisive factor influencing exercise intolerance. However, it is essential to consider that the severity

distribution in between groups may have affected this endpoint in such patients.
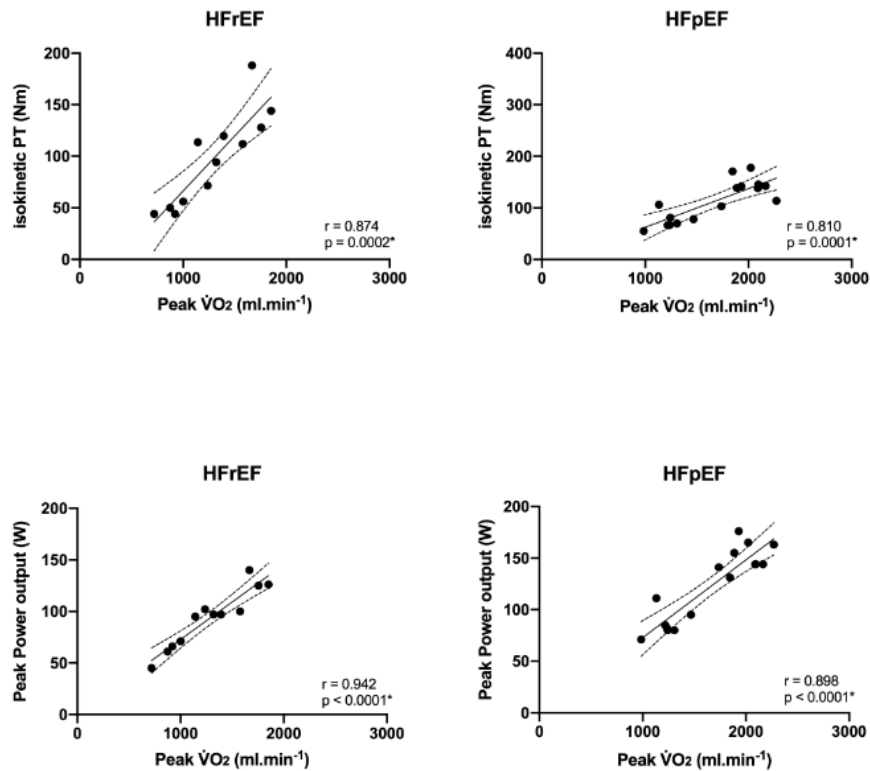
Fig 10. Association in between muscle strength and cardiorespiratory capacity.

In terms of muscle quality, this study (chapter 2) indicated the worst muscle quality in HFpEF - Weber C patients than those more severely affected in HFrEF. Attractive such worst muscle quality, was associated with the worst VO2 peak only in HFpEF patients classified as Weber C. Moreover, although muscular aspects were highlighted in chapter 2, muscle strength and ultrasound-derived thickness were not different between phenotypes nor between severities. However, a worse muscle quality was negatively associated with cardiorespiratory fitness in the same phenotype.

Hence, the preliminary findings suggested that peripheral muscle microcirculation dynamics can affect a strength-type exercise, like an aerobic-type exercise (194), in HFpEF reinforcing the scientific theory that exercise intolerance in HFpEF seems to be related to muscular microvascular dynamic, regardless the exercise modality.

Moving to chapter 3, first, we faced great difficulty in recruiting patients with heart failure in the central-western region in Brazil to develop this study. Therefore, unfortunately, it was not possible to address in such interventional study differences in between HF phenotypes in experimental clinical practice. Since the beginning of this doctorate trajectory, the primary

purpose and interest of Natalia Turri-Silva were to contribute to the exercise prescription area for patients with heart failure, checking how exercise prescription could affect exercise intolerance through a clinical approach. From the many opportunities about how to address such a topic, I choose the high-intensity field. By that time, guidelines worldwide did not include HIIT, and all its knowledge was growing. However, less attention was being given to resistance training modality. Some questions appeared: Do high-intensity protocols be positive in heart failure patients regardless of the exercise modality? Is there superiority between modalities, or are they similar in terms of benefits on exercise intolerance and other factors related to this aspect? Do high-intensity protocols influence the vascular dynamic regardless of the training modality?

Trying to answer such questions, we made the design of the second paper (chapter 3). This preliminary study showed the benefits of both high-intensity training modalities, aerobic and circuit-resistance training. However, regarding exercise intolerance benefits, HIIT seems to be a better approach for this population than high-intensity circuit-resistance training when applied to patients with NYHA 1 and 2, younger than 60 years old. The HIIT modality jointly improved cardiorespiratory capacity and muscle strength, both considering essential prognostic factors in HF. In addition, this modality was also able to provide benefits on functionality.

The third main paper of this thesis (chapter 4) was a systematic review with a metanalysis about exercise prescription in heart failure patients after heart transplantation. This review uncovered the clinical relevance and demand for a pooled and systemic analysis of the clinical studies utilizing exercise as a treatment intervention in the heart transplantation HTx population. The thirteen studies included in this systematic review demonstrate that aerobic training is currently the best modality after HTx, with a more significant impact on peak oxygen consumption arousing from high-intensity interval training (HIIT). Alternatively, both isolated resistance training and combined training improved muscle strength, a relevant clinical outcome. This first systematic review with meta-analysis provided:

Broader information regarding exercise use in HTx.

Affecting well-established outcome measures related to health status and quality of life.

Confirming the clinical meaning of the study.

Further clinical trials in the HTx field are needed to adjust the expected results, particularly addressing different resistance training modalities and aerobic intensities. Also, studies examining the impact of training modalities in other critical clinical outcomes measures (e.g.,

VE/V'CO2 slope and FMD) are required. Anyway, such new gaps could only be identified due to this study, opening readers' eyes to a new perspective in the field.

CONCLUSION: JOINTLY TAKE-HOME MESSAGE

- Microcirculatory dynamics demonstrated to be more impaired in heart failure with preserved ejection fraction and VO2 lower than 10 ml.kg.min (Weber C)
- Preliminary findings revealed that high exercise training intensities could reduce exercise intolerance in heart failure patients regardless of the training modality.
- Preliminary findings revealed that HIIT seems to be the best strategy to treat exercise intolerance in HF NYHA 1 and 2 compared to high intensity-circuit resistance training.
- HIIT current seems the best training modality to reduce exercise intolerance in HTx, regardless of the time post-transplantation

PhD TRAJECTORY

To make readers aware about how this PhD trajectory happened, this section explains the time frame events along the PhD.

This is the first Joint PhD (cotutelle) from "Programa de Pós-Graduação em Ciências e Tecnologias em Saúde da Universidade de Brasília".

Everything started during the clinical research conducted in Faculty of Ceilandia with heart failure individuals. This clinical research is described on chapter 3 of this thesis. By that time, this study was one center randomized controlled trial. Along its execution it become clear that it would not be possible to have an adequate sample size in Brasilia, since Faculty of Ceilandia did not have any formal partnership with hospitals. All Brazilian patients who included in the studies were indicated by physicians from public and private clinics from Federal District who have previous close relations to Professor Gerson (Brazilian promoter). Other patients came from Television announcement call. Also, the PhD candidate visited some hospitals in Brasilia, however this initiative was not enough.

To overcome the sample size limitation, the PhD candidate sent some emails to researchers around the globe who could be potentially interested to the project design. The proposal was to run the same study in a different center, and so, increasing the heart rate sample size.

One of the international partners was coming to the biggest Brazilian Congress in Cardiovascular area (Simpósio Internacional de Fisioterapia Cardiorrespiratória e Fisioterapia em Terapia Intensiva) and there the opportunity of a partnership came out. From that moment, by searching on partner institution's website the term "joint PhD" was found. Joint PhD means 2 PhD at the same time by following an agreement in between universities.

The term joint PhD was not included in the University of Brasilia website. Instead of "joint PhD" UnB apply the term "cotutelle". Firstly, it is important for those interested on follow this kind of accordance, to search in the partner university the terms and conditions. It is pivotal that, before the PhD candidate apply for it, a formal partnership in between universities involved happen.

At University of Brasilia, the department responsible for the international accordance's is called INT. They can provide information regarding the process. The total duration from the initial tasks for a joint PhD until the formal acceptance can take 1 year. As early as possible start the joint PhD/cotutelle steps, better it is. My personal recommendation is to start planning it from the first year.

Joint PhD candidates must follow the PhD requirements from both institutions. Promoters from both institutions together with the PhD candidate and PhD programs jointly decide the pathways. At the end of the accordance journey, promoters, copromoters, coordinators from both universities and rectors must sign (on person) the same documentation. In Brazil, after this step happen, this will be published in the "Diário Oficial da União".

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APPENDIX

Supplementaru figures and files from Chapter 3

S1 file. Consort checklist

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1, 2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3,4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	9, 10, 11, 12
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6, 7, 8, 9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Sample size	7a	How sample size was determined	12
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	5
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	5
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	5
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	7

CONSORT 2010 checklist   Page 1

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	n/a
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	12, 13
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	n/a
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Flow diagram
	13b	For each group, losses and exclusions after randomisation, together with reasons	Flow diagram
Recruitment	14a	Dates defining the periods of recruitment and follow-up	13
	14b	Why the trial ended or was stopped	limitations
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Table 1
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	All tables
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	n/a
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	n/a
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	n/a
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	18
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	18
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	16, 17, 18
Other information			
Registration	23	Registration number and name of trial registry	6
Protocol	24	Where the full trial protocol can be accessed, if available	n/a
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	tittle page

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

CONSORT 2010 checklist   Page 2

S2 file. Study protocol (in a separate doc file)

Doctoral Research Project

COMPARISON OF HIGH-INTENSITY VS. AEROBIC TRAINING TRAINNING VERSUSCIRCUIT RESISTANCE TRAINING ON ENDOTHELIAL FUNCTION AND THE OXYGEN KINETIC IN HEART FAILURE : a randomized controlled trial

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University of Brasilia - UnB , Faculty of Ceilândia - FCE . Project presented to the Graduate Program in Science and Technology in Saúde.Área concentration: Promotion, Prevention and Intervention in Saúde.Linha Research: Health, Functionality, Occupation and Cuidado.Temática : Clinical Exercise Physiology.

Advisor: Prof. Dr. Gerson Cipriano Júnior

Brasilia, December 2017

ABSTRACT

INTRODUCTION : Individuals with heart failure (HF) have dyspnea and fatigue, symptoms that decrease exercise tolerance and functional physical performance. Among the modalities of trainingphysical that can contribute to this framework, the aerobic training high intensity interval (TAAI) and resistance training circuit (TRC) are alternatives that have shown benefits . But there are still gaps important about the its effects on endothelial function (EF) and kinetics of oxygen ($\Delta VO2$) and fill this gap can bring relevant information quantotratamento these individuals. The potential improvement in EF and $\Delta VO2$ can result in a better blood and oxygen supply to peripheral muscles

. OBJECTIVE : To analyze and compare the TAAI and CRT modalities in the endothelial functionand oxygen kinetics outcomes in patients with HF. METHODS : Randomized controlled, longitudinal, parallel clinical trial involving HF patients with reduced ejection fraction aged over 35 years , divided into 3 groups: high intensity interval aerobic training, resistance circuit training and control group . The trainings will take place 3 times a week, totaling 36 sessions. The s reviews

of endothelial function and oxygen kinetics occur in times pre and post intervention. Theendothelial function will be assessed by flow-mediated dilation (DMF) and the assessment of oxygen kinetics will be performed on an exercise bike following an exercise protocol under constantload.

1 INTRODUCTION

Cardiovascular diseases have been the leading cause of death in Brazil since the late 1960s, amongwhich heart failure stands out for its higher prevalence (HF) (1) . The IC generates dyspnea and fatigue, symptoms that decrease exercise tolerance, r epercuti ing performance physical functions of these patients (1) . The physical training through exercises is essential for improving this situation

, and are strongly recommended (Class I indication) for patients after a cardiovascular event (2) . The literature indicates benefits obtained both by mode aeróbi to or resistid to, including aerobic training interval of high-intensity resistance training circuit (TRC) form part . However , it is not known which of these modalities generate better systemic responses in HF.

