

# **Exercise and Physical Activity in relation to Kinesiophobia and Cardiac Risk Markers in Coronary Artery Disease**

Maria Bäck

Department of Molecular and Clinical Medicine  
Institute of Medicine at Sahlgrenska Academy  
University of Gothenburg



UNIVERSITY OF GOTHENBURG

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Exercise and Physical Activity in relation to Kinesiophobia and Cardiac Risk  
Markers in Coronary Artery Disease

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Maria.m.back@vgregion.se

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*“The real voyage of discovery consists not in seeking new landscapes,  
but in having new eyes.”*

Marcel Proust

*To Jonas, Ida and Tilda, my family*

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## **ABSTRACT**

Coronary artery disease (CAD) is the leading cause of death worldwide. Patients who have survived a coronary event are the highest priority for secondary prevention. In the secondary prevention of CAD, strong evidence of the beneficial effects of exercise-based cardiac rehabilitation is confirmed. The positive effects of physical activity are well established in primary prevention, but the question of whether these effects also relate to patients with CAD still remains to be explored. It is theoretically possible that kinesiophobia, fear of movement, may prevent successful cardiac rehabilitation. The impact on kinesiophobia by rehabilitation outcomes in patients with CAD has not previously been investigated.

The overall aim of this thesis was to study the impact of exercise and physical activity in relation to kinesiophobia and cardiac risk markers in patients with CAD.

Study I evaluated the effects of high-frequency exercise before and after an elective percutaneous coronary intervention (PCI).

Study II examined the level of physical activity in patients with CAD and investigated the association between physical activity and cardiac risk markers.

Study III investigated the validity and reliability of the Tampa Scale for Kinesiophobia Heart (TSK-SV Heart), a brief questionnaire to detect kinesiophobia, in patients with CAD.

Study IV described the occurrence of kinesiophobia in patients with CAD



and investigated the impact on kinesiophobia by clinical variables with an influence on rehabilitation outcomes.

The main findings were that high-frequency exercise improved the maximum aerobic capacity and muscle function in patients treated with PCI, which may have clear advantages when it comes to preventing the progress of CAD. A relatively high level of physical activity was found among patients with CAD, six months after the cardiac event. After adjustment for confounders, statistically significant, yet weak, associations were found between physical activity and several cardiac risk markers. Support was found for the TSK-SV Heart as a reliable, valid questionnaire for measuring kinesiophobia in patients with CAD. A high level of kinesiophobia was found in 20% of patients with CAD, six months after the cardiac event. In addition, an impact on kinesiophobia was identified by clinical variables with an influence on rehabilitation outcomes in patients with CAD, representing medical variables, all components of the International Classification of Functioning, Disability and Health (ICF) and health-related quality of life.

In conclusion, high-frequency exercise in patients treated with PCI improved their maximum aerobic capacity and muscle function. Significant, yet weak, associations were identified between physical activity and cardiac risk markers in patients with CAD. Several important clinical findings with an impact on rehabilitation outcomes were found to be associated with a high level of kinesiophobia. Kinesiophobia therefore needs to be considered in cardiac rehabilitation and would benefit from future research.

**Keywords:** coronary artery disease, percutaneous coronary intervention, exercise, physical activity, cardiac rehabilitation, cardiac risk markers, kinesiophobia, psychometrics, International Classification of Functioning, Disability and Health

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# SAMMANFATTNING PÅ SVENSKA

## Bakgrund

Kranskärslssjukdom är den ledande dödsorsaken i världen.

Sekundärprevention syftar till att minska risken för upprepad hjärthändelse vid en redan etablerad hjärtsjukdom. Fysisk träning inom hjärtrehabilitering har evidensbaserade positiva effekter på dödlighet, sjuklighet, livskvalitet samt riskfaktorer för patienter med kranskärslssjukdom. Däremot är sambandet mellan vardaglig fysisk aktivitetsnivå och riskfaktorer mer osäkert i sekundärpreventivt syfte. Trots de bevisade positiva effekterna av fysisk träning är det en underutnyttjad behandling inom hjärtrehabilitering.

Rörelserädsla, eller kinesiofobi som det kallas i sin mer extrema form, har visat sig ha en negativ inverkan på rehabilitering i flera patientgrupper. Dess påverkan på hjärtrehabilitering är ännu inte undersökt.

## Syfte

Det övergripande syftet med avhandlingen var att studera betydelsen av fysisk träning och fysisk aktivitet i relation till kinesiofobi och riskmarkörer hos patienter med kranskärslssjukdom.

I den första studien utvärderades effekterna av högfrekvent fysisk träning för patienter behandlade med ballongvidgning (PCI). I den andra studien studerades förekomsten av fysisk aktivitet hos patienter med kranskärslssjukdom, sex månader efter hjärthändelsen, samt dess relation till riskfaktorer. Studie tre utvärderade tillförlitligheten (reliabiliteten) samt giltigheten (validiteten) av frågeformuläret, Tampaskalan för Kinesiofobi – Heart (TSK-SV Heart). I den fjärde studien undersöktes förekomsten av kinesiofobi hos patienter med kranskärslssjukdom samt dess relation till variabler som är kliniskt betydelsefulla inom hjärtrehabilitering.

## Resultat

De huvudsakliga fynden i avhandlingen var att högfrekvent fysisk träning ökade maximal arbetskapacitet och muskelfunktion hos patienter behandlade med ballongvidgning. En relativt hög nivå av fysisk aktivitet uppmättes bland patienter med kranskärslssjukdom, sex månader efter hjärthändelsen. Nivå av fysisk aktivitet hade statistiskt säkerställda, men svaga, samband med flera riskfaktorer. Vidare visade resultat att frågeformuläret TSK-SV Heart har god vetenskaplig kvalitet och kan därför användas för att identifiera kinesiofobi hos patienter med kranskärslssjukdom. Tjugo procent av en population patienter med kranskärslssjukdom hade en hög grad av kinesiofobi, sex månader efter hjärthändelsen. Patienterna med hög grad av kinesiofobi deltog i lägre utsträckning i hjärtrehabilitering, hade lägre nivå av fysisk aktivitet,

sämre muskelfunktion och hälsorelaterad livskvalitet samt högre grad av ångest och depression, jämfört med de patienterna som skattade låg grad av kinesiofobi.

