Exercise training and testing in patients with heart failure

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To *Janne*, my husband and
Johan, my deceased big brother, with love

“Lack of activity destroys the good condition of every human being, while
movement and methodical physical exercise save it and preserve it”
Plato 428-348 BC, Greek philosopher

CONTENTS

ABSTRACT	1
SVENSK SAMMANFATTNING	3
LIST OF PAPERS	5
ABBREVIATIONS.....	7
DEFINITIONS	9
INTRODUCTION.....	11
BACKGROUND.....	13
Heart failure	13
<i>Definition</i>	13
<i>Pathophysiology</i>	13
<i>Categories</i>	14
<i>Symptoms and severity</i>	15
<i>Skeletal muscle</i>	16
<i>Exercise intolerance and capacity</i>	17
<i>Treatment</i>	17
Physical activity and exercise.....	18
<i>Recommendations of physical activity and exercise</i>	18
<i>Aerobic exercise</i>	18
<i>Muscular exercise</i>	19
<i>Exercise training in patients with heart failure</i>	19
<i>Cardiac rehabilitation</i>	20
<i>Physiotherapy management exercise based cardiac rehabilitation</i>	21
Health-related quality of life	22
Adherence	23
AIM OF THE THESIS.....	25
Specific aims	25
METHODS	27
Measurements	28

<i>Six minute walk test</i>	28
<i>Symptom-limited bicycle ergometer test</i>	29
<i>Health-related quality of life</i>	29
Intervention	30
<i>Hospital-based training</i>	30
<i>Home-based training</i>	32
Statistics	33
Ethical considerations	34
RESULTS	35
Study I	35
Study II	35
Study III	37
Study IV	37
DISCUSSION	39
Exercise training	39
Functional testing	41
Health-related quality of life	43
Adherence and barriers	43
Home- and hospital setting	45
Life-long training programme	45
Limitations	46
CONCLUSIONS	49
Clinical implications	49
Future research and development	50
ACKNOWLEDGEMENT	51
REFERENCES	53

ABSTRACT

Patients with heart failure (HF) suffer from symptoms such as dyspnea, fatigue and reduced quality of life, which affect their physical function and often lead to immobilization and poor survival prognosis. Exercise training in cardiac rehabilitation should be offered to every patient with HF and can be performed both in a hospital-setting and with a home training programme. Exercise, in patients with HF, improves physical function and functional capacity as well as health-related quality of life (HRQoL) and reduces the need for hospital care. There are several barriers against participating in exercise based cardiac rehabilitation despite information about its benefits. The patient may anticipate not being able to exercise, that the exercise would be too hard, lives far away or has not been referred.

Aim: The aim of this thesis was to evaluate the effects of exercise in heart failure patients, of a one-year training programme, with hospital-based training followed by a home-based setting or only home-based, with special emphasis on peripheral muscle training (PMT). Furthermore, to study frequently used methods for evaluation of the effects, i.e the 6-minute walk test and instruments for estimating health-related quality of life.

Methods and findings: In **study I**, PMT was evaluated and the PMT programme in a hospital-setting (with equipment) and subsequent home-based training (with elastic bands) was compared with solely home-based training, over 1 year. At follow-up every third month, duplicated six minute walk test (6MWT) and two HRQoL questionnaires were used. The walking distance increased significantly after three months in both groups and was maintained thereafter. Also HRQoL increased but at different time points. In **study II**, PMT was compared with interval training on an ergometer bike/free walking. Both groups started under supervision of a physiotherapist in a hospital-setting, for three months and thereafter at home for nine months. The same measurements were used as in study I. Neither walking distance nor HRQoL changed over the study period. However, this may be regarded as a positive effect in the light of the known progressive nature of heart failure. In **study III**, the 6MWTs from study I and II were used to evaluate the necessity of performing duplicated 6MWTs in follow-ups clinically and for research purposes. We found that it is sufficient to perform one 6MWT. In **study IV**, both 6MWT and HRQoL forms from study I and II were used to investigate the relationship between walking distance and perceived HRQoL in HF patients. Patients with shorter walking distance, than the group median, experienced poorer general HRQoL but not HRQoL related to HF, than the higher performing

half of the study group. There were no longitudinal trends in these relationships.

Conclusion: PMT can be used as an exercise modality in patients with HF, both in hospital and at home, and may be evaluated with a single 6MWT. Shorter walking distance was related to a lower general HRQoL as judged by the patients but there was no significant relation between short walking distance and the HF-related HRQoL. Individualizing the training programme and methods, and offering the choice of exercise modality and the possibility of exercising at home, might be a way to increase adherence in cardiac rehabilitation.

SVENSK SAMMANFATTNING

Patienter med hjärtsvikt besväras av andfåddhet och trötthet vilket påverkar deras fysiska funktion och ofta leder till immobilisering, nedsatt livskvalitet och dålig prognos. Träning inom hjärtrehabilitering bör erbjudas alla patienter med hjärtsvikt och kan utföras såväl på sjukhus som hemma med hemträningsprogram. Träning vid hjärtsvikt förbättrar fysisk funktion och funktionell kapacitet, hälsorelaterad livskvalitet, och minskar behovet av vård på sjukhus. Det finns många barriärer till att delta i hjärtrehabilitering trots information om vinster, t ex att patienten tror sig inte klara av att träna, bor långt ifrån, har inte fått remiss för att nämna några.

Syfte: Syftet med avhandlingen var att utvärdera effekterna av ett träningsprogram för patienter med hjärtsvikt under 1 år, träning på sjukhus följt av hemträning eller enbart hemträning. Ett specifikt syfte var att utvärdera perifer muskelträning (PMT) som en möjlig, lämplig träningsmetod för hjärtsviktpatienter. Vidare var syftet att utvärdera effekten av sex minuters gångtest och hälsorelaterad livskvalitet.

Metod och resultat: I **studie I** utvärderades PMT och jämförde träning på sjukhus (med redskap) med efterföljande hemträning (med elastiska band) med enbart hemträning under 1 år. Vid utvärdering var tredje månad användes dubbla sex minuters gångtest och frågeformulär om livskvalitet. Gångsträckan ökade signifikant efter träning och höll i sig hela träningsperioden i båda grupperna. Även livskvaliteten ökade men vid olika tidpunkter. I **studie II**, jämfördes PMT med intervallträning på ergometercykel/promenader. Båda grupperna tränade under ledning av fysioterapeut i tre månader och därefter hemma upp till 1 år. Samma utvärdering som i studie I. Gångsträcka och livskvaliteten ändrade sig inte under studietiden. Det kan dock ses som en positiv effekt eftersom hjärtsviktpatienter vanligen försämrats över tid. I **studie III**, användes gångtesten från studie I och II för att utvärdera om det är nödvändighet att utföra dubbla sex minuters gångtest vid utvärdering. Ingen kliniskt betydelsefull skillnad sågs mellan gångtest ett och två. I **studie IV**, användes både gångtest och livskvalitetsformulär, från studie I och II, för att undersöka samband mellan gångsträcka och upplevd livskvalitet och om detta samband ändrades med tiden. Patienter med kortare gångsträcka upplevde sämre allmän hälsorelaterad livskvalitet men inte livskvalitet relaterad till hjärtsvikten, någon kliniskt signifikant förändring över tid kunde inte påvisas.

Konklusion: Perifer muskelträning kan användas som en säker träningsform för patienter med hjärtsvikt, både på sjukhus och som hemträning och kan utvärderas med endast ett sex minuters gångtest. Patienter med kortare gångsträcka upplever sämre allmän livskvalitet vilket förefaller relativt oberoende av de olika testtidpunkterna.

LIST OF PAPERS

- I. Lans C, Cider Å, Nylander E, Brudin L. *Peripheral muscle training with resistance exercise bands in patients with chronic heart failure. Long-term effects on walking distance and quality of life; a pilot study.* ESC Heart Failure 2018;5:241-248.
- II. Lans C, Cider Å, Nylander E, Brudin L. *Neither hospital-based nor home-based aerobic or peripheral muscle training improved walking distance or health-related quality of life during a one year follow-up in heart failure patients.* In manuscript.
- III. Lans C, Cider Å, Nylander E, Brudin L. *Test-retest reliability of six-minute walk tests over a one-year period in patients with chronic heart failure.* Clin Physiol Funct Imaging. 2020;40:284-289.
- IV. Lans C, Cider Å, Nylander E, Brudin L. *Six minute walk test versus health related quality of life in patients with chronic heart failure.* Submitted.