Regarding high-intensity interval aerobic training (TAAI) , a recent meta-analysis (Xie 2017) indicated better responses in cardiorespiratory capacity when compared to training with lower intensities in patients with HF (3) . In this meta-analysis, higher values of peak VO2 were observed

, which occurred regardless of age or anaerobic threshold (3) . This finding corroborates with the information that intensity seems to be an important predictor of the effectiveness of cardiac rehabilitation programs , even after adjusting for other training-related variables (4) . More recently, multicenter study showed no taai benefits in patients with HF compared ca moderate intensity. Andntretanto, this study 51% taai trained below the intensity adequate while 80% of moderate aerobic training trained intensity above the desired (5) . Thus, TAAI in this population still seems to be a therapeutic highlight (3,4,6) .

As for mode resistance training , although when isolated be beneficial to gain muscle strength, it isknown that this method exerts meno rinfluência of which the training aerobic to gain cardiorespiratory fitness (7) , thereby reinforcing the advantage of combining dest the d your training modalities . In this sense the TRC stands , po ise able to stimulate r also adaptations of aerobic and cardiovascular systems as demand higher values of heart rate during training (8) . Thisis because the maximum HR

values normally occur during the last repetitions of a series (8) . The TRC also has shown benefits in heart failure in muscular strength skeletal, VO2 peak (9-11) in addition to having been expressed strong correlation between the change in mitochondrial ATP production rate of skeletal muscle and the change in maximum oxygen consumption total body (peak VO2) (11) . Such findings demonstrate that CRT seems to be an interesting modality for patients with HF .

Despite the benefits already reported from both TAAI and TRC, there are still important gaps in the effects of both training on the CI population. Understand all the effects of the methods of physical training in the health of these patients is important because it contributes to the proper therapeutic choice in the rehabilitation of the same . In this regard we have not found studies evaluating the responses in endothelial function and either as the oxygen kinetics between these modes in these individuals . The importance of studying such outcomes will be elucidated in the following paragraphs.

The study of endothelial function in patients with HF is essential, since stasis is reduced. The reduction in endothelial function is the result of a lower production of nitric oxide (12) and an increase in oxidative stress (13–15) , which generates an increase in the response to vasoconstriction and vascular resistance . This compromises peripheral vasodilation assessed by means of flow- mediated dilation (DMF) , which leads to a reduction in blood supply to the muscle. Therapeutic resources, such as exercise, are able to improve endothelial function, which may result in a betterblood supply to the peripheral and cardiac muscles (15) (16) . The improvement in endothelial function reduces cardiac dysfunction in HF (12), which reinforces the relevance of its assessment in TAAI and CRT interventions.

In addition to the importance shown in studying endothelial function in patients with HF , studyingthe kinetics of oxygen consumption (Δ VO2), that is, the magnitude and nature of the adjustment in oxygen consumption during exercise (17,18) , is also important. also relevant for these patients . This is because the perfusion and

diffusion of oxygen (O2) is impaired in this population thanks todisturbances within the O2 transport path, which reduces the physical capacity of these individuals

(19) . The improvement in oxygen consumption kinetics minimizes the damage caused by HF in these individuals, emphasizing the relevance of its assessment after physical training interventions

(19) . This review can provide and and lucidar the adaptations within the O2 utilization and distribution system for skeletal muscle providing relevant information in the study of this population (19), in addition to providing r additional resources for interpretation ofcardiopulmonary exercise test.

The resolution of the mechanisms underlying skeletal muscle dysfunction and exercise intoleranceis essential for the development and improvement of the most effective treatments for patients withHF.

Taking into account the above, and seeking to remedy the gaps in the literature regarding TAAI and CRT, the present study will aim to analyze and compare such modalities in the endothelial function and oxygen kinetics outcomes in patients with heart failure.

The main hypothesis is that individuals allocated to TAAI group will promote better results compared to theTRC, generating greater increases in endothelial function and optimization of oxygen kinetic curve.

2 GENERAL OBJECTIVE
Analyze and compare high-intensity aerobic training and resistance circuit training in heart failurepatients

2.1 SPECIFIC
OBJECTIVES
Primary

Objective:

Analyze and compare endothelial function , oxygen kinetics and functional capacity before andafter physical training interventions (TAAI and CRT) and control group.

Secondary Objective:

Analyze and compare responses in autonomic modulation, body composition, muscle quality, quality of life, handgrip strength, muscle strength and functional physical capacity in patients withHF before and after physical training interventions (TAAI and CRT) and control group.

3 MATERIAL AND METHODS

3.1 DESIGN STUDY

This is a randomized controlled, multicentric, longitudinal, parallel clinical trial with a quantitative approach . Study will follow the recommendations issued by the CONSORT 16 for testing Clini c the high methodological quality, with the participation of IC holders of individuals allocated in three groups: training protocols of high intensity interval aerobic (TAAI) , protocol training resisted circuit (TRC) and control group without intervention (GC).

3.2 SAMPLE

The sample will be composed of individuals diagnosed with HF with reduced and preserved ejection fraction , hemodynamically stable , referred by cardiologists from Brasília and region (Federal District, Brazil) , as well as from the city of Hasselt (Belgium). According to data from a pilot study conducted in Brazil , a total sample of 42 individuals is required, considering an effect size of 0.36 alpha 0.05 power 0.8 considering the FMD outcome variable. To comply with the proposed sample size, the total sample will be composed of 18 participants in Brazil and 24 in Belgium.

3.3 INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria will be adopted: individuals diagnosed with HF with reduced and preserved ejection fraction , of both sexes (women in menopause), aged over 35 years , who should not have performed any type of physical activity the last 6 months, non-smoking individuals, absence of respiratory diseases and inflammatory or infectious lesion and process muscle tendon t nea or osteoarticular that desempenhasse exercise limitation . The regular accepted medications will only be used to control the necessary cardiovascular factors according to the cardiologist's indication . Exclusion criteria are: patients who perform any kind of physical activity in the rehabilitation period out those you s will be assigned, individuals who do not meet the periodization missing more than 25% of the sessions.

3.4 RESEARCH LOCATION

The research will be conducted at the University of Brasilia, Campus Ceilândia and also at the University of Hasselt , Campus Diepenbeek , and physical training will take place at the Gymnasium Therapeutic University and Reval (Bégica , Uhasselt) . The evaluations for the outcomes mentioned above will be carried out at the Laboratory of Physiology and Biophysics of the University of Brasília, Ceilândia Campus and also at Jess and Hospital, Hasselt , Belgium .

3.5 ETHICAL CONSIDERATIONS

All procedures used in this study will be forwarded to approve tion by the Ethics Committee of the Institution. Study participants will sign a free and informed consent form confirming their participation and proving their knowledge at all stages of the study, and if they choose, they may withdraw during the work.

3.6 EVALUATION PROCEDURES AND PROTOCOL

An independent researcher will prepare the allocation of randomized random sequence , which will be obtained through the software random.com . The allocation of the type of treatment will be carried out on the first visit to the physiotherapist,

at least two weeks before the beginning of the interventions. The responsible physiotherapist will know the intervention adopted by the volunteers, however the evaluator of each outcome will be blind.

The evaluations will be made in two moments for both groups: before starting the experimental protocol and after the end of it . The outcomes to be analyzed at these times will be: endothelial function, kinetics of oxygen consumption, functional capacity , quality of life, autonomic modulation , body composition , functional physical capacity , muscle quality , hand grip strength.

3.6.1 Flow-mediated vasodilation (DMF)

Previously, the subjects will be instructed to avoid any planned exercise sessions and will be askedto refrain from consuming caffeine / alcohol and to exercise for 24 hours before the tests. The subjects will be advised to participate in the assessment as long as at least 2 hours post-prandial. To avoid potential daytime variations, the tests will always be performed at the same time of day and in the same room with controlled temperature (~ 24 ° C).

Initially, individuals will rest in a supine position for a period of 15 min to ensure the achievementand stabilization of cardiovascular variables. The brachial artery diameter and blood velocity will be measured using high- resolution duplex-Doppler ultrasound (Ultrasound System HD11.XZ, 1 and 3 MHZ, Phillips, Barueri, SP, Brazil) following the present guidelines (20) . A 9 MHz linear matrix transducer will be placed over the brachial artery slightly proximal to the cubital fossa. The diameter and speed signals will be obtained simultaneously in duplex mode at a pulsed frequency of 5 MHz and corrected with an insonation angle of 60 °. The sample volume will be adjusted to cover the entire lumen of the vessel without extending beyond the walls and the slider will be adjusted in the middle of the vessel. The FMD of the brachial artery will be evaluated in the right arm in the supine position as previously described (21,22) .

Briefly, a cuff will be attached to the arm. For two minutes rest hemodinâmic data to be registrad them , and then the cuff is inflated to a pressure of 220 mmHg and maintained thus for 5 min. Themeasurements of continuous diameter and blood velocity will be recorded continuously for 3 min after rapid deflation of the cuff. The analysis of all vascular variables will be analyzed offline usingthe specialized edge detection software (Cardiovascular Suite , Quipu , Pisa, Italy). The variation in the percentage of DMF was normalized for the incremental area of shear rate under the curve upto the peak diameter (23) (24)

3.6.2 Incremental Cardiopulmonary Exercise Test

The assessment of functional capacity will be carried out by means of an ergospirometric examination carried out by a specialist doctor (blinded as to the allocation). This test will be important for determining the aerobic and anaerobic thresholds required for the prescription of TAAI , in addition to providing outcome measures for the groups, among which VO2 peak and VE / CO2 will be used, reported in a recent systematic review in training protocols. as the most widely used parameters and indicative of results (25) .

Patients will report to the Physiology and Biophysics Laboratory of Unb , to perform the incremental test limited by symptoms, on an electromagnetic bicycle with a 0-watt system (Corival

, Lode Co., Groningen, Netherlands) using a ramp protocol (5- 10 watts / minute). Before the startof each test, a period of 5 minutes will be observed for adaptation to the cycle ergometer and the stabilization of gas exchange. The 12-lead electrocardiogram will be monitored continuously (T12,Cosmed , Rome, Italy) with a record associated with the gas capture program 27. Blood pressure will be checked with a standard sphygmomanometer, with the patient sitting on the ergometer, every 2 minutes during the exam and up to 15 minutes after the end of the active part of the test. Exhaled gases will be collected in aliquots at each breath by a computerized gas analyzer (Quark CPET, Cosmed , Rome, Italy).

3.6.3 Evaluation of the kinetics of oxygen

The evaluation of oxygen kinetics will be performed on a stationary stationary bicycle. For this, thevolunteers will be instructed to remain seated, with a mask to capture the expired gases by a computerized gas analyzer (Quark CPET, Cosmed , Rome, Italy) . Volunteers will be instructed towear appropriate clothing for this exercise test prior to the assessment date . Not be will allowed the movement of people around the room during the performance test , in order to reduce the anxietyof individuals and capture errors.

The evaluation of oxygen kinetics will be performed according to the exercise protocol under constant load on the stationary stationary bike , performed with an initial phase without load (0 wattstart-up system, Lode , Netherlands) for three minutes and immediately after an initial exercise. with constant load, performed below the LA (anaerobic threshold), for 6 minutes with a constant sub-LA load (1st session). Shortly after the moderate exercise session, an interval of 15 minutes will be performed and a new exercise in the sequence, carried out with an initial load phase 0 wattfor three minutes and after that an exercise with supra-LA load (80% Δ VO2max) until the maximum possible (Tlim) and after the exercise the collection of the expired gases will be carriedthrough for 15 minutes.

During the test, oxygen consumption (O 2), carbon dioxide production (CO2), minute ventilation (E), tidal volume (VC), respiratory rate ($\square$), respiratory exchange ratio (R), will be analyzed , equivalent ventilation for oxygen (E / O2) and carbon dioxide (E / CO2), inspiratory time (TI), expiratory time (TE), and TI / TTOT ratio. The data will continue to be collected even after the endof the exercise, at least 15 minutes of passive recovery.

Throughout the protocol, the perceived effort index for fatigue of the lower limbs will be recorded.The 12-lead electrocardiogram will be continuously monitored. Individuals will be asked about thesensation of ventilatory effort and tiredness in the lower limbs every 2 minutes, according to the Borg scale . The system will be calibrated daily before each test.

3.6.4 Evaluation of Muscular Strength

Muscular strength will be assessed using the 1RM test, which will determine the maximum load that each individual will be able to perform during the movement required by the exercise in question, to later determine the training loads. This test represents the greatest resistance that can be moved through the full range of motion in a controlled manner and with good posture.

