Exercise-based cardiac rehabilitation, physical fitness, and physical activity in cardiac disease

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To Jessica and Mattias

"To experience is a part of the journey"

Jan Borland, modified by Hans Carlström

ABSTRACT

Background: Evidence suggests that individualised exercise-based cardiac rehabilitation should be offered to patients with ischemic heart disease and chronic heart failure (HF) because it improves physical fitness and health-related quality of life (HR-QoL), and reduces cardiac mortality and hospital admissions. If physiotherapist-led exercise-based cardiac rehabilitation (PT-X) can similarly improve physical fitness in patients with atrial fibrillation (AF), and improve physical activity levels in patients with chronic HF or permanent AF, has been sparsely studied. In addition, whether increased physical activity in patients with chronic HF or permanent AF can improve physical fitness in the same way as exercise has not been evaluated.

Aim: The general aim for this thesis was to investigate the effect of individually prescribed PT-X in elderly patients with chronic HF or permanent AF especially in regards to exercise modality, physical fitness, level of physical activity, HR-QoL, and metabolic risk factors.

Method and Main Findings: Study I. A randomised controlled trial (RCT) in patients with chronic HF and comorbidity investigating the effect of PT-X regarding the level of physical activity, physical fitness (i.e., exercise capacity and muscle function), and HR-QoL. Physical activity did not increase significantly after PT-X, though self-reported physically activity levels were higher. Physical fitness and HR-QoL improved significantly in the PT-X group compared to the control group. **Study II.** A RCT multicentre trial comparing PT-X and physical activity on prescription (PAP) with regard to physical fitness, level of physical activity, HR-QoL and metabolic risk markers in patients with permanent AF. Physical fitness improved significantly in PT-X compared to PAP. PAP increased energy expenditure but not physical fitness. No significant difference was found in HR-QoL or metabolic risk markers. **Study III.** A 3-month follow-up of study II investigating the effect of 3 months detraining with respect to physical fitness, level of physical activity, and HR-QoL in patients with permanent AF. The improvements achieved in physical fitness in the PT-X group decreased significantly with detraining, and HR-QoL was markedly reduced.

Conclusion: PT-X is well tolerated and safe and, therefore, should be used to improve physical fitness in patients with chronic HF or permanent AF. Neither PT-X nor PAP increases the physical activity level. PT-X improves HR-QoL in patients with chronic HF but not in patients with permanent AF. In patients with permanent AF, it is important to continue exercising because detraining reverses the gains in physical fitness obtained from PT-X and markedly decreases HR-QoL.

Keywords: exercise-based cardiac rehabilitation, exercise, physical fitness, physical activity, health-related quality of life, atrial fibrillation, heart failure.

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SAMMANFATTNING PÅ SVENSKA

Evidensen visar att individanpassad fysisk träning inom hjärtrehabilitering ska erbjudas samtliga patienter med ischemisk hjärtsjukdom och kronisk hjärtsvikt (HF), då det förbättrar fysisk kapacitet, hälsorelaterad livskvalitet (HR-QoL) samt minskar risken för kardiell mortalitet och antalet vårdtillfällen på sjukhus. Om fysioterapeut-ledd fysisk träning inom hjärtrehabilitering (PT-X) kan förbättra fysisk kapacitet hos patienter med förmaksflimmer (AF) på liknande sätt, och om PT-X kan öka den fysiska aktivitetsnivån hos patienter med kronisk HF är sparsamt studerat. I tillägg, är det inte utvärderat huruvida en ökad fysisk aktivitetsnivå hos patienter med kronisk HF eller permanent AF påverkar fysisk kapacitet positivt på samma vis som fysisk träning.

Syfte: Det övergripande syftet med avhandlingen var att undersöka effekterna av PT-X hos patienter med kronisk HF eller permanent AF med speciell referens till träningsform, fysisk kapacitet, fysisk aktivitetsnivå, HR-QoL och metabola riskmarkörer.

Metod och huvudresultat: Studie I. En randomiserad kontrollerad studie (RCT) undersökte effekten av PT-X avseende fysisk aktivitetsnivå, fysisk kapacitet (arbetskapacitet och muskelfunktion) och HR-QoL hos patienter med kronisk HF och samtidig medsjuklighet. Fysisk aktivitetsnivå ökade inte signifikant efter PT-X även om patienterna skattade sig mer aktiva. Fysisk kapacitet och HR-QoL förbättrades med PT-X jämfört med kontrollgruppen. **Studie II.** En RCT multicenterstudie jämförde PT-X och fysisk aktivitet på recept (PAP) avseende fysisk kapacitet, fysisk aktivitetsnivå, HR-QoL och metabola riskmarkörer hos patienter med permanent AF. Fysisk kapacitet förbättrades signifikant i gruppen som erhöll PT-X jämfört med PAP. Gruppen som erhöll PAP ökade sin energiförbrukning men inte fysisk kapacitet. **Studie III.** En 3 månaders uppföljning av studie II, undersökte effekten av 3 månaders träningsuppehåll avseende fysisk kapacitet, fysisk aktivitetsnivå och HR-QoL hos patienter med permanent AF. Förbättringarna avseende fysisk kapacitet som erhållits med PT-X var signifikant försämrade efter träningsuppehållet och HR-QoL var märkbart reducerad.

Konklusion: PT-X är väl tolererat och säkert och bör därför förskrivas till patienter med kronisk HF och permanent AF. Varken PT-X eller PAP ökar fysiska aktivitetsnivåer. PT-X förbättrar HR-QoL hos patienter med kronisk HF men inte hos patienter med permanent AF. Hos patienter med permanent AF är det viktigt att vidmakthålla träning då träningsuppehåll reducerar den förbättring av fysisk kapacitet som erhållits av PT-X och märkbart försämrar HR-QoL.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Borland M, Rosenkvist A, Cider Å. A group-based exercise programme did not improve physical activity in patients with chronic heart failure and comorbidity: a randomised controlled trial. J Rehabil Med. 2014;46(5):461-7.

II. Borland M, Bergfeldt L, Nordeman L, Bollano L, Andersson L, Rosenkvist A, Jakobsson M, Olsson K, Corin M, Landh L, Grüner Sveälv B, Scharin Täng M, Philip Wigh J, Lundwall A, Cider Å. Physiotherapist-led exercise-based cardiac rehabilitation versus physical activity on prescription for patients with permanent atrial fibrillation - a randomised controlled study focusing on physical fitness and physical activity. Submitted.

III. Borland M, Bergfeldt L, Cider Å, Rosenkvist A, Jakobsson M, Olsson K, Lundwall A, Andersson L, Nordeman L. Physiotherapist-led exercise within cardiac rehabilitation-induced improvement in physical fitness is “perishable goods” in patients with permanent atrial fibrillation. In manuscript.

CONTENT

ABBREVIATIONS

ACT	Aerobic continuous exercise training
AF	Atrial fibrillation
AIT	Aerobic interval exercise training
ATP	Adenosine triphosphate
$a\text{-}vO_2$ difference	Arteriovenous oxygen difference
CAD	Coronary artery disease
CO	Cardiac output
CR	Cardiac rehabilitation
DBP	Diastolic blood pressure
ECG	Electrocardiogram
EF	Ejection fraction
HF	Heart failure
HR	Heart rate
HRR	Heart rate reserve
HR-QoL	Health-related quality of life
ITT	Intention-to-treat analysis
LV	Left ventricle
MET	Metabolic equivalent of task
NYHA	New York Heart Association
PT-X	Physiotherapist-led exercise-based cardiac rehabilitation

PAP	Physical activity on prescription
RPE	Rate of perceived exertion (Borg´s scale 6-20)
SBP	Systolic blood pressure
SV	Stroke volume
TTE	Trans-thoracic echocardiography
VO_{2max}	Maximal rate of oxygen consumption
VO_{2peak}	Peak rate of oxygen consumption

DEFINITIONS IN SHORT

Aerobic	Oxygen-requiring energy reactions (1) .
Detraining	“Partial or complete loss of training-induced anatomical, physiological, and performance adaptations as a consequence of training reduction or cessation” (2), or a “cessation (stopping) or reduction of training or a decrease in physical performance caused by a cessation or reduction in training” (3).
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” (4).
MET	1 MET corresponds to the resting metabolic rate. VO_2 of 3.5 mL × kg^{-1} × min^{-1} (1) .
NYHA classification	Functional classification from I to IV based on symptom severity and the amount of exertion needed to provoke symptoms (5) .
Physical activity	“Any bodily movement produced by the skeletal muscles that results in energy expenditure” (4).
Physical fitness	A set of attributes that people have or achieve that relates to the ability to perform physical activity. Physical fitness can be either health-related physical fitness or skilled-related physical fitness (4).
Physical inactivity	An activity level insufficient to meet present recommendations (6).

Relative intensity	The percentage of maximal aerobic power, VO_{2max}, HR_{max} or HRR (1).
VO_{2max}	Maximal oxygen uptake. The highest oxygen uptake achieved despite increases in exercise intensity (1).
VO_{2peak}	Highest oxygen uptake achieved (1).

1 INTRODUCTION

The evidence for cardiac rehabilitation (CR) in patients with chronic heart failure (HF) is high, (7) and has been given priority 3 in the recommendations issued by the National Board of Health and Welfare in Sweden (8). In the clinical setting, patients with chronic HF have the opportunity to participate in physiotherapist-led group-based exercise within their CR (PT-X). Despite the high level of evidence, the participation rate is remarkably low. According to RiksSvikt, in 2015, only 5% of patients participated in PT-X. The participation rate was age-dependent; only 1% of patients >75 years old participated in PT-X (9). For patients with atrial fibrillation (AF), the overall evidence for PT-X is low, (10) and it is considered an area of research and development by the National Board of Health and Welfare in Sweden (8). For patients with AF, PT-X is non-existent, and individually prescribed PT-X is rare. During the last decade, the amount of research regarding the health effects of physical activity has grown, showing that sufficiently high levels of physical activity in healthy individuals can postpone the development of lifestyle-related disease. Therefore, during the last two decades in Sweden, physical activity on prescription (PAP) has been widely used within health care for primary and secondary prevention of several diseases (11, 12). However, the method has not been evaluated for patients with cardiac diseases. This thesis investigates the concepts of exercise and physical activity in elderly patients with chronic HF and permanent AF, which are two of the most common cardiac diseases in the elderly population (13). Chronic HF and AF often co-exist, sharing the same predisposing risk factors (13, 14) and similar symptoms, such as low physical fitness, dyspnoea, and fatigue (15). For patients with chronic HF, exercise improves the general well-being and ability to maintain independent living (16).