### Slutsats

Patienter behandlade med ballongvidgning ökade sin maximala arbetskapacitet och muskelfunktion av högfrekvent fysisk träning, under handledning av sjukgymnast. Däremot förblir sambandet mellan mer generell nivå av fysisk aktivitet och riskfaktorer för patienter med en etablerad kranskärslssjukdom fortfarande osäkert. En av fem patienter med kranskärslssjukdom hade en hög grad av kinesiofobi, sex månader efter hjärthändelsen. Eftersom resultaten indikerade att en hög grad av kinesiofobi har samband med flera variabler av betydelse inom hjärtrehabilitering och sekundärprevention, så bör kinesiofobi uppmärksammas bland patienter med kranskärslssjukom, samt prioriteras i framtida forskning.



# LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals. The papers have been printed with the kind permission of the publishers.

- I. Bäck M, Wennerblom B, Wittboldt S, Cider Å. Effects of high frequency exercise before and after elective percutaneous coronary intervention. *Eur J Cardiovasc Nurs*. 2008 Dec; 7(4):307-13.
- II. Bäck M, Cider Å, Gillström J, Herlitz J. Physical activity in relation to cardiac risk markers in secondary prevention of coronary artery disease. *Int J Cardiol*. 2012 Oct; doi: 10.1016/j.ijcard.2012.09.117.
- III. Bäck M, Jansson B, Cider Å, Herlitz J, Lundberg M. Validation of a questionnaire to detect kinesiophobia (fear of movement) in patients with coronary artery disease. *J Rehabil Med*. 2012 Apr; 44(4):363-9.
- IV. Bäck M, Cider Å, Herlitz J, Lundberg M, Jansson B. The impact on kinesiophobia (fear of movement) by clinical variables for patients with coronary artery disease. *Int J Cardiol*. 2012 Feb; doi: 10.1016/j.ijcard.2011.12.107.



# CONTENTS

ABBREVIATIONS .....	VI
BRIEF DEFINITIONS.....	VII
PERSONAL FOREWORD.....	IX
1 INTRODUCTION .....	1
1.1 Coronary artery disease.....	1
1.1.1 Percutaneous coronary intervention .....	2
1.1.2 Cardiac risk markers.....	3
1.2 Exercise and physical activity .....	4
1.2.1 General exercise principles.....	5
1.2.2 Recommendations for physical activity and exercise in the primary and secondary prevention of CAD .....	5
1.3 Association between physical activity and cardiac risk markers .....	7
1.3.1 Physical activity in primary prevention.....	7
1.3.2 Physical activity in secondary prevention .....	8
1.3.3 Body mass index, waist-hip ratio and physical activity .....	9
1.3.4 Glucose tolerance and physical activity .....	9
1.3.5 Lipids and physical activity.....	10
1.3.6 Twenty-four-hour blood pressure, heart rate and physical activity. .....	11
1.4 Cardiac rehabilitation .....	12
1.4.1 Effects of exercise-based cardiac rehabilitation .....	12
1.4.2 Adherence to exercise-based cardiac rehabilitation .....	13
1.5 Kinesiophobia .....	14
1.5.1 Kinesiophobia and avoidance behaviour.....	15
1.5.2 Definitions of related constructs.....	16
1.5.3 The Tampa Scale for Kinesiophobia – Heart .....	18
1.5.4 Occurrence of kinesiophobia.....	19
1.5.5 Kinesiophobia and rehabilitation.....	19

1.6	The physiotherapeutic perspective in exercise-based cardiac rehabilitation .....	20
1.7	International Classification of Functioning, Disability and Health.....	22
2	AIM.....	24
3	PATIENTS AND METHODS.....	25
3.1	Study population .....	25
3.2	Study design.....	27
3.3	Procedure .....	28
3.4	Intervention programme.....	29
3.5	Measurements .....	30
3.5.1	Body functions .....	30
3.5.2	Activities and participation .....	33
3.5.3	Personal factors .....	34
3.5.4	Health-related quality of life .....	34
3.6	Psychometrics .....	36
3.6.1	Reliability.....	36
3.6.2	Validity.....	38
3.7	Statistical analyses .....	41
3.8	Ethical considerations .....	44
4	RESULTS .....	45
4.1	High-frequency exercise before and after an elective PCI (Study I) ..	45
4.2	Physical activity and cardiac risk markers (Study II) .....	48
4.3	The validity and reliability of the TSK-SV Heart (Study III) .....	50
4.4	The impact on kinesiophobia by clinical variables (Study IV) .....	53
5	DISCUSSION.....	57
5.1.1	Are we taking full advantage of the documented value of exercise in patients with CAD? .....	57
5.1.2	Which dose of physical activity should we recommend to patients with CAD?.....	59
5.1.3	Is the TSK-SV Heart an optimal questionnaire for detecting kinesiophobia in CAD? .....	61



5.1.4	What is the impact on kinesiophobia by clinical variables in cardiac rehabilitation? .....	64
5.1.5	Methodological considerations.....	66
5.1.6	How do the selected endpoint variables affect the results? .....	68
5.1.7	Gender perspective .....	72
5.1.8	Clinical implications.....	73
6	CONCLUSIONS .....	76
7	FUTURE PERSPECTIVES .....	77
8	ACKNOWLEDGEMENTS .....	78
9	REFERENCES .....	82
10	APPENDIX.....	100

# ABBREVIATIONS

ACSM	American College of Sports Medicine
BMI	Body mass index
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CFA	Confirmatory factor analysis
DSM-IV	Diagnostic and Statistical Manual of the American Psychiatric Association, fourth edition
HADS	Hospital Anxiety and Depression Scale
HDL-C	High-density lipoprotein cholesterol
HRQoL	Health-related quality of life
ICF	International Classification of Functioning, Disability and Health
IPAQ	International Physical Activity Questionnaire
LDL-C	Low-density lipoprotein cholesterol
MET	Metabolic equivalent
PCI	Percutaneous coronary intervention
RM	Repetition maximum
SF-36	Short-Form 36
TSK	Tampa Scale for Kinesiophobia
TSK-SV Heart	Tampa Scale for Kinesiophobia – Heart (Swedish version)
WHR	Waist-hip ratio