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ABBREVIATIONS

6MWD	Six minute walking distance
6MWT	Six minute walk test
ATS	American Thoracic Society
CEG	Cycling Exercise Group, study II
COV	Coefficient of variation
CPET	Cardiopulmonary exercise test
CR-10	Borg scale, Category Ratio 0-10
EF	Ejection fraction
GT	Group-based training group, study I
HF	Chronic heart failure
HT	Home-based training group, study I
HRQoL	Health related quality of life
ICC	Intra class correlation
MLHFQ	Minnesota Living with Heart Failure Questionnaire
NYHA	New York Heart Association functional classification
PEG	Peripheral Exercise Group, study II
PMT	Peripheral muscle training
RPE	Borg scale, rating of perceived exertion 6-20
SF-36	SF-36v1™, Short Form-36 version1
PF	Physical Functioning
RP	Role-Physical
BP	Bodily Pain
GH	General Health
VT	Vitality
SF	Social Functioning
RE	Role-Emotional
MH	Mental Health
PCS	Physical component summary score
MCS	Mental component summary score

DEFINITIONS

Exercise	Physical activity that is planned, structured, repetitive, and purposive in the sense that improvement or maintenance of one or more components of physical fitness is an objective (1).
Exercise capacity	The maximum amount of physical exertion that a subject can sustain. Expressed as peak VO_2 (2).
Exercise intolerance	An impairment in the capacity to accomplish physical activities followed by increased breathing and fatigue (3).
Functional capacity	The ability to perform aerobic work as defined by the maximal oxygen uptake (2).
Health	A state of complete physical, mental and social well-being not merely the absence of disease or infirmity (4).
Physical function	The capacity of an individual to carry out the physical activities of daily living (5).
Physical activity	Any bodily movement, produced by skeletal muscles, that results in energy expenditure (1).
Physical fitness	Physical fitness is a set of attributes that people have or achieve which relate to the ability to perform physical activity (1).
Quality of life	An individual's perception of their position in life in the context of culture and value systems in which they live and in the relation to their goals, expectation, standards and concerns" is also an opportunity to achieve personal goals (6).
VO_2	Oxygen uptake (7).
$\text{VO}_{2\text{peak}}$	Highest oxygen uptake achieved (7).

INTRODUCTION

A sedentary behavior and physical inactivity are responsible for about 6% of all death globally and a risk factor for cardiovascular disease, but a modifiable risk factor (8). Physical activity and exercise in leisure time are described as the best buy for public health (9). Cardiac rehabilitation in patients with chronic heart failure (HF) is underused throughout the world (10) and a priority of class 1A recommendation in both the European and American guidelines (11-13). In the guidelines of heart disease and treatment by the National Board of Health and Welfare in Sweden there is a priority 3 on a recommendation scale (a 10-point scale, 1 has the highest priority, priority 1-3 is considered mandatory to the patient) which means that every patient with HF should be offered cardiac rehabilitation with a customized individually prescribed exercise programme (14). The implementation of cardiac rehabilitation is about to change and is now increasing in Europe. The ExtraHF survey study concluded that out of 170 centers in Europe (1 center in Sweden), 52% offered out-patient exercise training cardiac rehabilitation and 18% could also offer a home-based programme (15). Adherence to exercise training tends to decrease over time (16), therefore it is important to find an exercise modality that can meet exercise guidelines, patient's preferences, and which may be performed lifelong.

The studies in this thesis aimed at increasing the knowledge on different modes of exercise for use in cardiac rehabilitation in patients with heart failure, with focus on a long-term perspective, and to evaluate methods for characterising limitations and impairment of physical function coupled to heart failure.

BACKGROUND

Heart failure

Definition

The definition of heart failure (HF), according to European Society of Cardiology, is "a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress" (11). Heart failure means that there is an inability of the heart to maintain a cardiac output with normal filling pressure which is sufficient to provide the body tissues of adequate blood supply (17, 18).

The prevalence of HF is estimated, in the western world, to 1-2 % and increases considerably with age, (10, 17, 18) in Sweden prevalence is about 2% in the total population (19), and as high as 10% in patients above an age of 80 years (14, 20). The incidence is about 2-5 per 1000 habitants per year (19, 21). The prognosis of HF is poor, with a 5-year survival rate of approximately 50% (19).

Pathophysiology

Heart failure is a syndrome with a multifaceted complex pathophysiology.

Most heart diseases in advanced stages can cause HF, since HF itself is a syndrome and not an independent diagnosis (18, 22). Coronary artery disease, hypertension, atrial fibrillation, valve disease, separate or in combination, are the most common causes of HF in the western world (17, 22, 23). Therefore, it is important to find out the underlying cause of HF.

Heart failure is mainly caused by two different disorders of the heart function, diastolic and systolic dysfunction. In diastolic dysfunction the filling phase is disturbed and, in the case of systolic dysfunction the emptying capacity of the heart is reduced, most commonly due to decreased contractility (24, 25). The left ventricular ejection fraction (EF) is used to establish the degree of systolic ventricular function, calculated as the stroke volume divided by the end-diastolic volume in percent (17, 26). Ejection fraction is an important parameter since it has a prognostic value, lower EF

means worse prognosis and survival (23). However, it correlates poorly with exercise capacity (27).

Most often, the heart dilates as a result of increased filling pressure and thus filling volume in order to maintain the stroke volume according to the Frank-Starling principle (7, 26). Initially, this is an adequate compensation mechanism, but increased volume of the heart also leads to an increased load and reduced efficiency. To compensate for the disturbed ventricular function, the peripheral circulation relocates. The blood is redistributed to the most vital organs. Central mechanisms provide increased sympathetic tone which in turn leads to increased contractility and heart rate as well as a peripheral vasoconstriction. When the peripheral resistance increases, the heart also has an increased resistance, afterload, to work towards. This leads to progressive changes in the periphery (See section “Skeletal muscle”, page 16) (25, 28).

By tradition, HF has been defined as a failure of the contractile function, but later on it has been recognized that HF can occur even with a normal or near normal EF (23). Both diastolic and systolic dysfunction may occur at the same time (20, 22).

Categories

Heart failure is classified into three categories, Figure 1:

- Heart Failure with **REDUCED** left ventricular ejection fraction (HFrEF), the EF is 40% or less. Also classified as systolic heart failure. The pumping ability is reduced.
- Heart Failure with **PRESERVED** ejection fraction (HFpEF) where the EF is $\geq 50\%$. This is the diastolic heart failure. The pumping ability is normal but the filling function is impaired.
- Heart failure with **MID RANGE** ejection fraction (HFmrEF) where the EF is between 40 and 49%. This is a mix of the systolic and diastolic heart failure (11, 29, 30).

Figure 1. Categories of heart failure

Evidence for efficacious management and exercise training in patients with HFpEF is limited and less documented in literature than for patients with HFrEF (23, 31).

In this thesis, patients with HFrEF are studied.

Symptoms and severity

The clinical symptoms are often diffuse, especially in the early stages, and it can be difficult to differ HF from other diseases such as lung diseases. Early symptoms can be fatigue and dyspnea and may occur already with exertion at low workload or just in different body positions (25). The fatigue may be due to decreased cardiac output and dyspnea may be a sign of elevated filling pressure. Physical function is affected, for example, by immobilization and reduced health-related quality of life resulting in symptoms of exercise intolerance and increased time to recover after exercise, Table 1 (11, 12).

Table 1. Most typical symptoms and signs in HF (11, 32).

Clinical symptoms	Specific signs	Functional symptoms
Breathlessness	Elevated jugular venous pressure	Immobilized
Fatigue	Hepatojugular reflux	Reduced physical fitness
Orthopnea	Third heart sound (gallop rhythm)	Reduced exercise tolerance
Paroxysmal nocturnal dyspnea	Laterally displaced apical impulse	Fatigue, tiredness, ↑recover time after exercise
Ankle swelling		Low functional capacity
		Low quality of life

These are the most typical and specific symptoms and signs. In addition, there are less typical symptoms and less specific signs not mentioned here.