1.1 Heart Failure and Atrial Fibrillation

1.1.1 Heart failure

HF is a syndrome in which the heart fails to deliver oxygen and meet the metabolic requirements of the body tissues (17). HF is diagnosed in the presence of symptoms either during exertion or at rest and/or ankle swelling, together with objective evidence of cardiac dysfunction obtained by different imaging techniques, such as trans-thoracic echocardiography (TTE) (Table 1) (18). HF is usually accompanied by reduced cardiac output (CO) and/or elevated intracardiac pressure at rest and during exertion (18). The terminology includes HF with a left ventricular ejection fraction (LVEF) that is reduced (HFrEF), mid-range (HFmrEF), or preserved (HFpEF) (Table 2) (18). Congestive HF is a term that is sometimes used and may describe acute and chronic HF with evidence of volume overload (18). The severity of HF is described according to the New York Heart Association (NYHA) classification (Table 3) (5, 18). Chronic HF has a poor prognosis, with a 5-year survival rate of ≈ 50% and an even poorer prognosis in those with the worst symptoms (19) and low physical fitness (20). Ischemic heart disease, hypertension, and valvular disease are the most common causes of HF in western high income countries (21). The prevalence of chronic HF in Sweden is approximately 2-3% (19, 22). Pharmacological treatment in patients with HF aims to improve longevity, functional capacity, and health-related quality of life (HR-QoL) (18). The treatment of a patient with chronic HF includes pharmacological treatment, nurse-led receptions, and PT-X (18).

The pharmacological treatment includes beta-blockers, angiotensin-converting enzyme inhibitors, and mineralocorticoid/aldosterone receptor antagonist, which has been shown to improve survival, and diuretics, which reduce signs and symptoms of congestion in patients with HFrEF (18). Electronic devices, such as cardiac resynchronisation therapy (CRT) and implantable cardioverter-defibrillators (ICDs), are beneficial for some patients (18). As a medical treatment, PT-X should be offered to medically stable patients with chronic HF in NYHA classification II and III (7). Patients with chronic HF usually have skeletal muscle abnormities, such as reduced muscle fibre type I, decreased number of capillaries per muscle fibre, and mitochondrial dysfunction, which all contribute to reduced physical fitness (20, 23). Secondary to skeletal muscle abnormalities, the ergo receptors in the skeletal muscle become more sensitive, which relates to the ventilator response, dyspnoea, and sympathetic overdrive (24, 25). Increased inflammatory cytokines, especially tumour necrosis factor alpha (TNF-α) and interleukin 1β (IL-1 β), also play an important role in the alterations of skeletal muscles seen in chronic HF (20, 23).

Table 1. Typical symptoms and signs of heart failure, described by Ponikowski et al (18).

Typical symptoms of HF	**Specific signs of HF**
Breathlessness	Elevated jugular pressure
Orthopnoea	Hepatojugular reflux
Paroxysmal nocturnal dyspnoea	Third heart sound
Reduced exercise tolerance	Lateral displaced apical impulse
Fatigue, tiredness, increased time to recover after exercise	
Ankle swelling	
Less typical symptoms of HF	**Less specific signs of HF**
Nocturnal cough	Weight gain (>2 kg/week)
Wheezing	Weight loss (in advanced HF)
Bloated feeling	Tissue wasting (cachexia)
Loss of appetite	Cardiac murmur
Confusion (especially in the elderly)	Peripheral oedema (ankle, sacral, scrotal)
Depression	Pulmonary crepitation
Palpitations	Reduced air entry and dullness to percussion in lung bases (pleural effusion)
Dizziness	Tachycardia
Syncope	Irregular pulse
Bendopnea	Tackypnoea
	Cheyne-Stokes respiration
	Hepatomegaly
	Ascites
	Cold extremities
	Oliguria
	Narrow pulse pressure

HF: Heart failure.

Table 2. Definition of heart failure, described by Ponikowski et al (18).

Criterion	HFrEF	HFmrEF	HFpEF
1	Symptoms ± signs*	Symptoms ± signs*	Symptoms ± signs*
2	LVEF < 40%	LVEF 40-49%	LVEF ≥ 50%
3		1. Elevated levels of naturetic peptides 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE). b. diastolic dysfunction	1. Elevated levels of naturetic peptides 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE). b. diastolic dysfunction

HF: Heart failure, HFrEF: Heart failure with reduced ejection fraction, HFmrEF: Heart failure with mid-range ejection fraction, HFpEF: Heart failure with preserved ejection fraction, LAE: left atrial enlargement; LVEF: left ventricular ejection fraction; LVH: left ventricular hypertrophy. * Signs might not be present in the early stages of HF (especially in patients with HFpEF) or in patients treated with diuretics.

Table 3. New York Heart Association functional classification. Adapted from the criteria committee of the New York Heart Association (5) .

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

1.1.2 Atrial fibrillation

AF is the most common clinically significant arrhythmia in adults. AF is characterised by electrocardiogram (ECG) findings of irregular R-R intervals and an absence of distinct P waves. The chaotic atrial electrical activity in AF leads to a loss of atrial contraction and its contribution to ventricular diastolic filling (26, 27), as well as electrical and structural changes in the atria referred to as remodelling (26). The loss of atrial systole reduces stroke volume (SV) and, together with an irregular heart rate (HR), the CO (27). The HR is usually higher at rest than during sinus rhythm, and during exercise the HR increase is usually accelerated. The terminology includes five patterns of AF (Table 4) (28). The prevalence of AF in Sweden is approximately 3% in the adult population, but this may be underestimated (29). According to the Euro Heart survey, 30% of patients with AF are diagnosed with permanent AF (30). AF increases with age and is more common in men in each age group (29). The incidence of AF is expected to increase due to increasing longevity (31). AF is associated with a higher morbidity rate due to stroke (4-5 times increase) and HF (2-3 times increase) (28). The treatment of AF includes both acute and chronic management to reduce the risk of complications and alleviate symptoms (Table 5). Assessment of stroke risk and prevention by oral anticoagulation (65-70% risk reduction) is a major goal. Rate reduction and rhythm regulation are other goals to achieve haemodynamic stability and reduce symptoms. There is increasing awareness of the importance of managing precipitating factors, such as obesity and overconsumption of alcohol and nicotine, with lifestyle changes, as well as treatment of underlying cardiac and non-cardiac diseases, including hypertension and diabetes. Rate regulation reduces symptoms and the risk of tachycardia-induced HF, and is achieved by using beta-blockers, calcium channel antagonists (verapamil, diltiazem), and digitalis. For rhythm regulation, antiarrhythmic drugs, cardioversion, catheter ablation, and surgery for AF are alternatives (28). Several cardiovascular and other conditions are independently associated with AF, including hypertension, HF, valvular disease, myocardial infarction, thyroid dysfunction, obesity, diabetes mellitus, chronic obstructive lung disease, obstructive sleep apnoea, smoking, alcohol consumption, habitual vigorous exercise, and chronic kidney disease (28). Whether patients with AF have similar skeletal muscle abnormities as in chronic HF is unknown. However, patients with permanent AF have inspiratory muscle weakness (32), which suggests muscular alterations as one component of reduced physical fitness.

Table 4. Patterns of atrial fibrillation, described by Kirchhof et al (28).

Type of AF	Definition
First detected AF	AF that has not been diagnosed before, irrespective of the duration of the arrhythmia or the presence and severity of AF-related symptoms.
Paroxysmal AF	Self-terminating, in most cases within 48 hours. Some AF paroxysms may continue for up to 7 days. AF episodes that are cardioverted within 7 days should be considered paroxysmal.
Persistent AF	AF that lasts longer than 7 days, including episodes that are terminated by cardioversion, either with drugs or by direct current cardioversion, after 7 days or more.
Long-standing persistent AF	Continuous AF lasting for ≥ 1 year when it is decided to adopt a rhythm control strategy.
Permanent AF	AF that is accepted by the patient (and physician). Hence, rhythm control interventions are, by definition, not pursued in patients with permanent persistent AF. Should a rhythm control strategy be adopted, the arrhythmia would be re-classified as long-standing

AF: Atrial fibrillation

Table 5. Symptoms and signs of atrial fibrillation. Adapted from Riensta et al (33) and Morin et al (26).

Symptoms of AF*	Signs of AF on ECG
Palpitations	Presence of irregular RR intervals
Chest pain	Absence of distinct P-wave
Reduced exercise capacity	
Dyspnoea	
Fatigue	
Dizziness	

*AF: Atrial fibrillation, ECG: Electrocardiogram. *Approximately 15-30% of patients are asymptomatic. Asymptomatic AF is often discovered incidentally during population surveys or routine physical examinations.*

1.2 Exercise and Physical Activity

This thesis is investigating the effect of the concepts exercise and physical activity (4) and their effects on physical fitness in patients with chronic HF and permanent AF. The concepts are defined in Figure 1.

1.2.1 Exercise

Exercise is a subset of physical activity with the aim to improve or maintain one or more components of physical fitness (4). Exercise is not synonymous with physical activity, though it is sometimes used interchangeably.

1.2.2 Physical activity

Insufficient levels of physical activity is a leading risk factor for global mortality (6). Physical activity includes activities such as work-related physical activity, playing, carrying out household chores, transportation, and engaging in recreational pursuits (4). Physical activity can be measured objectively as body movement, such as steps taken, swimming, and cycling. The intensity, frequency, and duration of physical activity, both indoor and outdoor, and the energy expenditure of the physical activity can also be measured objectively. It is also possible to measure time in sleep and time spent sitting, though this is not physical activity. Furthermore, the patients' perceived level of physical activity can be assessed by questionnaires. These questionnaires include the patients' perceived intensity, frequency, and duration of physical activity. Measurements of physical activity are also often accompanied by a physical activity diary, which is used as a log for the performed physical activity. Different kinds of physical activity can be calculated as metabolic equivalents of task (METs) to determine the energy expenditure for the performed physical activity (34).

In this thesis, physical activity is measured both subjectively and objectively. In study I, the International Physical Activity Questionnaire (IPAQ) was used to subjectively measure physical activity together with a pedometer measuring steps per day. In studies II and III, the IPAQ was used together with an accelerometer to measure steps, the intensity of physical activity, and energy expenditure. These measurements are described under the Methods section.

The recommended levels of physical activity for adults are presented in Table 6 (35, 36).

The physical activity should be performed in bouts ≥ 10 minutes (36). Those who do not live up to the recommended levels of physical activity are inactive. Physical inactivity has recently been defined as “an activity level insufficient to meet present recommendations” (6).