## BRIEF DEFINITIONS

Cardiac rehabilitation	<p>The coordinated sum of interventions required to ensure the best physical, psychological and social conditions so that patients with chronic or post-acute cardiovascular disease may, by their own efforts, preserve or resume optimal functioning in society and, through improved health behaviours, slow or reverse the progression of disease.</p> <p><i>(Fletcher et al., 2001)</i></p>
Physical activity	<p>Any bodily movement, produced by skeletal muscles, that results in energy expenditure.</p> <p><i>(Caspersen et al., 1985)</i></p>
Exercise	<p>A subset of physical activity that is planned, structured, repetitive, and purposeful in the sense that the improvement or maintenance of physical fitness is the objective.</p> <p><i>(Caspersen et al., 1985)</i></p>
Aerobic exercise	<p>Any activity that uses large muscle groups, can be maintained continuously, and is rhythmic in nature.</p> <p><i>(ACSM, 2010)</i></p>
Muscular endurance	<p>Relates to the ability of muscle groups to exert external force for many repetitions or successive exertions.</p> <p><i>(Caspersen et al., 1985)</i></p>
Kinesiophobia	<p>An excessive, irrational, and debilitating fear of movement and activity resulting from a feeling of vulnerability to painful injury or re-injury.</p> <p><i>(Kori et al., 1990)</i></p>
Fear of movement	<p>Fear of movement/(re)injury, a specific fear of movement and physical activity that is (wrongfully) assumed to cause re-injury.</p> <p><i>(Vlaeyen et al., 1995)</i></p>

Psychometrics	<p>Psychometrics is the field of study concerned with the theory and technique of psychological measurement. The field is primarily concerned with the construction and validation of measurement instruments.</p> <p><i>(Portney et al., 2009)</i></p>
Reliability	<p>The extent to which a measurement is consistent and free from random error, the ability of a test to yield the same result under similar test conditions over time.</p> <p><i>(Nunnally et al., 1994, Kline et al., 1999)</i></p>
Validity	<p>Measurement validity relates to the extent to which an instrument measures what it is intended to measure.</p> <p><i>(Nunnally et al., 1994, Kline et al., 1999)</i></p>

# PERSONAL FOREWORD

Based on my clinical experience as a physiotherapist and on strong scientific evidence, I am convinced that patients with coronary artery disease (CAD) will benefit greatly from exercise-based cardiac rehabilitation. In this thesis, secondary prevention and cardiac rehabilitation are seen from a physiotherapeutic perspective and physical activity and exercise therefore run like common threads. However, it is also important to highlight the fact that cardiac rehabilitation is comprehensive and refers to coordinated, multifaceted interventions designed to optimize the physical, psychological and social function of patients with CAD.

I started my journey with an interest in the effects of physical activity and exercise on the secondary prevention of CAD from a biomedical perspective. Along the way, searching for factors influencing cardiac rehabilitation, the concept of kinesiophobia, fear of movement, was introduced to me. Based on clinical experience, certain patients with CAD appear to be afraid to move their body and consequently avoid physical activity and exercise. Kinesiophobia has been shown to have a negative influence on the outcome of rehabilitation in other patient groups, but its impact on cardiac rehabilitation in patients with CAD was not known.

The decision to add this perspective challenged me more than I first imagined and made me flash through unknown areas of knowledge and research methodology. Keeping the framework of a physiotherapist, the interdisciplinary collaboration in this thesis has made me broaden my mind and I believe that a bio-psycho-social perspective of health will add something more to patients. Regardless of unexpected directions of travel along the way, I have always known that my goal in the long run is to try to make a difference for these patients.



# 1 INTRODUCTION

Patients who have survived an acute coronary event are the highest priority for secondary prevention. Previous research has confirmed the strong evidence of the benefits of exercise-based cardiac rehabilitation, including positive effects on cardiac risk markers. The benefits associated with physical activity in the primary prevention of coronary artery disease (CAD) are well established. The question of whether these advantageous effects also relate to the secondary prevention of CAD still remains to be explored. The relationship between the level of physical activity and cardiac risk markers in relation to the secondary prevention of CAD was therefore focused on in this thesis.

Based on clinical experience, several patients with CAD appear to be afraid to move their body after a cardiac event and consequently avoid physical activity and exercise. Kinesiophobia, fear of movement, has been shown to have a negative influence on rehabilitation in other patient groups. However, the impact on kinesiophobia by rehabilitation outcomes in patients with CAD has not previously been investigated.

## 1.1 Coronary artery disease

Cardiovascular diseases, including CAD, are the most common causes of mortality and morbidity globally and are projected to remain so (1). As fatalities after an acute coronary event have fallen, partly as a result of improved medical care and public awareness, candidates for secondary prevention are growing in number.

CAD refers to the development of atherosclerotic plaques in the endothelium of coronary arteries forming blood-flow limiting stenosis leading to myocardial ischemia. The symptoms are typically first experienced during physical exertion or stress (stable angina pectoris). These atherosclerotic plaques can progress or rupture and trigger thrombosis, with the subsequent interruption of blood flow causing myocardial ischemia (acute coronary syndrome). Acute coronary syndrome includes the diagnosis of ST-elevation myocardial infarction, non-ST-elevation myocardial infarction and unstable angina pectoris (2, 3).