To specify the degree of HF, a subjective functional classification by the New York Heart Association, (NYHA) is commonly used in randomized trials and in the clinic. The level of severity and impairment of physical activity is divided into four classes (33), Table 2.

Table 2. New York Heart Association functional classification, adopted from Marvin HM (33).

Severity	Physical activity
Class I	No limitation of physical activity. Ordinary physical activity does not cause undue breathlessness, fatigue, or palpitations.
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in undue breathlessness, fatigue, or palpitations.
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in undue breathlessness, fatigue, or palpitations.
Class IV	Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken, discomfort is increased.

Skeletal muscle

Most patients with HF have developed skeletal muscle abnormalities. Skeletal muscle wasting, such as sarcopenia and myopathy occurs in 30-50% of patients with HFrEF, as a result of impaired mobility and symptoms (11, 34). Moreover there is a mitochondrial dysfunction, fewer muscle fibers type 1 (switch from type 1 to type 2 fiber), and decreased muscular capillary network which leads to impaired, both exercise and functional, capacity (28, 34, 35).

The muscle metabolism is altered in HF due to early accumulation of metabolites in the skeletal muscles and contributes to the reduced exercise tolerance. Breathlessness increases during exercise; breathing is controlled by several mechanisms, among others through afferent nerves (via chemoreceptors) from the skeletal muscles, the so-called ergo reflex or metaboreflex. The metaboreflex is over-activated in patients with HF, which leads to increased dyspnea already at low physical activity or even in rest (32, 36).

A key role of the periphery has emerged, generating the ‘muscle hypothesis’, where exertional dyspnea and fatigue are resulting from skeletal muscle pathophysiology, also because of deconditioning (28).

Exercise intolerance and capacity

A hallmark of HF is exercise intolerance. Exercise intolerance is defined as an impairment in the capacity to accomplish physical activities followed by increased breathing and fatigue (3, 37). Together the pathophysiological changes in the cardiovascular, muscular and respiratory systems contribute to the exercise intolerance, due to early onset of muscle fatigue, and a high degree of breathlessness (36, 38, 39).

Exercise intolerance is a feature in HF and is associated with low quality of life (QoL) and poor prognosis. Clinically, exercise intolerance appears as breathlessness and fatigue (37). Piepoli et al. (39) claim that exercise intolerance can be successfully tackled by regular exercising.

Exercise capacity and functional capacity are often used as the same term, and need to be defined. According to Arena et al. (2), exercise capacity could be defined as “the maximum amount of physical exertion that a subject can sustain” and functional capacity may be defined as “the ability to perform aerobic work as defined by the maximal oxygen uptake”. However, both exercise capacity and functional capacity are affected by limitations in the cardiovascular system (2, 3, 37).

Treatment

The aim of treatment of HFrEF is to alleviate symptoms, improve quality of life, prevent progression, decrease hospital readmission and prolong survival. The treatment should contain both pharmacological treatment and non-pharmacological treatment, such as nursing clinic (consists of information, medical titration, risk stratification, dietary advice etc) and participation in exercise based cardiac rehabilitation, led by a physiotherapist (40, 41). Recommended pharmacological treatment includes e.g. beta-blockers, ACE-inhibitors and diuretics (42, 43). Implantable cardiac device therapy, such as pacemaker, cardiac resynchronization therapy (CRT) and implantable cardioverter defibrillator (ICD) might be needed and is valuable for some patients with HF. In a more advanced stage there may be need for a mechanical assist device and heart transplantation (11).

Physical activity and exercise

Exercise is a subcategory of physical activity, not synonymous. Since the term physical activity often is used as a collective expression, there is a need to define different degrees of physical activity:

Physical activity is defined as any bodily movement, produced by skeletal muscles, that results in energy expenditure.

Exercise is physical activity that is planned, structured, repetitive, and purposive in the sense that improvement or maintenance of one or more components of physical fitness is an objective.

Physical fitness is a set of attributes that people have or achieve which relate to the ability to perform physical activity (1).

This thesis studies effects of exercise, not physical activity, in daily life.

Recommendations of physical activity and exercise

The global and national recommendations for physical activity and exercise in healthy adults and for patients with heart failure are similar (4, 11, 13).

Physical activity counselling for patients with HF is to be physical active at least 30-60 min/day at a moderate intensity most days of the week (41, 44). A study by Dontje et al. (45) showed that approximately half of the patients with HF had a sedentary lifestyle and took fewer than 5000 steps/day, and suggested that patients were sedentary if they performed less than 30 min/day of moderate to vigorous activities (45).

The latest recommendations of exercise consist of both aerobic and resistance training, and in elderly, balance exercises is added (8). All healthy adults and patients with cardiac disease should perform exercises for at least 150 minutes distributed over the week at a moderate level of exertion. Moreover, resistance exercises may be added, 2-3 week but should not replace the aerobic exercising (13).

If the recommendations cannot be achieved, due to age or disease, the recommendation is to be as active as the condition allows; activities may need to be adapted to the condition as well as to the individual (4).

Aerobic exercise

Simplified, aerobic exercise means exercising with enough oxygen supply and without oxygen deficit via the aerobic metabolism. In general, the intensity of the exercise should be moderate over a longer period of time.

This can be performed in different ways: continuous exercising or in intervals. Continuous exercising means training at a sustained low to moderate level throughout the training session; interval exercising means alternating the exercise intensity between higher and lower in different time intervals (7, 46, 47).

Muscular exercise

Muscular exercising involves both the peripheral muscles (upper and lower extremities) and the muscles of the torso (including postural muscles). The aim of the exercising can vary depending on the purpose of the training; this is regulated by the number of repetitions per exercise, sets and intensity (7, 46). The aim of muscular exercising might be to improve strength, endurance, maintenance of muscular effects and increase local circulation. In summary, the same muscles and exercises is used to achieve different purposes. Resistance training is defined, by Fleck and Kreamer (48), “as a type of exercise that requires the body’s musculature to move (or attempt to move) against an opposing force, usually presented by some type of equipment”.

The resistance training encompasses the use of own body weight, free weights or elastic band (48, 49).

Peripheral muscle training in this thesis aimed to use an isolated muscle mass with a low load and high number of repetitions to increase peripheral circulation in a specific skeletal muscle while imposing only a low load on the cardio-respiratory system (50-52).

Exercise training in patients with heart failure

Exercise training in patients with HF improves e.g. skeletal muscle, peripheral vascular function and central hemodynamic function, which together constitute VO_2 , as well as functional capacity and walking distance, Table 3 (53-55). Oxygen uptake (VO_2) is the result of cardiac output and arterio-venous oxygen ($a-v\text{O}_2$) difference at physical activity, higher workload requires higher VO_2 .

Better $\text{VO}_{2\text{peak}}$ (highest VO_2 achieved) is associated with lower mortality and hospitalizations (56, 57). The benefits of exercise training also include improved HRQoL (58).

Exercise training is broadly recognized as a valuable adjunct in the care of patients with HF and is a key component in cardiac rehabilitation (41, 56, 59, 60).

Table 3. Important effects of exercise training in HF (11, 61).

Aerobic training	Resistance training
↑ VO _{2peak} ↑ anaerobic threshold ↑ peripheral perfusion ↑ 6-minute walk distance ↑ quality of life ↓ hospital readmission	↑ muscle strength ↑ muscle endurance ↑ oxidative capacity ↑ 6 minute walk distance ↑ quality of life Different effects on VO _{2peak} ↑ ↓ and →

Table 4. Classification of intensity. Adapted from ACSM (46).

