Exercise Hemodynamics in Chronic Heart Failure

Physiological and Clinical Aspects

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Colofon

Exercise Hemodynamics in Chronic Heart Failure:
physiological and clinical aspects

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Exercise Hemodynamics in Chronic Heart Failure

Physiological and Clinical Aspects

Hemodynamiek tijdens inspanning bij Chronisch Hartfalen
fysiologische en klinische aspecten
(met een samenvatting in het Nederlands)

Proefschrift

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door

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te Venray

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CHAPTER 1

Introduction and outline of the thesis

Introduction

Chronic Heart Failure (CHF) is a complex and multi-faceted chronic disease with a high burden on healthcare.[1,2] The incidence and prevalence are increasing with age. As high as eighty percent of CHF patients are 65 years or older. It is estimated that there are currently about 227.000 CHF patients in the Netherlands. The prevalence will rapidly increase in the near future because of the ageing population and increasing prevalence of patients with diabetes, hypertension and obesity. In addition, better and faster diagnosis and improved pharmacological and non-pharmacological treatment will also contribute to the increasing CHF population.[3] Despite improved treatment modalities, CHF is still associated with a high mortality and morbidity rate. Annually, about 7700 deaths are related to CHF in the Netherlands.[3] Within the first year of diagnosis 17% patients die and survival rate is about 56% after 5 years, making the prognosis of CHF worse compared to some forms of prostate, colon or breast cancer.[1] Perhaps even more important from a patient perspective, CHF has a high morbidity rate. Patients suffer from fatigue and exercise intolerance which impairs daily life activity and increases the risk for functional dependence. Moreover, quality of life is reduced and depression is more prevalent compared to healthy controls.[4,5]

In addition, CHF has a high impact on society. In the Netherlands, there are yearly about 29000 hospital admissions related to CHF and 14% of patients are readmitted within 6 months. Of all diseases, CHF is the number one reason of readmission, leading to an enormous burden for healthcare. About 1 billion euro is spent each year on CHF related costs and because of the expected increase in prevalence, this figure will dramatically increase in the near future.[3] Therefore, it is important to develop strategies that improve quality of care for patients and/or reduce costs to achieve the best patient value.

Pathophysiology of exercise intolerance in Chronic Heart Failure

CHF is characterized by an impaired exercise tolerance. The pathophysiological background of exercise intolerance in CHF patients is a complex interplay of all factors affecting the oxygen transport and utilization chain from air to the exercising muscle.[2] According to the Fick equation, the reduced peak oxygen uptake ($\dot{V}O_{2k}$) is related to changes in cardiac output (Q) and (or) arterio-venous oxygen difference (a-vO_2) and their respective determinants. While it is generally conceived that in compensated CHF patients, oxygen diffusion in the lung is not limiting exercise capacity, there is still controversy whether central hemodynamics or peripheral oxygen extraction is the weakest link.[6] Originally, it was thought that the heart was the key determinant in exercise intolerance. Whereas

the CHF syndrome is initiated by a reduced pumping capacity leading to impaired tissue oxygenation, it is associated with a subsequent cascade of physiological adaptations involving activation of the RAAS system and sympathetic nerve activity (SNA), which serves to maintain stroke volume on the short term, but also induces several deleterious effects on skeletal muscle structure and function on the long term leading to exercise intolerance.[7] Since the muscle hypothesis by Coats et al, there was a paradigm shift towards a more central role for the skeletal muscle in the reduced exercise capacity of CHF patients.[8] Indeed, it was previously demonstrated that left ventricular ejection fraction (LVEF) at rest correlates poorly with exercise capacity.[9] However, in a disease that is characterized by a reduced *exercise* capacity, pathophysiological mechanisms underlying exercise intolerance should be studied during exercise. As such, previous studies in CHF patients showed that the hemodynamic response to exercise is markedly reduced and strongly relates to the impaired exercise capacity.[10,11,12] In fact, several studies demonstrated that a reduced hemodynamic response to exercise is one of the strongest predictors of worse prognosis.[10,13,14] Widespread use and implementation of exercise hemodynamics in clinical practice is currently hampered by several factors including the invasive and time consuming nature of the direct Fick method and/or technical difficulties precluding continuous and true maximal values in none invasive techniques as foreign gas rebreathing and bioimpedance cardiography. Moreover, comparison of hemodynamic data between studies is limited because of the lack of validation and accuracy of different techniques.[15,16,17] Yet, exercise hemodynamics provide not only prognostic information but also response to therapeutic interventions[18,19] and insight in the physiological determinants of exercise intolerance.[20] Determining the physiological profile of the patient may reveal the predominant limitation of exercise intolerance. For example, a patient with both a reduced peak $\dot{V}O_2$ and peak Q is considered to be centrally limited and may benefit from an intervention that improves cardiac function, like heart transplantation, left ventricular assist device (LVAD) or cardiac resynchronization therapy (CRT), while another patient with the same peak $\dot{V}O_2$ and a normal hemodynamic response to exercise may respond better to exercise training in order to improve peripheral derangements. Studies using such a physiological approach are limited and more research is necessary to establish its clinical usefulness in the current era of new pharmacological and non- pharmacological therapies.[10,21,22]

Although peak $\dot{V}O_2$ is considered to be the "gold standard" to measure aerobic capacity and is a strong predictor of prognosis in CHF,[23] the reliability of the attained maximal value can be influenced by patient motivation, encouragement and the test protocol.[24,25] In addition, daily life does not consist of repetitive activities at peak level. Therefore, submaximal exercise testing is considered to be a better indicator of functional capacity in CHF patients.[26,27] Oxygen uptake kinetics at the onset and recovery of a constant load test below the ventilatory aerobic threshold (VAT) are reliable and reproducible

submaximal parameters. $\dot{V}O_2$ onset and recovery kinetics can be used for prognosis and response to an intervention. Moreover, they are suitable for studying the physiological background of submaximal exercise performance in combination with validated measurements of central and peripheral determinants of $\dot{V}O_2$ kinetics.[28,29,30,31] At present, there is a discrepancy in the literature regarding the primary limitation of prolonged $\dot{V}O_2$ kinetics. This might be explained by the fact that studies did not measure central and peripheral parameters simultaneously during exercise.[32,33,34,35] Another explanation for these apparently conflicting results can be that there is a heterogenuous physiological response to submaximal exercise in CHF patients. In fact, computer modeling and animal studies provided evidence for heterogeneity,[36,37,38] but more studies are needed to confirm these results in CHF patients.

Role of exercise training in Chronic Heart Failure

It was only three decades ago, that the prevailing opinion among cardiologists was that exercise should be discouraged in CHF patients because of its deteriorating effects on the failing heart.[39,40] Nowadays, it is widely recognized that exercise training is safe and improves functional capacity by restoring central and peripheral disturbances. After a landmark study by Sullivan et al,[41] many studies showed the numerous positive effects of exercise training, such as increase in exercise capacity and quality of life, reducing hospital admissions and even improving prognosis.[42,43,44] As a consequence, exercise training has currently the highest class of recommendation (Ia) in heart failure guidelines.[45] The majority of original research, supporting aerobic exercise training, has investigated training programs that are continuous and at a moderate intensity relative to the maximal exercise capacity. However, more recently, the focus of research has shifted towards training programs at higher intensities. Initial evidence showed that high intensity interval training (HIT) could be performed safely in cardiac patients[46] and was superior to moderate continuous training (MCT) in terms of exercise capacity.[47] In addition, substantial reverse remodeling of the left ventricle in CHF patients was demonstrated.[48] Although animal and *in vitro* studies provided a physiological base for these results,[49,50,51] recent larger multicenter randomized clinical trials in coronary artery disease and CHF patients failed to show superiority in exercise capacity and cardiac function between HIT and MCT.[52,53] As a consequence, some controversy has risen about the beneficial effects of HIT. Yet, if HIT is still going to be used in cardiac rehabilitation, the phenotype of a responder and the mechanisms behind it, should be clarified. Moreover, the additional value of HIT in specific subgroups, such as CHF patients with cardiac resynchronization therapy (CRT) remains to be determined. Maximal and submaximal cardiopulmonary exercise testing (CPET) with contemporary measurements of central and peripheral determinants of $\dot{V}O_2$

can provide additional physiological insight in these mechanisms.[15,31] Knowledge about the contributors to the beneficial effects of a therapeutic intervention could lead to an individual based therapy and may yield significant clinical advancements.

Outline of the thesis

This thesis addresses the following themes:

1) Evaluation of the physiological heterogeneity of exercise intolerance in CHF patients by combining cardiopulmonary exercise testing with assessment of exercise hemodynamics and skeletal muscle oxygenation
2) Exploration of the clinical and physiological effects of high intensity interval training and cardiac resynchronization therapy in CHF patients

Part I discusses the first theme in chapters 2-5. The relative contribution of central versus peripheral factors in the reduced exercise capacity is still subject of debate and may have distinct therapeutic consequences. In chapter 2, we studied the heterogeneity in the nature of exercise intolerance by evaluating individual cardiac output (Q) patterns, with a failure to augment or a decrease in Q towards peak exercise being indicative of a central hemodynamic exercise limitation. In chapter 3, we evaluated the absolute and relative test-retest reliability of skeletal muscle oxygenation measurements in CHF patients. Near-infrared spectroscopy (NIRS) can be used in CHF patients for the identification of limitations in O_2 delivery or utilization at skeletal muscle level during exercise. Chapter 4 discusses the relation between central hemodynamics and skeletal muscle oxygenation during a submaximal exercise protocol which is indicative of normal daily activities, using the kinetics of cardiac output and the minimal value of the tissue saturation index (TSI), a NIRS parameter validated in the previous study. We hypothesized that in patients with a slowed hemodynamic response to exercise relative to metabolic demands, the degree of tissue deoxygenation increases as a compensation mechanism to attenuate the effect on $\dot{V}O_2$ kinetics. In the last chapter (chapter 5) of Part I, we evaluated the relation of exercise hemodynamics and the impaired oxygen pulse (OP) during recovery after maximal exercise. The cardiac output (Q) response to exercise is a useful marker to grade the prognosis and severity of CHF. The recovery of the oxygen pulse (OP) after maximal exercise is a non-invasive parameter, which is related to exercise capacity in cardiac patients. However, the relation between OP recovery and the Q response to exercise remains to be determined. We hypothesized that an impaired OP recovery is associated with a reduced Q response to exercise in CHF patients and may therefore be useful to grade central hemodynamic impairments non-invasively.

Part II discusses two randomized controlled trials in which we explored the physiological background of HIT and CRT on exercise capacity and its central and peripheral determinants. Previous studies demonstrated positive effects of HIT on cardiac remodeling and endothelial function; yet physiological measurements in these studies were performed at rest. In the HIT Central study (chapter 6), patients were randomized to either HIT or usual care. The aim of this explorative study was to investigate the effect

of HIT in CHF patients on maximal and submaximal exercise capacity and in particular to establish whether these improvements are mediated through improvements in exercising central hemodynamics and/or changes in microvascular oxygen delivery-to-utilization matching.

In chapter 7, the additional effects of HIT after CRT were studied. We hypothesized that HIT after CRT results in additive beneficial effects on exercise capacity through a synergistic effect in both central hemodynamic as well as peripheral factors.

Finally, in chapter 8, the main findings of this thesis are discussed and put into perspective. Implications for clinical practice and directions for future research are outlined.

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PART I

Physiological Aspects

CHAPTER 2

Characterization of exercise limitations by evaluating individual cardiac output patterns: a prospective cohort study in patients with chronic heart failure

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Abstract

Background Patients with chronic heart failure (CHF) suffer from exercise intolerance due to impaired central hemodynamics and subsequent alterations in peripheral skeletal muscle function and structure. The relative contribution of central versus peripheral factors in the reduced exercise capacity is still subject of debate. The main purpose was to investigate heterogeneity in the nature of exercise intolerance by evaluating individual cardiac output (Q) patterns. The secondary purpose was to evaluate whether patient and disease characteristics were associated with a central hemodynamic exercise limitation.

Methods Sixty-four stable CHF patients performed a symptom limited incremental exercise test with respiratory gas analysis and simultaneous assessment of Q, using a radial artery pulse contour analysis method. A central hemodynamic exercise limitation was defined as a plateau or decline in Q from 90 to 100% of exercise duration.

Results Data from 61 patients were analyzed. A central hemodynamic exercise limitation was observed in 21 patients (34%). In these patients, a higher occurrence of a plateau/decrease in oxygen uptake ($\dot{V}O_2$) (52% vs 23%, p=0.02), stroke volume (SV) (100% vs. 75%, p = 0.01) and chronotropic incompetence (31% vs. 2.5%, p = 0.01) was observed, while presence of a left bundle branch block (LBBB) occurred significantly less (19% vs 48%, p=0.03) There was no difference in disease characteristics such as etiology, duration, NYHA class, mitral regurgitation or ischemia.

Conclusions The study revealed considerable heterogeneity in the nature of exercise limitations between moderately impaired CHF patients. In one third of the study population a plateau or decrease in Q towards peak exercise was demonstrated, which is indicative of a central hemodynamic exercise limitation. A central hemodynamic exercise limitation was associated with an impairment to augment stroke volume and heart rate.

Background

Chronic heart failure (CHF) is a clinical syndrome resulting from inadequate tissue oxygenation due to impaired cardiac function. Although it is well established that patients with CHF suffer from exercise intolerance, the underlying pathophysiological mechanisms remain controversial. From a theoretical point of view, reduced exercise capacity may be the consequence of O_2 diffusion abnormalities in the lungs, impaired central hemodynamics or peripheral derangements such as a reduced skeletal muscle capillarization or metabolic capacity. Whereas it is generally accepted that pulmonary O_2 diffusion does not limit exercise capacity in compensated CHF patients, the role of central and peripheral factors is still under debate.[1] Previous studies showed associations between maximal exercise capacity and central hemodynamics,[2,3] whereas other studies revealed a relation between exercise capacity and skeletal muscle function.[4,5] A possible explanation for these seemingly discrepant findings is that the nature of exercise limitations differs between CHF patients. In fact, results from an animal study demonstrated that the primary response of microvascular oxygen pressure in the muscle was speeded in rats with moderate left ventricular (LV) dysfunction, while in rats with severe LV dysfunction, this response was significantly slowed.[6] These results suggest that the dynamic balance between oxygen delivery and utilization in the muscle is dependent of the severity of cardiac dysfunction, indicating physiological heterogeneity. Although additional physiological insight is needed in humans, some clinical studies suggested heterogeneity in exercise limitations. As such, CHF patients with a severe central hemodynamic limitation did not benefit from exercise training,[7] but may benefit most from a heart transplantation.[8] Characterization of exercise limitations in individual CHF patients and more knowledge on disease characteristics associated with the nature of these limitations may lead to a more tailored therapeutic strategy in CHF patients. An approach that can be used to characterize exercise limitations is to examine the pattern of the cardiac output (Q) response to symptom-limited exercise, with a failure to augment or a decrease in cardiac output towards peak exercise being indicative of a central hemodynamic exercise limitation.[9] Although previous studies investigated the cardiac output response to exercise with respect to prognosis,[10,11] no studies used cardiac output patterns during incremental exercise to characterize exercise limitations in CHF patients.

The primary goal of this study was to investigate the nature of the limitation of maximal exercise capacity in CHF patients by evaluation of cardiac output patterns. Furthermore we evaluated whether patient and disease characteristics are associated with a central hemodynamic exercise limitation.

Methods

The present study was designed as a prospective cohort study. All tests were conducted at the Department of Cardiology of the Máxima Medical Centre, the Netherlands. The research protocol was approved by the medical ethics committee of the Máxima Medical Centre. The study complies with the Declaration of Helsinki. All patients provided written and signed informed consent, prior to the study.

Population

All consecutive symptomatic CHF patients visiting the outpatient clinic of cardiology were considered for participation in the study. Additional inclusion criteria were: CHF secondary to ischemic or dilated cardiomyopathy, New York Heart Association functional class II-III, left ventricular ejection fraction ≤ 40% and optimized medical treatment. Exclusion criteria were: recent myocardial infarction, unstable angina (less than 3 months prior to inclusion), hemodynamically significant aortic valve disease, participation in a training program (≥2/week) in the last year, significant chronic obstructive pulmonary disease (FEV1/FVC<60%) and orthopedic or neuromuscular conditions limiting the ability to perform exercise.

Exercise testing

All patients performed a symptom-limited incremental exercise test on an electromagnetically braked cycle ergometer in an upright position (Corrival, Lode, Groningen, The Netherlands), using an individualized ramp protocol with a duration of 8 to 12 minutes. The test ended when a patient was not able to maintain the required pedaling frequency of 70 per minute. A 12-lead electrocardiogram was registered continuously. Ventilatory parameters were measured breath-by-breath (ZAN 680 USB, ZAN Messgeräte, Oberthulba, Germany). Volume and gas analyzers were calibrated before each test.

Assessment of central hemodynamics

Assessment of central hemodynamics was performed by a radial artery pulse contour analysis method (LiDCO, LiDCO Ltd, London, UK). This technique provides beat-to-beat changes in central hemodynamics, by calculating nominal stroke volume (SV) from a pressure-volume transform of the radial artery pressure waveform.[12] In order to convert nominal SV to absolute SV, the system has to be calibrated at rest for each subject by an independent method. We used echocardiography or lithium dilution for this purpose.[13,14] Before the exercise test, a 20-gauge arterial catheter was inserted into the radial artery. The radial artery catheter was connected to the LiDCO *plus* monitor. Subsequently, the calibration procedure to determine resting Q was performed in the supine position.

Thereafter patients were positioned upright on the cycle ergometer and the exercise protocol was started. Patients were instructed to keep the measured arm on the handlebar of the ergometer in the same position to keep an optimal arterial waveform. Previous studies showed that LiDCO is a reproducible and accurate method for assessment of cardiac output (Q) under a variety of physiological conditions.[15,16] Moreover, in a study using the Fick method as a reference, we showed that this technique is highly accurate for continuous assessment of Q during incremental symptom-limited exercise testing in CHF patients.[13]

Data analysis

Breath-to-breath data of oxygen uptake and beat-to-beat data of central hemodynamics were filtered for outliers using Python (Python 2.7, Python Software Foundation). Outliers were defined as values deviating more than three standard deviations from a calculated moving average.[17] All data were time aligned using manual set markers at the start of exercise and filtered using a central moving average filter with a window of 11 data points. In order to compare gas exchange and central hemodynamic variables during exercise between CHF patients, data were expressed as a percentage of total exercise time. Baseline values were calculated as the mean of the first 60 seconds of the unloaded phase prior to the start of loaded exercise. Peak values were defined as the average values during the final 20 seconds of the test. We characterized exercise limitations by using the pattern of the cardiac output response to maximal exercise. A failure to increase or a decrease in cardiac output towards the end of exercise was considered to be indicative of a central hemodynamic exercise limitation. A central hemodynamic exercise limitation was defined as a plateau or decline in Q from 90 to 100% of exercise time. Chronotropic incompetence was defined as a peak HR below 80% of the age-predicted heart rate, using the Brawner formula.[18]

Statistical analysis

Data were analyzed using SPSS 19.0.0 statistical software (SPSS Inc, Chicago, IL, USA). Continuous variables were tested for normality and presented as mean or mean ± SD. Between-group differences of continuous variables were evaluated by an independent t-test. Categorical variables are presented as absolute and relative frequencies. The $\chi 2$ test was used to evaluate differences between categorical data. Differences were presented as $\chi 2$ value with concomitant degree of freedom (df) Relations between variables were assessed by Pearson's correlation coefficient (r). For all statistical comparisons, the level of significance was set at $p < 0.05$.

Results

All 64 patients completed the combined hemodynamic and cardiopulmonary exercise test, without adverse events. Central hemodynamic data from 3 patients were excluded because of insufficient data quality due to excessive damping of the arterial pressure waveform during exercise. In total, data of 61 patients were analyzed.

The majority of the study population were males (84%); the mean age was 63 ± 9 years. At the time of inclusion, patients were diagnosed with CHF for a mean duration of 45 ± 51 months. Ninety-eight percent used ACE inhibitors or an angiotensin II receptor blocker, 93% used beta blockers. Thirty-four patients had an ischemic cardiomyopathy (due to one or more myocardial infarctions > 3 months prior to inclusion), 2 patients showed signs of myocardial ischemia during evaluation by non-invasive stress testing (i.e. positive exercise test or myocardial perfusion scintigraphy) or coronary angiography, which required percutaneous coronary intervention (PCI). Six patients had severe mitral regurgitation at resting echocardiography. Twenty-three patients had Left Bundle Branch Block (LBBB) and seven patients had atrial fibrillation.

	Baseline	Peak exercise
$\dot{V}O_2$ (mL min^{-1} kg^{-1})	4.3 ± 1.3	19.0 ± 5.9
HR (beats min^{-1})	80 ± 17	124 ± 26
SV (mL)	62 ± 14	87 ± 23
Q (L min^{-1})	4.9 ± 1.5	10.9 ± 4.1

TABLE 1 Hemodynamic and gas exchange variables at rest and during exercise (*n* =61). $\dot{V}O_2$ oxygen uptake, HR heart rate, SV stroke volume, Q Cardiac Output

Central hemodynamic and gas exchange variables at rest and maximal exercise

Gas exchange and hemodynamic variables at rest and peak exercise are presented in table 1.

The mean peak workload was 125 ± 49 Watt. The mean peak $\dot{V}O_2$ was 19.0 ± 5.9 mL min^{-1} kg^{-1} and $\dot{V}O_2$ at the ventilatory threshold was 11.9 ± 2.9 mL min^{-1} kg^{-1}, corresponding to 63% of peak $\dot{V}O_2$. Mean peak RER was 1.07 ± 0.1. There was a significant correlation between peak $\dot{V}O_2$ and peak Q (r =0.64, p<0.001).

Patterns of central hemodynamic variables during incremental exercise

Figures 1A and B show respectively, exercise-induced changes of $\dot{V}O_2$ and Q at a group level. Both $\dot{V}O_2$ and Q show a continuous increase throughout the exercise test. Looking at patterns of Q in individual patients, 21 patients (34%) showed a plateau or decrease in Q during the final 10% of exercise duration (fig 2B), while 40 patients (66%) showed a continuous increase in Q (Fig 2A).

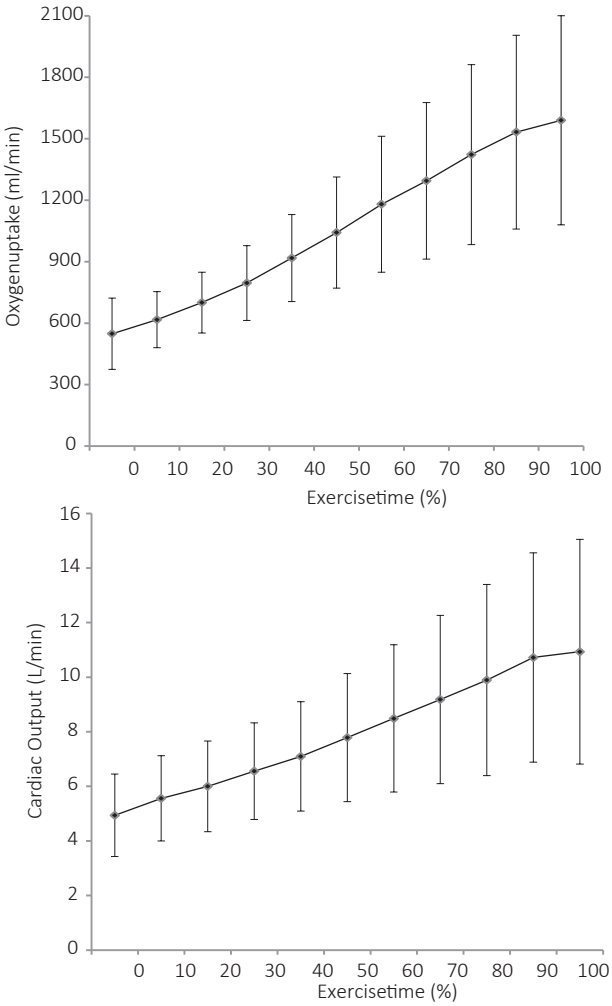

FIGURE 1A AND B: Mean oxygen uptake ($\dot{V}O_2$) and mean cardiac output (Q) response during a symptom limited exercise test. Error bars represent one standard deviation above and below the mean.

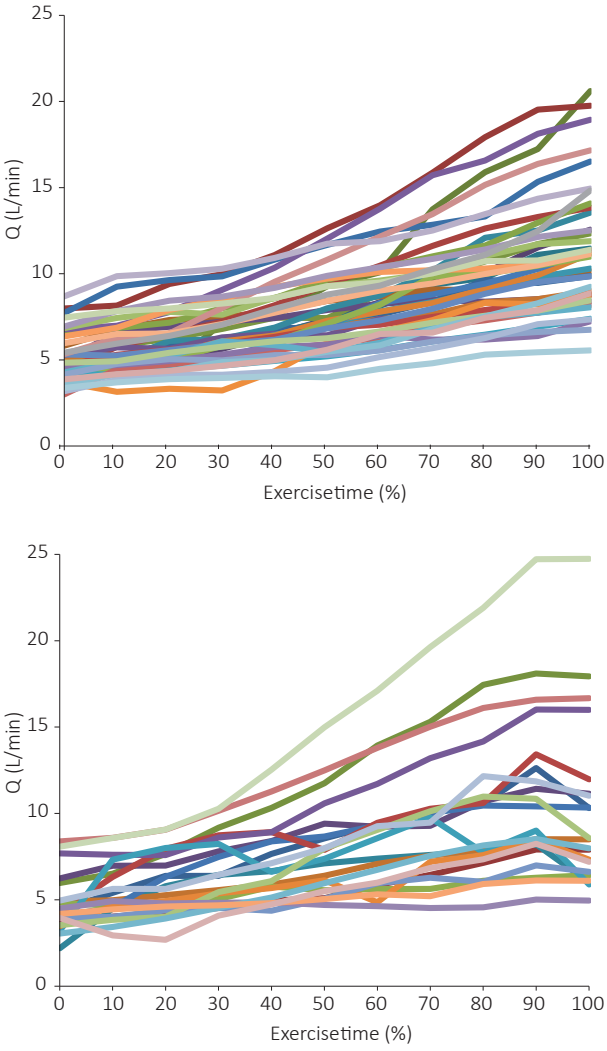

FIGURE 2A AND B Individual cardiac output (Q) responses with an continuous increase during exercise (*n* =40) and figure 2B individual cardiac output (Q) responses with a plateau or decrease during the final 10% of exercise during a symptom limited exercise test (*n* =21)

	Increase in Q (n = 40)	Plateau/decrease in Q (n = 21)	χ2 value(df)	*p-value*
Age (years)	63 ± 10	64 ± 9	n.a.	NS
Gender m/f (%)	33 (83)/7 (17)	18 (86)/3 (14)	0.10(1)	NS
ICM/DCM (%)	21 (53)/19 (47)	13 (62)/8 (38)	0.49(1)	NS
Duration CHF (months)	45 ± 50	46 ± 54	n.a.	NS
Beta blocker (%)	93	95	0.17(1)	NS
NYHA class II/III (%)	24 (60)/16 (40)	11 (52)/10 (48)	0.33(2)	NS
LVEF (%)	31 ± 8	33 ± 10	n.a.	NS
Peak$\dot{V}O_2$(mL min^{-1} kg^{1})	19.4 ± 6.0	18.2 ± 5.9	n.a.	NS
Peak Q (L min^{-1})	11.3± 3.6	10.2 ± 5.0	n.a.	NS
Peak SV (mL)	90 ± 24	83 ± 22	n.a.	NS
Plateau/decrease in $\dot{V}O_2$	9 (23%)	11 (52%)	5.58(1)	0.02
Plateau/decrease in SV	30 (75%)	21 (100%)	6.28(1)	0.01
Rest HR (beats min^{-1})	81±16	77±18	n.a.	NS
Peak HR (beats min^{-1})	126 ± 20	121 ± 35	n.a.	NS
Chronotropic incompetence	1 (2.5%)	5 (31%)	7.05(1)	0.01
Rhythm (SR, Afib, paced) (%)	35 (88)/2 (5)/3 (7)	15 (71)/5 (24)/1 (5)	4.85(2)	NS
LBBB	19 (48%)	4 (19%)	4.84(1)	0.03
Severe MR	3 (7.5%)	3 (14%)	0.72(1)	NS
Myocardial ischemia	2 (5%)	0 (0%)	1.09(2)	NS

TABLE 2 Characteristics comparison between subjects with increase in Q or plateau/decrease in Q (n=61) χ2 value, chi-squared value for categorical values, df degree of freedom, n.a. not applicable, ICM ischemic cardiomyopathy, DCM dilated cardiomyopathy, CHF chronic heart failure, NYHA New York Heart Association, LVEF left ventricular ejection fraction, $\dot{V}O_2$ oxygen uptake, Q cardiac output, SV stroke volume, HR heart rate, SR sinus rhythm, Afib atrial fibrillation, LBBB left bundle branch block, MR mitral regurgitation. NS non-significant

Table 2 shows a comparison of patient and disease characteristics between patients with a plateau/decrease in Q and patients with a continuous increase in Q. There was no significant between-group difference in beta blocker use (χ2 value 0.17, df=1, p =0.68). Peak $\dot{V}O_2$, peak Q and SV did not differ between both groups. In 11 of the 21 patients with a plateau/decrease in Q (52%), a plateau/decrease in $\dot{V}O_2$ was also observed. Nine out of 40 patients (23%) with a continuous increase in Q, showed a plateau/decrease in $\dot{V}O_2$ (χ2 value 5.58, df=1, p = 0.02 for between group comparison). In patients with a plateau/decrease in Q, all patients showed a plateau/ decrease in SV as opposed to 30 patients (75%) in the group with a continuous increase in Q (χ2 value 6.28, df=1, p = 0.01 for

between group comparison) (Table 2). Chronotropic incompetence was observed more often in patients with a plateau or decrease in Q (31% versus 2.5%, $\chi 2$ value 7.05, df=1, p<0.01). There was a higher occurrence of a plateau/decrease in SV in patients with chronotropic incompetence (83% versus 52%, p =0.047), but no significant difference in peak SV between patients with and without chronotropic incompetence (74± 22 versus 89±22 mL respectively, p =0.29). Left Bundle Branch Block was observed significantly less in patients with a Q plateau/ decrease ($\chi 2$ value 4.84, df=1,p=0.03). No differences between groups were observed for patients with severe mitral regurgitation at rest or myocardial ischemia.

Discussion

This is the first study in patients with CHF to characterize physiological limitations at maximal exercise by assessment of the pattern of Q during incremental exercise. In one third of the study population we demonstrated a failure to augment Q towards the end of the exercise test, (fig 2B) while a continuous increase was observed in the other patients (fig 2A). These results indicate that physiological heterogeneity in exercise limitations exists among CHF patients.

As the nature of the exercise limitation may be an important determinant for the selection of patients for specific treatments, (e.g. exercise training, heart transplantation, cardiac resynchronization therapy) these observations may be relevant for clinical practice.