### **1.1.1 Percutaneous coronary intervention**

Percutaneous coronary intervention (PCI) is the most frequently used revascularisation technique for patients with CAD (4). Primary PCI has been found to be more effective than thrombolytic therapy in the treatment of ST-elevation myocardial infarction (5). Further, it is suggested that PCI reduces the long-term rates of cardiovascular death or myocardial infarction in high-risk patients with non-ST-segment elevation acute coronary syndromes (6). The role of PCI in the management of patients with stable angina has been more controversial. Most meta-analyses report no effect on mortality or myocardial infarction when compared with medical therapy (7-9). However, PCI is a reasonable option for relieving symptoms for patients whose symptoms cannot be reduced by medical therapy. Despite its frequent use, PCI carries a high risk of restenosis, although the need for revascularisation has been reduced by the use of stents (10). In overall terms, these results support the presentation of recommendations to optimise medical therapy and lifestyle intervention, including exercise, as an initial management strategy in patients with stable angina pectoris (7).

### **Exercise studies in patients treated with PCI**

Although PCI is effective as a revascularisation procedure, it should be emphasised that these patients require lifelong secondary prevention, including exercise, to reduce the further progression of the disease. A low participation rate in cardiac rehabilitation programmes has been found among these patients (11). Given the rapid advances in coronary invasive technology, cardiac rehabilitation programmes must prepare for a growing number of patients treated with PCI.

Among the cardioprotective factors influenced by exercise, the endothelium is described as a major target (12). Several studies have found that exercise in patients with stable CAD improves coronary endothelial function, endothelium-dependent vasodilation and myocardial perfusion and slows the progression of CAD (13-17). As a continuation of this knowledge, a randomised study to compare the effects of exercise versus PCI in patients with stable CAD found that exercise intervention resulted in more event-free survival, higher exercise capacity, reduced re-hospitalisation and revascularisation, compared with controls (18).

When the exercise study in this thesis was designed, only a few previous studies that investigated the combined effects of PCI and exercise had been conducted. Some additional evidence has now been added. A recent systematic review, comprising six studies, investigated the effectiveness of



the combination of PCI and exercise compared with PCI alone in the secondary prevention of CAD (19). One study reported a lower mortality rate in the exercise group (20). Further, the incidence of non-fatal coronary events was found to be lower in the exercise group (20-23). All six studies reported the incidence of restenosis as an endpoint. One study showed no differences between the groups (24), while the other studies demonstrated significant differences in restenosis rate or residual diameter stenosis, favouring the exercise groups (20-23). Moreover, one study showed that quality of life was significantly higher in the patients that exercised (21). According to health-related quality of life (HRQoL), one study demonstrated that only the domain of physical role limitation in the Short-Form 36 (SF-36) was significantly better in the intervention group (24). Furthermore, most studies found a significant increase in maximum aerobic capacity in the exercise groups (21-25).

### **1.1.2 Cardiac risk markers**

Atherosclerosis begins in childhood and progresses at different rates, largely determined by genetics and risk factors (3, 26). A high proportion of potentially modifiable risk factors, which explain more than 90% of the overall risk of a myocardial infarction, have been identified (27). These risk factors include abnormal lipids, smoking, hypertension, type 2 diabetes mellitus, abdominal obesity, psychosocial factors, regular alcohol consumption, lack of daily consumption of fruit and physical inactivity. The effect of these risk factors is consistent in both genders, at all ages and in all regions of the world. It must be acknowledged, however, that the development of CAD is usually the product of multiple interacting risk factors (27).

Patients with CAD run an increased risk of a subsequent coronary event and are therefore a top priority for secondary prevention. Secondary prevention for the target group should aim to reduce mortality and the risk of further atherosclerotic events and improve quality of life (28, 29). Evidence of the effectiveness of secondary-prevention programmes to improve health outcomes, including mortality and morbidity, is well known (30). However, adherence to guidelines for secondary prevention is discouraging and this indicates that there is an urgent need for more extensive support for risk-factor reduction in patients with CAD (28). It is important to consider comprehensive lifestyle modifications in this target group; however, the scope of this thesis is limited to discussing the association between physical activity and cardiac risk markers.

## 1.2 Exercise and physical activity

Since exercise and physical activity are central constructs in this thesis, it is essential to note the theoretical distinction between them. These constructs are often used interchangeably, although physical activity is defined as “*any bodily movement, produced by skeletal muscles, that results in energy expenditure*”, while exercise is defined as “*a subset of physical activity that is planned, structured, repetitive, and purposeful in the sense that the improvement or maintenance of physical fitness is the objective*” (31). The definitions used in this thesis, related to exercise and physical activity, are described in Table 1.

*Table 1. Definitions of constructs related to physical activity and exercise*

Physical activity	Any bodily movement, produced by skeletal muscles, that results in energy expenditure (31)	Exercise	A subset of physical activity that is planned, structured, repetitive, and purposeful in the sense that the improvement or maintenance of physical fitness is the objective (31)
Physical fitness	Comprises sets of attributes that people have or achieve that relate to the ability to perform physical activity, often divided into two groups – <i>Health-related fitness includes:</i> cardiorespiratory endurance, muscular endurance and strength, body composition and flexibility – <i>Skill-related fitness includes:</i> Agility, balance, co-ordination, speed, power and reaction time (31)	Absolute intensity  Relative intensity	The rate of energy expenditure during exercise or physical activity, usually expressed in METs or kcal x min  The relative percentage of maximum aerobic power, e.g. $VO_{2max}$ , $HR_{max}$ , HRR, or according to RPE (26)
Aerobic exercise	Any activity that uses large muscle groups, can be maintained continuously and is rhythmic in nature (32)	Muscular endurance	Relates to the ability of muscle groups to exert external force for many repetitions or successive exertions (31)

MET, metabolic equivalent;  $VO_{2max}$ , maximum oxygen uptake;  $HR_{max}$ , maximum heart rate; HRR, heart rate reserve; RPE, rate of perceived exertion

### 1.2.1 General exercise principles

Aerobic exercise has two main goals, including the enhancement of central circulatory capacity to deliver oxygen and increasing the capacity of active muscle to consume oxygen. Several factors, such as the initial level of fitness, frequency, duration and intensity, influence the outcomes of exercise. It has been suggested that exercise intensity represents the most critical factor in successfully affecting  $\text{VO}_{2\text{max}}$  (26).

There are essentially four exercise principles to consider when conducting an exercise programme and subsequently interpreting the results of repeated exercise (26). They are as follows.