Intensity	%HR _{max}	RPE (6-20 scale)	RPE on CR-10 (1-10 scale)	Talk test
Light	<64	<12	3-4	Comfortable speech is possible
Moderate	64-77	12-13	5-6	Speech possible with some difficulty
Vigorous/Hard	77-94	14-16	7-8	Speech limited to short phrases
Very Hard	>94	17-20	>9	Speech is very difficult

HR, Heart Rate; RPE, Rating of Perceived Exertion; CR-10, Category Rating scale 0-10

Cardiac rehabilitation

Cardiac rehabilitation is a structured and multidimensional intervention with interplay of medical, psychological and behavioural factors facing the patients, managed by a multidisciplinary team, Figure 2 (41, 62). The multidisciplinary strategy is to e.g. stabilize or slow down disease progression, reduce symptoms and foster an active lifestyle (53, 63).

Figure 2. Services and key components in cardiac rehabilitation (CR). Adapted from Balady et al. (41).

Physiotherapy management exercise based cardiac rehabilitation

The main components in physiotherapy management is exercise training, and a cornerstone of cardiac rehabilitation (56). According to the guidelines (11-13), patients with heart failure should be offered participation in an exercise based cardiac rehabilitation, and yet it is underutilized. Before the onset of a cardiac rehabilitation programme, the patients precede through a clinical evaluation, risk stratification and physical testing (40, 44, 59). In Sweden the physical testing is usually performed by a physiotherapist. Participation in a hospital-setting rather than home-based training is the most common (60).

Based on the results of physical testing the physiotherapist gives the patients individualized exercise training recommendations consisting exercise training-, goals, content, method and frequency, intensity, time and type; these four components constitute the FITT-principle, Table 5 (64).

Table 5. FITT recommendations for patients with HF (13, 41, 46).

FITT		Aerobic activity	Resistance activity
	Frequency	3-5 times/week	2-3 times/week
	Intensity	40-80% $\text{VO}_{2\text{peak}}$ RPE 12-17	10-15 reps in 1-3 sets RPE <15 (40-60% of 1RM)
	Time	20-60 minutes, progressively increased	1-3 sets of 8-10 exercises, upper and lower body exercises, balance exercises should be included
	Type	Stationary cycling, free- walking, biking, running etc.	Machines, free weights, body weight, resistance band.
	Each session should include warm-up and cool-down exercises		

Health-related quality of life

There is no clear definition of the term health-related quality of life (HRQoL). Health-related quality of life and quality of life (QoL) are often used interchangeable (65). The definitions of health (from 1948) and QoL (from 1995), according to WHO:

Health: “A state of complete physical, mental and social well-being not merely the absence of disease or infirmity” (4).

QoL: “An individual’s perception of their position in life in the context of culture and value systems in which they live and in the relation to their goals, expectations, standards and concerns” is also an opportunity to achieve personal goals (6).

The concept of health and QoL encompasses most aspects of life and is difficult to provide a strict definition for the terms together in HRQoL (4, 6, 65). HRQoL is an evaluation of QoL and its relationship with health.

Both health and QoL are subjective parameters commonly used together as HRQoL as an outcome in studies in patients with HF. To cover the spectrum of health and QoL, both a generic and a disease-specific questionnaire can be chosen to measure HRQoL (66, 67), a generic with

reference values in healthy population for comparison and a disease-specific to evaluate the impact of an intervention.

Patients with HF experience low HRQoL due to persistent symptoms despite optimal treatment (67). Patients with HF estimate the second lowest physical health measured by the SF-36 compared to patients with other chronic diseases (68). Meta-analysis (58, 69) have found that exercise training improves the quality of life score measured with Minnesota living with heart failure questionnaire (MLHFQ).

Adherence

According to WHO (70) the definition of adherence is the extent to which a person's behavior is corresponding with agreed recommendations from a health care provider. The recommendations are not only about taking medication but also encompass lifestyle changes, as increasing physical activity.

According to the ExtraHF survey on implementation of exercise training in HF patients in Europe, which includes 41 countries, 170 centers and over 76 000 patients, about 50% are denied exercise therapy (15). Barriers for adherence in cardiac rehabilitation can be related to e.g. patient, health care team/system and condition, Table 6 (15, 71, 72).

Table 6. Barriers for exercise in patients with HF. Adapted from Conraads et al. (71).

	Barriers
Patient related	Older age Low level of education Low socio-economic status Anxiety and depression Logistical problems Lack of motivation Lack of insight into benefits Lack of time
Social and economics	Lack of resources and support Lack of reimbursement Transportation issues
Health care team/system	Lack of expertise in heart failure Lack of capacity Lack of referral Lack of education on the importance of exercise
Condition related	Severity of symptoms Level of disability Rate of disease progression Impact of co-morbidities, including depressive symptoms/cognitive problems
Therapy related	Lack of relevance of some exercise activities for daily life Difficulty to incorporate exercise into daily life

When patients have problems with adherence, the patients need to be supported, not blamed (70). There are several suggestions to help the patients increase adherence to exercise, such as face-to-face contact regularly with e.g. physiotherapist, group exercise sessions, feedback, exercise equipment provided for home-based training, to mention some (16).

AIM OF THE THESIS

The general aim of this thesis was to evaluate exercise training and testing in patients with chronic heart failure with focus on different exercise modalities, walking distance and HRQoL and the correlations between them. The overall goal was to contribute knowledge to this field, which would be applicable in clinical practice and thereby benefit patients with HF.

Specific aims

Study I: To describe a PMT programme with resistance bands in a home-based setting and to evaluate the effects on walked distance and HRQoL, in patients with HF, over a 12 month period. The second aim was to compare home-based training versus group-based supervised training (in a hospital-based setting during the first 3 months), subsequent over the 12 month period.

Study II: To compare the PMT programme from study I with an aerobic training programme. Initially, both groups started with supervised exercise training in a hospital-setting for 3 months and thereafter exercising in a home-based setting for 9 months.

Study III: To evaluate if it is necessary with duplicated walk tests for evaluation over time using test-retest reliability assessment of the 6MWT in patients with HF.

Study IV: To define the relationship between the 6 minute walked distance (measured with 6MWT) and self-reported HRQoL measured with both a generic and a disease specific questionnaire.

METHODS

This thesis is based on four studies described in Table 7 and Figure 3. All patients were recruited from the department of cardiology or department of clinical physiology, Kalmar county hospital. Both exercise testing and training were performed at the department of physiotherapy, Kalmar county hospital.

Table 7. Overview of studies I-IV.

Study	Design and study criteria
I	Prospective longitudinal randomized controlled study <i>Inclusion criteria:</i> Heart failure >3 months, stable drug therapy, NYHA II-III, EF $\leq$ 40%, Age $\leq$ 80 years <i>Exclusion criteria:</i> Physical or mental disorder limiting testing or training, concomitant disease e.g. chronic obstructive pulmonary disease and diabetes mellitus
II	Prospective longitudinal randomized controlled study <i>Inclusion criteria:</i> Heart failure >3 months, stable drug therapy, NYHA II-III, EF $\leq$ 40%, Age $\leq$ 80 years <i>Exclusion criteria:</i> Physical or mental disorder limiting testing or training, concomitant disease e.g. chronic obstructive pulmonary disease and diabetes mellitus
III	Longitudinal reliability study Data from study I and II
IV	Prospective experimental longitudinal study Data from study I and II

Figure 3. Flowchart over studies I-IV.

*1 patient, in study I, rejected further participation but gave permission to use baseline data. 6MWT, 6 minute walk test; MLHFQ, Minnesota Living with Heart Failure Questionnaire

Measurements

Six minute walk test

Walking distance was measured with an indoor standardized six minute walk test (6MWT). The 6MWT was performed in a flat, straight, 80-meter hospital corridor, without disturbance. Traffic cones were placed at each end of the course which was marked in 2.5 meter intervals to facilitate the distance count.

The standardized instructions were modified from ATS's recommendation (73), adapted for patients with HF. Before the 6MWT, oral instruction was given as to how to perform the test and how to use the Borg scales (74).

The patients were instructed to walk as far as possible in self-selected pace for 6 minutes. If needed, they were allowed to slow down or stop and rest, and continue walking when able to, but the time was still measured. They were not allowed to run. No encouragement was given during the test, but an oral signal was given when 1 minute remained.

