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Oxygen uptake kinetics in chronic heart failure

Clinical and physiological aspects

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Contents

Chapter 1

Introduction and outline of the thesis

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Chronic heart failure

Chronic heart failure (CHF) can be defined as a clinical syndrome resulting from the inability of the heart to maintain sufficient cardiac output for adequate tissue oxygenation. As a consequence, CHF patients suffer from exercise intolerance and fluid retention. One of the main determinants of reduced exercise capacity in these patients is systolic and / or diastolic left ventricular dysfunction, which causes an impaired hemodynamic response to exercise.[1] Other pathophysiological mechanisms include an impaired muscle blood flow caused by increased vasoconstriction[2,3] and / or an impaired local vasodilatory capacity,[4,5] muscle mitochondrial dysfunction,[6,7] an exaggerated ventilatory response to exercise,[8] and autonomic imbalance.[9] To what extent these mechanisms contribute separately to the functional capacity of CHF patients is not well established.

In 2003 the number of CHF patients in the Netherlands was estimated at about 180,000,[10] with a substantial increase in prevalence with age from about 1% in persons aged 55 to 64 years to 17% in those over the age of 85 years.[11] Also, the incidence rates of heart failure have been reported to increase with age, resulting in a lifetime risk of about 30% of developing heart failure over the age of 55 years.[11] It is expected that ageing of the population in the Western world will dramatically increase the number of CHF patients in the near future. Moreover, novel treatment modalities have improved the prognosis of CHF patients in the last decades,[12,13] leading to a further increase in the prevalence of heart failure. Nevertheless, despite therapeutic advances, the overall mortality of CHF patients remains high, with reported 5-year mortality rates ranging from 41% to 65%.[11-14] Therefore, the management of heart failure remains one of the most challenging areas in cardiology today.

The most frequent cause of heart failure in patients under 75 years old is coronary artery disease,[15] while in older patients hypertension may be a more predominant cause.[16] Less common causes include valvular disease, arrhythmias, hypertrophic or dilated cardiomyopathy, alcoholic cardiomyopathy, congenital heart disease, and metabolic disorders. In addition to the treatment of reversible causes of heart failure (e.g., by coronary revascularization, valve replacement, treatment of arrhythmias, or cessation of alcohol use), the management of CHF currently includes both pharmacological and non-pharmacological interventions. Regarding pharmacological therapy, betablockers,[17-19] angiotensin-converting enzyme inhibitors,[20] angiotensin II receptor blockers,[21] and aldosterone blockers[22,23] have all been shown to improve survival in CHF patients. However, the effects of these medications on their exercise capacity is less evident.[24-27] This has led to an emerging interest in non-pharmacological adjunct therapies. For example, cardiac resynchronization therapy (CRT) and physical training were shown to be effective in improving the exercise capacity of CHF patients. While the effect of CRT is mainly determined by an improvement of the central hemodynamic response to exercise,[28-30] the effect of

physical training is primarily determined by peripheral alterations, such as improvements in endothelial function[31,32] and the oxidative capacity of skeletal muscles.[33,34] Therefore, combining these treatment modalities could be particularly beneficial for CHF patients.[35] Currently, however, the application of CRT is limited to severely impaired CHF patients (New York Heart Association class III - IV) with ventricular dyssynchrony.[36] Furthermore, despite technological improvements, about 20 - 30% of selected CHF patients do not benefit from CRT.[37-39] Physical training has the advantage of being applicable to a wider population, but there is a considerable range in training responses among CHF patients, with reported numbers of non-responders exceeding 50%.[40] Unfortunately, previous studies failed to demonstrate a relation between training responses and clinical patient characteristics.[41-43] Therefore, additional research is needed to identify predictors of the effects of this treatment modality in CHF patients.

Exercise testing

One of the cardinal manifestations of CHF is a reduction in exercise capacity. Because resting indices of cardiac function[44,45] and the level of perceived exercise intolerance[46,47] correlate poorly with the exercise performance of these patients, exercise testing has become indispensable in the evaluation and monitoring of heart failure.

Traditionally, maximal oxygen uptake ($\dot{V}O_2$max) is considered the "gold standard" measure of aerobic fitness. In healthy individuals, $\dot{V}O_2$max is usually defined as the point at which $\dot{V}O_2$ reaches a plateau despite a further increase in work rate during a symptom-limited exercise test. However, in CHF patients such a plateau in $\dot{V}O_2$ is rarely seen, suggesting that most of these patients do not attain a maximal exercise level during symptom-limited exercise testing. Therefore, the highest attainable $\dot{V}O_2$ in CHF patients is referred to as peak $\dot{V}O_2$, rather than $\dot{V}O_2$max. It has been demonstrated that peak $\dot{V}O_2$ is a reliable indicator of the severity of heart failure[48] and a strong predictor of the prognosis in these patients.[49-52] For the assessment of exercise performance in CHF patients, however, the use of peak $\dot{V}O_2$ has several limitations. First, the reliability of the assessment of this exercise parameter is hampered by the influence of the patients' motivation,[53] the presence / absence of encouragement,[54] and the criteria used to terminate the test. Second, as daily life mainly consists of repetitive submaximal activities, the maximal exercise capacity may not reflect the functional capacity of these patients very well. This may explain the relatively low sensitivity of peak $\dot{V}O_2$ for evaluating the efficacy of therapeutic interventions in heart failure.[55,56] Therefore, there is a growing interest in submaximal exercise parameters to monitor changes in the functional capacity of CHF patients.

Frequently used submaximal exercise parameters are $\dot{V}O_2$ at the ventilatory threshold (VT) and the 6-min walking distance. The main limitation of the former is

that it cannot be detected in a substantial number of CHF patients due to ventilatory irregularities.[57] The value is also dependent on the exercise protocol used, making it difficult to compare figures from different centres.[58] In contrast, the 6-min walk test is well tolerated and easy to perform in CHF patients, but the outcome is substantially influenced by motivation and encouragement.[59] More importantly, the usefulness of the 6-min walking distance to assess changes in functional capacity is limited by a significant learning effect.[60] Other submaximal exercise variables that have been used to assess the functional capacity in CHF patients include the ventilatory response to incremental exercise, expressed as the $\dot{V}_E$ / $\dot{V}CO_2$ slope or the oxygen uptake efficiency slope (OUES), and oxygen (O_2) uptake kinetics during and after constant-load exercise with an intensity below the VT. Both $\dot{V}_E$ / $\dot{V}CO_2$ slope[41,61] and OUES[62,63] have been shown to be sensitive to the effects of physical training in CHF patients. However, as the assessment of these parameters requires exercise exceeding the anaerobic threshold, they should be considered more as parameters of maximal effort. Oxygen uptake kinetics during and after constant-load exercise below the VT represent a true measure of submaximal exercise capacity, but its clinical usefulness in CHF patients is not well established.

Oxygen uptake kinetics

Oxygen uptake kinetics describe the rate of change in $\dot{V}O_2$ during or after exercise (O_2 onset and recovery kinetics, respectively). According to Fick's law, $\dot{V}O_2$ is determined by cardiac output ($\dot{Q}$) and systemic O_2 extraction, which in turn is determined by arterial O_2 content and O_2 utilization in the metabolizing tissues. Therefore, O_2 onset and recovery kinetics can be considered to reflect the interaction of the cardiovascular, pulmonary, and metabolic systems during and after exercise.

Assessment of O_2 uptake kinetics

Symptom-limited exercise

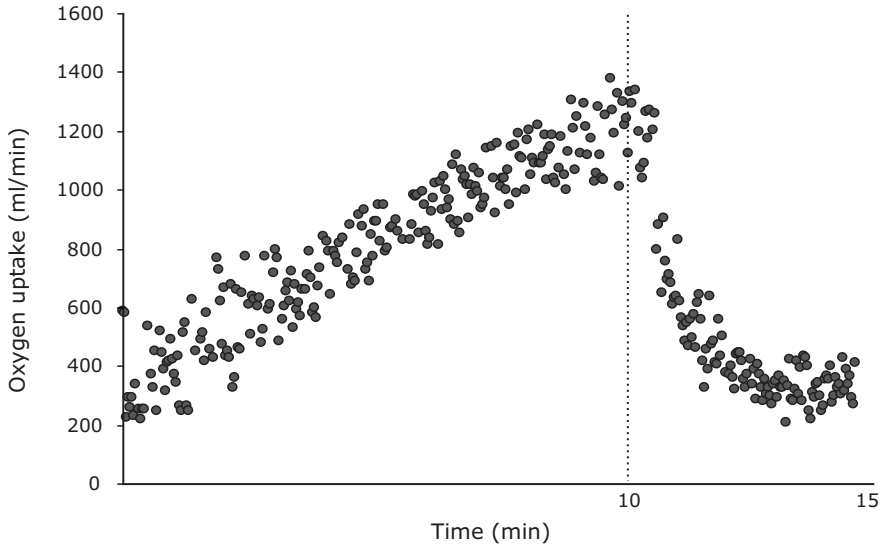
O_2 onset kinetics

Figure 1 shows an example of the time course of $\dot{V}O_2$ during and after a symptom-limited exercise test in a patient with CHF. During such a test, the increase in $\dot{V}O_2$ is linear until the VT is attained. The slope of the increase below the VT is mainly determined by the exercise protocol applied and is therefore of limited clinical value. The ratio between the increase in $\dot{V}O_2$ and the increase in workload ($\Delta\dot{V}O_2$ / ΔWR) has been shown to be reduced in severe heart failure.[64] This parameter is not addressed further in this thesis.

O_2 recovery kinetics

O_2 recovery kinetics following symptom-limited exercise are best described by a double exponential function.[65] However, as shown by Cohen-Solal et al. in a study with CHF patients,[66] the time required for a 50% fall in peak $\dot{V}O_2$ ($T½$-$\dot{V}O_2$) yields

Figure 1.



Time course of $\dot{V}O_2$ during and after a symptom-limited exercise test in a patient with chronic heart failure (New York Heart Assocation Class II). The dashed vertical line indicates the end of exercise.

information similar to exponential modelling and has an acceptable reproducibility. Given the fact that this method is easier to perform than complex multi-exponential modelling, T½-$\dot{V}O_2$ may be more suitable in clinical practice.

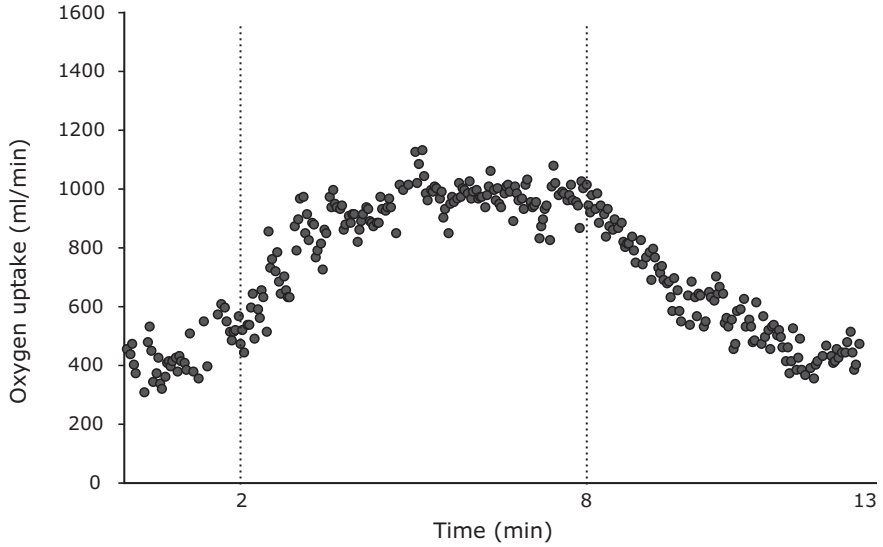
Submaximal constant-load exercise

Figure 2 shows an example of the time course of $\dot{V}O_2$ during and after constant-load exercise below the VT.

O_2 onset kinetics

Classically, O_2 onset kinetics during submaximal constant-load exercise are considered to consist of 3 phases. Phase I, or the cardiodynamic phase, reflects a fast increase in $\dot{V}O_2$ of approximately 15-20 sec as a consequence of an abrupt increase in pulmonary blood flow. Phase II reflects a mono-exponential increase in $\dot{V}O_2$, caused by an increase in cellular respiration at the skeletal muscle level. Phase III reflects a "steady state" situation when exercise is performed below the VT, or a slow linear $\dot{V}O_2$ increase with exercise above the VT.[67] Mathematically, O_2 onset kinetics during exercise below the VT in healthy individuals are well described by a simple mono-exponential model, provided that the cardiodynamic phase (i.e. the first 15 - 20 sec of the data) is omitted from the data.[65] This model has several limitations when applied to CHF patients, however. First, as a consequence of a

Figure 2.



Time course of $\dot{V}O_2$ during and after a constant-load exercise test of 6 min at 50% of the maximal workload with a recovery period of 5 min in a patient with chronic heart failure (New York Heart Assocation Class II). The first dashed vertical line indicates onset of exercise and the second vertical line the end of exercise.

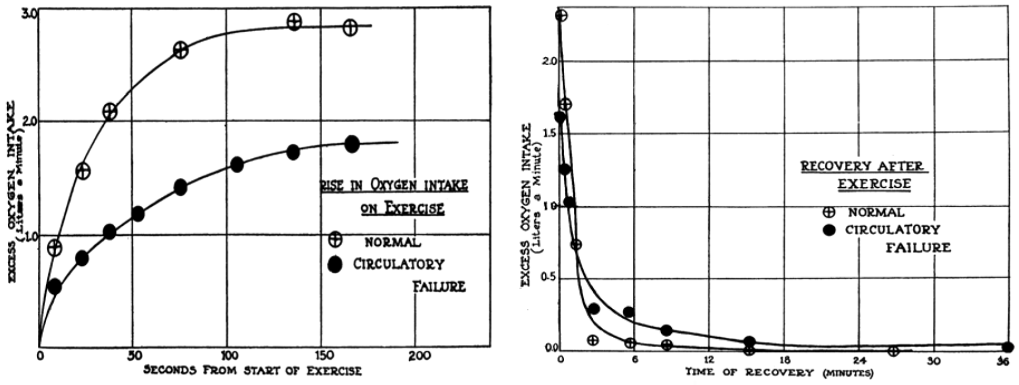
reduced ventilatory threshold, the exercise-related increase in $\dot{V}O_2$ is lower in CHF patients than in healthy subjects, and omitting phase I from the data leads to an even greater reduction of the $\dot{V}O_2$-amplitude. As pointed out by Lamarra et al., a relative low $\dot{V}O_2$-amplitude results in a low accuracy of mono-exponential modelling of O_2 onset kinetics, due to a relative low signal-to-noise ratio.[68] Second, the reliability of this method may be compromised by the typical ventilatory oscillations in CHF patients.[69] Therefore, O_2 onset kinetics have also been assessed by an algebraic method in CHF patients. This method involves calculating the cumulative sum of O_2 consumption in excess of baseline O_2 consumption (ΣVO_2). Subsequently, the O_2 deficit is calculated by subtracting this cumulative sum of O_2 consumption from the theoretical O_2 demand. The mean response time is calculated by dividing the O_2 deficit by the $\dot{V}O_2$-amplitude.[70,71] In the literature, the reliability of this method in CHF patients has not been compared with mono-exponential modelling.

<u>O_2 recovery kinetics</u>

O_2 recovery kinetics after submaximal exercise are generally considered to follow a mono-exponential course in both healthy subjects[65,72-74] and CHF patients.[75-77] A potential advantage of using O_2 recovery kinetics rather than O_2 onset kinetics to evaluate exercise performance is the fact that the $\dot{V}O_2$-amplitude that can be used for analysis is higher, due to a lesser influence of a cardiodynamic phase. In addition,

there may be a more stable breathing pattern and fewer motion artifacts during recovery from exercise.

Figure 3.



O_2 onset (left panel) and O_2 recovery kinetics (right panel) in a healthy subject and a patient with circulatory failure (adapted from Meakins et al.[78])

Clinical applications of O_2 uptake kinetics

In 1927 Meakins et al.[78] observed slower O_2 onset and recovery kinetics in a patient with circulatory failure as compared with a healthy subject (Figure 3). It was not until the 1990s that O_2 uptake kinetics were further evaluated as a potential instrument for objectively assessing the functional capacity of CHF patients. Most of these studies clearly demonstrated that O_2 onset kinetics during constant-load exercise below the VT are delayed in CHF patients, with slower O_2 uptake kinetics being associated with more fatigue due to a greater reliance on the anaerobic metabolism.[70,71,76,79-83] Although less attention has been paid to exercise recovery, several studies showed that O_2 recovery kinetics after submaximal[71,75-77] and maximal exercise[66,84,85] are prolonged in CHF patients, with the degree of the delay correlating with the functional impairment in these patients. Whether O_2 uptake kinetics are sensitive to the effects of therapeutic interventions in CHF patients is less well established. So far, preliminary studies with small sample sizes showed promising results for the application of O_2 onset kinetics to evaluate the effects of therapies in CHF patients such as beta-blocking agents,[86] physical training,[87] and heart transplantation.[88] In contrast, O_2 recovery kinetics following symptom-limited exercise proved not to be useful to measure the effects of high-intensity training in CHF patients.[89] To our knowledge, no studies have evaluated the clinical utility of O_2 recovery kinetics after submaximal exercise to assess the effect of therapeutic interventions in CHF patients.

In addition to grading functional impairments, O_2 uptake kinetics may also be used for risk stratification in CHF. Both O_2 onset kinetics during exercise below the VT[90,91] and O_2 recovery kinetics following symptom-limited exercise[92,93] were shown to be independent predictors of mortality in CHF. The prognostic value of O_2 onset kinetics may even be superior to peak $\dot{V}O_2$.[91] However, studies with large numbers of patients are needed to confirm this finding. The prognostic value of O_2 recovery kinetics after submaximal exercise has not yet been evaluated.

In all of the above-mentioned studies, standardization is lacking because different exercise protocols and calculation methods were used to assess O_2 uptake kinetics in CHF patients. Therefore, before using O_2 uptake kinetics in clinical practice, it is of crucial importance to establish uniform assessment methods. To achieve this, more data are needed on the accuracy of the modelling techniques currently being used in CHF patients, and the reproducibility of the various kinetic parameters should be assessed and compared. Furthermore, kinetic parameters should be investigated to discover which is best suited to serve various clinical purposes, such as assessment of prognosis or quantifying or predicting effects of therapeutic strategies (e.g. medications, physical training, CRT).

Physiological background of O_2 uptake kinetics

As mentioned before, O_2 uptake kinetics provide objective information on the ability of CHF patients to perform daily activities. Therefore, more knowledge of the physiological determinants of O_2 uptake kinetics may lead to a better understanding of the pathophysiological mechanisms causing functional impairments in these patients. This may eventually aid in the development of therapeutic approaches to improve the exercise capacity in CHF patients. Assessment of the physiological determinants of O_2 uptake kinetics may also be used to classify CHF patients better, allowing for a more appropriate treatment selection. For example, patients who are mainly limited by peripheral derangements may benefit from physical training,[40] while patients with more pronounced circulatory dysfunction during exercise may be better candidates for treatment to improve the central hemodynamics, such as CRT[94] or heart transplantation.[95]

Changes in $\dot{V}O_2$ during or after exercise are determined by tissue oxygenation (O_2 delivery) and the speed at which O_2 can be used for oxidative metabolism (O_2 utilization). O_2 delivery depends on O_2 transport and diffusion in the lungs, O_2 content of the blood, cardiac function, peripheral vasoconstriction, local vasodilatory capacity, capillary density, and diffusion of O_2 from the blood to the tissues. O_2 utilization is determined by the number of mitochondria, which is influenced by muscle fiber type distribution in skeletal muscles, and mitochondrial enzyme activity. Several mechanisms contribute to a reduction in O_2 delivery in CHF: cardiac insufficiency, elevated vasoconstriction due to increased sympathetic activity,[96] elevated plasma angiotensin[2] and endothelin levels[3], impaired nitric oxide-mediated vasodilatation,[5,97] and a blunted redistribution of blood flow from the non-exercising

tissues to the working skeletal muscles.[98] O_2 utilization may be limited by mitochondrial dysfunction and / or a reduction in the number of mitochondria due to muscle atrophy or a shift in muscle fiber type distribution to type II fibers.[99,100]

O_2 onset kinetics

Whereas impairments in both O_2 delivery and O_2 utilization may be present in CHF, the relative contribution of these factors to the delay in O_2 onset kinetics is not well established. Animal studies have previously demonstrated a delayed increase in muscle capillary blood flow[101] and a more rapid decrease in muscle microvascular O_2-pressure during submaximal exercise in rats with heart failure,[102] suggesting a limitation of O_2 onset kinetics by O_2 delivery. This notion is supported by human studies showing that the delay in O_2 onset kinetics during submaximal exercise ergometry in CHF patients is associated with a delayed increase in cardiac output.[103,104] Yet, studies evaluating the physiological determinants of O_2 uptake kinetics at a local muscle level showed that abnormalities in muscle metabolism are not associated with a reduced muscle blood flow during submaximal exercise in CHF patients.[105,106] The exercise protocols applied in these studies, however, involved small muscle groups (calf and forearm muscles respectively) and, therefore, the results of these studies may not be representative for exercise performed with larger muscle groups.

O_2 recovery kinetics

Data are even scarcer about the pathophysiological mechanisms underlying the delay in O_2 recovery kinetics in CHF. Rats with CHF showed a slower recovery of microvascular O_2-pressure following submaximal exercise than healthy controls,[107] suggesting that submaximal exercise recovery in CHF is limited by O_2 delivery. In another study with rats, this delayed recovery of microvascular O_2-pressure was shown to be associated with a diminished vascular NO availability, suggesting an important role for endothelial function in the delay of metabolic recovery in CHF. The results from human studies are conflicting. Toussaint et al. showed that a prolonged skeletal muscle metabolic recovery after submaximal exercise was associated with a reduction of reactive hyperemic blood flow and postulated that local circulatory dysfunction is an important contributor to the prolonged metabolic recovery in these patients.[108] Yet, Hanada et al. found that muscle metabolic recovery following submaximal exercise was more delayed than muscle tissue re-oxygenation in CHF patients and concluded that metabolic recovery in these patients is mainly limited by O_2 utilization.[109] In neither study were measurements of muscle metabolism and muscle perfusion / oxygenation performed simultaneously.

In conclusion, more knowledge of the physiological determinants of O_2 uptake kinetics in CHF patients may be useful for the development of treatments and an improved classification of these patients. However, data on this aspect are scarce and

sometimes contradictory. Therefore, more research is needed, preferably by performing measurements on O_2 delivery and O_2 utilization simultaneously. In addition, when performing these measurements at a local muscle level, measurements should be performed in the same muscle area.[110]

Outline of this thesis

This thesis addresses the following central questions:

1) Are O_2 uptake kinetics useful in clinical practice to quantify and predict the effects of physical training in CHF patients?

2) What are the physiological determinants of O_2 uptake kinetics in CHF patients?

Part I deals with the first question (**chapters 2-4**). Previous studies evaluating O_2 uptake kinetics in CHF patients used a variety of methods. For the assessment of O_2 recovery kinetics following symptom-limited exercise, T½-$\dot{V}O_2$ has been shown to be a reliable parameter that is easy to determine. For the evaluation of O_2 onset and recovery kinetics at submaximal exercise, however, the most accurate assessment method is not known. Therefore, in **chapter 2** the accuracy and reproducibility of several previously used calculation methods for the determination of O_2 uptake kinetics are compared. Using the parameters with the highest reproducibility, the utility of O_2 uptake kinetics to measure training effects in CHF patients is subsequently evaluated in **chapter 3**. In addition, this study compares training-related changes in O_2 uptake kinetics with changes in traditionally used variables such as peak $\dot{V}O_2$ and $\dot{V}O_2$ at the VT.

Although many studies have demonstrated favorable effects of physical training on the exercise capacity of CHF patients, it has also been recognized that a substantial number of CHF patients do not or only minimally respond to training. Therefore, it is of clinical interest to be able to predict the training responses. **Chapter 4** evaluates the prediction of training effects on maximal and submaximal exercise capacity in CHF patients. Together with commonly used clinical and physiological patient characteristics, O_2 uptake kinetics are also included as possible predictors of training effects in this study.

The second central question is addressed in Part II of this thesis (**chapters 5-8**). As outlined before, O_2 uptake kinetics are determined by O_2 delivery and O_2 utilization in metabolizing tissues. One approach to estimate the kinetics of O_2 delivery is by measuring cardiac output as an important factor for O_2 delivery. Currently, however, no reliable method for the continuous measurement of cardiac output in CHF patients is clinically available. Therefore, we evaluated the accuracy of 2 continuous cardiac output methods that are novel in their application in CHF patients: a radial arterial pulse contour analysis method (LiDCO) and an impedance cardiography technique (Physioflow) with the continuous Fick method as the gold standard. As the latter method requires continuous assessment of mixed venous oxygen saturation ($S\bar{v}O_2$), we first evaluated the reliability of the fiberoptic pulmonary artery catheter used for this purpose (**chapter 5**). **Chapter 6** evaluates the accuracy of LiDCO and Physioflow to assess absolute cardiac output values during

exercise as well as changes in cardiac output. In **chapter 7** the physiological determinants of O_2 uptake kinetics in CHF patients are examined by simultaneously assessing the kinetics of $\dot{V}O_2$ and cardiac output during onset and recovery from submaximal exercise. We postulate that a faster increase in cardiac output relative to the increase of $\dot{V}O_2$ during exercise onset, and a slower decrease of cardiac output relative to the decrease of $\dot{V}O_2$ during recovery, indicate an excess of blood flow relative to O_2 consumption, and thus a limitation of O_2 utilization rather than O_2 delivery. A difficulty with this approach is that it is not certain whether changes in cardiac output during and after exercise are representative of changes in O_2 delivery to the exercising muscles. Therefore, **chapter 8** addresses the physiological determinants of recovery from submaximal exercise at a local muscle level (i.e., vastus lateralis muscle). In this study, ^{31}P magnetic resonance spectroscopy and near-infrared spectroscopy are applied simultaneously. ^{31}P magnetic resonance spectroscopy assesses the rate of phosphocreatine resynthesis, reflecting muscle metabolic recovery, and near-infrared spectroscopy measures muscle tissue re-oxygenation.

In **chapter 9** the results presented in this thesis are discussed, and directions for future research are proposed.

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Part I

Clinical Aspects

Chapter 2

Reproducibility of onset and recovery oxygen uptake kinetics in moderately impaired patients with chronic heart failure

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Abstract

Background: Oxygen (O_2) uptake kinetics reflect the ability to adapt to or recover from exercise that is indicative of daily life. In patients with chronic heart failure (CHF), parameters of O_2 uptake kinetics have shown to be useful for clinical purposes like grading of functional impairment and assessment of prognosis. This study compared the goodness of fit and reproducibility of previously described methods to assess O_2 uptake kinetics in these patients.
Methods: Nineteen CHF patients, New York Heart Association class II-III, performed two constant-load tests on a cycle ergometer at 50% of the maximum workload. Time constants (τ) of O_2 uptake kinetics during and after exercise (O_2 onset and recovery kinetics, respectively) were calculated by mono-exponential modelling with 4 different sampling intervals (5 and 10 sec, 5 and 8 breaths). The goodness of fit was expressed as the coefficient of determination (R^2). O_2 onset kinetics were also evaluated by the mean response time (MRT).
Results: Considering O_2 onset kinetics, τ showed a significant inverse correlation with peak $\dot{V}O_2$ ($r = -0.88$, using 10 sec sampling intervals). The limits of agreement of both τ and MRT, however, were not clinically acceptable. O_2 recovery kinetics yielded better reproducibility and goodness of fit. Using the most optimal sampling interval (5 breaths), a change of at least 13 sec in τ is needed to exceed normal test-to-test variations.
Conclusion: O_2 recovery kinetics are more reproducible for clinical purposes than O_2 onset kinetics in moderately impaired patients with CHF. It should be recognized that this observation cannot be assumed to be generalizable to more severely impaired CHF patients.

Introduction

Oxygen (O_2) uptake kinetics describe the rate change of oxygen uptake during onset or recovery of exercise (O_2 onset and recovery kinetics, respectively) and reflect changes in cardiac output and tissue oxygen extraction. Compared to healthy individuals, patients with chronic heart failure (CHF) have slower O_2 onset and recovery kinetics, resulting in early fatigue and slow recovery after exertion due to a greater reliance on anaerobic metabolism.[1,2] Although peak oxygen uptake (peak $\dot{V}O_2$) is widely accepted as a reliable indicator of maximal aerobic capacity in CHF patients,[3,4] O_2 uptake kinetics provide additional objective information on the ability to adapt to and recover from exercise that is indicative of daily life.[2,5] Furthermore, O_2 uptake kinetics are potentially useful for risk stratification of CHF patients[6,7] and for measuring the effects of physical training, which has already been demonstrated in healthy individuals[8] and patients with chronic obstructive pulmonary disease (COPD).[9]

In order to use O_2 uptake kinetics for these clinical purposes it is necessary to know more about the applicability and reproducibility of these exercise parameters in this specific patient group. Until now there has been no uniformity in the assessment of O_2 uptake kinetics in patients with CHF.[10] In addition, the reproducibility of O_2 uptake kinetics at submaximal exercise in CHF patients has not been studied extensively. Two studies that assessed O_2 onset kinetics by different modelling techniques, suggest an acceptable reproducibility of nonlinear regression and an algebraic method.[11,12] In both studies, however, intra-class correlations and limits of agreement were not mentioned.

The purpose of this study was to evaluate the goodness of fit and reproducibility of previously described, clinically applicable methods to characterize O_2 onset and recovery kinetics in moderately impaired patients with CHF. Furthermore, we aimed to define interventional changes that are required to distinguish from the normal test-to-test variations.

Methods

Subjects

Nineteen patients (15 men, 4 women) with stable CHF (New York Heart Association class II-III and echocardiographic ejection fraction $\leq$ 40%) attributed to idiopathic dilated cardiomyopathy (n = 4) or ischemic heart disease due to myocardial infarction (n = 15) were selected at the cardiology outdoor clinic of Máxima Medical Centre (Veldhoven, The Netherlands). Fifteen patients were in NYHA functional class II and 4 in class III. Subject characteristics are listed in Table 1. Patients with recent myocardial infarction (< 3 months), angina pectoris at rest, atrial fibrillation, or atrial flutter were not included. All patients performed a

pulmonary function test using a spirometer (Masterlab, Jaeger, Würzburg, Germany) including measurement of forced expiratory volume in one sec (FEV_1) and forced vital capacity (FVC) during a maximal forced expiratory effort. Patients with chronic airways obstruction, defined as FEV_1 / FVC < 60% were excluded.

Fifteen patients used beta-blockers and angiotensin-converting enzyme inhibitors, 3 patients used an angiotensin-converting enzyme inhibitor only, and one patient used a beta-blocker only. Sixteen patients used diuretics. The average duration that patients were using beta-blockers was 34 ± 33 months (range 7 - 112 months) and 32 ± 29 months for ACE inhibitors (range 7 - 118 months). Patients who did not use beta-blockers were not different from the other patients with respect to age, peak $\dot{V}O_2$ or left ventricular ejection fraction.

The research protocol was approved by the local Research Ethics Committee of Máxima Medical Centre, and all patients provided written informed consent.

Table 1. *Characteristics of included patients with CHF (n = 19).*

Variable	Value	Range
Age (years)	62 ± 8	43 - 78
Height (cm)	172 ± 8	155 - 184
Weight (kg)	85 ± 10	54 - 97
Body Mass Index (kg/m^2)	29 ± 4	22 - 37
Fat mass (%) [a]	30 ± 7	20 - 43
Time since diagnosis (months)	20 ± 24	6 - 96
LVEF (%)	33 ± 7	19 - 40

Values are mean ± SD. LVEF = left ventricular ejection fraction.
[a] Fat mass was assessed by skinfold measurements (biceps, triceps, subscapular, and suprailiacal).[13]

Exercise testing

Subjects performed a symptom-limited, incremental exercise test, and on a separate day (at least 3 days later), a constant-load test at 50% of the maximum workload achieved at the first test. This test was repeated at the same time on another day within 2 weeks (mean difference between tests: 6.7 ± 3.9 days). All subjects took their medication at the usual time and were instructed not to perform any extra physical activity on testing days. During the testing period all patients were in sinus rhythm. None of the patients reported changes in symptoms, functional status or medication use. Therefore, they could be considered to be in a stable physical condition during the study period.

All exercise tests were performed in an upright seated position on an electromagnetically braked cycle ergometer (Corival, Lode, Groningen, The Netherlands). Measurements of $\dot{V}_E$, $\dot{V}O_2$ and carbon dioxide elimination ($\dot{V}CO_2$) were obtained breath by breath (Oxycon-α, Jaeger, Germany). Volumes and gas analysers were calibrated before each test.

The symptom-limited exercise test was performed using an individualized ramp protocol with a total test duration of 8 - 12 min.[14] During the tests all patients were instructed to maintain a pedaling frequency of 70/min. A 12-lead electrocardiogram was registered continuously, and blood pressure was measured every two min (Korotkoff sounds). The test was ended when the patient was not able to maintain the required pedaling frequency. Maximal workload was defined as the final registered workload, peak $\dot{V}O_2$ as the average $\dot{V}O_2$ of the last 30 sec of the test. Predicted value of peak $\dot{V}O_2$ was calculated with use of the Wasserman equation, normalizing peak $\dot{V}O_2$ for age, gender, weight and height.[15]

The ventilatory threshold was determined by two independent observers using the V-slope method as described by Beaver et al.[16] The constant-load tests included 2 min of rest, 2 min of unloaded pedaling, 6 min at 50% of the maximum workload and 5 min of rest.