*1. Individual differences principle*

All individuals do not respond similarly to a given exercise stimulus. Exercise programmes must therefore meet individual needs.

*2. Specificity principle*

To maximise the advantages of exercise, it must be performed in a way similar to the type of activity the person wants to improve.

*3. Overload principle*

Exercise must involve intensities greater than normal to progress to a higher work level.

*4. Reversibility principle*

The reversibility of exercise effects occurs relatively rapidly if exercise is discontinued or reduced too abruptly.

Physiological adaptations to exercise can be divided into acute and chronic responses. Acute responses involve the way the body responds to one bout of exercise, e.g. increased cardiac output and blood pressure and effects on neuromuscular and hormone systems. Chronic physiological adaptations are the way the body responds over time to the stress of repeated exercise bouts. This will subsequently lead to significant positive effects on several parts of the body, e.g. cardiovascular and pulmonary adaptations, effects on the nervous, skeletal, immune and hormone system (33).

### 1.2.2 Recommendations for physical activity and exercise in the primary and secondary prevention of CAD

International guidelines have established recommendations for physical activity and exercise in the primary and secondary prevention of CAD (34, 35). The differences between these guidelines are illustrated in Table 2.

*Table 2. Differences between physical activity and exercise recommendations in the primary and secondary prevention of coronary artery disease. Adapted from Garber (34) and Balady (35)*

	Primary prevention	Secondary prevention
Aerobic exercise	<p>F <math>\geq</math> 5 days/week  I = moderate  T <math>\geq</math> 30 min  <i>or</i>  F <math>\geq</math> 3 days/week  I = vigorous  T <math>\geq</math> 20 minutes</p> <p>Combinations of moderate- and vigorous-intensity exercise can be performed (<math>\geq</math> 10 min continuous exercise) to reach the total goal of energy expenditure <math>\geq</math> 1,000 kcal/week (<math>\geq</math> 500-1,000 METxmin/week). Progression of exercise volume until the desired goal is attained.</p>	<p>F = 3-5 days/week  I = 50-80% of VO<sub>2max</sub>  T = 20-60 min  M = interval or continuous  P = progressive updates to the exercise prescription are recommended</p> <p>Supplement the formal exercise regimen with guidelines for primary prevention on days with no exercise</p>
Resistance exercise	<p>F = 2-3 days/week  I = 60-70% of 1 RM  R = 8-12 for most adults, 10-15 for older persons  D = 1-3 sets of each major muscle group  P = progressive updates to the exercise prescription are recommended</p>	<p>F = 2-3 days/week  I = to moderate fatigue  R = 10-15 repetitions per set  D = 1-3 sets of 8-10 different upper and lower body exercises  P = progressive updates to the exercise prescription are recommended</p>
Flexibility	F = 2-3 days/week	F = should be included in each exercise session
Neuromotor exercise	Balance, agility, coordination exercise is recommended 2-3 days/week for older persons	Not specified

F, frequency; I, intensity; T, duration; M, modalities; P, progression; R, repetitions; VO<sub>2max</sub>, maximum oxygen uptake; MET, metabolic equivalent; RM, repetition maximum

Guidelines for exercise prescription in secondary prevention in CAD have also been suggested by Piepoli et al. (36). These guidelines are less clear and therefore not used as frequently in Swedish cardiac rehabilitation settings. However, these guidelines recommend continuous aerobic exercise at least 20-30 minutes (preferably 45-60 minutes/week), three days a week (preferably 6-7 days/week) at 50-80% of  $VO_{2max}$ . Furthermore, Perk et al. (29) emphasise that exercise prescription must be tailored to the clinical profile of the individual cardiac patient. According to these guidelines, moderate to vigorous exercise, 3-5 sessions a week, 30 minutes a session are suggested (29).

To comply with the current guidelines for primary prevention, in terms of pedometer steps, individuals are encouraged to walk a minimum of 3,000 steps in 30 minutes, five days a week (37). Three shorter sessions of 1,000 steps in 10 minutes, five days a week can also be used to meet the recommended goal. Other studies have suggested that  $\geq 7,000$  steps/day are recommended for further health benefits and  $> 10,000$  steps/day for weight loss (34).

The differences in the primary and secondary prevention guidelines can be basically found in the recommendations for aerobic exercise. While the main aim in primary prevention is to achieve a total energy expenditure of  $\geq 1,000$  kcal/week, the focus in the secondary prevention of CAD is to develop an individualised exercise prescription based on physical fitness evaluations (34, 35). In clinical practice in Sweden, it is unusual for patients to have performed a maximum exercise test or maximum ergospirometry. As a result, intensity can rarely be specified from a percentage of maximum heart rate or  $VO_{2max}$ . Instead, Borg's rate of perceived exertion scale (RPE) (38) is commonly used, showing established relationships between a percentage of  $VO_{2max}$ , heart rate and the RPE scale during exercise (33).

## **1.3 Association between physical activity and cardiac risk markers**

Previously related findings of associations between physical activity, exercise and risk markers in the primary and secondary prevention of CAD will now be briefly reported.

### **1.3.1 Physical activity in primary prevention**

The evidence demonstrating that a sufficient amount of physical activity has been shown to reduce the incidence of widespread disease (including

cardiovascular disease, type 2 diabetes mellitus, colon cancer, breast cancer, osteoporosis and depression) began with Hippocrates and continues with large epidemiological studies (39). In addition, improvements in metabolic function, hemodynamic, musculoskeletal and psychological functioning are a few of many established effects of increased physical activity (40). In the primary prevention of CAD, recent meta-analyses and guidelines have confirmed a graded, inverse relationship between physical activity levels and the risk of CAD and all-cause mortality (29, 41-43). The greatest benefits were seen in individuals moving from no activity to low levels of activity. In addition, walking pace has been suggested as a stronger predictor than walking volume of the risk of all-cause mortality (44).