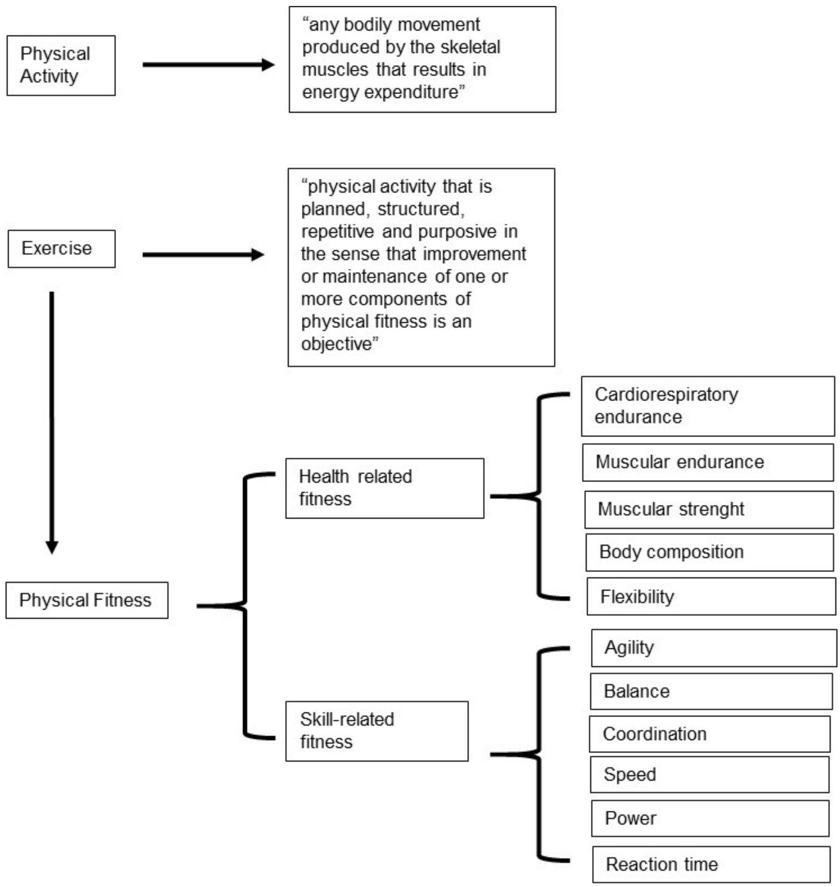
If an older adult cannot perform the recommended amount of physical activity due to health conditions, they should be as physically active as their abilities and conditions allow (35) . Whether less physical activity than stated in the guidelines will benefit the prognosis of people living with chronic HF has not yet been studied (37).

Table 6. Recommended levels of physical activity.

Aerobic physical activity			
Frequency	Intensity RPE		Duration/week
Most days of the week	12-13 * 14-17*		150 min 75 min
Muscle-strengthening activities			
Frequency, times/week	Intensity RPE	Major muscle groups, number of exercises	Number of repetitions
≥ 2	≥ 15	8-10	8-12
Balance exercises for persons ≥ 65 years.			

RPE: Rating of perceived exertion, Borg scale 6-20, * Aerobic moderate and vigorous physical activity could be performed separately or in combination.

Figure 1. Definition of exercise, physical activity and physical fitness. Adopted from Caspersen et al (4).



1.3 Cardiac Rehabilitation

Cardiac rehabilitation (CR) is defined by the WHO as the “sum of activity and interventions required to ensure the best possible physical, mental, and social conditions so that patients with chronic or post-acute coronary artery disease (CAD) may regain their proper place in society and live an active life” (38). The multidisciplinary approaches in CR/secondary prevention programmes are based on reducing cardiac events and decreasing disease progression (39). An overview of the core components in CR is presented in Table 7.

Table 7. Core components of cardiac rehabilitation/secondary prevention programmes. Adapted from Balady et al (40).

Patient assessment	Diabetes management
Nutritional counselling	Tobacco cessation
Weight management	Psychosocial management
Blood pressure management	Physical activity counselling
Lipid management	Exercise training

1.3.1 Physiotherapy

The tradition of physiotherapy in Sweden began in 1813, when Per Henrik Ling started the Royal Central Gymnastic Institute. Physiotherapy promotes health with the purpose of maintaining or improving inter alia physical fitness (41). Physiotherapy is the third largest health profession in Sweden and the Western world after physicians and nurses (41).

According to the World Confederation for Physical Therapy (WCPT), physiotherapy is “services provided by physiotherapist to individuals and populations to develop, maintain, and restore maximum movement and functional ability throughout the life span” (42). The WCPT states that physiotherapy involves the interaction between the physiotherapist patient, and other health professionals in identifying and maximising the quality of life and movement potential within the spheres of promotion, prevention, treatment/intervention, habilitation, and rehabilitation. These spheres encompass physical, psychological, emotional, and social well-being (42).

1.3.2 Physiotherapist-led group-based exercise within cardiac rehabilitation

Exercise training is one of the core components of CR (40, 43), strongly influencing all-cause and cardiovascular mortality and reducing hospital admissions in patients with CAD and chronic HF (7, 44). One meta-analysis showed that CR increased the cardiorespiratory physical fitness by 1.5 METs that corresponds to a cardiac mortality reduction of 16-54% (45). The physiotherapist is an exercise expert in the multidisciplinary team and has the task of prescribing individual-based exercise after clinical examination and risk stratification of each patient, as well as leading the group-based exercise (39, 46).

PT-X consists of continuous or interval aerobic exercise 3-5 days a week at 60-85% of the highest achieved oxygen uptake ($VO_{2\ peak}$) during 20-60 minute sessions, and muscular resistance exercises 2-3 days a week in 10-15 repetitions of 1-3 sets of 8-10 different upper and lower body exercises (40). Exercise-based CR should be medically supervised and include a clinical physical examination with blood pressure control, HR, and heart rhythm assessment before, during, and after exercise training (46). PT-X also includes an evaluation of possible exercise-limited comorbidities, assessment of behavioural characteristics (i.e., experience of exercise and physical activity, readiness to change behaviour, self-confidence, barriers, and social support), and the patient’s personal goals and exercise preferences (46).

1.3.3 Physical activity on prescription

PAP is one method used in health care to increase physical activity to reduce the risk of developing lifestyle-related diseases (11). This method is often used together with motivational interviewing, and all registered medical professions are allowed to prescribe PAP to patients with or without cardiac disease. PAP does not include any physiotherapist-led supervised exercise, and the patients are expected to exercise on their own.

1.4 Exercise Modalities within Physiotherapist-led Exercise within Cardiac Rehabilitation

PT-X includes both aerobic exercise and muscular resistance exercises. In this thesis, patients with chronic HF and AF performed aerobic exercise on an ergometer cycle. The aerobic exercise consisted of aerobic continuous exercise (ACT) in study I, and aerobic interval exercise (AIT) in study II. The muscular resistance exercise was performed as peripheral muscular exercise in study I, and as circuit training focusing on muscle endurance improvements in study II.

1.4.1 Aerobic exercise

Central circulatory aerobic exercise in PT-X includes ACT and/or AIT (1, 47). ACT is a submaximal, sustained, steady state aerobic exercise. AIT alternates high intensity with moderate to low intensity exercise. In aerobic exercise, the intensity must exceed the required energy system for improvements in cardiorespiratory fitness (1, 47). Studies have shown conflicting results regarding the favour of one concept in improving physical fitness over the other (48, 49).

1.4.2 Muscular resistance and endurance exercise

PT-X includes dynamic muscle work with a constant weight in the concentric and eccentric phase during each repetition (3). A resistance training programme includes exercise modalities with the aim of improving muscle cellular hypertrophy, strength, power, and endurance (3). The acute physiological responses and chronic adaptations to a resistance training programme depend on the choice and order of exercises, number of sets of an exercise, training intensity, and length of the rest periods between the sets and exercises (3). Exercises aiming to increase hypertrophy and muscle endurance are included in CR. The training programmes include concentric and eccentric muscle work in the lower and upper parts of the body at a given relative effort (50).

1.4.3 Peripheral muscle training

In peripheral muscle training, exercise is focused on working with a small muscle mass prescribed for use at the same time. This results in a high relative load on the individual muscle group with small cardiorespiratory stress (51). This training is suitable for patients with chronic HF and/or patients with low exercise capacity due to deconditioning or reduced CO (51-53).

1.5 Physiological Response to Physiotherapist-led Exercise within Cardiac Rehabilitation

Exercise involves acute responses and chronic adaptations in both central and peripheral functions in both healthy individuals and patients with heart disease (54). An improvement in VO_{2peak} is important because it strongly influences all cause and cardiovascular mortality in both healthy individuals and patients with cardiac disease (55, 56). Improvement in VO_{2peak} also improves prognosis and AF-related symptoms and episodes in patients with non-permanent AF (57, 58). An overview of the differences and similarities in chronic adaptations from exercise between healthy individuals, patients with chronic HF, and patients with AF is presented in Table 8 (54, 59-61).

Table 8. Overview of chronic adaptations from exercise. Adapted from Lavie et al (54), Piepoli et al (59), Hirari et al (60) and Reed et al (61).

	Healthy	Chronic HF	AF
Autonomic nervous system			
Sympathetic excitation		↓	
Heart			
LV size	↑	↓	
EF	↔	↑	
SV at rest and during exercise	↑	↑	
HR at rest	↓	↓	↓
HR, submaximal exercise	↓	↓↔	↓
HR maximal	↔	↑	
CO at rest and submaximal exercise	↔	↑	
Endothelium-mediated coronary dilation		↑	
Skeletal muscle			
Muscle fibre type I	↑	↑	
Mitochondria volume	↑	↑	
Oxidative enzyme activity	↑	↑	
O_2 delivery	↑	↑	
Vessels			
Vasoconstriction		↓	
Total peripheral resistance	↓	↓	
Systemic arterial compliance	↓	↑	
Endothelium-mediated vasodilation	↓	↑	
Circulating cytokines	↓	↓	
Metaboreflex (ergoreceptor)		↓	
Blood			
Blood flow	↑	↑	
Vascular resistance	↓	↓	
Plasma volume	↑	↑	
Capillaries per fibre	↑	↑	
Metabolics			
VO_{2max}	↑	↑	
VO_{2peak}	↑	↑	↑
a-v $O_{2\ diff}$	↑	↑	

HF: Heart failure, AF: Atrial fibrillation, LV: Left ventricular, EF: Ejection fraction, HR: Heart rate, SV: Stroke volume, CO: Cardiac output, O_2 delivery: Oxygen delivery, VO_{2max}: Maximal rate of oxygen consumption, VO_{2peak}: Peak rate of oxygen consumption, a-v $O_{2\ diff}$: Arteriovenous oxygen difference.

1.5.1 Cardiovascular system and metabolics

Cardiovascular function and the chronic effects of exercise are complex and multifactorial. In this thesis, the effects related to physical fitness are discussed. Other adaptations in the body are also important, but not focused on in this thesis. The chronic adaptations induced by aerobic exercise lead to an increased maximal oxygen uptake (VO_{2max}) of 20% on average in both healthy individuals and patients with chronic HF (62, 63).

Two major factors are important for both the improvement and limitation of VO_{2max}. The CO and/or capacity for active muscle to extract oxygen from the arterial blood (i.e., the arterial venous oxygen difference (a-vO_{2diff})). The limiting factor for VO_{2max} is the CO, and exercise can improve the CO in healthy individuals (64). The determinants of VO_{2max} are given in Fick's equation: $VO_{2max} = CO_{max} \times$ a-$vO_{2diff\ max}$ (1).

However, in patients with chronic HF, the ability to improve VO_{2max} through an increased CO is limited. Therefore, the most important factor to improve in these patients is the a-v O_{2diff} (62).

In patients with permanent AF, the chronic adaptations from aerobic exercise have been sparsely investigated. Studies have found a decreased HR at rest and submaximal exercise (61). One meta-analysis reported that exercise may have the potential to improve systolic function, especially in patients with AF and HFrEF (65).