Heart rate was monitored with a pulse transmitter attached to the chest with a display on the wrist (Polar®, Kempele, Finland), and was measured before and immediately after when walking stopped at 6 minutes. The

patients also rated, on Borg's scales (74), their perceived exertion (RPE 6-20) and feelings of breathlessness and chest pain (CR-10). The 6MWTs were performed by a physiotherapist not otherwise involved in the studies. The patients performed the 6MWT twice at each occasion on the same day with a 45 minutes rest, in a seated position, in between.

In study I the second 6MWT was analysed, but in study II the walk test with longest distance was used in the analysis.

Symptom-limited bicycle ergometer test

In study II, before starting exercising, the patients in the cycling exercise group (CEG) also performed a bicycle ergometer test. The purpose was to obtain the highest heart rate for calculating the correct heart rate span during the exercise class. The bicycle ergometer test was, therefore, not repeated during the study period. The workload started at 30Watt (W), for women, and 50W for men, and increased stepwise every minute with 5W (women) and 10W (men), respectively, until reaching 17 at Borg's RPE scale, which was the interruption criterion (75, 76).

Health-related quality of life

For evaluation of the health-related quality of life (HRQoL), validated and reliable Swedish versions of the short form Health Survey, SF-36v1™ (SF-36) and the Minnesota Living with Heart Failure Questionnaire (MLHFQ), were used to measure variations in generic (SF-36) and disease-specific (MLHFQ) health status during the study period. Both instruments are self-reported and were completed during the 45-minute seated rest between the walk tests (77, 78).

SF-36

The SF-36 consists of 36 items and comprises eight dimensions which in turn can be divided into two summary components, physical (PCS) and mental (MCS) component score. Each dimension extends a scale ranging from 0, worst perceived health status to 100, best perceived health status. The eight subscales are: Physical Functioning (PF), Role-Physical (RP), Bodily Pain (BP) and General Health (GH) forming the PCS, and Vitality (VT), Social Functioning (SF), Role-Emotional (RE), Mental Health (MH), constituting the MCS (78-80).

MLHFQ

The Minnesota Living with Heart Failure Questionnaire (MLHFQ) is a disease-specific questionnaire. A disease-specific form is designed to capture important aspects in a specific disease or group of patients, in this case adult patients with HF. The MLHFQ measures patients’ perception of symptoms’ impact on their daily life during the last month. The MLHFQ consists of 21 items in a total score of 0-105p: one physical domain (consists of 8 items, 0-40p), and one emotional domain (consists of 5 items, 0-25p); the other 8 items cover work, economics and sex, not included in a domain (81-83).

Intervention

In study I, both groups trained PMT, one group started in a hospital-setting followed by home-based training and the other group trained solely at home.

In study II, both groups started the exercise period in a hospital-based setting and continued with home-based training.

Both study I and II consisted of exercising and follow-ups during one year.

Hospital-based training

The exercise training programmes at the hospital were supervised by a physiotherapist and were conducted twice a week.

Table 8. Peripheral muscle training programme.

Peripheral muscle training - In hospital and at home	
Warm up Exercises in sitting and standing positions. At home: walking on the spot. Exercises with free weights or REP-band Unilaterally standing or sitting M. biceps brachii Wrist extensor group. M. Quadriceps Exercise using own body weight Bilaterally in erect position.	M. gastrocnemius Pulley exercises or REP-band Bilaterally in erect position M. pectoralis major M. intercostalis M. rhomboids M. triceps brachii M. gluteus maximus Cool down for 5-10 minutes Stretching exercises in both groups

REP-band, Resistive Elastic Product

Peripheral muscle training

The exercises were individually tailored for each patient, based on a restricted HR, to exceed no more than 30 beats over resting HR, monitored with a pulse transmitter on the chest, displayed on a pulse-watch on the wrist (Polar®, Kempele, Finland), to achieve a high number of repetitions/exercise (30 times) with a low load, performed in 2 sets (50, 51). In case of atrial fibrillation, the exercise intensity for each muscle was based solely on RPE 15 in the working phase. The training regime was designed to include leg, arm and chest muscles, using pulleys, free weights, and body weight as resistance and was performed in the gym at the physiotherapy department for 60 minutes per session, Table 8.

Table 9. Aerobic training programme.

Aerobic training - In hospital and at home		
Interval training at hospital	Duration	RPE/HR%
Warm up	5 minutes	11/40%
Interval circle consisting:	15-45 minutes	
High Interval	90 seconds	15/80%
Low Interval	30 seconds	13/60%
Cool down	5 minutes	11/40%
Free-walking at home		
Warm up	5 minutes	11
Free-walking	35 minutes	13-15
Cool down	5 minutes	11

RPE, rating of perceived exertion; HR, heart rate

Cycling exercise

The training protocol was adopted from an interval training study (84) on an ergometer bike. The patients accomplished an interval training program on an exercise bike, with 90 seconds of exercise and 30 seconds of active 'rest' but was modified to include a warm-up and a cool down period; in the active 'rest' between the intervals the patients continued biking but at a lower level of exhaustion.

The training programme was performed on an ergometer bike (Monark Ergonomic 818e, MonarkExercise, Vansbro, Sweden) and consisted of: five minutes warm-up at 40% of HRpeak or Borg RPE 11, a 90 s higher intensity interval and a 30 s active recovery phase (lower intensity) and finally a cool down for five minutes, at the same intensity as the warm-up phase, twice a week.

Patients in sinus rhythm exercised using a HR monitor on the chest displayed on a pulse-watch (Polar®, Kempele, Finland), corresponding to 80% of HRpeak at the baseline exercise test $\pm$ 5 beats, during each interval, and recovery phase 60% of HRpeak. For patients with atrial fibrillation, the exercise intensity was chosen to correspond to exhaustion grade 15 according to the Borg RPE scale (74), approximately 80% of maximum, and 60% in the recovery phase, Table 9.

The training time was gradually increased from 15 to 45 minutes by adding 15 minutes of intervals per month. With warm-up and cool-down phases included the total exercise sessions were between 25 and 55 minutes. Patients adjusted individually the speed and load to reach adequate HR or RPE.

Home-based training

After completing the first training period under supervision in a hospital-setting, a home-based training programme was tailored for each patients and prescribed for the remainder of the study period. Those patients in study I who began with home-based training, continued their training programme as before.

At follow-up, the load could be adjusted, but patients could contact the physiotherapist at any time if necessary. All patients were told to register the number of training sessions and perceived exertion in a logbook.

Peripheral muscle training

Patients who trained in the gym at the hospital continued with the same exercises but using elastic bands as resistance (REP-band®, (Resistive Elastic Product) Magister Corporation, Chattanooga, USA). The REP-bands are available in 5 different resistors and was individually tailored for each patient. The training programme was prescribed to be performed in one set, $\geq$ 3 times/week for 40 minutes per session, at an effort of RPE 13-15, Table 8.

Cycle training

Patients who exercised on an ergometer bike switched the training programme to free-walking for 45 minutes per session, $\geq$ 3 days/week, at an effort of RPE 13-15, Table 9.

Statistics

Statistical analysis was performed using Statistica version 12 (StatSoft®, Tulsa, OK, USA), MedCalc version 14.10 (MedCalc Software) and Excel 2013 (Microsoft Office, Redmond, WA, USA). The statistical significance level was set at $p < 0.05$ in all studies.

At baseline descriptive data, group differences were analysed using Fisher's exact test for categorical variables, and Mann-Whitney's U-test for continuous variables. The descriptive data was presented by numbers, percent, mean value and standard deviation, median and range, depending on characteristics and distribution of data (85, 86).

In study I and II, the power calculation was based on previously published results from similar studies; study II also included the results from study I for the power calculation. Calculations on an expected increase of 20% in walking distance with an SD of 30% indicated that a total of 24 patients should be included.

For comparison between groups over time, repeated measures ANOVA was used, with groups as categorical factors, and mixed factorial ANOVA followed by Duncan's post-hoc test in case of statistical significance (85, 86).

In study III, the Bland-Altman plot was used to describe the difference, in meters, between the paired 6MWTs (87). The intraclass correlation coefficient (ICC), and CI 95%, was used for correlation between the duplicated 6MWT performed by the same subject and measurement error (S_{method}) together with the coefficient of variation (in%) for intraindividual variability of the 6MWT (88). For interpretation of the ICC value > 0.75 was considered acceptable (89) and > 0.90 was considered excellent (90).