The test starts by receiving increments according to the subject's perception, until it is concluded when the volunteer reaches the maximum load, in which he can execute the movement without mechanical failure. No more than five attempts will be allowed to establish this maximum load and if this occurs, the test will be disregarded with scheduling a new date for evaluation. This variable will be collected at the baseline moment before the start of training and 72 hours after the end of the last session.

3.6.5 Evaluation of autonomic modulation

The evaluation of autonomic modulation will be performed through Heart Rate Variability (HRV).Therefore, volunteers will be directed to remain at rest, awake supine and spontaneous breathing for 30 minutes by cardiofrequency the Polar® RS800 (Polar Electro Oy, Finland) on the wrist , previously validated equipment as its use to capture the intervals between consecutive heartbeats (in ms) (26) . The volunteers will be guided by not consumption SNA 24 stimulants prior to this evaluation. People will not be allowed to move around the room during collections, in order to reduce individuals' anxiety and collection errors. The data obtained from HRV will be transferred to a computer using the Polar Pro Trainer software and, later, to calculate HRV indices, the KubiosHRV software - version 2.0 (Kubios , Biosignal Analysis and Medical Image Group , Departmentof Physics , University of Kuopio , Finland) , considering 1000 sinus intervals (minimum 95% sinus beats). This will occur after digital filtering (Polar Pro Trainer software) complemented by amanual (Microsoft Excel), to eliminate premature ectopic beats and artifacts.

For HRV analysis, linear indices will be used, obtained in the time domains (RMSSD and SDNN)

(27) , geometric indices (Poincaré plot , triangular interpolation of the NN intervals (TINN) (27) and triangular index (RRtri) (28) and in the frequency domain evaluated using the fast Fourier transform segmented at low frequency (LF - Frequency between 0.04 to 0.15Hz), high frequency (HF - Frequency between 0.15 to 0.4Hz) and LF ratio / HF expressed in normalized units and ms

(27) Non-linear methods already validated will also be used such as Recurrence (REC), Purified frequency analysis (DFA alpha 1 and alpha 2), Determinism (DET) and entropies (Apen and Sampen).

3.6.6 Assessment of body composition

Body composition will be estimated using DXA (DPX-MD, software 4.7; Lunar brand, Madizon ,WI, USA). The subject will be positioned in a supine position during the exam, which should be Property ions for a time of about 1 0 minutes. Fat mass (MG) and fat free mass (MLG) will be expressed in absolute values. To classify the groups in relation to body composition, due to the absence of cutoff points, the median of the greater or lesser amount of MG and MLG will be used

.

3.6.7 Evaluation of thickness and eco nicity muscle

The individuals will be evaluated in a supine position with the knee in passive extension and neutral rotation. A the aqueous solution , called transmission gel is applied to the head ultrasound to permitircontato sound without pressing the dermal surface. Two images are adquirid the s right leg : (1) image earlier: transducer placed perpendicular to the long axis of the thigh anterior two -thirds of the distance from the anterior superior iliac spine to superiorborda the patella

(29) , and (2) the side image: 5 cm laterally from the first image point. The edge image is obtainedin a field prolongadode view mode at a distance of 10 cm in a

running the direçãocrânio -caudal . To enable the replication of the image location in the post-training ultrasound , a mark will be drawnon the volunteer's leg and a photo will be registered for conference at the final moment . The imageswill be saved on the ultrasound hard disk and transferred for later analysis on a computer using the ImageJ software (NIH, Bethesda, MD) (30) .

All ultrasound measurements will be performed three times, with the average of the scores used in the final analyzes. In the previous image, muscle thickness and echogenicity of the vast intermediate

, rectus femoris , thickness of the subcutaneous tissue and transverse area of the rectus femoris willbe evaluated. Tod the parameters of espessuraserão measured cent e meters, and aarea transverse straight femoralserá medid the at cent t m at the widest point and muscle .

The echogenicity will be reported in pixels. The echogenicity will be determined using quantitativeanalyzes using computer quantified scales. A 2×2 cm square pattern for analysis of the rectus femoris and vastus intermedius muscles separately will be used to determine the region of interest

(ROI). The square method has a stronger confidence compared to the tracking method (where the evaluator highlights all the visible muscle area excluding epimysium and artifacts) to define the ROI (31) . If the area to be analyzed fo r smaller than 2×2 cm, the largest possible square within the anatomical limits of the muscle will be examined. Mean and standard deviation of theechogenicity of this ROI will be calculated using the histogram function of the ImageJ software (NIH, Bethesda, MD) and expressed as a value between 0 (= black) and 255 (= white) (32) . In thelateral image, the measurements will include vastus lateral thickness and penile angle of the vastuslateralis (angle in degrees between fascicles of muscle fibers and deep muscular aponeurosis) .

The ultrasound measurements will be carried out in two moments: before starting the training protocol and 72 hours after the end of the last session of the same.

3.6.8   Classification of states of functionality and disability (ICF)

The classification of the states of functionality and disability will be assessed through the CIF in itscomprehensive version, which consists of the application of all its codes. The assessment of the ICF will be in the form of an interview by a physiotherapist previously trained to use the instrument,according to Martins et al. 2010 (33) .

The ICF codes will be established based on the following components: I - Body functions; II Bodystructures; III - Activity and Participation; IV - Environmental Factors. Components I, II, and III are related to part 1 of the ICF, intended to classify functionality and disability and component IVare related to the classification of contextual factors.

The researcher will manually record the number of occurrences for all levels of coding, for all subjects. However, when processing the data, only the first level occurrences (chapters) will be considered for classification. Each specified code will be related to its respective qualifier, with qualifier being the determinant of functionality, that is, no deficiency for that code. Qualifiers 1 to4 will be considered as determinants of disability, as they classify the presence of disability from mild to complete. Qualifier 8 will be considered as unspecified, when the presence of a disability could not be determined, and qualifier 9, as not applicable, when the code was not applicable.

3.6.9 Force to hold palmar

To measure the handgrip strength, the handgrip instrument will be used .

The positioning of the participants will be in accordance with the American Society of HandTherapists Guide l ines (34) : subject seated with supporting arm , adducted

shoulders in neutral rotation, elbow flexed to 90 °, forearm in a neutral position and PU Nho between 0 and 30

Dorsiflexion °. Three measurements with the dominant and non-dominant hand will be performed. The highest value will be expressed in kg, and included in the analysis. The maneuvers must be carried out with 5 seconds of support, and 3 minutes of rest between them. We will instruct patients to maintain spontaneous breathing and to avoid performing the Valsalva maneuver , in conjunction with exercise.

Participants will be instructed to maintain positioning during tests and corrected by the examiner when necessary. Accessories such as watches, bracelets, rings and bracelets will be removed from both participants' upper limbs before testing begins. All participants will be assessed individually. Participants will be instructed not to look at the dynamometer display to avoid any visual feedback

.

3.6.10 Short battery of physical performance (SPPB)

The SPPB will be read, and applied, to the subjects in order to reduce the risk of bias. The domains explored by the questionnaires will be scored as foreseen by the SPPB.

Considering that the Short Physical Performance Battery (SPPB) is an instrument composed of three different tests , the evaluations will work as follows : 1) static balance - evaluated in three positions - side by side (feet together), semi tandem (one foot partially in front of the other) and tandem (one foot in front of the other); 2) walking speed (the time taken to cover three meters in a normal pace is timed); 3) strength of the lower limbs (the time spent to get up and sit on a chair for five consecutive times, without the aid of the hands). The score ranges from 0 to 4, for each of the tests and according to the time performed in each task, with 0 being the worst performance and 4 being the best performance. If it is impossible to carry out any of the steps, the score will be zero. (35)

The total score of the test is the result of the sum of the three tests already mentioned, that is, 12 points, with 0 being the worst performance and 12 the best performance. Score of 0 to 3 s and r willbe considered very poor performance or failure, score points are 4 to 6 ether shall considered poorperformance; 7 to 9 points s and r to the moderate performance and score points 10 to 12 s and r will considered good performance. (35)

3.6.11 Assessment of isokinetic muscle strength and peripheral oxygen extraction

For the assessment of isokinetic muscle strength, the dynamometer BIODEX System 3 PRO, NewYork will be used .

The subjects will be positioned with their hips at 90 ° with the articular axis aligned with the fulcrumof the dynamometer so that the knee of the evaluated member is free (distance of 2 fingers) and thesubject is with the entire gluteus close to the back of the chair. The alignment of the evaluated leg with the contralateral limb will be checked. All measurements of the subject's position on the dynamometer (chair height; chair base; chair back; distance from the dynamometer; distance fromthe arm) will be recorded on a form made by the researchers in order to make the measurement reproducible after the intervention. The subjects performed knee extension at 70 ° s-1 , to assess the peak isometric torque, 5 times for 4 seconds with a rest time of 30 seconds between repetitions.The average of the 3 highest values will be considered for analysis. For the measurement of dynamicstrength, the subjects will perform knee extension at 180 ° s-1 for up to 30 repetitions.

The evaluation of peripheral oxygen extraction will occur in a continuous and non-invasive way through the NIRS (Near-Infrared Spectroscopy Portamon (Artinis Medical Systems, Einsteinweg17, 6662 PW, Elst, The Netherlands). In the region close to the infrared, hemoglobin - including its two main variants: oxyhemoglobin (O_2Hb) and deoxyhemoglobin (HHb) - exhibit oxygen dependent absorption. Using a number of different wavelengths, relative changes in hemoglobin concentration can be displayed continuously. in the vastus lateralis muscle of the evaluated leg, visualized the site of the largest muscle belly after isometric

contraction, where the fixation of the device will be by means of velcro strips and covered with a black bandage to eliminate the ambientlight. This measurement will start 5 minutes before the procedures evaluation of isokinetic musclestrength, will be maintained throughout the evaluation, and 5 minutes after the end. the posicionament that of NIRS will be marked with a demographic pen and registered using a photographic camera. The variables analyzed will be tissue oxygenation index (TSI%), oxyhemoblogin (O 2 Hb), deoxyhemoglobin (HHb), total hemoglobin (tHb) and hemoglobin differentiation (HbDiff). The data will be analyzed with OxySoft Software (v2.1.2, Artinis Sistemas Médicos). The tissue saturation index (TSI) will be calculated using the equation below:

3.6.12 Lung function and respiratory muscle strength

Lung function and respiratory muscle strength are important assessments for the method of selection / respiratory assessment of patients (anamnesis) . Such assessments will be accessed by spirometry tests (MicroLab ML3500MK8, CareFusion , USA) , manovacuometer (MVD300, Globalmed , Brazil) and dynamic inspiratory pressure .

Individuals will be instructed to abstain from autonomic stimulants (alcoholic beverages, coffee, tea or caffeine-containing foods) for 24 hours before the assessment, as well as eating a light mealat least 2 hours before the measurement. Patients must rest 10 minutes before each test (spirometry,maximum respiratory pressures and dynamic inspiratory pressure). They will be placed on a benchwith legs bent at 90 degrees, upright posture, head in neutral position and nasal clip to prevent leaks.

Spirometry

Individuals will perform at least three forced expiration maneuvers according to the American Thoracic Society (ATS) / European Respiratory Society (ERS) technical procedures and acceptability and reproducibility criteria (36) . The spirometric evaluation will be performed to check for obstructive or restrictive patterns through

outcome measures: forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), peak expiratory flow (PEF), FEV1 / FVC ratio.

Blood pressure monitor

The MVD300® manovacuometer (Globalmed , Porto Alegre, RS, Brazil) was used to measure positive pressures (manometer) and negative pressures (vacuometer). The manovacuometer allowsthe static assessment of maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP) and plays an important role in the diagnosis and prognosis of chronic diseases (37) .

The manovacuometer will be previously calibrated in cmH_2O, with an operational limit of -300 to
+300 cmH_2O and scales ranging from 10 to 10 cmH_2O. The methods and criteria used will be thoserecommended by ATS / ERS (38) . To assess MIP , patients will be instructed to perform a maximum expiration, following a maximum inspiratory effort , so that the pressure is recorded close to the residual volume. For the assessment of MEP , a maximum inspiration will be requestedbefore the maximum expiratory effort to assess the pressure, close to the total lung capacity. A vigorous verbal command will be given during the assessment.