Although we demonstrated a continuous increase in Q throughout the incremental symptom-limited exercise test at group level, we observed a wide inter-individual variation in Q patterns. These observations are different from earlier findings in healthy individuals, showing a continuous increase in Q in all subjects.[19] Whereas individual Q patterns during symptom-limited exercise were not used previously to characterize exercise limitations in CHF patients, earlier studies did show heterogeneity in central hemodynamic responses to exercise in CHF populations by relating Q to $\dot{V}O_2$. In these studies, 32-55% of CHF patients were classified as having a central hemodynamic limitation of maximal exercise capacity,[7,8] which is in line with our study. Studies using other methods to investigate determinants of maximal exercise capacity in CHF patients demonstrated strong relations between maximal exercise capacity and both skeletal muscle function, e.g. reduced skeletal muscle metabolic capacity or peripheral O_2 transport,[4,5,20] as well as central hemodynamics.[2,3] However, these results did not allow to draw conclusions on the relative contributions of central and peripheral factors to impaired maximal exercise capacity, nor on the presence of physiological heterogeneity in CHF patients. Studies investigating the influence of peripheral and central factors on exercise capacity simultaneously are scarce and yielded conflicting results. Whereas

some of these studies indicate that intrinsic differences in skeletal muscle metabolism are the main determinants of a reduced exercise capacity,[21,22] other studies show that a reduced O_2 delivery to exercising muscles is the primary limiting factor.[23,24] Possible explanations for this discrepancy may be the variety in exercise protocols that were used but also physiological heterogeneity in exercise limitations in these study populations.

One third of our population showed a central hemodynamic limitation of maximal exercise capacity. This limitation was associated with a more frequent occurrence of a plateau/decrease in $\dot{V}O_2$. Furthermore a central exercise limitation was associated both with a higher occurrence of a plateau/decrease in SV and a higher occurrence of chronotropic incompetence. From a physiological point of view, the inability to augment forward SV may be caused by impaired global left atrial[25] or ventricular contractile reserve, regional contractility disorders due to ischemia, valvular disorders such as mitral regurgitation and dyssynchrony. As severe mitral regurgitation at rest and ischemia were not identified as determinants of a central exercise limitation, an impaired global contractile reserve is likely to be the most important determinant of impaired SV augmentation in our population. In addition to a failure to augment SV, a central exercise limitation was also associated with a higher occurrence of chronotropic incompetence . In theory, this observation may be caused by neurohormonal dysregulation or the use of beta blockers. Previous studies showed that the lower peak heart rate during long-term administration of beta blockers is associated with a higher peak SV.[26,27] In contrast, in our study population, patients with chronotropic incompetence, had a higher occurrence of failure to augment SV and a non-statistically significant lower peak SV. A previous study in CHF patients showed a significant correlation between peak oxygen uptake and change in heart rate, with no significant difference for patients with or without beta blockers.[28] As 93% patients in our study used beta blockers and there was no difference in beta blocker use in both groups, this could not explain the difference in occurrence of chronotropic incompetence . Therefore, we postulate that chronotropic incompetence based on neurohormonal dysregulation (i.e. an imbalance between sympathic and parasympathic nerve activity) can be a contributory factor limiting exercise capacity in patients with a central exercise limitation. Our results showed significantly less patients with LBBB in the centrally limited group. This could be explained by studies that provide evidence that left ventricular (i.e. mechanical) dyssynchrony is irrespective of the QRS duration. Moreover, it is suggested that dyssynchrony is a dynamic condition and may worsen during exercise.[29]
Characterization of exercise limitations may be beneficial in clinical practice for a better understanding of the causes of impairments in daily functioning. In addition, this approach may contribute to a more tailored therapeutic strategy in individual CHF patients. As such, Wilson et al. showed that patients with a reduced cardiac output response to exercise benefit less from a moderate intensity exercise training program

than patients with a normal cardiac output response.[7] Yet, other studies showed that patients with a more pronounced central exercise limitation may benefit more from interventions aimed at improving central hemodynamics such as heart transplantation[8] and cardiac resynchronization therapy.[30] Whether the approach used in the present study will contribute to a better prediction of treatment results in individual CHF remains to be determined.

Before drawing conclusion from this study, several limitations should be acknowledged. First, we used an arbitrary method to classify exercise limitations. In fact, some patients that were not classified as having a central exercise limitation showed only small increases in Q during the final part of exercise. Second, the limited sample size did not permit to perform additional subgroup analyses. For instance, due to the fact that most patients were moderately impaired, we were unable to test the hypothesis, generated from animal studies that patient with more severe left ventricular dysfunction at rest have a more pronounced peripheral limitation than those with moderate left ventricular dysfunction.[6] Third, assessment of valvular disease and dyssynchrony was performed by resting echocardiography. However, as both may worsen during exercise,[31] we cannot fully exclude that this factor played a role in the failure to augment SV and Q towards maximal exercise.

Conclusion

This study revealed heterogeneity in exercise limitations in CHF patients. In one third of the study population a plateau or decrease in Q towards peak exercise was demonstrated, which is indicative of a central exercise limitation. Factors associated with a central exercise limitation included a higher occurrence of a failure to augment SV and chronotropic incompetence, suggesting that both impaired contractile reserve and neurohormonal dysregulation are determinants of reduced exercise capacity in centrally limited patients. Future research should focus on the clinical utility of characterizing exercise limitations to predict treatment effects in CHF patients.

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CHAPTER 3

Test-retest reliability of skeletal muscle oxygenation measurements during submaximal cycling exercise in patients with chronic heart failure

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Abstract

The potential purpose of near-infrared spectroscopy (NIRS) as a clinical application in chronic heart failure (CHF) patients is the identification of limitations in O_2 delivery or utilization during exercise. The objective of this study was to evaluate absolute and relative test-retest reliability of skeletal muscle oxygenation measurements in CHF patients. Thirty patients with systolic heart failure (left ventricular ejection fraction 31±8%) performed 6-minute constant load cycling tests at 80% of the anaerobic threshold with tissue saturation index (TSI) measurement at the vastus lateralis. Tests were repeated after 10 ± 5 days to evaluate reliability. Absolute reliability was assessed with limits of agreement (LoA, expressed as bias ± random error) and coefficients of variation (CV) for absolute values (LoA range: 0.4±6.2% to 0.6±7.9%; CV range: 4.7-7.1%), amplitudes (LoA range -0.5±5.8% to -0.7±6.8%; CV range: 26.2-42.1%), onset and recovery kinetics (mean response times; LoA 0.4±9.5s, CV 23.5% and LoA -5.8±50.8s, CV 67.4% resp.), and overshoot characteristics (CV range 45.7-208.6%). Relative reliability was assessed with intraclass correlation coefficients (ICC) for absolute values (range 0.74-0.90), amplitudes (range 0.85-0.92), onset and recovery kinetics (0.53 and 0.51, resp.), and overshoot characteristics (range 0.17-0.74). In conclusion, absolute reliability of absolute values and onset kinetics seems acceptable for serial within-subject comparison, and as such, for evaluation of treatment effects. In contrast, absolute reliability of amplitudes and recovery kinetics is considered unsatisfactory. Relative reliability of absolute values and amplitudes is sufficient for purposes of physiological distinction between CHF patients. Despite lower relative reliability, kinetics may still be useful for clinical application as well.

Introduction

Chronic heart failure (CHF) is a clinical syndrome characterized by exercise intolerance. Key determinants of exercise intolerance in patients with CHF are a reduced cardiac output and skeletal muscle impairments. Evidence suggests that some patients are principally limited by derangements of oxygen utilization in exercising muscles on top of the diminished oxygen delivery capacity associated with their initial cardiac constraint.[1,2] While understanding a patient's principal limitation might improve allocation of therapeutic options (e.g. exercise training when impairments in oxygen (O_2) utilization are predominant and cardiac resynchronization therapy or improving nitric oxide bioavailability[3] when O_2 delivery is primarily impaired), to date no discriminating physiological measurement is available for the clinician dealing with these matters.

A useful approach that has been introduced to distinguish between limitations in O_2 delivery and utilization is characterization of the temporal profile of oxygenation in exercising skeletal muscles. Recent studies using computer simulations showed that limitations in O_2 delivery during the onset of exercise are reflected in a rapid transient decrease of muscle oxygenation below steady state levels (deoxygenation overshoot). In contrast, limitations in O_2 utilization are reflected in a slow decrease without overshoot.[4,5] In an animal study, using direct measurements of muscle microvascular O_2 pressure, it was shown that both patterns exist in CHF,[6] suggesting physiological heterogeneity. Moreover, the speed of recovery of microvascular O_2 pressure after exercise has been shown to slow with the degree of central hemodynamic impairment.[7] In humans, direct measurements of microvascular O_2 are not feasible as yet, especially during exercise. However, near infrared spectroscopy (NIRS) measurements of skeletal muscle have been shown to produce similar oxygenation patterns and to give comparable insights in exercise-induced changes of muscle oxygenation.[8,9,10] One of the more recent innovations in NIRS development, namely spatially resolved spectroscopy (SRS), allows for the NIRS device to acquire absolute saturation of oxygen of the chromophores in the tissue (mainly haemoglobin and myoglobin). The oxygen saturation is designated as muscle tissue oxygen saturation (SmO_2), and dependent on the device, as tissue saturation index (TSI) or tissue oxygenation index (TOI).[1,11,12] The additional advantage of the determination of absolute oxygenation values introduces the potential of identifying physiological 'critical' limits in working skeletal muscle. As such, application of SRS can greatly enhance the physiological characterization of CHF patients during exercise testing.

In order to be able to use NIRS as a routine measurement for clinical purposes, the issue of reliability needs to be addressed. Thus far, little research is done on test-retest reliability of NIRS parameters, and, to our knowledge, no studies concerning reliability of TSI kinetics and absolute values during cycling exercise in CHF patients have been performed. In particular, investigating parameters of absolute reliability is of interest when serial within-subject comparisons (e.g. evaluation of treatment effects) are

made, while relative reliability is of interest when one wants to distinguish CHF patients physiologically by NIRS measurements. As such, the evaluation of reliability is important for practical recommendations, meaningful interpretation of TSI measurements, and sample size calculation for future studies in this population. Therefore, the main objective of the study is to investigate the reliability of TSI measurements at rest and during submaximal cycling exercise in CHF patients.

Methods

Subjects

Thirty consecutive patients with CHF (24 men (81%) and 6 women) were recruited. Subject characteristics are listed in Table 1.

Variables	Values
Male / Female	24 / 6
Age (years)	64 ± 9
Height (cm)	176 ± 10
Weight (kg)	85 ± 16
BMI (kg/m^2)	27 ± 5
ATT (mm)	4.3 ± 2.4
LVEF (%)	31 ± 8
Etiology (ischemic CMP/dilated CMP)	17 / 13
Duration of HF (months)	73 ± 78
NYHA (II/III)	22 / 8
Cardiac device (pacemaker/ICD)	6 / 10
Medication	
Bèta Blocker	100 %
Diuretic	77 %
ACE-inhibitor	63 %
ARB	30 %
Digoxin	7 %
Anticoagulant	80 %

TABLE 1 Characteristics of included chronic heart failure patients (*N* = 30). Data are presented as means ± SD for continuous variables and as numbers (percentages) for dichotomous variables. Body Mass Index (BMI), Adipose Tissue Thickness (ATT), Left Ventricular Ejection Fraction (LVEF), Cardiomyopathy (CMP), Heart Failure (HF), New York Heart Association (NYHA), Implantable cardioverter defibrillator (ICD), Angiotensin Converting Enzyme (ACE), Angiotension II Receptor Blocker (ARB)

Criteria for eligibility were stable systolic heart failure attributed to either dilated cardiomyopathy or ischemic heart disease due to myocardial infarction, New York Heart Association (NYHA) functional Class II or III (without change in class or medication ≤ 3 months prior to inclusion) and left ventricular ejection fraction ≤ 40% (assessed by echocardiography or magnetic resonance imaging ≤ 2 months prior). Exclusion criteria were recent myocardial infarction (≤ 3 months prior), angina pectoris at rest, clinical signs of decompensated heart failure, pulmonary, neurological or orthopaedic disease limiting the ability to exercise and clinical signs of peripheral vascular disease.

The study protocol was approved by the local Research Ethics Committee of Máxima Medical Centre, Veldhoven, The Netherlands. The study was conducted according to the Helsinki Declaration of 1964 and all participants provided written informed consent.

Experimental protocol

Exercise testing was performed in an upright seated position on an electromagnetically braked cycle ergometer (Lode Corival, Lode BV, Groningen, The Netherlands). Saddle height was adjusted for optimal body position and recorded for replication on following occasions. A twelve lead electrocardiogram was registered continuously and blood pressure was measured every 2 minutes (Korotkoff sounds). Patients were instructed to maintain a pedalling frequency of 70 rotations per minute during all exercise phases.

Maximal exercise testing consisted of a symptom-limited test using an individualized ramp protocol aiming at a total test duration of 8-12 minutes. The test was preceded by 4 minutes of unloaded pedalling and was ended when the patient was not able to maintain the required pedalling frequency. Peak workload was defined as the final registered workload.

Submaximal cardiopulmonary exercise testing commenced with a 2 minute resting phase, passively maintaining the right leg in a fixed position. This was followed by a 6 minute exercise phase with a workload corresponding to 80% of the ventilatory threshold. When the ventilatory threshold could not be assessed exercise intensity was set at 50% of the peak workload.[13] Following the exercise phase, there was a 5 minute recovery phase with a fixed leg position identical to that of the resting period. Two tests, separated by 10 ± 5 days (range 5-21 days), were performed at the same time of day (S1 for day 1, and S2 for day 2). Patients were advised to refrain from strenuous exercise (48 hours), caffeine (4 hours) consuming a meal (2 hours) before testing and to take their medication as usual.

Respiratory gas measurements

Gas exchange and ventilatory parameters were measured breath-by-breath (ZAN 680 USB, ZAN Messgeräte, Oberthulba, Germany) and were averaged over 10 second intervals after removal of outliers (only values > 3 standard deviations (SDs) from the local mean were omitted).[14] Volume and gas analysers were calibrated before each test. Peak

pulmonary oxygen uptake ($\dot{V}O_2$) and peak respiratory exchange ratio (RER) were recorded as the final 30-second averaged value of the maximal exercise test. Anaerobic threshold (AT) was assessed by the V-slope method by two blinded experienced physicians, using the mean value.[15]

NIRS measurements

Near-infrared spectroscopy is a non-invasive measurement technique based on the oxygen dependency of absorption changes for near infrared light in haemoglobin and myoglobin, allowing an estimation of optical density changes of oxygenated (O_2Hb) and deoxygenated haemoglobin and myoglobin (HHb). The theoretical principles and clinical utility of NIRS have been described previously.[16] It is acknowledged that NIR light is absorbed by both haemoglobin and myoglobin. However, since their absorption spectra cannot be distinguished, and at present each relative contribution to absorption is unclear, for convenience, both will be referred to as haemoglobin [HHb].

In the present study, NIRS measurements were performed using a wireless continuous wave (CW) near-infrared spectrophotometer (Portamon, Artinis, Elst, The Netherlands) using modified Beer-Lambert Law and spatially resolved spectroscopy with 2 wavelengths of emitting light (760 and 841 nm). This specific device employs SRS by using 3 light emitting diodes and a detector photo diode, which are configured spatially to provide 3 source-detector distances (30, 35, and 40 mm). By using photon diffusion theory, an absolute measure of tissue oxygen saturation (tissue saturation index, which equals $[O_2Hb]/([O_2Hb]+[HHb]) \times 100$) can be calculated from the absorption coefficients derived from the slopes of light attenuation at different source-detector distances and wavelengths.[17] Because TSI is an absolute value, it may be viable for between-subject comparison and assessment of attainment of critical limits during exercise.[1] Furthermore, it may serve as a better estimate for muscle fractional O_2 extraction than does [HHb].[11] Therefore, the TSI is the main focus of this study. Additionally, after incorporating a differential path length factor of 4 (manufacturer recommendation) in the modified Beer-Lambert Law, [HHb] amplitudes (in μM) and kinetic values were also reported.

Before testing, the NIRS device was covered in a transparent plastic wrap, preventing moisture entering the device, and connected to the right leg with adhesive tape and a Velcro strap, 20 cm proximally from the lateral patellar edge over the centre of the vastus lateralis, and finally occluded from ambient light by cloth. Data were sampled at 10 Hz and stored for off-line analysis.

Because of potential confounding of the NIRS signal amplitude by the cutaneous and subcutaneous layers, the skinfold thickness at the site of NIRS measurement was recorded with a skinfold calliper (Harpenden, Baty International, West Sussex, UK) before each measurement session. The thickness of the measured double skinfold was divided by two to obtain an estimate of the adipose tissue thickness (ATT).

Data analysis

Absolute values

First, all TSI data of the constant-load tests were filtered using a central moving average filter with a window of 11 data points. Absolute values of TSI were calculated as the average of the last minute of the resting phase ($TSI_{baseline}$), the 5 second average of the minimally attained value after commencement of exercise ($TSI_{minimum}$), the average of the last minute of the exercise phase ($TSI_{end\text{-}exercise}$) and the 5 second average of the maximally attained value within the 5 minute recovery phase ($TSI_{maximum}$). The amplitude of the downward component of the TSI signal at exercise onset (ΔTSI_{onset}) was calculated as the difference between $TSI_{baseline}$ and $TSI_{minimum}$ and the amplitude of the upward component of recovery ($\Delta TSI_{recovery}$) as the difference between $TSI_{end\text{-}exercise}$ and $TSI_{maximum}$. The difference between $TSI_{baseline}$ and $TSI_{end\text{-}exercise}$ was defined as the overall TSI response to the submaximal constant load exercise ($\Delta TSI_{exercise}$). In addition, $\Delta[HHb]_{onset}$, $\Delta[HHb]_{recovery}$, and $\Delta[HHb]_{exercise}$ were calculated from their corresponding [HHb] values. Movement artefacts (e.g. unwanted movement of the leg, body posture changes) that were observed during the resting and recovery phases were deleted when these exceeded 50% of the onset or recovery response, respectively. In total, one movement artefact in the recovery phase had to be deleted.

Kinetics analysis

Time constants (τ) were calculated by fitting the TSI data to a first-order (mono-exponential) model using the non-linear least squares method (Python 2.7, Python Software Foundation). For exercise onset, the following equation was used:

$$Y(t) = Y_{baseline} - A * (1 - e^{-(t - Td)/\tau}) \quad (1)$$

Where $Y_{baseline}$ is $TSI_{baseline}$, A the TSI amplitude from $TSI_{baseline}$ to the end of the mono-exponential fit (calculated from the fit), T_d is the time delay and tau (τ) is the time constant of the mono-exponential function (in seconds).
For recovery, the following equation was used:

$$Y(t) = Y_{baseline} + A * (1 - e^{-(t - Td)/\tau}) \quad (2)$$

Where $Y_{baseline}$ is $TSI_{end\text{-}exercise}$, followed by the addition of the TSI amplitude of the fit from $TSI_{end\text{-}exercise}$ (A).
The time to the start of the mono-exponential fit (T_d) was determined using a matched filter method by sliding a mono-exponentially shaped kernel over the TSI signal, while calculating the cross-correlation. The time corresponding to the highest negative (onset) or positive (recovery) correlation yielded the T_d and the starting point for the

fitting procedure. The end of the mono-exponential fitting range was the lowest value (5 second average) after onset of exercise that was not succeeded by a lower value within 10 seconds in the first three minutes of exercise. The assumption is made that the primary phase of the deoxygenation kinetics is limited to maximally three minutes.[9,18] Finally, the mean response time was calculated as the sum of tau and time delay (MRT = $\tau + T_d$) and represents the time to reach 63% of the response from onset or cessation of exercise. The R squared measure of goodness of fit (coefficient of determination) of the mono-exponential fit was considered satisfactory when exceeding 0.85.[13]
For [HHb], kinetics analyses were performed similar to those for TSI, except that for onset the subtraction was replaced by an addition (exponential decrease) and for recovery by a subtraction (exponential rise).

Deoxygenation overshoot

An overshoot in the deoxygenation profile (or likewise, an undershoot in oxygenation) was defined as a rise in TSI of more than 10% of ΔTSI_{onset} occurring during the first three minutes of exercise following onset of exercise (Figure 1). The overshoot was assessed qualitatively (i.e. present or absent) in all subjects. When present, the overshoot was assessed quantitatively by calculation of the amplitude of the upward component ($\Delta TSI_{overshoot}$) as the difference between $TSI_{minimum}$ and the average TSI of the third minute after onset of exercise ($TSI_{end\text{-}overshoot}$). Furthermore, time constants of the upward component ($tau_{overshoot}$) were calculated using equation 2. $TSI_{minimum}$ was substituted for $Y_{baseline}$, followed by the addition of the amplitude (A), which was calculated from $TSI_{minimum}$ up to the third minute of exercise, while the time delay was omitted from the equation. The area of the overshoot ($Area_{overshoot}$ in %s) was calculated as the integral between the measured response and the TSI value at three minutes starting from the intersection with the onset curve.[5,18] Again, for [HHb], all analyses were performed similarly, taking into account the inverse response.
It should be noted that a reoxygenation overshoot was present in the recovery signal of multiple subjects. However, the duration of this response (before reaching a steady state value) exceeded the 5 minute recovery phase in most, consequently prohibiting an adequate fitting procedure. Therefore, the TSI overshoot during recovery of exercise was not evaluated qualitatively nor quantitatively.

Statistical analysis

All data were analysed using SPSS 22.0.0 statistical software (SPSS Inc, Chicago, IL, USA). Results are presented as mean value ± standard deviation (SD). Normality was assessed by skewness and kurtosis of the distribution, and by Shapiro Wilk tests. Thereafter, paired Student's t tests in case of a normal distribution, or Wilcoxon signed rank tests when appropriate, were performed to exclude significant systemic bias. Heteroscedasticity of

the data was assessed by Bland-Altman plots and confirmed by a diminishing positive correlation between the absolute error and the size of the measured value upon logarithmical transformation.[19] Absolute reliability was assessed by limits of agreement (in case of heteroscedastic data as ratios derived from logarithmical and subsequent antilog transformation) and coefficients of variation (CV), and interpreted as a characteristic of the performance of within-subject evaluation.[19,20] A CV below 30% was considered as acceptable absolute reliability. Acceptable thresholds for limits of agreement depend on the sensitivity of a specific parameter for detecting changes over time (e.g. due to an intervention) and are currently not available. Relative reliability was assessed by intra-class correlation coefficients ($ICC_{3,1}$) with 95% confidence interval (CI) and was considered a characteristic of the performance of discrimination between subjects.[21] Values larger than 0.50 indicate between-subject variability exceeding measurement error and values above 0.70 were classified as indicating good relative reliability.[20] Associations between categorical data were assessed by Pearson's chi-square test. When analysing correlations, Pearson's correlation coefficient (when normally distributed) or Spearman's rho (r_s) was assessed as a continuous variable throughout. A p-value < 0.05 was considered statistically significant for all tests.

Results

All patients successfully performed all exercise tests without any untoward events.

Maximal exercise tests

Maximal exercise testing resulted in an average maximum workload of 124 ± 44 W and peak $\dot{V}O_2$ was 19.7 ± 5.6 ml min^{-1} kg^{-1}. The ventilatory threshold could not be determined in seven patients (23%). In 23 patients the independent observers agreed on the determination of the ventilatory threshold (mean $\dot{V}O_2$ 14.7 ± 4.6 ml min^{-1} kg^{-1}).

Submaximal exercise tests

Submaximal exercise testing was performed at a workload of 62 ± 23 W, corresponding to 50 ± 7% of maximal workload.

NIRS measurements

Figure 1 shows a typical deoxygenation profile.

A paradoxical TSI profile was observed in two patients, as demonstrated by 1) a rise of TSI at exercise onset instead of a decline and 2) attainment of 100% oxygen saturation during the exercise phase in one of the two patients. Both patients were female, with a respective ATT of 9 and 18 mm, which are values among the five highest in the study

population. As it was assumed that these TSI responses were severely influenced by the overlying adipose tissue, they were excluded from further analysis. In addition, no satisfactory mono-exponential fit could be made for the [HHb] recovery response in six tests (five patients), as shown by time constants (tau) exceeding 500 seconds. The kinetic parameters of these recovery responses were omitted from the statistical analysis.

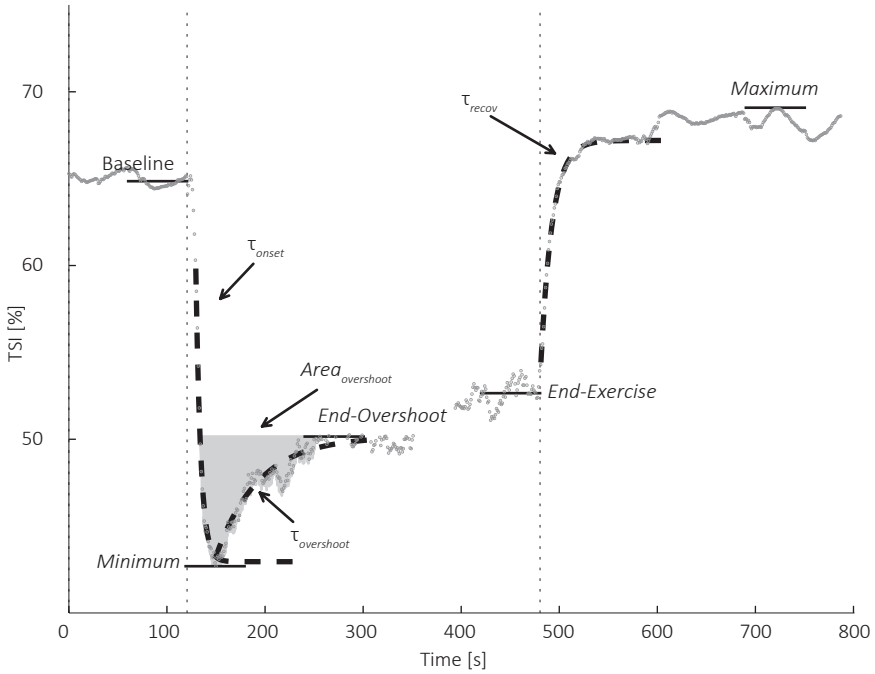

FIGURE 1 Example of Tissue Saturation Index (TSI) changes during submaximal exercise in a representative subject exhibiting a deoxygenation overshoot. The vertical dotted lines indicate (from left to right): start of exercise phase (t=120 s), start of recovery phase (t=480 s). The horizontal lines indicate (from left to right): baseline value (Baseline), minimum value (Minimum), end-overshoot value (End-overshoot), end-exercise value (End-exercise), maximum value (Maximum). The curved dashed lines represent the best fit of the mono-exponential model (tau) to the TSI response for (from left to right) onset (τ_{onset}), overshoot ($\tau_{overshoot}$) and recovery (τ_{recov}). The grey area represents the area of overshoot ($Area_{overshoot}$).Absolute values, amplitudes, kinetic parameters and overshoot characteristics for the submaximal exercise tests of both days (S1 and S2) for TSI and [HHb] are listed in Table 2.

Variables	S1	S2	S1	S2
Absolute values	TSI (%) (*N* = 28)		[HHb] (μM) (*N* = 28)	
Baseline	67.8 ± 4.0	67.4 ± 4.7	-	-
Minimum	57.7 ± 8.3	57.1 ± 9.5	-	-
End-exercise	60.9 ± 7.0	60.1 ± 7.8	-	-
Maximum	73.7 ± 5.3	73.6 ± 5.5	-	-
ΔOnset	-10.1 ± 6.1	-10.3 ± 6.7	6.4 ± 5.6	6.2 ± 6.1
ΔRecovery	12.8 ± 9.0	13.5 ± 8.7	-8.0 ± 6.8	-8.0 ± 7.6
ΔExercise	-6.8 ± 5.5	-7.3 ± 5.4	4.7 ± 5.4	4.8 ± 5.7
Overshoot characteristics	TSI (%)		[HHb] (μM)	
Overshoot *N* (%)	16 (57%)	18 (64%)	14 (50%)	14 (50%)
End-overshoot	62.1 ± 7.2	61.2 ± 8.3	1.7 ± 3.8	2.0 ± 4.1
ΔOvershoot	-3.8 ± 2.5	-3.5 ± 2.5	2.4 ± 1.5	1.8 ± 0.8
$Area_{overshoot}$ (%s / μMs)	150 ± 146	124 ± 162	77 ± 142	47 ± 61
$Tau_{overshoot}$	33.9 ± 18.8	37.1 ± 22.6	24.5 ± 20.5	50.5 ± 65.1
Kinetics	TSI (s) (*N* = 28)		[HHb] (s) (*N* = 28)	
Td_{onset}	14.0 ± 3.7	13.5 ± 3.6	13.0 ± 4.0 ‡	12.6 ± 4.1 §
Tau_{onset}	6.8 ± 2.9	6.9 ± 2.3	9.5 ± 6.0 §	8.3 ± 2.9 §
MRT_{onset}	20.8 ± 5.1	20.4 ± 4.9	22.4 ± 7.4	20.9 ± 5.7
$Td_{recovery}$	13.0 ± 11.4	13.2 ± 10.4	17.4 ± 10.4 †	16.4 ± 10.0 †
$Tau_{recovery}$	22.6 ± 14.6	28.1 ± 23.2	31.2 ± 31.6 †	28.7 ± 23.7 †
$MRT_{recovery}$	35.6 ± 22.7	41.4 ± 29.1	48.6 ± 36.7 †	45.0 ± 29.8 †
Coefficients of determination	TSI		[HHb]	
R^2 Tau_{onset}	0.95 ± 0.03	0.95 ± 0.04	0.91 ± 0.15	0.93 ± 0.08
R^2 $Tau_{recovery}$	0.97 ± 0.04	0.97 ± 0.06	0.87 ± 0.23 ‡	0.88 ± 0.21 ‡
R^2 $Tau_{overshoot}$	0.61 ± 0.39	0.54 ± 0.26	0.34 ± 0.48	0.38 ± 0.38

TABLE 2 Absolute and kinetic values of Tissue Saturation Index (TSI) and deoxygenated haemoglobin ([HHb]) for the tests of both days (S1 and S2). Values are means ± SD. Time delay (T_d), Time constant of mono-exponential model (Tau), Mean Response Time (MRT). † $N = 24$. ‡ $p < 0.05$ and § $p < 0.01$ for the difference between TSI and [HHb] calculated for kinetics and coefficients of determination (R^2)

The assumption of normality for TSI data could not be confirmed for TSI amplitudes, time constants, $Td_{recovery}$, and $MRT_{recovery}$ for [HHb] it could not be confirmed for any parameter. Kinetic responses of TSI and [HHb] were not different, except for T_d and tau for onset of exercise. A significant correlation between amplitudes of TSI and HHb was found (onset r_s=0.863, P<0.001; exercise r_s=0.822, P<0.001; recovery r_s=0.876, P<0.001). The coefficient of determination of the mono-exponential fit for onset, recovery and overshoot kinetics of TSI and [HHb] (Table 2) was considered satisfactory when exceeding 0.85. TSI onset and recovery measurements showed one unsatisfactory fit each (0.9%); for [HHb] there were 12 (10.7%) and 24 (21.4%), respectively. TSI overshoot kinetics showed 47 unsatisfactory fits for TSI (81.0%) and 35 (97.2%) for [HHb].