In study IV, each patient on each test occasion was allocated to a dichotomized group, based on the median walked distance, in percent, of all performed 6MWT of the predicted value.

The predicted walking distance in six minutes was calculated using Enright's formula (91):

Men = $(7.57 \times \text{height cm}) - (1.76 \times \text{weight kg}) - (5.02 \times \text{age}) - 309 \text{ m}$.

Women = $(2.11 \times \text{height cm}) - (2.29 \times \text{weight kg}) - (5.78 \times \text{age}) + 667 \text{ m}$.

Table 10. Overview of statistical methods.

Type of data and statistics	Study I	Study II	Study III	Study IV
Descriptive statistics	x	x	x	x
Mann-Whitney U	x	x	x	x
Fisher's exact test	x	x	x	x
Repeated measure ANOVA	x	x		
Bland-Altman plot			x	
Intraclass correlation			x	
Measurement error			x	
Mixed factorial ANOVA				x

Ethical considerations

The Regional Ethical Review Board of Linköping, approved the studies, Study I: Dnr99266 and Study II: Dnr02-041. Study III and IV were based on the collected results from study I and II. All included patients gave their written informed consent to participate after verbal and written information. The investigation conforms to the principles outlined in the Declaration of Helsinki. Both main studies lack a control group as exercise training is priority 3 according to The National Board of Health and Welfare guidelines (14), i.e. all patients with HF should be offered exercise training, therefore we considered it unethical to include a control group.

RESULTS

Study I

Peripheral muscle training with resistance exercise bands in patients with chronic heart failure. Long term effects on walking distance and quality of life; a pilot study

Twenty-two patients with stable HF (3 female) were randomized to individual home-based training (HT-group), or home-based training with a group-based start-up in a hospital-setting (GT-group), with baseline testing and four follow-up occasions, every third month over 1 year.

Exercise training resulted in statistically significant increased walking distance in both groups. There were no statistically significant differences between groups on any parameters or follow-ups. The HT-group increased on average (SD) 107 (80) meters from baseline to 12 months, and the GT-group by 100 (96) meters. Health-related quality of life, (MLHFQ and SF-36), reached statistically significant improvements in both groups but at different time points. The adherence to the prescribed exercise programme was high.

Study II

Neither hospital-based nor home-based aerobic or peripheral muscle training improved walking distance or health-related quality of life during a one year follow-up in heart failure patients.

Twenty-three patients (5 women), were randomized to either cycling/free-walking (CEG) or peripheral muscle training (PEG). Both groups began the training period in a hospital setting for three months and thereafter the exercising continued at home for the rest of the study period.

The exercise training did not significantly improve neither the walking distance nor HRQoL, measured with 6MWT, SF-36 and MLHFQ, during the year of exercising, despite relatively high, but decreasing, adherence, either within or between the groups.

Table 11. Study I and II.

Study I					Study II				
HT-group N=10		PT-group N=12			CEG N=13		PEG N=10		
Mean (SD)	p- value	Mean (SD)	p- value		Mean (SD)	p- value	Mean (SD)	p- value	
Six minute walk test, distance in meters									
Baseline	396 (96)		392 (130)		Baseline	445 (80)		420 (74)	
3 months	464 (118) **		490 (108) ***		3 months	457 (86) ns		444 (53) ns	
6 months	469 (117) ***		514 (97) ***		6 months	462 (95) ns		449 (65) ns	
9 months	481 (105) ***		497 (108) ***		9 months	439 (99) ns		409 (111) ns	
12 months	489 (107) ***		516 (119) ***		12 months	446 (97) ns		433 (99) ns	
MLHFQ Physical dimension, Score 0-40, Lower score represent better quality of life									
Baseline	17 (12)		19 (9)		Baseline	13 (11)		13 (8)	
3 months	14 (11) ns		13 (8) *		3 months	10 (7) ns		12 (8) ns	
6 months	12 (12) *		13 (9) *		6 months	8 (9) ns		14 (8) ns	
9 months	11 (11) *		13 (10) *		9 months	9 (10) ns		16 (11) ns	
12 months	13 (12) ns		12 (5) **		12 months	9 (9) ns		14 (10) ns	
MLHFQ Emotional dimension, Score 0-20, Lower score represent better quality of life									
Baseline	9 (8)		10 (4)		Baseline	6 (6)		6 (6)	
3 months	8 (6) ns		6 (4) *		3 months	6 (6) ns		5 (6) ns	
6 months	7 (6) ns		7 (4) ns		6 months	5 (5) ns		7 (5) ns	
9 months	7 (7) ns		7 (6) ns		9 months	6 (5) ns		7 (6) ns	
12 months	7 (6) ns		5 (5) **		12 months	6 (6) ns		8 (6) ns	
SF-36 - PCS, Score 0-100, Higher score represent better quality of life									
Baseline	54 (26)		45 (21)		Baseline	57 (24)		57 (19)	
3 months	57 (26) ns		56 (15) *		3 months	57 (26) ns		60 (16) ns	
6 months	60 (28) ns		62 (14) **		6 months	63 (24) ns		54 (24) ns	
9 months	64 (25) ns		56 (21) *		9 months	60 (24) ns		48 (17) ns	
12 months	65 (29) *		57 (16) *		12 months	58 (21) ns		55 (21) ns	
SF-36 - MCS, Score 0-100, Higher score represent better quality of life									
Baseline	58 (24)		50 (21)		Baseline	68 (25)		66 (20)	
3 months	62 (22) ns		60 (16) *		3 months	63 (25) ns		71 (12) ns	
6 months	66 (28) ns		65 (15) **		6 months	70 (22) ns		64 (23) ns	
9 months	69 (25) *		63 (21) **		9 months	65 (24) ns		60 (18) ns	
12 months	70 (27) *		62 (16) *		12 months	63 (22) ns		63 (21) ns	

HT-group, home training group; PT-group, physiotherapist-led group; CEG, cycling exercise group; PEG, peripheral exercise group; MLHFQ, Minnesota Living with Heart Failure Questionnaire; SF-36; Short Form 36 items; PCS, physical component summary score; MCS, mental component summary score

Study III

Test-retest reliability of six-minute walk tests over a one year period in patients with chronic heart failure

Forty-six patients (9 female) performed the 6MWT every third month for one year, in total 198 duplicated test (totally 396 6MWTs).

An improvement of 8.7 meters (1.9%) was seen in the second 6MWT calculated on all performed follow-ups. This was considered not to be of clinical significance. The average measurement error (S_{method}) ranged from 2.4 to 3.9% over the study period, and the relative test-retest reliability calculated as ICC was mean 0.98 (CI95% 0.96-0.99). The variation over time was not statistically significant.

Study IV

Six minute walk test versus health-related quality of life in patients with chronic heart failure

Forty-six patients (37 men and 9 female) performed 6MWT and administered the SF-36 and the MLHFQ on five occasions.

Patients were divided into two groups, below and above the median walked distance of 92% corresponding to the predicted value. $\text{Pred} < 92\%$; $403 \pm 77\text{m}$ ($76 \pm 13\%$ of the predicted value) and, $\text{Pred} \geq 92\%$; $517 \pm 67\text{m}$ ($104 \pm 10\%$ of the predicted value).

Patients with a walking distance lower than median $< 92\%$ of walking distance experienced a lower HRQoL than the higher performing half of the cohort, walking distance $> 92\%$, in four dimensions of the SF-36 (PR, RP, GH and RE) and both the physical and mental components score. No association, in either group, was seen between walked distance and MLHFQ.

Figure 4. Six minute walk test, study I versus study II.

Figure 5. Adherence to prescribed exercise, study I versus study II.

DISCUSSION

Historically, exercise training in patients with HF was proscribed until the late 1980s, when Sullivan et al. (92), for the first time, showed that exercise training for 12 weeks improved exercise tolerance. This study is a mainstay in research by changing the scientific approach to the relationship between HF and exercising.

The research in this thesis aims to evaluate and further develop exercise training and testing to make it more accessible and userfriendly for both clinical practice and heart failure patients.