Dynamic inspiratory pressure

The assessment of dynamic respiratory muscle strength will be performed using the POWERbreathe ® KH2 device (London, England, United Kingdom), in which the maximum inspiratory effort will be assessed from the residual volume. Maximum muscle strength (S-index) will be obtained during the dynamic contraction of the inspiratory muscles. Patients will be instructed to achieve the highest possible inspiratory flow rate after a previous expiration. To obtainthe S-index , the patient must be collaborative and able to respond to verbal commands (38) .

3.6.13 NT-pro-BNP

NT-pro-BNP will be used to characterize heart failure with preserved or reduced ejection fraction

(39) , specifying patient entry criteria along with other variables (anamnesis) according to theEuropean Society Cardiology Guidelines (40) .

Patients do not need to fast or have any special preparation for the test.

NT- proBNP serum will be measured using test strips (CARDIAC proBNP +, Roche Diagnostics ,Basel, Switzerland) containing monoclonal and polyclonal antibodies against epitopes of the NT- proBNP molecule in a point- of - care device (Cobas h232, Roche Diagnostics Basel, Switzerland).A sample of venous blood will be kept in heparinized (sodium) tubes (Vacuette from Greiner Bio-One , Roche Diagnostics , Basel, Switzerland) at room temperature and analyzed within 5 hours. The manufacturer's controls will be used to monitor quality control with acceptability limits definedby the manufacturer (4). Assessments will always be carried out in the physiology laboratory by qualified professionals (cardiologists collaborating with the research).

3.6.14 Echocardiographic evaluation

Individuals will be instructed to abstain from caffeine for 24 hours prior to the test. The strain echocardiographic examination with a 4-2 MHz transducer equipped with a second harmonic image (HDI 5000 2-4 MHZ, Philips ATL, Bothell , WA) will be used to access cardiac function through the DICOM (Digital Imaging and Communication format) in Medicine) (31) (anamnesis) . Outcome measures include left ventricular ejection fraction by Simpson (LEF,%), left atrial volume index (LAV, ml / m²), left ventricular mass index (IMVE, G / M²), diastolic diameter of the left ventricle left ventricle (LVDD, mm) and blood pressure (PAP, mmH) following recommendations by the American Society of Echocardiography and the European Association forCardiovascular Imaging (41,42)

3.7 INTERVENTION PROTOCOL

The experimental protocol for this study will be submitted to the national clinical trial registrationplatform http://www.ensaiosclinicos.gov.br/ .

It is important to note that a pilot study will be carried out as a miniature version of the main studyto test whether the components of this study (all evaluations and steps) can work concurrently. Thisprocedure will have all the outcomes of the main study that can contribute to the final analysis as well as sample calculation and, if necessary, adaptations will be made in the study design so that itis as appropriate as possible.

3.7.1 Cardiac rehabilitation

The study will consist of three randomized intervention groups: TAAI - high intensity aerobic training , CRT - resistance training in circuit (T RC) ; CG - control group.

The training groups will perform exercises three times a week, with an interval of at least 24 hoursbetween sessions until totaling 36 training sessions.

Previously, the training will be familiarized with the equipment as follows: for the TR C the individual will perform 10 repetitions with a load referred to as slightly intense (13 on the Borg scale) oriented in good posture; for TA AI the individual will be instructed to walk on the treadmillfor 15 minutes with somewhat intense perception (13 on the Borg scale) . These criteria will collaborate for volunteers to perform the movements with the best possible ease, adjusted s by physiotherapists during the familiarization period.

Exercises on the ground and global stretches will be used in order to warm up (15 minutes) , in order to avoid possible complications , reducing the risk of injury . The interval between the seriesof exercises will vary from 40 seconds to 1 and a half minutes, respecting the directly proportionalrelationship between time and exercise

load. Familiarization with the equipment will also take placeprior to the start of the sessions.

The muscle groups chosen for TR C will be: quadriceps, hamstrings, back, chest, shoulder, bicepsand triceps. The test of a maximum repetition (1RM) will be used to measure the maximum load ofeach individual, to later determine the RT loads. The loads of the TR C protocol will start at 30% of 1RM and gradually increase throughout the sessions up to 80% 1RM, (intensity between moderate and intense), always respecting the principles of adaptation and overload. The loads chosen to perform TA AI , which will occur on a treadmill and exercise bike will vary between twointensities, the highest above the first anaerobic threshold and the lowest below the first anaerobicthreshold obtained by the ergospirometric test, with the loads will be changed throughout the sessions according to the HR referring to reach the respective thresholds .

Already regarding the individuals the GC , they will attend lectures and will be instructed to performlight physical activity in an unsupervised manner, 3vezes week, both aerobic as resisted, and the intensity of both considered appropriate to below the first threshold obtained in the examination VO 2. For this, the individual will be previously instructed in the ergospirometric evaluation session regarding the perception of effort and the appropriate limit for exercises.

3.8 RISKS

Physical training will be held at the Gymnasium Therapy at the University of Brasilia, Campus Ceilandia by trained physiotherapists and during its execution will be accompanied by a medical

collaborator cardiologist (Dr. Alexandra CGB Lima) that will guarantee support physician throughout the work the in order to control the risks of patients.

During the sessions, blood pressure (BP), oxygen saturation (SATO2), effort perception scale (Borg) pre and post exercise scale and, if necessary, during the

performance will be performed. In addition, the individuals' heart rate (HR) will be assessed pre and post session in addition to being continuously monitored by a cardiofrequency meter throughout the entire session . C Abera the therapist to check the individual limits for each FC ind i vidual (which is previously obtained in accordance with the FC thresholds extracted from cardiopulmonary testing each participant).

The clinical signs and symptoms will be monitored throughout all sessions (Example: excessive tiredness, intense sweating, paleness, dizziness, vision blurred, palpitations , angina or pain pre cordial) and if the volunteer shows no indicative change risks for the year the training will be suspended and the volunteer will be sent to the responsible doctor for medical consultation .

Taking into account the complexity of the patient with heart failure and in order to attend any and all emergencies or complications, the Therapeutic Gymnasium at the University of Brasilia, where the physical training interventions will take place, will be equipped with all the necessary resources

. Resources will be available to therapists to contain events such as hypoglycemia / hyperglycemia and hypertension / hypotension crises (stethoscopes, sphygmomanometers, glucometer for checking blood glucose, emergency blood pressure and glycemic control medications) , and cardiorespiratory arrest (oxygen cylinder, masks for oxygenation, defibrillator) .

It is worth mentioning that in order to contain a possible cardiorespiratory arrest, all research therapists who will be during the patients' physical training, will have first aid knowledge. This knowledge will give professionals total autonomy to carefully perform cardiopulmonary resuscitation procedures as well as resuscitation, following the recommendations of basic life support for adults. All therapists will have sufficient knowledge to reduce the risk of complications from this event if it occurs.

The individuals allocated to the CG will be monitored over the telephone for symptoms and possiblediscomfort experienced with training once a month. Also, in face-to-face meetings that will take place on a monthly basis, individuals will be able to clear their doubts with health professionals, which will reduce risks throughout their participation in the research. If necessary, they will be consulted by the team's cardiologist at any time during the research.

We believe that these measures will be sufficient for monitoring patients during training and ensuring safety for these patients.

3.9 BENEFITS

Research participants will have direct benefits, since they will receive medical care with clinical and physical examinations, in addition to quality physiotherapeutic care throughout the entire cardiovascular rehabilitation protocol. The benefits of the rehabilitation protocol will happen regardless of the intervention group that the participant is selected (high intensity interval aerobic training and resistance training in circuit), since as the introduction of the present project, both modalities are known in the literature for their positive points. in rehabilitation in the population with HF. The rehabilitation protocol will help to reduce the clinical and functional symptoms caused by HF.

The GC not conduct intervention also have will benefit since they will receive medical care with conducting clinical and physical examinations. In addition, once a month they will receive lectureson how to deal with HF. The lectures will address topics such as nutrition, exercise, drug control, psychological aspects and will be held by professionals in the respective fields (nutritionist, physiotherapist, doctor and psychologist). Still, it is worth mentioning that after the research periodin which the individuals in the CG need to be sedentary, they will be invited to participate in the exercise protocols (without research purpose), and will receive care supervised by the professionalsinvolved in the study.

All patients, regardless of the group they are allocated, will receive a copy of all tests performed aswell as feedback on their health condition and guidance.

We understand that these benefits will be of paramount importance for these patients resulting in the quality of life of the same .

4 STATISTICAL ANALYSIS AND SAMPLE CALCULATION

The statistical analysis of the data will be descriptive to characterize the sample . The test of normality of the data will be by Shapiro Wilk. Parametric and / or non-parametric tests will be applied and broken down into tables according to normality. Comparative parametric and / or non-parametric tests will be applied and broken down between groups in tables according to normal (ANOVA two way or Kruskal Walllis). Possible correlations will be tested using Spearman's correlation . All analyzes will be performed using SPSS statistical software version 22.0 (SPSS, Inc. Chicago, IL, USA), and the significance level adopted is 5%.

5 OUTCOMES

5.1 PRIMARY OUTCOME

Verification of flow-mediated dilation variables: vessel diameter and blood flow velocity before after taai and trc and control group.

Analysis of oxygen kinetics variables before after taai and trc and control group: oxygen consumption (o2), carbon dioxide production (co2), minute ventilation (e), tidal volume (vc), respiratory rate (f), respiratory exchange ratio (r), ventilatory equivalents for oxygen (e / o2) and carbon dioxide (e / co2), inspiratory time (ti), expiratory time (te), and ti / ttot ratio

Verification of functional capacity by the ergospirometric test in the variables vo2 peak and ve / co2 before after taai and trc and control group.

5.2 SECONDARY OUTCOME

Analysis and comparison of autonomic modulation in patients with HF before and after TAAI andCRT using linear heart rate variability indices.

Analysis and comparison of body composition in patients with HF before and after TAAI and CRTby densitometry in the parameters% of body fat, lean mass (kg) and adipose mass (kg).

Characterization of the variation in muscle thickness and echo intensity by ultrasonography inpatients with HF before and after TAAI and CRT.

Evaluation of the quality of life responses of patients with HF by the classification of states offunctionality and disability (ICF) before and after interventions and control group.

Analysis of the effects of TAAI and CRT on handgrip strength by handgrip expressed in kilograms
/ strength
Analysis and functional physical capacity in patients with HF before and after interventions andcontrol group by the short physical performance battery (short physical vattery performance).

Analysis of the effects of TAAI and CRT on peripheral muscle strength using the test of 1 maximumrepetition (1RM)

Assessment of isokinetic muscle strength and peripheral

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Onderzoeksprotocol

Effects of High Intensity Interval Training versus Circuit Resistance Training on Endothelial Function and Cardiorespiratory Capacity in Patients with Heart Failure:A Randomized Trial

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Study protocol (version December 2019)

1 INTRODUCTION

Exercise physical training is strongly recommended as a therapeutic approach to treat individuals withHeart Failure (HF), an extremely prevalent cardiovascular disease impacting on patient's life and society. The present research proposal aims to verify the repercussion exercise training modalities high-intensity intervaltraining (HIIT) and circuit resistance training (CRT) in HF. Findings of those modalities have already indicatedimprovements in HF status, mainly by increasing cardiorespiratorycapacity. However, the mechanisms involved to increase functional capacity are not fully understoodin the scientific literature, especially over endothelial function and oxygen peripheral extraction. Improvements in those outcomes can impact the quality of life and prognosis of HF individuals positively, by improving dyspnea and fatigue symptoms, increasing exercise tolerance. In order to better understand the physiological pathways responsible for the benefits of HIIT and CRT physical training, we aim to explore the training repercussions over endothelial function (FE) and cardiorespiratory exercise capacity (CPET). Improved EF and increased oxygen supply may result inimproved vascular flow and peripheral oxygen extraction to peripheral musculature, justifying the benefits currently described in this population. Objective: To analyze and compare HIIT and CRT exercise modalities in endothelial function and cardiorespiratory capacity in patients with preserved and reduced HF. Methods: It is a multicenter randomized controlled trial involving patients with reduced and preserved HF, divided into HIIT, CRT and control groups (CG). Endothelial function and cardiorespiratory exercise capacity evaluations will occur on pre and post moments following standard recommendations. We hypothesized thatthere is no difference between HIIT and CRT for both outcomes based on interval training characteristic of both modalities, alternating pauses (CRT) or intensity reductions (HIIT) with higher exercise efforts impacting on intensity control. Oxidative metabolism is mainly required during HIIT to provide energy supply, positivelyinfluencing FMD andCPET, while for CRT those benefits can be related to cardiovascular demand and muscular alterations.