Reliability

No significantly large systemic bias between S1 and S2 was found for absolute TSI values amplitudes, kinetic parameters or deoxygenation overshoot characteristics. Figure 2 shows Bland Altman plots for $TSI_{baseline}$, $TSI_{minimum}$, and TSI kinetic parameters during onset and recovery of exercise with onset kinetics producing narrower (absolute and relative) 95% confidence intervals of the difference between tests. Visual inspection of the plots and improvement upon logarithmical transformation revealed heteroscedasticity for all kinetic parameters and overshoot characteristics, except for T_d of [HHb] onset and for $tau_{overshoot}$.

The intra-class correlation coefficients, coefficients of variation, and limits of agreement listed in Table 3, showed that absolute values and amplitudes provide better reliability compared to kinetic parameters and overshoot characteristics.

In Table 3 quantitative overshoot characteristics of S1 are compared with those of S2 for assessment of reliability in cases where one occurred in both. Percentage agreement of qualitative assessment of the overshoot in S1 and S2 was 54% for TSI ($\chi^2(1)$=0.324, P=0.569) and 79% for [HHb] ($\chi^2(1)$=5.60, P=0.002). Agreement between TSI and [HHb] for determination of an overshoot was 93% for S1 ($\chi^2(1)$=21.00, P<0.001) and 75% for S2 ($\chi^2(1)$=5.60, P=0.018).

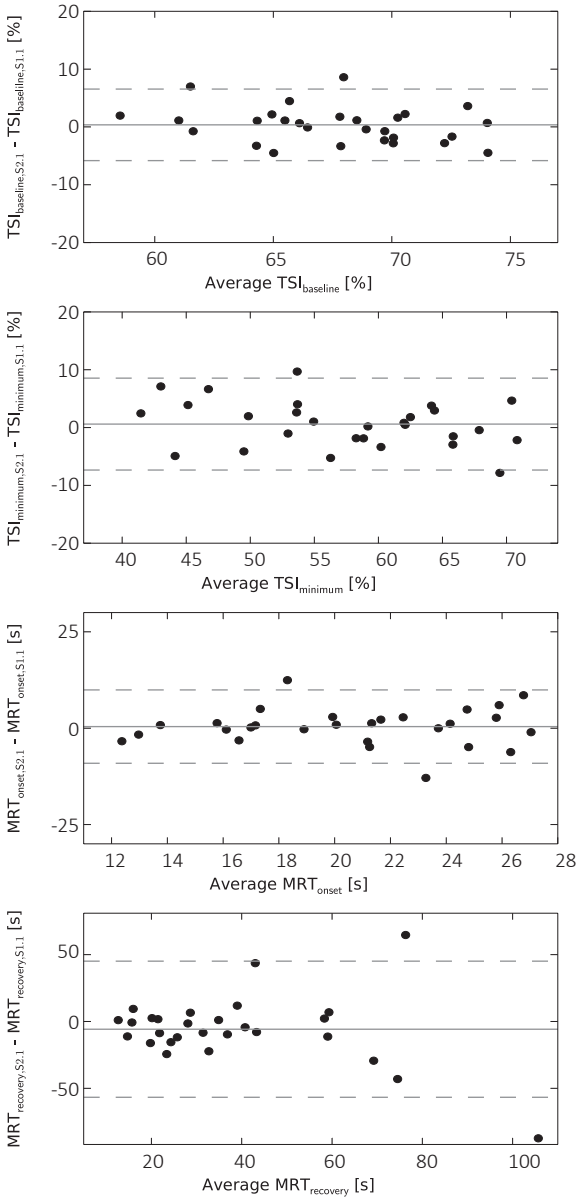

FIGURE 2 Bland-Altman plots showing the difference between the submaximal exercise tests of both days (S1 and S2) against the average value of the two test of (from top to bottom graph) resting Tissue Saturation Index values ($TSI_{baseline}$), minimum values after onset of exercise ($TSI_{minimum}$), and mean response times for onset (MRT_{onset}) and recovery kinetics ($MRT_{recovery}$) of TSI. The horizontal solid lines represent the mean differences between the values of the two tests. The horizontal dashed lines indicate the upper and lower limits of the 95% confidence intervals of the differences.

Variable	*N*	Bias ± random error (ratio)		CV (%)	ICC (95% CI)
TSI absolute values and amplitudes (%)					
$TSI_{baseline}$	28	0.4 ± 6.2		4.7	0.74 (0.51-0.87)
$TSI_{minimum}$	28	0.6 ± 7.9		7.1	0.90 (0.79-0.95)
$TSI_{end\text{-}overshoot}$	11	1.3 ± 6.5		5.5	0.90 (0.68-0.97)
$TSI_{end\text{-}exercise}$	28	0.8 ± 7.4		6.2	0.87 (0.74-0.94)
$TSI_{maximum}$	28	0.1 ± 7.0		4.8	0.78 (0.58-0.89)
ΔTSI_{onset}	28	-0.2 ± 6.5		32.7	0.87 (0.73-0.94)
$\Delta TSI_{recovery}$	28	-0.7 ± 6.8		26.2	0.92 (0.84-0.96)
$\Delta TSI_{exercise}$	28	-0.5 ± 5.8	†	42.1 †	0.85 (0.71-0.93)
$\Delta TSI_{overshoot}$	11	0.3 ± 3.8	(0.98 ×/÷ 1.59)	45.7	0.74 (0.29-0.92)
$Area_{overshoot}$ (%s)	11	27 ± 288	(0.91 ×/÷ 2.28)	84.1	0.65 (0.12-0.89)
[HHb] amplitudes (µM)					
$\Delta[HHb]_{onset}$	28	0.2 ± 5.7	†	46.2 †	0.88 (0.75-0.94)
$\Delta[HHb]_{recovery}$	28	-0.1 ± 5.8	†	37.1 †	0.92 (0.83-0.96)
$\Delta[HHb]_{exercise}$	28	-0.1 ± 4.9	†	52.8 †	0.90 (0.79-0.95)
$\Delta[HHb]_{overshoot}$	11	0.8 ± 2.3	(0.88 ×/÷ 1.35)	51.2	0.59 (0.02-0.87)
$Area_{overshoot}$ (µMs)	11	37 ± 305	(0.94 ×/÷ 2.98)	208.6	0.17 (-0.46-0.68)
TSI kinetics (s)					
Td_{onset}	28	0.4 ± 7.6	(0.98 ×/÷ 1.30)	28.0	0.44 (0.09-0.69)
Tau_{onset}	28	0.0 ± 5.3	(1.01 ×/÷ 1.31)	39.8	0.47 (0.12-0.71)
MRT_{onset}	28	0.4 ± 9.5	(0.99 ×/÷ 1.22)	23.5	0.53 (0.20-0.75)
$Td_{recovery}$	28	-0.2 ± 14.4	(1.07 ×/÷ 1.84)	56.2	0.77 (0.57-0.89)
$Tau_{recovery}$	28	-5.6 ± 50.1	(1.06 ×/÷ 1.72)	100.7	0.13 (-0.25-0.48)
$MRT_{recovery}$	28	-5.8 ± 50.8	(1.07 ×/÷ 1.57)	67.4	0.51 (0.17-0.74)
$Tau_{overshoot}$	11	-0.6 ± 43.1		57.8	0.42 (-0.21-0.80)
[HHb] kinetics (s)					
Td_{onset}	28	0.3 ± 9.7		38.9	0.26 (-0.12-0.57)
Tau_{onset}	28	1.2 ± 10.4	(0.97 ×/÷ 1.40)	60.0	0.36 (-0.01-0.64)
MRT_{onset}	28	1.5 ± 11.8	(0.97 ×/÷ 1.24)	27.7	0.59 (0.29-0.79)
$Td_{recovery}$	24	1.1 ± 18.3	(0.98 ×/÷ 1.68)	55.1	0.58 (0.24-0.80)
$Tau_{recovery}$	24	2.5 ± 51.9	(1.01 ×/÷ 2.52)	88.5	0.55 (0.20-0.78)
$MRT_{recovery}$	24	3.6 ± 59.2	(0.97 ×/÷ 1.68)	64.6	0.59 (0.25-0.80)
$Tau_{overshoot}$	11	-0.4 ± 51.1		93.7	0.28 (-0.36-0.74)

TABLE 3 Reliability of Tissue Saturation Index (TSI) and deoxygenated haemoglobin ([HHb]) for the tests of both days (S1 and S2). Limits of agreement are expressed as bias ± random error and in case of heteroscedasticity as ratio values derived from logarithmical transformation. Time delay (T_d); Time constant of mono-exponential model (Tau), Mean Response Time (MRT). † Negative values prohibit logarithmical transformation and meaningful CV interpretation

Discussion

This is the first study to evaluate test-retest reliability of NIRS derived absolute values of skeletal muscle oxygen saturation and its kinetics during submaximal cycling exercise in CHF patients. Reliability in the context of the current study consisted of an evaluation of absolute and relative reliability. Absolute reliability is related to similarity between repeated measures (expressed as limits of agreement and/or CV).[19,20] Relative reliability refers to the capability to assess differences between subjects when measurement errors are taken into account (expressed as ICC).[20,21] Relative reliability is always dependent on between-subject variability (i.e. higher in case of wider variability), and therefore only generalizable to population samples with comparable variation. As such, parameters of relative reliability are of interest when one wants to characterize CHF patients by NIRS measurements, while absolute reliability parameters are of interest in serial within-subject comparisons (e.g. evaluation of interventional changes).[20] In this light, absolute values of TSI showed good absolute and relative reliability, while amplitudes showed lower absolute reliability. Absolute and relative reliability of onset oxygenation kinetics were acceptable, as was relative reliability of recovery kinetics, while for overshoot characteristics both were poor.

Absolute values and amplitudes

In reliability studies in healthy adults, low CV values were reported for resting TSI in biceps brachii (2.4% to 4.4%, for three measurements) and vastus lateralis (5.8% and 5.2% versus 4.7% in our study),[22,23,24] confirming good absolute reliability. In contrast, Thiel et al. noted wider limits of agreement in vastus lateralis than found in our study (-13.9% to 12.2%, versus-5.9% to 6.7% in our study), possibly due to differences in measuring device (including calibration), measurement location and leg position.[23]

Concerning TSI amplitudes, comparable and acceptable absolute reliability for ΔTSI_{onset} (CV 31.5% versus 32.7% in our study) and $\Delta TSI_{recovery}$ (37.7% versus 26.2%) was reported in biceps brachii of healthy subjects performing repeated submaximal isometric contractions.[22]

When comparing reliability of absolute TSI values and amplitudes, respective values for ICCs and limits of agreement were similar in magnitude, albeit CVs were markedly higher for amplitudes. Hence, depending on the parameter for absolute reliability (i.e. limits of agreement or CV), different conclusions can be drawn with regard to absolute reliability of TSI amplitudes. Therefore we state that from a clinical point of view, a test is only useful for assessment of treatment effects when the limits of agreement fall within the expected effects of an intervention. However, currently the effect of specific interventions on TSI amplitudes in CHF patients has not been addressed. As such, the presented CV values for TSI amplitudes leads to the conclusion that absolute reliability seems unacceptable at this time.

Muscle oxygenation kinetics: onset kinetics

To our knowledge, no previous studies evaluated reliability of SRS-derived muscle oxygenation kinetics for submaximal cycling exercise. Our results showed that TSI onset kinetics produced acceptable absolute reliability (i.e. CV of MRT < 30%) and relative reliability measures (i.e. ICC of MRT > 0.50). Previous authors have reported reliability of [HHb] onset kinetics during moderate exercise in healthy adults, with the use of a fairly similar exercise protocol compared to our study. In the study of Spencer et al., the MRT for onset kinetics showed narrow 95% confidence intervals (±5.3 s versus -9.3 to 10.1 s for limits of agreement in our study).[25] When ensemble-averaging three or more transitions, confidence intervals became even narrower. The difference between average absolute workloads (119 ± 34 W compared to 62 ± 23 W in our study) might have contributed to a larger measured deoxygenation response to exercise. This facilitates fitting of the onset curve and may improve reliability. Sperandio et al. reported excellent measures of absolute reliability in a preliminary trial assessing reliability of [HHb] kinetic parameters of subjects performing heavy intensity cycling exercise (test-retest range of difference for tau was -0.3 to 0.8 s versus -9.4 to 11.8 s for limits of agreement in our study).[9] Possible explanations for their superior results are that spatial heterogeneity of muscle blood flow[26] and muscle deoxygenation decrease at the higher relative exercise intensities used (i.e. above the anaerobic threshold).[18,27,28] Another explanation might be a higher occurrence of a deoxygenation overshoot, resulting in lower values for onset kinetics and a reduction in between-subject variability of MRT_{onset}.[5] However, the studied population, exact measuring protocol, ICC, and occurrence rate of an overshoot (50% to 64% in our study) were not mentioned.

Deoxygenation overshoot

The present study is the first to assess reliability of the muscle deoxygenation overshoot at exercise onset, showing poor absolute and relative reliability of quantitative overshoot characteristics for TSI, as well as for [HHB]. Specifically, fitting of the upward component of the TSI response with a mono-exponential function was impaired. This may be the consequence of the low imposed absolute workload, resulting in a limited overshoot amplitude. Qualitative assessment of the overshoot showed acceptable absolute reliability for [HHb], however, not for TSI. Likewise, Bowen et al. recently demonstrated inconsistency of the incidence of the deoxygenation overshoot within and between healthy subjects, with no main effect on consistency after altering O_2 delivery by lowering the inspired O_2 concentration.[18]

Recovery kinetics

The present study showed similar relative reliability, however, inferior absolute reliability for recovery kinetics of TSI compared to onset kinetics. Problematic fitting of the mono-exponential function seems a key issue in the reliability of recovery kinetics, as has been confirmed by other authors.[12] It is especially troublesome for [HHb] recovery kinetics, where it was not feasible in six tests, with the remaining recovery responses producing lower coefficients of determination than for TSI. Sudden changes in muscle blood flow after termination of exercise and/or on-going kinetics at the point of cessation of the measurement might be important contributors to the problem.[12] Another contribution might lie in the fixed position of the device relative to the vastus lateralis during recovery, producing a localized measurement. In contrast, during onset the muscle moves underneath the skin resulting in an averaged response and a reduced effect of possible spatial heterogeneity.

Clinical implications

The potential purposes of NIRS as a clinical application in CHF patients are characterization (i.e. identification of limitations in O_2 delivery or utilization) and evaluation of muscle oxygenation changes over time (e.g. treatment effects). As such, several of the investigated parameters may have clinical consequences. For instance, animal studies have shown that resting microvascular oxygen pressure is lower in severe compared to moderate CHF,[6] and in CHF patients it is inversely related to the speed of pulmonary oxygen kinetics.[1,4] This might indicate that resting microvascular oxygenation (represented by $TSI_{baseline}$) facilitates local O_2 utilization and may serve as a marker for O_2 delivery. Similarly, the peak of deoxygenation during the exercise transient (represented by $TSI_{minimum}$) is associated with a limitation of oxidative energy provision,[18] because of temporary exhaustion and delayed replenishment of local O_2 stores.

TSI kinetics may particularly be useful for characterization of physiological limitations. In fact, it has been proposed that a MRT of approximately 20 seconds for muscle haemoglobin desaturation at exercise onset indicates sufficient matching of O_2 consumption and delivery.[1,16] As such, CHF patients are expected to exhibit slow deoxygenation at exercise onset when muscle O_2 consumption remains slow relative to accelerated microvascular O_2 delivery. Conversely, a (local) transient mismatch of O_2 delivery relative to O_2 utilization results in faster deoxygenation. Theoretically and effectively, this mismatch is frequently accompanied by a deoxygenation overshoot (70% for [HHb] and 87% for TSI in previous CHF studies versus 57% to 64% in this study).[1,5,6,9] However, computer simulations predict that the presence of a deoxygenation overshoot invalidates interpretation of the relation of O_2 delivery to utilization from the speed of deoxygenation.[5] Hence, this subject requires further investigation.

Fractional oxygen extraction

Previous investigations evaluating fractional O_2 extraction (i.e. the balance between O_2 delivery and utilization) in skeletal muscle employed both [HHb] and TSI as its proxy.[1,9] While there is an ongoing debate on which parameter serves this purpose best, no consensus exists on a preference of reporting either [HHb] or TSI.[11,29,30,31] The main arguments concern the influence of superficial tissue layers (i.e. skin and subcutaneous fat), where [HHb] is thought to be minimally influenced by skin blood flow because its concentration in superficial tissue layers is assumed to be much lower than in muscle tissue. Indeed, it was demonstrated that exercise-induced hyperemia of skin did not influence [HHb] However, it did not alter TSI either. Moreover, [HHb] was insensitive to exercise-induced hyperemia of skeletal muscle, as opposed to TSI.[11] The latter indicates insufficient capability of [HHb] to represent skeletal muscle fractional O_2 extraction because of insensitivity to increased O_2 delivery.

In the present study, differences between the responses of TSI and [HHb] to submaximal exercise could only be demonstrated for the time constant and time delay of exercise onset. However, the mean response times for onset and recovery were not significantly different, and amplitudes of both parameters showed a strong association, suggesting corresponding responses. Since studies comparing TSI and [HHb] data directly to fractional O_2 extraction measurements are lacking, no definite recommendation can be given on what NIRS parameter to use as a non-invasive alternative. However, given the physiological evidence and presented reliability, [HHb] seems less suitable for this purpose.

Study limitations

Several limitations should be acknowledged. First, a limited number of females were included, from which two were excluded because of a paradoxical TSI response, most likely due to large ATT. Furthermore, the majority of participants were moderately impaired. Therefore, the results cannot be generalized to female and more severely impaired patients. Second, above a certain ATT one must consider that NIRS measurements are representing skeletal muscle insufficiently, although, based on the present study results, an exact threshold cannot be given. Third, only one muscle (region) was investigated, instead of multiple sites. Performing spatially distributed measurements could possibly reduce the influence of local variations in perfusion and oxygen consumption and improve reliability.[32,33] Fourth, only one test for each day was used for analysis in our study, while averaging multiple subsequent tests (i.e. at least three) will possibly generate more satisfactory results for application in individual patients.[25] Fifth, the degree of compression of the muscle by the Velcro strap was not controlled, however, it has been

known to increase the recovery rate of muscle tissue oxygen saturation, and it increases oxygen availability during short term exercise.[34,35] Nevertheless, caution was taken to prevent compression to exceed the level that was necessary to reassure skin contact during exercise. Finally, only one specific NIRS device was used in the present study, while differences of measured muscle tissue oxygen saturation between devices have been reported, even in separate devices from a single manufacturer.[36,37] Comparability of the presented absolute values (e.g. group mean) is therefore limited to similar devices with matching calibration settings.

Conclusions

This study shows that relative test-retest reliability of absolute TSI values and amplitudes is sufficient for purposes of physiological distinction between moderately impaired CHF patients. Despite lower relative reliability, muscle oxygenation kinetics may still be useful for clinical application as well. Furthermore, absolute reliability of absolute TSI values and onset kinetics seems acceptable for serial within-subject comparison, and as such, for evaluation of treatment effects. In contrast, absolute reliability of amplitudes and recovery kinetics is considered unsatisfactory. Reliability of the deoxygenation overshoot is unacceptable for either purpose.

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CHAPTER 4

The relation between cardiac output kinetics and skeletal muscle oxygenation during moderate exercise in moderately impaired patients with chronic heart failure

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Abstract

Oxygen uptake ($\dot{V}O_2$) kinetics are prolonged in patients with chronic heart failure (CHF). This may be caused by impaired oxygen delivery or skeletal muscle derangements. We investigated whether impaired cardiac output (Q) kinetics limit skeletal muscle oxygen delivery relative to the metabolic demands at submaximal exercise in CHF patients by evaluating the relation between Q kinetics and skeletal muscle deoxygenation. Forty-three CHF patients, NYHA II-III, performed a constant-load exercise test at 80% of the VAT to assess $\dot{V}O_2$ kinetics ($\tau\dot{V}O_2$). Q kinetics (τQ) were assessed by a radial artery pulse contour analysis method. Skeletal muscle deoxygenation was assessed by near infrared spectroscopy at the m. vastus lateralis, using the minimal value of the tissue saturation index during onset of exercise (TSImin). Patients were categorized in slow and normal Q responders relative to metabolic demands ($\tau Q/ \dot{V}O_2 \geq 1$ and $\tau Q/ \dot{V}O_2 < 1$, respectively), τQ (62 +/- 29s) and $\tau\dot{V}O_2$ (60+/-21s) were significantly related (r=0.66, p= 0.001). There was a significant correlation between τQ and TSImin in the slow Q responders (r_s=-0.57, p=0.005, n=22 (51%)). In conclusion, in moderately impaired CHF patients with relatively slow Q kinetics, central hemodynamics may limit skeletal muscle oxygenation during moderate-intensity exercise.

Introduction

Patients with Chronic Heart Failure (CHF) suffer from fatigue and impaired exercise tolerance. These symptoms are particularly experienced during daily life, which mainly consists of repetitive submaximal activities. Previous studies in CHF patients have indeed shown that oxygen uptake kinetics are prolonged, compared to healthy individuals.[1,2] Therefore assessment of oxygen uptake kinetics as a measure for submaximal exercise is particularly indicative of the functional capacity and prognosis of CHF patients.[3]

From a clinical point of view, detailed knowledge on the pathophysiological mechanisms underlying impairments of submaximal oxygen uptake kinetics in individual CHF patients is important for tailoring of treatments and for development of new therapeutic strategies. Currently, however, there is still an on going debate whether oxygen uptake kinetics in CHF are primarily limited by central and/or microvascular oxygen delivery or intrinsic oxidative capacity of the skeletal muscle.[4,5] Whereas some studies showed that the inability to increase oxygen uptake during submaximal exercise was related to an impaired cardiac output (Q) response,[1,6,7] other studies found an impaired skeletal muscle function to be related to the reduced submaximal exercise capacity.[8,9] A possible explanation for these seemingly conflicting results may be that central and peripheral measurements were not performed simultaneously in these studies, making it difficult to distinguish the main limiting factor. Another explanation may be that physiological heterogeneity exists between different CHF subgroups. Recent animal studies showed that submaximal exercise capacity is only limited by oxygen delivery when microvascular oxygen pressure ($P_{m}\dot{V}O_2$) during exercise falls below a critical level at which oxygen diffusion into the myocyte becomes impaired.[10,11] Computer modelling studies of oxygen uptake dynamics revealed that such a "critical" $P_{m}\dot{V}O_2$ level was reached only when the rate of increase in muscle blood flow is slowed to a greater extent than the rate of increase in muscle metabolic demand.[12,13,14] Currently, it is not feasible to directly assess $P_{m}\dot{V}O_2$ in humans. However, Near infrared spectroscopy (NIRS), a technique using near infrared light to assess changes in tissue oxygenation, was shown to be a useful alternative to study exercise-induced changes of muscle oxygenation in humans[15] and may therefore be a valuable tool to study pathophysiological mechanisms of impaired oxygen uptake kinetics.[2]

In CHF patients, the role of central hemodynamics in relation to oxygen delivery to utilization (mis)matching in skeletal muscles during moderate-intensity exercise (i.e. an exercise intensity that is indicative of regular daily activities) has yet to be elucidated. Therefore, this study aimed to investigate whether the rate of increase in cardiac output during moderate exercise is related to the degree of skeletal muscle deoxygenation in patients with CHF. Based on the results of previous animal and computer modelling studies we hypothesized that in CHF patients with a relatively slow increase in cardiac

output relative to the metabolic demands, i.e. poor matching of Q and $\dot{V}O_2$, central hemodynamics have a more profound influence on skeletal muscle deoxygenation.

Methods

Subjects

Forty-three patients with CHF were recruited from our outpatient clinic from March 2012 till April 2014. Subject characteristics are listed in Table 1. Criteria for eligibility were stable systolic heart failure attributed to either dilated cardiomyopathy or ischemic heart disease due to myocardial infarction, New York Heart Association (NYHA) functional Class II or III (without change in class or medication ≤ 3 months prior to inclusion) and left ventricular ejection fraction ≤ 40% (assessed by echocardiography or cardiac MRI maximal 2 months prior to inclusion). Exclusion criteria were recent myocardial infarction (≤ 3 months prior), angina pectoris at rest, clinical signs of decompensated heart failure, pulmonary, neurological or orthopaedic disease limiting the ability to exercise and a history and/or clinical signs of peripheral vascular disease.

	Slow Q responder (*n* = 22)	Normal Q responder (*n* = 21)	P
Age (years)	66 +/- 11	64 +/- 6	Ns
Age category (<60/60-70/>70 years)	6/6/10	4/13/4	Ns
Gender (male/female)	18/4	18/3	Ns
Aetiology (ICM/DCM)	13/9	11/9	Ns
Duration (months)	44+/-46	64 +/- 64	Ns
NYHA class (II/III)	9/13	13/8	Ns
Weber class (A/B/C/D)	6/8/7/1	9/8/4/0	Ns
LVEF (%)	31+/-10	28+/-12	Ns
Beta blocker (n)	20	19	Ns
ACE/ARB (n)	21	21	Ns
Peak $\dot{V}O_2$ (mL min^{-1} kg^{-1})	17.7+/-6.1	20.5 +/- 6	Ns
Peak Q (L min^{-1})	10.9 +/- 4.7	11.1+/-3.9	Ns

TABLE 1 comparison of patient and disease characteristics between slow Q and normal Q responders. Values are presented as mean +/- SD or number. ICM ischemic cardiomyopathy, DCM dilated cardiomyopathy, BMI Body Mass Index, NYHA New York Heart Association, LVEF left ventricular ejection fraction, ACE angiotensin-converting enzyme inhibitor, ARB angiotensin II receptor blocker, $\dot{V}O_2$ oxygen uptake, Q cardiac output

The study protocol was approved by the local Research Ethics Committee of Máxima Medical Centre, Veldhoven, The Netherlands. The study was conducted according to the Helsinki Declaration and all participants provided written and signed informed consent.

Exercise testing

Exercise testing was performed in an upright seated position on an electromagnetically braked cycle ergometer (Lode Corrival, Lode BV, Groningen, The Netherlands). A twelve lead electrocardiogram (ECG) was registered continuously. Patients were instructed to maintain a pedalling frequency of 70 rotations per minute (RPM) during all exercise phases.

Maximal exercise testing was used to determine the workload for the submaximal exercise test. This test was performed at least 1 day before the submaximal test. It consisted of a symptom-limited test using an individualized ramp protocol aiming at total test duration of 8-12 minutes. The test was preceded by 4 minutes of unloaded pedalling and was ended when the patient was not able to maintain the required pedalling frequency. Peak workload was defined as the final registered workload.

Submaximal exercise testing commenced with a 2 minute resting period, passively maintaining the right leg in a fixed position, followed by a 6 minute bout at 80% of the workload corresponding to the ventilatory aerobic threshold (VAT), achieved during the maximal exercise test. Thereafter, there was a 5-minute recovery phase with the same fixed leg position as during the resting period.

During the tests ventilatory parameters were measured breath-by-breath (ZAN 680 USB, ZAN Messgeräte, Oberthulba, Germany) and were averaged over 10 second intervals after removal of outliers (values > 3 standard deviations (SD) from the local mean).[16] Volume and gas analysers were calibrated before each test. Peak$\dot{V}O_2$ and peak respiratory exchange ratio (RER) were defined as the final 30-second averaged value of the maximal exercise test. VAT was assessed by the V-slope method.[17]

Central hemodynamics

Assessment of cardiac output (Q) was performed by a radial artery pulse contour analysis method (LiDCO, LiDCO Ltd, London, UK). This technique determines beat-to-beat changes in central hemodynamics, by calculating nominal stroke volume (SV) from a pressure-volume transformation of the radial artery pressure waveform.

Before the exercise test, a 20-gauge arterial catheter was inserted into the radial artery. The radial artery catheter was connected to the LiDCO *plus* monitor. In order to convert nominal to absolute Q, the system was calibrated at rest in supine position by echocardiography (Philips CX50, handheld). Resting Q was calculated by assessing the product of heart rate (HR) and SV. SV was determined by the product of the Cross Sectional Area (CSA) and the Velocity Time Integral (VTI) of the Left Ventricular Outflow Tract (LVOT).[18] After the calibration procedure, patients were positioned upright on the

cycle ergometer and the exercise protocol was started. Data were sampled beat-by-beat and stored off line for analysis. Outliers were removed using a moving average filter with a window of 11 data points (Python 2.7, Python Software Foundation).
Previous studies showed that radial artery pulse contour analysis is a reproducible and accurate method for assessment of cardiac output (Q) under a variety of physiological conditions.[19,20] In particular, we showed, using the Fick method as a reference, that this technique is highly accurate for continuous assessment of Q during maximal and submaximal exercise testing in CHF patients.[19]

Skeletal muscle (de-) oxygenation

In the present study, NIRS measurements were performed using a portable continuous wave near-infrared spectrophotometer (Portamon, Artinis, Elst, The Netherlands). This technique is based on the modified Lambert-Beer law and is able to distinguish between oxygenated (O_2Hb) and deoxygenated haemoglobin (HHb) by measuring the absorption of emitted light at two different wavelengths (760nm for HHb and 841nm for O_2Hb). With the application of spatially resolved spectroscopy, the tissue saturation index (TSI) was used to estimate absolute values of skeletal muscle deoxygenation during constant load exercise (see also section data analysis). TSI equals the ratio of oxygenated haemoglobin (O_2Hb) divided by total Hb (tHb) and is expressed as a percentage. The theoretical principles and clinical utility of the measurement technique have been described elsewhere.[15]
The probe was connected to the right thigh with adhesive tape and kept in place by an elastic strap. It was located at 20 cm proximally from the lateral patellar edge over the centre of the m.vastus lateralis. A dark cloth impeded ambient light. Data were sampled at 10 Hz and stored for off-line analysis. Before the test, the skinfold thickness at the site of NIRS was measured with a skinfold calliper (Harpenden, Baty International, West Sussex, UK). The thickness of the measured double skinfold was divided by two to obtain an estimate of the adipose tissue thickness (ATT).

Data analysis

Kinetic analysis

The reproducibility and reliability of analysis of kinetics of $\dot{V}O_2$ and Q during onset of the constant-load tests were reported previously.[21] First, all data were resampled into 10-sec intervals. Considering exercise onset, the first 20 sec of the $\dot{V}O_2$ data set were omitted, as it is generally accepted that during this period (cardiodynamic phase) the increase in $\dot{V}O_2$ reflects merely an increase in pulmonary blood flow, rather than changes in tissue gas exchange. To calculate time constants of onset of $\dot{V}O_2$ and Q, a non-linear least squares regression procedure (Python 2.7, Python Software Foundation) was applied to the onset phase, using the following formula:

$$Y(t) = Y_{baseline} + A * (1- e- (t- Td)/\tau)$$

With Y = $\dot{V}O_2$ or Q, A = the amplitude during exercise onset, Td = time delay (s), and τ = time constant (s). The "goodness of fit" was determined by the coefficient of determination (R^2).