Since the 1980s, numerous studies have shown positive effects of exercise training in heart failure (93) and it has also become a class IA recommendation in both European and American guidelines (11, 12).

Despite this, only a small portion of patients with HF receives a customized individually based exercise program (10). This is about to change in Europe (15).

Exercise training

Patients with HF often experience poor physical function and impaired quality of life with low daily physical activity and immobilization as a result (94).

Promoting enhanced physical activity and physical exercise is important to gain benefits such as reduced mortality, reduced hospitalization, increased physical function and improved HRQoL (11-13). However, some patients with HF are difficult to engage in exercise training (39, 45, 71).

An exercise training programme in patients with HF should include both aerobic and resistance elements (13, 46). Since it is difficult for some patients to participate in cardiac rehabilitation in a hospital-setting we aimed to evaluate a training programme that would suite most patients. Moreover, participation in a supervised programme in a hospital-setting lasts for a limited period which means that patients with HF must find

another exercise setting after discharge from hospital based rehabilitation and training.

In study I, we evaluated a PMT programme in both a hospital- and a home-based setting. In both settings the patients increased their walking distance after three months of exercising and maintained the improvement over the 1-year study period, Figure 4. In this study, the walked distance was just below 400 meters in both groups at baseline, which is in line with similar studies (95). They increased their walked distance by about 100 meters, which was statistically significant, and more than average in similar studies (95-97). There were no significant differences regarding training effects between the 2 groups that received an initial period of hospital-based training or not. We could not repeat the improvements in study II, despite the similar approach, Figure 4. Nor was there any cardiac event reported, in study I and II, neither in the hospital-setting nor at home.

The fact that there was no significant change in either breathlessness according to the CR-10 scale, Borg's RPE or heart rate despite the increased walking distance, indicates that patients in study I had increased their maximum oxygen consumption. Although an increase of central circulatory capacity, probably based on a general increase in physical activity, cannot be excluded, a peripheral adaptation including e.g. improved muscle metabolism and capillarization, and thereby an increased maximal arterio-venous oxygen difference is likely to have contributed to the improvement (32).

The probable changes in the submaximal muscle endurance, obtained by low-intensive resistance training, may reflect the importance from the patient's perspective since most daily activities are done at submaximal force levels rather than maximal force production, gained by high-intensive strength training (98). This would favour a PMT programme.

To implement also an aerobic element of exercise, to reach exercise recommendations (11-13), we compared PMT with an aerobic training in study II. The mode of aerobic training was interval training on a bicycle ergometer in a hospital setting for 3 months, followed by free-walking in the home-based setting, as an attempt to find an accepted mode of aerobic exercising at home. This was compared with the PMT, also in hospital- and home-based setting in the same timeframe. The advantage of ergometer cycling is the possibility to measure and set the load individually, at for example 80% of HR which is in line with aerobic exercise recommendations (13, 46). It is harder to measure and set the load with

elastic bands, and the knowledge about the elastic bands properties is important to achieve the right load. This we could not measure. But the intensity can be adjusted by using the RPE scale, a useful way for patients to achieve the prescribed RPE when exercising (13), both in a hospital- and home based-setting. In study II, walking distance did not increase over the study period in either of the 2 groups.

It should however be borne in mind that HF has a progressive development (25) and that with age, the predicted walking distance and work capacity “normally” decreases (75, 99). In line with study II, earlier studies have shown none or poor improvement by an exercise programme in HF patients (100, 101). A lack of deterioration can thereby be interpreted as an improvement. This, and possible reasons for the different results in study I and study II, has been discussed more in-depth in Paper II.

Briefly, the mean age of the patients was higher in study II and despite this their 6-min walking distance was longer. Thus the potential to improve their physical function further may have been lower. One may also speculate whether one or two so called non-responders to training (102) may have participated in study II and reduced the group mean results. However, this was not the case since the results of the participating subjects were more homogenous.

Both modes of exercising were well tolerated and no cardiac events were reported.

Functional testing

Since HF is a syndrome with a progressive development and a poor long-term prognosis (18), it is valuable to detect changes over time (89).

CPET is the “gold standard” in measuring exercise capacity (103, 104) and probably the most frequently used exercise test in patients with HF; it is often recommended before starting cardiac rehabilitation (44, 105). Most patients will not undergo CPET before cardiac rehabilitation since the access to CPET is limited (106), e.g. in smaller hospitals or primary care. This may delay cardiac rehabilitation, and even lead to immobilization if there is no acceptable alternative test method before starting the rehabilitation period. In the absence of CPET, the 6MWT is recommended in different guidelines and reviews since it is a common functional test (39, 107, 108). It has also been suggested that 6MWT can predict VO₂ (109) using the following equation (110):

Mean Peak VO₂ (ml/kg/min) = (4.948+0.023)*Mean 6 MWD (meters)

There is a learning effect when the 6MWT is performed twice or more (111). Studies have shown that the walked distance has a tendency to increase with repeated 6MWT, indicating a learning effect by familiarization. The amount of learning effect differs between studies (112, 113). Singh et al. (114) showed a learning effect of 26 meters, but these pooled data were in patients with lung diseases, not studied in patients with HF. The learning effect has been described as an increase between 2 tests but there might also be a “negative learning effect”. If the first walk test is too physically demanding and feels overwhelming, this might affect the willingness to perform a second walk test (115).

In study III, we showed that the test-retest reliability was excellent over a one year period; this is important if measurements should be continued over time. The learning effect was 9 meters; this reached statistical significance but we interpreted that 9 meters was too small for a clinical significance. We interpret our results as in a clinic practice were it is enough to perform a single 6MWT, but in a study it could be valuable with more than a single test.

In both study I and II the patients performed two 6MWT with 45 minutes rest in between, at all test occasions, baseline and during follow-up. These data were in study III used to explore if it is necessary to perform the 6MWT twice. Since most of the patients with HF suffer from low physical function, it is inappropriate that the patients perform the 6MWT twice if it does not add any further information.

According to ATS (73) the straight surface at 6MWT can be 50-164 feet (~15-50 meters) with no significant effect on the walked distance. ATS recommend using a 30 meter flat corridor. In both study I and II the walking track was 80 meters long, which had the advantage of minimizing the number of turns. A potential disadvantage is that the track may feel overwhelming if the patient is in poor physical shape, but our patients generally had a longer walking distance, and this was not perceived as a problem.

The 6MWT can be used more frequently than other types of exercise testing because it is quick and easy, requires minimal equipment, and is well tolerated by patients. It is, however, still important to standardize the execution of the test, for patients with HF.

Opinions regarding encouragement during the 6MWT are divided. Encouragement is recommended but not imperative (73, 114, 116), e.g. the conclusion, in a frequently referenced study by Guyatt, (117) “there is no compelling reason to either give or not give encouragement, so long as tests

are conducted in a consistent manner". The study of Guyatt (117), enrolled 43 patients, 25 in the respiratory group and 18 in the cardiac group.

Neither in study I or II was encouragement given, since external pacing during the test situation, e.g. impaired hearing, may affect the test protocol (116).

Health-related quality of life

Health-related quality of life is impaired in patients with HF (67, 68), however, the HRQoL can increase in HF patients participating in an exercise training programme (58).

We evaluated the quality of life status before and after the exercise interventions in study I and II. The HRQoL did increase significantly in study I but not in study II despite similar training interventions. Whether this was coupled to the improved physical function, measured as improved 6MWD in study I is possible but not proven. The small number of participants in both studies may however also have contributed to the divergent results.

To shed more light on this, we decided to investigate the connection between perceived HRQoL and walking distance in study IV. Our hypothesis was that a shorter walked distance is related to a poorer HRQoL. This hypothesis could not fully be confirmed. Study IV showed that the relationship between HRQoL and walked distance was poor.

The median of walked distance of all patients was high, 92% of predicted value for healthy individuals, taking gender, age, height and weight into account. The score of the SF-36 in our patients was approximately 20 p lower than the SF-36 in a normal population (79). The patients with a lower walked distance than median had lower HRQoL by several dimensions of the SF- 36. No such relationship was seen in MLHFQ scores. This might reflect that our patients, stable on medical treatment, were not overtly symptomatic with classical heart failure symptoms, but still suffered some limitation in their daily life activities.