2 PURPOSES

- To analyze and compare the effects of HIIT and CRT on endothelial function andcardiorespiratoryexercise capacity in

patients with HF.

- To analyze and compare the effects of these modalities on skeletal muscle strength, musclequality,body composition, pulmonary function, autonomic modulation and functional capacity.

3 METHODS

Trial design

This multicentric randomized controlled trial is designed as longitudinal, parallel, and quantitative study following CONSORT recommendations (Consolidated Standards for Reporting) (1).

Group determination and study content

Heart failure patients will be recruited during the cardiology consultation. Suitable patients (based onthe decision of the cardiologist) will be introduced the content of the study by the researcher, after which the patient receives the informed consent. The patient will be called one week later to determinewhether he/she is willing to participate in the study. If the patient will not participate in the study, his/her contact details willbe removed after this phone call. Heart Failure patients will be allocated in three randomized (by closed envelope) groups: high-intensity interval training (HIIT), circuit-resistance training (CRT), and control group without exercise intervention (CG). Both training groupswill perform a 12 week intervention, personally supervised by a team of physiotherapists and biomedical scientists. Patients in the control group will get thestandard clinical treatment trajectory by their cardiologist, after which these patients will be invited to take part in the training intervention.All measurements will be performed at the start of the intervention and willbe repeated after the intervention period of 12 weeks (or the follow-up period of the control group). There will be two measurement days: one at the Jessa Hospital (Revalidatie- en Gezondheidscentrum) and one at Hasselt University (Revalidatie

Onderzoekscentrum). Both occasions will comprise about 2-3 hoursof testing.Each patient will receive an instruction card which includes the most important guidelines to take into account the days before the measurements. Instructions for the measurements are given at the measurement days.

Population

For this study, only stable heart failure patients (no changes in medication throughout the last three months;decision to be suitable for inclusion is based on cardiologists' opinion) with the following criteria can participate:

- Inclusion criteria

Individuals with HF diagnosis with reduced and preserved ejection fraction (HFrEF and HFpEF, respectively) according to 2016 ESC Guidelines (2), referred by doctors, both sex, older than 30 years,who did not participate in a previous exercise program six months before the protocol, non-smokers,non-Chagas disease, absence of exercise respiratory limitations according to spirometry (FEV1<50%)(3), absence of inflammatoryor infectious processes, absence of musculotendinous or osteoarticular lesions which could limit exercise performance.

- Exclusion criteria

Individuals who disagree participate to the research protocol. The follow up exclusion will occurfor thoseabstaining more than 25% of the 36 training sessions, or more than three consecutive training sessions.

Outcomes

Primary: 1) flow-mediated vasodilation (FMD) and 2) cardiorespiratory exercise capacity (CPET).

Secondary: 3) muscular strength, 4) body composition, 5) pulmonary function, 6) autonomicmodulation, 7)Muscle Quality 8) Short Physical Performance Battery.

Sample characterization only: 9) cardiac function (echocardiography), 10) NT-proBNP
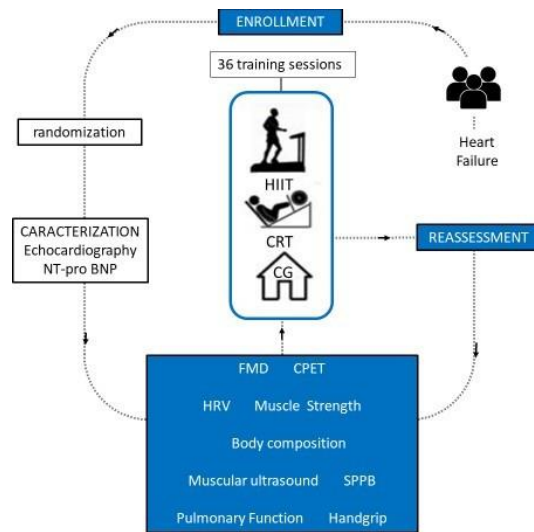

Figure 1: Study overview flowchart. HIIT, high-intensity interval training; CRT, circuit-resistance training; CG, control group; NT-pro BNP, brain natriuretic peptide; FMD, flow-mediated dilatation; CPET,cardiopulmonary exercise test; HRV, heart rate variability; M., muscular; DXA, dual-emission x-ray absorptiometry; SPPB, Short Physical Performance Battery.

4 FLOW-MEDIATED DILATION (FMD)

Flow-mediated dilation (FMD) is a non-invasive technique to evaluate endothelial function (9) and has beenconsidered an important prognostic variable for this population (10). The technique allows the visualization of Doppler waveform associated with arterial diameter measurements (11,12). Brachial endothelial dysfunction is associated with carotid thickness (13).

Subjects preparation: Subjects will start the experimental procedure at least 2 h after a light meal andabstained from caffeine, alcohol, and exercise for 24 h before testing. Tests will be performed at the same period of the day to avoid the circadian effect, and temperature will be controlled ($\sim 24°\,C / 75°F$). Subjectspreparation follows a previous standard recommendation (11).

Method Description: A cuff will be attached to the right arm of the subjects who will remain at rest supine position for 5 min for cardiovascular stabilization. Later, diameter and blood velocity of the brachial artery will be continuously measured by two minutes, according to Thijssen et al. 2011 (6), using high-resolution

Doppler duplex ultrasound equipment in Brazil (HD11.XZ, 1 and 3 MHZ, Phillips, Barueri, SP, Brazil) and at UHasselt (E95 Vivid, GE Healthcare, EUA)(12)(12)(8)(8). A 9 MHz linear matrix transducer will be positioned over the brachial artery discretely proximal to cubital fossa. Diameter and velocity signals will be obtained simultaneously in duplex mode at a pulse frequency of 5 MHz and corrected by an insonation angle of 60°. Sample volume will be adjusted to include the entire vessel's lumen without extending beyond the walls, andthe slider will be adjusted in the middle of thevessel. The FMD of the brachial artery will be evaluated on theright arm in the supine position, as previously described (14,15). After resting period evaluation, the cuff willbe inflated to a pressure of220 mmHg and maintained for 5 minutes. After

that, measurements of the diameter, and blood flow velocity will be recorded continuously for 3 min after rapid cuff deflation. All vascular variables willbe obtained by using specialized border detection software (Cardiovascular Suite, Quipu, Pisa, Italy). Percentage variation of FMD will be normalized (16). Baseline arterial Diameter, baseline blood velocity, temporal kinetics of arterial diameters, and blood velocities will be considered for analysis(11,17).

5   CARDIORESPIRATORY EXERCISE TEST

Cardiorespiratory exercise capacity will be obtained by the cardiorespiratory exercise test (CPX) within an incremental symptom-limited test on a 0-watt electro-magnetic bicycle (Corival, LODE BV Medical Technology Groningen - Netherlands) under a specialized physician supervision, blindedto allocation.

Subjects preparation: The subjects will be instructed to wear comfortable clothes without movementrestriction and instructed to abstain from caffeine for 24h before testing and have a light meal until 2hours earlier.

Method description: A breath-by-breath gas analyzer (CPET, Cosmed, Rome, Italy) will be used. This examination will determine ventilatory thresholds (18) for HIIT prescription (heart rate at the aerobic threshold and respiratory compensation point). Outcome measures including VO2, VCO2, HR, and VE and allkey variables for cardiorespiratory capacity assessment (19) will be determined.

6   MUSCLE STRENGTH

Muscle strength will be assessed through:

a) Isokinetic dynamometer;

b)1 RM;

c) Palmar hand grip.

For muscle strength assessment patients will be oriented to use a comfort short and perform the proceduresat least 2 hours after a light meal, and abstain from exercise for 24 hours prior to testing.

6.1 ISOKINETIC DYNAMOMETER

Subjects preparation: Patients will be instructed to adopt a seated position (90° hip) in a good posture.Beltswill be used to stabilize thigh, pelvis, and trunk. Joint axis will be aligned with the dynamometerallowing knee expose. Alignment between both legs will be verified. All patient measures and dynamometer position (as chair height, chair base, seat backrest, dynamometer distance, armsdistance) will be standardized at baseline and at post protocol evaluation (20).

Method description: Calibration of the equipment will be performed according to the manufacturer'sspecifications before every testing session. Patients will be carefully stabilized with Velcro belts, andthe rotational axis of the dynamometer arm will be oriented with the lateral condyle of the right participant's femur. In an angular adjustment of 75° s-1 (stimulating much increase on muscle strength in patients with heart failure) (20–23) the isometric familiarization will be performed. Familiarization consists of three voluntary submaximal contractions, each one with a 5s duration, including 30s of in between rest period, then, the test will be ready to start. The patients will be allowedto perform five contractions (considering 30 s between attempts), and the largest value will be considered for analysis.

After 3 minutes of rest, the patients start isokinetic familiarization by performing six maximal repetitions as fast as possible. Post 3 minutes of recovery, the endurance protocol starts, 20 repetitionsat 180 ° s-1, once (24). Peak torque (N-M); peak torque and body weight ratio (%); total repetition maximum work (J); total work (J); fatigue (%) and mean load (W) will be obtained by isokinetic dynamometer (Biodex System 3 PRO, Medical Inc., New York, EUA).

6.2 1RM TESTING

Subjects preparation: After checking blood pressure at rest and medication use, patients will initiate the 1RMprotocol.

Method description: Following a brief familiarization, patients will perform five repetitions of a lightto moderate load (~50% of predicted 1RM) in order to learn the movement amplitude motion. The patients will be instructed to graduate the load perception as: i) light, ii) light to moderate, iii) moderate, iv) moderate tointense, iv) intense. Familiarization and warm up consisted of 10 repetitionsof each exercise load only if referred as light to moderate. Later, the 1RM test starts with increments according to the subject's perception and finish when finding the maximal load in a good posture. After each successful performance, the weight increased until a failed attempt occurred. No more thanfive attempts will be allowed for each muscular group. The 1RM test will be performed for an

experienced therapist. In case more than five attempts are needed, another test day will be scheduledto finish the test. 1RM will be collected before starting exercise protocol for prescription purposes.

6.3   PALMAR HAND GRIP STRENGTH

Palmar handgrip strength has been used to predict cardiovascular events and mortality (25–27).

Subjects preparation: The patient will be seated at rest for palmar grip strength test evaluation using the Digital Hand Dynamometer (Jamar Plus+, Jamar) following the American Society of Hand Therapists Guidelines (28).

Method description: Subject seated with arm supported, shoulders adducted in neutral rotation, elbowflexed at 90°, forearm in the neutral position and wrist between 0 and 30° of dorsiflexion. Three measures with the dominant and non-dominant hands will be performed. The highest value shall be expressed in kg and included for analyzes. The movements should be performed for 5 seconds following 3 minutes of rest after each attempt. Patients will be instructed to maintain spontaneous breathing and posture alignment. Accessories such as watches, rings, and bracelets will be removed

from both participants' upper limbs prior to the test. Participants will be instructed not to look at the dynamometer display to avoid any visual feedback(28).

7 BODY COMPOSITION

Whole body composition will be estimated by dual-emission x-ray absorptiometry (DXA - Lunar Prodigy BoneDensitometers, GE Healthcare, USA) (29,30). a) Fat mass (MG), b) lean mass (MLG),and c) bone mass will beexpressed in absolute values and percentages.

Subjects preparation: The subjects will be instructed to wear gym clothes and remove all metal belongs(bracelets, rings, earring, watch) before the exam. Individuals with pacemakers are not eligible for the test. Method description: All subjects will have their weight and height measuredbefore to adopt a supineposition on DXA. During the exam, the patients will be stationary for 10 minutes average after assuming theadjusted position.

8 PULMONARY FUNCTION

Pulmonary function and respiratory muscle strength will be accessed by spirometry (MicroLab ML3500MK8,CareFusion, EUA) and manovacuometer (MVD300, Globalmed, Brazil) tests.