Data analysis

Mono-exponential model

Time constants (τ) were calculated by fitting the $\dot{V}O_2$ data of the constant-load tests to a first-order (mono-exponential) model using the non-linear least squares method.[17] Calculations were performed with breath-by-breath data averaged into 4 different sampling intervals that were used in previous studies: 5 sec,[18] 10 sec,[9] 5 breaths[2] and 8 breaths.[20] The following equations were used:

Onset kinetics: $\dot{V}O_{2\,(t)} = \dot{V}O_{2\,baseline} + A * (1 - e^{-(t - Td)/\tau})$

Recovery kinetics: $\dot{V}O_{2\,(t)} = \dot{V}O_{2\,steady\,state} - B * (1 - e^{-(t - Td)/\tau})$

with A = $\dot{V}O_2$-amplitude during exercise onset (ml/min), B = $\dot{V}O_2$-amplitude during exercise recovery (ml/min), Td = time delay (sec) and τ = time constant (sec), $\dot{V}O_{2\,baseline}$ = average $\dot{V}O_2$ of the last min of the unloaded-cycling stage (ml/min) and $\dot{V}O_{2\,steady\,state}$ = average $\dot{V}O_2$ of the last min of exercise (ml/min)

The time delay (Td) is a parameter allowed to vary in order to optimize the fit, representing the time between onset of exercise and the start of the mono-exponential increase of $\dot{V}O_2$ (or the time between the end of exercise and the mono-exponential decrease of $\dot{V}O_2$). One of the determinants of this time delay during exercise onset is the lag time between the computer signal to deliver the work rate and the actual response of the ergometer, which amounted to 2.2 ± 0.6 sec in this study. Occasional errant breaths (e.g., due to coughing, swallowing or talking) were deleted from the data set when $\dot{V}O_2$ exceeded three standard deviations of the mean, defined as the average of two following and two preceding sampling intervals.[21] In total, about 1% of the breaths had to be deleted.

Algebraic method

O_2 onset kinetics were also evaluated by an algebraic method calculating the mean response time (MRT).[12] This method involves calculating the cumulative sum of O_2 consumption in excess of baseline O_2 consumption ($\Sigma V O_2$). Subsequently, the O_2 deficit is calculated by subtracting this cumulative sum from the theoretical O_2 demand:

O_2 deficit (ml) = t * $\Delta \dot{V}O_2$ - ΣVO_2

with t = duration of constant-load test (i.e. 6 min), $\Delta \dot{V}O_2$ = $\dot{V}O_{2\ steady\ state}$ - $\dot{V}O_{2\ baseline}$ (ml/min) and ΣVO_2= cumulative sum of O_2 consumption in excess of baseline O_2 consumption (ml)

Mean response time (sec) = O_2 deficit/$\Delta \dot{V}O_2$

Statistical analysis

All data (presented as mean ± SD) were analyzed using a statistical software program (SPSS 11.0). The 'goodness of fit' for mono-exponential modelling was evaluated by the coefficient of determination (R^2). The fitting procedure was considered acceptable when $R^2 \geq 0.85$, as previously described by de Groote et al.[22] Differences between calculation methods were evaluated by one-way ANOVA with repeated measures and Bonferroni post hoc analyses. In order to assess differences between kinetic parameters of the two tests the paired Student's t test was used. Linear regression was used to define correlations between variables. Agreement between the kinetic parameters was assessed by intra-class correlation coefficients, limits of agreement (mean difference ± 1.96 x SD)[23] and coefficients of variation (SD of difference as a percentage of the mean value). Probability values < 0.05 were considered statistically significant.

Results

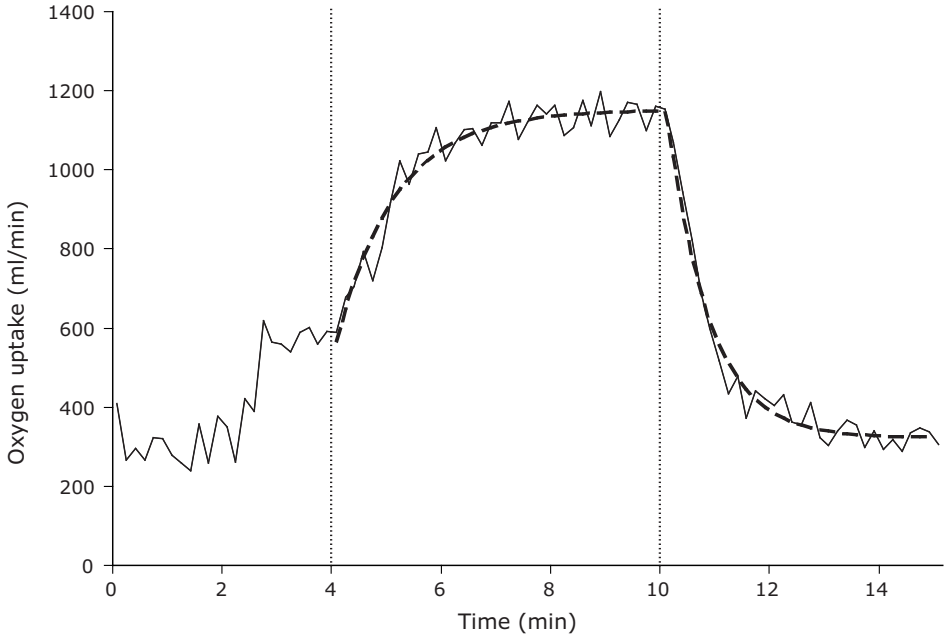
Symptom-limited exercise tests

All subjects completed the exercise tests. The maximum workload was 109 ± 32 Watt, peak $\dot{V}O_2$ was 20.0 ± 4.0 ml/min/kg (73 ± 9% of predicted peak $\dot{V}O_2$) and the maximal respiratory exchange ratio was 1.13 ± 0.13. The ventilatory threshold could not be determined in 3 patients (16%) because of excessive ventilatory oscillations. In the remaining 16 patients the independent observers agreed on the determination of the ventilatory threshold (mean $\dot{V}O_2$: 16.4 ± 3.2 ml/min/kg, 60 ± 11% of predicted peak $\dot{V}O_2$).

Constant-load exercise tests

The mean value of $\dot{V}O_2$ during the second min of unloaded pedaling was 655 ± 78 ml/min (30 ± 5% of predicted peak $\dot{V}O_2$), and the steady-state value at 50% of the maximal work load was 1185 ± 228 ml/min (53 ± 7% of predicted peak $\dot{V}O_2$). Figure 1 shows changes in $\dot{V}O_2$ during a constant-load test in a representative subject.

Figure 1.



$\dot{V}O_2$ response to constant-load exercise at 50 % of the maximal workload (50 Watt) in a representative subject. The solid line represents 10 sec averages of $\dot{V}O_2$. The curved dashed line is the computer-derived representation of the best fit of the mono-exponential model to the $\dot{V}O_2$ response. The first dashed vertical line indicates onset of exercise and the second vertical line the end of exercise.

In 16 subjects, in whom the ventilatory threshold could be determined reliably, steady-state-$\dot{V}O_2$ was below the ventilatory threshold. None of the other 3 subjects demonstrated a significant rise of $\dot{V}O_2$, defined as in increase from the third to the sixth min of exercise of more than 2 times the SD of the mean $\dot{V}O_2$ in the fourth min. This indicates that these 3 patients also exercised below the ventilatory threshold.[24]

Comparison of calculation methods

Concerning the onset phase, there were no significant differences between mono-exponential modelling and the algebraic method (differences between τ and MRT: -6.6 - +1 sec, SD: 11 - 17 sec). In the recovery phase, the use of different sampling intervals yielded significantly different time constants ($p < 0.001$). Paired comparisons showed that in two cases the time constants were not significantly different (5 sec versus 5 breaths, $p = 0.14$ and 10 sec versus 8 breaths, $p = 0.31$).

Table 2. *O_2 uptake kinetics using an algebraic method and a mono-exponential model with different sampling intervals (n = 19).*

Kinetic parameter	Value (sec)	Goodness of fit (R^2)	Useful measurements (%) [a]
Onset kinetics			
MRT	71 ± 19	-	-
τ-5s	67 ± 20	0.69 ± 0.15	26
τ-10s	74 ± 22	0.81 ± 0.12	42
τ-5b	75 ± 30	0.87 ± 0.08	79
τ-8b	74 ± 22	0.91 ± 0.07	84
Recovery kinetics			
τ-5s	60 ± 13	0.89 ± 0.06	84
τ-10s	66 ± 14	0.94 ± 0.04	100
τ-5b	61 ± 13	0.96 ± 0.03	100
τ-8b	64 ± 13	0.98 ± 0.02	100

Values are mean ± SD. MRT = mean response time; τ = time constant calculated with a mono-exponential model; 5s = 5 sec; 10s = 10 sec; 5b = 5 breaths; 8b = 8 breaths. Average duration of 5 breath sampling interval: 15.9 ± 3.6 sec at baseline, 13.0 ± 3.0 sec at steady-state. Average duration of 8 breath sampling interval: 25.0 ± 5.2 sec at baseline, 20.9 ± 4.7 sec at steady state. [a] The assessment of τ was considered useful when $R^2 \geq 0.85$.

When comparing the applicability of the mono-exponential model to the $\dot{V}O_2$-response during onset and recovery of exercise, the results indicate a better 'goodness of fit' during recovery ($p < 0.001$) (Table 2). Parameters of O_2 onset kinetics showed significant correlations with peak $\dot{V}O_2$ when calculating τ with sampling intervals of 10 sec, 5 breaths and 8 breaths (Table 3). However, the differences between these correlation coefficients were not statistically significant. During recovery of exercise τ was only correlated with peak $\dot{V}O_2$ when 5 breath sampling intervals were used.

Table 3. *Correlation coefficients between averaged kinetic parameters and peak $\dot{V}O_2$.*

Kinetic parameter	Correlation with peak $\dot{V}O_2$	95% confidence interval
Onset		
MRT	-0.33	-0.68 - 0.15
τ-5s	-	
τ-10s	-0.88 *	-0.99 - -0.24
τ-5b	-0.67 *	-0.90 - -0.16
τ-8b	-0.57 *	-0.83 - -0.10
Recovery		
τ-5s	-0.43	-0.76 - 0.08
τ-10s	-0.45	-0.75 - 0.01
τ-5b	-0.47 *	-0.76 - -0.02
τ-8b	-0.39	-0.72 - 0.08

MRT = mean response time; τ = time constant calculated with a mono-exponential model; 5s = 5 sec; 10s = 10 sec; 5b = 5 breaths; 8b = 8 breaths. Only data with $R^2 > 0.85$ when using a mono-exponential model were included. * $p < 0.05$

Table 4. *Comparison of kinetic parameters in two consecutive constant-load tests.*

Kinetic parameter	n	Difference between tests (sec)	Limits of agreement (sec)	Coefficient of variation (%)	Intraclass correlation coefficient
Onset					
MRT	19	2.8 ± 12.9	-23 - 29	18.4	0.86
τ-5s	0	-	-	-	-
τ-10s	6	9.3 ± 11.8	-14 - 33	17.1	0.79
τ-5b	12	5.9 ± 19.8	-34 - 46	28.4	0.63
τ-8b	16	5.6 ± 16.7	-28 - 39	23.0	0.77
Recovery					
τ-5s	16	-0.4 ± 7.2	-15 - 14	12.2	0.91
τ-10s	19	-0.9 ± 10.7	-22 - 21	16.3	0.86
τ-5b	19	-0.9 ± 6.4	-14 - 12	10.4	0.94
τ-8b	19	-0.4 ± 8.6	-19 - 16	13.4	0.91
$\dot{V}O_{2\ ss}$ (ml/min/kg)	19	0.1 ± 1.2	-2.3 - 2.5	8.5	0.97

Values are mean ± SD. $\dot{V}O_{2\ ss}$ = oxygen uptake at steady-state exercise; MRT = mean response time; τ = time constant calculated with a mono-exponential model; 5s = 5 sec; 10s = 10 sec; 5b = 5 breaths; 8b = 8 breaths. Only data with $R^2 > 0.85$ when using a mono-exponential model were included.

Reproducibility

In the two constant-load tests there were no statistically significant differences between $\dot{V}O_2$ during unloaded pedaling (655 ± 78 versus 633 ± 98 ml/min), $\dot{V}O_2$ at steady-state exercise (1185 ± 228 versus 1202 ± 235 ml/min), and respiratory exchange ratios at steady-state exercise (0.94 ± 0.04 versus 0.94 ± 0.06). In addition, there were no statistically significant differences between the kinetic parameters of both tests. Considering limits of agreement, coefficients of variation and intra-class correlation coefficients, recovery kinetics show better reproducibility than onset kinetics (Table 4).

Figures 2 shows Bland Altman plots of the kinetic parameters during onset and recovery of exercise with the highest intra-class correlation coefficients.

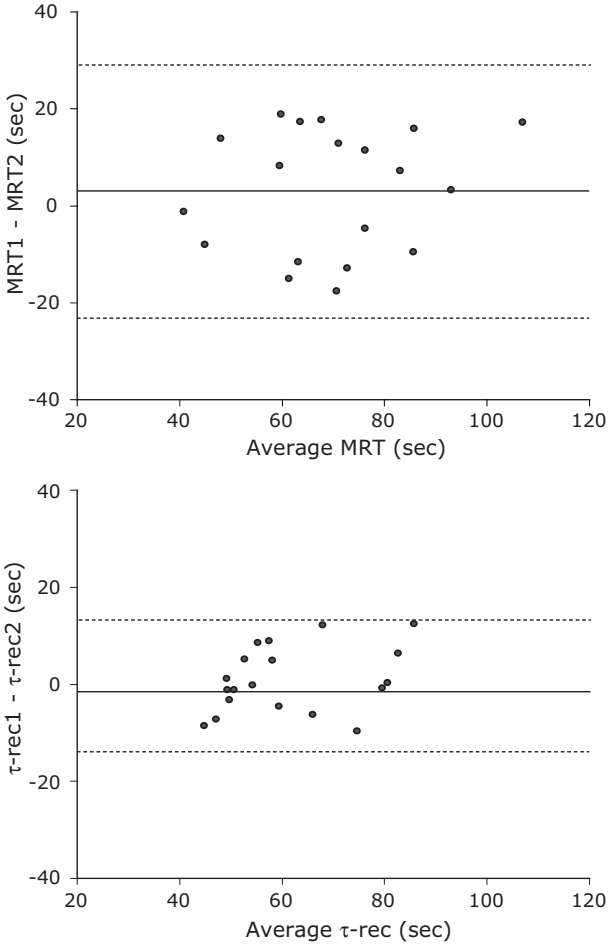
Discussion

The principal finding of this study is that, using the applied exercise protocol, O_2 recovery kinetics were more reproducible than O_2 onset kinetics in moderately impaired patients with CHF. It should be recognized, however, that this observation cannot be assumed to be generalizable to more severely impaired CHF patients.

O_2 onset kinetics

Because of the lack of standardized protocols, previous authors used both time constants (τ, non-linear regression)[2,11,18] and mean response times (MRT, algebraic method)[12] to assess O_2 onset kinetics in CHF patients. Considering non-linear regression, the use of 10 sec sampling intervals yielded the best results in terms of reproducibility in our study. However, the goodness of fit, which was comparable with the study of Arena et al.[19] (0.81 versus 0.78, respectively), was insufficient in 58% of the patients. Moreover, the wide limits of agreement restrict its use for clinical applications. While the calculation of τ with larger sampling intervals resulted in a better goodness of fit, their reproducibility was even lower. To our knowledge, only one study previously addressed reproducibility of O_2 onset kinetics using mono-exponential modelling in CHF patients. In that study, 5 patients with a peak $\dot{V}O_2$ that was comparable to our study performed 3 constant-load tests at a workload of 50 Watt, starting from unloaded cycling. Although the low mean difference between the tests (2 sec) suggests good reproducibility, the actual variability between the tests was not mentioned, making it impossible to compare these results to our study.[11] In spite of the fact that almost all of the onset procedures showed a significant correlation with peak $\dot{V}O_2$ (Table 3), differences between these correlations were not statistically significant. Therefore, one could not suggest a preferential use of one of the procedures.

Figure 2.



Bland Altman plots showing the difference of O_2 uptake kinetics between two constant-load tests during onset (upper graph) and recovery of exercise (lower graph), using an algebraic method and mono-exponential modelling with 5 breath sampling intervals respectively. The solid lines represent the mean difference between the two tests, the dashed lines indicate the 95% confidence intervals of the difference. MRT = mean response time; τ-rec = time constant of $\dot{V}O_2$ decrease during exercise recovery calculated with 5-breath sampling intervals.

Although showing a slightly higher intra-class correlation coefficient (Table 4), the wide limits of agreement of the MRT also indicate low reproducibility of this parameter. In addition, this parameter did not correlate significantly with peak $\dot{V}O_2$. Sietsema et al.[12] previously addressed reproducibility of the MRT in 18 CHF patients, reporting small mean differences between two tests. Again these results cannot be compared to our study, because intra-class correlations and limits of agreement were not mentioned.

When comparing reproducibility of O_2 onset kinetics in CHF patients with healthy subjects[25] and patients with COPD[26] we found a lower reproducibility of τ (coefficients of variation: 17.1%, 6.2% and 8.7% respectively). There are several physiological and methodological factors that may explain this discrepancy.

One significant physiological factor that may cause the large variability of O_2 onset kinetics in CHF patients is the influence of typical ventilatory oscillations, especially when small sampling intervals are used.[27] Although we did not quantify the effect of oscillations, we did observe ventilatory oscillations more clearly in patients with low coefficients of determination. Furthermore, it is postulated that ventilatory oscillations in patients with CHF increase in the transition from rest to exercise[28] and diminish with increasing exercise.[27] This suggests that these oscillations have a greater influence on O_2 onset kinetics than O_2 recovery kinetics. Based on our study, variations in τ during onset of at least 24 sec are needed to exceed the limits of the 95% confidence interval, whereas a change of only 13 sec in τ during recovery is sufficient to exceed the normal test-to-test variations. This latter variability is also observed during the on-transient response in patients with COPD,[26] which supports our view that the relatively large variability of the on-kinetic parameters was mainly caused by ventilatory oscillations.

Another explanation for the limited reproducibility of O_2 onset kinetics in CHF patients is their low exercise capacity, which reduces the $\dot{V}O_2$-amplitude, and consequently the reliability of the determination of the time constant.[21] Furthermore, the period between the tests (6.7 ± 3.9 days) could be a long enough period of time to induce changes in the cardio circulatory condition of the patients. However, all patients were in a stable clinical or functional condition during the study period.

Considering methodological factors, the fact that all patients started the constant-load test with unloaded pedaling in stead of rest resulted in a relatively low $\dot{V}O_2$-amplitude. This could be a major factor contributing to the relatively low reproducibility of the on-kinetic parameters found in this study. The reasons for the authors, however, to apply this exercise protocol were threefold. First, starting exercise from unloaded pedaling results in a reduction of the duration of the early rapid increase of oxygen uptake, representing an initial increase of pulmonary blood flow (cardiodynamic phase). Since in this phase the change of $\dot{V}O_2$ is functionally distinct from the subsequent mono-exponential increase of $\dot{V}O_2$ (phase II), reducing the relative contribution of this phase might result in a better fit of the mono-exponential model to the data. Second, starting exercise from unloaded cycling might reduce ventilatory oscillations at the onset of exercise because of a reduction in variation of pedaling frequency and upper limb muscle activity. Third, in daily life exercise will be frequently started from an active state. Given the results of this study, however, the authors feel that additional research is required to re-assess the reproducibility of O_2 onset kinetics using an exercise protocol starting from rest in stead of unloaded cycling. Starting exercise from rest might result in a better reproducibility of O_2 onset kinetics than observed in this study, which may in

particular be of importance for more severely impaired CHF patients than used in this study.

Another factor that may have influenced reproducibility of O_2 onset kinetics is the choice of the workload (i.e. 50% of the maximum workload). The approach to maximize $\dot{V}O_2$-amplitude by relating the workload to the ventilatory threshold (e.g. 90% of ventilatory threshold) was not used in this study, because it was postulated that such a fixed threshold cannot be determined reliably in a substantial number of CHF patients.[29] When looking at the patients of this study in whom determination of this threshold was successful, $\dot{V}O_2$ at steady state amounted to 86% of $\dot{V}O_2$ at the ventilatory threshold, with none of the patients exercising above this threshold. This suggests that the applied constant-load exercise protocol was adequate, because the exercise intensity remained below the ventilatory threshold.

O_2 recovery kinetics

O_2 recovery kinetics were more reproducible in moderately impaired patients with CHF than O_2 onset kinetics. This difference in reproducibility is at least partly explained by the larger $\dot{V}O_2$-amplitude in recovery due to the fact that subjects were not cycling in the recovery phase. From the results of this study it is difficult to conclude to what extent this difference between onset and recovery kinetics is caused by a smaller influence of the cardiodynamic phase during recovery or a more stable breathing pattern during recovery causing less ventilatory oscillations. Nevertheless, these observations are in line with previous studies in healthy individuals, which also reported a better reproducibility of O_2 recovery kinetics than O_2 onset kinetics.[25,30]

In terms of reproducibility, the most optimal method to characterize O_2 recovery kinetics was mono-exponential modelling with sampling intervals of 5 breaths (intra-class correlation: 0.94). Using this method a change of at least 13 sec in τ is needed to exceed the normal test-to-test variations. In addition, this method yielded an excellent goodness of fit (R^2: 0.96 ± 0.03). To our knowledge, other data on the reproducibility of the recovery kinetics after submaximal exercise in CHF patients are not available. Cohen-Solal et al.[31] studied reproducibility of O_2 recovery kinetics after maximal exercise in 10 patients with CHF (NYHA II-III) using a mono-exponential model with sampling intervals of 7 breaths. They found a coefficient of variation comparable to our study with 5 breath sampling intervals (12.3% versus 10.4%, respectively).

Conclusion

This study shows that the reproducibility of O_2 onset kinetics assessed by mono-exponential modelling is too low to warrant their use for measuring effects of therapeutic interventions in moderately impaired patients with CHF. This might be mainly attributable to physiological factors like ventilatory oscillations and the applied exercise protocol. Future studies should address the effect of different exercise protocols.

The determination of time constants of O_2 recovery kinetics has been shown to be feasible and reproducible when using mono-exponential modelling with 5 breath sampling intervals. Since this variable represents recovery from exercise that is indicative of daily life, it is potentially useful for clinical purposes like grading of functional impairment in patients with CHF and measuring effects of therapeutic interventions.

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Chapter 3

Physical training accelerates post-exercise oxygen uptake kinetics in patients with chronic heart failure

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Submitted

Abstract

Background: Oxygen (O_2) uptake kinetics correlate well with the functional capacity of chronic heart failure (CHF) patients. The present study evaluated the clinical usefulness of O_2 uptake kinetics to assess training effects in CHF patients.
Methods: In a prospective semi-crossover design, 32 CHF patients (NYHA class II / III) were randomized to an intervention group (n = 16), that performed a 12-week training program (cycle interval and resistance training), or to a control group (n = 16) that started this program after a 12-week control period. Training effects were expressed as changes in peak workload, peak $\dot{V}O_2$, $\dot{V}O_2$ at the ventilatory threshold (VT), and O_2 onset and recovery kinetics at submaximal and maximal cycle ergometry.
Results: During symptom-limited exercise, peak workload, peak $\dot{V}O_2$, and $\dot{V}O_2$ at the VT were increased significantly after training. Only $\dot{V}O_2$ at the VT showed a significant training-related between-group change (and training-related within-group change for the control group) ($p \leq 0.05$). Concerning O_2 uptake kinetics, both the time constant of $\dot{V}O_2$ recovery after submaximal exercise (τ-rec) and the recovery half-time of peak $\dot{V}O_2$ decreased after training. However, only τ-rec showed consistently training-related between-group changes ($p \leq 0.005$). In contrast to the assessment of the VT (percentage of failure: 13%), assessment of τ-rec was successful in all patients.
Conclusion: Training effects in CHF patients were manifested consistently at a submaximal exercise level in improvements of τ-rec and $\dot{V}O_2$ at the VT. Since τ-rec could be better assessed, this parameter can be recommended in clinical practice for evaluation of training effects in CHF patients.

Introduction

Physical training has been shown to improve exercise performance and quality of life in patients with chronic heart failure (CHF).[1,2] These beneficial effects are determined by multiple factors, such as improvements in skeletal muscle function, endothelial function, autonomic balance, ventilatory function and left ventricular diastolic filling.[3] Traditionally, the effects of physical training are evaluated by measuring the peak $\dot{V}O_2$ at the end of a symptom-limited incremental exercise test or the $\dot{V}O_2$ at the ventilatory threshold (VT) during treadmill or cycle ergometry.

Since normal daily life of CHF patients is characterized mainly by submaximal activities, changes in variables measured at maximal exercise may not be representative for changes in daily physical activity. Moreover, the outcome of maximal exercise tests can be influenced by the patient's motivation, the presence of encouragement[4] and the criteria used by the physician to terminate the exercise test. Therefore, submaximal exercise parameters may be more representative and even more sensitive to detect changes in functional capacity in CHF patients than peak $\dot{V}O_2$.[5] As such, the $\dot{V}O_2$ at the VT has the advantage of being an objective parameter not requiring maximal exercise. However, it's clinical use is hampered because ventilatory oscillations in these patients interfere with a reliable determination.[6]

The rate of change of $\dot{V}O_2$ during or after exercise (O_2 onset and recovery kinetics, respectively) reflects the ability to adapt to and recover from exercise. This rate is determined by changes in cardiac output and tissue oxygen extraction. It is well established that both O_2 onset kinetics during and O_2 recovery kinetics after constant-load exercise[7,8] as well as O_2 recovery kinetics after maximal exercise[9] are delayed in patients with CHF. This delay correlates well with the functional capacity of these patients.[10,11] Studies in healthy subjects have shown that O_2 onset[12,13] and recovery kinetics[14,15] are useful markers for measuring training effects. However, it is not ascertained whether this also applies to CHF patients. For example, Myers et al.[16] reported that high-intensity training in CHF patients did not result in faster O_2 recovery kinetics following maximal exercise, whereas recently Roditis et al.[17] reported that in CHF patients the O_2 onset kinetics were improved by a continuous cycle training, but not by an interval training program. Neither study assessed changes in O_2 recovery kinetics after submaximal exercise.

The objectives of this study were to assess the effects of physical training on the functional capacity of CHF patients, and to examine the clinical usefulness of O_2 onset and O_2 recovery kinetics as training effect parameters.

Methods

Study protocol

This study was designed as a prospective randomized semi-crossover trial. All patients signed a written informed consent form for participation in this study, which was approved by the local Research Ethics Committee. Patients were randomized into two groups: an intervention group that performed a 12-week physical training program and a control group that maintained their normal daily life style in the first 12 weeks and started the 12-week training program thereafter. In both groups, measurements were performed at baseline and after 12 weeks. In the original control group, measurements were also performed after 24 weeks (i.e., after 12 weeks of training).

Subjects

Thirty nine patients with CHF, referred for physical training by their cardiologist, were recruited. In- and exclusion criteria are described in Chapter 2.

No significant differences in baseline characteristics were observed between the intervention and control group (Table 1). During the study period all patients continued to use their medication.

Table 1. *Clinical characteristics of patient groups and dropouts.*

Variable	Intervention Group (n = 16)	Control Group (n = 16)	Dropouts (n = 7)
Male / female (n)	13 / 3	11 / 5	5 / 2
Age (years)	64 ± 8	61 ± 11	63 ± 16
Height (cm)	174 ± 6	173 ± 11	169 ± 7
Weight (kg)	81 ± 9	81 ± 15	78 ± 15
Body Mass Index (kg/m^2)	27 ± 3	27 ± 4	27 ± 4
LVEF (%)	31 ± 5	33 ± 5	32 ± 6
NYHA class II / III (n)	12 / 4	11 / 5	4 / 3
Etiology: ICM / DCM (n)	11 / 5	11 / 5	6 / 1
Medication (n)			
Diuretics	14	13	7
ACE inhibitors / ARBs	15	16	6
Beta-blockers	16	14	6
Digoxin	2	1	2
Amiodarone	0	0	1
Oral anticoagulation	9	8	5

Values are mean ± SD or n. LVEF = left ventricular ejection fraction; NYHA = NewYork Heart Association; ICM = ischemic cardiomyopathy; DCM = dilated cardiomyopathy; ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker.

Exercise testing

All patients performed 2 types of exercise tests. The first was a symptom-limited exercise test in an upright seated position on an electromagnetically braked cycle ergometer (Corival, Lode, Groningen, The Netherlands). The second, which occurred on a separate day in the same week, was a constant-load test at 50% of the peak workload achieved at the first test. On these days, patients were instructed to take their medication at the usual time and not to perform any extra physical activity. In both tests ventilatory parameters were measured breath-by-breath (Oxycon-α, Jaeger, Hoechberg, Germany). Volumes and gas analyzers were calibrated before each test.

The incremental exercise test was performed using an individualized ramp protocol with a total test duration of 8 - 12 min.[18] During the tests all patients were instructed to maintain a pedaling frequency of 70/min. A 12-lead electrocardiogram was registered continuously, and blood pressure was measured every two min (Korotkoff sounds). The test was ended when the patient was not able to maintain the required pedaling frequency. Peak workload was defined as the final registered workload and peak $\dot{V}O_2$ as the average $\dot{V}O_2$ of the last 30 sec of the test. The $\dot{V}O_2$ at the ventilatory threshold (VT) was determined by the V-slope method,[19] using the average value obtained by two independent observers.

The constant-load test included 2 min of rest, 2 min of unloaded pedaling, 6 min at 50% of the maximum workload, and 5 min of rest.

O_2 uptake kinetics

No accepted reliable methods are currently available to characterize O_2 onset kinetics during an incremental exercise test. Therefore, we only assessed O_2 recovery kinetics after the symptom-limited test. Because the decrease of $\dot{V}O_2$ after maximal exercise is not always correctly described by a mono-exponential model, we used the recovery half-time of $\dot{V}O_2$ (T½-$\dot{V}O_2$), defined as the time required for a 50% fall from peak $\dot{V}O_2$. Recovery half-time been shown to be reproducible in patients with CHF (coefficient of variation: 5.9%).[20]

The methods used for characterizing O_2 uptake kinetics at constant-load exercise in this study were based on a previous study investigating the feasibility and reproducibility of different methods to assess O_2 uptake kinetics in CHF patients.[21] This study showed that O_2 onset kinetics cannot be reliably assessed by mono-exponential modelling in a substantial number of patients. Therefore, we used an algebraic method, as previously described by Sietsema et al.[22] In brief, the cumulative sum of O_2 consumption in excess of baseline O_2 consumption was calculated by using breath by breath data. Subsequently the O_2 deficit was calculated by subtracting this cumulative sum from the theoretical O_2 demand, which was defined as the product of the $\dot{V}O_2$-amplitude and the duration of the exercise test. The mean response time (MRT) was calculated by dividing O_2 deficit to $\dot{V}O_2$-amplitude. The equations that were used are shown in Chapter 2.

Oxygen recovery kinetics after constant-load exercise were assessed by using a mono-exponential model. Occasional errant breaths (eg, due to coughing, swallowing or talking) were deleted from the data set when $\dot{V}O_2$ exceeded three standard deviations of the local mean, defined as the average of two following and two preceding breaths.[23] The time constant (τ-rec) was calculated by fitting the $\dot{V}O_2$ data, after having been averaged into 5 breaths sampling intervals, to a first-order (mono-exponential) model using the non-linear least squares method. The equation that was used to calculate τ-rec is shown in Chapter 2.

Training protocol

The 12-week training program was based on the recommendations of the Working Group on Cardiac Rehabilitation & Exercise Physiology and Working Group on Heart Failure of the European Society of Cardiology,[3] and consisted of cycle interval, resistance and inspiratory muscle training (three 1-hour sessions per week). All training sessions took place at the Department of Physical Therapy under supervision of a physical therapist and commenced with cycling training on an electromagnetically braked cycle ergometer with a warm up phase of 5 min, followed by 15 min of interval training with work phases of 30 sec and recovery phases of 60 sec (10 work phases). The intensity of the work phases was 50% of the maximum short-term exercise capacity (MSEC), which was assessed by a steep ramp test (increase of work rate by 25 W every 10 sec until exhaustion). The steep ramp test was performed at the start of the program and repeated every 4 weeks to adjust training intensity. After the cycling training patients performed resistance training (leg press, leg curl, biceps curl, triceps extension, calf raise), using 2 sets of 12 repetitions at 70% of the 1-repetition maximum, which was determined at the start of the program and subsequently every 4 weeks. In addition, all patients were instructed to perform resistive inspiratory muscle training at home, using the Threshold inspiratory muscle trainer (Healthscan, New Jersey, NJ, USA) 5 times per week during 30 min at 30% of their maximum inspiratory pressure.[3]

Daily physical activity

To assess changes in daily physical activity (DPA) a modified Baecke questionnaire was used. This questionnaire, consisting of scores in household activities, sports activities and other leisure time activities, has been validated for the Dutch elderly population.[24] Training hours were not included in the DPA score. Higher scores correspond to higher activity levels. The questionnaire was administered at baseline and at 12 weeks in both groups and repeated at 24 weeks in the control group.