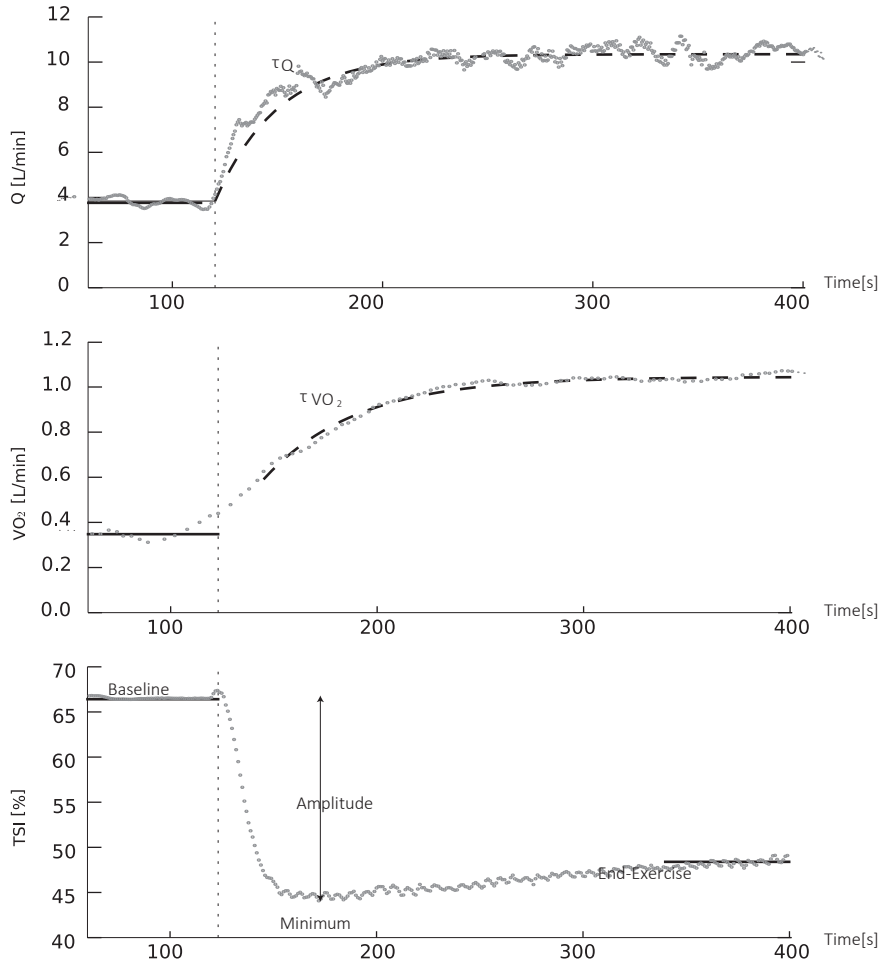

FIGURE 1 example of oxygen uptake ($\dot{V}O_2$), cardiac output (Q) and skeletal muscle deoxygenation (TSI) respons at the onset of submaximal exercise. Measured study parameters are shown in the figure

TSI values

In a previous study, we demonstrated that absolute values of TSI showed better relative reliability compared to kinetic values. As such, absolute TSI values (described below) may be more appropriate for determining physiological differences between patients.[22]

Absolute baseline values of TSI were defined as the average values during the last minute of the resting period, and end exercise values as the average values during the last minute of exercise ($TSI_{endexercise}$). The minimal value of TSI (TSImin) was defined as the lowest 5 second averaged value during the initial decay. The amplitude of TSI (TSIamp) was defined as TSI baseline minus TSImin. Figure 1 shows an example of calculation and fitting of absolute and kinetic parameters for Q, $\dot{V}O_2$ and TSI.

Q response relative to metabolic demand

Patients were categorized in two groups: patients with a relatively slow increase in cardiac output relative to the metabolic demands (ratio of $\tau Q/ \dot{V}O_2 \geq 1$, slow Q responders), and normal Q responders (ratio of $\tau Q/ \dot{V}O_2 < 1$). From a physiological point of view, a ratio exceeding 1 reflects poor matching of oxygen delivery and consumption, which necessitates greater fractional oxygen extraction to sustain a given metabolic rate.[10,23]

Statistical analysis

All data were analysed using SPSS 19.0.0 statistical software (SPSS Inc, Chicago, IL, USA). Results are presented as mean value ± standard deviation (SD) or numbers (n). Distribution of data was checked for normality by skewness and kurtosis. The independent t-test was used for unpaired observations. Differences between categorical data were assessed by the Chi-square test. Relations between variables were assessed by Pearson correlation coefficient for normal distributed data and Spearmans rho (r_s) for not normal distributed data. For all statistical comparisons the level of significance was set at $p< 0.05$.

Results

All 43 patients successfully performed both maximal and submaximal exercise tests without any untoward events. Mean peak $\dot{V}O_2$ was 19.1 +/-6 ml/min/kg, mean peak Q was 11 +/- 4.3 L/min and mean peak workload corresponded to 127 +/- 54 W.

Table 2 shows the results of the submaximal exercise test. The mean workload for slow Q responders was 53W (+/- 24W) and for normal Q responders 57 +/- 23W This was at respectively 41% (+/- 8) and 47% (+/- 11%) of the maximal achieved workload.The mean coefficient of determination (R^2) of $\dot{V}O_2$ onset kinetics was 0.87 (+/- 0.11) and 0.80 (+/- 0.20) for Q onset kinetics. The time constant of $\dot{V}O_2$ ($\tau\dot{V}O_2$) was significantly correlated with the time constant of Q (τQ) ($r=0.66$, $p<0.0001$).

	Slow Q responder (*n* = 22)	Normal Q responder (*n* = 21)	P
τQ(s)	76+/-24	47+/-27	0.01
$\tau\dot{V}O_2$ (s)	56+/-19	63+/-23	Ns
$\dot{V}O_2$ baseline (ml/min)	337+/-85	341+/-77	Ns
$\dot{V}O_2$ steady state (ml/min)	1080+/-334	1228+/-309	Ns
Q baseline (L/min)	4.3+/-1.3	3.8+/-1.2	Ns
Q steady state (L/min)	8.0+/-2.7	7.9+/-2.8	Ns
TSI bl (%)	67+/-5	67+/-6	Ns
TSI min (%)	60+/-7.6	58+/-10	Ns
TSI end exercise (%)	63+/-6.0	62+/-7.7	Ns
TSI amp (%)	7.2+/-5.0	8.4+/-5.9	Ns

TABLE 2 comparison of submaximal exercise data of $\dot{V}O_2$, Q and skeletal muscle deoxygenation between slow Q and fast Q responders. Values are presented as mean +/- SD. Q Cardiac Output, $\dot{V}O_2$ oxygen uptake, tau time constant, TSI_{bl} baseline value of tissue saturation index (TSI), TSI_{min} minimal value of TSI, $TSI_{endexercise}$ TSI value at end of exercise, TSI_{amp} amplitude of the TSI response between the baseline and minimal value.

Patient and disease characteristics between slow and normal Q responders

Table 1 represents a comparison between slow and normal Q responders. No statistical differences in disease characteristics as for instance aetiology, duration of heart failure, NYHA, Weber class, presence of ischemia, mitral regurgitation or dyssynchrony were observed. The median duration of CHF in Slow Q responders was 37 months (range 4-192), while in normal Q responders the median duration of CHF was 18 months (range 3-130). This was not statistical significant. The use of beta-blockers and ACE inhibitors/ angiotensin II receptor blocker was similar in both groups.

Relationship between cardiac output and muscle deoxygenation

There were no statistical significant correlations between TSI parameters and $\tau\dot{V}O_2$ or τQ. Twenty-two (51%) patients were categorized as slow Q responders ($\tau Q/\tau\dot{V}O_2$ >1) and 21 patients (49%) as normal Q responders ($\tau Q/\tau\dot{V}O_2$ <1).

Figure 2 a and b show the relation between τQ and the minimal attained value of TSI. In slow Q responders, both TSImin and TSIamp were significantly correlated to τQ (respectively r_s= - 0.57, p<0.005 and r= 0.44, p=0.04), while no significant correlations were observed in normal Q responders (r_s=0.15, p= 0.52 and r_s = 0.09, p=0.7 respectively). The absolute values of TSI parameters did not differ statistically in both groups (Table 2).

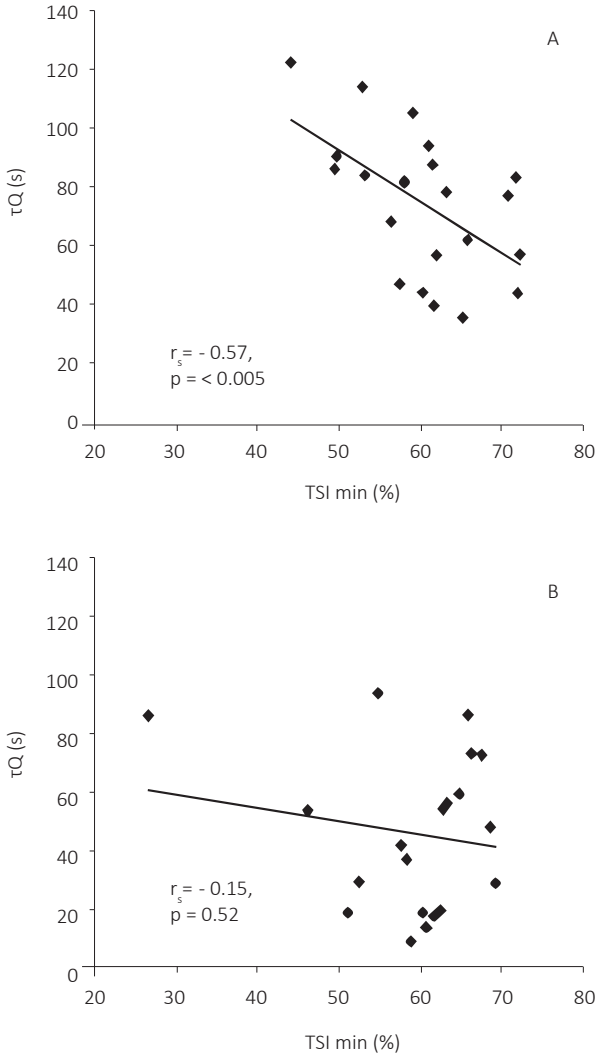

FIGURE 2 A AND B relationship between the rate of increase in cardiac output (τQ) and the minimal value of skeletal muscle deoxygenation (TSImin) in panel A: slow Q responders (τQ/τ $\dot{V}O_2$ >1) and panel B: normal Q responders (τQ/τ$\dot{V}O_2$ <1) r_s = Spearmans correlation coefficient, p= level of significance

Discussion

This study showed that in moderately impaired CHF patients with a slow cardiac output increase relative to the increase in whole body oxygen uptake (i.e. poor matching of Q and $\dot{V}O_2$), slower cardiac output kinetics were related to a higher degree of skeletal

muscle deoxygenation during moderate-intensity exercise. In contrast, cardiac output kinetics were not related to the degree of skeletal muscle deoxygenation in patients with relative fast cardiac output kinetics. These findings suggest heterogeneity in the pathophysiological determinants of delayed oxygen uptake kinetics of CHF patients. This different response could not be predicted by patient or disease characteristics such as age, aetiology, NYHA class or medication use.

The lack of correlation between the amount of skeletal muscle deoxygenation and cardiac output kinetics in relative fast Q responders suggests that the ability to increase cardiac output is not necessarily the main determinant of the amount of deoxygenation in exercising skeletal muscles. These results seem to be in contrast with the findings of Sperandio et al., who observed a high correlation between the kinetics of cardiac output and microvascular blood flow.[2] This discrepancy could be explained by several factors. First, substantially higher exercise intensity was used, which may have compromised blood flow to exercising muscles to a greater extent, resulting in a more pronounced discrepancy between microvascular oxygen delivery and the metabolic demands. These findings are in line with an earlier study by Sullivan et al., showing that, compared to healthy individuals, exercising leg blood flow in CHF patients was reduced, relatively more at maximal compared to submaximal exercise.[24] Second, our study population has a considerable higher maximal exercise capacity at baseline (peak $\dot{V}O_2$ 19.1 +/-6 ml/min/kg vs 15.1 +/- 2.8 ml/min/kg). It is known from animal studies that severe heart failure is associated with an impaired skeletal muscle oxygenation.[23] Therefore this baseline difference in exercise capacity may limit comparison of both studies. Third, methodological differences may have played a role. For instance, deoxygenated haemoglobin (HHb) was measured, compared to TSI in our study, to assess skeletal muscle deoxygenation. Although the optimal assessment parameter is still under debate,[25,26] a major concern of using HHb to assess changes in skeletal muscle oxygenation is that it is less sensitive to exercise-induced hyperaemia than TSI.[27] Also, the NIRS technique used by Sperandio did not permit assessment of absolute values. Yet, it was shown recently that the use of relative concentrations of HHb resulted in exaggerated deoxygenation responses as compared to using absolute values.[28] In addition, kinetic analysis may be less suitable to assess exercising skeletal deoxygenation in CHF patients than evaluation of absolute values.[22] Finally, Barbosa et al. showed that mono exponential fitting may be inadequate to characterize deoxygenation onset kinetics in the presence of an overshoot, which is frequently present in CHF patients.[12]

From a physiological point of view, the lack of correlation between the rate of cardiac output increase and skeletal muscle deoxygenation in the moderate-intensity domain in normal Q responders may have different explanations. First, the impaired oxygen uptake kinetics may be primarily determined by a reduced ability to utilize oxygen. This view is supported by a study in isolated canine gastrocnemius muscle preparations,

showing that improvement in oxygen delivery did not result in faster oxygen uptake kinetics.[29] Although human studies in CHF patients using this approach are not available, numerous studies demonstrated intrinsical skeletal muscle abnormalities (e.g. decreased oxidative enzymes and mitochondria), suggesting that skeletal muscle myopathy plays a major role in the reduced exercise capacity.[30,31,32,33] A second explanation may be that changes in microvascular blood flow and cardiac output during moderate exercise are not directly related. Although previous studies in CHF patients demonstrated a clear relation between exercise-induced changes in cardiac output and leg blood flow,[24,34] studies investigating the relation between leg blood flow and microvascular blood flow in exercising muscles in CHF patients are scarce. Theoretically, several factors may constrain microvascular muscle blood flow in CHF patients, including mechanical (e.g. vascular stiffness, decreased perfusion pressure), neurohumoral (e.g increased levels of endothelin, angiotensin and catecholamines) and inflammatory factors (e.g. TNFα, ROS). In a study in healthy humans it was shown that the onset kinetics of femoral leg blood flow were faster than microvascular blood flow, suggesting that leg blood flow in conduit arteries may not be a representative of microvascular blood flow.[35] In addition, both animal and human studies demonstrated heterogeneity in blood flow responses within and between skeletal muscles.[36,37] Yet, the fact that we did observe a significant correlation between the amount of deoxygenation and the prolonged cardiac output response in slow Q responders, would argue against a complete uncoupling between central and microvascular blood flow.

The most important finding of this study is that, in contrast to patients with a normal increase in cardiac output relative to the metabolic demands, we did observe a significant correlation between the rate of increase in cardiac output and the amount of skeletal muscle deoxygenation (TSImin) in patients with poor matching of Q and $\dot{V}O_2$ kinetics. This finding confirms our hypothesis and suggests that in these patients the delayed increase in cardiac output induces a compensatory increase in skeletal muscular oxygen extraction. This concept was demonstrated before in an animal study.[10] Whether our findings reflect an actual central hemodynamic limitation of oxygen uptake kinetics is difficult to establish from our data since the critical level of TSI below which the blood-myocyte O_2 flux compromises mitochondrial control is currently not known.[38] Moreover TSI is a surrogate for $Pm\dot{V}O_2$ and it is not clear if it represents absolute values of $Pm\dot{V}O_2$. Nevertheless, our results indicate that in a subset of relatively young, well-treated patients with moderately impaired exercise capacity, the cardiac output response may be a limiting factor, even during moderate-intensity exercise. Although this does not detract the fact that treatment strategies aiming at improvement of daily exercise performance should be directed at improving the skeletal muscle metabolic capacity (e.g. the intra-myocyte milieu, mitochondrial mass, etc), these findings suggest that improving the “central pump” in CHF patients should also be an important treatment

goal. Clinical predictors of pathophysiological limitations to exercise capacity might be useful for customizing care and thereby improving the response to treatment.[39,40] In the present study, however, we did not find an association between disease and demographic characteristics and the rate of increase in cardiac output. Yet, in a previous animal study, it was shown that more severe heart failure was associated with a more pronounced skeletal muscle deoxygenation.[11] Since we evaluated moderately impaired CHF patients (peak $\dot{V}O_2$ 19.1 +/-6 ml/min/kg), future studies evaluating clinical predictors of pathophysiological limitations to exercise should also include CHF patients with lower exercise capacities.

Limitations

Before drawing definite conclusions from this study, some limitations should be acknowledged. First, the sample size was too low to draw definite conclusions on clinical and disease predictors for the heterogeneity in submaximal exercise capacity.

Our patients resembled a "typical" CHF study population of predominantly moderately impaired, middle aged men. Whether our results can be extrapolated to an older population, women or more severely impaired patients remains to be determined. A second limitation concerns the performance of one submaximal exercise bout. More repeats are definitely needed in case of a low number of study participants (e.g. $n < 10$) and when individual patients are evaluated. However, in this rather larger group of CHF patients the influence of bout-to-bout variability will likely not influence between group analysis to a large degree. In addition, in clinical practice, multiple bouts would be time consuming and costly, which hampers implementation of submaximal exercise testing.

The third limitation would be the application of NIRS. Although we standardized the location of the NIRS sensors at the m vastus lateralis, TSI responses may have been influenced by different muscle fibre type distribution under the area of investigation between subjects as Type II fibre differ in their deoxygenation response from type I.[41] Also capillary recruitment patterns in the skeletal muscle at the onset of exercise may have varied between subjects.[38,42] These factors may have contributed to the differences seen in the relationship between τQ and TSI amplitude.

Finally, the pulse contour wave analysis method, used in our study to assess cardiac output kinetics, should be used with caution in patients with an important aortic regurgitation. This may overestimate absolute values. However, this did not apply to our study, as there were no patients with severe aortic regurgitation (determined with echocardiography or MRI). In addition, the morphology of the arterial waveform may be altered by damping or other technical errors. Although studies do not report measurement error as a result of this phenomenon, this may be a source of error in any form of pulse contour analysis.[43]

Because cardiac output is estimated every cardiac cycle, atrial fibrillation may result in irregular data output, however as data was filtered with a moving average filter this did not result in exclusion of data. Moreover, we showed in a previous study that this method is an accurate measurement for stroke volume with low variability compared to the direct Fick method in CHF patients in the moderate intensity domain.[19]

Conclusion

The present study demonstrated a slow cardiac output increase relative to the increase in whole body oxygen uptake during moderate-intensity exercise in a substantial subset of moderately impaired CHF patients. In this group, cardiac output kinetics were related to the amount of skeletal muscle deoxygenation, suggesting that central hemodynamics may limit muscle oxygenation during moderate-intensity exercise in these patients.

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CHAPTER 5

The utility of the oxygen pulse recovery as a marker of the cardiac output response to exercise in patients with Chronic Heart Failure

SUBMITTED

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Abstract

Background Chronic heart failure (CHF) is characterized by exercise intolerance, which is partly attributed to impaired central hemodynamics. The cardiac output (CO) response to exercise is a useful marker to grade the prognosis and severity of CHF, albeit difficult to assess in daily clinical practice. The recovery of the oxygen pulse (OP) after maximal exercise is a non-invasive parameter, which is related to exercise capacity in cardiac patients. However, the relation between OP recovery and the central hemodynamic response to exercise remains to be determined. We hypothesized that an impaired OP recovery is associated with a reduced CO response to exercise in CHF patients.

Methods 61 CHF patients performed a symptom limited cardiopulmonary exercise test with simultaneous measurement of CO. Impaired OP recovery was defined as an overshoot during the first minute of recovery. Furthermore, OP recovery was evaluated by the OP relative recovery (i.e. OP at 1 min recovery as a percentage of peak OP).

Results An OP overshoot was observed in 9% (n=5) of patients. In these patients, peak CO and $\dot{V}O_2$ were significantly lower (peak CO 7.9±0.8 vs 11.2±4.3 L/min and peak $\dot{V}O_2$ 14.1±4.7 vs 19.6±5.8 ml/min/kg, p=0.001 and 0.03). Mean relative recovery of OP was 78 ± 20%. A slow OP recovery (OP_{RR} >100%) was seen in 13% (n=8) of patients. Peak CO and $\dot{V}O_2$ were significant lower in the OP_{RR}>100 group (11+/-4 vs 8+/-0.7 L/min, p=0.03 and 19.7+/- 5.9 vs 14.6 +/- 3.7ml/kg/min, p=0.01, respectively) Weber class was significant lower in patients with an OP overshoot (p=0.004) and with an OP_{RR}>100 (p=0.03). There was a significant relation between OP_{RR} and SV_{RR} (r=0.57, p=0.001), as well as between OP_{RR} and a-v O_2 diff $_{RR}$ (r_s=0.4, p=0.001).

Conclusion An impaired OP recovery is associated with a reduced CO response to exercise and worse functional status. Therefore the OP recovery can be used to grade the severity of CHF.

Introduction

Chronic Heart Failure (CHF) is characterized by an impaired exercise capacity. The underlying pathophysiological mechanisms are constituted by a complex interplay between central hemodynamic and peripheral factors.[1] Several studies have shown that the cardiac output (CO) response to exercise is impaired in CHF patients and bears important prognostic information.[2,3,4] In addition, the rate of post-exercise recovery of stroke volume (SV) and CO were shown to be related to the CO response during exercise and disease severity in CHF patients.[5] Despite the potential clinical utility of exercising hemodynamics for the assessment and treatment of CHF patients, measurement of CO during exercise is not implemented in daily clinical practice due to the fact that most available methods are either invasive, expensive, not feasible or lacking accuracy at maximal exercise in this specific patient group.[6,7,8,9] The ratio between oxygen uptake ($\dot{V}O_2$) and heart rate (HR) is named the oxygen pulse (OP) and is a non-invasive parameter, which can be determined by cardiopulmonary exercise testing (CPET). According to the modified Fick's principle, the OP is the product of SV and the systemic arteriovenous oxygen difference (a-v O_2 diff). Previous studies showed that the OP could be used as an estimate for SV at peak exercise in healthy individuals as peak a-v O_2 diff is relatively constant in these subjects.[10,11] In contrast, peak a-v O_2 diff is not a constant value in CHF patients and depends on disease severity.[11,12] Therefore, the peak OP response can be heterogeneous and does not simply reflect peak SV. The OP response during recovery may be more suitable to characterize exercise hemodynamics.[13,14,15,16] As such, Suzuki et al. demonstrated, in a mixed population of cardiac patients, an OP overshoot during recovery in 19% of the study population, which correlated with lower exercise capacity and resting left ventricular ejection fraction (LVEF).[17] However, there have been no studies evaluating the relation of post-exercise OP recovery with the central hemodynamic response to exercise in CHF patients. The aim of the study was to evaluate the relation between the OP response during recovery and the severity of CHF, as determined by central exercise hemodynamics and clinical parameters. Furthermore, we aimed to investigate the pathophysiological background of delayed OP recovery.

Methods

In this cohort study, we analyzed the baseline data of CHF patients who participated in our cardiac rehabilitation program. All subjects performed a cardiopulmonary exercise test with simultaneous measurement of central hemodynamics at the Department of Cardiology of the Máxima Medical Center between 2008 and 2014 All participants provided written and signed informed consent. The study was conducted according to

the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act.

Study population

In total, 61 CHF patients were enrolled in the study. Inclusion criteria were: CHF secondary to ischemic or dilated cardiomyopathy, New York Heart Association functional class II-III, left ventricular ejection fraction ≤ 40% (assessed by echocardiography and/ or cardiac MRI) and Optimized Medical Treatment (OMT) according to current guidelines.[18] Exclusion criteria were: recent myocardial infarction, unstable angina (less than 3 months prior to inclusion), hemodynamically significant valvular heart disease, significant chronic obstructive pulmonary disease and other conditions limiting the ability to perform exercise.

Exercise testing

All subjects performed a symptom-limited maximal exercise test on an electromagnetically braked cycle ergometer in an upright position (Corrival, Lode, Groningen, The Netherlands), using an individualized ramp protocol with duration of 8 to 12 minutes.[19] The subjects were instructed to maintain a pedaling rate of 70-90 per minute. The test was terminated when the subject was not able to maintain the required pedaling rate. After termination of exercise the CHF patients remained on the cycle ergometer in seated position for 5 minutes, without pedaling. In all subjects a 12-lead electrocardiogram was registered continuously. Ventilatory parameters were measured breath-by-breath (Zan 680 USB, Oberthulba, Germany). Volume and gas analyzers were calibrated before each test.

Assessment of central hemodynamics

Assessment of cardiac output (CO) was performed by a radial artery pulse wave contour analysis method (LiDCO, LiDCO Ltd, London, UK). This technique provides beat-to-beat changes in central hemodynamics, by calculating nominal stroke volume (SV) from a pressure-volume transform of the radial artery pressure waveform. In order to convert nominal CO to absolute CO, the system was calibrated at rest by echocardiography (Philips CX50, handheld). Resting CO was calculated by assessing the product of heart rate (HR) and SV. SV was determined by the product of the Cross Sectional Area (CSA) and the Velocity Time Integral (VTI) of the Left Ventricular Outflow Tract (LVOT).[20] Before the exercise test, a 20-gauge arterial catheter was inserted into the radial artery. The radial artery catheter was connected to the LiDCO plus monitor. After the calibration procedure, patients were positioned upright on the cycle ergometer and the exercise protocol was started. Previous studies showed that radial artery pulse contour analysis is a reproducible and accurate method for assessment of CO under a variety of physiological

conditions.[21,22,23] In particular, using the Fick method as a reference, we showed that this technique is highly accurate for continuous assessment of the CO during an incremental symptom limited exercise testing in CHF patients.[7]

Definition of recovery parameters

The relative recovery of the OP was assessed by the ratio between the OP after 1 minute of recovery and the OP at peak exercise, expressed as a percentage (OP_{RR}). The same was done for SV and a-v O_2 diff. For identifying overshoots we used the method described by Suzuki et al.[17] First, two independent blinded researchers visually identified overshoots after excluding artifacts (e.g. breathing, noise). In case of disagreement, a third independent observer decided whether data was taken into the final analysis. Second, the overshoot was confirmed by a higher mean value during the first 60 seconds of recovery compared to the peak value. This method was determined to have a more objective definition of an overshoot, though in daily practice, overshoots are mostly visually identified.

Data analysis

Breath-to-breath data of oxygen uptake and beat-to-beat data of central hemodynamics were filtered for outliers. Outliers were defined as points deviating more than two standard deviations from a calculated moving average with a window of 11 data points using Python 2.7, (Python Software Foundation). All data were time aligned using manually set markers at the start of exercise and resampled in intervals of 10 seconds. Resting values were calculated as the mean of the first 60 seconds of the resting phase prior to the start of exercise. Peak values were defined as the average values during the final 30 seconds of the test.

Statistical Analysis

Data were analyzed using SPSS 22.0.0 statistical software (SPSS Inc, Chicago, IL, USA). Continuous variables are presented as mean ± SD and categorical variables as absolute and/ or relative frequencies. Normality was checked by skewness and kurtosis of the distribution. Relations between variables were assessed by Pearson correlation coefficient for normal distributed data and Spearmans rho (r_s) for abnormally distributed data. The Goodman and Kruskal Tau test was used as a measure for association between nominal variables. Between-group differences of continuous variables were evaluated by an independent t-test for normal distributed data. The $\chi 2$ test and Fisher Exact test were used to evaluate differences between categorical data. For all statistical comparisons the level of significance was set at $p< 0.05$.

Results

In total 61 patients were included for analysis. Baseline characteristics of CHF patients are presented in Table 1.

Age (years)	63 ± 9
Gender male/female (%)	51/10 (84/16)
Etiology ICM/DCM (%)	34/27 (56/44)
Duration CHF (months)	45 ± 51
NYHA class II/III (%)	35/26 (57/43)
Weber class A/B/C/D (%)	22/23/15/1 (36/38/24/2)
LVEF (%)	32 ± 8
Chronotropic incompetence (%)	55/6 (90/10)
Rhythm (SR, Afib, paced) (%)	50/7/4 (82/11/7)
LBBB (%)	23 (38)
Severe mitral regurgitation (%)	6 (10)
Myocardial ischemia (%)	2 (3)
Beta blocker (%)	57 (93)
ACE/ARB (%)	60 (98)

TABLE 1 Baseline Characteristics (n=61)Values are presented as mean +/- SD or number. ICM ischemic cardiomyopathy, DCM dilated cardiomyopathy, BMI Body Mass Index, NYHA New York Heart Association, LVEF left ventricular ejection fraction, SR sinus rhythm, Afib atrial fibrillation, LBBB left bundle branch block, ACE angiotensin-converting enzyme inhibitor, ARB angiotensin II receptor blocker

The study population was predominantly male and the mean age was 63 ± 9 years. Ninety-three percent of patients were treated with a beta-blocker and 98% with an ACE inhibitor or AT II blocker. Hemodynamic and gas exchange variables are presented in Table 2. Peak $\dot{V}O_2$ was 19.0 ± 5.9 ml/min/kg, peak CO was 10.9 ± 4.1 L/min.

	Baseline	Peak exercise
$\dot{V}O_2$ (ml min^{-1} kg^{-1})	4.3 ± 1.3	19.0 ± 5.9
HR (beats min^{-1})	80 ± 17	124 ± 26
SV (ml)	62 ± 14	87 ± 23
CO (L min^{-1})	4.9 ± 1.5	10.9 ± 4.1
OP (ml/beat)	7 ± 2.1	13 ± 3.7

TABLE 2 Hemodynamic and gas exchange variables (*n* =61) $\dot{V}O_2$ oxygen uptake, HR heart rate, SV stroke volume, CO Cardiac Output. OP Oxygen Pulse

Data of 4 patients were of insufficient quality to assess an OP overshoot. An OP overshoot was identified in 5 of the remaining 57 patients (9%). SV overshoot was found in 16 of 61 CHF patients (26%). There was no relation between the prevalence of an OP and SV overshoot. (Goodman and Kruskal tau=0.007, p=0.54) In patients with an OP overshoot, peak CO and $\dot{V}O_2$ were significantly lower compared to patients without an OP overshoot (peak CO 7.9±0.8 vs 11.2±4.3 L/min and peak $\dot{V}O_2$ 14.1±4.7 vs 19.6±5.8 ml/min/kg, p=0.01 and p=0.04 respectively). Also, patients with an OP overshoot were in a lower Weber class (21/20/11/0 vs 0/2/2/1, p=0.004). There was no significant difference in peak SV or peak HR, or in other clinical parameters.Relative recovery of OP was 78 ± 20% and for SV 88 ± 13%. There was a significant relation between OP_{RR} and SV_{RR} (r=0.57, p=0.001, figure 1), as well as between OP_{RR} and a-v O_2 diff $_{RR}$ (r_s=0.4, p=0.001, figure 2).