1.5.2 Skeletal muscle adaptation

In chronic HF, exercise induces alterations in the skeletal muscle, such as increased mitochondrial volume and density, oxidative enzyme activity, and increased capillary per muscle fibre ratio. Exercise also produces a shift to a larger proportion of oxidative muscle fibre type 1 with a greater muscle fibre area. The lactate threshold will increase and the O_2 cost decrease (60). This leads to a decreased ventilator drive and enhanced muscle ergo reflex (59).

In patients with permanent AF, the effect of aerobic exercise on the muscular system has not been investigated.

1.5.3 Detraining

Cessation of exercise causes detraining alterations in both the short term (< 4 weeks) and longer term (> 4 weeks). Detraining was defined by Mujika et al (2) as “the partial or complete loss of training-induced anatomical, physiological, and performance adaptations as a consequence of training reduction or cessation”. According to Kramer et al (3), detraining is “a cessation (stopping) or reduction of training or a decrease in physical performance caused by a cessation or reduction in training”. In this thesis, the effects of 3 months detraining were studied in patients with permanent AF. The physiological effects of detraining in patients with permanent AF have not previously been studied. However, the effects of detraining in healthy athletes and recently trained individuals have been investigated (2, 66). The cardiorespiratory characteristics and muscular characteristics of long-term detraining in recently trained healthy individuals are presented in Table 9.

Table 9. Overview of the effects of detraining in healthy, recently trained individuals. Adapted from Mujika et al (2, 66).

Detraining characteristics	Recently trained healthy individuals
Cardiovascular characteristics	
Blood volume	↓
HR submaximal	↑
SV during exercise	↓
CO max	↓
Blood pressure (MAP)	↑
Muscular characteristics	
Capillary density	↓
Oxidative enzyme activity	↓
Mean fibre cross sectional area	↓
Muscle mass	↓
Strength and power performance	↓
Metabolics	
A-$VO_{2\ diff}$	Not investigated in recently trained. ↓ in athletes
VO_{2max}	↓
VO_{2peak}	↓

HR: Heart rate, SV: Stroke volume, CO: Cardiac output, MAP: Mean arterial blood pressure, VO_{2max}: Maximal rate of oxygen consumption, VO_{2peak}: Peak rate of oxygen consumption, a-v $O_{2\ diff}$: Arteriovenous oxygen difference.

1.5.4 Cardiovascular system

VO_{2max} reverses to pre-training levels, but different degrees of retention have been reported. Detraining results in a higher HR at rest and submaximal exercise and, consequently, decreased CO (66). A decrease in red blood cell volume and plasma volume has been observed in young recently trained individuals (67), which can partially explain the decline in VO_{2max}.

1.5.5 Skeletal muscle system

In skeletal muscle, detraining causes a decline in muscular capillaries. Whether a decline in the a-v $O_{2\ diff}$ occurs in recently trained individuals has not been investigated. However, a-v $O_{2\ diff}$ is reversed in athletes, and mitochondrial adenosine triphosphate (ATP) production is reversed in recently trained individuals in the short term (< 4 week), so it can be assumed that this is also possible in the long term (2, 66).

1.6 Health-related Quality of Life

The term HR-QoL is not defined in the literature, and measures of health status often use the terms HR-QoL and quality of life interchangeably (68). The importance of measuring quality of life was highlighted in the 1960s when medical treatment was able to extend the length of life, sometimes at the expense of quality of life, and the measurement of death rates was not enough to measure the population's health (68, 69). The term HR-QoL was developed from quality of life to include the individual's health status, experience with disease, and process of natural aging. According to Karimi et al (68), HR-QoL overlaps the terms health and quality of life, and is often used as the individual self-perceived health status. According to the WHO, health is defined as "a state of complete physical, mental, and social well-being, and not merely the absence of disease and infirmity"(70) . The WHO has defined quality of life as "the individual's perception of their position of life in the context of their culture and value systems in which they live and in relation to their personal goals, expectations, standards, and concern" (71).

Even though advanced medical techniques are available, patients with chronic HF have a severe symptom burden and high mortality rates as well as frequent hospital admissions. HR-QoL is worse in patients with chronic HF than in other chronic cardiac and non-cardiac diseases (72, 73). The main symptoms of chronic HF are breathlessness and fatigue; other symptoms are presented in Table 1, several of which greatly impact HR-QoL (74-76). Patients with chronic HF are often symptom-limited, have low physical fitness and a limited ability to perform a wide range of daily physical activities and exercise (74, 75, 77). In patients with chronic HF, reduced HR-QoL has been associated with a younger age and the severity of symptoms, which restrict physical activity and social functioning and cannot be normalised with optimal medical treatment (74).

Similarly, patients with AF often experience symptom-related limitations, which affect HR-QoL. The severity of symptoms and type of AF are related to a greater negative impact on HR-QoL (73, 78, 79), despite advanced pharmacotherapy and electrotherapy treatments. The occurrence of arrhythmia, and the frequency and duration of the attack can be unpredictable and require emergency hospital admissions, which negatively influence the patients’ HR-QoL. Dorian et al (80) reported that 90% of patients with non-permanent AF have symptoms during AF episodes. Symptoms of AF negatively affect the patient’s physical fitness, social life, professional life, and activities of daily living (33, 78, 81, 82), as well as HR-QoL, and increase the risk of depression in patients with all types of AF (82, 83).

1.6.1 General exercise principles

There are six exercise principles for the prescription and planning of exercise to optimise its effects (84).

- *Individuality:* not all individuals respond the same way to exercise stimuli; therefore, it is important that the exercise programme meet the individual's needs.

- *Specificity:* physiological responses adjust to the exercise performed; to achieve improvements, the exercise must be adjusted to meet the desired demand.

- *Overload:* the relationship between exercise intensity and desired effect; the exercise programme must include intensities greater than normal to progress to a higher work level.

- *Reversibility or disuse:* reversibility of the effects of physiological exercise will occur if exercise is ceased (i.e., detraining).

- *Hard and easy:* a period of hard exercise is followed by a period of easier exercise.

- *Periodisation:* exercise is planned and divided into periods, enabling athletes to be at their best when needed.

  In PT-X, four principles are considered when conducting an exercise programme. The principles of hard/easy and periodisation are not commonly used in PT-X. The exercise programme is individually prescribed according to the patients' medical status and include the mode, frequency, duration, intensity, and progression of exercise (85).

2 GAPS OF KNOWLEDGE WITHIN EXERCISE-BASED CARDIAC REHABILITATION REGARDING CHRONIC HEART FAILURE AND ATRIAL FIBRILLATION

There are some gaps in the knowledge regarding PT-X in patients with chronic HF and AF. In this thesis, some of these gaps are studied, but not all. When I started my PhD project, PT-X had high evidence in patients with chronic HF, but not in patients with AF. As I have worked on this project, the knowledge has increased regarding the importance of lifestyle management for patients with AF (28). However, knowledge gaps still exist regarding PT-X and its effect on mortality and hospital admissions in patients with AF (10), and if it should be included in the multidisciplinary management of patients with AF (8, 28).

When I started my PhD project, ACT was the superior form of aerobic exercise within PT-X. Today, AIT with higher exercise intensities is more common and widely used within PT-X (47). However, which exercise regimen will benefit patients with chronic HF in the long term and patients with permanent AF in the short and long term remains unknown.

During the years I have worked as a physiotherapist on PT-X, it has become more common that different medical professions recommend patients to increase their physical activity level. This is often achieved with an alternative to PT-X when patients are unable to participate for different reasons. There are still knowledge gaps regarding the amount of physical activity and dose response relationship of the physical activity needed to achieve improved physical fitness.

3 AIMS AND HYPOTHESIS OF THE THESIS

3.1 General Aims

The general aim of this thesis was to investigate the effect of individually prescribed PT-X in elderly patients with chronic HF or permanent AF, especially in regards to exercise modality, physical fitness, level of physical activity, HR-QoL, and metabolic risk factors.

3.2 Specific Aims and Hypothesis

Study I aim: To assess the impact of PT-X on the level of physical activity, physical fitness, and HR-QoL in patients with chronic HF and comorbidity, and to assess the correlations between baseline values for physical activity, physical fitness, sitting time, and HR-QoL.

Primary outcome measure: steps per day.

Hypothesis: PT-X will increase the physical activity level in patients with chronic HF.

Study II aim: To assess and compare the impact of PT-X or PAP on physical fitness, the level of physical activity, HR-QoL, metabolic risk markers, and safety in patients with permanent AF.

Primary outcome measure: exercise capacity in Watts.

Hypothesis: PT-X will increase physical fitness significantly more than PAP in patients with permanent AF.

Study III aim: To assess the impact of a 3-month detraining after PT-X or PAP regarding physical fitness, the level of physical activity, and HR-QoL in patients with permanent AF, and if any variable could predict the possible change in physical fitness.

Hypothesis: Detraining will affect physical fitness in patients with permanent AF.

4 PATIENTS AND METHODS

This thesis is based on the three studies described below, Table 10. The patients were recruited from both rural and urban hospitals and primary health care in Region Västra Götaland in Sweden. For studies I and II, the randomisation tickets were kept in sealed envelopes constructed by a person not working at the clinic.

Table 10. Overview of studies I-III.

Study	Patients
I	48 patients (10 women), mean age 71 ± 8 years, EF 27 ± 10%, with chronic HF and comorbidities in NYHA functional class II-III. 42 patients completed the study, 6 dropped out.
II	96 patients (28 women), mean age 74 ± 5 years with permanent AF. 87 patients completed the study, 9 dropped out.
III	80 patients (22 women), mean age 74 ± 5 years with permanent AF.

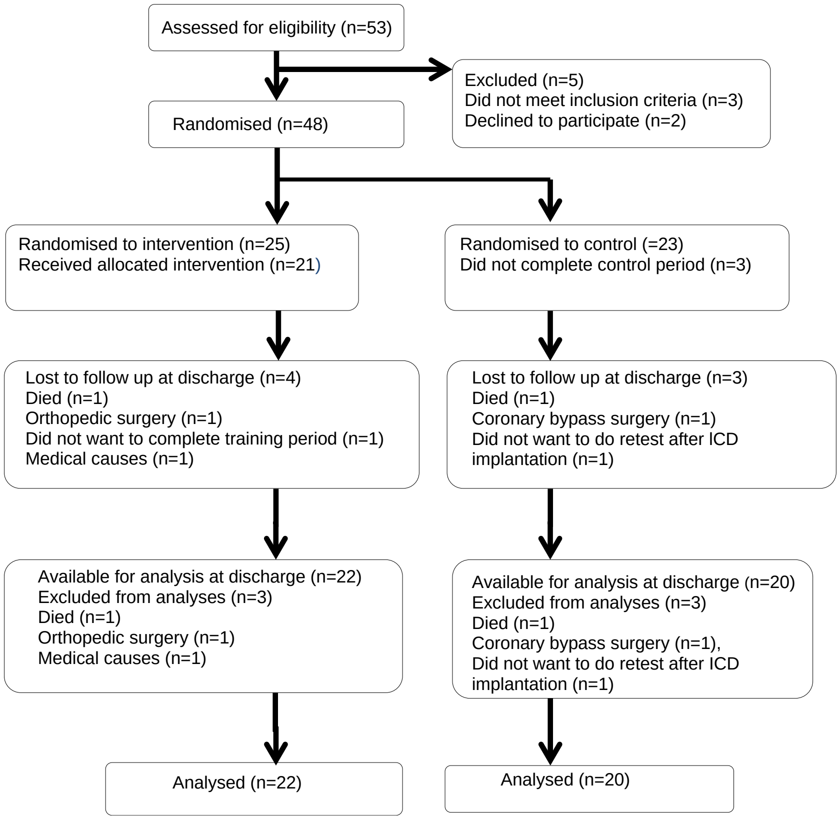
4.1 Study Design

Studies I-III: Experimental randomised controlled trial.