Statistical analysis

All data (presented as mean ± SD) were analyzed using SPSS 12.0 statistical software (SPSS Inc, Chicago, IL, USA). Between-group differences of continuous variables were assessed by the Mann-Whitney U test or by Kruskal-Wallis test (for

multiple independent group comparisons), and the χ^2 test was used to evaluate differences between categorical data. The Wilcoxon signed rank test was used to analyze within-group differences. The 'goodness of fit' for mono-exponential modelling of O_2 recovery kinetics was evaluated by the coefficient of determination (R^2). Variables were not included in the analysis if R^2 was less than 0.85.[21] For all statistical comparisons, the level of significance was set at $p < 0.05$.

Results

Subjects

Three patients from the intervention group and 4 patients from the control group did not complete the training program because of different reasons: large time commitment (n = 2), orthopaedic complaints (n = 2), motivational problems (n = 2), and ventricular arrhythmia's at rest (n = 1). They did not differ from the other patients in baseline characteristics (Table 1), but were not further analyzed. The remaining 32 patients attended more than 80% of the training sessions.

Symptom-limited exercise test

Two patients did not perform this test after their training periods: one from the control group and the other from the intervention group because of admission to our hospital (unstable angina pectoris and gastro-intestinal bleeding, respectively). The VT could not be determined in 4 patients (13%): 3 patients from the intervention group and 1 patient in the control group.

Exercise data at baseline and after 12 weeks are presented in Table 2. Focussing on physiologic variables, there were no significant differences in these variables at baseline between the control group and the intervention group, with the exception of heart rate at maximal exercise (Table 2). In spite of latter finding, no difference in exercise effort could be observed, as the maximal respiratory exchange ratio (RER) was not significantly different at baseline between the intervention and the control group (1.07 ± 0.07 versus 1.12 ± 0.08, respectively). Whereas there was no significant increase in peak $\dot{V}O_2$ in the intervention group ($p = 0.06$), the peak workload and $\dot{V}O_2$ at the VT improved significantly (Table 2). The control group did not show any significant changes in exercise parameters after the 12-week control period. For between-group differences, only $\dot{V}O_2$ at the VT increased significantly in the intervention group.

When comparing changes during the control period with changes in the training period for the control group, the $\dot{V}O_2$ at the VT was also the only physiologic variable that showed a significant improvement during symptom-limited exercise (Table 3). Combined pre- and post-training data from the intervention and the control group are presented in Table 4, showing significant increases in peak-$\dot{V}O_2$, peak workload and $\dot{V}O_2$ at the VT during symptom-limited exercise.

Table 2. *Physiologic and kinetic variables in the intervention (n = 16) and control group (n = 16) at baseline and after 12 weeks.*

Variable	Intervention Group		Control Group		p-value between-group difference
	Baseline	12 wks	Baseline	12 wks	
Symptom-limited exercise [a]					
Peak $\dot{V}O_2$ (ml/kg/min)	16.2 ± 3.6	17.4 ± 4.4	18.1 ± 4.0	17.9 ± 2.9	0.14
Peak Workload (W)	94 ± 28	101 ± 32 *	104 ± 35	111 ± 34	0.74
HR (beats/min)	117 ± 23	116 ± 23	138 ± 22 +	132 ± 21	0.52
$\dot{V}O_2$ at the VT(ml/kg/min) [b]	11.8 ± 2.0	13.1 ± 2.6 *	13.3 ± 2.8	12.6 ± 2.1	0.02
T½-$\dot{V}O_2$ (sec)	120 ± 41	115 ± 43	107 ± 42	96 ± 30	0.79
Constant-load exercise					
MRT (sec)	77 ± 29	79 ± 24	78 ± 26	78 ± 23	0.67
τ-rec (sec)	91 ± 36	78 ± 24 *	75 ± 25	80 ± 27	0.005

Values are mean ± SD. HR = maximum heart rate; VT = ventilatory threshold; T½-$\dot{V}O_2$ = half time recovery of $\dot{V}O_2$ after maximal exercise; MRT = mean response time; τ-rec = time constant of recovery of $\dot{V}O_2$. [a] n = 31 (15 patients in intervention group, 16 patients in control group); [b] n = 27 (12 patients in intervention group, 15 patients in control group).
*Significantly different from previous test within-group ($p < 0.05$); +Significantly different from baseline value of intervention group ($p < 0.05$).

Table 3. *Changes of physiologic and kinetic variables in the control group (n = 16) during the control and training periods.*

Variable	Change in control period	Change in training period	p-value between change in control and training period
Symptom-limited exercise [a]			
Peak $\dot{V}O_2$ (ml/kg/min)	-0.2 ± 3.1	2.3 ± 2.8 *	0.06
Peak Workload (W)	7 ± 15	9 ± 10 *	0.55
HR (beats/min)	-6 ± 19	2 ± 12	0.24
$\dot{V}O_2$ at the VT(ml/kg/min) [b]	-0.7 ± 2.2	1.5 ± 2.1	0.048
T½-$\dot{V}O_2$ (sec)	–11 ± 33	-12 ± 18 *	0.96
Constant-load exercise			
MRT (sec)	0 ± 26	1 ± 26	0.68
τ-rec (sec)	5 ± 11	-8 ± 11 *	0.005

Values are mean ± SD. HR = peak heart rate; VT = ventilatory threshold; T½-$\dot{V}O_2$ = half time recovery of O_2 after maximal exercise; MRT = mean response time; τ-rec = time constant of recovery of O_2. [a] n = 15. [b] n = 14. *Significant change ($p < 0.05$).

Table 4. *Post-training changes in physiologic and kinetic variables in all patients (n = 32).*

Variable	Before training	After training	p-value
Symptom-limited exercise [a]			
Peak $\dot{V}O_2$(ml/kg/min)	17.0 ± 3.3	18.8 ± 4.0	0.002
Peak Workload (W)	101 ± 31	109 ± 33	0.001
HR (beats/min)	124 ± 23	125 ± 23	0.49
$\dot{V}O_2$ at the VT(ml/kg/min) [b]	12.3 ± 2.1	13.7 ± 2.7	0.004
T½-$\dot{V}O_2$ (sec)	109 ± 37	101 ± 40	0.02
Constant-load exercise			
MRT (sec)	78 ± 25	79 ± 22	0.55
τ-rec (sec)	85 ± 32	76 ± 27	0.001

Values are mean ± SD. HR = peak heart rate; VT = ventilatory threshold; T½-$\dot{V}O_2$ = half time recovery of $\dot{V}O_2$ after maximal exercise; MRT = mean response time; τ-rec = time constant of recovery of $\dot{V}O_2$. [a] n = 30; [b] n = 26.

Constant-load exercise test

All patient performed the constant-load exercise tests. At baseline, the heart rate during the constant-load exercise test was higher in the control group than in the intervention group (118 ± 16 beats/min vs 99 ± 18 beats/min, p = 0.004). No significant within-group changes in exercising heart rate were observed in either group during the first 12 weeks, nor during the subsequent training period of the control group. In addition, no between-group differences in changes in heart rate were observed.

Oxygen uptake kinetics

There were no significant training-related within- or between-group differences in O_2 recovery kinetics after maximal exercise (T½-$\dot{V}O_2$), nor in O_2 onset kinetics (MRT) in the first 12 weeks. In contrast, the time constant of O_2 recovery kinetics after submaximal exercise (τ-rec) decreased significantly in the intervention group, whereas the control group did not show any significant change (Table 2). This between-group difference was highly significant (p = 0.005). During the training period of the control group, both T½-$\dot{V}O_2$ and τ-rec decreased significantly (Table 3). However, compared to the changes during the control period, only τ-rec showed a significant decrease, which is similar to the post-training findings in the intervention group. Considering post-training changes in both groups together, O_2 recovery kinetics after submaximal as well as maximal exercise improved significantly, without a change in O_2 onset kinetics (Table 4).

The coefficient of determination (R^2) of τ-rec exceeded 0.85 in all cases (mean value: 0.95 ± 0.03), indicating a good fit of the data to the mono-exponential model.

Daily physical activity

After 12 weeks, there were no significant changes in DPA scores in the intervention group (mean baseline score: 24 ± 10 versus 23 ± 11 post-training), and in the control group (mean value:18 ± 9 versus 18 ± 9 after 12 weeks), nor during the subsequent training period of the control group (mean value:18 ± 9 versus 18 ± 7).

Discussion

This study is the first to show that physical training in moderately impaired patients with CHF accelerates O_2 recovery kinetics after submaximal exercise. This observation is in line with previous studies in healthy individuals.[14,15] A number of physiological mechanisms may be responsible for the acceleration of O_2 recovery kinetics: enhanced O_2 utilization in the muscles and / or an improvement of O_2 delivery through changes in local peripheral vasodilatory capacity or cardiac output kinetics. Currently, there are no training studies in CHF patients that have assessed these etiological factors of oxygen flux simultaneously, so it is difficult to say which of the mechanisms is the most important one. Because most daily tasks consist of adaptations to and recovery from submaximal activities, an acceleration of O_2 recovery kinetics may very well be directly related to improvements of the functional capacity of CHF patients. Moreover, the assessment of the time constant of O_2 recovery kinetics is relatively easy to perform and does not require maximal exercise. Therefore, this parameter can be useful in clinical practice for evaluation of training effects in CHF patients

Most studies evaluating the effects of physical training in CHF patients used peak $\dot{V}O_2$ as an outcome measure. The improvements of peak $\dot{V}O_2$ reported in those studies showed a substantial variety with a range of 4 - 31%.[1,2,25-29] In our study, peak $\dot{V}O_2$ did not improve significantly in the intervention group, whereas it did in the control group during the training period after the cross-over. Both groups did not differ in clinical or physiological characteristics, except for heart rate at maximal and constant-load exercise. We do not have an explanation for the lower heart rate in the intervention group, as this cannot be explained by a difference in medication, i.e. the use of beta-blockers (Table 1), or a difference in exercise effort (see Results: symptom-limited test). In addition, there were no significant changes in DPA in both groups. Despite the inconsistency in training responses of both groups, there was a highly significant post-training increase in peak $\dot{V}O_2$ of 11% when the results of both groups were combined ($p = 0.002$). Such an increase is comparable to other studies using an almost similar cycle interval training program (8% in both studies).[17,30] While the post-training improvements of peak $\dot{V}O_2$ and peak workload were not concomitant in both groups, we observed a consistent, highly significant, post-training acceleration of O_2 recovery kinetics after submaximal exercise. These results indicate that, in agreement with other randomized controlled trials,[2,29] the effects of

physical training in CHF patients manifest themselves mainly in improvements of submaximal rather than maximal exercise performance.

Another well accepted method to measure changes in the functional capacity in CHF patients is the assessment of $\dot{V}O_2$ at the VT. There are, however, several drawbacks to the clinical use of this method. First, the VT cannot be determined in a substantial number of CHF patients due to excessive respiratory oscillations. The percentage of failure in our study was 13%, whereas a rate of up to about 25% has been reported in more severely impaired CHF patients.[6] Second, the observed training-induced increases in $\dot{V}O_2$ at the VT in CHF patients are often small[2,27] and insufficient to exceed the normal test-to-test variation that was previously estimated at 3.5 ml/min/kg.[31] This was also the case in our study.

We did not observe a significant training-induced change in O_2 onset kinetics after constant-load exercise. To our knowledge, only one study has previously evaluated the effects of physical training on O_2 onset kinetics in CHF patients.[17] That study used a 12-week interval training protocol that was almost similar to the one we used, only differing in recovery time (30 sec vs 60 sec, respectively). To improve the reliability of the assessment of O_2 onset kinetics, the authors averaged the $\dot{V}O_2$ responses of 3 subsequent constant-load tests.[17] Our results confirm their findings that effects of interval training were not reflected in an acceleration of O_2 onset kinetics in moderately impaired CHF patients. Yet, Roditis et al.[17] observed a faster time constant of onset kinetics after a continuous training program, and argued that this result was obtained because such a program is more effective in increasing skeletal muscle capillarization and / or mitochondrial capacity than interval training, as was previously demonstrated in healthy individuals.[32] However, the fact that we observed a highly significant improvement in O_2 recovery kinetics suggests that the training program that we used, which also included resistance training, did induce an improvement in local O_2 delivery and / or utilization. That this did not result in an acceleration of O_2 onset kinetics cannot be fully explained from our study, but may be related to the relatively low reproducibility of O_2 onset kinetics as compared to O_2 recovery kinetics in CHF patients.[21]

Concerning O_2 recovery kinetics after maximal exercise, we found a small but significant post-training decrease of $T½\text{-}\dot{V}O_2$ after pooling of the data of both groups (Table 4). There were, however, no significant between-group changes for trained versus non-trained conditions. In a previous study, Myers et al.[16] could not demonstrate a significant improvement in $T½\text{-}\dot{V}O_2$ and postulated that the substantial variability in responses, presumably caused by the irregular breathing pattern of these patients, contributed to the impossibility to demonstrate post-training changes in this variable. Furthermore, the relatively low sensitivity of O_2 recovery kinetics after maximal exercise to detect effects of physical training may have a physiological background. In CHF patients, O_2 uptake kinetics after maximal exercise have been shown to be more related to central hemodynamics, such as peak cardiac index and recovery of cardiac output after exercise,[33] than to peripheral

factors. In fact, it has been shown that training-induced changes of the exercise capacity of CHF patients depend mainly on improvements of peripheral derangements rather than improvements of central hemodynamics.[34,35]

Limitations

Before drawing conclusions from this study, there are limitations that must be acknowledged. The small sample size may limit the reliability of the findings. Therefore, our results should be considered preliminary, and future studies with a larger number of patients to confirm our findings will be needed. A strategy to increase the reproducibility of results in cases of a limited sample size is to average responses to multiple exercise tests.[23] We did not use this approach because it is time consuming and, therefore, not suited for clinical practice. Moreover, it is not known whether in a multiple exercise protocol effects of previous exercises influence the O_2 uptake kinetics in CHF patients. Finally, the results of this study are not generalizable to more severely impaired CHF patients or to different training programs.

Conclusions

Despite the limitations of this study, our findings showed that the effects of a combined cycle interval and resistance training program in CHF patients are consistently manifested in improvements of O_2 recovery kinetics after submaximal exercise and the $\dot{V}O_2$ at the VT. Since submaximal exercise is representative of daily physical activities, we postulate that for clinical practice both markers are useful for evaluating effects of physical training in patients with CHF. However, as the time constant of O_2 recovery can be better assessed than the VT in these patients, we recommend the use of the time constant. Future studies in CHF patients should be conducted to unravel the underlying mechanisms of training-induced changes in O_2 uptake kinetics.

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Chapter 4

Predicting effects of exercise training in patients with heart failure secondary to ischemic or idiopathic dilated cardiomyopathy

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Abstract

Aims: The purpose of this study was to investigate which patient characteristics may predict training effects on maximal and submaximal exercise performance in patients with chronic heart failure (CHF). Together with commonly used clinical and performance-related variables, oxygen (O_2) uptake kinetics during exercise recovery were included as possible predictors.

Methods: Fifty CHF patients (New York Heart Association, NYHA, class II-III) performed a 12-week training program (cycle interval, resistance and inspiratory muscle training). Training effects were expressed as changes in peak oxygen uptake (peak $\dot{V}O_2$), $\dot{V}O_2$ at the ventilatory threshold (VT), and the time constant of $\dot{V}O_2$ recovery after submaximal exercise (τ-rec).

Results: After training, peak $\dot{V}O_2$, $\dot{V}O_2$ at the VT and τ-rec improved significantly, with a wide variety in training responses. Changes in peak $\dot{V}O_2$ were related to changes in $\dot{V}O_2$ at the VT ($r = 0.79$, $p < 0.001$), but both changes were not related to changes in τ-rec. Using multivariate regression analyses, post-training changes in peak $\dot{V}O_2$ could be predicted by recovery half-time of peak $\dot{V}O_2$ (T½- $\dot{V}O_2$), peak $\dot{V}O_2$ (% of predicted) and peak respiratory exchange ratio (R^2: 36%). Post-training changes in $\dot{V}O_2$ at the VT could be predicted by T½-$\dot{V}O_2$ and VT (predicted) (R^2: 29%), whereas changes in τ-rec could be predicted only by τ-rec at baseline (R^2: 34%).

Conclusion: O_2 recovery kinetics after maximal and submaximal exercise substantially add to the prediction of training effects in CHF patients, presumably because of their relations with, respectively, central and peripheral impairments of exercise capacity. However, the explained variance in training effects is not sufficient to make a definite distinction between training responders and non-responders.

Introduction

Previous studies in patients with chronic heart failure (CHF), looking for predictors of training responses, failed to demonstrate a significant relationship between training effects and clinical patient characteristics, such as age, gender, body mass index, functional status, cause of CHF and left ventricular ejection fraction.[1-3] The evaluation of variables assessed by cardiopulmonary exercise testing yielded conflicting results. Whereas it has been reported that CHF patients with a relatively low baseline exercise capacity, expressed as oxygen uptake ($\dot{V}O_2$) at the ventilatory threshold (VT)[4] or at peak exercise,[5,6] benefit more from a training program than patients with a better exercise capacity, these results could not be confirmed by other investigators.[1-3] In all mentioned studies, training effects were defined as improvements at a maximal exercise level or at the level of the VT, which can also be regarded as an indicator of the maximal exercise performance, as shown by its strong correlation with peak $\dot{V}O_2$ in CHF patients ($r = 0.89$).[7] However, as maximal exercise performance may not reflect the ability to perform daily tasks correctly, training-related changes in submaximal exercise capacity are probably more indicative of improvements in daily functional capacity of these patients.[2,8] Therefore, it may be of even greater clinical relevance to identify predictors of training effects at a submaximal than at a maximal exercise level. The present study was performed to investigate the prediction of training effects on maximal and submaximal exercise capacity in CHF patients. Together with commonly used baseline patient variables, such as age, left ventricular ejection fraction, body mass index, peak $\dot{V}O_2$ and $\dot{V}O_2$ at the VT, we also included O_2 recovery kinetics after submaximal and maximal exercise as possible predictors of training effects.

Methods

In this prospective study, all patients performed a 12-week training program. All subjects provided informed consent, and the study was approved by the local Research Ethics Committee. Originally, 60 CHF patients who were referred for physical training were included, but actually a number of 50 completed the training program (see Results). 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) class II or III, left ventricular ejection fraction $\leq$ 40% (assessed by echocardiography or radionuclide ventriculography $\leq$ 2 months prior), and sinus rhythm. Exclusion criteria were recent myocardial infarction (< 3 months prior), angina pectoris at rest, peripheral vascular, neurological, orthopedic or pulmonary disease limiting the ability to exercise. During the study period all patients continued to use their medication.

Before and after the training program, all patients performed 2 exercise tests in

an upright seated position on an electromagnetically braked cycle ergometer (Corival, Lode, Groningen, The Netherlands). During the tests patients were instructed to maintain a pedaling frequency of 70/min. A 12-lead electrocardiogram was registered continuously, and blood pressure was measured every two min (Korotkoff sounds). Ventilatory parameters were measured breath-by-breath (Oxycon-α, Jaeger, Hoechberg, Germany). Volumes and gas analyzers were calibrated before each test. On testing days, patients were instructed to take their medication at the usual time and not to perform any extra physical activity.

The first test session consisted of a symptom-limited exercise test, using an individualized ramp protocol with a total test duration of 8 - 12 min.[9] The test was ended when the patient was not able to maintain the required pedaling frequency, or when the patient was restricted by symptoms or signs of myocardial ischemia. Peak workload was defined as the final registered workload and peak $\dot{V}O_2$ and peak heart rate as the average $\dot{V}O_2$ and heart rate of the last 30 sec of the test. Peak $\dot{V}O_2$ was also expressed as a % of the predicted value.[10] The ventilatory threshold (VT) was determined by the V-slope method,[11] using the average value obtained by two independent observers. The chronotropic response to exercise was assessed by calculating the difference between peak heart rate and resting heart rate (average heart rate in the last 30 sec of the resting period).

On a second occasion within the same week, subjects performed a constant-load test, consisting of 2 min of unloaded pedaling, 6 min at 50% of the peak workload achieved at the first test, and a recovery period of 5 min. $\dot{V}O_2$ and heart rate at steady state were defined as the mean value during the last min of exercise. After the training period, patients exercised at the same absolute workload in stead of the same relative intensity. We chose this strategy because it does not require the repetition of a symptom-limited exercise test after training, making it easier to integrate such an approach in daily clinical practice. Previous studies showed that training induces faster O_2 recovery kinetics both at the same absolute[12] and relative intensity levels.[13]

Since the rate of decrease of $\dot{V}O_2$ after maximal exercise cannot always be correctly described by a mono-exponential model, we used the recovery half-time of $\dot{V}O_2$ ($T½\text{-}\dot{V}O_2$), defined as the time required for a 50% fall from peak $\dot{V}O_2$, to assess O_2 recovery kinetics after the symptom-limited exercise test.[14] As the rate of decline of $\dot{V}O_2$ after submaximal exercise follows a mono-exponential course,[15] O_2 recovery kinetics after the constant-load test were evaluated by calculating a time constant (τ-rec) from the end of exercise until 5 min of recovery. After deleting occasional errant breaths (e.g., due to coughing, swallowing or talking) from the data set when $\dot{V}O_2$ exceeded three standard deviations of the local mean,[16] $\dot{V}O_2$ data were re-sampled into 5 breaths sampling intervals. Subsequently, the data were fit to a mono-exponential model, using the non-linear least squares method as previously described.[17]

The following equation was used:

$$\dot{V}O_{2\ (t)} = \dot{V}O_{2\ \text{steady state}} - A * (1 - e^{-(t - Td)/\tau\text{-rec}})$$

with A = $\dot{V}O_2$-amplitude during exercise recovery (ml/min), Td = time delay (sec) and τ-rec = time constant (sec)

As already mentioned, steady state $\dot{V}O_2$ was defined as the average $\dot{V}O_2$ during the last min of exercise. The other parameters in the fitting procedure (A, τ-rec and Td) were used as free parameters that were allowed to vary to optimize the fit. The 'goodness of fit' was determined by the coefficient of determination (R^2).

The 12-week training program was based on recommendations of the European Society of Cardiology,[18] and consisted of cycle interval, resistance and inspiratory muscle training (1-hour sessions, 3 times per week). All training sessions took place at the Department of Physical Therapy and commenced with cycling training on an ergometer with a warm up phase of 5 min, followed by 15 min of interval training with work phases of 30 sec and recovery phases of 60 sec. The intensity of the work phases was set at 50% of the maximum short-term exercise capacity, which was assessed by a steep ramp test (increase of work rate by 25 W every 10 sec until exhaustion) every 4 weeks. This interval training program has previously been proven to be effective in CHF patients.[19,20] After the cycling training, patients performed resistance training (leg press, leg curl, biceps curl, triceps extension, calf raise), using 2 sets of 12 repetitions at 70% of the 1-repetition maximum, which was determined every 4 weeks. In addition, all patients were instructed to perform resistive inspiratory muscle training at home, using the Threshold inspiratory muscle trainer (Healthscan, New Jersey, NJ, USA) 5 times per week during 30 min at 30% of their maximum inspiratory pressure.[18]

Feelings of well-being were assessed by a validated Dutch translation of the Minnesota Living with Heart Failure Questionnaire (MLHF).[21] The lower the MLHF scores, the higher the quality of life (QOL).

Data were analyzed using SPSS 16.0 statistical software (SPSS Inc, Chicago, IL, USA). Continuous variables are presented as mean ± SD, categorical variables as absolute frequencies. Data distributions were tested for normality by calculation of the coefficients of skewness and kurtosis and by the Shapiro-Wilk test. If necessary, square root transformations were performed to normalize the data. Only if the transformed variables altered the multivariate predictions of the training effect parameters, the transformed variables were used and specifically marked in the section 'Results'. Training-related within-group changes were analyzed by the paired Student's t test and between-group differences in training effects were assessed by the unpaired Student's t test. Relations between variables were evaluated by univariate regression analysis. Baseline patient variables that were selected as possible predictors of a training effect were T½-$\dot{V}O_2$, τ-rec, as well as clinical and

physiological variables that were used in previous studies.[1-6,22,23] Baseline variables with $p < 0.20$ in univariate analysis were used in a multivariate regression model (backward stepwise regression, removal criteria: $p > 0.05$). The goodness-of-fit was evaluated by using R^2. The level of significance was set at $p < 0.05$.

Results

Ten patients did not complete the training program because of medical reasons (n = 4) and non-compliance (n = 6). These patients were not different from the other patients with respect to age, gender, left ventricular ejection fraction, NYHA class and peak $\dot{V}O_2$. The remaining 50 patients attended > 80% of the training sessions. Baseline characteristics are shown in Table 1. Two patients did not perform the symptom-limited exercise test after their training periods due to medical reasons. The VT could not be determined on at least one occasion in 3 patients. The analysis of O_2 recovery kinetics after the constant-load test showed a R^2 of 0.95 ± 0.03, indicating a good fit of the mono-exponential model. QOL scores were not obtained after training in 2 patients due to non-compliance.

Table 1. *Baseline clinical characteristics in patients with CHF (n = 50).*

Variable	Value
Male / female (n)	38 / 12
Age (years)	62 ± 9
Height (cm)	173 ± 8
Weight (kg)	83 ± 13
Body Mass Index (kg/m^2)	28 ± 4
LVEF (%)	31 ± 7
NYHA class II / III (n)	38 / 12
Etiology: ICM / DCM (n)	36 / 14
ICD (n)	12
Biventricular pacemaker (n)	7
Medication (n)	
Diuretics	43
ACE inhibitors / ARBs	49
Beta-blockers	44
Digoxin	5
Amiodarone	5
Oral anticoagulation	29

Values are mean ± SD or n. LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; ICM = ischemic cardiomyopathy; DCM = dilated cardiomyopathy; ICD = Implantable Cardioverter Defibrillator; ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker.

The effects of training on exercise performance and QOL are presented in Table 2. Since analysis of the original data yielded the same results as for the transformed data, only the results of original data are presented. When comparing patients with ischemic and dilated cardiomyopathy, no differences in training-related changes were observed in peak $\dot{V}O_2$ (+1.7 ± 1.8 ml/min/kg vs +1.8 ± 2.4 ml/min/kg, respectively, p = 0.87), $\dot{V}O_2$ at the VT (+1.2 ± 1.7 ml/min/kg vs +1.6 ± 1.6 ml/min/kg, respectively, p = 0.51), τ-rec (-10 ± 20 sec vs -10 ± 21 sec, respectively, p = 0.97), nor in the other variables presented in Table 2. The ranges in post-training changes of the outcome variables indicate a considerable variety in individual training responses (Table 2). When a cut-off value of 10% change was used to divide patients into responders and non-responders,[4,24] 50% of the patients could be classified as responder for changes in peak $\dot{V}O_2$, 49% for changes in $\dot{V}O_2$ at the VT, and 48% for changes in τ-rec. Training-induced changes in peak $\dot{V}O_2$ were significantly related to changes in $\dot{V}O_2$ at the VT (r = 0.79, p < 0.001), whereas changes in these variables were not related to changes in τ-rec (r = -0.15, p = 0.32, and r = -0.19, p = 0.21, respectively).

Table 2. *Physiologic variables and quality of life before and after a 12-week training program in CHF patients.*

Variable	Before training	After training	Range of change	p-value
Symptom-limited exercise test (n = 48)				
$\dot{V}O_2$ at the VT (ml/kg/min) [a]	12.3 ± 1.8	13.6 ± 2.3	-1.6 - 4.9	< 0.001
HR at the VT (beats/min) [a]	98 ± 17	101 ± 18	-23 - 43	0.16
Peak workload (W)	105 ± 31	114 ± 34	-21 - 43	< 0.001
Exercise time (sec)	639 ± 151	706 ± 176	-105 - 215	< 0.001
Peak $\dot{V}O_2$ (ml/kg/min)	17.4 ± 3.1	19.1 ± 3.6	-1.7 - 7.4	< 0.001
Peak RER	1.13 ± 0.11	1.15 ± 0.12	-0.29 - 0.28	0.09
Peak HR (beats/min)	126 ± 22	126 ± 22	-32 - 22	0.87
Chronotropic response (Δbeats/min)	44 ± 16	46 ± 18	-19 - 42	0.16
T½-$\dot{V}O_2$ (sec)	104 ± 36	95 ± 35	-48 - 25	0.002
Constant-load exercise test (n = 50)				
$\dot{V}O_2$ at steady state (ml/kg/min)	13.4 ± 2.5	13.4 ± 2.5	-3.8 - 3.5	0.92
Heart rate at steady state (beats/min)	103 ± 16	98 ± 17	-29 - 25	0.01
τ-rec (sec)	81 ± 29	71 ± 24	-99 - 12	0.001
Quality of life (n = 48)				
MLHF score	26 ± 17	20 ± 18	-51 - 27	0.005

Values are mean ± SD. VT = ventilatory threshold; HR = maximum heart rate; RER = Respiratory Exchange Ratio; T½-$\dot{V}O_2$ = half time recovery of $\dot{V}O_2$ after maximal exercise; τ-rec = time constant of recovery of $\dot{V}O_2$; MLHF = Minnesota Living with Heart Failure Questionnaire. [a] n = 45.

Table 3 shows that, using univariate regression analysis, there were no significant relations between baseline clinical variables and training effects. From the variables selected for multivariate regression analysis, T½-$\dot{V}O_2$ was the strongest independent predictor of changes in both peak $\dot{V}O_2$ and $\dot{V}O_2$ at the VT (Table 4). Both in univariate and multivariate analyses, τ-rec was the only significant predictor of training-induced change of τ-rec (Figure 1, Tables 3 and 4).

Table 3. *Univariate linear regression analyses of the relation between baseline variables and training effects in CHF patients.*

	ΔPeak $\dot{V}O_2$ (n = 48)		**$\Delta\dot{V}O_2$ at the VT (n = 45)**		**$\Delta\tau$-rec (n = 50)**	
	Regression coefficient	**R^2**	**Regression coefficient**	**R^2**	**Regression coefficient**	**R^2**
Clinical variables						
Age (years)	-0.02	0.0004	+0.15	0.02	-0.07	0.005
Gender (Male / Female)	+0.04	0.002	+0.05	0.003	+0.07	0.005
Body Mass Index (kg/m^2)	-0.23 *	0.05	-0.26 *	0.07	-0.07	0.005
LVEF (%)	+0.15	0.02	+0.04	0.002	-0.03	0.0009
NYHA class (II / III)	+0.03	0.0009	+0.21 *	0.04	+0.03	0.0009
Etiology (ICM / DCM)	+0.02	0.0004	+0.10	0.01	+0.01	0.0001
Diuretics	+0.02	0.0004	+0.17	0.029	+0.15	0.023
ACE inhibitors / ARBs	+0.17	0.03	+0.17	0.029	+0.03	0.0009
Beta-blockers	+0.14	0.02	-0.08	0.006	+0.23 *	0.05
Digoxin	+0.05	0.003	+0.07	0.005	+0.22 *	0.05
Amiodarone	+0.17	0.03	+0.22 *	0.05	+0.06	0.004
Oral anticoagulation	+0.06	0.004	+0.03	0.0009	+0.14	0.002
Physiological variables						
Peak workload (W)	-0.10	0.01	+0.13	0.02	+0.17	0.03
Peak $\dot{V}O_2$ (ml/min/kg)	-0.04	0.002	+0.07	0.005	+0.12	0.01
Peak $\dot{V}O_2$ (% predicted)	-0.25 *	0.06	-0.11	0.01	+0.09	0.01
Chronotropic response (Δbeats/min)	+0.12	0.01	+0.08	0.006	+0.17	0.03
Peak RER	+0.33 †	0.11	+0.13	0.02	+0.14	0.02
$\dot{V}O_2$ at the VT(ml/min/kg)	-0.06	0.004	-0.14	0.02	+0.17	0.03
$\dot{V}O_2$ at the VT (% predicted)	-0.25 *	0.06	-0.26 *	0.07	+0.11	0.01
HR at the VT (beats/min)	-0.10	0.01	-0.07	0.005	+0.11	0.01
T½-$\dot{V}O_2$ (sec)	-0.26 *	0.07	-0.42 ‡	0.18	+0.05	0.003
τ-rec (sec)	-0.06	0.004	-0.03	0.001	-0.59 ‡	0.35

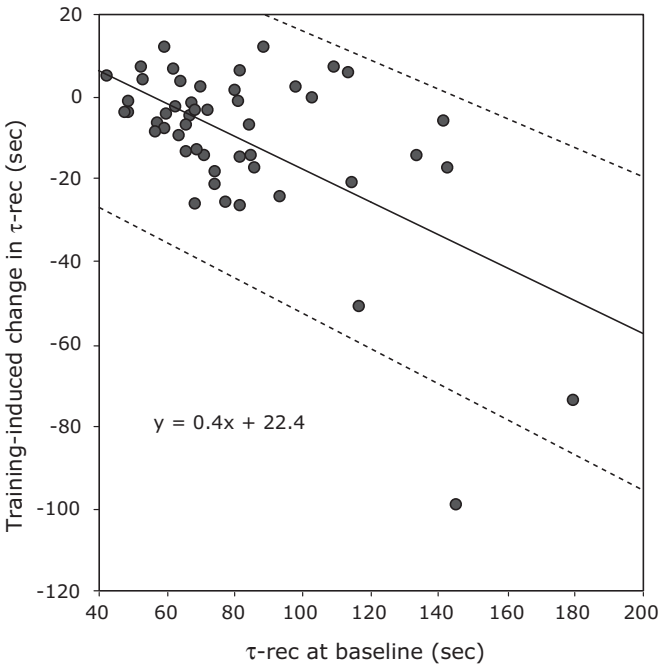
LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; ICM = ischemic cardiomyopathy; DCM = dilated cardiomyopathy; ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; RER = Respiratory Exchange Ratio; VT = ventilatory threshold; HR = heart rate; T½-$\dot{V}O_2$ = half time recovery of $\dot{V}O_2$ after maximal exercise; τ-rec = time constant of recovery of $\dot{V}O_2$. * $p < 0.20$; † $p < 0.05$; ‡ $p < 0.01$.