Subjects preparation: Subjects will be instructed to abstain from autonomic stimulants (alcoholic drinks, coffee, tea or food containing caffeine) during 24h preceding the evaluation, as well as to ingest a light mealat least 2h before measurement. Patients shall rest 10 minutes before each test (spirometry, maximum respiratory pressures, and dynamic inspiratory pressure). They will then be placed sitting on a bench with their legs bent 90 degrees, erect posture, head in a neutral position, andnasal clip placed to prevent leakage(31).

8.1 SPIROMETRY

Method Description: Individuals will perform at least three forced expiration maneuvers according to the technical procedures and criteria of acceptability and reproducibility of American Thoracic Society (ATS) / European Respiratory Society (ERS)(31). Spirometry evaluation will be performed to check obstructive or restrictive patterns through outcome measures: forced expiratory volume in 1second (FEV1), forced vital capacity (FVC), expiratory peak flow (EPF), FEV1/FVC ratio.

8.2 MANOVACUOMETER

The MVD300® manovacuometer (Globalmed, Porto Alegre, RS, Brazil) was utilized to measure thepositive pressures (manometer) and negative pressures (vacuometer). Manovacuometer allows the static evaluation of maximum inspiratory pressure (MIP) and the maximum expiratory pressure (MEP) and play an importantrole in the diagnosis and prognosis of chronic diseases (25).

Method Description: The manovacuometer will be previously calibrated in cmH2O, with an operational limitof -300 to +300 cmH2O and scales ranging from 10 to 10 cmH2O. The methods andcriteria used will be thoserecommended by ATS / ERS (24). To assess the MIP, patients will be instructed to perform a maximal expiration, following a maximal inspiratory effort so the pressure will be recorded close to the residual volume. For the assessment of MEP, a maximum inspiration willbe requested before the maximal expiratoryeffort to evaluate the pressure, close to total lung capacity.A vigorous verbal command will be given duringthe evaluation.

8.3 DYNAMIC INSPIRATORY PRESSURE

Method Description: The evaluation of the dynamic respiratory muscle strength will be performed using thePOWERbreathe® KH2 device (London, England, UK), in which the maximal inspiratory effort will be assessed from residual volume. The maximum muscle strength (S-Index) will be obtained during the dynamic contraction of the inspiratory muscles. Patients will be instructed to achieve the highest possible inspiratoryflow rate after a previous expiration. In order to obtain the S-index, the patient must be collaborative and able to respond to verbal commands (24).

9 HEART RATE VARIABILITY

Autonomic modulation will be accessed by heart rate variability (HRV) method using heart rate monitor (Polar® RS800, Polar Electro OY, Finland) following linear index analysis in the time and frequency domains (56).

Subjects preparation: Subjects will be instructed to abstain from autonomic stimulants (alcoholic drinks, coffee, tea or food containing caffeine) during 24h preceding the evaluation, as well as to ingest a light mealat least 2h before measurement. In order to reduce anxiety during HRV evaluation,the volunteers will be kept alone in a comfort, quiet, and climate room. Subjects will be oriented to keep in silence and awake, at rest, breathing spontaneously for 30 minutes in the supine position duringevaluation by Polar RS800 monitor(Polar Electro®, Finland).

Method description: HRV data acquisition will be conducted in the morning to prevent circadian changes. The room temperature will be controlled (21 to 23º C / 70 to 73º F) and relative air humiditybetween 40% and 60%. Only period contained more than 95% sino-atrial node beats will be recordedand analyzed in the study. Stationary frames of 1000 R-R intervals (RRi) will be selected, accordingto the most stable signal of data acquisition. The Kubios software will be used to run HRV analysis (Biosignal Analysis and Medical Image Group, Department of Physics, University of Kuopio, Finland)(32).

Time domain analysis includes mean RR intervals (reflecting global variability); the square root of the mean squared difference between adjacent RR intervals (RMSSD) - reflecting parasympathetic modulations of HR; the standard deviation of all normal RR intervals (SDNN) - reflecting global variability. The geometric indexesfrom Poincaré plot (SD1 and SD2, reflecting parasympathetic andglobal modulations of HR, respectively);

triangular interpolation of normal to normal RR intervals (TINN) and triangular index (RRtri) both reflecting global variability. (33,34)

For the frequency domain, low frequency (LF: between 0.04 and 0.15Hz), high frequency (HF: between 0.15to 0.4Hz) and the relationship LF/HF will be computed. The spectral analysis includes Fast Fourier Transformcalculations. Spectral indexes will be expressed in absolute units (ms2) and normalized units (HFnu and LFnu).The power in the LF band is modulated by both the sympathetic and the parasympathetic branches of the autonomic nervous system and the power in the HF band iscorrelated with vagal modulation (33,34)

10 MUSCLE QUALITY ASSESSMENT

Subjects preparation: Patients will be previously oriented to wear shorts.

Method description: Ultrasound imaging will be captured using ultrasound (HD11XE, Phillips, Amsterdam, The Netherlands) with 7.5-MHz linear array transducers.

Individuals will be evaluated in the supine position with the knee in passive extension and neutral rotation. Water-gel will be applied to the ultrasound transducer to allow acoustic contact without pressing the dermalsurface. The images will be acquired in the right leg (rectus femoris - knee at 45 °),with the transducer placedtransversely and perpendicular to the long axis of the anterior thigh (rectusfemoris and vastus lateralis: 50%of the distance between the iliac spine anterior superior to upper anterior patellar border, anterior tibial: 25% of distance between medial condyle of tibia to lateral malleolus (35). The images will be saved on the ultrasound hard disk and transferred for later analysison a computer using ImageJ software (bundled with 64- bit Java 1.8.0_112, 70 MB, NIH, Bethesda, USA) (36).

All ultrasound measurements will be performed three times, using the mean of the scores for the finalanalyses. According to the images, the muscular thickness, echo intensity (minimum, maximum andaverage of the grayscale) and thickness of the subcutaneous tissue will be evaluated. All thickness parameters will bemeasured in centimeters.

The echo intensity will be reported in pixels. The echo intensity will be determined using computer quantitative scales. A 2×2cm square pattern for analysis of the rectus femoris and vastus lateralis will be used to determine the ROI. The square method has stronger confidence compared to the tracking method (where the evaluator highlights the entire visible muscle area, excluding epimysiumand artifacts) to define ROI80 (37). If the area to be analyzed is smaller than 2×2 cm, the largest possible square within the anatomical limits of the muscle will be examined. Mean, and standard deviation of the echo intensity of thisROI will be calculated using the ImageJ software histogram function (bundled with 64-bit Java 1.8.0_112, 70MB, NIH, Bethesda, USA) and expressed as a valuebetween 0 (black) and 255 (white)(38).

11 SHORT PHYSICAL PERFORMANCE BATTERY

The Short Physical Performance Battery (SPPB), is considered a brief performance battery based on short distance walking, repeated chair stands, and a set of balance tests (39). SPPB is a validated assessment tool able to measure lower extremity function which has been widely used in both clinical and research settings (40,41). Mainly used in aging studies, low scores in the SPPB is associated with a wide range of health outcomes such as hospitalization, length of hospital stay, mobility loss, disability, nursing home admission, and death (42,43).

Subjects preparation: Patients will be previously oriented to wear sports clothes.

Method description: SPPB execution will follow previous recommendations (39). Firstly, patients will perform a static equilibrium test based on three different positions held for 10 seconds: side by side (parallel feet); semi-tandem (one foot partially in front of the other) and tandem (one foot positioned in front of the other). The maximum total score possible for equilibrium tests is 4 points, in which two points are attributable to the last task.

Further, patients will perform twice the walking speed test, considering the time spent to walk along three meters corridor in their usual step. The shortest time will be considered for analysis. Scores rates as follow: if the walking time is less than 4.82 seconds = 4 points; between 4.82 and 6.20 seconds = 3 points; between 6,21 and 8,70 = 2 points; greater than 8.70 = 1 point. If the patient does not perform the walk, so no punctuation is awarded.

Finally, the third test of the battery evaluates lower limbs strength (the time spent to stand up and sit down on a chair for five consecutive times, without the aid of hands). Patients must perform five

consecutive attempts without using upper limbs. The maximum score assigned is 4 points for a test time of 11.19 seconds or less; 3 points for a time of 11.20 to 13.69 seconds; 2 points for a test time of

13.70 to 16.69 seconds and

1 point for 16.70 seconds or more. If patients are unable to perform the test within 60 seconds, or if the patient is not able to get up from the chair five times, the score assigned is zero.

The total score of SPPB is a result of the sum of equilibrium, walking speed and lower limb strength,totalizing12 points. Scores from 0 to 3 points are considered incapacity or very poor performance, scores from 4 to 6 points are considered low performance; from 7 to 9 points means moderate performance and from 10 to 12points are considered good performance.

12 TRAINING INTERVENTION PROTOCOL

Training protocols will occur three times per week during 36 sessions with a matched session duration(≈40 minutes). Training familiarization for both modalities will be established for the patient's adaptation, with a duration of 6 sessions. In case a patient requires more than 6 familiarization sessions to reach the adequateHIIT or CRT protocol intensities, the number of familiarization sessionswill be recorded for further analysis. The exercises on the CRT group will be conducted on six largemuscle groups, according to the established sequence: pull down, leg press, pectoralis machine, flexorchair, shoulder press, and extensor chair machines.Before the CRT sessions, 10 minutes of warmingup will be guided by the therapist, 5 minutes focusing on muscle stretching, and 5 minutes on dynamicmovements to promotes HR and blood flow increase. CRT will be performed in resistive stations, as (EN-Dynamic, Enraf-Nonius, Rotterdam). Exercise order will vary cyclically ineach session, but respecting exercise sequence. During the six sessions of familiarization on CRT, training load will be set at 50% of 1RM, with 3 circuit series of 12 repetitions. After the familiarizationperiod, the workloads will be set as 60% 1RMnin the 1st month; 70%1RM in the 2nd monthand 80%1RM in the 3rd month, following adaptation and overload principles (57). Repetitions: 6 to 12 repetitions in the first two weeks of each month and 15 to 20 in the last two weeks of each month. 3 circuit series of each exercise with 1 min of rest between exercises will be performed.

During the familiarization period on HIIT, the moderate intensity will be performed daily-alternated on a treadmill (T150, COSMED, EUA) and at an ergometric bicycle

(Corival, LODE BV Medical Technology Groningen - Netherlands), in which the heart rate should reach values higher than the 1st ventilatory

threshold for 30 minutes. HIIT will be gradually incorporated during familiarization toguarantee an adequateHR response during the research protocol. Before starts HIIT protocol, individuals will perform 10 minutes of warm-up at 10% above the HR equivalent to the 1st ventilatory threshold obtained by previous CPX. HIIT loads should vary between two intensities, 10% above the 1st (low-intensity) and 10% higher the 2nd ventilatory threshold (high-intensity) obtained from CPX. HIIT protocol will be applied by 4 minutes at low intensity followed by 3 minutes at high-intensity protocol, totalizing four cycles of 7 minutes. in 28 minutes of HIIT (44).

Polar Software will continuously register HR monitorization during training sessions.

Results information

Only clinically validated results will be communicated to the patient as well as their corresponding cardiologist.

2

Insurance and costs

Participation in the study will not result in additional costs for the patient. All costs willbe handled by the researchers. If any problem occurs throughout the study period, as aresult of the study participation, an insurance policy can be consulted.

Data handling and protection

All data will be handled confidentially and coded uniquely. A subject identification listwill be used to link data to the subjects. The key to the

code will be safeguarded by an independent investigator that is not involved in the study. All collected data will be stored in digital Case Report Forms at the Google Drive File Stream (protected by Hasselt University) and only the responsible researcher will have access to the source data. The participants have the right to ask the researchers for which data are being collected and what is the purpose of these obtained data. Participants can always ask to take a look in the obtained data and to correct these in case of necessity. Source data will be stored for 25 years in accordance with GCP standards to re-use them or to validate results. Future research in line with the current study (re-use of the data) will only be conducted with subject's approval on the informed consent form for re-use of the data and approval of the new study by the ethical committee.

The obtained personal data will not contain such elements that would make it possible to identify individual patients, which is in accordance with the EU guidelines (2016/679) and GDPR guidelines concerning personal data protection. Anonymized research data can, provided that permission has been obtained, only be evaluated by authorized collaborators of the research institute or the ethical committee via the responsible researcher Dominique Hansen.