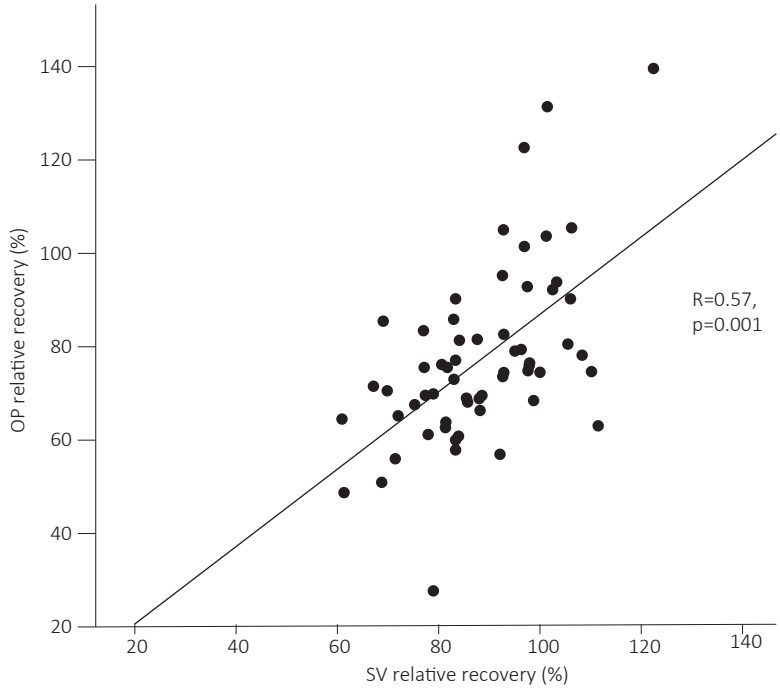

FIGURE 1 Relation between the Oxygen Pulse Relative Recovery (%) and Stroke Volume Relative Recovery (%) (n=61) R= Pearsons correlation coefficient, p= level of significance

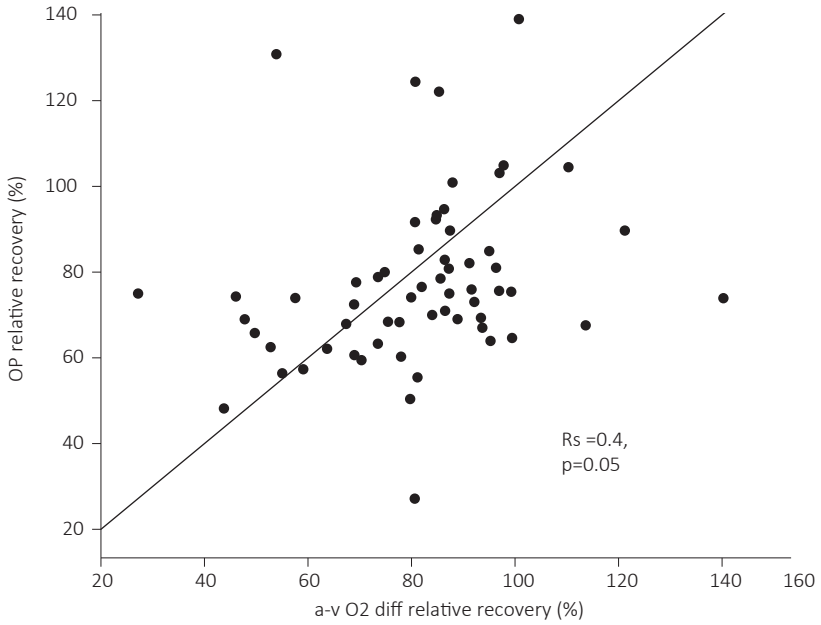

FIGURE 2 Relation between the Oxygen Pulse Relative Recovery (%) and Arteriovenous Oxygen Content Difference Relative Recovery (%) (n=61) R_s = Spearmans correlation coefficient, p= level of significance

Table 3 shows a comparison between patients with an OP_{RR} > and < 100%. In the OP_{RR} > 100% group (i.e. slow response), peak CO and $\dot{V}O_2$ were significant lower (respectively 8+/-0.7 vs 11+/-4 L/min, p=0.03 and 14.6 +/- 3.7 vs 19.7+/- 5.9 ml/kg/min, p=0.01). SV_{RR} was 103+/-10% in the OP_{RR} > 100% group. SV_{RR} was significantly higher compared to SV_{RR} in the OP_{RR} < 100% group (87+/-12%, p=0.001). Relative recovery of a-v O_2 diff showed a trend towards a significant higher value in the slow OP_{RR} group (94+/-10 vs 79+/-19.7%, p=0.05). Weber class was significant lower in the group with a slow OP recovery (p =0.03). Other clinical parameters, such as age, etiology, medication use or duration of heart failure did not differ significantly between both groups.

OP Relative Recovery	<100% (n=53)	>100% (n=8)	P
$\dot{V}O_{2\ peak}$ (ml min^{-1} kg^{-1})	19.7+/- 5.9	14.6 +/- 3.7	0.01
Weber A/B/C/D	21/20/12/0	1/3/3/1	0.03
CO_{peak}(L min^{-1})	11+/-4	8+/-0.7	0.03
SV_{peak} (ml)	90+/-23	71+/-12	0.001
$SV_{relative\ recovery}$(%)	87+/-12	103+/-10	0.001

TABLE 3 comparison between patients with and without an impaired Oxygen Pulse recovery in the first minute after cessation of exercise expressed as Oxygen Pulse Relative Recovery of respectively below and above 100%

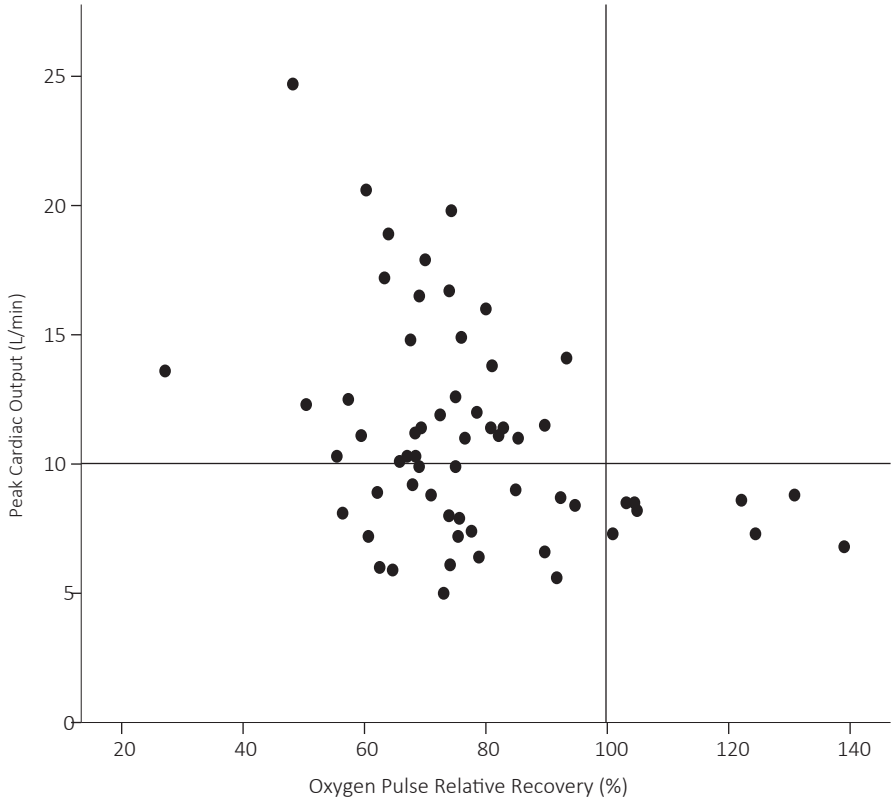

FIGURE 3 Scatter plot of Peak Cardiac Output (L/min) versus Relative Recovery of the Oxygen Pulse (%) (n=61). Solid line on X-axis divides subjects with an OP relative recovery above and below 100%. Solid line on the Y-axis divides subjects with a peak CO above and below 10L/min.

As shown in figure 3, all patients with an OP_{RR}> 100% had a peak CO below <10 L/min, while in patients with an OP_{RR} < 100%, peak CO exceeded 10L/min in 33 patients (62 %). An SV_{RR}>100% was observed in 13/61 patients (21%). There was no difference in peak CO between the SV_{RR}>100% or <100% (9.4±3.9 vs 11.4±4.1L/min, p=0.11); Peak SV was significantly lower (76±21ml vs 90±23ml, p=0.04), and the increase of CO, $\dot{V}O_2$ and SV during exercise were significantly lower than in the group with a SV_{RR} <100%. (delta CO 4.6±2.4 vs 6.4±3.5L/min, $\dot{V}O_2$ 835±334 vs 1097±494ml/min, SV 12±12 vs 29±16ml). In the SV_{RR}>100% ischemic cardiomyopathy was more prevalent (n=23 vs 11, p=0.02), other clinical variables did not differ between groups.

Discussion

The results of this study demonstrated that an impaired OP relative recovery is associated with a more severely impaired CO response to exercise in CHF patients, suggesting that OP recovery is a useful marker for exercising hemodynamics in this patient population. Moreover, patients with an impaired OP recovery had a lower peak $\dot{V}O_2$ and were in a lower Weber class, reflecting worse functional status compared to patients with a more rapid decrease in the OP after cessation of exercise. From a physiological point of view, slow OP recovery was associated with both slow SV and a-v O_2 diff recovery, which may indicate a prolonged replenishment of oxygen debt due to a higher oxygen deficit during exercise. Whether a prolonged OP relative recovery can serve as an independent prognostic marker remains to be determined in future larger studies.

Studies evaluating the OP overshoot phenomenon during recovery of exercise in cardiac patients are scarce. Suzuki et al. reported on the overshoot phenomena of respiratory gas variables during exercise recovery in a heterogeneous population and found an OP overshoot in 19%. However, they did not evaluate central hemodynamics during or after exercise.[17] The difference in the prevalence of OP overshoots as compared to our study (19% vs 9%, respectively), may be attributed to the fact that in our study only CHF patients were included, whereas Suzuki et al. included a heterogeneous population of cardiac diseases including coronary artery disease, valvular disease and hypertrophic cardiomyopathy. Nonetheless, in their study, an overshoot was related to impaired exercise capacity and lower LV ejection fraction, suggesting that an OP overshoot is a marker of cardiac dysfunction. This is in line with the results of our study, showing that patients with an overshoot of OP (or SV) had a reduced peak CO and $\dot{V}O_2$. Yet, in our study population, an OP overshoot was observed less frequently than an OP_{RR} >100% (5 vs 8 patients). Furthermore, an overshoot could not be determined in 4 patients (8%) due to artefacts. This suggests that for clinical purposes, relative recovery (RR) after 1 minute may be preferable.

The physiological background of a prolonged OP recovery or OP overshoot in CHF patients is not clearly understood. According to the modified Fick equation, the OP equals the product of SV and a-v O_2 diff, indicating that both a delayed SV and OP recovery may play a role. Concerning SV recovery, we observed an SV overshoot in 26% of the subjects. In addition, an SV_{RR} >100% was seen in 21% of our patients. Although the prevalence of an SV overshoot was higher as compared to an OP overshoot (26 vs 9%), there was a highly significant relation between OP_{RR} and SV_{RR} (r=0.57, p=0.001, figure 2). These findings suggest that a delayed SV decrease during recovery contributes, at least partly, to an impaired OP recovery. An impaired SV_{RR}, in its turn, was related to a reduced SV response during exercise. An impaired SV response during exercise may be explained by decreased contractility during exercise due to e.g. ischemia, dyssynchrony

or mitral regurgitation.[24,25,26] In our study, ischemic cardiomyopathy was more prevalent than dilated cardiomyopathy in the SV_{RR} > 100% group. A delayed SV recovery in these subjects may be explained by the fact that an exercise-induced decease in contractility is often followed by a sudden increase during early exercise-recovery, resulting in an OP overshoot or delayed recovery. In line with these findings, Koike et al demonstrated in cardiac patients that an SV overshoot occurred during recovery.[27] They stated that this increase in SV was due to imbalance between sustained cardiac contractility and sudden decrease in afterload.

A second determinant of an OP overshoot/ impaired recovery may be a delayed decrease of the a-v O_2 diff during recovery. We observed a trend towards significance of a slower relative recovery of a-v O_2 diff in the slowed OP_{RR} group (94+/-10 vs 79+/-19.7%, p=0.05). Moreover, the OP_{RR} was significantly related to the relative recovery of a-v O_2 diff (r_s=0.4, p=0.001, figure 3), suggesting that a delayed decrease in a-v O_2 diff during recovery also contributes to the slowed OP response. This might be explained by the fact that in CHF patients, a large oxygen deficit has occurred during exercise and during recovery a prolonged SV and/or a-v O_2 diff response is physiologically needed to replenish the oxygen debt. This concept has been shown in submaximal exercise studies in CHF patients where prolonged $\dot{V}O_2$ onset kinetics (i.e. increased O_2 deficit) are strongly correlated with prolonged $\dot{V}O_2$ recovery kinetics (i.e. increased O_2 debt).[28] In line with these findings, Tanabe et al demonstrated that an impaired CO response during a symptom limited exercise test was closely related to a prolonged CO recovery. In patients with a CO overshoot, they found that systemic vessel resistance (SVR) was significant higher at peak exercise but significant lower during recovery compared to patients without a CO overshoot, with the latter presumably serving as a compensatory mechanism to improve post-exercise leg blood flow in order to repay the O_2 debt. This decrease in SVR may be driven by local mechanisms controlling peripheral circulation, including neurohormonal, metabolic and endothelium-derived factors that regulate vascular tone and redistribution of blood flow to the recovering skeletal muscles. In this way, the level of microvascular O_2 pressure may persist to maintain O_2 delivery to utilization matching. In summary, in CHF patients with a reduced CO response to exercise a prolonged OP response during recovery may be a functional compensatory response of both central hemodynamics and peripheral factors.

Clinical Implications

A non-invasive and easy-to-use marker of circulatory impairment may be useful in clinical practice for assessment of prognosis and tailoring of therapeutic interventions. For example, Wilson et al showed that in CHF patients with a peak CO below 10L/min,

the non-response to exercise training was substantially higher than in patients with a higher peak CO.[29] In addition, it was demonstrated that CRT candidates with a worse hemodynamic status respond better to CRT.[30] Finally, exercise hemodynamics are strong predictors of mortality.[2,3] Therefore, future studies should include the OP relative recovery as a predictor for response to therapy and/ or prognosis.

Limitations

This study has a relative small sample size and consisted predominantly of moderately impaired middle-aged male patients. Therefore, these results cannot be generalized to more severely impaired CHF patients and women. Second, we studied passive recovery, in other words, patients stopped pedaling after maximal exercise. It remains to be determined what the role of active recovery is on hemodynamics and gas exchange parameters. For example, SVR may drop more instantly during passive recovery, which may influence overshoot phenomena. Therefore, the results of this study may not be applicable to exercise protocols using active recovery.
Third, the prevalence of an impaired recovery depends partly on the constraints of the definition. For relative recovery we used a cutoff value of 100% and for determination of the overshoot, we used the definition by Suzuki et al, consisting of visual inspection followed by the confirmation of a higher mean value of the first minute of recovery compared to the peak value of the last 30 seconds of exercise. These variables should be evaluated in prospective studies with a larger population to evaluate prognostic significance.

Conclusion

In patients with Chronic Heart Failure, an impaired recovery of the oxygen pulse is associated with a reduced cardiac output response to exercise and worse functional status. Therefore, OP recovery may be useful to grade the hemodynamic severity and prognosis of CHF. From a physiological point of view, slow OP recovery was associated with both slow SV and a-v O_2 diff recovery, which may indicate a prolonged replenishment of oxygen debt due to a higher oxygen deficit during exercise.

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PART II

Clinical Aspects

CHAPTER 6

Effects of High Intensity Interval Training on Central Hemodynamics and Skeletal Muscle Oxygenation During Exercise in Patients with Chronic Heart Failure: the HIT Central study

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Abstract

Background High intensity Interval Training (HIT) improves exercise capacity in patients with chronic heart failure (CHF). Moreover, HIT was associated with improved resting cardiac function. However, it remains to be elucidated to what extent these improvements actually contribute to training-induced changes in exercise capacity. Therefore, we evaluated effects of HIT on exercising central hemodynamics and skeletal muscle oxygenation.

Methods Twenty-six CHF patients were randomized to a 12-week 4x4 min HIT program at 85-95% of peak$\dot{V}O_2$ or usual care (UC). Patients performed maximal and submaximal cardiopulmonary exercise testing with simultaneous assessment of cardiac output and skeletal muscle oxygenation by Near InfraRed Spectroscopy, using the amplitude of the Tissue Saturation Index (TSIamp).

Results Peak workload increased with 11% after HIT (p between group =0.01) with a non-significant increase in peak $\dot{V}O_2$ (+7%, p between group=0.19). Cardiac reserve (CR) increased by 37% after HIT (p within group =0.03, p between group =0.08); this increase was not related to improvements in peak workload. Oxygen uptake recovery kinetics after submaximal exercise accelerated by 20%, (p between-group = 0.02); this improvement was related to a decrease in TSIamp (r=0.71 p=0.03), but not to changes in cardiac output kinetics.

Conclusion HIT induced improvements in maximal exercise capacity and exercising hemodynamics at peak exercise. Improvements in recovery after submaximal exercise were associated with attenuated skeletal muscle de-oxygenation during submaximal exercise but not with changes in cardiac output kinetics, suggesting that the effect of HIT on submaximal exercise capacity is mediated by improved microvascular oxygen delivery-to-utilization matching.

Introduction

It is widely recognized that exercise training improves functional capacity and quality of life in chronic heart failure (CHF) patients. Furthermore exercise training is safe and has beneficial effects on prognosis.[1,2,3] For this reason, exercise training is highly recommended in international guidelines for CHF patients.[4,5] Nevertheless, to date, it remains unclear what the optimal training characteristics should be.[6,7] In a randomized controlled trial in elderly CHF patients, high intensity interval training (HIT) was shown to have superior effects on exercise capacity and quality of life as compared to moderate continuous training (MCT).[8] In this study, HIT was not only associated with improvements in skeletal muscle function, but also with a marked reduction in left ventricular size (reverse remodelling) and improvement in cardiac function. However, as resting hemodynamics correlate poorly with exercise capacity, it remains unclear to what extent hemodynamics during exercise contributes to the improvement in exercise capacity.

From a physiological standpoint, a reduced cardiac output (Q) response to exercise (i.e. bulk oxygen delivery) may compromise peripheral oxygen delivery (i.e. micro vascular blood flow; Qm) and subsequently impair the ratio between microvascular oxygen delivery and metabolic demands in skeletal muscles (QmO_2-to-$\dot{V}O_2$ matching), resulting in impaired contractile performance and exercise capacity.[9,10] Therefore, in order to investigate whether HIT-induced improvements in central hemodynamics actually contribute to improved skeletal muscle oxygenation, it is essential to assess both exercising cardiac function and QO_2-to- $\dot{V}O_2$ matching in skeletal muscles. Previously, Near InfraRed Spectroscopy (NIRS) has been used in humans to asses skeletal muscle oxygenation and is considered to be a proxy of microvascular oxygen delivery-to-utilization (QO_2-to-$\dot{V}O_2$) matching during dynamic transitions.[11,12] It was shown that continuous moderate-intensity training improves QO_2-to- $\dot{V}O_2$ matching in healthy subjects and animal models of CHF.[13] However, these studies did not investigate whether this improvement was mediated through improvements in central hemodynamics or improved peripheral oxygen delivery, as exercising central hemodynamics were not assessed. Also, studies investigating the effects of HIT on microvascular oxygen delivery-to-utilization matching in CHF patients are lacking.

The purpose of this explorative study was to investigate the effect of HIT in CHF patients on maximal and submaximal exercise capacity and in particular to establish whether these improvements are mediated through improvements in exercising central hemodynamics and/or changes in microvascular oxygen delivery-to-utilization matching.

Methods

The study was designed as a prospective randomized controlled trial. Baseline assessment consisted of cardiac MRI and/or echocardiography, (sub) maximal exercise testing with respiratory gas analysis and simultaneously cardiac output measurements using a pulse wave contour analysis method. In addition changes in skeletal muscle tissue oxygenation during and after (sub) maximal exercise were assessed by Near Infrared Spectroscopy (NIRS). After the intervention all subjects underwent the same assessment. All tests were conducted at the Department of Cardiology of the Máxima Medical Center. The research protocol was approved by the medical ethics committee of the Máxima Medical Center, Veldhoven, the Netherlands. The study complies with the Declaration of Helsinki. All patients provided written and signed informed consent.

Population

Consecutive patients with CHF who were referred to the department of cardiac rehabilitation in the Máxima Medical Center were screened for eligibility. Patients with stable (≥ 3 months) CHF were considered eligible for participation in the study. Additional inclusion criteria were: CHF secondary to ischemic or dilated cardiomyopathy, New York Heart Association functional class II-III, left ventricular ejection fraction ≤ 40% and optimized medical treatment. Exclusion criteria were: recent myocardial infarction, unstable angina (≤ 3 months prior to inclusion), hemodynamically significant valve disease, participation in a training program (≥2/week) in the last year, significant chronic obstructive pulmonary disease (FEV1/FVC<60%) and orthopedic or neuromuscular conditions limiting the ability to perform exercise.

Randomization, blinding and treatment allocation

Randomization was performed after completion of baseline measurements. Sealed envelopes were used to allocate the patient to the training or usual care group (1:1 ratio). The study physician was blinded for the treatment allocation. Blinded physicians or technicians analyzed testing results.

High Intensity Interval Training (HIT)

Exercise training was performed 3 times a week during 12 weeks. The HIT program was adapted from the study of Wisløff et al. in elderly CHF patients.[8] In contrast to the original treadmill based program, study participants performed the HIT protocol on a bicycle ergometer. Training commenced with a 5 minute warming up period. Subsequently, subjects performed 4 intervals of 4 minutes with a workload corresponding to 85-95% of peak$\dot{V}O_2$ achieved at the maximal exercise test. The intervals were separated by 3-minute active pauses. After completion of the interval sessions there was a 5-minute

cool down. All subjects were trained in the hospital under direct supervision of trained physiotherapists. The control group was advised to remain physically active according to recommendations for physical activity.[14]

Cardiopulmonary exercise testing

Exercise testing was performed in an upright seated position on an electromagnetically braked cycle ergometer (Lode Corrival, Lode BV, Groningen, The Netherlands). A twelve lead electrocardiogram (ECG) was registered continuously. During the test ventilatory parameters were measured breath-by-breath (ZAN 680 USB, ZAN Messgeräte, Oberthulba, Germany) and were averaged over 10 second intervals after removal of outliers (values > 3 standard deviations (SD) from the local mean).[15] Volume and gas analysers were calibrated before each test.

Maximal exercise testing consisted of a symptom-limited test using an individualized ramp protocol aiming at total test duration of 8-12 minutes. The test was preceded by 4 minutes of unloaded pedalling and was ended when the patient was not able to maintain the required pedalling frequency. The results of this baseline test were used to determine the workload for the submaximal exercise test. Peak workload was defined as the final registered workload. Peak$\dot{V}O_2$ was defined as the final 20-second averaged value of the maximal exercise test. The ventilatory aerobic threshold (VAT) was assessed by the V-slope method.[16]

Submaximal constant load exercise testing commenced with a 2 minute resting period, passively maintaining the right leg in a fixed position, followed by a 6 minute bout at 80% of the workload corresponding to the VAT, achieved during the maximal exercise test. Patients were instructed to maintain a pedalling frequency of 70 rotations per minute. (RPM) After the load phase, there was a 5-minute recovery phase with the same fixed leg position as during the resting period.

Skeletal muscle deoxygenation

NIRS measurements were performed using a portable continuous wave near-infrared spectrophotometer (Portamon, Artinis, Elst, The Netherlands). This technique is based on the modified Lambert-Beer law and spatially resolved spectroscopy. The theoretical principles and clinical utility of the measurement technique have been described elsewhere.[11] To distinguish between oxygenated (O_2Hb) and deoxygenated haemoglobin (HHb), the device emitted light at two different wavelengths (760nm for HHb and 841nm for O_2Hb). We used the tissue saturation index (TSI) during submaximal exercise to measure absolute values of skeletal muscle deoxygenation (see also section data analysis). TSI is the ratio of oxygenated haemoglobin (O_2Hb) divided by total Hb (tHb) and expressed as a percentage.

In a previous study, we demonstrated that absolute values of TSI showed a better relative reliability compared to kinetic values (TSI Intraclass Correlation Coefficient range 0.74-0.90 for absolute values versus 0.53 for onset and 0.51 for recovery kinetics).[17] The NIRS probe was connected to the right thigh with adhesive tape and kept in place by an elastic strap. It was located at 20 cm proximally from the lateral patellar edge over the centre of the m.vastus lateralis. Ambient light was impeded by a dark cloth. Data were sampled at 10 Hz and stored for off-line analysis. Absolute baseline values of TSI were defined as the average values during the last minute of the resting period, steady state values as the average values during the last minute of exercise (TSIss). The amplitude of TSI (TSIamp) during submaximal exercise was defined as TSI baseline minus the lowest 5 second averaged value (TSImin). Regarding maximal exercise testing, TSI peak was defined as the average of the last 20 seconds. The difference between TSI baseline and TSI peak was defined as TSI delta.

Assessment of exercise hemodynamics

Assessment of exercise hemodynamics was performed by a radial artery pulse contour analysis method (LiDCO, LiDCO Ltd, London, UK). This technique provides beat-to-beat changes in central hemodynamics, by calculating nominal stroke volume (SV) from a pressure-volume transform of the radial artery pressure waveform.[18] Previous studies showed that LiDCO is a reproducible and accurate method for assessment of cardiac output (Q) under a variety of physiological conditions.[19,20] Moreover, in a study using the Fick method as a reference, we showed that this technique is highly accurate for continuous assessment of Q during incremental symptom-limited exercise testing in CHF patients.[21]

Before the exercise test, a 20-gauge arterial catheter was inserted into the radial artery. The radial artery catheter was connected to the LiDCO *plus* monitor. In order to convert nominal SV to absolute SV, the system had to be calibrated at rest by an independent method. For this purpose, we used echocardiography and determined resting SV according to international recommendations.[22] Directly after calibration, patients were positioned upright on the cycle ergometer and the exercise protocol was started. Resting Q was defined as the average of 60 seconds during the resting phase and peak Q as the average of the last 20 seconds at the end of maximal exercise. Cardiac reserve (CR) was defined as peak minus baseline Q.

Cardiac Magnetic Resonance Imaging (CMR)

CMR was performed on a clinical whole-body 1.5 Tesla scanner (Philips Achieva. Best, the Netherlands) with acquisition of 2-chamber, 4-chamber and short-axis cineloops. Left ventricular end diastolic (LVEDV) and end systolic volumina (LVESV) were determined using the modified Simpson's rule algorhythm by tracing the short axis 2D

areas. Quantative flow (Qflow) of the proximal aorta was used as a reference for SV measurements. Analysis was done post-hoc by a blinded physician using cardiac analysis software (Cardiac Explorer, Philips, Best, The Netherlands).

Echocardiography at rest

In patients with a contra indication for CMR, such as an ICD or pacemaker, echocardiography was used to determine cardiac volumina and function (Philips IE33, Best, The Netherlands) Volumina and left ventricular ejection fraction were determined using the modified biplane Simpson's rule algorhythm by tracing endocardial borders at end systole and diastole in a apical 2 and 4 chamber view, according to international recommendations.[22] Analysis was done post-hoc by a blinded echocardiographist using cardiac analysis software (TomTec Arena, Munich, Germany).

Data analysis

Kinetic analysis

The analysis of kinetics of $\dot{V}O_2$ and Q during onset and recovery of the constant load tests was reported previously.[23] First, all data were resampled into 10-sec intervals. Considering exercise onset, the first 20 sec of the $\dot{V}O_2$ data set were omitted, as it is generally accepted that during this period (cardiodynamic phase) the increase in $\dot{V}O_2$ reflects merely an increase in pulmonary blood flow, rather than changes in tissue gas exchange. To calculate time constants of onset of $\dot{V}O_2$ and Q, a non-linear least squares regression procedure (Python 2.7, Python Software Foundation) was applied to the onset phase, using the following formula:

$$Y(t) = Y_{baseline} + A * (1- e- (t- Td)/\tau)$$

with Y = $\dot{V}O_2$ or Q, A = the amplitude during exercise onset, Td = time delay (s), and τ = time constant (s). For the recovery phase of $\dot{V}O_2$ and Q, the following formula was used:

$$Y(t) = Y_{steadystate} - A * (1- e- (t- Td)/\tau)$$

with Y = $\dot{V}O_2$ or Q, A = the amplitude during recovery from steady state, Td = time delay (s), and τ = time constant (s).