Table 4. *Multivariate regression models predicting training effects in CHF patients.*

Training effect	Predictors of training effect	Standardized β Coefficient	t-value	p-value	Total R^2
ΔPeak $\dot{V}O_2$	T½-$\dot{V}O_2$ (sec)	-0.48	-3.5	0.001	0.36
(ml/min/kg)	Peak $\dot{V}O_2$ (% predicted)	-0.39	-2.8	0.007	
(n = 48)	Maximal RER	0.34	2.7	0.01	
Δ$\dot{V}O_2$ at the VT	T½-$\dot{V}O_2$ (sec)	-0.48	-3.6	0.001	0.29
(ml/min/kg)	$\dot{V}O_2$ at the VT	-0.35	-2.6	0.01	
(n = 45)	(% predicted)				
Δτ-rec (sec)	τ-rec (sec)	-0.59	-5.0	< 0.001	0.34
(n = 50)					

T½-$\dot{V}O_2$= half time recovery of $\dot{V}O_2$ after maximal exercise; RER = Respiratory Exchange Ratio; VT = ventilatory threshold; τ-rec = time constant of recovery of $\dot{V}O_2$.

Figure 1.



Relation between the time constant of O_2 recovery kinetics after submaximal exercise at baseline (τ-rec) and training-induced changes in τ-rec in a group of 50 patients with CHF. The least squares regression line with lines showing 95% CI, and the regression equation are depicted.

Discussion

The present study demonstrated that both at maximal and submaximal exercise levels, the response to physical training varied considerably among CHF patients, underlining the importance of identifying predictors of training effects in these patients. Whereas initial clinical patient characteristics proved not to be useful for this purpose, several variables obtained by baseline exercise testing, could be identified as independent predictors.

To be able to draw conclusions from this study, the efficacy of the training program should be addressed first. Although some studies reported greater increases in peak $\dot{V}O_2$ and $\dot{V}O_2$ at the VT,[3,6] the improvements that were observed in the present study (10% and 11% respectively) are comparable to other studies in CHF patients.[1,2,23] Concerning submaximal exercise-related variables, we found a significant decrease in heart rate, which was also observed in other studies.[3,23] In addition, we demonstrated an acceleration of O_2 recovery kinetics after training. This finding is in agreement with studies in healthy subjects[12,13] and recent post-training findings in CHF patients in our laboratory (Chapter 3).

In line with other studies in CHF patients,[1-3] we did not observe a relationship between training-induced changes in peak $\dot{V}O_2$ and clinical patients characteristics. Considering physiological variables, multivariate regression analysis identified 3 independent predictors of the increase in peak $\dot{V}O_2$, with a total explained variance of 36% (Table 4). The first predictor is baseline peak $\dot{V}O_2$ (% of predicted). A relatively low peak $\dot{V}O_2$ was associated with a relatively large increase in peak $\dot{V}O_2$ after training. A similar relationship was found in some studies,[5,6] but not in others,[1-3] which may be explained by different patient selections. Meyer et al., who included more severely impaired CHF patients (peak 12.2 ± 0.7 ml/min/kg), observed a strong negative correlation between baseline peak $\dot{V}O_2$ and training-related changes in peak $\dot{V}O_2$ ($r = -0.74$).[5] Studies in patients with a higher baseline peak $\dot{V}O_2$ reported lower or even absent associations between these variables,[1-3] suggesting that the predictive value of baseline peak $\dot{V}O_2$ is higher in more severely impaired CHF patients. From a physiological point of view, this outcome may be explained by the fact that in mild to moderate heart failure peak $\dot{V}O_2$ is mainly determined by central hemodynamics,[7] whereas peripheral derangements play a greater role in severe heart failure,[25] the latter being more susceptible to physical training.[3] The second predictor is the rate of recovery of peak $\dot{V}O_2$, which was not evaluated in previous studies. A relatively slow recovery, and thus a long lasting T½-$\dot{V}O_2$ at baseline, was associated with a relatively small training-related increase in peak $\dot{V}O_2$. As it was shown that T½-$\dot{V}O_2$ is negatively correlated with the maximal cardiac index in CHF patients,[26] our results suggest that patients with a more pronounced circulatory dysfunction are less likely to respond to physical training. This finding is in agreement with studies directly assessing cardiac output.[24,27] The third predictor is the maximal RER. Patients who reached a relatively high RER

showed relatively large improvements in peak $\dot{V}O_2$. An explanation may be that these patients invested greater efforts at the tests used to adjust the training workload, indicating that these patients trained at a relatively high intensity.

Whereas clinical patient characteristics were not related to training-related changes in $\dot{V}O_2$ at the VT, 2 physiological variables were identified as independent predictors (Table 4). First, patients with slower O_2 recovery kinetics after maximal exercise at baseline showed a lower training effect. As mentioned before, this may be explained by more severe hemodynamic dysfunction in these patients. The second predictor was the initial $\dot{V}O_2$ at the VT (% of predicted). Meyer et al., who studied more severely impaired CHF patients observed an even stronger relation between these variables ($r = -0.74$),[4] suggesting that post-training changes in $\dot{V}O_2$ at the VT can be best predicted by its baseline value in these CHF patients. Given the strong correlation between changes in $\dot{V}O_2$ at the VT and peak $\dot{V}O_2$ ($r = 0.79$), the explanation for the initial $\dot{V}O_2$ at the VT as predictor may be similar to that for the interaction between post-training changes in peak $\dot{V}O_2$ and its baseline value.

The only variable predicting post-training changes in τ-rec was τ-rec at baseline. In previous studies it was demonstrated that delayed O_2 recovery kinetics after submaximal exercise in CHF patients reflect peripheral derangements such as impaired local vasodilatory capacity[28] and slower muscle metabolic recovery.[29] Therefore, it is not surprising that patients with a relatively slow O_2 recovery kinetics at baseline benefit most from physical training.

A potential limitation of this study is that, besides clinical patient characteristics, only variables obtained from cardiopulmonary exercise testing were evaluated. Although these variables provide reliable objective information on the submaximal and maximal exercise capacity of these patients, the relative contribution of peripheral and central impairments to performance capacity cannot be evaluated in this way. Preliminary studies, however, suggest that such information may add to the prediction of training effects in CHF patients.[24,27] In addition, genetic factors, which according to data from healthy individuals,[30] may also contribute to the heterogeneity in training responses were not assessed. Another limitation of this study concerns the lack of a control group. However, as the observed post-training changes in the exercise variables correspond to those reported in several controlled studies,[1,2,23] it can be assumed that the improvements in exercise performance in this study are mainly attributed to the training program. Furthermore, as a result of the sample size of this study we were unable to evaluate adequately the training effects in patients with ischemic and dilated cardiomyopathy separately.

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Part II

Physiological aspects

Chapter 5

The reliability of continuous measurement of mixed venous oxygen saturation during exercise in patients with chronic heart failure

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Abstract

Background: Continuous assessment of mixed venous oxygen saturation ($cS\bar{v}O_2$) during exercise using a fiberoptic pulmonary artery catheter can provide valuable information on the physiological determinants of the exercise capacity in patients with chronic heart failure (CHF). Since its accuracy is not well established during exercise, this study evaluated the reliability of a fiberoptic pulmonary artery catheter for measuring $S\bar{v}O_2$ during exercise in CHF patients.
Methods: Ten patients with stable CHF performed steady state exercise tests at 30% and 80% of the ventilatory threshold and consequently a symptom-limited incremental exercise test. During the tests $S\bar{v}O_2$ was monitored continuously using a fiberoptic pulmonary artery catheter (CCOmbo, Edwards Lifesciences, Irvine, CA, USA) and by oximetric analysis of mixed venous blood samples obtained at rest (n = 26), constant-load (n = 17) and peak exercise (n = 8).
Results: There was a significant correlation between oximetrically determined $S\bar{v}O_2$ and $cS\bar{v}O_2$ values (r = 0.97). The bias between both methods was 0.6% with limits of agreement from -8% to 9%. The limits of agreement for $S\bar{v}O_2$ values < 30% (n = 16) were slightly wider than for $S\bar{v}O_2$ values > 30% (n = 35) (-10% - 12% and -7% - 8%, respectively).
Conclusion: Continuous measurement of $S\bar{v}O_2$ during exercise using a fiberoptic pulmonary catheter is reliable in patients with CHF, with somewhat less accurate measurements of $S\bar{v}O_2$ below 30%.

Introduction

The development of fiberoptic pulmonary artery catheters has enabled continuous measurement of mixed venous oxygen saturation ($S\bar{v}O_2$).[1] This measurement technique has been shown to be accurate and useful in the management of critically ill patients,[2-4] pediatric patients[5] and patients undergoing cardiac surgery.[6] Continuous measurements of $S\bar{v}O_2$ are also potentially useful in patients with left ventricular dysfunction for studying physiological mechanisms determining the response to exercise,[7] recovery from exercise[8] and for the assessment of continuous cardiac output during exercise using the continuous Fick method.[9,10] However, the reliability of continuous $S\bar{v}O_2$ measurements during exercise in these patients is not well established. Previous studies in patients with chronic obstructive pulmonary disease[11] and patients with chronic heart failure (CHF)[12] have reported that fiberoptic pulmonary artery catheters are reliable at $S\bar{v}O_2$ levels above 50%, but systematically underestimate lower values. After the publication of these studies, technological advances may have improved the accuracy of these measurements. Therefore, this study was conducted to evaluate the reliability of a fiberoptic pulmonary artery catheter for continuous measurement of $S\bar{v}O_2$ during steady state and incremental exercise in patients with CHF.

Methods

Subjects

Ten male patients with stable CHF were selected at the cardiology outdoor clinic of Máxima Medical Centre (Veldhoven, The Netherlands). 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) Class II or III, left ventricular ejection fraction ≤ 40% (assessed by echocardiography or radionuclide ventriculography) and sinus rhythm. Exclusion criteria were recent myocardial infarction (< 3 months prior), angina pectoris at rest, peripheral vascular, neurological or orthopaedic disease limiting the ability to exercise and chronic airway obstruction, defined as FEV_1 / FVC < 60%. Subject characteristics are listed in Table 1.

The research protocol was approved by the local Research Ethics Committee of Máxima Medical Centre, and all patients provided written informed consent.

Exercise testing

On entering the study, all patients performed a familiarization symptom-limited, incremental exercise test with continuous measurement of $\dot{V}O_2$ and $\dot{V}CO_2$ (Zan 680 USB, Germany) on an electromagnetically braked cycle ergometer (Corival, Lode, Groningen, The Netherlands), using an individualized ramp protocol.[13] The ventilatory threshold was determined by the V-slope method.[14]

Table 1. *Characteristics of included patients with CHF (n =10).*

Variable	Value
Age (years)	63 ± 8
Height (cm)	178 ± 8
Weight (kg)	89 ± 4
Body Mass Index (kg/m^2)	28 ± 4
LVEF (%)	33 ± 7
NYHA class II / III (n)	6 / 4
Etiology: ICM / DCM (n)	9 / 1
Medication (n)	
Diuretics	9
ACE inhibitors / ARBs	10
Beta-blockers	9
Digoxin	0

Values are mean ± SD or n. LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; ICM = ischaemic cardiomyopathy; DCM = dilated cardiomyopathy; ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker.

On a separate day, patients underwent exercise testing with $S\bar{v}O_2$ measurements. After arrival in the Cardiac Catheterization Room, a 7.5 F Swan-Ganz catheter (CCOmbo, Edwards Lifesciences, Irvine, CA, USA) was inserted into the right antecubital vein and positioned in the right pulmonary artery under fluoroscopic guidance. The pulmonary catheter was connected to a hemodynamical monitor (Vigilance II, Edwards, Irvine, USA). After a resting period of 20 min, an in-vivo calibration of the fiberoptic catheter was performed using hematocrit and oxygen saturation values obtained from a pulmonary artery blood sample analyzed by an in-vitro oximeter (ABL800 Flex, Radiometer America Inc., Copenhagen, Denmark). After the patient had been seated at least 5 min on the ergometer, exercise testing started with unloaded cycling for 2 min, followed by a minimum of 5 min at 30% and thereafter 5 min at 80% of the previously determined ventilatory threshold. If the patient did not reach a steady state after 5 min, the test was continued for another 5 min. After a resting period of at least 15 min a symptom-limited exercise test was performed. Blood samples were drawn from the distal port of the pulmonary artery catheter and collected in a heparinized syringe at rest (2 times with 5 min-intervals), at the end of both constant-load tests, before the symptom-limited exercise test and in the last minute of this test. The samples were immediately analyzed for hemoglobin, hematocrit and O_2 saturation (ABL800 Flex, Radiometer America Inc., Copenhagen, Denmark) and compared afterwards to the average of continuously measured $S\bar{v}O_2$ ($cS\bar{v}O_2$) values of 15 sec before and 15 sec after blood sample collection.

Statistical analysis

All data (presented as mean ± SD) were analyzed using a statistical software program (SPSS 12.0). Differences between continuous variables were evaluated by the paired Student's t test. Linear regression was used to define correlations between variables. Agreement between $S\bar{v}O_2$ and $cS\bar{v}O_2$ was assessed by the limits of agreement (mean difference ± 1.96 x SD).[15] Probability values < 0.05 were considered statistically significant.

Results

All subjects completed the exercise tests. The maximum workload was 108 ± 46 Watt and peak $\dot{V}O_2$ was 16.4 ± 5 ml/min/kg. In total, 59 blood samples were taken from the pulmonary catheter. Of these samples, 8 could not be included in the analysis because of blood clot formation in the syringe in 4 cases (in 3 patients) and an unstable $cS\bar{v}O_2$ signal in 4 cases (in 1 patient), leaving a total of 51 samples (26 at rest, 17 at steady state exercise and 8 at maximal exercise).

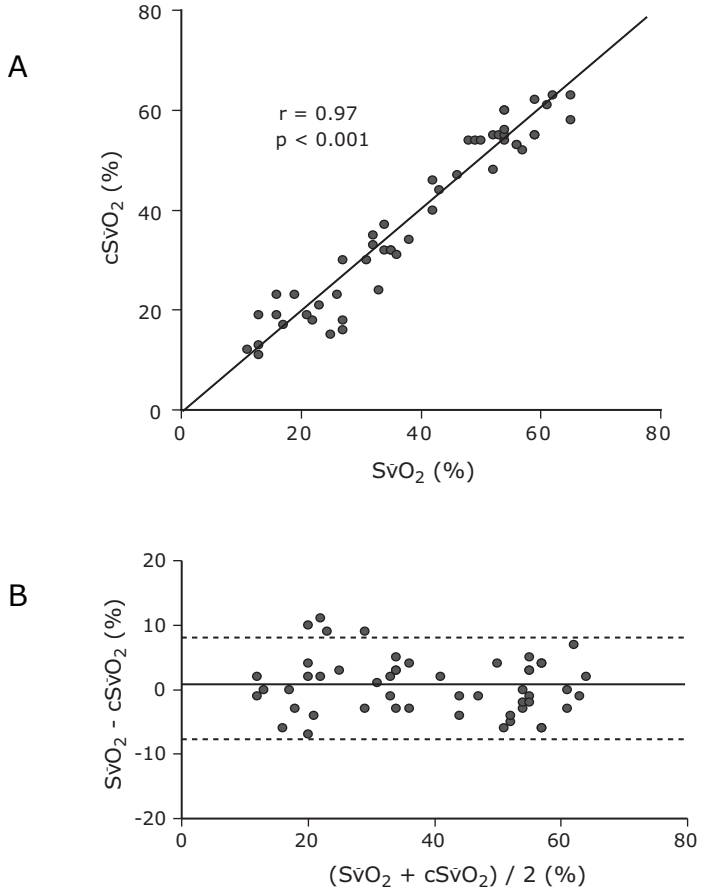
A comparison between oximetrically determined $S\bar{v}O_2$ and $cS\bar{v}O_2$ values is shown in Figure 1A,B. The linear correlation coefficient between the two methods was r = 0.97 ($p < 0.001$, Figure 1A). The bias between both methods was 0.6% with limits of agreement from -8% to 9% (Figure 1B). Visual inspection of the Bland Altman plot reveals that the variability of the difference between both measurement methods increases slightly with $S\bar{v}O_2$ values < 30% (n = 16). The limits of agreement for these values in the lower range were wider than for $S\bar{v}O_2$ values > 30% (n = 35) (from -10% - 12% and from -7% - 8% respectively). There was no significant difference between oximetrically determined $S\bar{v}O_2$ and $cS\bar{v}O_2$ in the range below 30% (1.2 ± 5.4%, p = ns).

Discussion

This study showed that continuous measurement of mixed venous oxygen saturation is feasible and reliable during exercise in patients with CHF. In contrast to other studies that used a different fiberoptic catheter,[11,12] there was no systemic underestimation of $S\bar{v}O_2$ by the fiberoptic catheter at low values in our study. We did, however, observe a slightly larger variation of the difference with oximetrically determined $S\bar{v}O_2$ values in the range below 30%, seemingly indicating somewhat lower accuracy in this range.

A possible physiological explanation for this may be that exercise causes an increase in hematocrit.[16] Since the hematocrit value that is entered during calibration at rest determines the calibration curve, the fact that we did not recalibrate the fiberoptic catheter during exercise could theoretically result in an underestimation of $S\bar{v}O_2$ during exercise. Nevertheless, although we did find a

Figure 1.



Comparison of continuously measured $Sv\bar{v}O_2$ ($cSv\bar{v}O_2$) and oximetrically determined $Sv\bar{v}O_2$ ($Sv\bar{v}O_2$) (n = 51). ***A*** *Correlation plot between $cSv\bar{v}O_2$ and $Sv\bar{v}O_2$. The line of identity is shown.* ***B*** *Bland Altman plot 15 showing the difference between $cSv\bar{v}O_2$ and $Sv\bar{v}O_2$ vs their mean. The solid line represents the mean difference between the two tests, the dashed lines indicate the 95% confidence intervals of the difference.*

significant increase of the hematocrit at maximal exercise (41% ± 4% at rest vs 45% ± 5% at maximal exercise, $p < 0.05$), there was no such a systemic underestimation of $Sv\bar{v}O_2$ by the fiberoptic catheter in the lower range in our study, ruling out a marked influence of this factor.

Another aspect possibly affecting the accuracy of continuous $Sv\bar{v}O_2$ measurement during exercise is the effect of body movements on catheter tip position. Yet, we did not observe exercise-induced changes in the pressure waveform indicating catheter tip migration. In addition, $Sv\bar{v}O_2$ signal intensity was insufficient in only one patient.

Finally, the apparent lower accuracy of the fiberoptic catheter in the lower range could be the consequence of the fact that measurements at maximal exercise were

performed in a non-steady state situation. Since $cS\bar{v}O_2$ and oximetrically determined $S\bar{v}O_2$ cannot be obtained exactly simultaneously due to signal instability of the fiberoptic catheter during blood sampling, we may have underestimated the reliability of $cS\bar{v}O_2$ measurements during maximal exercise.

In conclusion, continuous measurement of $S\bar{v}O_2$ during exercise is reliable in patients with CHF. Although values < 30% seem somewhat less accurate, there is no systemic underestimation in this lower range.

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Chapter 6

Evaluation of two methods for continuous cardiac output assessment during exercise in chronic heart failure patients

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Abstract

Aims: The purpose of this study was to evaluate the accuracy of 2 techniques for the continuous assessment of cardiac output in patients with chronic heart failure (CHF): a radial artery pulse contour analysis method which uses an indicator dilution method for calibration (LiDCO) and an impedance cardiography technique (Physioflow), using the Fick method as a reference.
Methods: Ten male CHF patients (New York Heart Association class II-III) were included. At rest, cardiac output values obtained by LiDCO and Physioflow were compared with those of the direct Fick method. During exercise, the continuous Fick method was used as a reference. Exercise, performed on a cycle ergometer in upright position, consisted of 2 constant-load tests at 30% and 80% of the ventilatory threshold, and a symptom-limited maximal test.
Results: Both at rest and during exercise LiDCO showed good agreement with reference values (bias ± limits of agreement (LOA), -1% ± 28% and 2% ± 28%, respectively). In contrast, Physioflow overestimated reference values both at rest and during exercise (bias ± LOA, 48% ± 60% and 48% ± 52%, respectively). Exercise-related within-patient changes of cardiac output, expressed as a % change, showed for both techniques clinically acceptable agreement with reference values (bias ± LOA: 2% ± 26% for LiDCO, and -2% ± 36% for Physioflow, respectively).
Conclusion: Although the limits of agreement with the Fick method are pretty broad, LiDCO provides accurate measurements of cardiac output during rest and exercise in CHF patients. Although Physioflow overestimates cardiac output, this method may still be useful to estimate relative changes during exercise.

Introduction

Commonly accepted methods to accurately assess cardiac output in patients with chronic heart failure (CHF) include the direct Fick method and thermodilution.[1,2] However, because these methods require cardiac catheterization they are unsuitable for daily clinical use. Therefore, numerous studies have investigated the clinical utility of less invasive measures, such as radionuclear methods, Doppler cardiography, gas rebreathing techniques, and impedance cardiography.[3,4] Because radionuclear methods require steady state conditions, they are unsuitable for measurements during maximal exercise.[3] The widespread use of Doppler cardiography is limited because its accuracy (i.e., agreement with the gold standard) highly depends on the skills of the operator.[3] Studies evaluating the accuracy of impedance cardiography in the heart failure population yielded conflicting results.[5,6] Although foreign gas rebreathing techniques have shown promising results in CHF patients,[7,8] these methods do not provide continuous cardiac output measurements. We aimed to evaluate techniques for continuous estimation of the cardiac output, because of its merit for studying the pathophysiological mechanisms underlying exercise intolerance in CHF.[9-11]

Two methods have recently been introduced for real-time continuous cardiac output measurement. One method is based on radial artery pulse contour analysis, using an indicator dilution method to calibrate the system (LiDCO, London, UK). Up to the present, the accuracy of this method for the assessment of cardiac output during exercise has not been evaluated. The other method is an impedance technique (Physioflow, Manatec Biomedical, Petit Ebersviller, France). This method is different from previously used impedance methods. The algorithm that is used does not require basal thoracic impedance measurement or the estimation of blood resistivity and the position of the electrodes is not critical for the accuracy of the measurements. Previous studies showed that Physioflow provides accurate cardiac output measurements during steady state and maximal exercise in healthy subjects.[12,13] However, in patients with chronic obstructive pulmonary disease (COPD) cardiac output was systematically overestimated.[14] The authors of latter study hypothesized that this might be due to specific characteristics of COPD patients, such as hyperinflation and changes in the distribution of lung volumes. The sensitivity of Physioflow to detect changes in cardiac output was not addressed in this study. Currently, no studies have evaluated the accuracy and sensitivity of this technique in CHF patients.

The purpose of this study was to evaluate the accuracy of LiDCO and Physioflow at rest and during exercise, using the Fick method as reference. In addition, we investigated the sensitivity of both techniques by evaluating within-patient changes in cardiac output.

Methods

The study was conducted at the Department of Cardiology of the Máxima Medical Centre. The research protocol was approved by the local Research Ethics Committee, and all patients provided written informed consent.

Subjects

Ten male patients with stable CHF were recruited to participate in the study. In- and exclusion criteria are described in Chapter 5. Subject characteristics are listed in Table 1. During the study period, there were no changes in medication use.

Exercise protocol

All patients performed exercise tests on 2 occasions using an electromagnetically braked cycle ergometer in an upright position (Corival, Lode, Groningen, The Netherlands). In both tests ventilatory parameters were measured breath-by-breath (Zan 680 USB, Oberthulba, Germany). Volume and gas analyzers were calibrated before each test. A 12-lead electrocardiogram was registered continuously. The mean duration between both occasions was 7.8 ± 4.9 days.

During the first session, patients underwent a symptom-limited incremental exercise test, using an individualized ramp protocol, with a duration of 8 - 12 min.[15] The test was ended when a patient was not able to maintain the required pedaling frequency of 70 per minute. Peak oxygen uptake ($\dot{V}O_2$) was defined as the average values of the last 30 sec of the test. The $\dot{V}O_2$ at the ventilatory threshold (VT) was

Table 1. *Clinical characteristics of the study population (n = 10).*

Variable	Value
Age (years)	63 ± 8
Height (cm)	177 ± 12
Weight (kg)	89 ± 14
Body mass index (kg/m^2)	28 ± 3
LVEF (%)	33 ± 7
NYHA class II / III (n)	6 / 4
Etiology: ICM / DCM	9 / 1
Medication (n)	
Diuretics	9
ACE inhibitors / ARBs	10
Beta-blockers	9
Digoxin	0
Oral anticoagulation	2

Values are mean ± SD or n. LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; ICM = ischemic cardiomyopathy; DCM = dilated cardiomyopathy; ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker.

determined by the V-slope method, using the average value obtained by two independent observers.[16] From this test the individual workload for the two constant-load tests was calculated (see below).

The second session was performed to evaluate the accuracy of the cardiac output assessment methods under different conditions: at rest, during light and moderate steady state exercise, and maximal exercise. The session started with a resting period, in which cardiac output measurements were performed (see cardiac output assessment). Thereafter, patients started exercising with 2 min cycling at the lowest intensity of the ergometer (7 Watt), followed by 2 subsequent 5-min bouts at a light and moderate constant-load intensity of 30% and 80% of the workload of the VT, respectively. Based on our previous experience with CHF patients, a workload of 30% of VT is the lowest workload at which significant changes in $\dot{V}O_2$ and cardiac output ($\dot{Q}$) occur, and a workload higher than 80% of VT does not ensure a steady state for all patients. Steady state was defined as a stable heart rate (increase < 5%) during the last 2 min of exercise. Finally, a symptom-limited incremental exercise test was performed after a resting period of at least 15 min (average duration between tests: 81 ± 47 min), in order to assess cardiac output at maximal exercise

Cardiac output assessment

Fick method

First, a 7.5F fiberoptic catheter (CCOmbo, Edwards Lifesciences, Irvine, CA, USA) was positioned in the right pulmonary artery under fluoroscopic guidance through the antecubital vein and connected to a hemodynamic monitor (Vigilance II, Edwards Lifesciences). A 20-gauge arterial catheter was then placed into the radial artery and connected to a pressure monitor (SC9000, Siemens Medical Systems Inc, Erlangen, Germany), using a disposable pressure transducer (Safedraw, Becton, Dickinson and Co, Franklin Lakes, NJ, USA). In addition, a pulse oximeter (Onyx 9500, Nonin Medical Inc, Plymouth, MN, USA) was attached to the index or middle finger to monitor arterial oxygen saturation (SaO_2) continuously. A picture of the experimental setup is shown in Figure 1.

Cardiac output ($\dot{Q}$) was calculated using the Fick equation:

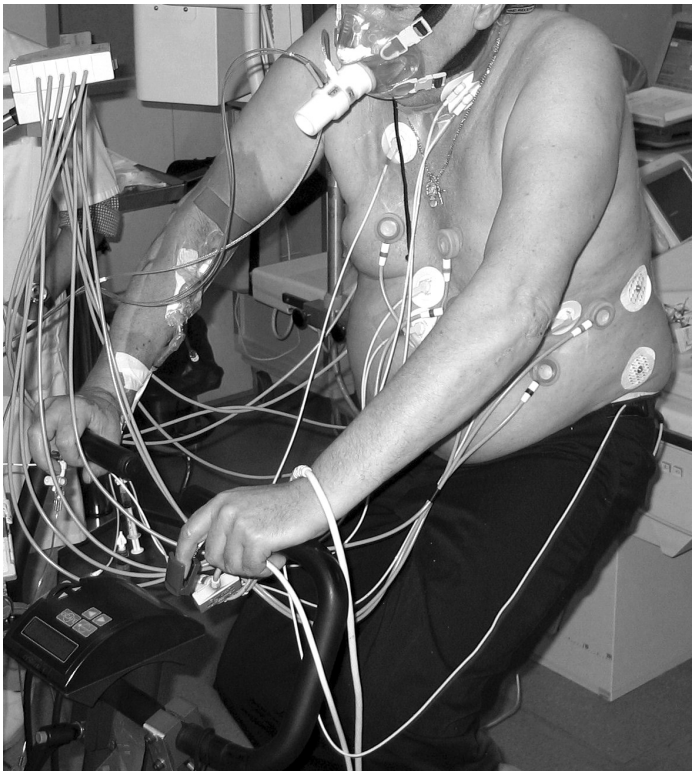
$$\dot{Q}\ (l/min) = \dot{V}O_2\ (ml/min) / (CaO_2 - C\bar{v}O_2)\ (ml/l)$$

with CaO_2 = arterial oxygen content (ml/l) and $C\bar{v}O_2$ = mixed venous oxygen content (ml/l)
and:
Oxygen content of blood = $\alpha PO_2 + SO_2 \times Hb \times 1.34$

with α = solubility coefficient of oxygen in blood at 37° C, PO_2 = partial pressure of oxygen, SO_2 = oxygen saturation, Hb = hemoglobin (g/dl), and 1.34 = the volume of oxygen (ml) which can combine with 1 g of Hb. The oxygen in physical solution was

ignored, because of the small value of α for blood (0.003 ml/100 ml per mm Hg). Stroke volume (SV) was calculated by dividing $\dot{Q}$ by heart rate.

Figure 1.



Picture of the experimental setup for the assessment of cardiac output during exercise using the Fick method. A fiberoptic pulmonary artery catheter was inserted through the right antecubital vein and an arterial catheter through the right radial artery. A pulse oximeter is attached to the left index finger. Respiratory gases are collected through a face-mask.

For cardiac output assessments at rest, the direct Fick method ($\dot{Q}_{dF}$) was applied as reference, using Hb and SO_2 values obtained from blood samples drawn from the radial and pulmonary artery that were analyzed by an in vitro oximeter (ABL800 Flex, Radiometer America Inc, Copenhagen, Denmark). These measurements were performed twice in an upright position before the start of the constant-load exercise tests (time interval about 5 min), and repeated during the preceding resting period of the symptom-limited maximal test.

During exercise, the continuous Fick method was applied as a reference method, using continuously measured $\dot{V}O_2$, SaO_2 and $S\bar{v}O_2$ data. After the tests, these data were resampled into 0.5 sec intervals, and synchronized by using event markers. The second resting Hb measurement was used to calculate cardiac output ($\dot{Q}_{cF}$). The

continuous Fick method was used because it allows multiple paired comparisons with the other methods. Previous studies demonstrated that this method is feasible and accurate during exercise in patients with left ventricular dysfunction.[17,18]

Pulse contour analysis (LiDCO)

The pulse contour analysis method (LiDCO Ltd, London, UK) provides beat-to-beat changes in stroke volume, by calculating nominal stroke volume from a pressure-volume transform of the radial artery pressure waveform. Heart rate is calculated by the duration between subsequent pressure waveforms. In order to convert nominal stroke volume to absolute stroke volume, the system needs to be calibrated. An advantage of this method is that a calibration method (indicator dilution) is already incorporated. The indicator, lithium chloride, can be administered through a central or peripheral vein.[19] The indicator dilution curve is generated by a flow-through cell containing a lithium selective electrode, which is attached to the arterial line.[20] Cardiac output is calculated from the dilution curve, using the following equation:

$\dot{Q}$ (l/min) = LiCl dose (mmol) × 60 / (area under the curve × [1-PCV])

with PCV = packed cell volume = Hb (g/dl)/34

After the patient was properly positioned on the ergometer, the calibration procedure started. First, the LiDCO plus monitor was connected to the SC9000 pressure monitor which, in its turn, was connected to the radial artery catheter. Subsequently, 2 ml lithium chloride (30 mmol LiCl) was injected into the right atrium through the pulmonary artery catheter. This measurement was repeated after 5 min and during the resting period preceding the symptom-limited exercise test. These resting measurements were used for comparison with the other cardiac output measurement methods. Immediately after each lithium dilution measurement, blood samples were drawn for determination of the reference $\dot{Q}_{dF}$. Therefore, the direct Fick method and lithium dilution were not performed simultaneously (delay: 10 to 15 sec). Normally, only 1 lithium dilution measurement is required for calibration. We used the second lithium dilution measurement for this purpose, because this was the last measurement before the start of the exercise protocol. After the calibration procedure, uncalibrated cardiac output values were automatically corrected to calibrated values.