4.2 Selection of Participants, Inclusion and Exclusion Criteria

Study I: Fifty-three patients were assessed for eligibility from Alingsås hospital and the primary healthcare in south-western Sweden between 2009 and 2011. Forty-eight patients fulfilled the inclusion criteria, consented to participate, and were recruited for baseline testing. After baseline testing, the patients were randomised and included in the study. The inclusion criteria were stable chronic HF, NYHA functional class II-III. The exclusion criteria were difficulties participating in the test procedure or insufficient command of the Swedish language. The inclusion process and reasons for exclusion and drop-out are presented in Figure 2.

Figure 2. Flowchart over the inclusion process study I.



Study II: Five hundred and thirty-eight patients were assessed for eligibility to participate in a multi-centre study at Alingsås Hospital, Sahlgrenska University Hospital, and primary healthcare in south-western Sweden between 2014 and 2016. Patients were also recruited via advertisements in local papers. A total of 98 patients fulfilled the inclusion criteria, consented to participate, and were recruited for baseline testing. At baseline, one patient was excluded due to ventricular bigeminy. Therefore, 97 patients were randomised. One patient was excluded during the intervention because an ECG showed sinus rhythm, resulting in 96 patients being enrolled in the study. Inclusion criteria were permanent AF verified by ECG and LVEF ≥ 45%. Exclusion criteria were significant valvular lesions, coronary event within 3 months prior to inclusion, stroke with residual symptoms, pacemaker, or not being able to participate in the test procedure or read Swedish. The inclusion process and reasons for exclusion and drop-out are presented in Figure 3.

Study III: Eighty-seven patients completed study II and were assessed for eligibility in the 3-month follow-up. Out of these, 80 patients completed a 3-month detraining period and were included in the study. The patients followed their earlier randomisation. The inclusion process and reasons for drop-out are presented in Figure 4.

Figure 3. Flowchart over the inclusion process in study II.

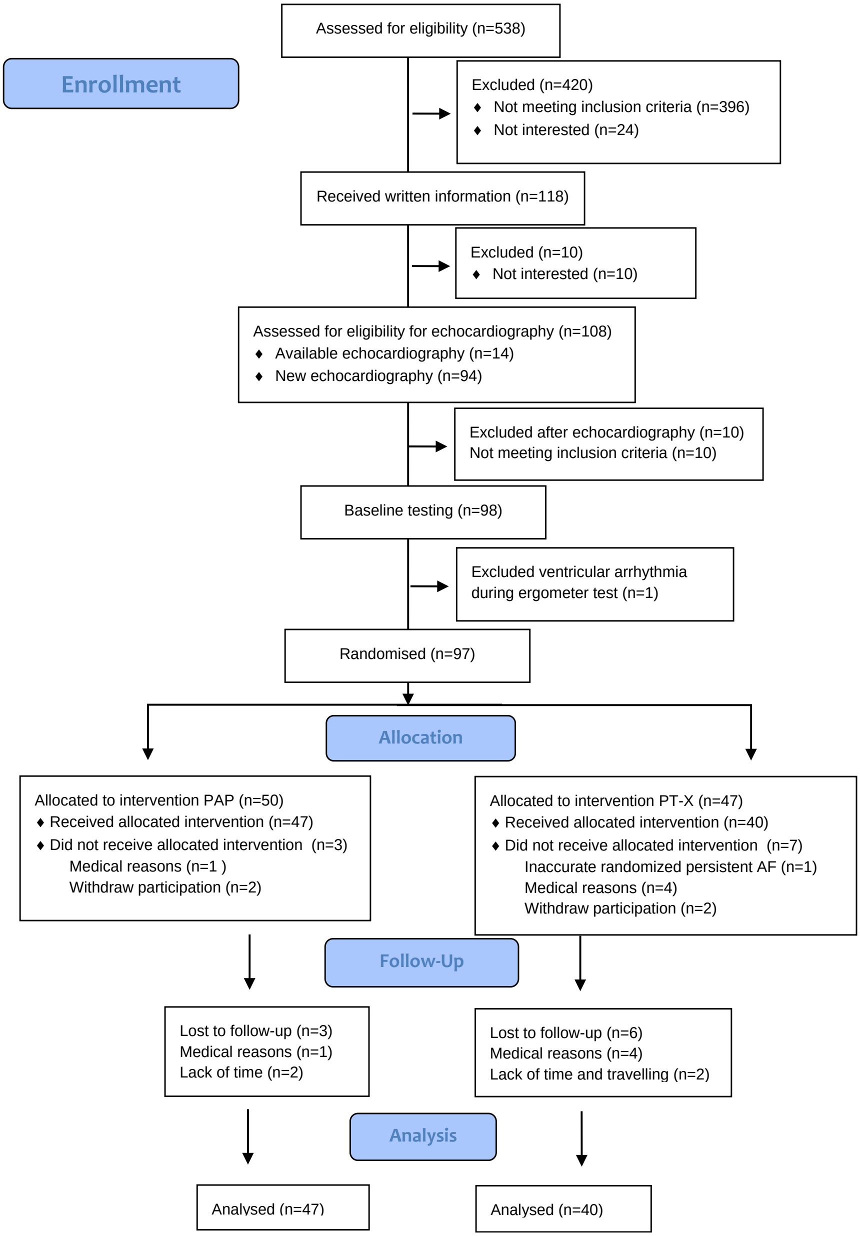
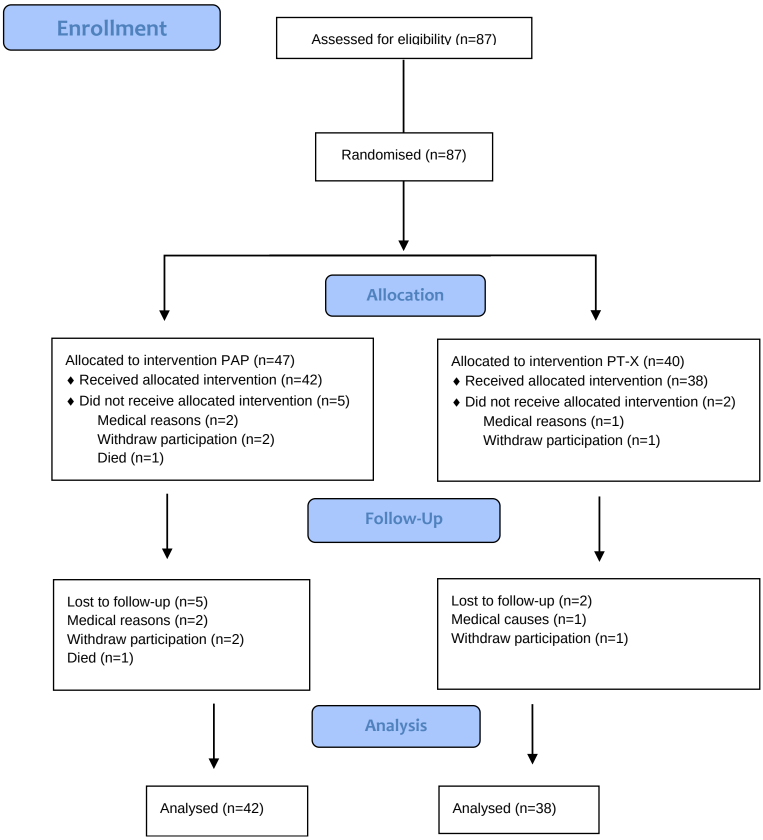


Figure 4. Flowchart over the inclusion process in study III.



4.3 Data Collection

The outcome measurements included in this thesis are presented below in detail and listed in Table 11. As much as possible, the measurements were collected by the same physiotherapist blinded to group assessment at the same hour of the day at baseline, after intervention, and at follow-up.

Table 11. Overview of outcome measurements.

Measurements	Study I	Study II	Study III
BMI [kg/m^2]		x	x
TTE		x	
Blood samples			
Plasma glucose		x	
Cholesterol mmol/L		x	
HDL mmol/L		x	
LDL mmol/L		x	
Triglycerides mmol/L		x	
HbA1$_C$ mmol/mol		x	
Physical fitness test			
Symptom-limited ergometercycle test	x	x	x
6MWT	x		
Unilateral isoinertial shoulder flexion	x	x	x
Bilateral isometric shoulder abduction	x	x	x
Unilateral isoinertial heel-lift	x	x	x
RPE	x	x	x
CR10	x	x	x
Physical activity			
Keep walking pedometer	x		
Actigraph accelerometer GT3x		x	x
IPAQ	x	x	x
Saltin-Grimby Physical Activity level 6 grade scale			x
Health-related quality of life			
Short form SF-36	x	x	x

BMI: Body mass index, TTE: Trans-thoracic echocardiography, HDL: High density lipoprotein, LDL: Low density lipoprotein, HbA1$_C$: Glycated haemoglobin A$_{1c}$, Borg RPE: Rating of perceived exertion, Borg scale 6-20, 6MWT: Six-minute walk test, Borg CR10: Borg category ratio scale for rating of dyspnoea and pain, IPAQ: International Physical Activity Questionnaire, SF-36: Short form health survey SF-36

4.3.1 Measurements

Body mass index (BMI) (studies II, III): Body weight and height were assessed upon clinical examination and BMI calculated as the weight in kilograms divided by the height in meters squared [kg/m^2] (1).

Age and gender (studies I, II, III) were used to describe the study population in all studies and for stratification.

Trans-thoracic echocardiography (study II): LV-EF, LV volume, and valvular function were evaluated by both visual estimates and using the apical two- and four-chamber view according to the biplane method of disks (Simpson’s rule) to determine the end-diastolic volume and end-systolic volume. Two-dimensional Doppler echocardiography (Vidid 7 and Vivid E9, General Electric Medical systems, Horten, Norway) was performed using a phased-array transducer (1.5-4.0 MHz). Images were obtained from the parasternal long axis and apical four- and two-chamber views. Pulsed and continuous Doppler flow velocities across the mitral valve and left ventricular outflow tract were acquired according to the American Society of Echocardiography (86). Offline analysis was performed using commercially available Echopac PC software (General Electric Ultrasound, Horten, Norway).

Venous blood sampling for cardiac risk markers (study II): Plasma glucose, glycated haemoglobin A1*c* (HbA1c), total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), and triglycerides were measured. Blood was collected after an overnight fast and analysed according to the European accreditation system (87). The blood test results were received only as a laboratory report on paper, and no blood samples were reposted for later use.