Figure 1 shows an example of the responses of $\dot{V}O_2$, Q and TSI during submaximal exercise in a representative subject

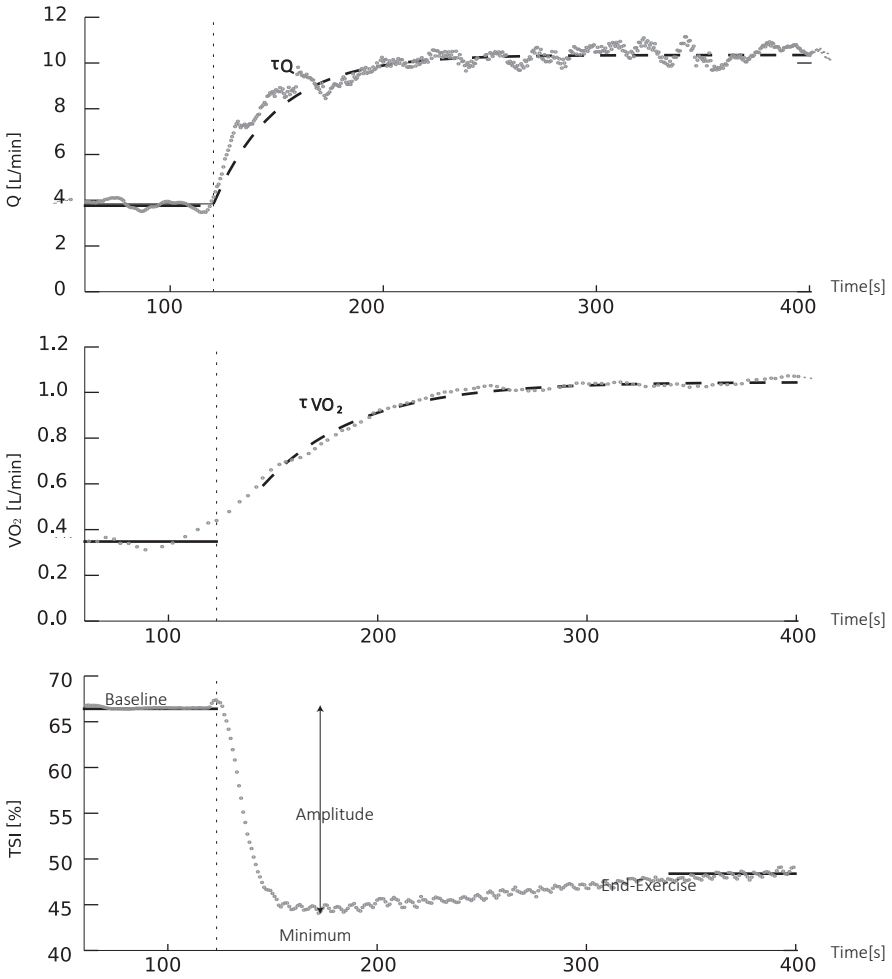

FIGURE 1 example of oxygen uptake ($\dot{V}O_2$), cardiac output (Q) and skeletal muscle deoxygenation (TSI) respons at the onset of submaximal exercise. Measured study parameters are presented in the figure

Statistical analysis

Data were analyzed using SPSS 19.0.0 statistical software (SPSS Inc, Chicago, IL, USA). Continuous variables describing the patient sample are presented as mean with standard deviation and dichotomous data as numbers and percentages. Data was analyzed by paired *t* tests for within group differences and by independent *t* tests for between group differences. A p-value less than 0.05 was considered to be statistically significant. Relations between variables were assessed by Pearson's correlation coefficient. The "goodness of fit" was determined by the coefficient of determination (R^2).

Results

In total, 31 eligible patients consented to participate. Five patients were excluded from final analysis: two patients had ventricular arrhythmias requiring hospitalization (one from the control group and one from the intervention group) and two patients from the intervention group died (progressive renal and heart failure after a severe gastro enteritis in 1 subject and progressive heart failure and personal decision to refrain from further medical services in another subject). Finally, one patient stopped after 10 training sessions because of lack of motivation. Twenty-six patients finished the study protocol. Twelve completed the HIT protocol; all subjects attended >80% of training sessions. Fourteen patients were allocated to the control group. Table 1 represents baseline characteristics of the included subjects. Except for age, no statistical significant differences were observed between categories.

	HIT (n=12)	Control (n=14)	p
Age (years)	58 +/- 7.8	66.5 +/- 8.7	0.02
Gender (male/female)	10/2	13/1	0.48
Weight (kg)	83+/-12	89+/-13	0.23
Height (cm)	175+/-8	177+/-7	0.25
Etiology(ICM/DCM)	8/4	6/8	0.38
Duration (months)	47+/- 43	38+/-61	0.66
NYHA class (II/III)	9/3	7/7	0.25
LVEF (%)	33+/-9	32+/-12	0.81
ICD/CRT-D/PM	7/1/0	1/2/1	0.07
Rhythm(SR,AF,PM)	10/1/1	8/5/1	0.25
Beta blocker (%)	92	100	0.30
ACE/ARB (%)	100	93	0.51
MRA (%)	33	29	0.80

TABLE 1 subject characteristics at baseline. Values are presented as mean +/- SD, number or percentage. BMI Body Mass Index, ICM ischemic cardiomyopathy, DCM dilated cardiomyopathy, NYHA New York Heart Association, LVEF left ventricular ejection fraction, ICD Internal Cardiac Defibrillator CRT-D Cardiac Resynchronization Therapy with defibrillator, PM pacemaker, SR sinus rhythm, AF atrial fibrillation, ACE angiotensin-converting enzyme inhibitor, ARB angiotensin II receptor blocker, MRA Mineralocorticoid Receptor Antagonist

Exercise testing

All study procedures were performed without adverse events. Cardiac output assessment at the final evaluation was not performed in 2 patients due to refusal and unsuccessful arterial cannulation respectively. Cardiac output data from another patient could not be used due to damping of the arterial pressure waveform. Oxygen uptake recovery kinetics could not be adequately determined due to insufficient data quality in one patient in the intervention group at the final assessment. TSI values could not be determined at baseline in one patient in the intervention group due to technical problems. Four out of 52 maximal TSI tests could not be analyzed due to insufficient data quality.

Resting hemodynamics

Table 2 represents the data obtained from the baseline and final assessments in both groups. There were no significant training-induced changes in left ventricular volumes and function at rest. Changes in these parameters were not related to changes in exercising hemodynamics, oxygen uptake or TSI parameters.

Maximal exercise capacity

There was a significant within- and between-group increase in peak workload, but no significant change in maximal oxygen uptake and oxygen uptake at the ventilatory aerobic threshold (Table 2). Although the increase in peak Q did not reach statistical significance, there was a 37% increase in cardiac reserve (CR) in the intervention group (2.3+/-3.2 L/min, p =0.03), which did not reach statistical significance at a between-group level. There were no significant within- and between-group changes in peak skeletal muscle deoxygenation or in the amplitudes during the symptom limited exercise test.

The training induced change in workload correlated significantly with changes in peak $\dot{V}O_2$ and $\dot{V}O_2$ at VAT (r=0.7, p=0.01 and r=0.77, p=0.004), but not with changes in peak Q and CR (r=0.55, p=0.08 and r=0.56, p=0.09) nor with changes in peak skeletal muscle deoxygenation (r=-0.40, p=0.29) or amplitude (r=0.13, p=0.7)

Submaximal exercise data

Physiological and kinetic variables at submaximal exercise in both groups are shown in Table 2.Whereas $\dot{V}O_2$ onset kinetics showed no significant improvement after HIT, there was a significant within- and between group acceleration of $\dot{V}O_2$ recovery kinetics (p=0.02, Table 2). In the HIT group, there was a non-significant acceleration in Q onset kinetics (p=0.11). There were no significant within and between-group differences in the amplitudes of skeletal muscle deoxygenation (TSIamp) and minimal TSI values (TSI min). Training-induced changes in $\dot{V}O_2$ recovery kinetics correlated significantly with changes in TSI amplitude (r=0.71 p=0.03) (Fig 2) but not with Q onset or recovery kinetics. Also TSI parameters were not correlated with Q kinetics.

	HIT (n=12)		Control(n=14)		p
	Before	After	Before	After	between
			Rest		
EF(%)	32.8+/-8.6	33.5+/-10.4	32.9+/-11.7	35.5+/-12.4	0.53
ESV(ml)	150+/-43	150+/-53	179+/-97	169+/-84	0.58
EDV(ml)	219+/-42	221+/-48	251+/-103	244+/-100	0.62
			Submaximal		
$\tau\dot{V}O_2$ on(s)	57+/-22	49+/-17	60+/-28	56+/-23	0.72
$\tau\dot{V}O_2$rec(s)	71+/-19	**59+/-14***	68+/-23	69+/-24	**0.02**
τQ on(s)	62+/-27	49+/-17	52+/-39	48+/-31	0.38
τQ rec (s)	52+/-23	55+/-23	66+/-49	60+/-25	0.58
TSI bl(%)	65+/-4.4	65.4+/-7	67.8+/-4.9	66.7+/-4.6	0.43
TSI min(%)	54.9+/-10.6	56.2+/-10	60.4+/-7.1	57.8+/-8.2	0.06
TSI amp(%)	10.1+/-7.2	9.2+/-4.6	7.4+/-5.2	8.9+/-5.7	0.17
			Maximal		
P peak(W)	135+/-47	**150+/-51***	130+/-57	132+/-64	**0.01**
$\dot{V}O_2$ peak(ml/min/kg)	20.8+/-5.4	22.2+/-5.3	20.2+/-6.0	19.9+/-6.7	0.19
$\dot{V}O_2$ VAT (ml/min/kg)	13.9+/-3.2	14.9+/-3.1	13.8+/-4.4	13.8+/-4.3	0.39
Q peak(L/min)	12.4+/-3.8	15+/-4.4	10.6+/-5.2	11.1+/-7.3	0.20
Q bl(L/min)	5.3+/-2.2	5.7+/-1.5	4.8+/-1.7	5.3+/-1.7	0.87
CR(L/min)	7.2+/-2.6	**9.7+/-4.1***	5.8+/-4.3	5.8+/-5.7	0.08
TSI bl max (%)	70.7+/-4.2	68.9+/-2.1	70.7+/-5.9	69.6+/-7.0	0.96
TSI peak(%)	57.5+/-6.4	56.5+/-3.7	56.1+/-6.8	55.3+/-7.9	0.65
TSI delta(%)	13.2+/-4.4	12.4+/-2.9	14.6+/-5.2	14.3+/-4.5	0.81

TABLE 2 Physiological and kinetic variables at rest, submaximal and maximal exercise at baseline and follow up.Values are presented as mean +/- SD, HIT High Intensity interval Training, EF Ejection Fraction, ESV End Systolic Volume, EDV End Diastolic Volume, $\tau\dot{V}O_2$ time constant of oxygen uptake, τQ time constant of cardiac output, TSI Tissue saturation index, TSI min: minimal value of tissue saturation index, TSIamp amplitude of the TSI response between the baseline and minimal value. Pmax peak workload, $\dot{V}O_2$ oxygen uptake, VAT Ventilatory Aerobic Threshold, Q Cardiac Output, CR Cardiac Reserve (peak minus baseline value), TSI bl max. TSI baseline value from the maximal exercise test, TSI peak, TSI value at the end of maximal exercise, TSI delta, amplitude between baseline and peak TSI *A * represents within group statistical significance with a p value <0.05*

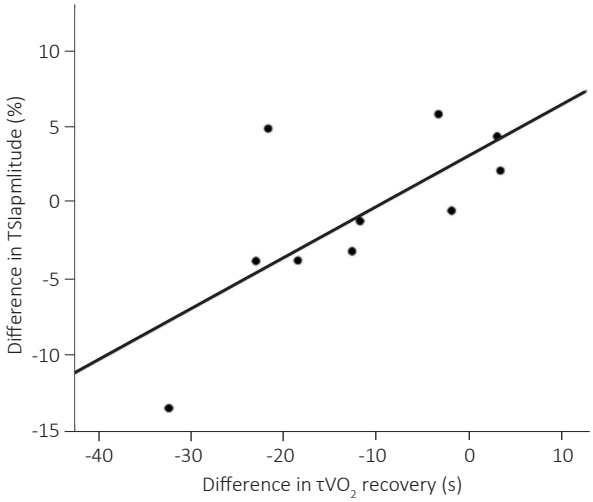

FIGURE 2 relation between training induced changes in submaximal oxygen uptake recovery kinetics and training induced changes in skeletal muscle deoxygenation amplitude in the HIT Group (n=10, r=0.71, p=0.03)

Discussion

The results of this study demonstrate that high intensity interval training in CHF patients induces improvements in the maximally achieved workload and the rate of recovery from submaximal exercise. The increase in maximal workload was associated with an increase in $\dot{V}O_2$ but there was no correlation with changes in resting or exercising hemodynamics. The acceleration of recovery after submaximal exercise was related to a decrease in skeletal muscle de-oxygenation during submaximal exercise, suggesting that the effect of HIT on submaximal exercise capacity is mediated at least partly by improved microvascular oxygen delivery-to-utilization matching and not by improved central hemodynamics.

Resting hemodynamics

Our results did not demonstrate any signs of left ventricular reverse remodeling after HIT. These findings are in contrast to the study by Wisloff et al, showing substantial improvements in cardiac size and function. The mechanistic base for LV reverse remodeling is supported by previous animal and in vitro studies, showing improved calcium handling and myocyte contractility.[24,25] This discrepancy might be explained by several factors. First, the population in the study by Wisløff was considerably different. It consisted of older males (mean age of 75.5 +/- 11) with an ischemic cardiomyopathy and a severely impaired exercise capacity (mean peak $\dot{V}O_2$ 13ml/kg/min) In comparison, our study

population consisted of both male and females, was younger (58 +/- 7.8), included both ischemic and dilated cardiomyopathies and were moderately impaired (peak $\dot{V}O_2$ 20.8+/- 5.4 ml/kg/min). However, the non-significant increase in resting cardiac output (7%) and the improvement of cardiac reserve capacity during exercise suggests LV remodeling/ improved contractility to some extent. Moreover, looking at individual patients, we observed responders and non-responders of HIT (e.g improvement of ejection fraction, reduced end systolic volume), but at group level this was non-significant. Because of the small study sample a subgroup analysis was not performed. Our results are in line with studies in coronary artery disease [26,27] and heart failure [28] which also failed to demonstrate superior effects of HIT on LV reverse remodeling. Future studies should therefore focus on physiological and clinical characteristics predicting effects of HIT in CHF patients, so that HIT can be prescribed more individually.

Maximal exercise

Despite the lack of change in resting hemodynamics after HIT, we did observe a significant and substantial improvement in CR (35%). An improvement in exercising hemodynamics after a comparable HIT protocol was also demonstrated by Fu et al. (e.g. peak Q increased 31%).[29] The ability to increase Q from baseline to peak values is an important marker of cardiac function.[30] Moreover, exercising hemodynamics provide substantial additional information regarding to prognosis and prediction of treatment effects.[31,32,33,34] Therefore improvement of the central hemodynamic performance at peak exercise induced by HIT may be of clinical importance. From a physiological point of view, an increase in bulk O_2 delivery during exercise may improve microvascular QO_2-to-$\dot{V}O_2$ matching in skeletal muscles, which leads to improved exercise capacity.[10,35] Although we did not observe a direct relation between improved exercising hemodynamics and maximal exercising capacity, the fact that skeletal muscle de-oxygenation did not increase despite a higher maximally achieved workload suggests an increase in the microvascular oxygen delivery-to-utilization ratio.

Submaximal exercise

Regarding submaximal exercise, the present study demonstrated a significant acceleration of $\dot{V}O_2$ recovery kinetics after HIT. This finding is clinically relevant as many CHF patients are hindered by prolonged fatigue after repetitive daily activities. Although the positive effects of aerobic exercise on oxygen uptake kinetics in CHF patients have already been described in previous studies,[36,37] studies evaluating the effect of HIT on submaximal exercise capacity in CHF patients are scarce. A previous study using a training protocol with shorter intervals of higher intensity, also demonstrated accelerated post- exercise oxygen uptake recovery kinetics after exercise training in CHF patients.[38] However, the physiological mechanism of these training effects was not evaluated. Theoretically,

training-induced acceleration of oxygen uptake recovery kinetics can be explained by an improved oxygen delivery or a faster decline in the rate of tissue oxygen utilization.[23] TSI represents the dynamic balance between oxygen delivery and utilization (QO_2-to- $\dot{V}O_2$) at the skeletal muscle level. Therefore, the fact that we observed a significant relation between training-related changes in the amplitude of skeletal muscle deoxygenation and acceleration of oxygen uptake recovery kinetics (i.e. a decrease in deoxygenation is associated with improved recovery), suggests that an increase in the ratio between microvascular oxygen delivery and utilization is a determinant of the training effect. This concept is in agreement with results from previous studies, showing an increase in microvascular blood flow to exercising muscles after HIT.[8,29] Moreover, it is in line with studies showing that the rate of submaximal exercise recovery in CHF is primarily limited by reduced skeletal muscle oxygen delivery.[39,40] Possible mechanisms underlying HIT-induced improvements of peripheral oxygen delivery that are postulated, include improved endothelial function by an increased anti-oxidant status, indicating lower levels of reactive oxygen species and higher production of nitric oxide (e.g. improved NO bio availability). In addition, HIT has been shown to increase levels of PGC-1α, [8] which is associated with up regulation of capillary and oxidative capacity.[41] Greater capillary and red blood cell flux adjacent to contracting myocytes may serve to reduce spatial heterogeneity of microvascular blood flow and enhance oxygen delivery and diffusion capacity. Theoretically, the relation between acceleration of $\dot{V}O_2$ recovery kinetics and decreased muscle de-oxygenation could also be mediated by improved central hemodynamics. However, given the lack of correlation between cardiac output kinetics and CR with both $\dot{V}O_2$ recovery kinetics and skeletal muscle de-oxygenation, central hemodynamic improvements do not seem to play a role in HIT-induced improvements in submaximal exercise capacity in the present study.

Limitations

Before drawing definite conclusion to our study results some limitations have to be addressed. First, the study population was relative small, limiting the ability to evaluate subgroups for differences in response (e.g. etiology, severity). However the sample size is in line with most CHF training studies. Furthermore, because of the explorative nature of the study, we feel that the results extend the current understanding of the benefits of HIT in CHF patients. Second, a relative high dropout rate of 25% (n=4) was observed in the intervention group. However, individual analysis of these cases did not reveal a causal relation between the dropout reason and HIT, but accentuates the fact that it is a fragile population with an unpredictable course of the disease itself. On the other hand, in a large study in cardiac rehabilitation a low risk of cardiovascular events during HIT

in CHF patients was found.[42] Third, the measurement techniques used in our study to assess cardiac output and local oxygen delivery-to- utilization provide estimation rather than absolute values. However both the pulse wave contour method as well as NIRS were validated in a comparable cohort in previous studies.[17,21] Furthermore we did not evaluate haemoglobin (Hb) before and after HIT. An increase in Hb after training might have a positive influence on oxygen delivery. Finally, our results cannot be extrapolated to different interval training protocols and more severely impaired patients, as we included predominantly moderately impaired patients.

Conclusion

This study showed that high intensity interval training is effective in improving maximal and submaximal exercise capacity in CHF patients. In contrast with resting hemodynamics, a significant within-group improvement in cardiac reserve was observed during *maximal* exercise. At *submaximal* exercise level, the acceleration of $\dot{V}O_2$ recovery kinetics was correlated with a decrease in skeletal muscle deoxygenation during submaximal exercise but not with cardiac output kinetics or cardiac reserve. Therefore, these results suggest that the effect of HIT on submaximal exercise capacity is mediated at least partly through improved microvascular oxygen delivery-to-utilization matching and not through improved central hemodynamics.

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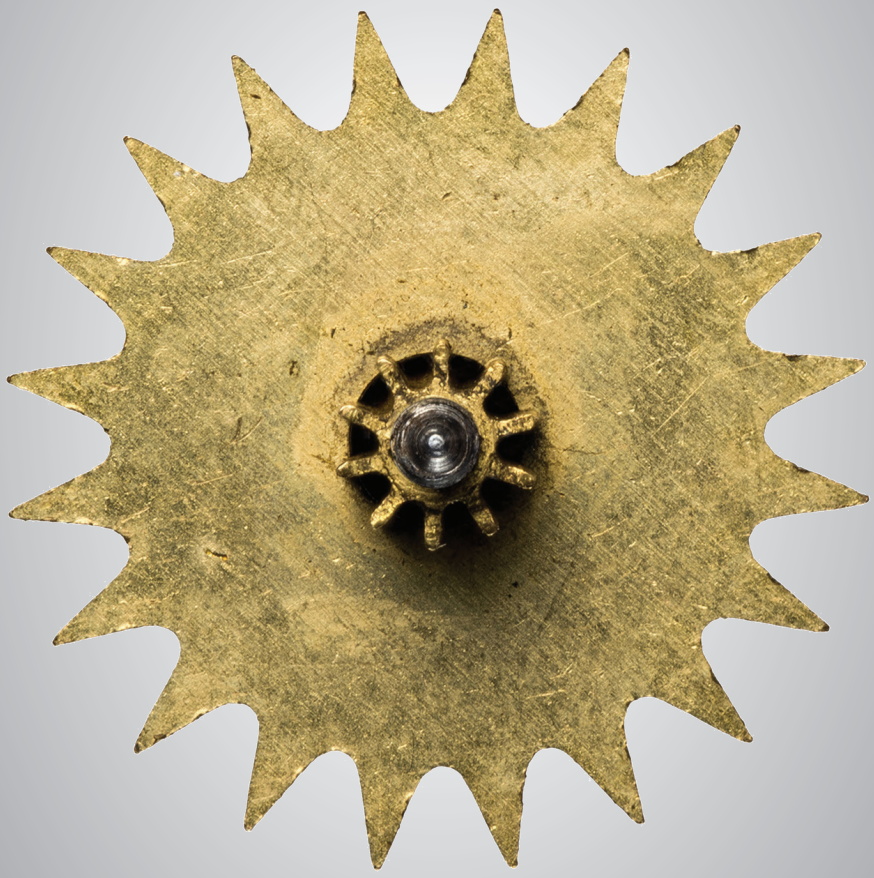
CHAPTER 7



High Intensity Interval Training after Cardiac Resynchronization Therapy: an explorative randomized controlled trial: the HIT CRT study

SUBMITTED

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Abstract

Background Cardiac Resynchronization Therapy (CRT) leads to a substantial improvement in exercise capacity, cardiac function and mortality in selected Chronic Heart Failure (CHF) patients. Preliminary studies showed that exercise capacity may improve to an even greater extent by combining this therapy with moderate-intensity exercise training (ET). However, the effect of high-intensity interval training (HIT) as an adjunct therapy to CRT has not yet been established. Given the complementary peripheral physiological effects of HIT, we hypothesized that this particular training modality may have additional effects on exercise capacity when combined with CRT.

Methods 24 CHF patients, NYHA class II or III and accepted for CRT underwent an echocardiogram, QoL questionnaire and cardiopulmonary exercise test (CPET) with simultaneous measurement of cardiac output before implantation, at 3 and 6 months. After 3 months, patients were randomized to usual care (UC) or HIT, consisting of 3 sessions a week during 3 months at 85-95% of peak $\dot{V}O_2$.

Results Peak $\dot{V}O_2$ increased after CRT (17+/-5.3 to 18.7+/-6.2 ml/kg/min ,$p<0.05$); after HIT there was an additional increase of 1.4 ml/kg/min that did not reach statistical significance (p=0.12). Peak workload increased after CRT (109+/-45 to 118+/-44, p=0.001) and there was an additional significant within- and between group increase after HIT in the intervention group (128+/-42 to 148+/-48W, versus 110+/-50 to 110+/-50, respectively, p= 0.03). Peak cardiac output did not change significantly after CRT or HIT. $\dot{V}O_2$ recovery kinetics speeded by 27% after CRT (p=0.04), no further improvement after HIT was observed. LVEF increased 25% after CRT (p=0.0001), no additional increase was seen after HIT.

Conclusion This study demonstrates that HIT provides additional improvement of exercise capacity without a concomitant change in peak $\dot{V}O_2$ or cardiac output suggesting that the additional effect of HIT is mainly mediated by an improvement of anaerobic performance.

Introduction

The management of Chronic Heart Failure (CHF) currently includes both pharmacological and non-pharmacological interventions. Whereas pharmacological therapy improves survival in CHF patients,[1,2,3,4] the effects of these medications on exercise performance are less evident.[4,5,6,7,8] This has led to an emerging interest in non-pharmacological adjunct therapies. In this respect, cardiac resynchronization therapy (CRT) was not only shown to be effective in improving mortality and morbidity, but also in improving exercise capacity. This beneficial effect is predominantly mediated by an improvement in central hemodynamics.[9] However, the amount of CRT non-responders is still substantial.[10] Another therapy aiming at an improvement of functional status which is often underused in CHF patients is exercise training (ET).[11] ET not only improves central hemodynamics,[12] but also peripheral components of the oxygen transport chain, leading to an improved exercise capacity.[13] Previously, Patwala et al. demonstrated that a moderate intensity continuous training (MCT) program following CRT led to an additional increase in exercise capacity.[14] Yet, given its distinct physiological effects, high intensity interval training (HIT) after CRT may be even more effective. As such, previous studies demonstrated that HIT was associated with greater improvements on endothelial function than MCT, which may lead to improved redistribution of blood flow to exercising muscles.[16] Furthermore, although a recent multicenter trial comparing effects of HIT and MCT failed to demonstrate an effect on resting left ventricular (LV) function in either group,[15] we recently did observe an improvement in exercising hemodynamics after HIT.[18] This effect may be explained by an improved calcium-handling of the cardiomyocyte, induced by HIT.[17]

The aim of our study was to evaluate the additional effect of HIT on exercise capacity, 3 months after implantation of a CRT device in CHF patients. We hypothesized that HIT after CRT results in additive beneficial effects on exercise capacity through a synergistic effect in both central hemodynamic as well as peripheral factors.

Methods

The study was designed as a prospective randomized controlled multicenter trial and was conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act. The study was approved by the Medical Ethical Committee of the Máxima Medical Center Veldhoven, the Netherlands. The trial was registered in the open access Dutch trial register NTR with number NTR2527. All patients provided written and signed informed consent before study procedures. Implantation of the CRT devices was performed, according to standard techniques and local protocols, in the Catharina Hospital, Eindhoven (CHE) and University Medical

Center, Utrecht (UMCU), the Netherlands. Hemodynamic exercise testing was performed in the UMCU and the Máxima Medical Center. Exercise training was performed in the local referring hospitals.

Patient population

Patients eligible for CRT were screened in the abovementioned hospitals and asked to participate in the study between February 2011 and April 2014. Inclusion criteria were based on the ESC guideline at time of inclusion**:** QRS width >120ms with a Left Bundle Branch Block (LBBB) morphology, heart failure with reduced ejection fraction (HFREF) due to ischemic, dilating or pacing-induced cardiomyopathy with a left ventricular ejection fraction (LVEF) < 35% and NYHA class II or III before CRT. Exclusion criteria were myocardial infarction or unstable angina less than 3 months prior to inclusion, clinical signs of decompensated heart failure, ventricular tachycardia or ischemia during exercise, participation in a training program (≥2/week) in the last year, intracardiac shunts or congenital heart disease limiting exercise capacity, orthopaedic, vascular, pulmonary, neuromuscular and other disease limiting exercise capacity.

Study protocol

Before implantation of the CRT device, a baseline assessment was performed, which consisted of a physical examination, the Minnesota living with heart failure (MLWHFQ) questionnaire, an echocardiogram, a constant load exercise test and a symptom limited cardiopulmonary exercise test (CPET) with simultaneous measurement of exercise hemodynamics. These tests were repeated after 3 and 6 months. At baseline, an extra CPET was performed for familiarization of the test procedure and to determine the workload for the constant load test (80% of the ventilatory threshold). The same workload was used for the 3 and 6-month constant load test.

Randomization was performed after the 3 months' assessment, using sealed envelopes. Patients were allocated to the training or usual care group (1:1 ratio). Due to the design, patients and physicians could not be blinded.

Study procedures

Cardiopulmonary Exercise Testing

Maximal exercise testing consisted of a symptom limited exercise test with respiratory gas analysis on a cycle ergometer (Lode Corrival, Groningen), using an individualized ramp protocol until voluntary exhaustion aiming at a total test duration of 8-12 minutes.[19] Patients were instructed to maintain a pedalling frequency of 70/min. A twelve lead ECG was registered continuously. Peak oxygen uptake was defined as the average value of oxygen uptake during the last 30 seconds of exercise. Ventilatory threshold was assessed by the V-slope method by two blinded physicians, using the mean value.[20]

Submaximal exercise testing with respiratory gas analysis

Submaximal cardiopulmonary exercise testing started with a 2-minute resting period, followed by a 6-minute bout at 80% of the workload corresponding to the ventilatory threshold. Thereafter, there was a 5-minute recovery phase with no movement of the legs in order to assess $\dot{V}O_2$ kinetics.

Echocardiography

Echocardiography was analysed by 2 blinded physicians. Standard two-dimensional, colour and spectral Doppler measurements were performed. Left ventricular dimensions were measured on a parasternal long axis two-dimensional (2D) image. LVEF was determined using the Simpson's rule algorithm by tracing the left ventricular 2D-area in standard apical two- and four-chamber view at end-systole and end-diastole.[21] A reduction of 15% or more in LVESV was considered an echocardiographic response to CRT.

Exercise hemodynamics

Assessment of exercise hemodynamics was performed by a pulse wave contour analysis method (LiDCO, LiDCO Ltd, London, UK). This technique provides beat-to-beat changes in central hemodynamics, by calculating nominal stroke volume (SV) from a pressure-volume transform of the radial artery pressure waveform.[22] Previous studies showed that LiDCO is a reproducible and accurate method for assessment of cardiac output (Q) under a variety of physiological conditions.[23,24] Moreover, using the Fick method as a reference, we showed that this technique is highly accurate for continuous assessment of Q during incremental symptom-limited exercise testing in CHF patients.[25]

Before the exercise test, a 20-gauge arterial catheter was inserted into the radial artery. The radial artery catheter was connected to the LiDCO *plus* monitor. In order to convert nominal SV to absolute SV, the system had to be calibrated at rest by an independent method. For this purpose, we used echocardiography and determined resting SV according to international recommendations.[21] Directly after supine calibration, patients were positioned upright on the cycle ergometer and the exercise protocol was started. Resting Q was defined as the average of 60 seconds during the resting phase and peak Q as the average of the last 20 seconds at the end of maximal exercise. Cardiac reserve (CR) was defined as peak minus baseline Q. Cardiac Power Output (CPO) was determined by the product of peak Q, mean arterial pressure (MAP) and a constant K, where K ($2.22x10^{-3}$) is the conversion factor into Watts.[26]

Kinetic analysis

The analysis of kinetics of $\dot{V}O_2$ and Q during onset and recovery of the constant load tests was reported previously.[27] To determine the kinetics of oxygen uptake ($\dot{V}O_2$) and cardiac output (Q) during onset and recovery of the constant load tests, all data were

resampled into 10-sec intervals. Considering exercise onset, the first 20 sec of the data set were omitted, as during this period (cardiodynamic phase) the increase in Vo_2 reflects merely an increase in pulmonary blood flow, rather than changes in tissue gas exchange. To calculate time constants of onset and recovery kinetics, a non-linear least squares regression procedure was applied to the onset phase (from 20 seconds after the start of exercise until 6 min ofexercise) and the recovery phase (from the end of exercise until 5 min of recovery), using mono-exponential functions of the following format:

Onset kinetics: Y(t) = Y baseline + A * (1- e- (t- Td)/τ)

Recovery kinetics: Y(t) = Y steady state- B * (1- e- (t- Td)/τ)

Y= $\dot{V}O_2$ or Q, A = the amplitude during exercise onset, B = the amplitude during exercise recovery, Td = time delay (sec), and τ = time constant (sec)

High intensity Interval Training (HIT)

Exercise training was performed 3 times a week during 3 months. Patients performed the training program at the department of physical therapy of their own (local) hospital. All training sessions were performed on a cycle ergometer. Training started with a 5 minute warming up period, subsequently, subjects performed 4 intervals of 4 minutes with a workload corresponding to 85-95% of peak $\dot{V}O_2$ achieved at the maximal exercise test. The intervals were separated by 3-minute active pauses. After completion of the interval sessions there was a 5-minute cool down. Several precautions were taken to minimize the risk of training. First, all subjects trained in the hospital under direct supervision of trained and experienced physiotherapists. Second, all subjects performed a maximal exercise test at baseline; in this way, patients with ischemia or ventricular arrhythmias during high-intensity exercise were excluded. Third, in patients with a CRT-D, the maximal heart rate during HIT was set at 20bpm under the zone for anti-tachycardia pacing or shock therapy (usually >180 bpm or 188 bpm, depending on ICD manufacturer/brand), to minimize the risk for inappropriate interventions of the defibrillator.