During the exercise protocol, cardiac output ($\dot{Q}_{Li}$) and stroke volume values (SV_{Li}) were stored beat-to-beat for offline analysis.

Physioflow

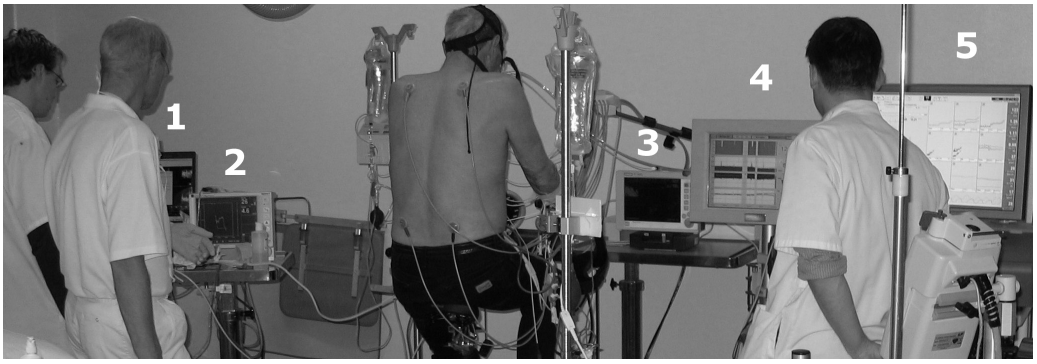
Physioflow is an impedance technique based on the principle that variations in the impedance to a high-frequency (75 kHz) low-magnitude (1.8 mA) alternating current

across the thorax during cardiac ejection result in a waveform from which SV can be calculated. Initially, stroke volume index is calculated at rest by evaluating 24 consecutive heart beats (autocalibration procedure), using measurements of the largest impedance difference during systole, the largest rate of variation of the impedance signal (contractility index), the thoracic fluid inversion time, heart rate, and the pulse pressure (= difference between systolic and diastolic arterial pressure).[12] Cardiac output is then calculated by multiplying the stroke volume index with body surface area and heart rate, which is obtained from the R-R interval determined on the ECG first derivative.[12] As compared to the commonly used Sramek-Bernstein approach,[21] Physioflow does not require estimations of baseline thoracic impedance or blood resistivity. Furthermore, as already stated, the position of the electrodes is not critical for the accuracy of the measurements.

After cleaning the skin, 2 pairs of electrodes (FS50, Skintact, Innsbruck, Austria) were positioned at the left base of the neck and along the xiphoid for transmitting and receiving electrical currents. Two electrodes were also placed on the chest (V1 / V6 position) to obtain the ECG signal. The autocalibration procedure was started after a period of at least 5 min, in which patients were sitting immobile on the cycling ergometer. The SV (SV_{Ph}) and cardiac output ($\dot{Q}_{Ph}$) values were stored beat-to-beat.

A picture of the complete experimental setup is shown in Figure 2.

Figure 2.



Picture of the complete experimental setup, showing the Physioflow impedance cardiography device (1), the hemodynamic monitor (2) which is connected to the pulmonary artery catheter for assessment of mixed venous oxygen saturation, the pressure monitor (3) which is connected to the radial artery catheter and to the LiDCO plus monitor (4), and finally the monitor which is connected to the respiratory gas analyser (5).

Data analysis

All cardiac output data were imported into MATLAB (Mathworks Inc, Natick, MA, USA). After removal of outliers,[22] data were synchronized by cross-correlating the heart rate data of the different assessment methods. Subsequently, data were

averaged into 30-sec intervals. Resting cardiac output and SV values obtained by LiDCO and Physioflow were compared with the direct Fick method at three different time moments, resulting in 30 measurements (10 patients x 3 measurements). During exercise, comparisons of simultaneous measurements were made during the last 2 min of constant-load exercise, resulting in 4 comparisons at both exercise intensities (i.e., a total of 80 measurements: 10 patients x 8 measurements), and during the last minute of the symptom-limited maximal test, resulting in 2 comparisons (i.e., a total of 20 measurements).

As outlined by Linton et al., the between-patient variability in cardiac output can have a substantial influence on the agreement between different assessment methods of absolute cardiac output values.[23] One may expect that the presence of within-patient changes in cardiac output may be of even greater relevance for the clinical utility of a cardiac output assessment method. Therefore, as in other studies,[6,24] we evaluated within-patient changes in cardiac output by calculating relative rather than absolute changes (i.e. % increase relative to the second resting cardiac output value). An advantage of this approach is that comparisons with other studies can be made irrespective of the absolute resting cardiac output values.

Statistical analysis

All data were analyzed using SPSS 12.0 statistical software (SPSS Inc, Chicago, III). Differences between continuous data were evaluated by the paired Student t test. Pearson's correlation coefficient (r) was calculated to quantify relations between variables. Differences between the assessment methods at rest and during exercise were evaluated by one-way ANOVA with Bonferroni post hoc analyses. The variation between measurements at rest and during steady state exercise (repeatability) was evaluated by the coefficient of variation (SD of difference as a percentage of the mean). Agreement between methods was assessed by the approach described by Bland and Altman.[25] The bias and limits of agreement (= bias ± 1.96 SD) among the methods are presented as a percentage of the mean values rather than as absolute values. This was done because it allows for a better evaluation of the relationship between cardiac output values and the size of the error.[26] Because there was no difference in heart rate among the different methods, bias and limits of agreement are equal for cardiac output and SV, and therefore only provided for cardiac output. Data are presented as mean ± SD. P values of less then 0.05 were considered statistically significant.

Results

At rest, 5 out of 30 $\dot{Q}_{dF}$ measurements could not be analyzed because of blood clot formation in the syringe (n = 3) or technical problems (n = 2). The indicator dilution measurements were not performed in 2 patients owing to logistic reasons. Because of aberrant shapes of the dilution curves, 4 of the remaining 24

measurements could not be used for further analysis, with at least 1 valid measurement in each of the remaining 8 patients. A total of 6 out of 30 resting $\dot{Q}_{Ph}$ measurements could not be analyzed because of an insufficient quality of the impedance signal. The mean coefficients of variation of the measurements at rest were 12.1% for the direct Fick method, 9.0% for lithium dilution, and 7.4% for Physioflow.

All subjects completed the exercise tests. During exercise, 8 out of 100 $\dot{Q}_{cF}$ measurements could not be used because of an unstable SO_2 signal from the fiberoptic catheter. As stated before, indicator dilution measurements could not be performed in 2 patients, resulting in a total of 80 available calibrated LiDCO measurements ($\dot{Q}_{Li}$). Of these measurements, 13 had to be excluded from further analysis due to damping or motion artifacts of the radial artery pressure tracing, with at least 2 remaining valid measurements per exercise intensity level in each patient. An insufficient quality of the impedance signal was observed in 24 out of 100 $\dot{Q}_{ph}$ measurements. The mean coefficients of variation of consecutive measurements at light steady state exercise were 4.5% for the continuous Fick method, 1.8% for LiDCO, and 2.4% for Physioflow. At moderate steady state exercise these coefficients of variations were 5.9%, 2.3% and 3.6%, respectively.

Table 2 summarizes cardiac output and SV values of the different methods at rest, during light and moderate constant-load exercise, and at peak exercise with corresponding $\dot{V}O_2$ and workload values. Considering the constant-load exercise tests, none of the subjects showed an increase in heart rate of more than 5% during the final 2 min of exercise (mean change: +0.9%, range: -4% - +4%). The mean

Table 2. Workload, oxygen uptake ($\dot{V}O_2$), cardiac output ($\dot{Q}$) and stroke volume (SV) values at rest, light and moderate constant-load exercise, and peak exercise in 10 CHF patients.

Variable	Rest	Light	Moderate	Peak
Workload (W)	-	26 ± 9	73 ± 23	108 ± 46
$\dot{V}O_2$ (ml/min)	302 ± 62	790 ± 142	1274 ± 330	1415 ± 396
$\dot{V}O_2$ (ml/min/kg)	3.5 ± 0.9	9.2 ± 2.5	14.8 ± 4.8	16.4 ± 5.1
$\dot{Q}$ (l/min)				
Fick [a]	3.8 ± 0.7	6.2 ± 1.3	9.0 ± 1.8	9.6 ± 2.3
LiDCO	3.8 ± 0.5	6.4 ± 1.4	9.0 ± 2.4	9.3 ± 2.4
Physioflow	6.3 ± 1.6	10.5 ± 2.6	13.7 ± 4.0	15.6 ± 5.4
SV (ml)				
Fick [a]	57 ± 15	79 ± 12	88 ± 13	87 ± 18
LiDCO	55 ± 10	75 ± 10	85 ± 16	84 ± 22
Physioflow	95 ± 15	134 ± 24	139 ± 27	140 ± 26

Values are mean ± SD. Light = constant-load exercise at 30% of the ventilatory threshold; Moderate = constant-load exercise at 80% of the ventilatory threshold; Peak = peak exercise.
[a] The direct Fick method was used at rest and the continuous Fick method during exercise.

change in $\dot{V}O_2$ during this period was +0.5% (range: -9% - +5%). This indicates that a steady state was attained in both constant-load tests.

Comparison of methods at rest

ANOVA revealed overall differences in $\dot{Q}$ and SV values at rest between the 3 assessment methods ($p < 0.001$); post hoc testing showed only significant differences in $\dot{Q}$ and SV values between Physioflow and both other methods ($p < 0.001$). Table 3 summarizes the bias and limits of agreement among the different methods. Both $\dot{Q}_{Li}$ and SV_{Li} were positively correlated with $\dot{Q}_{dF}$ and SV_{dF} ($r = 0.50$, $p = 0.04$ and $r = 0.71$, $p = 0.001$, respectively). Neither $\dot{Q}_{Ph}$ nor SV_{Ph} was significantly correlated with values obtained by the other methods.

Table 3. *Comparison of different methods for assessing cardiac output in CHF patients.*

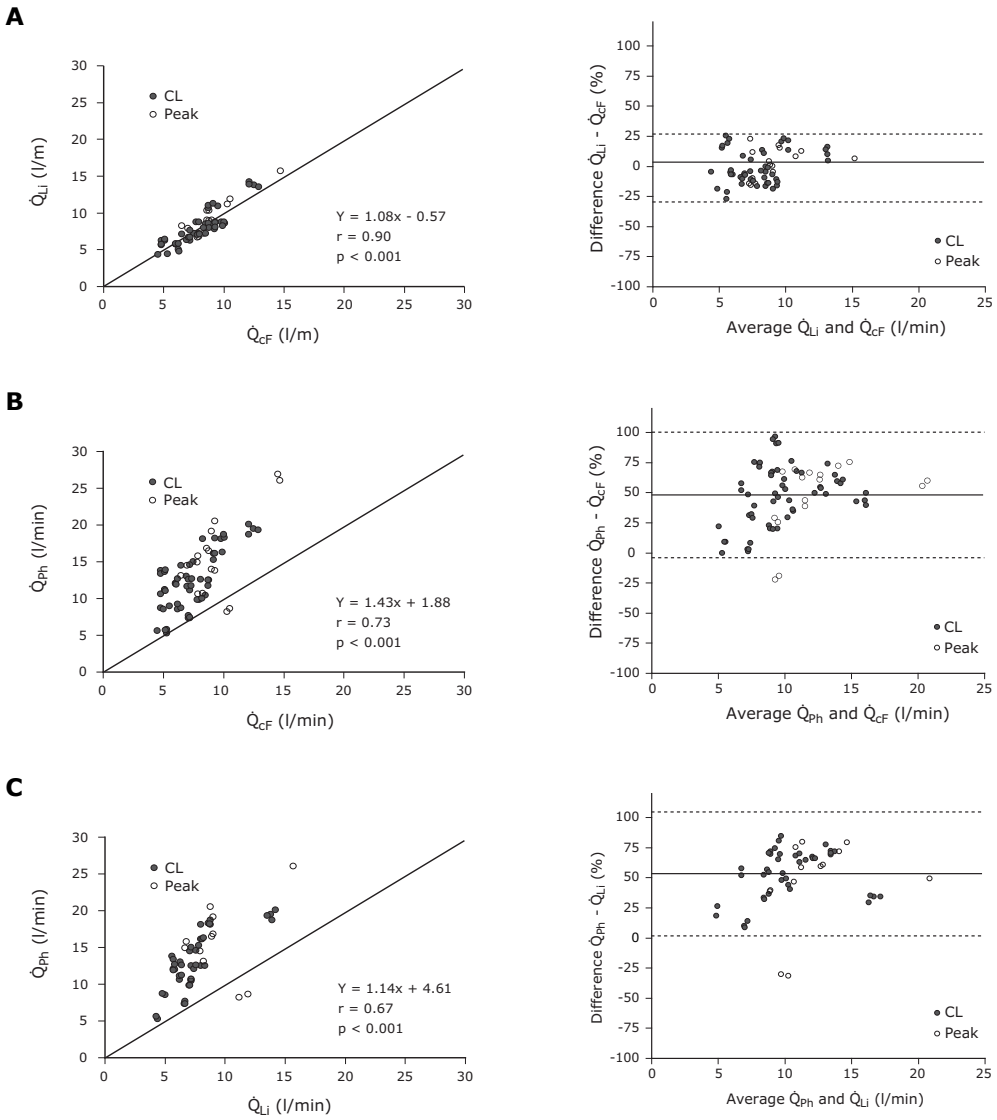
	LiDCO vs Fick [a]			Physioflow vs Fick [a]			Physioflow vs LiDCO		
	n	Bias (%)	LOA (%)	n	Bias (%)	LOA (%)	n	Bias (%)	LOA (%)
Rest	17	-1	-29 - 26	21	48	-12 - 108	18	52	6 - 98
Light	22	-1	-30 - 29	30	53	0 - 105	17	58	22 - 95
Moderate	26	-1	-28 - 26	27	42	-12 - 87	25	50	6 - 93
Peak	15	3	-22 - 28	16	47	-14 - 107	13	46	-28 - 120

Light = constant-load exercise at 30% of the ventilatory threshold; Moderate = constant-load exercise at 80% of the ventilatory threshold; Peak = peak exercise; Bias = mean difference between methods expressed as percentage of their mean values; LOA = limits of agreement (bias ± 1.96 SD) expressed as percentage. [a] The direct Fick method was used at rest and the continuous Fick method during exercise.

Comparison of methods during exercise

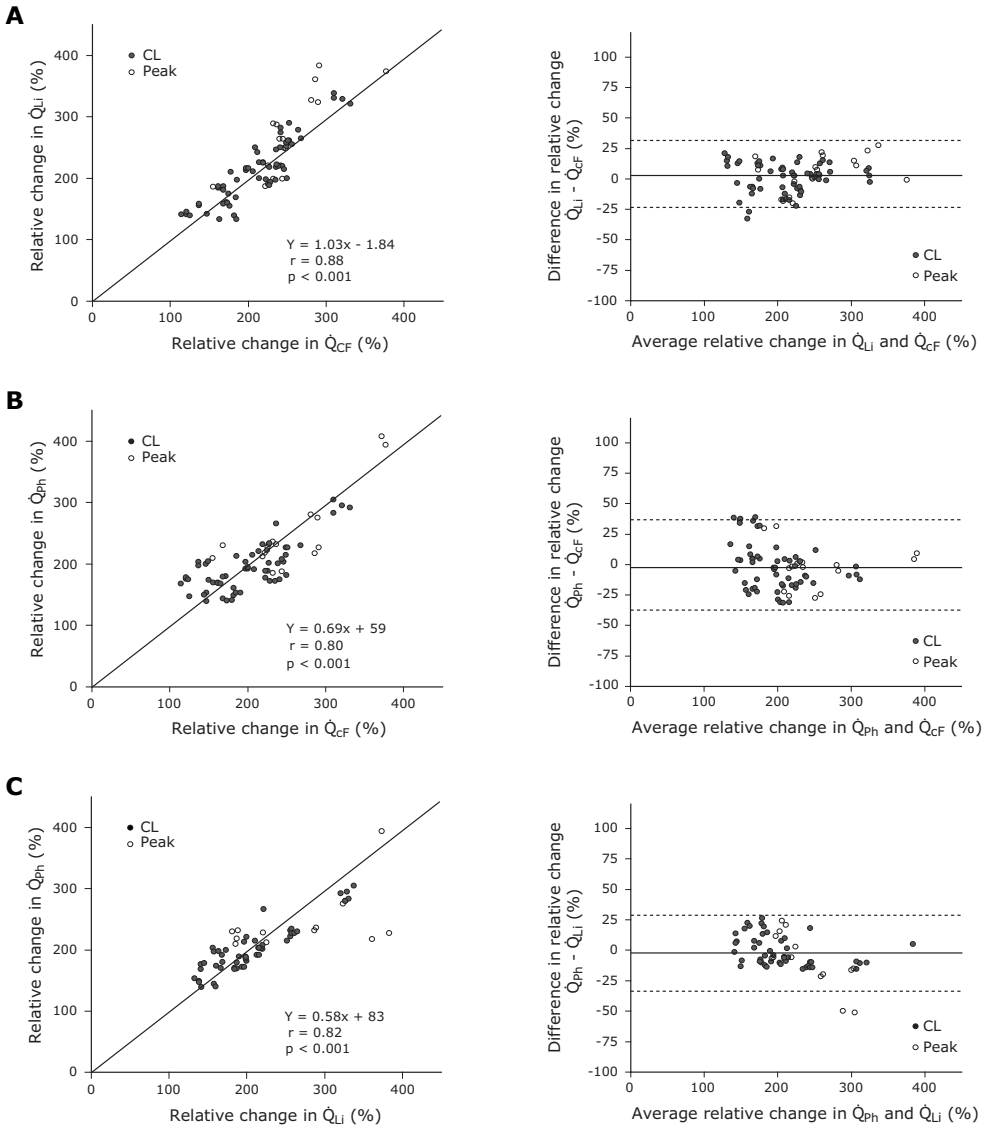
ANOVA revealed overall differences in $\dot{Q}$ and SV values among the methods ($p < 0.001$); post hoc testing revealed that only $\dot{Q}_{Ph}$ and SV_{Ph} were significantly different from values obtained from LiDCO or the continuous Fick method ($p < 0.001$). The bias and limits of agreement between the methods at different exercise levels are summarized in Table 3, and Figure 3 provides a graphic representation. A positive correlation was found between $\dot{Q}_{Ph}$ and $\dot{Q}_{cF}$ during exercise ($r = 0.73$, $p < 0.001$, Figure 3B, left); however, SV values of these methods were not significantly correlated. There were highly significant positive correlations between $\dot{Q}_{Li}$ and $\dot{Q}_{cF}$ ($r = 0.90$, $p < 0.001$, Figure 3A, left) and also between SV_{Li} and SV_{cF} ($r = 0.76$, $p < 0.001$). The lowest bias and narrowest limits of agreement were observed between $\dot{Q}_{Li}$ and $\dot{Q}_{cF}$ (0% ± 27%, Figure 3A, right). Bias and limits of agreement between $\dot{Q}_{Ph}$ and both other methods were from the same order of magnitude (48% ± 52% for $\dot{Q}_{Ph}$ versus $\dot{Q}_{cF}$ and 52% ± 50% for $\dot{Q}_{Ph}$ versus $\dot{Q}_{Li}$, Figure 3B and C, right).

Figure 3.



*Scatter diagrams (left panel) and corresponding Bland Altman plots (right panel) for cardiac output measurements during constant-load (CL) and peak exercise (Peak), comparing LiDCO ($\dot{Q}_{Li}$) with the continuous Fick method ($\dot{Q}_{cF}$) (**A**), Physioflow ($\dot{Q}_{Ph}$) with $\dot{Q}_{cF}$ (**B**), and $\dot{Q}_{Ph}$ with $\dot{Q}_{Li}$ (**C**). In the scatter diagrams the lines of identity are shown. The solid lines in the Bland Altman plots represent the mean difference between the tests, and the dashed lines indicate the 95% confidence intervals of the difference, expressed as a percentage of their mean values.*

Figure 4.



*Scatter diagrams (left panel) and corresponding Bland Altman plots (right panel) for relative changes in cardiac output, expressed as a % of the resting value, during constant-load (CL) and peak exercise (Peak), comparing LiDCO ($\dot{Q}_{Li}$) with the continuous Fick method ($\dot{Q}_{cF}$) (**A**), Physioflow ($\dot{Q}_{Ph}$) with $\dot{Q}_{cF}$ (**B**), and $\dot{Q}_{Ph}$ with $\dot{Q}_{Li}$ (**C**). In the scatter diagrams the lines of identity are shown. The solid lines in the Bland Altman plots represent the mean difference between the tests and the dashed lines indicate the 95% confidence intervals of the difference, expressed as a percentage of their mean values.*

Comparison of changes of cardiac output during exercise

When comparing relative within-patient changes in $\dot{Q}$, ANOVA showed no significant overall differences between the methods. However, significant differences between changes in SV values were observed ($p = 0.02$), with only a significant difference between Physioflow and LiDCO in post hoc analysis ($p = 0.03$). Correlations and Bland Altman plots comparing within-patient changes of cardiac output are depicted in Figure 4. The limits of agreement between changes of $\dot{Q}_{cF}$ and $\dot{Q}_{Li}$ (± 26%) were somewhat narrower than in the other comparisons ($\dot{Q}_{cF}$ versus $\dot{Q}_{Ph}$: ± 36%, and $\dot{Q}_{Li}$ versus $\dot{Q}_{Ph}$: ± 31%). In all comparisons the bias was close to zero (2%, -2%, and -3%, respectively). Significant correlations were observed among the different methods (Figure 4A-C left). In addition, changes of both SV_{Li} and SV_{Ph} showed positive correlations with changes of the reference SV_{cF} ($r = 0.67$, $p < 0.001$ and $r = 0.41$, $p < 0.001$, respectively), as well as with each other ($r = 0.51$, $p < 0.001$). Considering the transition from "rest" to light steady state exercise (i.e., the smallest increase in exercise intensity), there were no significant differences between relative changes among the methods. Bias and limits of agreement for changes at this transition were 2% ± 27% for $\dot{Q}_{cF}$ versus $\dot{Q}_{Li}$, -4% ± 42% for $\dot{Q}_{cF}$ versus $\dot{Q}_{Ph}$, and -4% ± 25% for $\dot{Q}_{Li}$ versus $\dot{Q}_{Ph}$.

Discussion

To decide whether a cardiac output measurement technique is useful in clinical practice, it is crucial to know the accuracy of the used reference method.[26] In the present study, we used the Fick method as the gold standard. Although this method is generally considered to be reliable in healthy individuals[4] and in CHF patients,[1,2] its accuracy during exercise is not well established. Theoretically, the Fick principle only applies to steady state conditions in which the time lag in the response of $\dot{V}O_2$ with respect to SaO_2 and $S\bar{v}O_2$[27] can be compensated. Therefore, it is questionable whether the Fick principle can be applied during peak exercise. Yamabe et al.,[18] however, reported that cardiac output obtained by the continuous Fick method during ramp exercise showed good agreement with values during steady-state exercise at the same intensity in CHF patients, suggesting that the Fick principle can also be applied during peak exercise in these patients.

The accuracy of the continuous Fick method mainly depends on operator-related factors and the summated inaccuracies of the measurements of $\dot{V}O_2$, SaO_2, $S\bar{v}O_2$, and Hb. According to the manufacturer's specifications, the gas exchange monitor for assessment of $\dot{V}O_2$ had a precision error of 1.5% (defined as 1 SD of the difference with the actual value). The used fiberoptic catheter had a precision error of 4%.[28] Assuming precision errors of 3% for SaO_2[29] and 2% for Hb,[30] we calculated a theoretic precision error of 11% for the continuous Fick method, with corresponding limits of error of 22%.[31] Because we considered a measuring method clinically useful when its limits of error approximated the continuous Fick method, limits of

agreement up to 31% were accepted.[26] It should be recognized that these limits only apply to the comparison of absolute values and not to the changes of cardiac output, because the precision error of the continuous Fick method to detect these changes is not exactly known.

Although LiDCO has been shown to be useful to assess cardiac output in patients undergoing major surgery,[24,32] its accuracy during exercise conditions has not been evaluated previously. In a study using a different pulse contour analysis method, it was shown that this method is not suitable for measuring absolute cardiac output values during exercise in healthy individuals.[33] However, it was also demonstrated that initial calibration with another method improved the accuracy substantially.[34] As already stated, an advantage of our method is that an indicator dilution method as calibration, is already incorporated. Although not all calibration measurements were successful in our study (failure rate of 17%), at least 1 valid measurement could be obtained in all patients. As only 1 calibration is required, this failure % does not have any impact on the potency of this technique in clinical practice. In agreement with other studies,[35,36] we observed an acceptable level of agreement with the reference method, and the repeatability of measurements was higher than the reference method (coefficient of variations: 9.0% and 12.1%, respectively). However, despite the high accuracy of the lithium dilution technique, there are some drawbacks to its clinical use. First, it is relatively time-consuming and expensive. Second, it requires an additional peripheral intravenous access for administration of lithium chloride.[19] Therefore, it is valuable to consider the use of non-invasive methods for calibration of this technique, such as Doppler cardiography[37] or open-circuit inert gas techniques.[38]

A major advantage of using LiDCO is that, once calibrated, it provides real-time beat-to-beat cardiac output data at rest and during exercise. However, an essential prerequisite remains a good quality of the radial artery pressure waveform. In our study, 16% of the calibrated measurements could not be used for further analysis because of the influence of damping or motion artifacts on the waveform during exercise. Yet, we could obtain two or more valid measurements at each exercise intensity level in all subjects, indicating that this technique is feasible during exercise in CHF patients. Considering the accuracy, we observed a low bias and acceptable limits of agreement between this technique and the continuous Fick method, both for the assessment of absolute values as well as for changes in cardiac output. However, this technique may somewhat overestimate cardiac output values exceeding 10 l/min (Figure 3A, left), possibly due to an overestimation of resting cardiac output during the calibration procedure. This view is supported by the observation that an obvious overestimation of changes in cardiac output in the higher range is lacking (Figure 4A, left). Another explanation for the possible overestimation of higher cardiac output values may be related to the fact that the algorithm that is used to transfer changes in arterial pressure to changes in volume is based on data obtained from healthy individuals. Yet, it was shown previously that exercise-induced changes

in the relation between arterial pressure and flow (arterial input impedance) in CHF patients were not different from changes in healthy individuals,[39,40] suggesting that the algorithm is also suitable for CHF patients.

Despite the possible overestimation of cardiac output values exceeding 10 l/min, this study showed that LiDCO is accurate for assessment of absolute cardiac output values in a range, which is normally obtained in CHF patients. Importantly, this technique was also able to detect accurately relatively small changes in cardiac output. Therefore, we postulate that pulse contour analysis is potentially useful for clinical purposes, such as assessment of prognosis or selection of candidates for heart transplantation[41], and for research purposes such as investigating the physiological determinants of exercise tolerance in CHF patients.[9-11]

Impedance cardiography is a simple, inexpensive and completely non-invasive method to assess cardiac output. The accuracy of impedance cardiography during exercise has been an issue of debate for many years, despite advancements in technology. Common problems which may compromise the quality of the impedance signal are movement and respiration artifacts,[3] as well as the presence of pulmonary congestion.[42] In the present study, 24% of the measurements obtained during exercise could not be analyzed because of insufficient quality of the signal. This relatively high % percentage of failure may have been caused mainly by an irregular or oscillatory breathing pattern.[43] As none of our CHF patients showed any clinical signs of pulmonary congestion we believe that this did not significantly affect our study results. Moreover, pulmonary congestion has been shown to cause an underestimation of cardiac output by impedance cardiography,[42] rather than an overestimation which we observed. Despite the relatively high failure rate of Physioflow in our study, we obtained successful measurements at all exercise intensity levels in 8 patients.

Considering the accuracy of Physioflow during exercise, previous studies in healthy individuals demonstrated a high level of agreement between Physioflow and the direct Fick method.[12,13] In contrast, the results of our study showed poor agreement with the reference method, with a systemic overestimation of SV by Physioflow. However, as shown by Bland Altman analysis, the relative bias (i.e. expressed as a % of the mean value) between Physioflow and the reference method was almost similar under rest and exercise conditions (Table 3). This suggests that the discrepancy between both methods during exercise is mainly caused by an overestimation of SV during the calibration procedure. This notion is supported by the fact that the bias between Physioflow and the reference method for estimating relative changes is negligible (Figure 4B, right). In a recent study with COPD patients, SV assessed by the Fick method was also overestimated by Physioflow.[14] It is striking that the mean resting SV value in these COPD patients was comparable with the CHF patients in our study (60 ml and 57 ml, respectively). As no significant bias between Physioflow and the Fick method was observed in healthy individuals

with higher SV values,[12,13] we postulate that the autocalibration algorithm of Physioflow is less suited for patients with relatively low SV values.

Despite the low accuracy of Physioflow for the assessment of absolute cardiac output values, we demonstrated a reasonable overall agreement between Physioflow and the reference method for the assessment of relative changes in cardiac output and SV. However, as shown by the Bland Altman plot (Figure 4B, right) and the relative wide limits of agreement between both methods for cardiac output changes from rest to light constant load exercise (± 42%), the accuracy of Physioflow to detect subtle changes in cardiac output is limited. Yet, as greater changes in cardiac output (i.e. > 200%) can be assessed with reasonable accuracy (Figure 4B, right), Physioflow may still be useful for clinical purposes such as the evaluation of the cardiac output response to maximal exercise in mild to moderate heart failure, or the evaluation of exertional dyspnea during cardiopulmonary exercise testing.

To our knowledge, there are no studies that have evaluated reproducibility of LiDCO and Physioflow during exercise in CHF patients, and also our study design did not permit an assessment of day-to-day reproducibility of these methods. However, we evaluated the variation of subsequent measurements of the different methods. Both at rest and during constant-load exercise, the mean coefficients of variation of LiDCO and Physioflow were lower than those obtained from the reference method. Another limitation of this study is that only moderately impaired male patients were included. Consequently, our observations cannot be generalized to women or more severely impaired patients.

In conclusion, although the limits of agreement with the Fick method are pretty broad, the accuracy of LiDCO is clinically acceptable for the assessment of absolute values of cardiac output as well as within-patient changes during exercise in a range which is normally obtained by CHF patients. There may, however, be a slight overestimation by values exceeding 10 l/min. While Physioflow offers the advantage of being completely non-invasive, relatively inexpensive and easy to use, it systematically overestimates cardiac output during exercise, due to an overestimation of stroke volume at rest. However, provided that changes in cardiac output are not too small (i.e. < 200%), this method may still be used to assess the relative increase in cardiac output during exercise in CHF patients. Although the failure rates of both LiDCO and Physioflow during exercise were relatively high (16% and 24%, respectively), the number of valid measurements was sufficient for these methods to be feasible in clinical practice.

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Chapter 7

Are oxygen uptake kinetics in chronic heart failure limited by oxygen delivery or oxygen utilization?

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Submitted

Abstract

Background: The delay in oxygen (O_2) uptake kinetics during and after submaximal physical activity (O_2 onset and recovery kinetics, respectively) correlates well with the functional capacity of patients with chronic heart failure (CHF). This study examined the physiological background of this delay in moderately impaired CHF patients by comparing kinetics of cardiac output ($\dot{Q}$) and O_2 uptake ($\dot{V}O_2$).
Methods: Fourteen stable CHF patients (New York Heart Association class II-III) and 8 healthy subjects, matched for age and body mass index, were included. All subjects performed a submaximal constant-load exercise test to assess O_2 uptake kinetics. Furthermore, in 10 CHF patients $\dot{Q}$ was measured by a radial artery pulse contour analysis method, which enabled the simultaneous modelling of exercise-related kinetics of $\dot{Q}$ and $\dot{V}O_2$.
Results: Both O_2 onset and recovery kinetics were delayed in the patient group. There were no significant differences between the time constants of $\dot{Q}$ and $\dot{V}O_2$ during exercise onset (62 ± 25 sec versus 59 ± 28 sec, $p = 0.51$) or recovery (61 ± 25 sec versus 57 ± 20 sec, $p = 0.38$) in the patient group, suggesting that O_2 delivery was not in excess of the metabolic demands in these patients.
Conclusion: The delay in O_2 onset and recovery kinetics in moderately impaired CHF patients is suggested to be due to limitations in O_2 delivery. Therefore, strategies aimed at improving exercise performance of these patients should focus more on improvements of O_2 delivery than on O_2 utilization.

Introduction

The rates of changes in oxygen uptake ($\dot{V}O_2$) during and after submaximal exercise (O_2 onset and O_2 recovery kinetics, respectively) have shown to provide objective information on exercise tolerance of patients with chronic heart failure (CHF),[1-3] with slower O_2 uptake kinetics being associated with more fatigue due to a greater reliance on anaerobic metabolism. In addition, O_2 uptake kinetics are related to prognosis of CHF patients.[4] Yet, the physiological mechanisms underlying the impairments of O_2 uptake kinetics in CHF patients are not well understood. More knowledge on this issue may contribute to the development of therapeutic strategies aiming at improvement of the functional capacity of these patients.