### **1.3.2 Physical activity in secondary prevention**

To date, physical activity in secondary prevention of CAD is often regarded as an exercise intervention. The available data deal almost exclusively with physical fitness measurements and not with evaluations of physical activity levels per se (29). Even though the expected outcomes of physical activity in secondary prevention for patients with CAD have been discussed in relation to improved psychosocial well-being, the enhancement of opportunities for independent self-care and the prevention of disability, studies are limited (36). A few studies have established an inverse graded relationship between physical activity and mortality in patients with CAD (45-49). However, no meta-analyses are available. In addition, it has been shown that patients who improved their physical activity level reduced their risk of death, in contrast to those patients with a declining physical activity level, who were observed to run an increased risk (47, 48).

Studies have attempted to establish the amount of leisure time physical activity that is needed to accomplish effects on cardiorespiratory fitness and coronary atherosclerotic lesions in patients with CAD (16, 50). It has been suggested that a measurable improvement in cardiorespiratory fitness requires 1,400 kcal/week of leisure time physical activity (50). Furthermore, the progression of CAD was negatively associated with the amount of leisure time physical activity and regression only occurred in patients expending more than 2,200 kcal/week (16, 50).

However, in patients with CAD, there are few studies investigating the association between physical activity and cardiac risk markers. Increasing knowledge within this area is very important when it comes to the physical activity advice we should give patients with CAD in terms of secondary prevention.

### **1.3.3 Body mass index, waist-hip ratio and physical activity**

There has been a substantial rise in obesity in patients with CAD during the last few years (28). Obesity is regarded as a major risk factor for several chronic diseases, such as type 2 diabetes mellitus and hypertension (51). However, according to the obesity paradox, overweight has been associated with reduced mortality in some chronic diseases, including patients with CAD (52). Furthermore, obesity is not a risk factor for mortality in fit men (52). On the other hand, central obesity has independently and cumulatively been associated with increased mortality in patients with CAD (53). Systematic reviews (51, 54) have confirmed that exercise results in small weight losses, when compared with no treatment, in adults with overweight or obesity. Favourable changes in cardiac risk markers can occur, even in the absence of weight reduction. In comparison between high- versus low-intensity exercise for weight loss, all the trials favoured high-intensity exercise (51). However, to achieve long-term weight reduction, exercise in combination with diet appears to produce the most encouraging results (51, 54). In patients with CAD, a meta-analysis showed that anthropometric outcomes were no better among the physical activity intervention group than among controls, in the absence of a diet intervention (55).

### **1.3.4 Glucose tolerance and physical activity**

Impaired glucose tolerance is a marker of early-developing insulin resistance (56). Compared with normoglycaemia, impaired glucose tolerance is an independent predictor of all-cause and CAD mortality (57). An abnormal glucose metabolism is common in patients with CAD and there has been an increase in undetected diabetes over time (28, 58). Several studies have shown that admission hyperglycaemia is a strong predictor of an adverse outcome in patients with acute coronary syndromes (59, 60).

Physical activity has beneficial effects on both insulin sensitivity and glucose metabolism (61). There is strong evidence that physical activity can prevent or delay progression to type 2 diabetes in patients with impaired glucose tolerance (62). In patients with type 2 diabetes, structured aerobic exercise, resistance exercise, or both combined, were each associated with declines in haemoglobinA<sub>1c</sub> (HbA<sub>1c</sub>). An exercise volume of more than 150 minutes a week was associated with a greater decline in HbA<sub>1c</sub> compared with exercise for 150 minutes or less a week. Physical activity advice alone was only related to lower HbA<sub>1c</sub>, if combined with diet (63).

Few studies have investigated the effects of physical activity on impaired glucose tolerance in patients with CAD. One study, however, showed no result in terms of insulin resistance after twelve weeks of moderate exercise, in the absence of weight loss (64). Further studies are needed to achieve consensus on the optimal exercise prescription to establish positive effects on glucose metabolism in patients with CAD.

### **1.3.5 Lipids and physical activity**

For patients with CAD, lipid management is important and lifestyle adaptations are recommended (28). The effect of physical activity and exercise on lipid levels is an area of active research. One study in patients with CAD demonstrated no significant correlation between the degree of leisure time physical activity and changes in cholesterol, high-density lipoprotein cholesterol (HDL-C) and triglycerides, as compared with positive effects on these parameters in patients performing daily high-intensity exercise (50). Another recent study in patients with CAD showed that blood lipids did not change with increasing levels of physical activity (65). In contrast, a meta-analysis found that aerobic exercise increased HDL-C and reduced triglycerides in patients with CAD (66). Furthermore, meta-analyses of exercise-based cardiac rehabilitation have confirmed advantageous effects on blood lipids (67, 68).

Conflicting results have been reported regarding the effects of physical activity and exercise on lipids in primary prevention as well. A meta-analysis has concluded that physical activity (walking) reduces low-density lipoprotein cholesterol (LDL-C) and total cholesterol/HDL-C (69). However, no significant improvements in total cholesterol, HDL-C and triglycerides were found, independent of changes in body composition. The most recent meta-analysis concluded that aerobic exercise significantly improved triglycerides but not total cholesterol, LDL-C or HDL-C (70). In contrast, other studies have found that aerobic exercise primarily increased HDL-C (71, 72). In a recent systematic review, a comparison of the effects of different intensities of aerobic exercise on blood lipids only resulted in a favourable influence in connection with high-intensity aerobic exercise in contrast to moderate-intensity aerobic exercise, independently of the total volume of exercise (73). Greater improvements in HDL-C and less frequently in triglycerides, total cholesterol and LDL-C were observed. These findings are also supported by the most recent review (74), including samples from the primary and secondary prevention of CAD, which concluded that regular exercise had a positive impact on apolipoprotein B, triglycerides and HDL-C. Although this review indicates no effect on serum LDL-C concentrations,



there is evidence of alterations in LDL particle size as a result of exercise. Further conclusions regarding ideal exercise intensity, duration and frequency response to serum lipoprotein changes have yet to be confirmed.