Statistical analysis

Continuous variables were presented as the mean with standard deviation and dichotomous data as numbers and percentages. Data distributions were tested for normality by calculation of the coefficients of skewness and kurtosis and by the Shapiro-Wilk test. Data with a normal distribution was evaluated by paired *t* tests for within group differences and by independent *t* tests for between group differences. Data with a non-normal distribution were evaluated by nonparametric tests: Wilcoxon signed rank sum test for paired observations of continuous data, and Mann-Whitney U test for unpaired comparisons. A p-value less than 0.05 was considered as statistically significant

Results

In total, thirty eligible patients gave informed consent. Two patients were excluded at baseline: one patient had a severe anxiety disorder, which precluded adequate exercise testing. In the other patient, baseline echocardiogram demonstrated an improved LVEF>35%, so the indication for CRT was no longer appropriate. Another two patients were excluded before randomization. One patient died due to progressive heart failure and one patient withdrew from the study due to transportation difficulties. Finally, two patients who were randomized to the training group could not complete the protocol because of orthopaedic complaints (respectively back- and knee). Twenty-four patients completed the 6 months' study protocol. The study population consisted of 79% male subjects with a mean age of 69 years. The majority of patients were in NYHA class III and on optimal medical treatment according to the ESC heart failure guideline, applicable at the time of the study. Baseline characteristics are presented in table 1

	Total	HIT	CON	P
Age (years)	68.9 +/-6.4	68.9+/-6.7	68.8+/-6.5	0.98
Gender (male/female)	19/5	12/0	7/5	**0.002**
Etiology (ICM/DCM)	12/12	8/4	4/8	0.10
Duration of heart failure (months)	42+/-47	56+/-49	28+/-41	0.14
QRS morphology (LBBB*, Paced LBBB, IVCD, RBBB)	18/3/3/0	7/2/3/0	11/1/0/0	0.12
QRS width (ms)	152+/-16	150+/-12	155+/-20	0.45
NYHA class (II/III)	6/18	5/7	1/11	0.06
Weber class (A/B/C/D)	5/10/8/1	2/6/4	3/4/4/1	0.57
LVEF (%)	28.6+/-7.3	26.9+/-7.9	30.2+/-6.6	0.29
Rhythm (SR,AF)	19/5	9/3	10/2	0.32
Beta blocker (%)	92	83	100	0.14
ACE/ARB (%)	100	100	100	n.a.

TABLE 1 Subject characteristics at baseline (n=24) and after randomization (n=12). Values are presented as mean +/- SD, number or percentage, ICM ischemic cardiomyopathy, DCM dilated cardiomyopathy, LBBB Left Bundle Branch Block, *= LBBB was classified according to Strauss's ECG criteria
IVCD Intraventricular Conduction Delay, RBBB Right Bundle Branch Block, NYHA New York Heart Association, LVEF left ventricular ejection fraction, SR sinus rhythm, AF atrial fibrillation, ACE angiotensin-converting enzyme inhibitor, ARB angiotensin II receptor blocker

Baseline versus 3 months after CRT

Measurements at baseline and 3 months after CRT are presented in table 2. Three months after CRT, a significant increase in LVEF of 6.9% and a decrease in LVESV and LVEDV of 26% and 17%, were observed (p<0.001 for all comparisons). LVESV decreased more than

15% in 13 of 24 patients (54%). Peak $\dot{V}O_2$ increased significantly from 17+/-5.3 to 18.7+/-6.2 ml/kg/min (p=0.005) but there was no significant increase in $\dot{V}O_2$ at the ventilatory threshold. Also, significant improvements in the VE/VCO2 slope (34.8+/-8.7 to 32.6+/-6.8, p=0.01) and increase in the Oxygen Uptake Efficiency Slope (OUES, 1618+/-500 to 1882+/-557, p=0.001) were observed. Exercise hemodynamics did not demonstrate a significant change after CRT. Peak Q, as well as Cardiac Reserve (CR) and Cardiac Power Output (CPO) remained unchanged. Quality of life, as determined by the MLWHFQ did not change significantly (24+/-17 to 20+/-25, p=0.58). Regarding submaximal exercise, $\dot{V}O_2$ recovery kinetics accelerated significantly by 27% (decrease in τ from 80s to 63s, p =0.04). No significant differences were observed in onset kinetics of $\dot{V}O_2$ and Q or in Q recovery kinetics.

	Before CRT	3 months after CRT	p
	Rest		
EF (%)	28.6+/-7.3	35.7+/-11.3	0.0001
ESV (ml)	191+/-83	153+/-90	0.0001
EDV (ml)	257+/-88	220+/-95	0.0001
	Submaximal		
$\tau\dot{V}O_2$ on (s)	76.5+/-38	72.6+/-41	0.7
$\tau\dot{V}O_2$rec (s)	80+/-41	63+/-19	0.04
τQ on (s)	64+/-33	71+/-37	0.43
τQ rec (s)	77+/-64	59+/-26	0.25
	Maximal		
P peak (W)	109+/-45	118+/-44	0.001
$\dot{V}O_2$peak (ml/kg/min)	17+/-5.3	18.7+/-6.2	0.005
$\dot{V}O_2$VAT (ml/kg/min)	12.0+/-3.8	12.8+/-3.3	0.12
OUES	1618+/-500	1882+/-557	0.0001
VE/VCO2 slope	34.8+/-8.7	32.6+/-6.8	0.01
Q peak (L/min)	11.1+/-4.0	10.8+/-5.0	0.75
Q bl (L/min)	5.2+/-1.5	4.9+/-1.6	0.19
CR (L/min)	5.9+/-2.9	5.9+/-3.8	0.89
CPO (W)	2.5+/-1.0	2.6+/-1.0	0.63

TABLE 2 Gas exchange, hemodynamic and kinetic variables before and 3 months after CRT (n=24) Values are presented as mean +/- SD, EF Ejection Fraction, ESV End Systolic Volume, EDV End Diastolic Volume, $\tau\ \dot{V}O_2$ time constant of oxygen uptake, τQ time constant of cardiac output, Pmax peak workload, $\dot{V}O_2$ oxygen uptake, VAT Ventilatory Aerobic Threshold, Q Cardiac Output, CR Cardiac Reserve (peak minus baseline value). CPO cardiac power output

HIT versus control

After 3 months, 12 patients were randomized to the HIT group and 12 to the control group. In the control group, significant more females were included (5 vs 0, p<0.001) and the duration of heart failure was significantly shorter (28+/- 41 vs 56+/- 49 months, p=0.01). On average, ninety-two percent of training sessions were followed and no serious cardiovascular events occurred during HIT. The results after 6 months are presented in table 3.

	HIT (n=12)		Control (n=12)		P change between group
	Before	After	Before	After	
			Rest		
EF (%)	33+/-12	31+/-11	38+/-11	42+/-13*	**0.01**
ESV (ml)	163+/-98	166+/-106	139+/-80	121+/-78	**0.048**
EDV (ml)	235+/-99	230+/-109	212+/-92	196+/-94	0.33
			Submaximal		
$\tau\dot{V}O_2$ on (s)	79+/-50	58+/-9	66+/-30	49+/-36	0.46
$\tau\dot{V}O_2$rec (s)	64+/-16	59+/-11	62+/-22	59+/-24	0.36
τQ on (s)	69+/-26	67+/-40	80+/-51	77+/-41	0.67
τQ rec (s)	70+/-17	66+/-22	53+/-33	50+/-22	0.97
			Maximal		
P peak(W)	128+/-42	148+/-48*	110+/-50	110+/-50	**0.03**
$\dot{V}O_2$ peak (ml/kg/min)	19.4+/-6.7	20.8+/-7.0	18.5+/-6.3	18.4+/-5.6	0.14
$\dot{V}O_2$ VAT (ml/kg/min)	13.2+/-4.2	14.2+/-5.0	12.8+/-3.4	12.9+/-2.7	0.20
RER	1.08+/0.07	1.14+/-0.14	1.04+/-0.12	1.07+/-0.13	0.41
Q peak (L/min)	12.5+/-5.4	14.1+/-8.6	8.6+/-3.0	9.6+/-3.4	0.64
Q bl (L/min)	5.7+/-1.8	5.6+/-1.7	4.3+/-1.0	4.6+/-1.3	0.49
CR (L/min)	6.8+/-4.3	8.6+/-7.1	4.3+/-2.5	5.0+/-2.7	0.33
CPO (W)	2.9+/-1.1	3.3+/-1.8	2.3+/-0.8	2.6+/-0.9	0.20

TABLE 3 Exercise and hemodynamic variables at rest, submaximal and maximal exercise after randomization. Values are presented as mean +/- SD, HIT High Intensity interval Training, EF Ejection Fraction, ESV End Systolic Volume, EDV End Diastolic Volume, $\tau\ \dot{V}O_2$ time constant of oxygen uptake, τQ time constant of cardiac output, Pmax peak workload, $\dot{V}O_2$ oxygen uptake, VAT Ventilatory Aerobic Threshold, RER Respiratory Equivalent Ratio, Q Cardiac Output, CR Cardiac Reserve (peak minus baseline value) CPO Cardiac Power Output
*A * represents within group statistical significance with a p value <0.05*

LVEF increased significantly in the control group as compared to the HIT groups (+4 vs -2%, p=0.01). This was accompanied by a decrease in LVESV (-18ml vs +3ml, p=0.048). Peak workload improved significantly in the HIT group only (within-group difference: 128+/-42W to148+/-48W, p=0.01, between group difference: +20W vs 0W, p=0.03). We observed non-significant increases in peak $\dot{V}O_{2,}$ $\dot{V}O_2$ at the ventilatory threshold (p=0.09) and RER (p=0.09) in the HIT group, with no between-group differences. Also, the 13% and 26% increase in peak Q and CR in the HIT group were not statistically significant and no significant relations were observed between these variables. Regarding submaximal exercise, we observed no significant change in $\dot{V}O_2$ or Q onset and recovery kinetics in both groups. The MLWHQ score after 3 months was 34.5+/-38 in the control group and 10+/-8 in the HIT group, after 6 months this was respectively 11.3+/-16 and 10+/-10, within and between group changes were not statistical significant (within control: p=0.13, within HIT: p=0.96, between groups: p=0.08)

Discussion

In this study, we demonstrated that the addition of HIT after CRT results in a substantial additional improvement in peak workload without significant concomitant improvements in peak oxygen uptake and exercise hemodynamics. At a submaximal exercise level, we showed that CRT induced accelerated oxygen uptake recovery kinetics without an additional improvement after HIT.

Maximal exercise capacity

Studies evaluating the effect of exercise training after CRT are scarce. In a pilot study, Conraads et al. observed a significant additional increase in peak $\dot{V}O_2$ when CRT was followed by a MCT program.[28] In a larger trial, Patwala et al, also demonstrated beneficial effects of an MCT program 3 months after CRT. While CRT predominantly improved cardiac function, the addition of exercise training improved both cardiac function as well as skeletal muscle function resulting in a significant increase in exercise capacity.[14] Based on previous studies, demonstrating superior effects of HIT compared to MCT on endothelial function, skeletal muscular oxidative capacity and exercise hemodynamics, we hypothesized that additional HIT after CRT may have a synergistic effect.[29] We observed a significant increase in peak workload 3 months after CRT, which improved even further after HIT. From a physiological standpoint, the additional increase in peak workload after HIT may be attributed to improvements in the O_2 transport chain from lungs to skeletal muscles and/or O_2 utilization, including (exercising) central hemodynamics, blood flow redistribution, macro- and microvascular endothelial function and skeletal muscle oxidative capacity. Alternatively, the increase in peak workload may be explained

by improved anaerobic performance or (biomechanical) efficiency. Regarding central hemodynamics, we demonstrated an increase in resting LVEF and a decrease in LVESV and LVEDV after CRT, however no additional reverse remodelling was demonstrated after HIT. Furthermore, the increase in peak Q or CR after HIT was not statistical significant (p=0.09) nor were these parameters related to the change in peak workload (r=0.21, p=0.65), suggesting that (exercising) central hemodynamics were not primarily related to the increase in workload. Another physiological explanation for the additional improvement of peak workload after HIT may be an improved redistribution of blood flow to exercising muscles, which in turn improves microvascular oxygen delivery and utilization matching in the skeletal muscle. Moreover, it has been shown in previous studies that HIT improves endothelial function and may therefore decrease peripheral vasoconstriction. These factors can attenuate sympathetic nerve activity (SNR) and could (partially) restore neurohormonal imbalance, which is a strong mediator for the reversal of the skeletal myopathy found in CHF patients[30,31] Although endothelial function was not assessed in our study, the fact that peak $\dot{V}O_2$ and $\dot{V}O_2$ kinetics, which are actually the "end products" of changes in the abovementioned factors, did not show an additional improvement after HIT suggests that endothelial function was not a determinant of the improvement in exercise performance. Also, the lack of improvement in maximal aerobic capacity argues against a role of an improvement in skeletal muscular oxidative metabolism. In contrast with our findings, Patwala et al. did demonstrate an additional improvement in peak $\dot{V}O_2$, suggesting that, at a group level, MCT may be more effective in improving aerobic capacity.

Finally, the additional increase in peak workload after HIT may be related to an improvement in anaerobic performance. Although we did not include specific anaerobic test to test this hypothesis, the fact that we did not observe a concomitant significant increase in peak $\dot{V}O_2$ suggests that HIT is not a pure form of aerobic training, but that its effect is also mediated by an improvement in anaerobic performance and power output. Moreover, these findings are in line with recent HIT studies in non-CRT heart failure patients.[18,35]

Submaximal exercise

As daily life exists of a continuum of submaximal activities, like walking and cycling, we evaluated submaximal exercise performance by determining $\dot{V}O_2$ onset and recovery kinetics.[36] In contrast with previous studies in non-CRT patients with CHF,[18,38] we could not demonstrate an additional acceleration in $\dot{V}O_2$ onset and recovery kinetics after HIT in the present study. These results suggest that submaximal aerobic capacity is not improved by HIT after CRT. To our knowledge, no other studies investigated the additional effect of post-CRT exercise training on submaximal exercise performance. While a significant speeding of $\dot{V}O_2$ recovery kinetics after 3 months of CRT was observed,

there was no further improvement observed after HIT. The fact that $\dot{V}O_2$ recovery kinetics did not show an additional improvement after HIT could be explained by a "ceiling" effect, where further improvement after CRT cannot be achieved. In fact, we recently demonstrated speeding of $\dot{V}O_2$ recovery kinetics after a high intensity interval training program in non-CRT CHF patients.[18] In line with this study, Q onset and recovery kinetics did not show significant changes nor were related to the speeding of $\dot{V}O_2$ recovery after CRT, or HIT. This suggests that bulk O_2 delivery by improving the central pump is not the key factor for speeding $\dot{V}O_2$ recovery kinetics and suggest that other mechanisms as local O_2 delivery- utilization matching in the skeletal muscle may play an important role. Another explanation might be that a lack of change after HIT at group level is caused by heterogeneity of the population. In fact, looking at an individual level some patients showed speeding and some slowing of respectively $\dot{V}O_2$ and Q kinetics. Unfortunately, the small sample size precluded adequate subgroup analysis to differentiate between responders and non-responders.

Limitations

Before drawing definitive conclusions, several limitations have to be acknowledged. First, the sample size was limited. It could be that our sample size may have lacked sufficient statistical power to demonstrate a statistically significant increase in peak $\dot{V}O_2$ after HIT. In fact, the absolute increase in peak $\dot{V}O_2$ after exercise training was comparable with the observation of Patwala et al. Second, all females (5) were randomized to the control group by chance. In addition, the control group consisted of more DCM patients compared to an ischemic aetiology in the HIT group. Since it is known that these patients respond better to CRT this may have influenced the results.[40,41] Moreover, the process of reverse remodelling is not restricted to 3 months and may last until 12-18 months after device implantation. This effect may have been more prominent in the control group.[10] Third, there was no optimization protocol during exercise and automatic rate adaptive AV and VV setting were not available during the study.[42,43]

Future directions

Although literature on effects of exercise training after CRT is scarce, all available studies point out that exercise training, regardless of intensity, is an effective adjunct therapy after CRT to optimize benefits.[14,28] In our study, exercise training was evaluated as a monodisciplinary intervention. A multidisciplinary cardiac rehabilitation program with dietary consultation, self-management skills and optimization of medication and device

after implantation could be even more beneficial.[44] In order to improve the response to both modalities it is important to identify predictors of response. While most patients are asymptomatic at rest, functional, exercise related parameters would be preferable to identify the limiting factor causing exercise intolerance. This could lead to a more tailored therapeutic approach. For example, in patients who are predominantly limited by skeletal muscle function, exercise training preceding CRT might result in a better response or even defer CRT in selected cases.

Conclusion

This study shows that HIT after CRT has a substantial additional effect on peak workload without a concomitant change in peak $\dot{V}O_2$ or cardiac output suggesting that HIT after CRT predominantly improves anaerobic performance.

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CHAPTER 8

General discussion and future directions

General Discussion

Chronic heart failure is intrinsically associated with exercise intolerance. Understanding the pathophysiological background of exercise intolerance is essential for optimizing the response to current and future therapies aiming at an improvement of exercise capacity. Each step in the oxygen transport chain and the rate of oxygen utilization can be responsible for the reduced exercise capacity in CHF patients.[1] In this thesis, additional physiological insight is provided by characterizing central and peripheral determinants of oxygen uptake during (sub)maximal exercise and recovery. In addition, the clinical effects and its underlying mechanisms of high-intensity interval training (HIT) with or without cardiac resynchronization therapy (CRT) were explored. This chapter addresses the main findings of the conducted studies in the context of the central themes as outlined in the introduction. Furthermore, clinical implications of the results and directions for future research will be discussed.

1) *Evaluation of the physiological heterogeneity of exercise intolerance in CHF patients by combining cardiopulmonary exercise testing with assessment of exercise hemodynamics and skeletal muscle oxygenation*

There is still controversy in the literature regarding the relative contributions of central hemodynamics and peripheral oxygen delivery and utilization to the impaired oxygen uptake during exercise in CHF patients.[2,3] Whereas some studies provide evidence for a primary exercise limitation in the skeletal muscle, others suggest that central hemodynamic impairments play a predominant role.[4,5,6,7,8] A limitation of most studies is that central and peripheral parameters were not assessed simultaneously, hampering a direct comparison. Another explanation for these seemingly discrepant findings might be that measurements are often performed at rest, while it is well known that rest indices of cardiac function, like left ventricular ejection fraction, are not related with aerobic capacity.[9] A third explanation is that in CHF patients heterogeneity may exist with respect to exercise limitations, resulting in a heterogeneous response to exercise training.[10,11] Therefore, a personalized approach using a combination of validated central and peripheral measurements may be warranted to clarify the main limitation in the individual patient and to optimize patient selection for interventions aiming at an improvement of exercise capacity. In chapter 2, we used hemodynamic patterns during maximal exercise as a novel approach in CHF patients to characterize the exercise limitation. The previously validated radial artery pulse wave contour method measuring stroke volume (SV), heart rate (HR), cardiac output (Q) and arterial blood pressure beat by beat, was used to generate a hemodynamic profile during incremental, symptom limited exercise.[12] A central limitation was defined as a plateau or decline in Q during the

last 10 % of exercise. At a group level, we observed a continuous increase in both $\dot{V}O_2$ and Q throughout the test. These patterns were similar to a previously studied healthy population.[13,14] However, a third of our study population showed a central limitation. This central limitation was related to a plateau/decline in stroke volume (SV) and chronotropic incompetence, suggesting that both impaired contractility during exercise and neurohormonal dysregulation are determinants of the reduced exercise capacity in CHF patients with a central limitation. Whether hemodynamic patterns can be used in clinical decision making remains to be determined in future studies.

The ability to increase the rate of oxygen consumption during exercise is, besides central hemodynamics, also dependent on the metabolic oxidative capacity of skeletal muscles and peripheral vascular function. Peripheral vascular function, in its turn, may be limited by impaired redistribution of blood flow due to excessive vasoconstriction or inefficient vasodilation and heterogeneity in capillary recruitment patterns leading to disturbances in local matching of O_2 delivery and utilization in skeletal muscles.[1,15,16] In animal and computer modelling studies it was shown that $\dot{V}O_2$ kinetics are limited by O_2 delivery only when microvascular O_2 pressure in the capillaries was below a critical level.[10,17,18] At present, it is not feasible to assess microvascular O_2 pressure directly in humans. However, Near infrared spectroscopy (NIRS) can serve as a clinical application to identify limitations in O_2 delivery and utilization during exercise.[19] In fact, NIRS derived parameters as the tissue saturation index (TSI) have shown similar deoxygenation patterns and is considered to be a non- invasive proxy of microvascular O_2 pressure.[17,20,21] As such, it can be used to characterize patients physiologically and evaluate the effects of treatment on skeletal muscle oxygenation. However, at least a sufficient reliability of TSI is needed before it can be used as a routine measurement. Therefore, we assessed the absolute and relative reliability of amplitudes, absolute and kinetic values of (TSI) at the onset and recovery of submaximal exercise at two different days in 30 CHF patients. In this study we demonstrated that the relative test-retest reliability of TSI amplitudes and absolute values is sufficient to characterize CHF patients physiologically. Absolute reliability, which is used for within subject comparison and evaluation of treatment effects, was acceptable for absolute TSI values and onset kinetics. The results of this study were applied in chapter 4 in which we evaluated the relation between cardiac output (Q) kinetics and skeletal muscle deoxygenation during moderate-intensity exercise. Based on the results of the previous mentioned computer modelling and animal studies, we evaluated the determinants of impaired $\dot{V}O_2$ kinetics and tested the hypothesis that impaired matching of Q to the metabolic demands during submaximal exercise, defined as a slower increase in Q as compared to the increase in $\dot{V}O_2$, is associated with a higher degree of skeletal muscle deoxygenation.[10,17,22] An impaired Q-to-$\dot{V}O_2$ matching was found in 51% of our study population. In these subset of patients, a slow increase in Q was indeed related to a higher degree of deoxygenation of TSI, suggesting that Q was limiting peripheral O_2

delivery. Patient and disease characteristics, such as age, etiology, NYHA class or medical therapy were not different between groups with normal and impaired matching of Q and $\dot{V}O_2$. In conclusion, our findings demonstrated heterogeneity in hemodynamic exercise responses during moderate-intensity exercise. It remains to be determined whether this approach can be used to predict the response to therapies aiming at improvement of cardiac function during exercise.

In chapter 5 we focused on the utility of the oxygen pulse (OP) during recovery after maximal exercise to predict the central hemodynamic response to exercise. Exercising hemodynamics have shown their potential utility regarding prognosis and clinical decision making.[23,24,25,26] However, currently it is underused in daily practice due to several barriers in available methods.[12,27,28] Ideally, a hemodynamic measurement should be non-invasive, reliable, accurate, easy to use and provide continuous data during exercise and recovery. The OP meets most of these criteria. According to the modified Fick's principle, the OP equals the product of SV and arteriovenous oxygen content difference (a-vO_2diff). It was previously demonstrated that in the healthy population, the OP can be used a proxy for SV as the a-vO_2diff is constant at peak level.[29,30] However, this cannot be extrapolated to CHF patients, where peak a-vO_2diff is different between individuals and depends on disease severity.[31] Yet, the OP response during recovery was related to impaired exercise capacity in CHF patients, but its relation with the central hemodynamic response to exercise was unclear.[32,33,34,35] Our study demonstrated that an impaired OP recovery is related to a reduced Q during exercise and may be useful to grade the hemodynamic severity of CHF. Furthermore, we observed a significant relation between a slow OP recovery and a slow SV as well as a slow a-vO_2diff recovery, suggesting that both central and peripheral factors are responsible for restoring the oxygen debt during recovery that was accumulated during exercise.

In conclusion, in part I we demonstrated physiological heterogeneity during maximal exercise (chapter 2), submaximal exercise (chapter 4) and recovery after maximal exercise (chapter 5).

Additional insight in the pathophysiology of exercise intolerance in CHF is essential for developing novel therapies. Moreover, characterization of the nature of exercise limitations is needed to ascertain which determinant should be primarily targeted for therapy. We investigated several new exercise related parameters (Q patterns, ratio of Q-to-$\dot{V}O_2$, SmO_2 amplitude and OP relative recovery) that can be used to identify the main limitation. Further research is necessary to explore the clinical usefulness and prognostic significance of these novel approaches.

2) *Exploration of the clinical and physiological effects of high intensity interval training and cardiac resynchronization therapy in CHF patients*

A large body of evidence supports the use of exercise training in CHF patients.[36,37,38] Most of these studies were performed with moderate-intensity continuous training (MCT) programs. In the last decade, research has also focused on the effects of high-intensity interval training (HIT). Initial small studies demonstrated superior effects on exercise capacity and cardiac function, however these results could not be reproduced in recent larger randomized trials.[39,40,41,42] In clinical practice, training effects are evaluated by improvement in peak $\dot{V}O_2$ without knowing whether this is mediated by central or peripheral mechanisms. Although peak $\dot{V}O_2$ is a reliable indicator of peak aerobic capacity, it is less suitable to evaluate the performance in daily life, as this consists mainly of submaximal activities. As such, it has been demonstrated that $\dot{V}O_2$ kinetics at the onset and recovery of submaximal exercise are reliable and reproducible parameters and can be used for risk stratification and evaluation of training effects.[43,44,45,46] The aim of the HIT Central study (chapter 6) was to evaluate the relative contribution of exercising hemodynamics and skeletal muscle oxygenation in HIT-induced effects on (sub) maximal exercise capacity. At maximal exercise, a significant increase in peak workload and cardiac reserve (CR) capacity was demonstrated after 3 months of HIT. The change in workload was related to the change in peak $\dot{V}O_2$ but not to changes in CR. At submaximal level, $\dot{V}O_2$ recovery kinetics were significantly speeded after HIT. This acceleration was related to a decrease in skeletal muscle deoxygenation suggesting that HIT improves local QO_2-to-$\dot{V}O_2$ matching. As exercising hemodynamics did not relate to the improved QO_2-to-$\dot{V}O_2$ matching, the underlying mechanism may be related to improved endothelial function by an increased anti-oxidant status and nitric oxide bioavailibility.[47] Another explanation could be that HIT improves local QO_2-to-$\dot{V}O_2$ matching by an increased level of PGC-1alfa,[39] a key regulator in cellular energy metabolism which has been associated with upregulation of capillary and oxidative capacity.[48] Besides additional physiological insight, our results have also clinical relevance. As many CHF patients are impaired by prolonged fatigue after daily life activities, accelerated $\dot{V}O_2$ recovery kinetics might help to improve their physical activity level.

Although there was an improvement at a group level, the results also revealed a considerable variation in training effects between patients. Unfortunately, the small sample size did not allow to analyse subgroups to identify the phenotype of a responder or non-responder. Larger studies are needed to clarify this important issue. In chapter 7 we explored the additional effects of HIT in a special subgroup of CHF patients with an indication for cardiac resynchronization therapy (CRT). In these CHF patients, cardiac function is (partly) reduced due to dyssynchrony leading to adverse remodeling of the ventricles which can be restored by synchronized pacing. It is known that CRT improves

exercise capacity, which is predominantly mediated by central hemodynamics.[49,50] However, the non-response to CRT is still substantial.[51,52] Previous studies have shown that moderate-intensity continuous training after CRT has additional effects on exercise capacity.[53,54] Yet, given the distinct physiological mechanisms of HIT and CRT, we hypothesized that HIT after CRT might be even more effective. In line with previous CRT studies, we observed a significant improvement of peak $\dot{V}O_2$, workload, $\dot{V}O_2$ recovery kinetics and resting indices of cardiac function 3 months after CRT.[50,55,56] The results after HIT demonstrated a significant additional increase in peak workload, without a concomitant change in peak $\dot{V}O_2$,$\dot{V}O_2$ kinetics or exercising hemodynamics, suggesting that the effects of HIT after CRT are mainly mediated by an improvement in anaerobic performance. To investigate this hypothesis, future studies should also evaluate changes in structural characteristics of skeletal muscles (e.g. increase in type II fibres). Nevertheless, this study showed that HIT is useful in clinical practice as an adjunct therapy to optimize the benefits of CRT, but more research is needed to identify the predictors of response to both therapies.

Future directions

In part I of this thesis it was demonstrated that physiological heterogeneity exists among CHF patients with respect to limitations to different intensities of exercise using gas exchange analysis in combination with assessment of exercising hemodynamics. Previously, exercise hemodynamics have been shown to be the strongest predictor of prognosis in CHF patients.[23] However, to implement exercise hemodynamics in clinical decision making, larger multi center trials are needed. In addition, the clinical utility of the proposed methods in this thesis to identify heterogeneity in CHF patients should be evaluated. In particular, application of exercising hemodynamics could be used to select appropriate candidates for current and novel therapies that improve central hemodynamics (e.g. left ventricular assist device (LVAD) or mitraclip) or peripheral skeletal muscle function (e.g. improved QO_2-to-$\dot{V}O_2$ matching due to increased NO bioavailiability by administering phosphodiesterase inhibitors such as sildenafil or nutritional supplements).[57] Finally, future studies should evaluate the proposed methods in other patient groups such as heart failure with preserved ejection fraction (HFPEF) with a presumably different pathophysiological background.[58]

In this thesis, we focused on central hemodynamics and skeletal muscle oxygenation during exercise. However, from a physiological point of view, the role of macrovascular and microvascular redistribution of blood flow to and within the skeletal muscle was not fully explored. It was demonstrated previously that leg blood flow was reduced in CHF patients, not only by the reduced cardiac output but also a reduced redistribution of

blood flow to the exercising muscles by multiple factors such as impaired vasodilation by reduced endothelial function.[59] Because these studies were conducted in the pre ACE-inhibitor and beta-blocker era, it is not known whether the results can be extrapolated to contemporary CHF patients. At present, a non-invase measurement, such as phase contrast magnetic resonance imaging (PC-MRI) can be used to evaluate cardiac output and peripheral blood flow.[60] Simultaneous measurement during exercise has not been performed yet, but may provide new insights in the relation between cardiac output and redistribution of macrovascular leg blood flow in CHF patients. Furthermore, the relative contribution of microvascular blood flow to exercise intolerance in CHF patients has not been fully elucidated. In the last decade it has been proposed that temporal and spatial matching of Q-to-$\dot{V}O_2$ is essential for effective skeletal muscle and exercise performance. In CHF, arteriolar dysfunction and considerable reduction of red blood cell flux in the capillaries impair QO_2-to-$\dot{V}O_2$ matching.[16,61] As outlined in this thesis, NIRS derived parameters as the tissue saturation index (TSI) can be used to evaluate QO_2-to-$\dot{V}O_2$ matching. However, as TSI represents the ratio between local oxygen delivery and utilization, it cannot be used to assess absolute microvascular blood flow or oxygen utilization separately. The oxygen utilization capacity can be estimated by the oxidative function and capacity of the myocyte, but this requires muscle biopsy and cannot be performed during exercise. On the other hand, microvascular blood flow may be quantified by novel promising techniques, such as Power Doppler which measures changes in blood flow in the skeletal muscle area of interest. In combination with the assessment of pulmonary oxygen uptake, exercising hemodynamics, the macrovascular redistribution factor and TSI, it may be feasible to analyze the complete oxygen transport chain in combination with oxygen utilization during exercise, enabling a more complete understanding of determinants of exercise intolerance in CHF patients.[62]

In part II, we evaluated HIT induced effects on exercise capacity and its physiological determinants in CHF patients with or without CRT. Although we observed benefits at a group level of several maximal and submaximal exercise parameters, there was still a considerable variation between individual patients. In future studies, the clinical and physiological profile of a responder to both CRT and exercise training should be clarified to enable a more tailored therapeutic approach. A prediction model with exercise related parameters such as proposed in this thesis could optimize benefits for individual patients and lead to lower healthcare costs. For example, by selecting responders to exercise training, a HIT program before CRT may optimize benefits or even defer CRT. Moreover, a predicted non-responder will not be exposed to an expensive treatment with potential adverse side effects. In the light of the emerging heart failure population, an individual phsyiologically based approach could therefore act as a double edged sword.