In theory, O_2 uptake kinetics depend on the rate of tissue oxygenation (O_2 delivery), and the ability to utilize O_2. Therefore, derangements of O_2 delivery and / or O_2 utilization may be responsible for the prolonged O_2 uptake kinetics in CHF. Possible mechanisms contributing to an impairment of O_2 delivery in CHF include cardiac insufficiency, vasoconstriction due to increased sympathetic activity,[5] elevated plasma angiotensin[6] and endothelin levels,[7] impaired nitric oxide-mediated vasodilatation,[8] and / or a blunted redistribution of blood flow from the non-exercising tissues to the working skeletal muscles.[9] Considering a limited O_2 utilization, previous studies reported in CHF patients an impaired skeletal muscle metabolism that was independent of a reduced blood flow.[10,11]

A useful approach to investigate the relative influence of impaired O_2 delivery and O_2 utilization on O_2 uptake kinetics is to compare the kinetics of cardiac output ($\dot{Q}$) and $\dot{V}O_2$. Studies in sedentary individuals showed that the increase in $\dot{Q}$ during submaximal exercise is faster than the increase in $\dot{V}O_2$.[12,13] As changes in $\dot{Q}$ have been shown to reflect changes in muscle blood flow,[14] these results indicate that O_2 delivery to skeletal muscles is in excess of the metabolic demands during exercise-onset. Therefore, it was postulated that O_2 onset kinetics in healthy sedentary individuals are limited by O_2 utilization.[13] Accordingly, the decrease in $\dot{Q}$ following submaximal exercise was shown to be slower than the decrease in $\dot{V}O_2$,[13,15] suggesting that in healthy sedentary subjects O_2 recovery kinetics are also limited by O_2 utilization. In contrast, in CHF patients the onset kinetics of $\dot{Q}$ were shown not to be faster than O_2 onset kinetics, suggesting a limitation of O_2 onset kinetics by O_2 delivery.[16,17] O_2 recovery kinetics were not evaluated in those studies. However, as we previously demonstrated that O_2 recovery kinetics are more reproducible and can be assessed more reliably than O_2 onset kinetics in CHF patients,[18] these kinetics may be even more suitable for investigating the physiological background of functional impairments in CHF. Therefore, this study was designed to investigate the physiological mechanisms underlying the delay in exercise-related O_2 onset and recovery kinetics in CHF patients by comparing the temporal profiles of $\dot{V}O_2$ and $\dot{Q}$.

Methods

Subjects

Fourteen patients with stable CHF were studied. Inclusion criteria were: heart failure secondary to ischemic or dilated cardiomyopathy, New York Heart Association class II or III, left ventricular ejection fraction of 40% or less (assessed by echocardiography), and sinus rhythm. Exclusion criteria were recent myocardial infarction (< 3 months prior), unstable angina pectoris, severe valvular heart disease, current involvement in a regular training program ≥ 2 times per week), significant chronic obstructive pulmonary disease and other disorders limiting the ability to exercise. In order to quantify the delay in O_2 uptake kinetics in CHF patients, measurements were also performed in a control group, consisting of 8 healthy subjects, matched for age and body mass index (BMI). None of these subjects were involved in competitive sports, and none were receiving any medication. Clinical characteristics of patient and control groups are listed in Table 1. The research protocol was approved by the local Research Ethics Committee, and all participants provided written informed consent.

Table 1. *Clinical characteristics of the study population.*

Variable	CHF patients (n = 14)	Control subjects (n = 8)	p-value
Male / female (n)	12 / 2	7 / 1	0.91
Age (years)	60 ± 13	59 ± 13	0.86
Body mass index, (kg/m^2)	28 ± 3	28 ± 4	0.58
LVEF (%)	36 ± 5	-	
NYHA class II / III (n)	12 / 2	-	
ICM / DCM (n)	6 / 8	-	
Medication (n)			
Diuretics	6	-	
Spironolactone	5	-	
ACE inhibitors / ARBs	14	-	
Beta-blockers	14	-	
Digoxin	0	-	
Oral anticoagulation	6	-	

Values are mean ± SD or n. LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; ICM = ischemic cardiomyopathy; DCM = dilated cardiomyopathy; ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker.

Exercise protocol

Exercise testing was performed in an upright position on an electromagnetically braked cycle ergometer (Corival, Lode, Groningen, The Netherlands). Ventilatory parameters were measured breath-by-breath (Zan 680 USB, Oberthulba, Germany).

Volume and gas analyzers were calibrated before each test. On testing days, patients were instructed to take their medication at the usual time and not to perform any extra physical activity.

In order to determine the ventilatory threshold, all patients and controls first underwent a symptom-limited exercise test, using an individualized ramp protocol.[19] This test was ended when the required pedaling frequency of 70/min could not be maintained, or when the patient was restricted by symptoms or signs of myocardial ischemia. Peak oxygen uptake ($\dot{V}O_2$) was defined as the average value of the last 30 sec of the test. The $\dot{V}O_2$ at the ventilatory threshold (VT) was determined using the V-slope method.[20]

On a second occasion within 1 week, a 6-min constant-load exercise test was performed at 80% of the workload corresponding to the VT of the symptom-limited exercise test. This intensity level was chosen to ensure that patients exercised below the VT, with sufficient $\dot{V}O_2$-amplitude remaining for the analysis of O_2 uptake kinetics. The test was preceded by a resting period of 2 min, and followed by a recovery period of 5 min. During this test, cardiac output measurements were performed simultaneously in the patient group.

Cardiac output assessment

Cardiac output ($\dot{Q}$) measurements were performed by using a radial artery pulse contour analysis method (LiDCO, LiDCO Ltd, London, UK), which was described in detail previously.[21] This technique provides beat-to-beat changes in stroke volume, by calculating nominal stroke volume from a pressure-volume transform of the radial artery pressure waveform. In order to convert nominal stroke volume to absolute stroke volume, the system needs to be calibrated at rest. We applied an indicator dilution method for this purpose. The indicator, lithium chloride (LiCl), can be administered through a peripheral vein. The indicator dilution curve is generated by a flow-through cell containing a lithium selective electrode, which is attached to the arterial line. Cardiac output is calculated from the dilution curve (the equation is shown in Chapter 6). In a recent study, using submaximal and maximal exercise in CHF patients, the assessment of $\dot{Q}$ by this method correlated highly with the Fick method (Chapter 6, Figure 3A).

Before the exercise test, a 20-gauge arterial catheter was inserted into the radial artery and a venous cannule into the antecubital vein. The radial artery catheter was connected to the LiDCO *plus* monitor. Subsequently, the calibration procedure was performed in the supine position. For this measurement, 2 ml LiCl (30 mmol) was injected into the antecubital vein. Immediately after the calibration procedure, patients were positioned on the cycle ergometer and the exercise protocol was started. For medical ethical reasons, cardiac output measurements were not performed in the control group

Kinetic analysis

To determine the kinetics of $\dot{V}O_2$ and $\dot{Q}$ during onset and recovery of the constant-load tests, all data were resampled into 10-sec intervals. Occasional errant $\dot{V}O_2$ values (e.g., due to coughing, swallowing or talking) were first deleted from the data set when $\dot{V}O_2$ exceeded three standard deviations of the local mean, defined as the average of two following and two preceding breaths.[22] Considering exercise onset, the first 20 sec of the data set were omitted, as 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.[23] To calculate time constants of onset and recovery kinetics of $\dot{V}O_2$ and $\dot{Q}$, a non-linear least squares regression procedure was applied to the onset phase (from 20 sec after the start of exercise until 6 min of exercise) and the recovery phase (from the end of exercise until 5 min of recovery), using mono-exponential functions of the following format:[13]

Onset kinetics: $Y_{(t)} = Y_{baseline} + A * (1 - e^{- (t - Td)/\tau)}$

Recovery kinetics: $Y_{(t)} = Y_{steady\ state} - B * (1- e^{- (t - Td)/\tau)}$

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

Baseline values were defined as the average values during the last min of the resting period, and steady state values as the average values during the last min of exercise. The other parameters in the fitting procedure (A, B, t and Td) were used as free parameters that were allowed to vary to optimize the fit. The 'goodness of fit' was determined by the coefficient of determination (R^2).

Statistical analysis

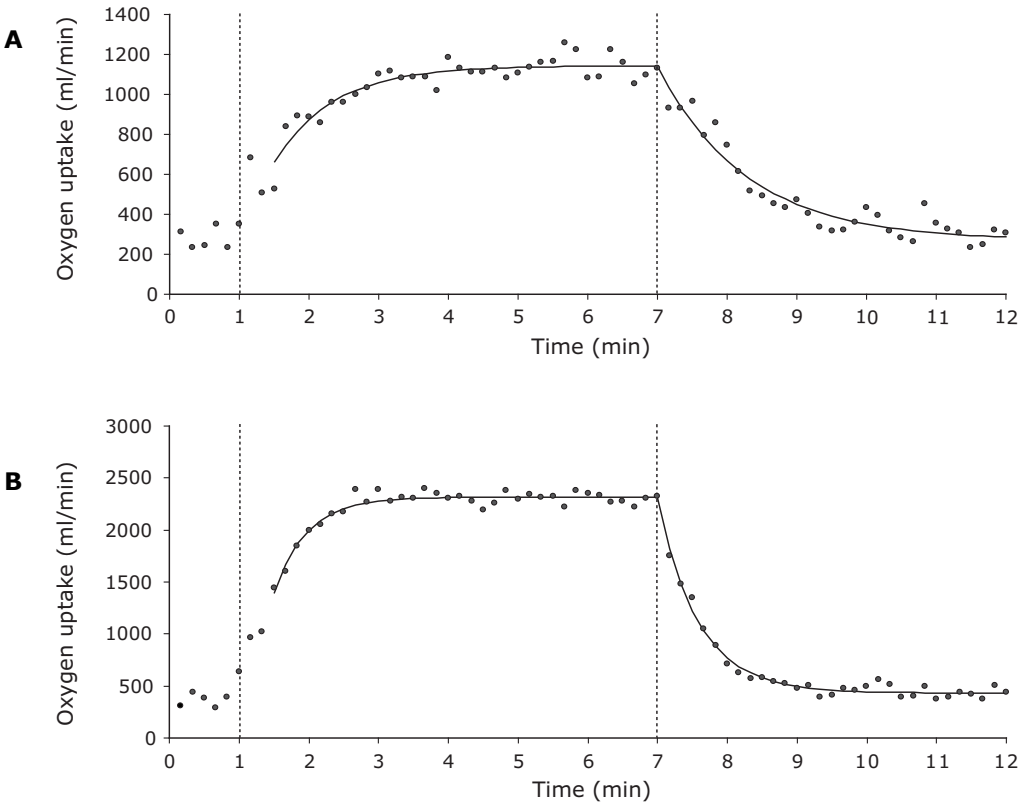
Data were analyzed using SPSS 16.0 statistical software (SPSS Inc, Chicago, IL, USA). Continuous variables are presented as mean ± SD. Categorical variables are presented as absolute frequencies. Owing to the small study population, non-parametric tests were used for analysis of the data. Wilcoxon signed rank sum test was used for paired observations of continuous data, and Mann-Whitney U test for unpaired comparisons. Differences between categorical data were evaluated by the χ^2 test. Relations between variables were assessed by Spearman correlation coefficients (r_s). For all statistical comparisons, the level of significance was set at $p < 0.05$.

Results

All subjects completed both exercise tests. As compared to the control group, CHF patients had a lower peak $\dot{V}O_2$ (20.2 ± 4.7 versus 36.7 ± 14.2 ml/kg/min, p = 0.006), peak workload (123 ± 30 versus 255 ± 87 W, p < 0.001), and $\dot{V}O_2$ at the VT (13.9 ± 1.8 versus 25.9 ± 11.0 ml/kg/min, p = 0.008).

The mean coefficient of determination (R^2) of O_2 onset kinetics was 0.91 ± 0.06 for the control group and 0.86 ± 0.07 for the patient group. Regarding O_2 recovery kinetics, R^2 was higher than for O_2 onset kinetics, both in the control group (0.97 ± 0.02 versus 0.91 ± 0.06, p = 0.01) and the patient group (0.94 ± 0.05 versus 0.86 ± 0.07, p = 0.001). Examples of exercise-related O_2 uptake kinetics in a CHF patient and a healthy control subject are shown in Figure 1.

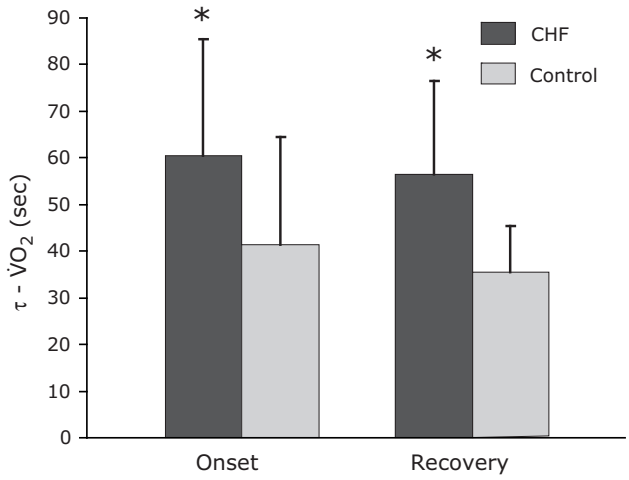
Figure 1.



*Changes in oxygen uptake during and after the constant-load test in a patient with chronic heart failure (**A**) and a healthy control subject (**B**). The curved line represent the mono-exponential model fit. The first vertical line indicates onset of exercise and the second vertical line the end of exercise.*

Figure 2 shows that the time constants of both O_2 onset and recovery kinetics lasted longer in CHF patients (60 ± 25 versus 41 ± 23 sec, p = 0.02, and 55 ± 19 versus 35 ± 10 sec, p = 0.004, respectively). There was no significant difference between O_2 onset and recovery kinetics in the patient group (p = 0.68), nor in the control group (p = 0.78).

Figure 2.

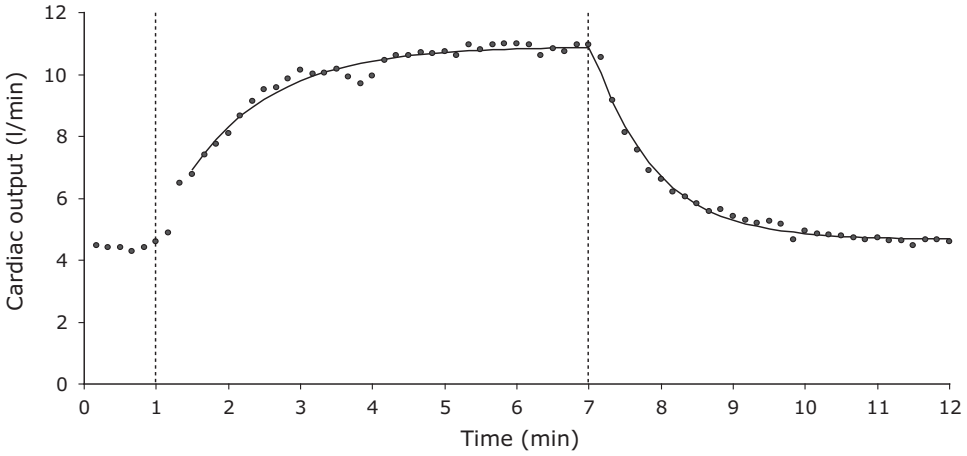


Mean and standard deviation of time constants of oxygen uptake (τ-$\dot{V}O_2$) during onset and recovery of the constant-load test in chronic heart failure (CHF) patients (n = 14) and healthy controls (n = 8).
** p < 0.05 compared to control group.*

Cardiac output ($\dot{Q}$) measurements could not be performed in 4 CHF patients due to technical difficulties (n = 2), vasovagal collapse (n = 1) and refusal (n = 1). These patients did not differ from the other patients with respect to age, BMI, peak $\dot{V}O_2$ and LVEF. In the remaining 10 patients the mean resting $\dot{Q}$ was 4.2 ± 1.5 l/min and at steady state exercise $\dot{Q}$ was 8.6 ± 2.6 l/min. The mean coefficient of determination of the time constant of $\dot{Q}$ was 0.94 ± 0.04 for exercise-onset and 0.96 ± 0.04 for recovery. An example of onset and recovery kinetics of $\dot{Q}$ is shown in Figure 3. There was no difference between $\dot{Q}$ onset and recovery kinetics (time constant: 62 ± 25 and 61 ± 25 sec, respectively, p = 0.72).

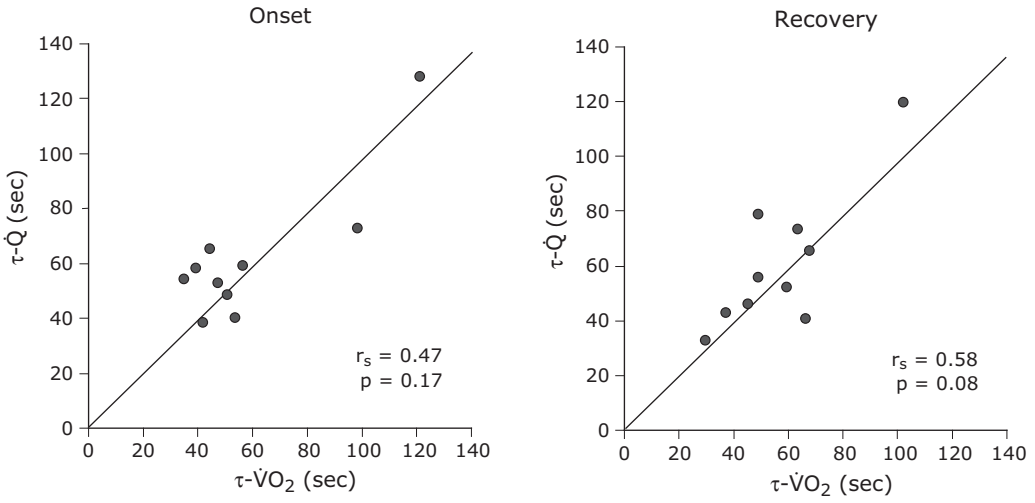
Comparing the kinetics of $\dot{Q}$ and $\dot{V}O_2$, no difference was observed between the time constants of $\dot{Q}$ and $\dot{V}O_2$ both during exercise onset (62 ± 25 versus 59 ± 28 sec, respectively, p = 0.51) and recovery (61 ± 25 versus 57 ± 20 sec, respectively, p = 0.38). Figure 4 shows scatterplots of individual values of the time constants of $\dot{Q}$ and $\dot{V}O_2$ during exercise-onset and recovery. No significant correlations between these variables were observed.

Figure 3.



Changes in cardiac output during and after constant-load test in a patient with chronic heart failure. The curved line represent the mono-exponential model fit. The first dashed vertical line indicates onset of exercise and the second vertical line the end of exercise.

Figure 4.



Relationship between the time constants (τ) of oxygen uptake ($\dot{V}O_2$) and cardiac output ($\dot{Q}$) during onset (left panel) and recovery (right panel) from the constant-load exercise test (n = 10). The line of identity is shown.

Discussion

The present study demonstrated that both exercise-related O_2 onset and recovery kinetics are delayed in moderately impaired CHF patients. Concerning the physiological background of this delay, it was shown that there was no difference between the kinetic responses of $\dot{Q}$ and $\dot{V}O_2$, suggesting that O_2 delivery is not in excess of the metabolic demands during and after submaximal exercise in these patients.

Our finding that O_2 onset kinetics during exercise below the anaerobic threshold are prolonged in CHF patients is in agreement with other studies addressing this issue.[1-3] However, the physiological mechanisms causing this delay are not well established. Richardson et al.[24] demonstrated that the rate of increase in skeletal muscle blood flow during exercise-onset was prolonged in CHF rats, suggesting that an impairment of O_2 delivery plays an important role in the delay in O_2 onset kinetics in CHF. This notion is supported by another study, showing that the microvascular O_2 -pressure in muscles, reflecting the ratio between local O_2 delivery and the rate at which O_2 is consumed, decreased more rapidly during exercise in CHF rats than in healthy controls.[25] To estimate the ratio of O_2 delivery to O_2 consumption in our study, we examined the temporal profiles of $\dot{Q}$ and $\dot{V}O_2$ in CHF patients. Previous studies using this approach in healthy individuals, reported faster onset kinetics of $\dot{Q}$ as compared to $\dot{V}O_2$,[12,13] indicating an excess of blood flow to the muscles relative to the metabolic rate. This suggests a limitation of O_2 utilization rather than O_2 delivery. Compared to these studies, we observed a considerably longer time constant of $\dot{Q}$ in CHF patients (62 sec versus lower than 30 sec), which is in close agreement with data of Koike et al.,[16] who used a comparable exercise protocol and study population. They reported a time constant of $\dot{Q}$ of 63 sec. In agreement with other studies,[16,17] we observed no difference between the onset kinetics of $\dot{Q}$ and $\dot{V}O_2$ in CHF patients, indicating a lower O_2 delivery rate relative to the metabolic demands than observed in healthy individuals, and thus suggesting a limitation of O_2 delivery rather than O_2 utilization during onset of submaximal exercise in moderately impaired CHF patients.

O_2 recovery kinetics after submaximal exercise were also prolonged in moderately impaired CHF patients as compared to healthy control subjects. This finding is in agreement with previous studies.[2,3] As daily life consists of a repetition of different submaximal activities, O_2 recovery kinetics are important for daily functioning of CHF patients. Moreover, O_2 recovery kinetics can be assessed more reliably than O_2 onset kinetics in CHF patients, as indicated by a higher coefficient of determination in the present study (0.94 ± 0.05 versus 0.86 ± 0.07, $p = 0.001$). Therefore, O_2 recovery kinetics may be particularly useful to grade functional impairments in CHF patients. However, there is a lack of knowledge about the physiological determinants of O_2 recovery kinetics in CHF. McDonough et al.[26] found a slower recovery of microvascular O_2-pressure following submaximal exercise in CHF rats than in healthy

controls, indicating a reduced O_2 delivery relative to the metabolic rate. Studies in healthy individuals, using measurements of $\dot{Q}$ to estimate the rate of change in O_2 delivery, demonstrated asymmetry of exercise-related $\dot{Q}$ kinetics, with recovery kinetics being appreciably slower than onset kinetics.[13,15] Yoshida et al. postulated that this delay in $\dot{Q}$ recovery kinetics serves to maintain sufficient O_2 delivery to skeletal muscles for a high oxygen uptake.[13] Studies in CHF patients using near infrared spectroscopy to estimate the temporal profile of local O_2 delivery during recovery of exercise, yielded conflicting results.[27,28] In the present study, we did not observe a difference between $\dot{Q}$ onset and recovery kinetics. Moreover, recovery kinetics of $\dot{Q}$ were not slower than O_2 recovery kinetics in our group of CHF patients, suggesting that there was no excess in O_2 delivery relative to the metabolic demands. Therefore, we postulate that in moderately impaired CHF patients O_2 recovery kinetics following submaximal exercise are limited by O_2 delivery rather than O_2 utilization.

Before drawing definitive conclusions from this study, some limitations should be acknowledged. First, we used cardiac output measurements to estimate the time course of O_2 delivery. It is, however, not certain if changes in $\dot{Q}$ during and after exercise resemble changes in local blood flow in the exercising muscles in CHF patients. In fact, in CHF patients with a severely depressed cardiac output response to exercise, exercise induces a greater shift in blood flow from non-exercising tissues to working muscles than in less impaired patients.[29] However, in CHF patients with a relatively high peak $\dot{V}O_2$, Sullivan et al. demonstrated that the proportion of cardiac output distributed to exercising muscles was similar to healthy subjects.[30] Since we included only moderately impaired CHF patients, we believe that exercise-induced redistribution of blood flow did not have a marked influence on the results.

Second, despite the inclusion of only moderately impaired patients (NYHA class II-III), the present study showed a limited number of patients with faster onset kinetics of $\dot{Q}$ than $\dot{V}O_2$, and / or slower recovery kinetics of $\dot{Q}$ than $\dot{V}O_2$ (Figure 4), suggesting that also limitations in O_2 utilization may play a role. Therefore, studies with a larger number of subjects are needed to evaluate patient's characteristics that may predict different limitations in exercise-related responses (e.g different etiology or medication use).

Third, it should be noted that the approach that we used to differentiate between physiological determinants that limit exercise tolerance does not permit a direct comparison between the contributions of impairments by O_2 delivery or by O_2 utilization. In fact, patients whose exercise capacity is limited by O_2 delivery, may also have an impaired muscle oxidative capacity. Therefore, to obtain a more complete picture of the pathophysiological changes in moderate heart failure, future studies should also focus on measurements of muscle oxidative capacity.

Finally, as the majority of the included patients were in NYHA class II (i.e., 86%), the results of this study are not generalizable to more severely impaired CHF patients.

In conclusion, the results of this study suggest that the delayed O_2 onset and recovery kinetics at submaximal exercise in moderately impaired CHF patients are mostly limited by an impairment of O_2 delivery to exercising muscles rather than O_2 utilization. In order to improve the exercise capacity of these patients therapeutic interventions should thus primarily be aimed at an increase in muscle blood flow.

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Chapter 8

Is skeletal muscle metabolic recovery following submaximal exercise in patients with chronic heart failure limited by oxygen delivery or oxygen utilization?

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Submitted

Abstract

Aims: To investigate the pathophysiological background of delayed skeletal muscle metabolic recovery following submaximal exercise in moderately impaired patients with chronic heart failure (CHF).

Methods: Thirteen stable CHF patients (New York Heart Association class II-III) and 8 healthy subjects, matched for age and BMI, performed repetitive submaximal dynamic single-leg extensions in the supine position. Post-exercise phosphocreatine (PCr) resynthesis was assessed by ^{31}P magnetic resonance spectroscopy (vastus lateralis muscle). PCr recovery kinetics were calculated by mono-exponential modelling. Near-infrared spectroscopy was applied simultaneously in the same muscle region, using the rate of decrease in deoxygenated hemoglobin (HHb) as an index of post-exercise muscle re-oxygenation. Recovery kinetics of HHb were calculated by the mean response time.

Results: PCr recovery was slower in CHF patients than in control subjects (time constant: 47.3 ± 10.0 sec versus 35.2 ± 12.0 sec, $p = 0.04$), and HHb recovery kinetics were prolonged (mean response time: 74.4 ± 41.2 sec versus 43.6 ± 17.1 sec, $p = 0.04$). In the patient group, HHb recovery kinetics were slower than PCr recovery kinetics ($p = 0.02$), while no difference existed in the control group ($p = 0.32$).

Conclusion: The slower muscle re-oxygenation compared to metabolic recovery in moderately impaired CHF patients indicates a lower O_2 delivery relative to metabolic demands. Therefore, we postulate that the impaired ability to perform repetitive daily activities in these patients depends more on a reduced muscle blood flow than on limitations in O_2 utilization.

Introduction

Chronic heart failure (CHF) has been shown to be associated with a prolonged recovery of skeletal muscle energy stores after submaximal exercise.[1-4] As daily life is characterized by repetitive submaximal activities, it can be assumed that this delayed recovery is an important contributor to exercise intolerance in these patients. Therefore, more insight into the physiological determinants of metabolic recovery is crucial for a better understanding of the pathophysiological basis of exertional fatigue in CHF patients and, moreover, it may help improving therapeutic approaches in these patients.

Factors influencing the rate of recovery of muscle energy stores are O_2 delivery and O_2 utilization. Whereas O_2 delivery is determined by muscle blood flow and arterial O_2 content, O_2 utilization is associated with oxidative capacity of skeletal muscles. Studies in healthy untrained individuals have provided evidence that metabolic recovery is limited by O_2 utilization, rather than O_2 delivery.[5-7] In CHF patients, both impairments of muscle blood flow[8,9] and muscle oxidative capacity[10,11] have been documented. To what extent these derangements contribute to the delayed muscle metabolic recovery in these patients, however, is not well established.

Near-infrared spectroscopy (NIRS) is a non-invasive method providing a continuous assessment of changes in tissue oxygenation. This technique is based on the principle that oxygenated (O_2Hb) and deoxygenated hemoglobin (HHb) have different absorption characteristics for near-infrared light. Assuming a constant O_2 content in arterial blood, changes in these parameters reflect changes in the ratio between muscle blood flow and local O_2 uptake. Therefore, in combination with assessment of muscle metabolism, NIRS is potentially useful to investigate the relative influence of O_2 delivery and O_2 utilization on muscle metabolic recovery.[12] Provided that muscle acidosis is not severe, ^{31}P magnetic resonance spectroscopy (^{31}P MRS) measurements of phosphocreatine resynthesis (PCr) can be used to evaluate the time course of the muscle metabolic rate.[13-15] To our knowledge, only one study combined NIRS and ^{31}P MRS measurements during exercise recovery in CHF patients.[1] In that study, CHF patients were found to have slower recovery of both PCr resynthesis and muscle tissue oxygenation. In contrast with healthy controls, PCr resynthesis was even slower than tissue re-oxygenation in the patient group, suggesting that metabolic recovery in CHF is mainly limited by O_2 utilization.

The present study was conducted to quantify the delay in muscle metabolic recovery following submaximal exercise in moderately impaired CHF patients, and to examine the pathophysiological background of this delay by performing simultaneous measurements of ^{31}P MRS and NIRS in CHF patients and healthy individuals.

Methods

Subjects

Thirteen patients with stable CHF were recruited. In- and exclusion criteria are described in Chapter 7. Additional exclusion criteria were the presence of a pacemaker or implantable cardioverter defibrillator and claustrophobia. The control group consisted of 8 age- and body mass index matched healthy subjects. These subjects were not receiving any medication, and none were competitive athletes. Subject characteristics are listed in Table 1.

Table 1. *Clinical characteristics of the study population.*

Variable	CHF patients (n = 13)	Control subjects (n = 8)	p-value
Male / female (n)	12 / 1	7 / 1	0.72
Age (years)	60 ± 14	59 ± 13	0.75
Body mass index (kg/m^2)	28 ± 3	28 ± 4	0.80
LVEF (%)	36 ± 5	-	
NYHA class II / III (n)	11 / 2	-	
ICM / DCM (n)	6 / 7	-	
Medication (n)			
Diuretics	6	-	
Spironolactone	5	-	
ACE inhibitor / ARBs	13	-	
Beta-blockers	13	-	
Digoxin	0	-	
Oral anticoagulation	6	-	

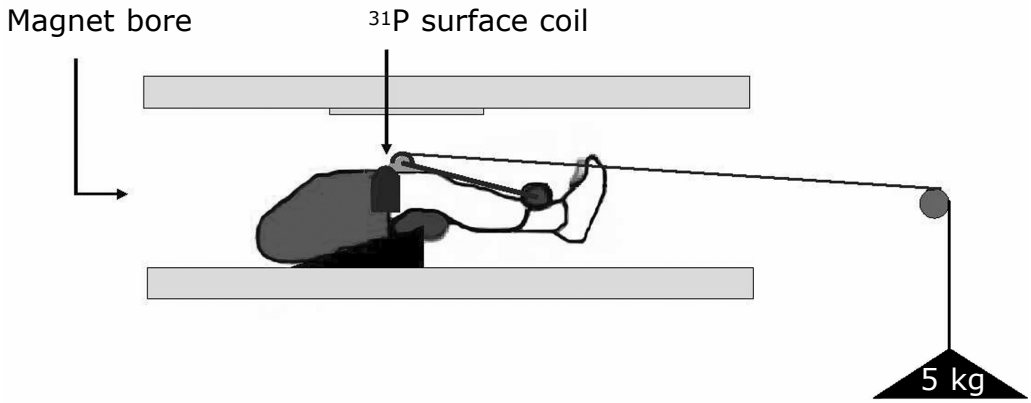
Values are mean ± SD or n. LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; ICM = ischemic cardiomyopathy; DCM = dilated cardiomyopathy; ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker.

The research protocol was approved by the local Research Ethics Committee, and all subjects provided written informed consent.

Exercise protocol

Exercise consisted of dynamic single leg extensions in the supine position. The right upper leg was immobilized with Velcro straps with the knee supported in approximately 90 degrees of flexion. Subjects were instructed to lift a lever resting on the lower leg which was attached to a weight via a pulley system (Figure 1). One contraction was performed every 1.5 sec, paced by a digital metronome. All subjects performed exercise tests on 2 occasions within 1 week.

Figure 1.



Schematic drawing of a subject performing dynamic single leg extensions inside the MRI scanner. ^{31}P signals are obtained by using a surface coil which is placed over the vastus lateralis muscle.

During the first session, patients underwent an exercise test until exhaustion with 1 min incremental steps. The initial weight applied and the incremental steps were set individually, aiming at a total test duration of 4 to 6 min. In addition to familiarizing subjects with the procedure, this test was used to determine the duration and workload during the second session.

During this second visit, the exercise protocol was adjusted individually such that phosphocreatine (PCr) depletion approximated 50% at the end of the test (see ^{31}P magnetic resonance spectroscopy). In addition, a drop of intra-cellular pH below 6.8 was avoided in order to minimize the influence of muscular acidosis on PCr recovery kinetics.[16-18] Exercise was followed by a recovery period of at least 5 min, in which PCr recovery kinetics were assessed.