13 STATISTICAL ANALYSIS

Descriptive analysis will be used for sample characterization. Shapiro Wilk test will check data normality. Parametric or non-parametric tests will be applied according to standard or non-standard data distribution (ANOVA two way with Tukey post-test or Kruskal Wallis with Newman Keuls post-test). Possible correlations will be tested using Spearman or Pearson correlation. Statistical software SPSS version 22.0 (SPSS, Inc.

Chicago, IL, USA) will be used following a 5% significance level. Sample size calculation made by Manova repeated measures, between factors from pilot data (n=11) and based on baseline arterial diameter (mm) indicated a minimum total sample size of 15 individuals (α err prob =0,05; power 1-β err prob = 0,95, effect size f = 0,914).

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Correspondent

Campus Virga Jesse

Stadsomvaart 11

3500 Hasselt

Ethical Review Committee

Advice Form

(X) Study Protocol

( ) Amendement protocol

( ) Medican need program

ONS KENMERK

Hasselt, 5 december 2019

Title Protocol: Effects of High Intensity Interval Training versus Circuit Resistance Training on Endothelial Function and Cardiorespiratory Capacity inPatients with Heart Failure:A Randomized Trial

Belgish registration: B243201942026
Lead Researcher: Prof. Dr. Dominique Hansen

FINAL APPROVAL OF ETHICS REVIEW COMMITTEE JESSA

Dear Colleague,

On 21/11/2019, the Ethics Review Committee made comments regarding the submitted study file. We hereby confirm that we have received your modified study application:

■ 19.94-REVA19.06_Reasons_adjustments

■ Application form_01122019_first adjustments

■ InformedConsent_December2019

■ Instruction sheet

The amended documents comply with the stated comments and will comply with the study file being added. The Ethics Review Committee hereby gives its final approval for the start of the research. This approval applies to all participating sites, as stated in the preliminar advice. This approval is valid until 31/12/2020.

The Ethical Review Committee is organized and acts according to the guidelines of GCP / ICH.

After the advice on the initial / file has been issued by the Ethical Review Committee, you can there is no amendment to add a new research site for 3 months were submitted.

If there are changes to the study and / or approved documents, the investigator is required to report these changes to the Ethics Review Committee, as stipulated in the internationally established guidelines by the International Conference on Harmonization; ICH E6: Good Clinical Practice, Consolidated Guideline CPMP / ICH / 135/95:

The researcher refrains from deviating from the protocol or implementing changes without permission from the sponsor and review / approval by the appropriate ethical commission, except when it concerns an immediate threat to the participant or When it concerns administrative changes (such as change of telephone number, ...).

The investigator is required to immediately report to the Ethics Review Committee, in following cases:

- Deviating or changing the protocol to pose an immediate danger to the participant appearance.
- Changing the protocol which increases the risk for the participant or whichincreases the course of the study changes significantly.
- Preventing Adverse Drug Reactions (Adverse Drug Reactions) that are serious and unexpected.
- New information that can affect the safety of the participant.

Inform the Ethics Review Committee if a study is not started or when it is closed or interrupted prematurely (with reasons). If the inclusion has not started one year after approval, approval for the study expires and must be completed a new application was submitted to the Ethics Review Committee for approval. In addition, the Ethics Review Committee asks the researcher to inform faar / ifks were kept from the course of the study. If this is done with, the approval will expire the stud1e. In addition, the Ethics Review Committee asks that upon termination, the following be taken:

- the end of the study (end date, number of treated / patients, possible complications and my overall impression).
- any publicatles.

Please find attached the list of members of the Ethical Review Committee.

With best regards,

For approval,

Vo te Assessment Committee

Jes is

December 5, 2019

Members of the Ethics Review Committee 2019

Dr. Koen Magerman, clinical bio / eye (chair)

Mieke Bieghs, pharmacist / substitute Inge Dreesen

Joyce Bollen - nurse and lie. moraa / sciences

Dr. Martin Herklots, neurologist

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HOPITAL

Rosita Jakers, psycho / age / alternates Hanne Heymans / Kelly Pauwels

Dr. Herman Kuppers - general practitioner

Anne / a Lintermans - patient representative

Fabienne Mertens - head nurse

Dr. Jean-Luc Rummens, clinical bio / eye

Dr. Geert Souverijns, radiologist

Dr. Bjorn Stesse / - Anesthetist

Kimberly Vanhees - operational manager biobank

Ohr. Pros Vanhe / mont - lawyer

Dr. Johan Vanwal! Eghem, nephro / eye (vice-chair)

Dr. Pascal Vranckx - cardiologist, expert pharmacology, pharmacotherapy, pharmacokinetics and clinical trial

design methodology expert

Dr. Renate Zeevaert - pediatrician

JESSA
Z I E K E N H U I S

Ethische Toetsingscommissie

ADVIESFORMULIER

- ■ studieprotocol
- ☐ amendement protocol
- ☐ medical need program

VOORZITTER
dr. Koen Magerman

SECRETARIAAT
Veerle Vanderhenst
veerle.vanderhenst@jessazh.be

CONTACT
ethische.toetsingscommissie@jessazh.be

ONS KENMERK
19.94-REVA19.06

Hasselt, 5 december 2019

Titel protocol:	**Effecten van hoog intense interval training versus krachttraining op endotheelfunctie en fysieke fitheid bij hartfalenpatiënten: een gerandomiseerde studie**
Belgisch registratien°:	B243201942026
Hoofdonderzoeker:	Prof. dr. Dominique Hansen

DEFINITIEVE GOEDKEURING ETHISCHE TOETSINGSCOMMISSIE JESSA

Geachte collega,

Op 21/11/2019 maakte de Ethische Toetsingscommissie opmerkingen in verband met het ingediende studiedossier.
Hierbij bevestigen wij dat we uw **aangepaste** studieaanvraag ontvingen:

- ■ 19.94-REVA19.06_Motivering_aanpassingen
- ■ Aanvraagformulier_01122019_eerste aanpassingen
- ■ InformedConsent_December2019
- ■ Instructiefiche

De gewijzigde documenten voldoen aan de gestelde opmerkingen en zullen aan het studiedossier toegevoegd worden.
De Ethische Toetsingscommissie geeft hierbij haar **definitieve goedkeuring** voor de start van het onderzoek. Deze goedkeuring geldt voor alle deelnemende sites, zoals vermeld in het voorlopig advies. Deze goedkeuring is geldig tot **31/12/2020**.

De Ethische Toetsingscommissie is georganiseerd en handelt volgens de richtlijnen van GCP/ICH.

Na het uitbrengen van het advies over het initieel dossier door de Ethische Toetsingscommissie, kan er gedurende 3 maanden geen amendement voor het toevoegen van een nieuwe onderzoekslocatie worden ingediend.

Als er wijzigingen zijn in de studie en/of goedgekeurde documenten, is de onderzoeker verplicht deze wijzigingen te melden aan de Ethische Toetsingscommissie, zoals gestipuleerd in de

adviesformulier versie 11_21/10/2019 – studie19.94-REVA19.06

De vzw Jessa Ziekenhuis is een fusie tussen het
Virga Jesseziekenhuis en het Salvator-St.-Ursulaziekenhuis

Maatschappelijke zetel:
Salvatorstraat 20, 3500 Hasselt

1/3

internationaal vastgestelde richtsnoeren door de 'International Conference on Harmonisation', ICH E6: Good Clinical Practice, Consolidated Guideline CPMP/ICH/135/95:

De onderzoeker onthoudt zich van afwijken van het protocol of implementeren van wijzigingen zonder toestemming van de opdrachtgever en herziening/goedkeuring door de bevoegde ethische commissie, behalve wanneer het gaat over onmiddellijke dreiging voor de deelnemer of wanneer het gaat over administratieve wijzigingen (zoals wijziging telefoonnummer, ...).

De onderzoeker is verplicht onmiddellijk een melding te doen bij de Ethische Toetsingscommissie, in volgende gevallen:

- *Afwijken of wijzigen van het protocol om een onmiddellijk gevaar voor de deelnemer te voorkomen.*

- *Wijzigen van het protocol waarbij de risico's voor de deelnemer verhoogt of waarbij het verloop van de studie significant wijzigt.*

- *Voorkomen van nadelige effecten (Adverse Drug Reactions), die ernstig en onverwacht zijn.*

- *Nieuwe informatie die de veiligheid van de deelnemer kan beïnvloeden.*

Gelieve de Ethische Toetsingscommissie mee te delen indien een studie niet wordt aangevat of wanneer ze wordt afgesloten of vroegtijdig wordt onderbroken (met opgave van reden). Indien de inclusie niet gestart is een jaar na de goedkeuring vervalt de goedkeuring op de studie en moet er een nieuwe aanvraag ter goedkeuring voorgelegd worden aan de Ethische Toetsingscommissie.

Daarnaast vraagt de Ethische Toetsingscommissie aan de onderzoeker jaarlijks op de hoogte te worden gehouden van het verloop van de studie. Indien dit niet gebeurt vervalt de goedkeuring op de studie. Verder vraagt de Ethische Toetsingscommissie om bij beëindiging volgende te melden:

- *het einde van de studie (einddatum, aantal behandelde patiënten, eventuele complicaties en mijn globale indruk).*

- *eventuele publicaties.*

In bijlage vindt u de ledenlijst van de Ethische Toetsingscommissie.

Met vriendelijke groeten,
Ter goedkeuring,

Dr. Koen Magerman   5 december 2019
Voorzitter Ethische Toetsingscommissie
Jessa Ziekenhuis

adviesformulier versie 11_21/10/2019 – studie19.94-REVA19.06

De vzw Jessa Ziekenhuis is een fusie tussen het
Virga Jesseziekenhuis en het Salvator-St.-Ursulaziekenhuis

Maatschappelijke zetel:
Salvatorstraat 20, 3500 Hasselt

2/3

Leden Ethische Toetsingscommissie 2019
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Joyce Bollen - verpleegkundige en lic. moraalwetenschappen
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Dhr. Pros Vanhelmont – jurist
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Dr. Pascal Vranckx – cardioloog, deskundige farmacologie, farmacotherapie, farmacokinetiek en clinical trial design methodology expert
Dr. Renate Zeevaert – pediater

S3 file. Chronological dates of the study steps

Supporting informations

Chronological dates of the study steps:

- March 21st, 2018 - approval on Brazilian Ethical Commite
- May 21st, 2018   - approval on Study Registration Platform – REBEC
- June 1st, 2018   - first date for enrollment in Brazil
- September 8th, 2019 - last date for enrollment in Brazil
- December 5th, 2020 - approval on Belgic Ethical Commite

This study did not started as a multicentric one, but along the PhD of the main researcher there was an opportunity to make it, stablishing a joint PhD partnership between Brazil and Belgium.

Changes were made in the initial protocol in order to adapt the trial to a multicentric one. The outcomes initially cited on Brazilian Ethical Committe "quality of life" and "oxygen extraction" were not included on Belgic ethical Commite due to technical limitations. In addition, the outcomes "autonomic modulation", "muscle ultrasound" and "pulmonar function" were not included on this paper, but they were obtained and can be presented in a future pape or upon reasonable request.