4.3.2 Physical fitness

Exercise capacity (studies I, II, III) was measured by a symptom-limited ergometer cycle test based on the WHO protocol (88) performed on a Monark ergometer 839e (Monark, Varberg, Sweden). The workload began at 25 W and was increased by 25 W every 4.5 min. The Borg scale (RPE 6-20) was used to assess the rate of exertion (89). HR was recorded every 2nd minute, and blood pressure was measured manually using a sphygmometer and stethoscope on the right arm every 3rd minute during each interval. If the patient did not sustain the final step, the maximal power was adjusted according to Strandell's formula: maximal power = (submaximal power) + (25×n/4.5) (90, 91). Thus, in this thesis, maximal power = (maximal Watts achieved - 25 W) + (25×time in max Watts/4.5).

In study I, the workload increased until the patient rated 15-17 on the RPE scale. In studies II and III, the workload increased until the patient rated RPE 17. Symptoms, such as dyspnoea and pain, were assessed with the Borg category ratio scale (CR-10) (89).

The instructions to the patient before testing were to avoid nicotine, coffee, tea, or any drinks containing caffeine at least 2 hours before examination. Furthermore, the patients were requested to not perform strenuous physical activity the day before testing.

Exercise capacity related to activities of daily living (study I) was measured by a standardised 6-minute walking test (6MWT). The instructions were to walk on a pre-marked 30-m corridor for 6 min, covering as much distance as possible. No encouragement or coaching was provided during the test. Distance walked and HR were measured using a sport-tester pulse watch (Polar Electro OY, Kempele, Finland). For rating of perceived exertion and dyspnoea, the RPE scale and Borg CR-10 scale (89) were recorded. The test has an inverse relationship with NYHA classification and strongly correlates with VO_{2peak}, which is a prognostic marker in patients with HF (92). The 6MWT has good validity and reliability for patients with chronic HF (92, 93).

Muscular endurance (studies I, II, and III) was measured with three clinic-based tests. These tests have been proven to be reliable for measuring muscle endurance in patients with chronic HF and CAD (94, 95).

Unilateral isoinertial shoulder flexion: The patient sat on a stool with their back touching the wall, holding a 2 kg (women) or 3 kg (men) dumbbell in their hand. Twenty shoulder flexions/minute were performed at a pace of 40 beats per minute (bpm) set by a metronome (Taktell, Wittner, Germany (study I) or Seiko instruments, Chiba, Japan (studies II and III)). The patient was told to do as many repetitions as possible.

Bilateral isometric shoulder abduction: The patient held a 1 kg dumbbell in each hand using the same body position as in shoulder flexion. The patient was asked to elevate both arms to 90° of shoulder abduction and maintain this position as long as possible. After being reminded once when losing the position, the test was ended and the time recorded.

Unilateral isoinertial heel lift: Touching the wall for balance, with shoes on, the patients performed a maximal unilateral heel lift as high as possible with a straight knee on a 10° tilted wedge. Thirty heel lifts/minute were performed and the metronome kept a 60 bpm pace.

4.3.3 Physical activity

Physical activity level was measured both objectively and subjectively.

Pedometer (study I): Steps per day were measured by a Keepwalking LS2000 pedometer (KeepWalking Scandinavia, Kalmar, Sweden). The pedometer was placed on the patient´s hip and worn for 7 days except when showering or bathing. Overweight patients were instructed to place the pedometer on their ankles. Patients were instructed to record the total number of steps on a log sheet at bedtime and reset the device to zero each morning (96). A pedometer counts the uniaxial vertical movement of the hip (97). The validity and reliability of this pedometer has been shown to be satisfactory in adult populations (98).

Accelerometer (studies II and III): Daily physical activity was measured by an accelerometer (Actigraph® GT3x+, Actigraph, Pensacola, Florida, USA) placed on the patient´s hip and worn throughout the whole day for 7 days except when showering or bathing (97). Actigraph GT3x is a tri-axial accelerometer detecting acceleration (difference in velocity/time, m/s^2) in three axes (vertical, medio-lateral, and anterial-posterial). The accelerations were collected as activity counts, with accelerations due to body movement at different intensities to predict energy expenditure (99, 100). The amount of physical activity and sedentary time were determined by classifying activity counts accumulated over a specific length of time (epoch length) (100). The accelerometer data were analysed according to the algorithm created by Choi et al (99). These monitors are reliable and valid in the adult population (97, 101-104).

Self-reported physical activity (studies I, II, and III) was measured by the Swedish version of the IPAQ (105). The IPAQ was developed to compare measurements of self-reported physical activity across countries in epidemiological studies. In the questionnaire, three types of physical activity are requested (walking, moderate-intensity activities, and vigorous physical activities) in four domains: leisure-time physical activity, domestic and gardening (yard) activities, work-related physical activity, and transport-related physical activity. The intensity of physical activity is classified as 3 (high level, 1 hour of at least moderate physical activity above the basal level of physical activity or half an hour of vigorous physical activity, e.g., 12 500 steps/day or the equivalent in moderate or intense physical activity) 2 (moderate level, defined as performing some activities more often than in the lowest category or the equivalent of half an hour of at least moderately intense physical activity on most days), or 1 (low level of physical activity, defined as not meeting the criteria for either of the previous categories). Metabolic expenditure is measured by equivalent METs per day (MET×minutes×day) and per week (MET×minutes×week) by weighting the reported minutes per week by the total expenditure (METs) estimate assigned to each category of activity. The total Kcal per week is calculated by the reported minutes per week and the person's weight. The instrument also includes a question regarding time sitting (105). The IPAQ has been found to be valid and reliable, and measures physical activity over a 7-day period in METs, including sitting time (105).

Self-reported physical activity level during detraining (study III): To assess physical activity during detraining, Saltin-Grimby´s 6-grade physical activity scale was used (106). The scale is divided into six categories ranging from 1 (hardly any physical activity) to 6 (hard to very hard exercise). Household activities are also included in the scale. The scale has good reliability and validity in older populations and has been used in several studies including elderly patients with different medical conditions (107). The patients were instructed to rate the category that corresponded to their physical activity level during the 3-month detraining period.

4.3.4 Health-related quality of life

Health-related quality of life (studies I, II, and III): To measure general HR-QoL, the short form Health Survey Questionnaire (SF-36) (108) was used. This questionnaire has been used in several studies of chronic HF and AF (109). SF-36 contains 36 questions in eight dimensions rated from 0 (lowest health status) to 100 points (highest health status). The points summarise to two summary scores, each with a maximum 50 points. The eight dimensions are physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), social functioning (SF), role-emotional (RE), vitality (VT), and mental health (MH). The two summary scores representing the overall index for physical and mental health are: the physical component summa score (PCS) comprising PF, RP, BP, and GH, and the mental component summa score (MCS) comprising SF, RE, VT, and MH (110). SF-36 has good validity and reliability, and there are reference values for the Swedish general population (111).

4.4 Interventions

PT-X was designed based on the results of the ergometer test and the patient's individual requirements and comorbidities using the RPE scale and CR-10 scale (89) to obtain the correct relative intensity of the exercise programme. The exercise programme included aerobic exercise and muscular endurance exercise in studies I and II. Study II included individually prescribed PAP. Exercise and PAP were prescribed according to guidelines. No exercise programme was conducted in study III, as the patients were instructed to avoid participation in any structured and organised exercise.

4.4.1 Exercise programme in study I

PT-X consisted of two 60-minute sessions per week for 3 months of central circulatory exercise, peripheral muscular, and balance exercises. The control group was instructed to continue with their usual life during the 3-month study period, and thereafter were invited to participate in the exercise programme. The exercise programme is described in detail in Table 12.

4.4.2 Exercise programme in study II

PT-X included central circulatory interval exercise and circuit exercise, two sessions per week, for 60 minutes, and two home-based exercise sessions. PAP included active walking, four sessions a week, for 40 minutes. The patients kept a diary for the home-based exercise and PAP. The exercise programmes for PT-X and prescription of PAP are described in detail in Table 13.

Table 12. Exercise programme in study I.

Exercises	Duration	Repetitions	RPE	Set
Aerobic exercise	15 min	1	12-13	
Resistance exercises				
Seated row in cable pulley		10-12	12-13	2
Leg extension		10-12	12-13	2
Heel lift on wedge		10-12	12-13	2
Elbow flexion with dumbbell		10-12	12-13	2
Elbow extension with dumbbell		10-12	12-13	2
Bench press		10-12	12-13	2
Balance exercise with and without eyes closed				
Standing with feet close together		2		
One leg standing		2		
Standing on different surface		2		

RPE: Rating of perceived exertion, Borg scale 6-20.

Table 13. Exercise programme in the PT-X group and active walking in the PAP group in study II.

Interval exercise on ergometer cycle, PT-X	**Duration, min**	**Repetitions**	**RPE**
Warm-up period	6	1	11
Interval I	2	4	15-17
Interval II	2	4	13
Cooldown period	2	1	11
Resistance exercises, PT-X	**Duration, s exercise/rest/change**	**Repetitions**	**RPE**
Straight arm pull down in cable pulley	45/15/30	2	13-15
Leg extension	45/15/30	2	13-15
Heel lift on wedge	45/15/30	2	13-15
Step-up	45/15/30	2	13-15
Shoulder flexion with dumbbell	45/15/30	2	13-15
Shoulder abduction with dumbbell	45/15/30	2	13-15
Bench press	45/15/30	2	13-15
Squats with exercise ball against the wall	45/15/30	2	13-15
Wide grip push down in cable pulley	45/15/30	2	13-15
Home exercise programme, PT-X	**Duration, s exercise/rest/change**	**Repetitions**	**RPE**
Warm-up period with step-up	120		13-15
Step-up, between exercises	120		13-15
Elbow flexion, M. biceps	45/15/30	2	13-15
Straight arm shoulder flexion	45/15/30	2	13-15
Shoulder abduction	45/15/30	2	13-15
Standing row	45/15/30	2	13-15
Heel lift	45/15/30	2	13-15
Sit up	45/15/30	2	13-15
Active walking PAP	**Duration, min**	**Repetitions**	**RPE**
Warm-up period	5	1	11
Active walking	30	1	13-15
Cool down period	5	1	11

RPE: Rating of perceived exertion, Borg scale 6-20.

4.5 Statistics

An overview of the statistical tests used in all studies is presented in Table 14. The level of significance was $p < 0.05$ in all three studies. Analyses were performed in study I according to the protocol analysis. In studies II and III, a partial intention-to-treat (ITT) analysis was performed. For sensitive analysis in study II, a full ITT analysis was performed with baseline values carried forward, showing no effect on the results from the partial analysis. SPSS Windows version 19.0 and 22.0 was used for statistical analyses.

Table 14. Overview of the statistical methods.

Statistical test	Study I	Study II	Study III
Descriptive statistics	x	x	x
Chi squared (x^2)	x	x	x
Yates correlation	x		
Wilcoxon signed rank test	x	x	
Mann-Whitney U-test	x	x	x
Spearman's bivariate correlation coefficient test	x		x
Cohen's *d*		x	x
Mixed effect model			x

4.5.1 Statistical power

In studies I and II, the statistical power was calculated using a power (β) of 80% and a significance level of (α) 5%.