^{31}P magnetic resonance spectroscopy

During recovery from exercise, PCr is resynthesized purely as a consequence of adenosine triphosphate (ATP) generation, mainly by oxidation reactions within mitochondria. Because the creatine kinase reaction is much faster than ATP production, the PCr resynthesis rate is considered to reflect mitochondrial oxidative phosphorylation flux.[13-15]

In this study, ^{31}P magnetic resonance spectroscopy was performed with a 1.5-T whole-body magnet (Gyroscan S15 / ACS, Philips Medical Systems, Best, The Netherlands). The spectroscopy procedures that were used have been described previously.[18,19] In brief, after the magnetic field homogeneity was optimized by localized shimming on the proton signal, ^{31}P signals were collected using a 6-cm diameter surface coil placed over the vastus lateralis muscle of the right leg (mid

thigh level, Figure 1). Data were acquired following a 90° adiabatic excitation pulse with a sweep width of 2 kHz and 1,024 data points. First, a fully relaxed spectrum was obtained at rest with a repetition time of 30 sec and 24 scans. During the exercise protocol, spectra were acquired with a repetition time of 3 sec.

Spectral analysis

Zero- and first-order phase corrections were determined from the rest spectra and then also applied to the time series. Spectra were fitted in the time domain by using a nonlinear least-squares algorithm (AMARES)[20] in the jMRUI software package.[21] PCr, inorganic phosphate (Pi), ATP, and phosphodiester (PDE) signals were fitted to Lorentzian line shapes as described by Praet et al.[19]

Absolute concentrations of PCr were calculated after correction for partial saturation and assuming that the ATP concentration is 8.2 mmol/l at rest.[22] PCr depletion was defined as the difference between resting and end exercise PCr concentrations divided by the resting value. Intracellular pH was calculated from the chemical-shift difference between the Pi and PCr resonances as described previously.[15]

For analysis of PCr recovery kinetics, data were averaged into 6 sec intervals (2 scans), and subsequently fit to a mono-exponential model of the following format:

$$[PCr]_{(t)} = [PCr]_{(EE)} + A * (1- e^{-(t/\tau)})$$

with $[PCr]_{(EE)}$ = the PCr concentration (mmol/l) at the end of the exercise test, A is the amplitude of the post-exercise increase in [PCr], and τ is the time constant (sec).

The 'goodness of fit' of the model was determined by the coefficient of determination (R^2).

Near Infrared Spectroscopy

Near-infrared spectroscopy is based on the O_2 dependency of absorption changes for near infrared light in hemoglobin and myoglobin, allowing a noninvasive estimation of concentration changes of oxygenated (O_2Hb) and deoxygenated hemoglobin (HHb). The theoretical principles and clinical utility of this measurement technique have been described previously.[23,24]

In the present study, NIRS measurements were performed by a single channel continuous-wave near-infrared spectrophotometer (OXYMON, Artinis, Zetten, The Netherlands) with 2 wavelengths of emitting light (775 and 850 nm). The light source and detectors were connected to the leg with 2 nonmagnetic fiberoptic light guides. In order to obtain NIRS and ^{31}P MRS measurements from the same region in the vastus lateralis muscle, the light guides were integrated into the MRS-coil. Data were sampled at 50 Hz and stored for off-line analysis.

Unlike other studies in CHF patients,[1,25] we used deoxygenated hemoglobin

(HHb) to evaluate the recovery kinetics of muscle oxygenation. This approach was chosen because it has been demonstrated that exercise-induced changes in total arterial blood volume under the NIRS probe significantly influence the kinetics of oxygenated hemoglobin (O_2Hb), irrespective of changes in tissue oxygenation.[23,26,27] Since the amount of HHb in arterial blood is low when assuming a normal arterial O_2 saturation, changes in arterial blood volume can be expected to have a relatively low impact on HHb kinetics. Therefore, HHb kinetics are considered a more accurate marker of muscle tissue oxygenation than O_2Hb kinetics.[23,26,27]

As demonstrated by Ferreira et al.,[5] HHb recovery kinetics following submaximal exercise can be adequately assessed by the mean response time (i.e. time delay + time constant of mono-exponential decrease), approximating the time to reach 63% of the response. To calculate this mean response time (MRT-HHb), we first re-sampled the HHb data into 1 sec intervals. The time delay (Td_{HHb}) was defined as the time until HHb dropped more than 1 SD below the end-exercise HHb value.[28] End-exercise HHb was defined as the average value of the last 20 sec of exercise. To calculate the time constant of the subsequent HHb decrease until 5 min of recovery (τ), a mono-exponential function of the following format was applied:

$$[HHb]_{(t)} = [HHb]_{(BL)} - A * (1- e^{-(t - Td)/\tau})$$

with $[HHb]_{(BL)}$ = the baseline HHb concentration (arbitrary units, a.u.) at the point from which the data were fitted, A is the amplitude of the post-exercise decrease in [HHb], Td is the time delay (sec), and τ is the time constant (sec).

The 'goodness of fit' of the model was assessed by R^2.
Finally, as already stated MRT-HHb was calculated as $\tau + Td_{HHb}$.

Statistical analysis

Data were analyzed using SPSS 16.0 statistical software (SPSS Inc, Chicago, IL, USA). Continuous variables are presented as mean ± SD, categorical variables as absolute frequencies. Because of the relatively small study populations, non-parametric tests were used for analysis of the data. Wilcoxon signed rank sum test was used for paired observations of continuous data, and Mann-Whitney U test for unpaired comparisons. Differences between categorical data were evaluated by the χ^2 test. Relations between variables were assessed by Spearman correlation coefficients (r_s). For all statistical comparisons, the level of significance was set at $p < 0.05$.

Results

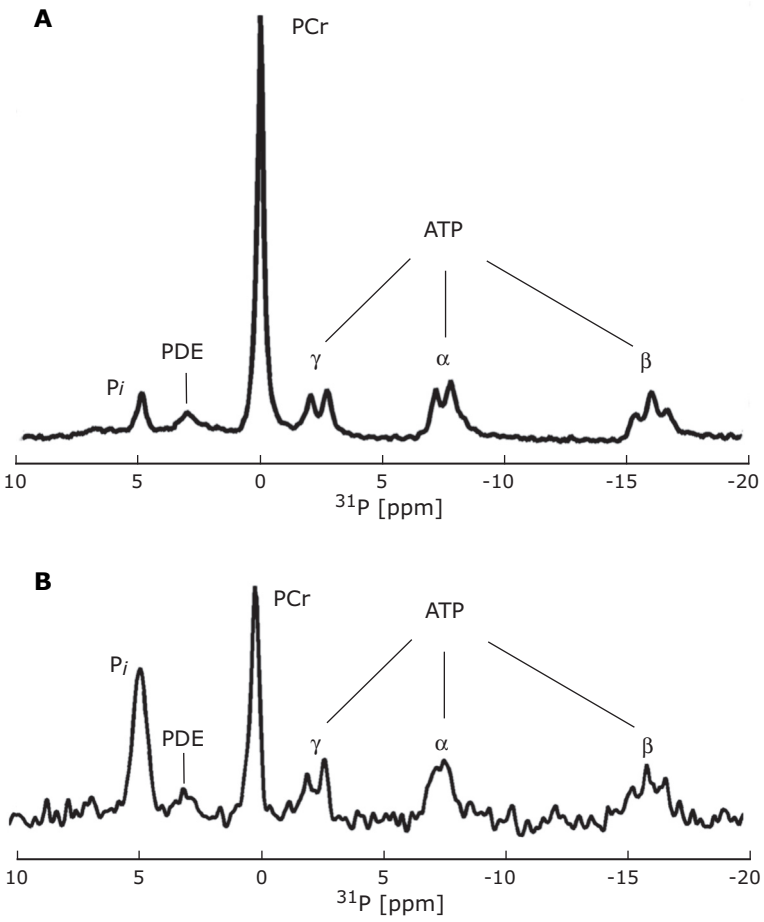
All subjects completed the exercise tests. Measurements obtained by ^{31}P MRS at rest and at the end of exercise are shown in Table 2.

Table 2. *Parameters obtained by ^{31}MRS at rest and the end of exercise.*

Variable	CHF patients (n = 13)	Control subjects (n = 8)	p-value
Rest			
PCr (mmol/l)	38.6 ± 2.7	35.3 ± 2.6	0.03
pH	7.06 ± 0.02	7.07 ± 0.02	0.29
Exercise			
PCr (mmol/l)	19.7 ± 4.0	18.2 ± 4.6	0.41
pH	6.93 ± 0.04	6.92 ± 0.05	0.75
PCr depletion	0.49 ± 0.09	0.48 ± 0.13	1.00

Values are mean ± SD; PCr = phosphocreatine.

Figure 2.

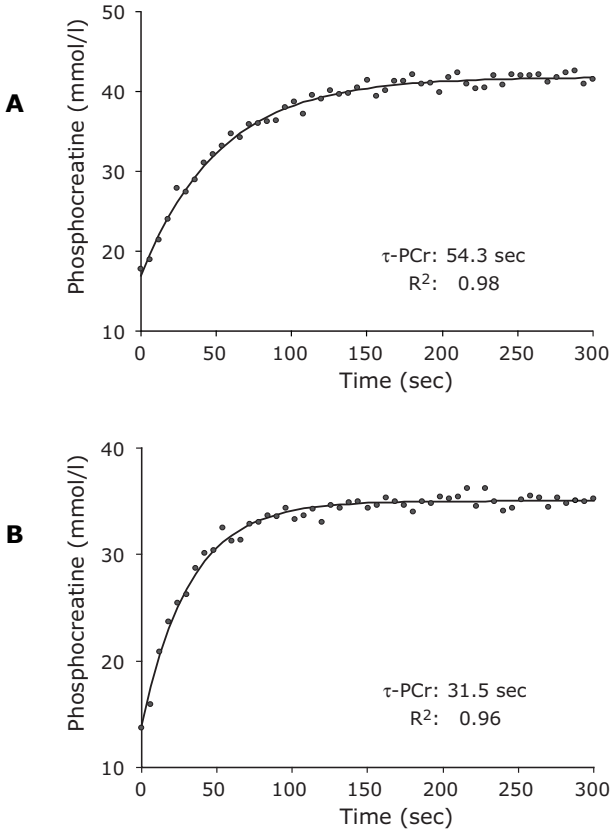


*^{31}P MRS spectra at rest (**A**, average of 60 scans) and at the end of exercise (**B**, average of 2 scans). PCr = phosphocreatine; Pi = inorganic phosphate; PDE = phosphodiesters; ATP = adenosine triphosphate.*

Resting PCr concentrations were significantly lower in the control group, but there was no difference in PCr depletion during exercise, indicating that both groups exercised at the same relative exercise intensity. In addition, there were no significant differences in exercise duration (4.9 ± 1.5 min versus 4.6 ± 1.9 min, p = 0.94) or intracellular pH at the end of exercise between patient and control groups (Table 2). Typical examples of phosphorus spectra at rest and at the end of exercise are shown in Figure 2.

The coefficient of determination (R^2) of the mono-exponential fits of PCr recovery was 0.96 ± 0.02 (range: 0.92 - 0.98) in the patient group and 0.94 ± 0.03 (range: 0.89 - 0.97) in the control group, indicating a good fit of the mono-exponential model to the data in both groups. Figure 3 shows representative examples of the time courses of PCr during recovery from exercise in a CHF patient and a healthy subject.

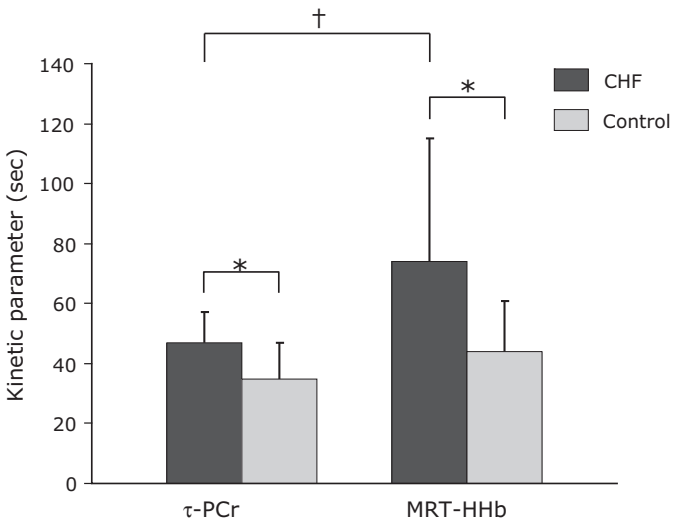
Figure 3.



*Representative examples of the time course of phosphocreatine (PCr) during recovery from single leg extensions in a patient with chronic heart failure (**A**) and a healthy control subject (**B**). The curved line represents the mono-exponential model fit. Calculated values of the time constant (τ-PCr) and the coefficient of determination (R^2) are shown in the Figure.*

As shown in Figure 4, the time constant of PCr recovery (τ-PCr) in the patient group was significantly greater than in the control group (47.3 ± 10.0 sec vs 35.2 ± 12.0 sec, respectively, with p = 0.04), indicating a slower muscle metabolic recovery in the patient group.

Figure 4.

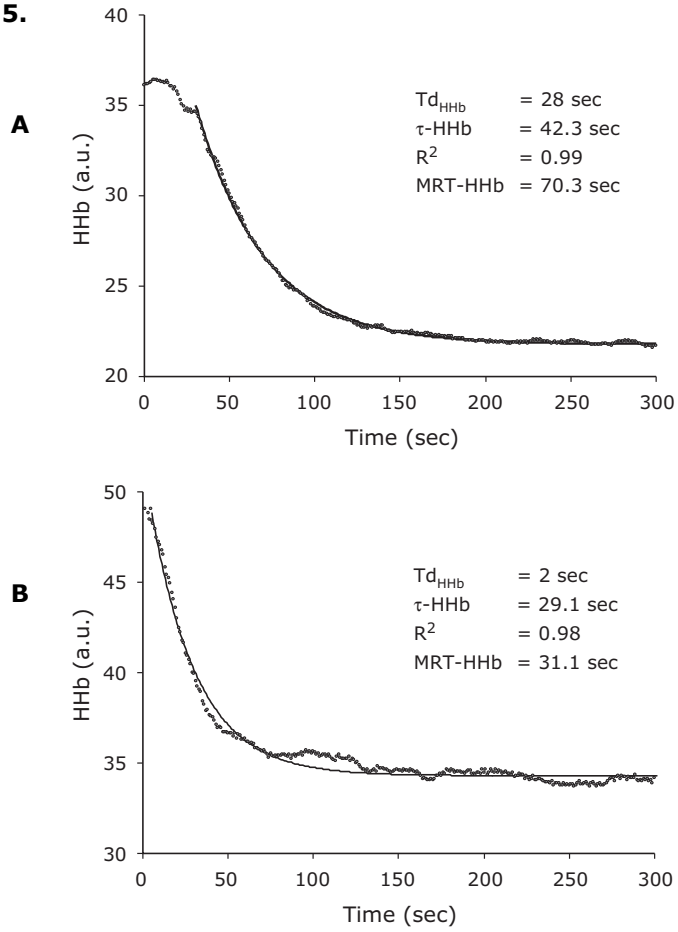


*Kinetic parameters of phosphocreatine (time constant, τ-PCr) and deoxygenated hemoglobin (mean response time, MRT-HHb) during recovery from submaximal single leg extension in chronic heart failure (CHF) patients (n = 13) and healthy controls (Control, n = 8). * p < 0.05 between CHF patients and healthy controls; † p < 0.05 between τ-PCr and MRT-HHb*

NIRS data were successfully obtained and analyzed in all patients. In both groups, R^2 for the determination of the time constant of the post-exercise HHb decrease (τ-HHb) exceeded 0.90 in all cases (patient group: 0.98 ± 0.02, control group: 0.98 ± 0.01). Representative examples of HHb recovery following exercise are shown in Figure 5. Comparing patient and control groups, there were no significant differences in Td_{HHB} (19.0 ± 21.7 sec vs 5.4 ± 4.6 sec respectively with p = 0.37) or τ-HHb (53.9 ± 38.2 sec vs 38.2 ± 15.0 sec respectively with p = 0.41). However, MRT-HHb was significantly greater in the patient group (74.4 ± 41.2 sec vs 43.6 ± 17.1 sec, respectively, with p = 0.045, Figure 4).

As shown in Figure 4, MRT-HHb lasted longer than τ-PCr in the patient group (74.4 ± 41.2 sec vs 47.2 ± 10.0 sec, respectively with p = 0.02), while there was no significant difference between these parameters in the control group (43.6 ± 17.2 sec vs 35.2 ± 12.0 sec respectively with p = 0.32). There were no significant relations between MRT-HHb and τ-PCr in both groups (patient group: r_s = 0.35, p = 0.25; control group: r_s = -0.14, p = 0.74).

Figure 5.



*Representative examples of the time course of deoxygenated hemoglobin (HHb) during recovery from single leg extensions from the same subjects as in Figure 2: a patient with chronic heart failure (**A**) and a healthy control subject (**B**). The curved line represents the mono-exponential model fit. Calculated values of the time delay (Td_{HHb}), time constant (τ-HHb), coefficient of determination (R^2), and mean response time (MRT-HHb) are shown in the Figure.*

Discussion

To our knowledge, this is the first study to simultaneously assess the kinetics of skeletal muscle re-oxygenation and muscle metabolic recovery after submaximal exercise in patients with CHF. The main findings were that both PCr resynthesis and muscle re-oxygenation were delayed in CHF compared to healthy subjects. Importantly, muscle re-oxygenation was slower than PCr recovery kinetics only in the

patient group. These findings suggest that the observed delay in the recovery of muscle energy stores in CHF patients is determined by an impairment of O_2 delivery rather than O_2 utilization.

Considering ^{31}P magnetic resonance spectroscopy measurements, we found slightly higher resting PCr concentrations in CHF patients than in healthy individuals, which is in contrast with other studies.[1,3] As it was shown that intracellular PCr concentrations are higher in type II muscle fibers than in type I muscle fibers,[29] this finding may indicate that the patients that we included had a higher % of type II muscle fibers than the healthy controls, which is in agreement with other studies.[10,30] Considering muscle metabolic recovery, we observed a slower PCr recovery in CHF patients than in healthy subjects, which is in agreement with previous studies.[1-4,31,32] Only 2 of these studies applied a mono-exponential model to assess PCr recovery, both reporting greater time constants than in our study (74.6 ± 11.3 sec and 76.3 ± 30.2 sec vs 47.2 ± 10 sec respectively). However, in one of these studies more severely impaired CHF patients (NYHA class III-IV) were included.[4] In the other study, the exercise-induced decrease in muscle pH was greater than in our study (6.56 ± 0.01 vs 6.93 ± 0.04).[1] Yet, it was demonstrated that severe intramuscular acidosis considerably delays the rate of PCr resynthesis.[16-18]

Only few studies have examined the relative influence of impairments of local O_2 delivery and O_2 utilization on submaximal exercise capacity in CHF. Studies focusing on exercise onset yielded conflicting results. Animal studies demonstrated a delayed exercise-related increase in skeletal muscle capillary blood flow[33] and a more rapid lowering in microvascular pO_2 in CHF as compared to healthy controls,[34] pointing at a limiting role of O_2 delivery. In contrast, human studies showed that abnormalities in muscle metabolism are not associated with a reduced muscle blood flow during submaximal exercise in CHF patients.[35,36] The exercise protocols applied in those studies, however, involved small muscle groups (calf and forearm muscles respectively) and, therefore, the results of those studies may not be representative for exercise performed with larger muscle groups. Studies evaluating the physiological determinants of metabolic recovery from submaximal exercise in CHF patients are scarce. In a study with severely impaired CHF patients, Toussaint et al. showed that prolonged PCr recovery kinetics were associated with a reduction of reactive hyperemic blood flow, suggesting that local circulatory dysfunction contributes to the prolonged metabolic recovery in these patients.[4] The measurement techniques used in that study, however, did not permit simultaneous assessment of perfusion and metabolism in the same muscle area. Moreover, muscle perfusion could not be measured continuously during exercise recovery. In a study, using direct measurements of microvascular O_2-pressure in the exercising muscle of rats, McDonough et al. found a slower muscle re-oxygenation following submaximal exercise in CHF.[37] Using Near Infrared Spectroscopy (NIRS), we also found a delay in post-exercise muscle re-oxygenation in humans with CHF, which is in agreement

with other studies in CHF patients.[1,25] From a physiological point of view, changes in tissue oxygenation are determined by changes in the ratio between local O_2 delivery and O_2 uptake. Accordingly, the observed delay in post-exercise muscle re-oxygenation in CHF patients indicates a reduced ratio of O_2 delivery to the metabolic demands in these patients, suggesting that an impairment of O_2 delivery plays an important role in the delay in metabolic recovery in moderately impaired CHF patients. Still, additional research is needed to establish a definite causal relationship, for example by investigating the effect of alterations of muscle blood flow on muscle metabolic recovery.

When comparing the kinetics of muscle metabolic recovery and muscle re-oxygenation, we observed a slower muscle-reoxygenation in CHF patients, whereas no difference in these kinetics existed in healthy subjects, providing further evidence for the notion that impairments of muscle blood flow are responsible for the prolonged metabolic recovery in these patients. This finding is in contrast with that of Hanada et al.,[1] who reported faster muscle re-oxygenation than PCr resynthesis in CHF patients, while no difference was observed in healthy subjects. Several methodological differences may have contributed to this discrepancy with our results. First, the exercise protocol that we used was different from that used by Hanada et al. In our study, exercise involved a larger muscle group (quadriceps versus calf muscles) and, therefore, impairments of O_2 delivery may have had a greater influence on metabolic recovery. Also, we adjusted the exercise intensity based on individual phosphocreatine depletion, therefore standardizing metabolic responses during recovery in patient and control groups. In contrast, Hanada et al. used a percentage of maximal workload to determine exercise intensity. However, this approach resulted in a greater exercise-related phosphocreatine depletion and muscle pH drop in the patient group as compared to the control group. As several studies have shown that severe intracellular acidosis delays PCr recovery due to an increased proton efflux rate,[16-18] this may explain, at least in part, the discrepancy with our study. Another important methodological difference with our study is the fact that Hanada et al. did not perform ^{31}P MRS and NIRS measurements simultaneously. This may have lead to differences in muscle sample areas. Yet, as shown recently, small differences in muscle sample areas may lead to considerable differences in microvascular oxygenation kinetics.[38] In addition, although Hanada et al. used similar exercise protocols for ^{31}P MRS and NIRS measurements, their patients may have performed exercise more efficiently during the second test. Finally, considering the analysis of the NIRS data, Hanada et al. did not include a time delay in the evaluation of the kinetics of muscle tissue re-oxygenation. However, our results indicate that such a time delay can be of considerable magnitude in CHF patients (19.0 ± 21.7 sec) and should therefore be included in the overall kinetic analysis of muscle tissue oxygenation.

Clinical implications

The results of this study suggest that recovery from daily physical activity is delayed by a reduction in O_2 delivery in moderately impaired CHF patients. This implies that, in order to increase the functional capacity of these patients, therapeutic interventions should primarily be aimed at increasing local skeletal muscle blood flow. This can be achieved by reducing local vasoconstriction, by improving local endothelial function (e.g. by endurance training),[39,40] or by improving the distribution of blood flow to exercising limbs through an improvement of the metabolic efficiency in other tissues (e.g. by inspiratory muscle training).[41]

Study limitations

Although we demonstrated a difference in the kinetics of muscle metabolic recovery and muscle re-oxygenation between CHF patients and healthy subjects at a group level, the wide variations and lack of correlation between the kinetic variables indicate that there is a physiological heterogeneity in both patient and control groups. Therefore, studies with larger numbers of subjects are needed to identify subgroups with different physiological profiles and different underlying mechanisms of exercise tolerance.

Another limitation of this study is the fact that the exercise protocol involved single leg extensions in the supine position. It is, therefore, not certain whether the results of this study also apply to whole body exercise in an upright position. However, as the present study suggest that recovery from local exercise is already limited by muscle blood flow, it can be expected that this also applies to whole body exercise. Indeed, Belardinelli et al. demonstrated a slower recovery of muscle tissue oxygenation following upright submaximal cycling exercise in CHF patients.[25] Nevertheless, future studies investigating the pathophysiological mechanisms of delayed metabolic recovery in CHF patients should also include whole body exercise.

Conclusions

The present study showed that muscle metabolic recovery following submaximal single leg extension is delayed in moderately impaired CHF patients. This prolonged metabolic recovery is associated with an even slower muscle tissue re-oxygenation, suggesting that recovery from submaximal exercise in these patients is limited by a reduced muscle blood flow, rather than an impaired O_2 utilization. The underlying physiological mechanisms, such as excessive vasoconstriction, a reduction of local vasodilatory capacity or redistribution of blood flow, remain to be determined.

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Chapter 9

Discussion and future directions

One of the hallmark symptoms of patients with chronic heart failure (CHF) is exercise intolerance. Since clinical symptoms are not reliable indicators of the functional capacity of these patients, exercise testing has become indispensable.[1] Although the introduction of breath-by-breath respiratory gas analysis during ergometry has substantially improved our ability to evaluate the maximal aerobic capacity (peak $\dot{V}O_2$), it is still not clear which exercise parameters are most indicative of the functional capacity of CHF patients.[2] O_2 uptake kinetics, reflecting the ability to adapt to and recover from exercise, have been shown to be potentially useful for grading functional impairments in these patients.[3-5] However, their evaluation in the CHF population is not a routine part of daily clinical practice. Possible reasons for this include insufficient knowledge on the reliability and reproducibility of assessment techniques and a lack of studies addressing the sensitivity of O_2 uptake kinetics for assessing interventional changes in functional capacity in CHF patients, such as those evoked by physical training. In addition, our knowledge of the controlling mechanisms of O_2 uptake kinetics in these patients is incomplete. This thesis addresses both clinical potency (Part I) and physiological aspects (Part II) of O_2 uptake kinetics in CHF patients. The findings of the studies from this thesis and the answers to the central questions as formulated in the introduction are summarized and discussed here.

1) Are O_2 uptake kinetics useful in clinical practice to quantify and predict the effects of physical training in CHF patients?

In the past two decades, numerous studies have documented favorable effects of physical training on exercise performance in CHF patients.[6-13] For both clinical and research purposes, it is of crucial importance that parameters are used which can evaluate the effects of physical training objectively. These parameters should reflect the ability to perform daily activities. In this respect, studies in healthy subjects have shown that O_2 onset[14,15] and recovery kinetics[16,17] are useful objective markers for the assessment of training-related changes in exercise capacity. However, it is not well established whether this applies to CHF patients. An important prerequisite is that these parameters can be obtained reliably and that their reproducibility is acceptable.

Calculation methods

To date, many different calculation methods have been used to assess O_2 uptake kinetics in CHF patients.[4,18-21] The applicability and reproducibility of these methods have not been compared previously. Therefore, we evaluated the goodness-of-fit and reproducibility of previously described methods to characterize O_2 onset and recovery kinetics at submaximal exercise in 19 moderately impaired CHF patients (**chapter 2**). This study revealed that the assessment of O_2 recovery kinetics is feasible and reproducible, in contrast to O_2 onset kinetics, which showed a

substantially lower reproducibility. By using a mono-exponential model with 5 breath sampling intervals to calculate the time constant of the $\dot{V}O_2$ decrement (τ-rec) during recovery, it was shown that an interventional change of at least 13 sec in τ is needed to exceed normal test-to-test variations.

Possible explanations for the difference in reproducibility between O_2 onset and recovery kinetics include a relatively great influence of movement artefacts and typical ventilatory oscillations during exercise onset.[22] As ventilatory oscillations in CHF patients are most pronounced during the transition from rest to exercise,[23] they may have a greater influence on the reliability of the assessment of O_2 onset kinetics than O_2 recovery kinetics.[23] Another explanation for the low reproducibility of O_2 onset kinetics may be the fact that our exercise protocol commenced with unloaded pedaling instead of rest. This results in a relatively low $\dot{V}O_2$-amplitude and, consequently, a relative low signal-to-noise ratio.[24] Notwithstanding this disadvantage, the main reason for using such an exercise protocol was to reduce the duration of the early rapid increase of oxygen uptake (phase I or cardiodynamic phase). Since the change of $\dot{V}O_2$ during phase I is functionally distinct from the subsequent mono-exponential increase of $\dot{V}O_2$ (phase II), we presumed that a reduction of the relative contribution of this phase might result in a better fit of the mono-exponential model. Given the results of this study, however, we feel that future studies should also evaluate the reproducibility of O_2 onset kinetics during rest-exercise transitions. A strategy that may be used to increase the signal-to-noise ratio involves averaging the $\dot{V}O_2$ responses from multiple exercise tests.[24] As such an approach is complicated and time-consuming, it is questionable whether it would be used in clinical practice.

In conclusion, O_2 recovery kinetics show acceptable reproducibility in moderately impaired CHF patients. Using the presented exercise protocol, the reproducibility of O_2 onset kinetics is too low to warrant their use for clinical purposes such as the grading of functional impairments or the assessment of effects of therapeutic interventions.

Assessment of training effects

Traditionally, training effects in CHF patients are evaluated by measuring peak $\dot{V}O_2$. However, as maximal exercise performance may not reflect the ability to perform daily tasks correctly, training-related changes in submaximal exercise capacity are probably more indicative of improvements in daily functioning.[2] Therefore, we evaluated the utility of O_2 onset and recovery kinetics at submaximal exercise to assess training effects in 39 CHF patients (**chapter 3**), using the kinetic parameters with the highest reproducibility as presented in **chapter 2**. In addition, recovery kinetics after maximal exercise were assessed. In a randomized trial with a semi-crossover design, we showed that a 12-week training program resulted in significant within- and between-group improvements of the parameters τ-rec (the time constant during recovery from submaximal exercise) and $\dot{V}O_2$ at the ventilatory

threshold (VT). There was, however, no significant between-group improvement in peak $\dot{V}O_2$, peak workload, or O_2 recovery kinetics following maximal exercise. In line with other randomized controlled trials,[13,25] this indicates that the effects of physical training in CHF patients are manifested more clearly in improvements at a submaximal exercise level than at a maximal exercise level. Comparing the clinical utility of τ-rec or $\dot{V}O_2$ at the VT, τ-rec offers the advantage of being easier to determine (failure rate 0% versus 13%, respectively).

In contrast with O_2 recovery kinetics after submaximal exercise, O_2 onset kinetics were not accelerated after the training period. Recently, Roditis et al. also failed to demonstrate an acceleration of phase II O_2 onset kinetics in CHF patients after cycle interval training, but observed a significant improvement of these kinetics after continuous cycle training. The authors postulated that this discrepancy in training responses may be due to the fact that cycle interval training is less effective than continuous training in increasing skeletal muscle capillarization and / or mitochondrial content and function.[26] However, we observed a highly significant improvement in O_2 recovery kinetics, suggesting that our training program, which also included resistance training, induced an improvement in local O_2 delivery and / or utilization. Hence, the lack of improvement in O_2 onset kinetics in our study with a relatively low sample size is more likely to be related to the low accuracy and reproducibility of these kinetics (**see chapter 2**) than to an absent training response.

In conclusion, evaluation of O_2 recovery kinetics following submaximal exercise is useful for the assessment of the effects of physical training in CHF patients. With the exercise protocol applied, the sensitivity of O_2 onset kinetics is too low for the detection of training effects in CHF patients. Other strategies that are available to assess O_2 onset kinetics in these patients (e.g. by averaging the $\dot{V}O_2$ responses from multiple exercise tests) are time-consuming and therefore only useful for further research, but not for daily clinical practice.

Prediction of training effects

While physical training has been shown to improve the exercise tolerance in CHF patients at a group level, a substantial number of these patients do not or only minimally respond to training.[27,28] As a consequence, one may expect a considerable heterogeneity in training responses in these patients. Since the physical training of CHF patients requires considerable effort from both patients and clinicians, is expensive and not completely without risks, it is of clinical interest to be able to predict beforehand whether training responses are to be expected.[29,30] In a study with 50 CHF patients, we evaluated the potential of both clinical and exercise-related parameters to predict the effects of a 12-week training program (**chapter 4**). As we showed that the effects of physical training were manifested mainly at a submaximal exercise level (**chapter 3**), training effects were not only expressed as a change in maximal exercise capacity (peak $\dot{V}O_2$), but also as changes in submaximal exercise-

related parameters (τ-rec and $\dot{V}O_2$ at the VT). After training, peak $\dot{V}O_2$, $\dot{V}O_2$ at the VT, and τ-rec improved significantly, with a substantial number of non-responders (i.e., improvement < 10%) for these outcome measures (50%, 49%, and 48%, respectively). In agreement with previous studies,[13,31,32] clinical parameters (i.e., age, gender, body mass index, left ventricular ejection fraction, NYHA functional class, etiology of heart failure, medication use) did not predict the training effects. However, about one-third of the variation in training responses could be predicted by parameters from baseline maximal and submaximal cardiopulmonary exercise testing. In particular, O_2 recovery kinetics following maximal exercise, expressed as the recovery half-time of peak $\dot{V}O_2$ (T½-$\dot{V}O_2$), proved to be the strongest predictor of improvements in peak $\dot{V}O_2$ and $\dot{V}O_2$ at the VT, with slower kinetics being associated with a lower training effect. As T½-$\dot{V}O_2$ has been shown to be negatively correlated with the central hemodynamic response to exercise in CHF patients,[33] our results suggest that patients with more pronounced circulatory dysfunction are less likely to respond to physical training than moderately impaired patients. This finding is in agreement with studies directly assessing the cardiac output response to exercise.[27,28] The only baseline variable predicting post-training changes in τ-rec after submaximal exercise was τ-rec, with slower kinetics at baseline being associated with a higher training effect. In previous studies, it was demonstrated that delayed O_2 recovery kinetics after submaximal exercise in CHF patients reflect peripheral derangements in skeletal muscles rather central hemodynamic dysfunction.[34,35] As physical training has been shown to mainly affect peripheral muscle function rather than central hemodynamics,[32,36] it is not surprising that patients with slower O_2 recovery kinetics, and thus more pronounced skeletal muscle derangements, benefit more from a training program than patients with faster O_2 recovery kinetics.