Natália Turri-Silva

(on behalf of all coauthors)

S1 Figure. Individual dynamic of flow-mediated dilation
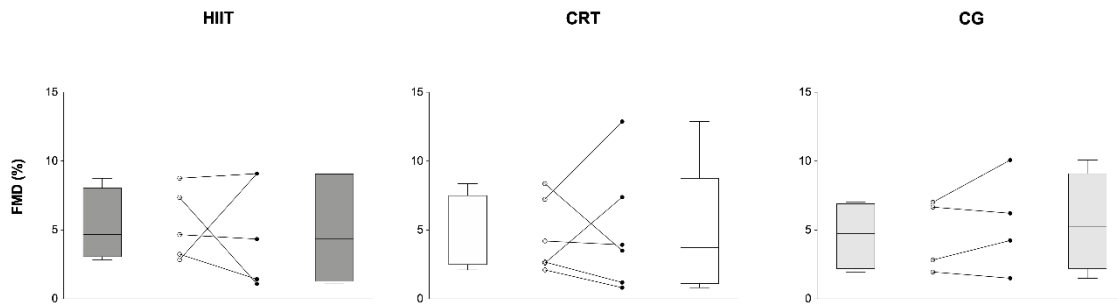
S1 Table. Body composition parameters in heart failure

DXA	HIIT (n=4)		CRT (n=4)		CG (n=7)		group*time interaction	group interaction	time interaction
	pre	post	pre	post	pre	p value	p value	p value	p value
Total fat mass (%)	36,9 ± 0,5	37,1 ± 1,7	40,2 ± 8,2	39,9 ± 8,6	33,9 ± 3,8	33.2 ± 4,2	0,611	0,156	0,566
95% CI	[36.0;37.7]	[34.4;39.9]	[27.2;53.1]	[22.2;53.5]	[30.4;37.4]	[29.3;37.1]			
Total lean mass (%)	60,5 ± 0,6	61,2 ± 1,5	57,8 ± 8,1	58,6 ± 7,8	63,8 ± 3,9	64,1 ± 3,6	0,878	0,183	0,201
95% CI	[59.5;61.5]	[58.7;63.6]	[45.0;70.7]	[46.2;70.9]	[60.2;67.5]	[60.8;67.5]			

Legends: DXA (dual x-ray absorptiometry); **HIIT** (high-intensity interval training); **CRT** (circuit-resistance training); **CG** (control group). Comparisons between groups were analyzed by the Two-way ANOVA (group*time interaction and group interaction). The baseline and post were analyzed by Kruskall-Wallis Test. The normality was analyzed by Kolmogorov-Smirnov test. Values are expressed as mean ± standard deviation (SD). A statistically significant difference was considered when there was a p value <0.05.

Eletronic Supplementary Material - chapter 3

Search strategy

The search strategy included the cross-checking of the keywords, according to the Medical Subjects Headings (Mesh), from the United States National Library of Medicine. We chose the keywords following the intervention and population criteria and included filters to limit the search only to randomized clinical trials. There was no language restriction. The full electronic search strategy followed the keywords: (i) population: "Heart-Lung Transplantation"[Mesh] OR "Heart Transplantation"[Mesh] (ii) intervention: "Warm-Up Exercise"[Mesh] OR "Cool-Down Exercise"[Mesh] OR "Plyometric Exercise"[Mesh] OR "Exercise Muscle Stretching Exercises"[Mesh] OR "Exercise"[Mesh] OR "Physical Therapy"[Mesh] OR "Exercise Tolerance"[Mesh] OR "Exercise Therapy"[Mesh] OR "Resistance Training"[Mesh] OR "Physical Therapy Specialty "[Mesh] OR "Circuit-Resistance Training"[Mesh] OR "High-Intensity Interval Training"[Mesh]).

The research was limited to Randomized Controlled Trials (RCTs) in humans above 19 years old in the following languages: Dutch, English. French and Portuguese.

The studies were selected according to the Cochrane handbook (152). The authors initially assessed the title and abstract for screening, followed eligibility criteria, including the type of study design, description of the population, and information on interventions.

Quality of the trials

Quality assessment was performed by two independent reviewers (WCCR and JSF) (and a third reviewer (GCJ) in case of disparities). PEDro scale was used (Table and detailed Pedro score on Electronic Supplemental Material Table S1). On this scale, 11 questions were answered as 'yes' (score 1) or 'no' (score 0) to obtain more information about the internal and external validity of the study and interpretability of the statistical results (Pedro). According to Pedro guidelines, item 1 from the Pedro scale was not used to calculate the score, which resulted in a total score maximum of 10.

According to the Pedro scale, specific information per domain is below in Table S1.

Study	Study quality criteria										
	2	3	4	5	6	7	8	9	10	11	**Total**
Braith et al.	1	0	1	0	0	1	0	0	1	1	**5**
Bernardi et al.	1	0	1	0	0	0	0	0	1	1	**4**
Haykowsky et al.	1	0	0	0	0	0	1	0	1	1	**4**
Hermann et al.	1	1	1	0	0	1	1	0	1	1	**7**
Kobachigawa et al.	1	1	1	0	0	0	1	0	1	0	**5**
Nytrøen et al.	1	0	1	0	0	0	1	0	1	1	**5**
Pascoalino et al.	1	0	1	0	0	1	1	0	1	1	**6**
Pierce et al.	1	0	1	0	0	0	0	0	1	1	**4**
Tegtbur et al.	1	0	1	0	0	0	0	0	1	1	**4**
Wu et al.	1	0	1	0	0	0	0	1	1	1	**5**
Braith et al.	0	0	1	0	0	1	0	0	1	1	**4**
Braith et al.	1	0	1	0	0	1	1	0	1	1	**6**
Dall et al.	1	1	1	0	0	1	1	0	1	1	**7**
Karapolat et al.	1	0	1	0	0	0	0	0	1	0	**3**

Table S1 *Physiotherapy Evidence Database (PEDro) scores for each of the 12 included studies in the metanalysis. 1 = criterion is satisfied; 0 = criterion not satisfied*

Other papers during the PhD period

Effects of resistance training protocols on nonlinear analysis of heart rate variability in metabolic syndrome

N. Turri-Silva; D.M. GarnerS; H. Moosavi; A.L. Ricci-Vitor; D.G.D. Christofaro; J. Netto Junior; L.M. Vanzella; L.C.M. Vanderlei

Journal: Braz. J. Med. Biol. Res. 51 (8) • 2018

Analysis of function and disability in heart failure patients

CARVALHO, Karen Gomes; VALLE, Giovanna Oliveira1; MARTINS, Gabriela de Sousa; SILVA, **Natalia Turri-Silva**, Marianne Lucena da; MORAIS, Letícia de Araújo; CIPRIANO JR, Gerson; MARTINS, Wagner; CIPRIANO, Graziella França Bernardelli.

Journal: ASSOBRAFIR Ciência. 2019 Ago;10(2):25-36

Functional Resistance Training Superiority Over Conventional Training in Metabolic Syndrome: A Randomized Clinical Trial

Natália Turri-Silva, Ana Laura Ricci-Vitor, Gerson Cipriano Jr., David Garner, Jaime Netto Jr, Thaís Giacon, Diego Giulliano Destro Christofaro & Luiz Carlos Marques Vanderlei

Journal: Research Quarterly for Exercise and Sport, 91:3, 415-424, DOI: 10.1080/02701367.2019.1679333

Peripheral Components and Body Composition Impair Oxygen Kinetics in Heart Failure with Preserved Ejection Fraction"

Gerson Cipriano Jr, Marianne Lucena, Dominique Hansen, Sergio Ramalho, **Natália Turri-Silva**, Amanda Vale-Lira, Gaspar Chiappa.

Journal: Submitted to Plos One

A Randomized Controlled Crossover Trial of Virtual Reality in Maintenance Cardiovascular Rehabilitation in a Low-Resource Setting: Impact on Adherence, Motivation, and Engagement

Mayara Moura Alves da Cruz, Ana Laura Ricci-Vitor, Giovanna Lombardi Bonini Borges, Paula Fernanda da Silva, **Natália Turri-Silva,** Carolina Takahashi, Sherry L Grace, Luiz Carlos Marques Vanderlei

Journal: *Physical Therapy*, Volume 101, Issue 5, May 2021, pzab071

Is mat pilates training supplemented with aerobic exercise better for improve blood pressure in hypertensive women? A randomized and controlled clinical trial

Isabella da Silva Almeida, PTa,b; Letícia de Souza Andrade, PT1; Alessandra Martins Melo de Sousa, PTa; Gerson Cipriano Junior, PT, PhDa,c; Natália Turri da Silva, PTc; Dahan da Cunha Nascimento, PhDd; Yomara Lima Mota PT, PhDe, João Luiz Luiz Quagliotti Durigan, PT, PhDa

Journal: Physical Therapy, 2021

Short-Term Effects of a Resistance Training Program Using Elastic Tubing in Patients with Heart Disease
João Pedro Lucas Neves Silva, Tamara Iasmin de Sá Ferreira, Gabriela Côrtes Cavalleri, Mayara Moura Alves da Cruz, Bianca Pinhal Galindo, Natália Turri da Silva, Bruna Spolador de Alencar Silva, Marceli Rocha Leite, Ana Paula Coelho Figueira Freire, Ercy Mara Cipulo Ramos, Luiz Carlos Marques Vanderlei, Francis Lopes Pacagnelli

Journal: International Journal of Cardiovascular Sciences. 2021; 34(2):149-156

Congresses/conferences participation and abstract accepted

CENTROFIR 2017: Efeitos do treinamento resistido com uma e múltiplas articulações na síndrome metabólica.

DEIC 2018: "Reabilitação cardiovascular semi-supervisionada mantém a capacidade cardiorrespiratória após programa supervisionado em pacientes com insuficiência cardíaca"

SIFR 2018: "Perfil clínico e funcional de idosos durante internação em UTIs adulto: Estudo de Coorte" and "Análise do pico de fluxo expiratório de pacientes críticos durante permanência em UTI: Estudo coorte prospectivo"

V JOBRAFIR 2019: "Influência da reabilitação cardiopulmonar na força muscular esquelética: um estudo piloto" e "Efeito da reabilitação cardiopulmonar na capacidade físico funcional: estudo piloto"

ESC Preventive Cardiology 2019: "The effect of high intensity interval training on left atrial volume index in heart failure patients" and "The behavior of cardiorespiratory capacity after a semi-supervised cardiovascular rehabilitation program in heart failure patients - a pilot study"

ESC Preventive Cardiology 2020: "Aerobic and resistance high- intensity exercise protocols in heart failure: a preliminary study" e "Peripheral components impair oxygen uptake kinetics in heart failure with preserved ejection fraction: a case-control study"
ESC Preventive Cardiology 2021: participation as listener

American Heart Associations's Scientific Sessions 2021: "Muscular Microcirculatory Dynamics During Lower Limb Strength Exercise Testing In Heart Failure With Preserved Ejection Fraction"

Congresso Internacional e XVII Nacional do DERC 2021 - Da prevenção ao tratamento: participation as listener.

Extra activities during PhD period

Ambulatory Coordination, clinical practice, and research projects
- PRECAP – University of Brasilia
  Supervision of students, education, assessments, rehabilitation
- Genk Hospital: project ongoing with heart failure patients (interventional study)
  What is the effect of low- or moderate-intensity strength training with addition of endurance training in people with heart failure?– University of Hasselt

Master degree co-supervisions:
- Tom Gillissen – Maastrich University and University of Hasselt
  The adaptive response of skeletal muscle function and structure post high-intensity interval training versus circuit resistance training in human heart failure

- Lore Timmers and Lieze Nouwen - University of Hasselt
  The difference between low and moderate intense resistance training, combined with aerobic endurance training, on exercise tolerance and functional capacity in patients with heart failure

- Lise Machiels and Lennert Verdonck - University of Hasselt
  To what extent does the effect on strength, exercise tolerance and hemodynamic parameters differ between an aerobic exercise program in combination with a low-intensity strength training program and an aerobic exercise program in combination with a moderate-to-high intensity strength training program in patients with heart failure?

- Amanda Vale-Lira – University of Brasilia (collaboration)
  Morphofunctional aspects of the musculoskeletal system in patients with heart failure with reduced and preserved ejection fraction: performance, muscle architecture and peripheral oxygen extraction

Bachelor's degree thesis co-supervision:
- Amanda Rafaely – University of Brasilia
  Effects of a cardiovascular rehabilitation program on muscular strength of patients with heart failure: a pilot study

- Julia Fontenele and Daniele Stefanie – University of Brasilia
  Effect of cardiovascular rehabilitation on the functional physical capacity of patients with heart failure: a pilot study

- Jessica Desirre – University of Brasilia
  Skeletal muscle strength in heart failure with preserved and reduced ejection fraction: a cross-sectional study

Publication rules of the journal in which the scientific articles were submitted, and qualis of the journal in the Interdisciplinary area

International Journal of Environmental Research and Public Health
Impact factor: 3.39
Qualis Interdisciplinary area: A2

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<u>Plos One</u>
Impact factor: 3.240
Qualis Interdisciplinary area: A1

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Impact factor: 2.43
Qualis Interdisciplinary area: A2

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Journal Rank: JCR - Q2 (Medicine, General & Internal) / CiteScore - Q2 (General Medicine)

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