Adherence and barriers

It has been reported that patients with heart failure have difficulty following recommendations for exercise. Evangelista et al. showed that 61% of patients with HF estimated adhering to an exercise recommendation harder than to other recommendations, e.g. medicine, dietary. Barriers for participating in cardiac rehabilitation and exercise

training could be lack of motivation, lack of energy and presence of symptoms (31, 71, 72, 118).

It is difficult to measure adherence to home-based training according to no consensus in measurement (119, 120) but still and surprisingly there seems to be a tendency towards higher adherence to exercise in a home-based setting rather than in a hospital/center-based setting (120, 121).

In study I and II, the patients kept a logbook over exercise sessions, time and RPE per session and we noticed the difficulty in measuring adherence. Despite detailed oral and written information about completion of the logbook, patients interpreted this differently and several patients had also counted time for activities such as housekeeping. However, this time was excluded from the analysis.

Many patients are unable to participate in a training programme in a hospital-setting because they live far away, have problems of transportation or cannot afford to pay the fee for training at hospital (122, 123). For these patients a home-based exercise training programme could be an alternative.

In study I, the adherence was good, according to the logbook, in both intervention groups. In the group which started exercising under supervision for 3 months, the adherence decreased over the period. The home-based training group exercised 3 times per week over the study period, but they also lost in adherence over time. Supervised exercise in the hospital-setting was twice per week and after discharge the training sessions were increased to 3 times per week. However, the group continued to exercise twice a week, probably because of the habit to do so. This was not the case in study II; the adherence was good in both intervention groups but decreased over time as well. The adherence tends to decrease over time in trials as well as in real life (71, 118).

According to long-term low adherence and barriers to exercise training, like lack of time and energy (71) it seems necessary to monitor and optimize exercise modalities to increase adherence and overcome barriers in patients with HF.

More importantly, an item which has caught our attention in recent years, is that elderly patients show low confidence to exercise (124-126). Confidence to exercise is an individual's belief in their own ability to initiate or maintain regular physical activity (125). Many older patients have no experience of exercising and are worried about not being able to cope with the exercise programme, which may reflect a low confidence to exercise. It is important that intensity of the exercise programme is challenging but not

overwhelming; the patient must experience a sense in success of mastering the exercise and thus increase their confidence to exercise. It seems more likely that we accomplished that in study I than in study II.

Home- and hospital setting

Most previous studies have evaluated exercise training programs in a hospital-setting, for a shorter limited period (50, 84, 127-130). It seems like there is a quite rapid deterioration after finished exercise training in a hospital-setting (131, 132). Only a few studies with long-term follow-up for a year or longer are reported (133-135).

Home-based training programs have been reported and have focused on walking or bicycling (123, 133, 135-137). Studies using center-based training followed by a home-based training program compared to a solely home-based training program are rare (135, 138, 139). In addition, only a few long-term studies of home-based peripheral muscle training have been reported (123, 135, 137).

In study I, the patients gained walked distance and increased HRQoL and maintained this over the study period regardless of introductory period.

In a meta-analysis by Buckingham et al. based on a Cochrane report, it was concluded that both home-based and hospital/center-based cardiac rehabilitation had same benefits in patients with HF (120, 140), and that patient's choice of exercise setting according to their preferences may increase adherence (120, 121).

According to this, home-based training seems to be a good alternative to supervised training after discharge from cardiac rehabilitation, or solely if wanted, according to patients' choice.

Life-long training programme

A long-term exercise program (141, 142) can be difficult for patients with HF when symptoms of dyspnea and fatigue occur already with light physical/daily activity and therefore may limit the patients' willingness to exercise (93).

In recent years, attempts to streamline exercise training with shorter bouts of exercise have been made, e.g. aerobic interval training (AIT) with higher intensity (143) or low-volume time-efficient resistance training (96). Wisloff et al. (143) showed that AIT on treadmill with as high as 95% of peak HR in older patients with HF (76.5±9 years) was well tolerated compared with moderate continuous walking at an intensity of 70-75% of peak HR. The increase in VO₂ was larger in the AIT group (46%) than in

the continuous walking group (14%). Both groups also increased HRQoL. Munch et al. (96) on the other hand, had a different approach, comparing moderate continuous cycling for 45 minutes (75% of $\text{Watt}_{\text{peak}}$), with low-volume resistance training for 25 minutes (4 sets, 1 set at 25% and 3 sets at 40% of 1RM. Exercise time include warm-up period. Both improved equally regarding VO_2 , $\text{Watt}_{\text{peak}}$, 6MWD and HRQoL. However, the patients in this study were younger 61 ± 3 years. Aerobic interval training has been shown to be more efficient than aerobic continuous training for increasing VO_2 (60).

Shah et al. (144) showed the impact of holiday winter time, like Christmas, was associated with increased HF events directly after the holiday, associated with i.a. reduced exercise. Another study (145) confirmed the seasonal variation with lower physical activity during the winter period among patients with HF. During winter time it can be hard with a free-walking exercise programme, due to e.g. risk of fall; with a PMT programme it is easy to continue exercising.

We think that we have found an exercise mode (PMT with elastic bands) that patients are able to adhere to over seasons and holidays. Exercising with elastic bands is easy and can be adjusted after degree of symptoms; when feeling better the patients can tighten the elastic bands, and with feeling worse can slacken the elastic bands and can still estimate perceived exertion on the RPE scale.

Finally, the selection of the exercise modality should take into account the patient's age, concomitant diseases, leisure and working habits, preferences and abilities, logistical restraints, and the availability of exercise facilities and equipment (39, 40). An exercise modality such as walking and resistance training with body weight or elastic bands, a long-term exercise training to be performed at home, for older patients with HF, might be recommended.

Based on our results, we suggest that peripheral muscle training could promote improved daily living, such as quality of life and walking distance over time.

Limitations

There is a difficulty in attracting women to participate in studies. This might be attributed to the fact that women are older when having the diagnosis of heart failure, and then more often with preserved EF.

The lack of a control group is based on the national and international recommendation for physical activity, partly for healthy individuals but especially for patients with HF.

There is limited evidence of the benefits of exercise in patients with HF and preserved EF and our results cannot be generalized to that population.

CONCLUSIONS

Peripheral muscle training resulted in improved physical function and health-related quality of life in one study and absence of deterioration in another, indicating that peripheral muscle training is useful and effective in the training of heart failure patients.

The effects over a one-year follow-up were similar whether starting with a 3-months hospital-based training period or not.

When comparing one group of heart failure patients having PMT and another performing aerobic exercise, the outcome in terms of walking distance and health-related quality of life was equal.

Duplicating the 6-minute walk test with 45 minutes rest in between gave a slightly, albeit significantly longer walking distance at the second test, a clinically unimportant difference of only 9 meters (2%). This was the case also at follow-up every 3rd month over the one year follow-up.

A shorter walking distance was related to an inferior rating of health-related quality of life evaluated by the generic instrument SF-36 but to a much lesser degree by the disease-specific Minnesota Living with Heart Failure Questionnaire.

Clinical implications

Home-based training is a possible alternative to hospital-based and can, with regular follow-up, be the solution of the need for long-term training in these patients.

Peripheral muscle training is effective and useful in heart failure patients.

Patients should thus be offered to choose exercise modality, and hospital/center based or home-based training, based on their preferences.

Six minute walk tests need not to be duplicated in clinical practise.

For the evaluation of severity of heart failure symptoms and effects of treatment it is important to be aware that the different evaluation tools measure different aspects of the spectrum of functional impairment.

Future research and development

There is a need for strategies to get patients with heart failure to participate in cardiac rehabilitation and to overcome barriers for participation.

Solutions for increasing adherence to exercise, such as smartphone applications, websites, validated logbook should be developed and evaluated.

The lack of opportunities for prolonging exercise training after discharge from cardiac rehabilitation, especially for older patients should be addressed. Involving of community services, and involving sports clubs to establish special “heart patient visits” with an exercise instructor present, are some examples.

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