### **1.3.6 Twenty-four-hour blood pressure, heart rate and physical activity**

In primary prevention, the effect of physical activity and aerobic exercise in reducing clinical and ambulatory monitored blood pressure is well known (75-77). However, the optimal exercise prescription is still a matter of debate, as differences in changes in blood pressure have not been found to be dependent on frequency, duration, or intensity (76). Based on current evidence, the physical activity guidelines from the American College of Sports Medicine (ACSM) (34) apply to individuals at risk of developing high blood pressure or those with high blood pressure (78).

It is unclear whether the ACSM physical activity recommendations are sufficient for lowering blood pressure in established CAD. In a meta-analysis that measured physical activity outcomes in patients with CAD, there were no significant differences between patients who received treatment and controls (55). This was also confirmed by an additional study which reported no significant relationship between clinical blood pressure and habitual physical activity (65). To the best of our knowledge, studies of the relationship between ambulatory monitored blood pressure and physical activity are lacking in patients with CAD. Nevertheless, the effect of aerobic exercise in reducing clinical and ambulatory monitored blood pressure is well known in this target group (67, 68).

Results relating to ambulatory heart rate recording are sparsely reported in patients with CAD. However, it is well known from current physiological findings that a decrease in resting and submaximum heart rate at the same exercise intensity is one manifestation of sufficient physical activity, partly due to a change in autonomic balance and an increase in stroke volume. Practical implications include (1) an increase in cardiac reserve which enhances aerobic capacity, (2) a decrease in rate pressure product at any given submaximum exercise level, thus reducing the likelihood of myocardial ischemia, and (3) a lengthening of the diastolic phase of the cardiac cycle, facilitating myocardial perfusion (26, 61).

## 1.4 Cardiac rehabilitation

Today, exercise is fundamental in cardiac rehabilitation with strong scientific evidence of a reduction in morbidity and mortality and with positive effects on psychological well-being (67, 68, 79, 80). However, it was not until the 1950s that previous advice on bed rest and the avoidance of exercise and physical activity was questioned. In the 1960s, several studies showed that early activity after a myocardial infarction safely negates the adverse effects associated with prolonged bed rest. By the end of the 1960s, outpatient cardiac rehabilitation programmes, including exercise, had been developed (81).

Cardiac rehabilitation has been defined as the *“coordinated sum of interventions required to ensure the best physical, psychological and social conditions so that patients with chronic or post-acute cardiovascular disease may, by their own efforts, preserve or resume optimal functioning in society and, through improved health behaviours, slow or reverse the progression of disease”* (82). The core components of cardiac rehabilitation include baseline patient assessment, nutritional counselling, risk factor management, psychosocial interventions, physical activity counselling and exercise (35). International guidelines consistently identify exercise as a cornerstone in cardiac rehabilitation (35, 83).

### 1.4.1 Effects of exercise-based cardiac rehabilitation

An extensive review of all the effects of exercise-based cardiac rehabilitation far exceeds the scope of this thesis. This introductory description is limited to the results of meta-analyses and results relevant to the present thesis.

Meta-analyses clearly confirm the benefits of exercise-based cardiac rehabilitation in terms of marked reductions in cardiac and all-cause mortality (30, 67, 68, 79), as well as a reduced risk of a subsequent myocardial infarction (30, 68). Furthermore, exercise-based cardiac rehabilitation has favourable effects on cardiac risk markers, including smoking, blood pressure and lipid profile (67, 68).

Supervised exercise, according to recommended guidelines (35), for three to six months is generally reported to increase peak oxygen uptake, with the greatest improvements in the most deconditioned patients (84). Since peak aerobic exercise capacity is a strong predictor of mortality in patients with

CAD, a small gain in oxygen uptake may improve not only functional capacity and quality of life but also survival prospects (84, 85).

Given the heterogeneity of health-related quality of life (HRQoL) measures, meta-analyses have not been conducted. However, in the majority of reviewed studies, there was evidence of a significantly higher level of HRQoL with exercise-based cardiac rehabilitation compared with standard care (30, 79). Furthermore, considerable evidence indicates the adverse effects of psychosocial risk factors in the pathogenesis and recovery from CAD (80). Substantial data have demonstrated the impact of exercise and multifactorial cardiac rehabilitation on improving psychological factors, including depression and anxiety (80, 86, 87).

On the other hand, one recent randomised trial suggested that comprehensive cardiac rehabilitation after myocardial infarction had no important effects on mortality, morbidity, risk factors and quality of life after exercise-based cardiac rehabilitation, in comparison with standard care (88). However, this study has been extensively criticised for a number of methodological limitations (89). The most important criticism includes an insufficient sample size due to power calculations for the primary endpoint variable of mortality. Furthermore, the heterogeneity of invalid exercise programme delivery, not in line with guidelines, limits the conclusions that can be drawn.

### **1.4.2 Adherence to exercise-based cardiac rehabilitation**

Despite the well-established positive effects of exercise-based cardiac rehabilitation, uptake and adherence in patients with CAD are sub-optimal (90). In Sweden, the average participation rate for exercise-based cardiac rehabilitation was 40% in 2011 (91). There are many barriers to uptake and adherence and they may vary between individuals. Factors identified as predicting adherence include health belief variables, age, gender, level of education, cardiac functional status, mood state and social support (11, 90). At present, there are few practical recommendations for increasing the uptake of and adherence to cardiac rehabilitation. Some evidence suggests that interventions involving motivational communication and coping strategies targeting barriers to adherence may be effective (90, 92). A current position statement has addressed several barriers to exercise in heart failure, e.g. patient related, social and economic factors, condition related and therapy related (93). Consequently, tailored interventions targeting patient-identified barriers to uptake and adherence are warranted (90, 93).

## 1.5 Kinesiophobia

Based on clinical experience, several patients with CAD are afraid to move their body after a cardiac event and consequently avoid physical activity and exercise. It has been shown in other patient groups that kinesiophobia has a negative influence on the outcome of rehabilitation (94-96). However, the impact on kinesiophobia by clinical variables and rehabilitation outcomes for patients with CAD has so far not been thoroughly investigated.