In studies I and II, an independent person not participating in the projects calculated and created the randomisation plots. The calculations were performed by a computer-based randomiser in Microsoft Excel as high and low plots. The patients received one or two points depending on age, gender, and 6MWT or exercise capacity. This was done in order to avoid the possibility of a homogeneous sample size.

In study I, the statistical power was calculated based on an assumption of a 10% improvement in steps per day in the PT-X group and 4% in the control group; therefore, at least 48 patients (24 patients in each group) were needed. The patients were randomised to the PT-X or control group in a 1:1 ratio stratified for gender, age, and distance walked in the 6MWT.

In study II, the statistical power was calculated based on an assumption of a difference of 10 ± 15 W in the improvement in exercise capacity in the PT-X group vs. the PAP group; therefore, at least 82 patients were needed, 41 patients in each group. A dropout rate of 8% was estimated and we aimed to enrol ≥ 90 participants. The patients were randomised to PT-X or PAP in a 1:1 ratio stratified for gender, age, and exercise capacity.

4.5.2 Descriptive data

Descriptive statistics were used to present group characteristics. Ratio and interval data are presented as mean ± 1 standard deviation (SD), ordinal data are presented as median minimum and maximum values, and nominal data are presented in absolute and relative numbers.

4.5.3 Comparison between groups

The X^2 test and Mann-Whitney *U*-test were used to analyse differences between groups. To analyse comorbidities, pharmacotherapy, and pacemaker data in study I, Yates correlation was used.

4.5.4 Correlation

Spearman's bivariate correlation coefficient was used for correlations concerning physical activity and physical fitness and HR-QoL at baseline. The correlation was interpreted according to Munro (112): 0.00-0.25 as little if any correlation, 0.26-0.49 as low correlation, 0.50-0.69 as moderate correlation, 0.70-0.89 as high correlation, and 0.90-1.00 as very high correlation.

4.5.5 Effect size

Cohen's *d* was used to calculate the effect size using the mean difference between groups and pooled SD of the mean differences of both groups. The effect size was considered small for $d = 0.2 – 0.3$, medium for $d = 0.5$, and large for $d = 0.8$ (113).

4.5.6 Predictors of change in physical fitness

A mixed effect model was used to determine predictors of change in physical fitness. The independent variables were checked pairwise for possible collinearity, using Spearman $r \geq 0.7$. In addition, for variable pairs with one categorical variable with few categories, we checked that boxplots overlapped. If both variables were categorical with few categories, we checked cross tables for > 80% observations in diagonal and cells with < 5 observations. Three models were created, and each variable was checked stepwise and carried forward if $p<0.20$: model 1, intervention × time; model 2, model 1 variable with addition of possible confounders (age, sex, and BMI); model 3, included secondary explanatory variables for physical fitness at baseline, mean value for heel lift left and right leg, SF -36 PF, IPAQ category, and moderate to vigorous physical activity measured by an accelerometer. The final model 3 consisted of model 1 variable, significant model 2 variables (age and sex), and significant secondary explanatory variables (SF-36 PF and moderate-vigorous physical activity measured by accelerometer). Variables in models were considered significant if $p<0.05$.

4.6 Ethical Considerations

The investigations conformed to the declaration of Helsinki and were approved by the Regional Ethics Committee of Gothenburg (study I, DNR 808-8; study II, DNR 074-13, T-652-13, ClinicalTrials.gov NCT02493387; and study III, DNR 074-13, ClinicalTrials.gov NCT02493400). All patients received written and verbal information about the studies and provided written informed consent. All patients were informed that they could withdraw their participation without a given cause. The withdrawal did not impact further treatment of their health and diseases. Whether it is ethically correct to allow patients to participate in detraining when the evidence for improved physical fitness is high as previously discussed can be debated.

5 RESULTS

The results of the studies included in this thesis are presented in the manuscripts attached to the printed version. Studies II and III are yet to be published.

5.1 Study I

A group-based exercise programme did not improve physical activity in patients with chronic heart failure and comorbidity: a randomised controlled trial.

Forty-two patients completed the study; 6 patients dropped out (PT-X = 3, control = 3). PT-X was well tolerated and no adverse events occurred during the intervention. The physical activity level assessed as steps/day did not increase significantly after intervention (p=0.351), though the patients rated themselves as more physically active on the IPAQ (p=0.008). Physical fitness increased in exercise capacity on the ergometer cycle (p=0.001), walking distance on the 6MWT (p=0.014), and muscular endurance in shoulder abduction (p=0.028) and heel lift (p<0.0001). HR-QoL (p=0.018) also improved significantly in the PT-X group compared to controls.

5.2 Study II

Physiotherapist-led exercise-based cardiac rehabilitation versus physical activity on prescription for patients with permanent atrial fibrillation - a randomised controlled study focusing on physical fitness and physical activity.

Eighty-seven patients completed the study; 9 patients dropped out (PT-X = 6, PAP = 3). No serious adverse events occurred during the study period in any group. Physical fitness improved significantly more after PT-X vs. PAP based on the exercise capacity on an ergometer cycle (p<0.0001) and muscle endurance in shoulder flexion left arm (p<0.001), shoulder abduction (p=0.010), and heel lift right leg (p<0.05) and left leg (p<0.001). The PAP group spent significantly more kilocalories and time in moderate and moderate to vigorous physical activity but did not have improved physical fitness. HR-QoL and lab tests did not significantly differ between the two groups.

5.3 Study III

Physiotherapist-led exercise within cardiac rehabilitation-induced improvement in physical fitness is "perishable goods" in patients with permanent atrial fibrillation.

Eighty of the 87 patients completing the intervention study (92%) participated (22 women; age 74 (±5) years). Physical fitness decreased significantly in the PT-X group (n=38) compared to the PAP group (n=42) in regards to exercise capacity on an ergometer cycle ($p<0.0001$) and muscle endurance in shoulder flexion ($p<0.001$). HR-QoL (SF-36 and RE function) was markedly reduced after detraining ($p<0.010$).

The mixed effect model showed physical fitness changes over time, and that this change is different depending on the intervention. The pattern of change showed that the improved physical fitness achieved by PT-X was reversed after detraining, but was not equal to baseline values. The physical fitness in the PAP group remained relatively unchanged over time. This was confirmed after adjusting for confounders (age and sex) and the secondary explanatory variables SF- 36 PF and moderate to vigorous physical activity measured by an accelerometer.

6 DISCUSSION

6.1 Discussion of Methods and Results

The results of the studies included in this thesis clearly confirm that PT-X improves physical fitness in patients with chronic HF and comorbidities. In patients with permanent AF, PT-X is safe and improves physical fitness, whereas an individually prescribed PAP does not. The results also show that PT-X does not improve the physical activity level in patients with chronic HF and permanent AF, though the patients with chronic HF rated themselves as more physically active. Furthermore, cessation of PT-X can reverse the benefits achieved by PT-X in regards to physical fitness in patients with permanent AF.

In study I, the patients were recruited from Alingsås Hospital and primary health care. In study II, the patients were recruited from Alingsås Hospital and Sahlgrenska University Hospital, primary health care, and from advertising in different local newspapers. These patients followed earlier randomisation in study III. Recruiting a mixed population from a small hospital outside Gothenburg, a university hospital, and primary health care makes it possible to generalise the results in a broader population compared to a narrower selection of patients from one hospital (114). The possibility of reaching the required number of patients more rapidly with a multicentre study also improves the external validity (114).

6.1.1 Intention-to-treat and per protocol analysis

Missing participant data in RCT trials is commonly occurring (115). It is rare that every patient enrolled in a clinical trial follows the study protocol and complete all the allocated treatments and assessments. In the studies included in this thesis, the exercise duration consisted of 3 months PT-X or PAP. The adherence was good but some patients cancelled some of their exercise sessions, and a few withdrew their participation. In RCT studies, the ITT analysis is the gold standard method to analyse data (116). The ITT principle states that the analysis should include all study participants in the group to which they were originally allocated (116). This means that every patient who has entered the study is included in the final data analysis according to the treatment they were intended to have (112, 116).

ITT helps to preserve the benefits of a randomisation, which is intended to ensure that all the benefits in the outcome is solely an effect of the treatment (116) . However, when analysing the results, the missing participant data must be taken into account. There are different ways that data can be interpreted, the most commonly used is a single imputation as the last observation carried forward, but also mixed models for repeated measures and/or multiple imputations are used (117). In study I, we decided to analyse the data as per protocol (117). In study II, we analysed the results as a partial ITT including all available outcome measures howsoever adherence to the study protocol (117). For sensitive analysis in study II a full ITT analysis with last observation carried forward was performed, which did not alter the result compared to the partial ITT. Therefore, we decided to present the results from the partial ITT. It can be debated whether the result from the full ITT and not the partial ITT should be presented. However, we thought that by presenting the results from the partial ITT analysis, the real impact of the treatment for those who completed the study is shown.

6.1.2 Physical fitness

The importance of high physical fitness regarding longevity and prognosis is well known in healthy individuals, as well as in patients with chronic HF and non-permanent AF (56, 57, 118, 119). A low VO_{2peak}, exercise duration, and percentage of predicted VO_{2peak} predicts the likelihood of premature death and a higher rate of hospital admissions in patients with chronic HF (118, 120). Low VO_{2peak} correlates with a high risk of mortality and/or stroke in patients with non-permanent AF (119). In study I, the patients with chronic HF and comorbidities had a low exercise capacity at baseline, corresponding to a poor prognosis; this was also indicated by the 6MWT and the results from the pedometer (92, 121). In study II, the patients with permanent AF had lower physical fitness than a healthy reference population (122).

There are major health benefits to improving physical fitness with PT-X. In patients with chronic HF and all types of AF, exercise-based CR increases VO_{2peak} (7, 10), and the health benefits of increased physical fitness have been confirmed by several studies (7, 55, 57, 58). Exercise-based CR reduces the mortality risk and hospital admissions in patients with chronic HF (7). Pathak et al (57) showed that an improvement in exercise capacity of $\geq$ 2 METs is an independent factor for arrhythmia freedom without drugs controlling arrhythmia and/or ablation when adjusted for weight loss in obese patients with non-permanent AF.

Increased VO_{2peak} is also associated with reduced symptom burden in patients with non-permanent AF (57, 58). In patients with coronary heart disease, an increase in VO_{2peak} is associated with an approximately 15% reduction in the risk of mortality (55). However, the evidence for mortality and serious adverse events in PT-X is still lacking for patients with AF (10).

In study I, the patients improved their exercise capacity 15 W on average. In study II, the patients with permanent AF increased their exercise capacity an average of 16 W. Participating in PT-X also improved muscle endurance in patients with chronic HF and permanent AF. It is important for elderly patients to postpone a reduction in muscle function, as it improves activities of daily living and reduces the risk of falls (50).