In conclusion, this study confirmed previous observations that there is a considerable heterogeneity in training responses in moderately impaired CHF patients. Although we showed that O_2 recovery kinetics following maximal and submaximal exercise substantially contribute to the prediction of training effects in these patients, the explained variance in training effects by all variables obtained from cardiopulmonary exercise testing was too low to make a definite distinction between training responders and non-responders. Therefore, we recommend that future studies combine cardiopulmonary exercise testing with other possible predictors of training effects, such as the cardiac output response to maximal exercise[27,28] or genetic factors.[37]

2) What are the physiological determinants of O_2 uptake kinetics in CHF patients?

Daily life is characterized by repetitive submaximal activities. Accordingly, it can be assumed that prolonged O_2 onset and recovery kinetics at submaximal exercise, reflecting a delay in the adaptation to and recovery from daily physical activities, are important contributors to exercise intolerance in CHF. Therefore, more knowledge of the physiological determinants of O_2 uptake kinetics in these patients may contribute to the development of therapeutic strategies aimed at improving their functional capacity.

As outlined in the introduction, O_2 uptake kinetics are determined by the rate of O_2 delivery and the ability to utilize O_2. Whereas O_2 delivery is determined by local blood flow and arterial O_2 content, O_2 utilization reflects the oxidative capacity of tissues. To date, it has not been clearly established whether O_2 uptake kinetics at submaximal exercise in CHF patients are limited by O_2 delivery or O_2 utilization. The ideal approach to investigate this issue would be to measure the dynamics of microvascular O_2-pressure (PO_2m) in exercising muscles, reflecting changes in the balance between O_2 delivery and O_2 utilization. At this stage, however, PO_2m measurements can only be done in animals.[38,39] Other strategies should be used to estimate this balance during submaximal exercise in humans. One such strategy is to compare the exercise-related kinetics of cardiac output and $\dot{V}O_2$. An important prerequisite for using this approach is that cardiac output can be assessed reliably during exercise in non-steady-state situations. Commonly accepted methods of cardiac output assessment in patients with CHF include the direct Fick method and thermodilution.[40,41] However, because these methods require the insertion of a pulmonary artery catheter, they are unsuitable for routine clinical use during exercise. Several less invasive techniques, such as radionuclear methods and Doppler cardiography, cannot be performed reliably during non-steady-state situations. Although foreign gas rebreathing techniques have shown promising results in CHF patients during exercise,[42,43] these methods do not provide continuous cardiac output measurements and are therefore not ideal for the analysis of kinetics. Studies evaluating the accuracy of impedance cardiography in the CHF population have yielded conflicting results.[44,45] Therefore, we examined the accuracy of two techniques for the continuous assessment of cardiac output: a radial artery pulse contour analysis method which uses an indicator dilution method for calibration (LiDCO), and an impedance cardiography technique using a novel algorithm (Physioflow) (**chapters 5 and 6**). Both techniques had not been validated before during exercise in CHF patients. The continuous Fick method was used as the "gold standard". As this technique requires continuous measurement of mixed venous O_2 saturation ($cS\bar{v}O_2$), we first evaluated the accuracy of the fiberoptic pulmonary artery catheter used to assess $cS\bar{v}O_2$. We observed a high measurement accuracy during exercise in CHF patients (**chapter 5**). Subsequently, we showed that the

accuracy of LiDCO is clinically acceptable for the continuous assessment of cardiac output ($\dot{Q}$) during exercise, while Physioflow systematically overestimates $\dot{Q}$ (**chapter 6**). Therefore, LiDCO was used to investigate the physiological determinants of O_2 uptake kinetics in CHF patients (**chapter 7**). As expected, this study showed that both O_2 onset and recovery kinetics at submaximal exercise were delayed in CHF patients compared with healthy subjects, matched for age and body mass index. In the patient group, no differences were observed between onset kinetics of $\dot{Q}$ and $\dot{V}O_2$, which is in agreement with other studies in CHF patients.[18,46] Also, no difference was observed in the patient group between $\dot{Q}$ and O_2 recovery kinetics, and onset and recovery kinetics of $\dot{Q}$ were virtually identical. These results differ from studies in healthy individuals, showing faster kinetics of $\dot{Q}$ relative to $\dot{V}O_2$ at exercise onset[47-49] and slower $\dot{Q}$ recovery kinetics compared with $\dot{Q}$ onset kinetics.[49,50] Therefore, our results indicate that during onset and recovery from submaximal exercise, the rate of O_2 delivery is relatively low with respect to the metabolic demands, suggesting a functional limitation in moderately impaired CHF patients through impairment of O_2 delivery.

A potential limitation of the strategy used in **chapter 7** is that it is not certain whether the kinetics of $\dot{Q}$ actually reflect the kinetics of O_2 delivery to exercising muscles. In fact, it has been shown that blood flow distribution between exercising muscles and less active tissues may be different between severe heart failure patients and healthy individuals.[51] For this reason, we also investigated the physiological determinants of submaximal O_2 uptake kinetics at the local muscle level in CHF patients and healthy subjects (**chapter 8**). We used near-infrared spectroscopy (NIRS) to assess local oxygenation in the vastus lateralis muscle. Assuming a constant O_2 content in the arterial blood, changes in local oxygenation reflect changes in the balance between O_2 delivery and O_2 utilization. To assess the rate of skeletal muscle metabolism, ^{31}P magnetic resonance spectroscopy (^{31}P MRS) was applied simultaneously in the same muscle region by measuring the rate of phosphocreatine (PCr) resynthesis. Exercise consisted of incremental dynamic single-leg extensions in the supine position until a PCr depletion of approximately 50%. As this protocol did not permit participants to attain a steady-state condition, we did not evaluate the onset kinetics. The results showed that both muscle metabolic recovery and muscle re-oxygenation were delayed in patients with CHF compared with healthy individuals. Only in the patient group we observed that muscle re-oxygenation was slower than metabolic recovery. These results indicate that during exercise recovery, the ratio of O_2 delivery to O_2 utilization is lower in CHF patients than in controls, suggesting a limitation of skeletal muscle metabolic recovery by O_2 delivery, which is in line with the findings of **chapter 7**. In contrast to our results, Hanada et al., also using a combination of NIRS and ^{31}P MRS measurements, observed a slower muscle metabolic recovery than tissue re-oxygenation in CHF patients, while there was no difference in healthy controls.[35] This discrepancy can be accounted for by several methodological differences with our

study. First, Hanada et al. studied a smaller muscle group (calf muscles versus quadriceps muscles in our study). Second, NIRS and ^{31}P MRS were not performed simultaneously in that study. Third, in contrast with our study, Hanada et al. did not standardize metabolic responses during exercise recovery. This resulted in a greater PCr depletion and a lower end-exercise pH in CHF patients compared with their control group. Severe muscle acidosis has been shown to delay PCr resynthesis due to an increased proton efflux rate.[52-54] Therefore, given the fact that in our study there was no difference in muscular acidosis between CHF patients and healthy subjects, it is difficult to compare these results with our study. Finally, considering the analysis of the NIRS data, Hanada et al. did not include a time delay in the overall kinetic analysis of muscle tissue oxygenation, which may lead to an overestimation of the rate of tissue re-oxygenation.

In conclusion, the results of the studies reported in **chapters 7 and 8** suggest that the adaptation to and recovery from submaximal exercise in moderately impaired CHF patients are limited by O_2 delivery rather than O_2 utilization. These results appear to be in line with animal studies.[38,39,55] From a clinical point of view, these findings imply that therapeutic interventions aiming at improvements in the functional capacity of these patients should primarily be aimed at increasing local skeletal muscle blood flow, e.g., by improving local endothelial function through endurance training,[9,56] high intensity interval training,[57] or by improving the distribution of blood flow to skeletal muscles through an increase in metabolic efficiency in other tissues (e.g., by inspiratory muscle training).[58]

Future directions

The studies presented in Part I of this thesis showed that O_2 recovery kinetics may be useful in clinical practice for the assessment and prediction of training effects in CHF patients. However, before these exercise parameters can be implemented on a wide scale, analysis of O_2 uptake kinetics should be incorporated in the software of commercially available breath-by-breath respiratory systems. Furthermore, in order to use O_2 recovery kinetics to assess the level of functional disability of CHF patients, reference values should be developed, corrected for age, gender, and body composition. Considering other clinical applications, future research should also focus on the utility of O_2 recovery kinetics for the evaluation and prediction of effects of other therapeutic interventions aiming at an improvement of the exercise tolerance of CHF patients (e.g., cardiac resynchronization therapy). In addition, the prognostic value of O_2 recovery kinetics should be explored.

Considering the physiological background of the delay in O_2 uptake kinetics in moderately impaired CHF patients, the results of the studies presented in Part II of this thesis suggest that O_2 delivery is the rate-limiting process. Further research is needed to determine the underlying mechanisms of this impairment of O_2 delivery, such as cardiac insufficiency, excessive vasoconstriction,[59-61] impaired nitric oxide-mediated vasodilatation,[62] and / or a blunted redistribution of blood flow from the non-exercising tissues to the working skeletal muscles.[63] It should also be acknowledged that the results of these studies cannot be generalized to severely impaired CHF patients. In fact, it has been shown in an animal study that in severe heart failure, decrements in the muscle oxidative capacity play a more predominant role in the delay in metabolic recovery than they do in moderate heart failure.[38] If this observation holds true for humans, it may imply that patients with severe heart failure will benefit more from therapeutic interventions aimed at improving O_2 utilization, such as endurance training,[64] high intensity interval training,[65] and more specifically, localized muscle training.[66,67] Therefore, future studies should compare the physiological background of O_2 uptake kinetics between patients with moderate and severe heart failure.

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List of abbreviations

List of abbreviations

a.u.	arbitrary units
ACE	angiotensin-converting enzyme
ARB	angiotensin II receptor blocker
ATP	adenosine triphosphate
BMI	body mass index
C	Celsius
CaO_2	arterial oxygen content
CHF	chronic heart failure
COPD	chronic obstructive pulmonary disease
CRT	cardiac resynchronization therapy
$cS\breve{v}O_2$	continuously measured mixed venous oxygen saturation
$C\breve{v}O_2$	mixed venous oxygen content
DCM	dilated cardiomyopathy
dl	deciliter(s)
DPA	daily physical activity
F	French
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
g	gram(s)
Hb	hemoglobin
HHb	deoxygenated hemoglobin
HR	heart rate
ICD	implantable cardioverter defibrillator
ICM	ischemic cardiomyopathy
kg	kilogram(s)
kHz	kiloherz
l	liter(s)
LiCl	lithium chloride
LOA	limits of agreement
LVEF	left ventricular ejection fraction
mA	miliampère
min	minute(s)
ml	mililiter(s)
MLHF	Minnesota Living with Heart Failure Questionnaire
mm	milimeter
mmol	milimole(s)
MRT	mean response time
MSEC	maximum short-term exercise capacity
NIRS	near-infrared spectroscopy
NYHA	New York Heart Association

O_2	oxygen
O_2Hb	oxygenated hemoglobin
O_2 onset kinetics	rate of increase in oxygen uptake during exercise onset
O_2 recovery kinetics	rate of decrease in oxygen uptake during recovery from exercise
OUES	oxygen uptake efficiency slope
Peak $\dot{V}O_2$	oxygen uptake at the end of a symptom limited exercise test
PCr	phosphocreatine
PCV	packed cell volume
PDE	phosphodiesters
Pi	inorganic phosphate
^{31}P MRS	phosphorus-31 magnetic resonance spectroscopy
	cardiac output
QOL	quality of life
RER	respiratory exchange ratio
SaO_2	arterial oxygen saturation
sec	second(s)
SV	stroke volume
$S\bar{v}O_2$	mixed venous oxygen saturation
τ	time constant
τ-HHb	time constant of HHb recovery kinetics
τ-PCr	time constant of PCr recovery kinetics
τ-rec	time constants of O_2 recovery kinetics
T½-$\dot{V}O_2$	recovery half-time of peak O_2
Td	time delay
Td_{HHb}	time delay until mono-exponential decrease in deoxygenated hemoglobin following exercise
$\dot{V}CO_2$	carbon dioxide elimination
$\dot{V}_E$	minute ventilation
$\dot{V}O_2$	oxygen uptake
$\Delta\dot{V}O_2$ / ΔWR	ratio between the increase in oxygen uptake and the increase in workload
VT	ventilatory threshold
W	Watt(s)
wks	weeks

Summary
Samenvatting

Summary

Chronic heart failure (CHF) is a clinical syndrome characterized by exercise intolerance. Because resting indices of cardiac function and the level of perceived exercise intolerance correlate poorly with the exercise performance of these patients, exercise testing has become an important tool for the evaluation and monitoring of heart failure. Whereas the maximal aerobic capacity (peak $\dot{V}O_2$) has been shown to be a reliable indicator of the severity and prognosis of heart failure, submaximal exercise parameters may better reflect the ability to perform daily physical activities. Oxygen (O_2) uptake kinetics describe the rate of change in oxygen uptake ($\dot{V}O_2$) during onset or recovery of exercise (O_2 onset and recovery kinetics, respectively). Previous studies showed that, compared to healthy individuals, CHF patients have slower O_2 onset and recovery kinetics, with the degree of the delay correlating with the functional impairment in these patients. However, it is not well established whether O_2 uptake kinetics are sensitive to the effects of therapeutic interventions in CHF patients. Moreover, knowledge is lacking on the pathophysiological background of the delay in O_2 uptake kinetics in CHF patients.
This thesis addressed the following central questions:

1. **Are O_2 uptake kinetics useful in clinical practice to quantify and predict the effects of physical training in CHF patients?**
2. **What are the physiological determinants of O_2 uptake kinetics in CHF patients?**

Ad 1. Are O_2 uptake kinetics useful in clinical practice to quantify and predict the effects of physical training in CHF patients?

In previous studies, various calculation methods have been used to assess O_2 uptake kinetics at submaximal exercise in CHF patients. In order to determine which assessment method is most appropriate for clinical use, we compared the accuracy and reproducibility of these methods in 19 moderately impaired CHF patients (**chapter 2**). The assessment of O_2 recovery kinetics proved to be feasible and reproducible. The most optimal method to characterize O_2 recovery kinetics was mono-exponential modelling with sampling intervals of 5 breaths. In contrast, O_2 onset kinetics could not be assessed reliably by mono-exponential modelling and the reproducibility of O_2 onset kinetics was substantially lower than O_2 recovery kinetics, both when using mono-exponential modelling and an algebraic method calculating the mean response time.

Physical training has been shown to improve exercise performance and quality of life in CHF patients. As O_2 onset and recovery kinetics reflect the rate of adaptation to and recovery from daily physical activities, these exercise parameters are potentially useful to assess training-induced effects on the functional capacity of CHF patients. Using the parameters with the highest accuracy and reproducibility as

presented in **chapter 2**, we performed a randomized controlled trial with semi-crossover design to evaluate the utility of O_2 uptake kinetics to assess effects of physical training in CHF patients (**chapter 3**). After a combined cycle interval and resistance training program with a duration of 12 weeks, we did not observe a significant improvement in O_2 onset kinetics during submaximal exercise. Improvements in peak $\dot{V}O_2$ and O_2 recovery kinetic following maximal exercise only reached statistical significance when the training results of the intervention and control groups were pooled (n = 32). There were, however, significant between-group changes in the time constant of O_2 recovery kinetics following submaximal exercise (τ-rec) and $\dot{V}O_2$ at the ventilatory threshold (VT). The determination of τ-rec was successful in all cases, whereas the VT could not be determined in 13% of the patients. Therefore, τ-rec can be recommended in clinical practice for evaluation of training effects in CHF patients.

Previous studies showed that there is a considerable heterogeneity in responses to physical training in CHF patients. In **chapter 4** we investigated the prediction of training effects in 50 CHF patients, using both clinical patient characteristics and exercise parameters as possible predictors. Training effects were defined as changes at a maximal exercise level (peak $\dot{V}O_2$) and at a submaximal exercise level ($\dot{V}O_2$ at the VT and τ-rec). After a combined cycle interval and resistance training program with a duration of 12 weeks, there were significant improvements in these parameters with a considerable variety in training responses. Whereas clinical patient characteristics did not predict training effects, multivariate regression analysis revealed that about one-third of the variation in training responses could be predicted by parameters from baseline maximal and submaximal cardiopulmonary exercise testing. O_2 recovery kinetics after maximal exercise, expressed as recovery half time of peak $\dot{V}O_2$, proved to be the strongest independent predictor of training-related changes in peak $\dot{V}O_2$ and $\dot{V}O_2$ at the VT, and τ-rec was the only predictor of training-related changes in τ-rec. It was concluded that, although O_2 recovery kinetics substantially add to the prediction of training effects in CHF patients, the explained variance in training effects is not sufficient to make a definite distinction between training responders and non-responders.

Ad 2. What are the physiological determinants of O_2 uptake kinetics in CHF patients?

More knowledge of the physiological determinants of O_2 uptake kinetics may lead to a better understanding of the pathophysiological mechanisms causing functional impairments in CHF patients. This may eventually aid in the development of therapeutic approaches to improve the exercise capacity in CHF patients. Theoretically, O_2 uptake kinetics are determined by the rate of tissue oxygenation (O_2 delivery) and the rate at which O_2 can be used for oxidative metabolism (O_2 utilization). An useful approach to investigate the relative influence of impaired O_2 delivery and O_2 utilization on O_2 uptake kinetics is to compare the kinetics of cardiac

output ($\dot{Q}$) and $\dot{V}O_2$. This approach requires a continuous cardiac output assessment method that is feasible and reliable during exercise in non-steady state conditions in CHF patients. As such a method was not clinically available at the time of our study, we evaluated the accuracy of 2 techniques for the continuous assessment of cardiac output that are novel in their application to chronic heart failure (CHF): a radial artery pulse contour analysis method that uses an indicator dilution method for calibration (LiDCO) and an impedance cardiography technique (Physioflow). The continuous Fick method was used as the "gold standard". As this technique requires continuous measurement of mixed venous O_2 saturation ($cS\bar{v}O_2$), the accuracy of the fiberoptic pulmonary artery catheter used to assess $cS\bar{v}O_2$ was evaluated first (**chapter 5**). We observed a high measurement accuracy of this catheter during exercise in CHF patients. In **chapter 6** we showed that LiDCO provided accurate measurements of cardiac output during exercise in CHF patients, both under steady state and non-steady state conditions. Although Physioflow overestimated cardiac output, it was concluded that this method may still be useful to estimate relative changes during exercise.

In **chapter 7**, we investigated the physiological determinants of O_2 uptake kinetics in CHF patients by comparing the temporal profiles of $\dot{V}O_2$ and $\dot{Q}$ (assessed by LiDCO). Both O_2 onset and recovery kinetics at submaximal exercise were delayed in CHF patients as compared to healthy controls. In the patient group, no differences were observed between the kinetics of $\dot{Q}$ and $\dot{V}O_2$, both during exercise onset and recovery. As previous studies in healthy individuals demonstrated faster kinetics of $\dot{Q}$ relative to $\dot{V}O_2$ during exercise onset and slower kinetics of $\dot{Q}$ relative to $\dot{V}O_2$ during exercise recovery, our findings indicate a lower O_2 delivery rate relative to the metabolic demands in CHF patients. Therefore, it is suggested that O_2 onset and recovery kinetics in CHF patients are mainly limited by O_2 delivery rather than O_2 utilization.

In **chapter 8**, physiological determinants of exercise recovery were also investigated at the local muscle level. ^{31}P magnetic resonance spectroscopy was used to assess skeletal muscle metabolic recovery, and near-infrared spectroscopy to measure muscle tissue re-oxygenation. Measurements were performed simultaneously in the vastus lateralis muscle during recovery from submaximal dynamic single leg extensions in the supine position. Both muscle metabolic recovery and muscle re-oxygenation were delayed in CHF as compared to healthy individuals. Importantly, muscle re-oxygenation was slower than PCr recovery kinetics only in the patient group. In line with the findings of **chapter 7**, this finding suggests that the observed delay in the recovery of muscle energy stores in CHF patients is determined by an impairment of O_2 delivery rather than O_2 utilization.

Finally, **chapter 9** summarizes the results from this thesis, discusses clinical implications and provides recommendations for future research.

Samenvatting

Chronisch hartfalen (CHF) is een klinisch syndroom dat wordt gekenmerkt door een verminderd inspanningsvermogen. Omdat de hartpompfunctie in rust en de subjectieve beleving van de beperkte inspanningstolerantie niet goed overeenkomen met het inspanningsvermogen van deze patiënten, is inspanningsdiagnostiek een belangrijk instrument geworden voor de evaluatie en follow-up van CHF patiënten. Terwijl het maximale zuurstofopnamevermogen (peak $\dot{V}O_2$) een betrouwbare maat is gebleken voor de ernst en de prognose van hartfalen, geven submaximale inspanningsparameters mogelijk een beter beeld van het vermogen om dagelijkse inspanningen te leveren. Zuurstofopname kinetiek beschrijft de snelheid van verandering in $\dot{V}O_2$ tijdens en na inspanning (O_2 onset en O_2 herstel kinetiek respectievelijk). Uit eerdere studies is gebleken dat zowel O_2 onset kinetiek als O_2 herstel kinetiek tijdens en na submaximale inspanning vertraagd zijn bij CHF patiënten, waarbij de mate van vertraging goed overeenkomt met de functionele beperking van deze patiënten. Het is echter onvoldoende onderzocht of O_2 opname kinetiek in deze patiëntengroep bruikbaar is om de effecten van therapeutische interventies te monitoren. Daarnaast ontbreekt kennis over de pathofysiologische achtergrond van de vertraging in O_2 opname kinetiek bij CHF patiënten.
Dit proefschrift behandelt de volgende centrale vragen:

1. **Is O_2 opname kinetiek in de klinische praktijk bruikbaar om effecten van fysieke training bij CHF patiënten te kwantificeren en te voorspellen?**
2. **Wat zijn de fysiologische determinanten van O_2 opname kinetiek bij CHF patiënten?**

Ad 1. Is O_2 opname kinetiek in de klinische praktijk bruikbaar om effecten van fysieke training bij CHF patiënten te kwantificeren en te voorspellen?

In voorgaande studies werden verscheidene rekenmodellen gebruikt om O_2 opname kinetiek tijdens en na submaximale inspanning bij CHF patiënten te kwantificeren. Om te bepalen welke methode het meest geschikt is voor klinisch gebruik vergeleken we de nauwkeurigheid en reproduceerbaarheid van deze methoden in een groep van 19 matige beperkte CHF patiënten (**hoofdstuk 2**). Het kwantificeren van O_2 herstel kinetiek bleek praktisch uitvoerbaar en reproduceerbaar met als optimale methode een mono-exponentieel model met middeling van de data in intervallen van 5 ademteugen. In tegenstelling tot O_2 herstel kinetiek, kon O_2 onset kinetiek niet adequaat worden beschreven met een mono-expontieel model en de reproduceerbaarheid van de bepaling van O_2 onset kinetiek was ook beduidend lager dan van O_2 herstel kinetiek, zowel bij gebruik van een mono-exponentieel als een algebraïsch rekenmodel.

Het is aangetoond dat fysieke training positieve effecten heeft op het inspanningsvermogen en de kwaliteit van leven van CHF patiënten. Aangezien O_2

onset en herstel kinetiek een weerspiegeling zijn van de adaptatie aan en herstel van dagelijkse inspanningen, zijn deze parameters potentieel bruikbaar voor het meten van veranderingen van de functionele capaciteit van deze patiënten. In **hoofdstuk 3** wordt een gerandomiseerde gecontroleerde studie beschreven met semi-crossover design waarin de klinische bruikbaarheid van O_2 opname kinetiek voor het meten van trainingseffecten bij CHF patiënten werd onderzocht. Voor bepaling van O_2 onset en herstel kinetiek werd gebruik gemaakt van de rekenmethoden met de hoogste nauwkeurigheid en reproduceerbaarheid zoals beschreven in **hoofdstuk 2**. Na een gecombineerd interval- en krachttrainingsprogramma van 12 weken werd geen significante verbetering gezien van O_2 onset kinetiek tijdens submaximale inspanning. Alleen na het samenvoegen van de trainingsresultaten van interventie- en controlegroep werden significante verbeteringen gezien van peak $\dot{V}O_2$ en O_2 herstel kinetiek na maximale inspanning (n = 32). Bij vergelijking van de interventie- en controlegroep tijdens de eerste 12 weken, werden alleen significante verbeteringen gezien van O_2 herstel kinetiek na submaximale inspanning en de zuurstofopname bij de ventilatoire drempel (VD). Gezien het feit dat de tijdsconstante van O_2 herstel kinetiek na submaximale inspanning (τ-rec) bij alle patiënten kon worden bepaald, terwijl de VD niet kon worden bepaald in 13% van de patiënten, kan τ-rec worden aanbevolen voor de evaluatie van trainingseffecten bij CHF patiënten.

Voorgaande studies hebben aangetoond dat er een aanzienlijke spreiding is van trainingseffecten bij CHF patiënten. In **hoofdstuk 4** wordt verslag gedaan van een studie naar de voorspelbaarheid van trainingseffecten bij 50 CHF patiënten, waarbij zowel klinische patiënten eigenschappen als inspanningsvariabelen als mogelijke voorspellers werden gebruikt. Trainingseffecten werden gedefinieerd als veranderingen op maximaal inspanningsniveau (peak $\dot{V}O_2$) en op submaximaal inspanningsniveau ($\dot{V}O_2$ bij de VD en τ-rec). Na een gecombineerd interval- en krachttrainingsprogramma van 12 weken traden significante verbeteringen op van deze parameters met, zoals verwacht, een aanzienlijke spreiding van de trainingseffecten. Terwijl klinische patiënten eigenschappen niet bruikbaar bleken te zijn voor het voorspellen van trainingseffecten, werd m.b.v. multivariate regressie analyse gevonden dat ca. 1/3 van de variatie in trainingseffecten kon worden voorspeld met submaximale en maximale inspanningsvariabelen. O_2 herstel kinetiek na maximale inspanning, uitgedrukt als de halfwaardetijd van de daling van de peak $\dot{V}O_2$, was de sterkste onafhankelijke voorspeller van trainingseffecten op peak $\dot{V}O_2$ en $\dot{V}O_2$ bij de VD; τ-rec was de enige voorspeller van trainingsgerelateerde veranderingen in O_2 herstel kinetiek na submaximale inspanning. Concluderend kan worden gesteld dat, hoewel O_2 herstel kinetiek duidelijk bijdraagt aan het voorspellen van trainingseffecten bij CHF patiënten, de verklaarde variatie niet voldoende is om responders en non-responders van elkaar te onderscheiden.

Ad 2. Wat zijn de fysiologische determinanten van O_2 opname kinetiek bij CHF patiënten?

Meer kennis over de fysiologische determinanten van O_2 opname kinetiek kan leiden tot een beter begrip van de pathofysiologische mechanismen die verantwoordelijk zijn voor functionele beperkingen van CHF patiënten. Uiteindelijk kan dergelijke kennis bijdragen aan de ontwikkeling van therapieën die gericht zijn op een verbetering van het inspanningsvermogen van CHF patiënten. In theorie wordt O_2 opname kinetiek enerzijds bepaald door de snelheid van O_2 aanvoer naar de aktieve spieren en anderzijds door de snelheid waarmee O_2 kan worden gebruikt voor metabolisme in de spier (O_2 verbruik). Een bruikbare manier om de relatieve invloed van beperkingen van O_2 aanvoer en O_2 verbruik op O_2 opname kinetiek bij CHF patiënten te onderzoeken is door de snelheid van veranderingen van $\dot{V}O_2$ en cardiac output ($\dot{Q}$) tijdens en na inspanning met elkaar te vergelijken. Deze aanpak vereist een continue cardiac output meetmethode die bij CHF patiënten tijdens inspanning uitvoerbaar is en nauwkeurige metingen oplevert in niet-steady state situaties. Omdat een dergelijke meetmethode niet klinisch beschikbaar was onderzochten we de nauwkeurigheid van 2 continue cardiac output meetmethoden die niet eerder waren geëvalueerd bij CHF patiënten: 1) een pulse contour analyse methode van de arteria radialis met een indicator dilutie methode om het systeem te kalibreren (LiDCO) en 2) een impedantie cardiografie methode (Physioflow). De continue Fick methode werd gebruikt als "gouden standaard". Aangezien bij deze methode een continue meting van de zuurstofsaturatie in de pulmonaal arterie (gemengd veneuze saturatie) nodig is, werd eerst de betrouwbaarheid van de gebruikte fiberoptische catheter onderzocht (**hoofdstuk 5**). Hierbij werd een hoge meetnauwkeurigheid van deze catheter gevonden tijdens inspanning bij CHF patiënten. **Hoofdstuk 6** laat zien dat LiDCO klinisch acceptabele cardiac output metingen oplevert tijdens inspanning bij CHF patiënten, zowel in steady state als in niet-steady state situaties. Hoewel Physioflow bij deze patiënten een systematische overschatting gaf van de cardiac output, is deze methode wel potentieel bruikbaar om relatieve veranderingen in cardiac output tijdens inspanning te schatten.

Hoofdstuk 7 beschrijft een studie waarin bij CHF patiënten de fysiologische determinanten van O_2 opname kinetiek tijdens en na submaximale inspanning werden onderzocht door de snelheid van veranderingen van $\dot{V}O_2$ en $\dot{Q}$ (gemeten m.b.v. LiDCO) met elkaar te vergelijken. Zoals verwacht, waren zowel O_2 onset als O_2 herstel kinetiek vertraagd bij CHF patiënten t.o.v. gezonde controle personen. In de patiëntengroep werden tijdens en na inspanning geen verschillen gezien tussen de kinetiek van $\dot{V}O_2$ en $\dot{Q}$. Aangezien in eerdere studies bij gezonden een snellere stijging van $\dot{Q}$ t.o.v. $\dot{V}O_2$ tijdens inspanning en een tragere daling van $\dot{Q}$ t.o.v. $\dot{V}O_2$ na inspanning werd waargenomen, geven onze bevindingen aan dat er bij CHF patiënten een lagere O_2 aanvoer is t.o.v. de metabole behoefte tijdens en na submaximale inspanning. Dit suggereert dat O_2 onset en herstel kinetiek bij CHF patiënten voornamelijk worden beperkt door een verminderde O_2 aanvoer.

In **hoofdstuk 8** wordt een studie beschreven waarin de fysiologische determinanten van herstel na submaximale inspanning ook werden onderzocht op lokaal spierniveau. ^{31}P magnetische resonantie spectroscopie werd gebruikt om het metabole herstel in de skeletspier te bepalen en het herstel van de oxygenatie van de skeletspier werd geschat m.b.v. nabij-infrarood spectroscopie. De metingen werden verricht in liggende positie in een dijbeenspier (vastus lateralis spier) tijdens herstel van herhaalde strekkingen van het been tegen weerstand. Zowel het metabole herstel als de re-oxygenatie in de spier waren vertraagd bij CHF patiënten t.o.v. gezonde controle personen. Een andere opvallende bevinding was dat in de patiëntengroep de re-oxygenatie in de spier nog trager was dan het metabole herstel, terwijl een dergelijk verschil niet te zien was in de controlegroep. In overeenstemming met de resultaten van **hoofdstuk 7**, suggereren deze bevindingen dat de vertraging in het metabole herstel na submaximale inspanning bij CHF patiënten wordt bepaald door een beperking van O_2 aanvoer in plaats van O_2 verbruik.

Hoofdstuk 9 geeft een overzicht van de resultaten van dit proefschrift en bespreekt enkele klinische implicaties. Daarnaast worden aanbevelingen gedaan voor toekomstig onderzoek.

Dankwoord
Curriculum vitae

Dankwoord

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Curriculum vitae

The author of this thesis was born on July 25th, 1972 in Nuenen, The Netherlands. In 1990 he obtained his gymnasium diploma at the Lorentz Lyceum in Eindhoven. He entered Medical School at the University of Utrecht in 1990 and received his medical degree in 1997.

From 1997 until 1998 he worked as a resident at the Emergency Department of the Carolus Hospital in 's-Hertogenbosch. In 1998 he started his training in Sports Medicine in the St. Joseph Hospital in Veldhoven. During this period he worked as a team physician of the professional soccer teams FC Den Bosch and VVV Venlo. After he was registered as a Sports Physician in 2002 he commenced his training in Cardiology at the Catharina Hospital in Eindhoven under the supervision of dr. J.M. van Dantzig and prof. dr. N.H.J. Pijls. The research for this thesis was started in 2003 at the Departments of Sports Medicine and Cardiology of Máxima Medical Centre in Veldhoven. He expects to be registered as a Cardiologist on December 1th 2009. The author currently lives in 's-Hertogenbosch with his wife Dareczka and their son Oscar.