From a broader perspective, besides the discussion what the ideal training characteristics should be for CHF patients, exercise training is vastly underused. The uptake of cardiac rehabilitation for CHF patients was shown to be only 4% in the Netherlands.[63] Obviously, there is large gap between knowledge and practice. This may be caused by several barrieres, including lack of adherence to guidelines from healthcare professionals or patient related factors as low socio-economic status, lack of time or financial reimbursement.[64] Future prediction models with digital decision support systems for clinicians may be helpful to increase adherence to guidelines. From a patient perspective, adherence to training, particularly in the long term is quite low and methods to improve adherence should be developed. Remote patient monitoring may improve physical fitness and help the patient to implement physical activity in daily life.[65] Especially in CHF patients, exercise training is a lifelong medicine and prescribed at the right dose, it will improve exercise capacity, quality of life and reduce hospital admissions. Therefore, policy makers should consider the macroeconomic benefits of lifelong reimbursement of supervised ET. Indeed, the HF-action trial showed that only 30% of patients continue to exercise after a supervised program.[66] Naturally, patients should be intrinsically motivated to exercise in the first place, but periodic coaching to keep the patient motivated and physical active is essential. Moreover, CHF has an unpredictable course and ageing goes alone with multiple co- morbidities, so exercise training should be a dynamic proces tailored to the patients' needs and their clinical status.

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APPENDIX

Nederlandse samenvatting
Dankwoord
Curriculum Vitae
List of publications

Nederlandse samenvatting

Chronisch hartfalen (CHF) is een syndroom dat wordt gekenmerkt door een tekortschietende pompfunctie van het hart en uiteindelijk leidt tot een verminderde inspanningscapaciteit. Het is essentieel om meer inzicht in de pathofysiologische mechanismen van het verminderd inspanningsvermogen te verkrijgen om de resultaten van huidige en toekomstige behandelingen te kunnen optimaliseren. Elke stap in de zuurstoftransportketen van longen naar de actieve spier kan verantwoordelijk zijn voor de verminderde inspanningscapaciteit. In dit proefschrift hebben we meer inzicht verkregen in de inspannings(patho)fysiologie van patiënten met chronisch hartfalen door het karakteriseren van de centrale (hart) en perifere (spier) determinanten van zuurstofopname tijdens inspanning. Daarnaast is er meer inzicht verkregen in de onderliggende mechanismen van de effecten van hoog intensieve intervaltraining (HIT) bij patiënten met chronisch hartfalen met en zonder cardiale resynchronisatie therapie (CRT). In dit hoofdstuk zullen aan de hand van de twee centrale thema's van het onderzoek de belangrijkste bevindingen van de uitgevoerde studies worden samengevat. Daarnaast zullen de klinische implicaties en richtingen voor toekomstig onderzoek worden besproken.

In deel I "fysiologische aspecten van de inspanningshemodynamiek bij chronisch hartfalen" staat het volgende onderwerp centraal.

1) Evaluatie van de fysiologische heterogeniteit van de verminderde zuurstofopnamecapaciteit bij patiënten met chronisch hartfalen door het combineren van inspanningstesten met ademgasanalyse, metingen van de hemodynamiek en zuurstofvoorziening van de actieve skeletspier.

In de literatuur bestaat er nog steeds een controverse over de relatieve bijdrage van de centrale hemodynamiek en de perifere zuurstoftoevoer en-verbruik ten aanzien van de verminderde zuurstofopnamecapaciteit bij chronisch hartfalen. Sommige studies laten een centrale beperking zien, terwijl anderen suggereren dat perifere factoren het meest beperkend zijn. Deze schijnbare tegenstelling kan op verschillende manieren worden verklaard. Ten eerste, in de meeste studies worden centrale en perifere factoren niet gelijktijdig bepaald waardoor een direct vergelijk niet goed mogelijk is. Ten tweede, worden hemodynamische metingen vaak in rust uitgevoerd, terwijl het bekend is dat rustmetingen, zoals de ejectiefractie van de linkerkamer, niet goed overeenkomen met de inspanningscapaciteit van patiënten. Als derde verklaring kan worden aangevoerd dat patiënten met chronisch hartfalen ten aanzien van de beperkende factor van het verminderde inspanningsvermogen daadwerkelijk een heterogene groep vormen dat

leidt tot een verschillende uitkomst op behandelingen zoals fysieke training. Daarom is een geïndividualiseerde benadering met gevalideerde en simultane metingen van de centrale hemodynamiek en oxygenatie van de actieve spier aangewezen om meer inzicht te krijgen in de onderliggende beperking in de individuele patiënt met als doel het optimaliseren van patiëntselectie voor behandelingen die gericht zijn op het verbeteren van het inspanningsvermogen.

In hoofdstuk 2 hebben we gebruik gemaakt van hemodynamische patronen als een nieuwe benadering om de inspanningsbeperking bij patiënten met chronisch hartfalen te karakteriseren. Hiervoor hebben we gebruikt gemaakt van de zogenaamde polsgolf contour analyse. Deze methode hebben we in eerder onderzoek gevalideerd met de "Fick methode" als gouden standaard. Met deze polsgolf contour analyse kunnen we van slag tot slag zowel de hartslag, het slagvolume, het hartminuutvolume (cardiac output) als de arteriële bloeddruk meten. Tijdens een maximale inspanningstest met ademgasanalyse kan op deze manier een hemodynamisch profiel van de patiënt worden opgesteld, waarbij een centrale beperking werd gedefinieerd als een plateau of daling van de cardiac output in de laatste 10% van de inspanningstest. Op groepsniveau wordt er een continue stijging gezien tot het einde van de test van de zowel de zuurstofopname als de cardiac output. Deze resultaten komen overeen met bevindingen bij de gezonde populatie in een ander onderzoek. Echter in een derde (1/3) van onze studiepopulatie blijkt sprake te zijn van een centrale beperking volgens eerdergenoemde definitie. Deze centrale beperking is gerelateerd aan een plateau/ daling van het slagvolume en chronotrope incompetentie (niet oplopen van de hartslag bij inspanning). Deze bevindingen suggereren dat zowel een afgenomen contractiliteit tijdens inspanning als neurohormonale disregulatie een rol spelen bij de afgenomen inspanningscapaciteit bij patiënten met een centrale beperking. Uit toekomstig onderzoek zal moeten blijken of deze hemodynamische patronen gebruikt kunnen worden voor beslisvorming in de klinische praktijk.

Naast de centrale hemodynamiek spelen ook factoren, zoals de perifere vaatfunctie en de metabole oxidatieve capaciteit van de skeletspieren een belangrijke rol in de beperkte zuurstofopnamecapaciteit bij patiënten met chronisch hartfalen. De perifere vaatfunctie kan beperkt zijn door onder andere een afgenomen redistributie van bloedstroom naar de actieve spier als gevolg van excessieve vasoconstrictie of inefficiënte vasodilatatie. Daarnaast kan er sprake zijn van heterogeniteit van gerekruteerde capillairen in de actieve skeletspier dat leidt tot een verstoorde lokale balans tussen zuurstofaanvoer en -verbruik. Uit dierstudies en computermodellen is gebleken dat de kinetiek van zuurstofopname alleen beperkt is door lokale zuurstofaanvoer wanneer de zuurstofdruk in de capillairen onder een kritische grens komt. Op dit moment is het nog niet mogelijk om bij mensen de zuurstofdruk in de capillairen direct te meten. Echter, Near Infrared

Spectroscopy (NIRS) kan worden gebruikt als een surrogaatmeting. Een afgeleide parameter van NIRS is de zogenaamde Tissue Saturation Index (TSI). Hiermee kan de lokale balans tussen zuurstofaanvoer en zuurstofverbruik tijdens of na inspanning worden gemeten in de skeletspier. Uit eerder onderzoek is gebleken dat de direct gemeten zuurstofdruk in de capillairen vergelijkbare patronen vertoont als TSI tijdens en na inspanning. Als zodanig kan de TSI gebruikt worden om meer inzicht te krijgen in de fysiologische achtergronden van het zuurstofopnamevermogen. Echter voordat deze toepassing in de praktijk gebruikt kan worden, dient de betrouwbaarheid en reproduceerbaarheid van deze meting getest te zijn. In hoofdstuk 3 hebben we de absolute en relatieve betrouwbaarheid van TSI-metingen tijdens en na submaximale inspanning getest op 2 verschillende tijdstippen en dagen bij 30 patiënten. Hieruit komt naar voren dat de absolute betrouwbaarheid, die belangrijk is voor het vergelijken van metingen binnen een persoon en het evalueren van behandeleffecten, acceptabel is voor absolute TSI waarden en de TSI kinetiek bij aanvang van submaximale inspanning. De resultaten van dit onderzoek worden toegepast in hoofdstuk 4. Hierin wordt de relatie tussen de cardiac output kinetiek en de mate van deoxygenatie in de skeletspier tijdens submaximale inspanning bestudeerd door gelijktijdig gebruik te maken van de voorgenoemde polsgolf contour analyse en de TSI. Gebaseerd op dierstudies en computermodellen, was de hypothese dat een verstoorde balans tussen zuurstofaanvoer en zuurstofverbuik, gedefinieerd als een tragere stijging van de cardiac output ten opzichte van de zuurstofopname, zou leiden tot een verhoogde mate van deoxygenatie in de skeletspier (lagere TSI waarde). Een verstoorde balans werd gevonden bij 51% van de patiënten. In deze groep werd inderdaad een relatie tussen de trage stijging in cardiac output en een lagere TSI waarde gevonden. Deze resultaten suggereren dat in deze groep een centrale beperking ook leidt tot een perifere beperking van zuurstofaanvoer. Patiënt-en ziektekarakteristieken zoals leeftijd, etiologie, ernst van het hartfalen (NYHA-klasse) of medicatiegebruik bleken niet verschillend te zijn tussen de 2 groepen. Onze bevindingen tonen heterogeniteit in de hemodynamiek tijdens submaximale inspanning bij patienten met chronisch hartfalen. Uit toekomstig onderzoek zal moeten blijken of deze benadering ook gebruikt kan worden om het effect van behandelingen, die gericht zijn op het verbeteren van de pompfunctie, te kunnen voorspellen.

In hoofdstuk 5 ligt de focus op de bruikbaarheid van het herstel van de zuurstofpols na maximale inspanning als voorspeller van de hemodynamiek tijdens inspanning. De hemodynamiek tijdens inspanning is een belangrijke voorspeller van de prognose en kan worden ingezet in klinische beslisvorming, bijvoorbeeld bij selectie voor harttransplantatie. Echter op dit moment worden hemodynamische inspanningsmetingen nauwelijks gebruikt in de praktijk vanwege allerlei tekortkomingen van de beschikbare methodes. Idealiter zou een hemodynamische inspanningsmeting niet invasief, betrouwbaar,

accuraat, gemakkelijk te gebruiken en continue data moeten genereren tijdens en na inspanning. De zuurstofpols voldoet aan de meeste van deze criteria. Volgens de gemodificeerde vergelijking van Fick is de zuurstofpols het product van het slagvolume en het arterioveneus zuurstofverschil. Uit eerder onderzoek bij gezonde proefpersonen is gebleken dat de zuurstofpols als een goede maat voor het slagvolume gebruikt kan worden. Echter dit kan niet worden geëxtrapoleerd naar patiënten met chronisch hartfalen, waarin het maximale arterioveneus zuurstofverschil tussen individuen sterk kan verschillen en afhankelijk is van de ernst van de ziekte. Het herstel van de zuurstofpols na inspanning daarentegen blijkt sterk te relateren aan het inspanningsvermogen, maar de relatie met de hemodynamiek tijdens inspanning is nog onopgehelderd. De resultaten van deze studie laten zien dat een vertraagd herstel van de zuurstofpols gerelateerd is aan een afgenomen cardiac output respons tijdens inspanning. Daarnaast blijkt er een significante relatie te bestaan tussen een relatief vertraagd herstel van de zuurstofpols en vertraagd herstel van zowel het slagvolume als het arterioveneus zuurstofverschil. Deze bevindingen suggereren dat zowel centrale als perifere factoren betrokken zijn bij het herstellen van de zuurstofschuld die is opgebouwd tijdens inspanning. Samengevat kan worden gesteld dat in deel I fysiologische heterogeniteit tussen patiënten met hartfalen wordt aangetoond zowel tijdens maximale en submaximale inspanning als tijdens de herstelfase. Additionele fysiologische inzichten in de inspanningsbeperking bij patiënten met chronisch hartfalen zijn essentieel om nieuwe behandelingen te ontwikkelen. Daarnaast is het karakteriseren van de inspanningsbeperking bij het individu nodig om de behandeling te richten op de primaire beperking. We hebben meerdere nieuwe inspanningsgerelateerde parameters onderzocht, die gebruikt kunnen worden om de belangrijkste beperking te identificeren. Toekomstig onderzoek is nodig om de bruikbaarheid in de klinische praktijk en de prognostische waarde te evalueren.

In deel II worden de klinische aspecten belicht van de inspanningshemodynamiek bij patiënten met chronisch hartfalen met als centraal thema:

2) Onderzoek naar de klinische en inspanningsfysiologische effecten van hoog intensieve intervaltraining en cardiale resynchronisatie therapie bij patiënten met chronisch hartfalen.

Er is reeds veel bewijs in de literatuur voor de positieve effecten van fysieke training bij patiënten met chronisch hartfalen. Veruit de meeste studies zijn echter gedaan met matig intensieve duurtraining. Het laatste decennium is er steeds meer aandacht gekomen voor hoog intensieve intervaltraining (HIT). Enkele kleinere studies laten superieure effecten zien met betrekking tot het inspanningsvermogen en de hartfunctie. In recente grotere gerandomiseerde studies kunnen deze resultaten echter niet

bevestigd worden. In de klinische praktijk wordt het effect van fysieke training vaak gemeten door een verbetering van de zuurstofopnamecapaciteit zonder te weten of dit met name door centrale of perifere factoren bepaald wordt. Hoewel de maximale zuurstofopnamecapaciteit een betrouwbare en belangrijke indicator is van het aerobe vermogen, is het minder geschikt om de conditie van activiteiten in het dagelijks leven te meten, omdat dit met name bestaat uit verschillende submaximale inspanningen. Hiervoor kan beter gebruik worden gemaakt van zuurstofopname kinetiek, waarin de snelheid van zuurstofopname tijdens en de snelheid van daling na een submaximale inspanning gemeten wordt. Zuurstofopname kinetiek is daarnaast een reproduceerbare maat die ook geschikt is voor risicostratificatie en het meten van trainingseffecten. Het doel van de HIT Centraal studie (hoofdstuk 6) is het evalueren van de relatieve bijdrage van inspanningshemodynamiek en skeletspieroxygenatie op HIT geïnduceerde effecten op het (sub) maximale inspanningsvermogen. Na 3 maanden HIT blijkt er een significante verbetering te zijn van het inspanningsvermogen en de reservecapaciteit van het hart (maximale cardiac output minus rust cardiac output) tijdens maximale inspanning. De verbetering van het vermogen is gerelateerd aan verandering van de zuurstofopnamecapaciteit, maar niet in veranderingen van de reservecapaciteit van het hart. Op submaximaal niveau blijkt er sprake te zijn van een significant sneller herstel van de zuurstofopname kinetiek na 3 maanden HIT. Deze versnelling is gerelateerd aan een verbetering van de skeletspieroxygenatie. Deze bevindingen suggereren dat HIT leidt tot een verbetering van de lokale balans tussen zuurstofaanvoer en-verbruik. Gezien het feit dat de centrale hemodynamiek tijdens inspanning niet gerelateerd is aan de verbetering van de lokale balans tussen zuurstofaanvoer en -verbruik, zou het onderliggende mechanisme verklaard kunnen worden door een verbeterde endotheelfunctie door toegenomen anti-oxidatieve status en biologische beschikbaarheid van stikstofmonoxide. Een andere verklaring zou kunnen zijn dat HIT leidt tot een toename van PGC-1 alfa, een belangrijk moderator in het energiemetabolisme van de cel, die gerelateerd is aan toename van capillairen en oxidatieve capaciteit. Afgezien van additionele fysiologische inzichten, hebben deze resultaten ook klinische relevantie. Veel patiënten met chronisch hartfalen ervaren een langdurige vermoeidheid na dagelijkse inspanningen, een sneller herstel van de zuurstofopname kinetiek na submaximale inspanning kan resulteren in een verbetering van de fysieke activiteiten in het dagelijkse leven. Hoewel er op groepsniveau een verbetering te zien is, is er ook een aanzienlijke variatie van trainingseffecten tussen patiënten. Helaas bleek de studiepopulatie te klein om subgroepen te onderscheiden waarin het fenotype van een responder of non responder van HIT kon worden geïdentificeerd. Grotere studies zijn nodig om dit belangrijke aspect te verkennen. In hoofdstuk 7 hebben we de additionele effecten van HIT onderzocht in een speciale subgroep van patiënten met chronisch hartfalen met een indicatie voor cardiale resynchronisatie therapie (CRT). Bij deze groep patiënten is de hartfunctie

(deels) afgenomen als gevolg van asynchrone contracties van beide ventrikels, dat weer hersteld kan worden door een speciale pacemaker die beide ventrikels synchroon pacet (CRT). Uit eerder onderzoek is gebleken dat CRT leidt tot een verbetering van het inspanningsvermogen, dat met name het gevolg is van een verbeterde hemodynamiek. Het aantal non responders op CRT is echter nog substantieel. Voorgaande onderzoeken hebben aangetoond dat een programma met matig intensieve duurtraining leidt tot een additionele verbetering van de conditie. Gezien de verschillende fysiologische achtergronden van duurtraining en hoog intensieve intervaltraining, is onze hypothese dat HIT na CRT mogelijk nog effectiever zou kunnen zijn. Overeenkomstig met eerdere CRT studies hebben we 3 maanden na implantatie van de CRT pacemaker een significante verbetering gezien van de zuurstofopname capaciteit, kinetiek en de hartfunctie in rust. De resultaten na 3 maanden met een HIT programma laten een additionele verbetering van het inspanningsvermogen zien zonder een bijkomende verbetering van de zuurstofopnamevermogen, kinetiek of de hemodynamiek in rust of tijdens inspanning. Deze resultaten suggereren dat de effecten van HIT na CRT met name gemedieerd zijn door een verbetering van het anaerobe vermogen. Om deze hypothese te toetsen zullen toekomstige studies ook structurele veranderingen van de skeletspier moeten meten (bijvoorbeeld afnemen van spierbiopten om verandering in type en functie van spiervezels te bekijken) Desalniettemin laat dit onderzoek zien dat HIT bruikbaar is in de klinische praktijk als een aanvullende behandeling na CRT om de effecten te optimaliseren. Meer onderzoek is echter nodig om de voorspellers van respons op beide interventies beter te identificeren.

Aanbevelingen voor toekomstig onderzoek

In deel I van dit proefschrift hebben we de fysiologische heterogeniteit van het inspanningsvermogen bij verschillende intensiteiten bij patiënten met chronisch hartfalen aangetoond. Eerder is gebleken dat de centrale hemodynamiek tijdens inspanning een van de belangrijkste voorspellers is van de prognose. Echter om deze hemodynamische metingen te implementeren in de praktijk, zullen er grotere multicenter onderzoeken nodig zijn. Mede om de klinische bruikbaarheid te testen van de, in dit proefschrift voorgestelde, methoden om heterogeniteit te evalueren. Metingen van de hemodynamiek tijdens inspanning zouden gebruikt kunnen worden om geschikte kandidaten te selecteren voor huidige en toekomstige behandelingen die een verbetering geven van de centrale hemodynamiek (denk aan het steunhart of een harttransplantatie) of perifere vaat- of skeletspierfunctie (bijvoorbeeld combinatie van fysieke training en het toevoegen van bepaalde supplementen die de beschikbaarheid van stikstofmonoxide verhogen). Ten slotte kunnen de voorgestelde benaderingen in dit proefschrift geëvalueerd worden bij patiënten met hartfalen en een behouden linkerventrikelfunctie (zogenaamd HFPEF) met een waarschijnlijk verschillende fysiologische achtergrond van het afgenomen inspanningsvermogen.

In dit proefschrift heeft met name de focus gelegen op de rol van de centrale hemodynamiek en de perifere skeletspieroxygenatie. De rol van macro- en microvasculaire redistributie van de bloedstroom naar en in de skeletspier is onderbelicht gebleven.

Het is bekend dat bij patiënten met chronisch hartfalen de redistributie van bloed naar de actieve spier verminderd is ten op zichte van gezonde proefpersonen. Echter deze onderzoeken zijn gedaan in een tijd voordat medicamenten zoals ACE-remmers en bètablokkers hun intrede maakten. Het is daardoor niet duidelijk of voorgenoemde resultaten in het huidig tijdperk van toepassing zijn. Met huidige technieken zoals fase-contrast MRI kan de cardiac output en perifere bloedstroom worden gemeten. Simultane metingen in de MRI tijdens inspanning zouden meer inzicht kunnen geven in de relatie tussen de centrale hemodynamiek en de redistributie van bloedstroom naar de grote vaten.

Daarnaast is de laatste jaren uit onderzoek gebleken dat de microvasculaire balans tussen zuurstofaanvoer en -verbruik een belangrijke rol speelt in de beperkte inspanningstolerantie bij patiënten met chronisch hartfalen. Zoals in dit proefschrift naar voren is gekomen, kan NIRS afgeleide parameters, zoals de TSI, een belangrijke bijdrage leveren om meer inzicht te krijgen in de fysiologische achtergronden. Echter TSI heeft de beperking dat het een ratio betreft tussen zuurstofaanvoer en -verbruik en niet gebruikt kan worden om onafhankelijk de microvasculaire bloedstroom of zuurstofverbruik in de spiercel te meten. Nieuwe veelbelovende technieken, zoals Power Doppler, zouden gebruikt kunnen worden om veranderingen in de microvasculaire bloedstroom van de actieve skeletspier te meten. In combinatie met de reeds gebruikte

methoden in dit proefschrift kan een completer beeld van de zuurstoftransportketen worden bepaald en daarmee meer inzicht in de beperkende factor van het inspanningsvermogen bij het individu.
In deel II hebben we de effecten van HIT op het inspanningsvermogen onderzocht bij patiënten met en zonder CRT. Hoewel er op groepsniveau significante verbeteringen worden gezien op (verschillende onderdelen van) het inspanningsvermogen, is er sprake van een aanzienlijke variatie tussen individuele patiënten. In toekomstige studies dienen de fysiologische en klinische profielen van een responder (en ook non responder) op zowel HIT als CRT verder onderzocht te worden om te komen tot een behandeling die op maat gemaakt is. Bijvoorbeeld door het selecteren van responders van fysieke training, zou een HIT programma voorafgaand aan CRT kunnen leiden tot een verbetering van de respons op CRT of mogelijk zelfs kunnen uitstellen. Hierdoor hoeven patiënten niet blootgesteld te worden aan dure behandelingen met potentiele bijwerkingen en complicaties. In het licht van de groeiende populatie van patiënten met chronisch hartfalen, snijdt het mes met een dergelijke individuele benadering aan twee kanten. Vanuit een breder perspectief gezien, is het niet alleen belangrijk om te kijken naar specifieke trainingskarakteristieken, maar ook naar de instroom van hartfalen patiënten binnen de hartrevalidatie. In Nederland bestaat maar 4% van de deelnemers aan hartrevalidatie uit patiënten met chronisch hartfalen. Er is hier duidelijk sprake van een discrepantie tussen de aanwezige kennis over de positieve effecten van fysieke training en de klinische praktijk. Dit komt onder andere door een gebrek aan het volgen van de richtlijnen door zorgverleners, alsmede patiënt gerelateerde factoren zoals lage sociaaleconomische status, gebrek aan tijd, vervoer of financiële vergoeding. Toekomstige voorspelmodellen met beslisondersteuning voor de zorgverlener kunnen leiden tot een verbetering van richtlijnadherentie. Daarnaast speelt mee dat patiënten in veel gevallen de aanbevolen beweegactiviteiten op de lange termijn niet volhouden. Er is gebleken dat de fysieke activiteit bij hartpatiënten verbetert met behulp van nieuwe technieken zoals remote patiënt monitoring (begeleiden van patiënten in de eigen omgeving) en het bovendien fysieke training kan integreren in het dagelijks leven van de patiënt. Met name bij patiënten met chronisch hartfalen is gebleken dat fysieke training een levenslang medicijn is en als het op de juiste manier is voorgeschreven, het leidt tot een verbetering van het inspanningsvermogen, kwaliteit van leven en afname van angst en depressies, ziekenhuisopnames en wellicht overleving. Daarom zouden beleidsmakers meer aandacht moeten hebben voor de macro economische voordelen van een langdurige vergoeding voor hartfalenrevalidatie. Natuurlijk moeten patiënten ook intrinsiek gemotiveerd zijn om deel te nemen, maar periodieke coaching is essentieel om de patiënt fysiek actief en gemotiveerd te houden. Bovendien heeft chronisch hartfalen een onvoorspelbaar en grillig beloop en ouder worden gaat gepaard met comorbiditeit, daarom is (het voorschrijven van) fysieke training een dynamisch proces en zou moeten worden afgestemd op de behoeften en actuele klinische status van de patiënt.

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Victor, mister muscle, mijn medevluchter uit het peloton. Wat een weg hebben we afgelegd! Vele uren samen op de fietskamer. In de wandelgangen werden we vaak circus Ruud en Victor genoemd. Ons werkterrein leek voor een buitenstaander (of patiënt?) soms op een bloederige middeleeuwse martelkamer. Arteriële lijnen die niet altijd lukten,

spierbiopten met botte naalden, NIRS, MRI, MRS etc, etc. Het viel in het begin niet altijd mee om ons gedachtegoed te verspreiden in de tijdschriften, maar op karakter(iseren) zijn we doorgegaan.

Geachte leden van de leescommissie, hartelijk dank voor de kritische beoordeling van het manuscript.

Team Flow, collega promovendi. Tom “Feijenooit” Vromen, Danny “Oeh” vd Sanden, Thijs “Skutsie” Schoots, Rutger “Wodka Brewers”, Dr. Jozua Kraal, Yvette “rebound stretch” van der Linden. Wat een mooie club en wat een geweldige tijd hebben we de afgelopen jaren samen beleefd op de Europese toer. Ik hoop dat mijn inspirerende speech als de “randomizer” tijdens de promovendi BBQ bij Hareld het vuurtje heeft aangewakkerd bij jullie.

Vakgroep Cardiologie, beste maten. Hareld, Jan, Ron, Eric, Robert, Luc, Simone, Sabine en Anne-Rosine. Bedankt voor het vertrouwen en het geduld dat jullie betracht hebben. Al vanaf de beginfase kon ik bij jullie terecht als het nodig was. Eerst in de jeugdploeg van het MMC en uiteindelijk doorgestroomd naar de selectie. Een scenario uit een mooi jongensboek. Nu kunnen we samen het glas gaan heffen!

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Uiteraard alle patiënten, die zeer flexibel en enthousiast hebben deelgenomen aan de onderzoeken, ook al hebben ze daar niet altijd zelf direct baat bij. In het bijzonder mijn vaste fietsmaatje Rob van der Zanden voor de jaarlijkse tandemtocht. We gaan nog zeker een keer samen spinnen.

Deze rit ben ik begonnen tijdens mijn opleiding in het Catharina ziekenhuis, ik wil dan ook mijn toenmalige opleiders dr. van Dantzig en prof.dr. Pijls bedanken voor de mogelijkheid om dit onderzoek naast de opleiding te faciliteren. Ook mijn collega arts-assistenten, die inmiddels als cardiologen verspreid zijn over het land.

Last but not least, vrienden en familie. Zij die dicht bij je staan en je over het dode punt heen helpen als het nodig is. Al jarenlang ben ik door jullie aangemoedigd langs de kant van de weg en kreeg ik regelmatig de vraag: wanneer is het zover? Jawel, nu is het zover! Tijd voor een mooi fisje nie?

Lieve pap en mam, jullie leerden mij fietsen waardoor ik mij nu staande kon houden in het peloton. Elke etappe stonden jullie met de camper langs de weg en hadden jullie aanmoedigingen op de weg geschilderd. Ik had niet altijd de tijd om ze te lezen, maar heb het altijd zeer gewaardeerd. Bedankt pap, bedankt mam. Tijd voor een goed Belgisch biertje.

Lieve Yvonne, lieve zus, er voor elkaar zijn in goede en slechte tijden, daar is familie voor! Dank je dat mijn paranimf wilt zijn.

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……En daar is dan de finish, nog even omkijken, shirtje straktrekken voor de sponsoren, kushandje maken en dan de handen in de lucht. C’est fini. Merci à tous…..

Curriculum Vitae

The author of this thesis was born on September 14th 1977 in Venray, the Netherlands. In 1995, he obtained his gymnasium diploma at the Boschveldcollege in Venray. He entered medical school at the Radboud University in Nijmegen in 1995 and graduated in 2002. In 2003 he started a specialist training in Sports Medicine at the Laurentius Hospital in Roermond. In 2005 he switched to a residency in Cardiology at the Máxima Medical Centre Veldhoven and started his specialist training Cardiology in 2007 at the Catharina Hospital Eindhoven. In 2010 he started the research for this thesis at the Department of Cardiology at the Máxima Medical Centre and the University Medical Centre in Utrecht. In 2015 he finished his specialty in Cardiology and performed a fellowship Cardiac MRI in Berlin, Germany. Thereafter, he started working as a cardiologist at the Máxima Medical Centre with a special interest in Cardiac Rehabilitation, Heart Failure and Sports Cardiology. In 2016 he was awarded as best reviewer for the Dekker grants by the Dutch Heart Foundation. Since 2016 he is a Sports Cardiology consultant for professional soccer club PSV Eindhoven.

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