To assess exercise capacity and determine the intensity of exercise and physical activity in the studies included in this thesis, we used a symptom-limited ergometer cycle test with a steady state protocol instead of a maximal cardiopulmonary ergospirometry test (CPX) with a ramp protocol. The symptom-limited ergometer cycle test is less expensive than a CPX, but the CPX is the gold standard of exercise tests (123). The symptom-limited test was based on the clinical aspect, and this is the standard test used at physiotherapy clinics in Sweden and performed without a physician present. A symptom-limited steady state test can also be more appropriate than a maximal ramp test in order to prescribe exercise (91).

6.1.3 Physical activity

A low physical activity level in healthy people leads to reduced physical fitness and is associated with an increased risk of premature morbidity and mortality in several diseases (12). To increase their physical activity level, the patient can receive an individually prescribed PAP according to the guidelines given in *Physical activity in the prevention and treatment of disease (FYSS)* (11). In study II, PT-X was compared to PAP (11). The patients received an individually prescribed PAP consisting of active walking, which is the most common PAP prescription given by the medical profession (124, 125). PAP is most often prescribed without knowledge of the patients' physical fitness or how to prescribe individual-based exercise. Active walking was used for comparisons to PT-X because we wanted to come as close to the clinical reality for the patients as possible. Whether active walking is the optimum way to prescribe PAP can be debated, as the recommendations in FYSS include aerobic central circulatory exercise and muscular resistance and endurance exercise, even though it is called physical activity (11).

Walking is considered a safe, daily, and feasible activity that can be performed easily by patients. However, a “brisk” walk can be of too strenuous intensity and unattainable for patients with very low physical fitness (< 3 METs) (126) and too low to improve physical fitness in patients with high physical fitness.

Although the patients with permanent AF in the PAP group in study II increased the intensity of their physical activity, it was not enough to increase physical fitness. The patients in the PAP group spent more time in moderate and moderate to vigorous physical activity and achieved a higher energy expenditure as assessed by an accelerometer with no effect on physical fitness. The prescription of PAP included an individual visit with a physiotherapist and a 6-week follow-up return visit by the same physiotherapist. Leijon et al (127) has shown that adherence to PAP is low in the least active individuals due to multiple factors. It is recommended that PAP should be accompanied by motivational support, adjustment of the intervention, and evaluation (11, 128). At this visit, the ability to perform active walking was discussed, as well as the intensity, hinders, and barriers to performing the PAP. Conflicting results regarding the effect of PAP are found in the literature. Positive effects of PAP have been reported for metabolic risk factors, HR-QoL, and self-reported physical activity (129, 130), whereas others have found no effect with respect to VO_{2max} (130).

Neither patients with chronic HF nor patients with permanent AF increased their physical activity level as assessed by steps per day or total step counts after participating in PT-X. Two meta-analyses reported conflicting results regarding whether exercise-based CR leads to a more active lifestyle. When comparing CR programmes, including centre-based exercise or home-based exercise, for patients after acute coronary syndrome, centre-based CR was not sufficient to increase and maintain the physical activity level. However, the result was more promising for home-based exercise CR (131). It may be easier to incorporate physical activity in daily life with home-based exercise programmes. None of the CR programmes improved physical activity levels in the longer term (≥ 6 months after completion) (131). On the other hand, Dibben et al (132) found moderate evidence that exercise-based CR improved physical activity levels. In this meta-analysis, patients with coronary heart disease and patients with HF were included, and the patients with HF were less likely to improve their physical activity level (132).

Dibben et al (132) discussed whether the mean improvement of 1423 steps/day found in their meta-analysis is clinically meaningful and whether CR leads to an improvement in physical activity according to the guidelines of 150 minutes/week of moderate intensity physical activity. People living with chronic diseases are known to be less physically active (126). One study investigating whether patients with HF meet the recommended levels of physical activity found that no one managed to achieve the recommended levels of physical activity as measured by accelerometer data (133). According to accelerometer data, the patients were primarily engaged in light activities, but even this activity level was low (133). Patients with AF were not included in these studies. However, the recommended levels of physical activity in the WHO guidelines do not include patients with chronic HF and AF. The question remains, if patients with cardiac disease should focus on improving physical activity level or physical fitness.

The lack of improvement in physical fitness with PAP can be due to the recommended levels for physical activity are insufficient to improve physical fitness. Elliot et al (134) stated that the recommended levels of physical activity are insufficient for health benefits in patients with non-permanent AF. They discuss whether a higher volume of exercise (equivalent to 210 minutes/week) with the inclusion of vigorous exercise (≥ 6 METs) could be more appropriate. This supports the intensity of the physical activity being the most important factor for cardiorespiratory physical fitness and not the physical activity per se (56).

In study I, the pedometer was used as an objective measure of physical activity based on the economic frame of the study. Pedometers have well-known difficulties capturing slow walk and fast physical activity, such as jogging (97). There are also considerations in how to attach the pedometer in patients who are overweight or obese (97). In studies II and III, the pedometer was exchanged for an accelerometer for the objective measurement of physical activity. The accelerometer was worn in the same way as the pedometer, as there is less of a problem with attachment with a triaxial accelerometer in which the output is expressed as vector magnitude (97). The accelerometer has been proven to be more valid than the pedometer (97, 103).

When measuring physical activity with a pedometer or accelerometer, we must take into account that we are not able to measure non-ambulatory physical activity, such as cycling and swimming. In all studies, the patients were told to take the device off when taking a bath, shower, or swimming, but there was no restriction for cycling. It is possible to convert non-ambulatory physical activity to METs (34, 135), but this was not done in these studies because our main interest was steps per day and no other forms of physical activity. If we had converted different kinds of physical activity, we may have obtained another result.

In all studies, the objective measurement of physical activity was compared to the patient’s subjective rating of their physical activity level. For this purpose, the IPAQ was used (105). This questionnaire is considered a weak indicator of physical activity (136) but, together with an objective measurement, can be used to describe an individual’s physical activity level over 7 days. The difficulties with measuring self-reported physical activity are well known; Dyrstad et al (137) found that patients over-report physical activity compared to accelerometer data, especially at higher intensity levels. The results from study I concluded that the patients rated themselves as more physically active. This is congruent with Yates et al (133), as 38% of the patients rated themselves as physically active according to guidelines, though this was not confirmed by the accelerometer data. The reason for this discrepancy may be related to the increment in physical fitness, which may have improved the ability to perform physical activity with less effort and symptoms of breathlessness and fatigue. This may not increase the steps measured by the pedometer, which was our primary outcome measure; for example, performing household activities with less effort does not necessarily include more steps.

6.1.4 Health-related quality of life

Exercise-based CR clearly improves HR-QoL in patients with chronic HF (7). In this thesis, patients with chronic HF and comorbidities had improved SF-36 PCS scores. A high prevalence of symptoms and symptom burden are associated with low HR-QoL in patients with chronic HF (74-76). In addition, VO_{2peak} is associated with physical function in the elderly population (138). In study I, the patients had improved physical fitness and self-reported physical activity despite no increase in steps per day. It is possible that the patients felt fewer symptoms and, therefore, scored an improved PCS score for HR-QoL. Tierney et al (16) found that patients with HF associated an improvement in physical fitness with well-being and maintaining independent living.

In study II, no significant difference was found in HR-QoL in patients with permanent AF. This was congruent with the study by Risom et al (10), who found no evidence that exercise-based CR improves HR-QoL. However, another meta-analysis found improvements in some dimensions of SF-36, GH and VT, with exercise-based CR (65). As in patients with HF, the degree of symptom burden has been associated with low HR-QoL in patients with AF (73, 78). Guglin et al (15) found that the prevalence of symptoms in patients with AF increases with time in AF until the patient spends almost all the time in AF, then the symptom burden seems to decrease. In this study, the patients were well medicated and diagnosed with permanent AF. Patients with permanent AF have fewer symptoms than patients with non-permanent AF (33). These results are congruent with our study, as the patients with permanent AF rated their HR-QoL as similar to that of healthy Swedish individuals of the same age (110) .

In this thesis, we chose to use a non-specific generic instrument to measure HR-QoL, the SF-36 (108). We are aware of the ability to use a diagnosis-specific instrument, and there are some instruments for patients with HF or AF. However, the use of a generic instrument rather than a disease-specific instrument allows us to compare the patients across diseases and with the normative population of the same age. It allows us to investigate the patients' preserved health from a perspective apart from disease. Furthermore, a disease-specific instrument may not detect unforeseen side effects of the target condition (139).

6.1.5 Metabolic risk markers

CR includes, besides PTX and physical activity counselling, other core components that also allude to reduce the risk factors for cardio vascular disease (40). In study II neither PTX nor PAP reduced blood glucose and cholesterol. It must be taken into account that these patients already had blood glucose and cholesterol within reference limits at baseline, and therefore further improvement in these variables was unexpected.

6.1.6 Detraining

In study III, a 3-month period of detraining showed that the increment in physical fitness achieved by PT-X and the HR-QoL RE score were significantly reduced in patients with permanent AF. Other studies have found similar effects regarding the effect of detraining on VO_{2peak} and muscular strength in patients with CAD and in older adults (140, 141). In this study, we wanted to come as close to the clinical reality as possible, and although exercise-based CR improves physical fitness, the exercise needs to be continued on one's own accord after the programme is completed. Unfortunately, studies in patients with CAD and chronic HF have shown the difficulty for patients to continue exercising and be physically active after finishing the rehabilitation with PTX (142, 143) or PAP (130, 144). It is also difficult to adhere to PT-X, and various regimens have been compared but none seem to be effective (145).

7 CONCLUSION

This thesis shows that PT-X improves physical fitness in patients with chronic HF and comorbidities and in patients with permanent AF. PT-X is also superior over PAP regarding improvement in physical fitness in patients with permanent AF. PT-X should therefore be offered as a part of the medical treatment.

PT-X is well tolerated and safe in patients with permanent AF.

Individually prescribed PAP such as active walking increases energy expenditure but not physical fitness in patients with permanent AF.

Participating in PT-X do not augment the physical activity level in patients with chronic HF or in patients with permanent AF.

PT-X improves HR-QoL in patients with chronic HF but not in patients with permanent AF.

Detraining markedly decreased HR-QoL and reversed the gains in physical fitness acquired after 12 weeks of PTX -X in patients with permanent AF.

8 FUTURE PERSPECTIVES

The knowledge of lifestyle management has grown and its importance is now mentioned in every guideline regarding chronic HF and all types of AF. This raise many further research questions, each of them important for patients with cardiac diseases.

We found that patients with permanent AF improved physical fitness but not HR-QoL or metabolic risk markers. These patients were well medicated and with similar HR-QoL as the normative population. It would therefore be of further interest to investigate the effect of PT-X in patients with paroxysmal or persistent AF. These patients are often more symptomatic and the effect of PT-X is sparsely investigated.

To keep up the good habits after cessation from an exercise period is difficult either you are a healthy person or living with a chronic disease. Several techniques have been tested, but none has been superior over the other. What happens in the body organs in patients with chronic HF and AF when you stop exercise, and how can we support the patients in the best way? These questions require more research to be able to answer.

Although the evidence for PT-X is high, it is still an underused medical treatment. The amount of physiotherapists working within PT-X in Sweden and the amount of potential patients with cardiac diseases that should benefit from PT-X needs further investigation.

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