Kinesiophobia was introduced in the field of chronic pain in 1990 (97) and the most research has been performed in this area. Kinesiophobia was originally defined by Kori et al. as *“an excessive, irrational, and debilitating fear of movement and activity resulting from a feeling of vulnerability to painful injury or re-injury”* (97). The phenomenon has since been elaborated on by Vlaeyen et al. and alternatively described as *“fear of movement/(re)injury, a specific fear of movement and physical activity that is (wrongfully) assumed to cause re-injury”* (98).

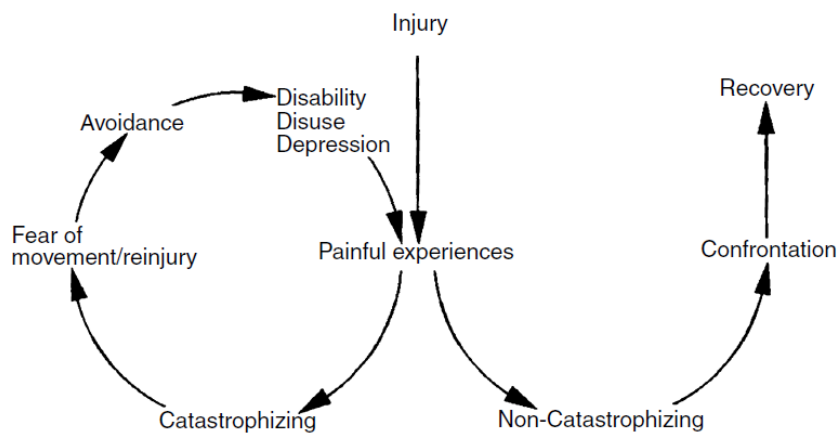
The terms “kinesiophobia” and “fear of movement” are used synonymously in the literature, although there is a psychological difference between them. Kinesiophobia is used in the most extreme form of fear of movement (97). An acute coronary event may be frightening and traumatic. So, in the acute stages after a cardiac event, fear and associated avoidance behaviours may be regarded as a normal psychological reaction. In patients with chronic pain, avoidance behaviour has been shown to be adaptive as a natural response to injury (99). Among these patients, there appears to be a group that, based on different factors, are unable to cope with their fear, which subsequently results in long-term avoidance behaviour with negative physical and psychological consequences (96, 98). Future studies are needed to investigate whether these findings also relate to patients with CAD. Since my interest was primarily to study excessive fear of movement after a coronary event, kinesiophobia was chosen as the conceptual definition in this thesis.

*Table 3. The original definitions of kinesiophobia and fear of movement*

<i>Kinesiophobia</i>	<i>Fear of movement/(re)injury</i>
An excessive, irrational and debilitating fear of movement and activity resulting from a feeling of vulnerability to painful injury or re-injury (Kori et al., 1990)	A specific fear of movement and physical activity that is (wrongfully) assumed to cause re-injury. (Vlaeyen et al., 1995)

### 1.5.1 Kinesiophobia and avoidance behaviour

In patients with chronic pain, kinesiophobia has often been described in relation to the cognitive-behavioural fear-avoidance model (98). It postulates two opposing behavioural responses to injury: confrontation and avoidance and presents possible pathways by which injured patients may increase avoidance behaviours. For the individual person, catastrophising, anxiety sensitivity and negative affectivity are examples of negative precursors to developing fear-avoidance behaviour (96, 100). In contrast, confrontation with daily activities and physical activity is likely to lead to fast recovery. Avoidance concepts have not been carefully evaluated in patients with CAD. However, it is reasonable to suppose that similar processes may operate and play an important role in cardiac rehabilitation. In accordance with the fear-avoidance model (98), confrontation with physical activity and fast referral to exercise-based cardiac rehabilitation appear to be essential after an acute coronary event, in order to stimulate recovery. There is therefore a need for future studies to identify patients with CAD, who run the risk of developing kinesiophobia and avoidance behaviours, and to explore appropriate treatment interventions.



*Figure 1. The cognitive-behavioral fear-avoidance model by Vlaeyen JWS, Kole-Snijders AMJ, Boeren RGB, van Eek H. Fear of movement/(re)injury in chronic low back pain and its relation to behavioral performance. Pain. 1995 Sept 62(3); 363-72. This figure has been reproduced with kind permission of the International Association for the Study of Pain® (IASP). The figure may not be reproduced for any other purpose without permission.*

## 1.5.2 Definitions of related constructs

Kinesiophobia is a construct rather than an actual disease or a pathological state (101). To establish kinesiophobia more firmly as a meaningful clinical concept for patients with CAD, it is important to distinguish it from other related constructs. A short overview and definition of relevant constructs will now be presented.

Fear and anxiety are strongly related. They are, however, separate and distinct constructs and it is important to understand their differences (101-103). Fear is defined as *“the usually unpleasant feeling that arises as a normal response to realistic danger”* (104). Fear is, however, not limited to the perceived threat of an object or situation that is external to the self. Individuals can also fear internal states related to somatic arousal or threats to the self-concept, like fear of a potential (re)injury (101). Anxiety, on the other hand, is *“the apprehensive anticipation of future danger or misfortune accompanied by a feeling of dysphoria or somatic symptoms of tension”* (105). Anxiety has also been described as *“a future-oriented state arising without any objective source of danger”* (104). The concept of anxiety is also elaborated in theories of personality, where anxiety is conceptualised as a personality trait (106). Trait anxiety indicates a habitual tendency to be anxious over a long period of time in many situations – *“I usually feel anxious”*. State anxiety refers to anxiety felt at a particular moment – *“I am anxious right now”* (104, 106).

Phobia is defined as *“fear of the situation that is out of proportion to its danger, can neither be explained nor reasoned away, is largely beyond voluntary control and leads to avoidance of the feared situation”* (104). In the Diagnostic and Statistical Manual of the American Psychiatric Association, fourth edition (DSM-IV) (105), a specific phobia is defined as a *“circumscribed, persistent and unreasonable fear of a particular object or situation”*. In relation to kinesiophobia, the excessive fear would be fear of movement. It is not known whether patients with an excessive fear of movement after a coronary event fully recognise the irrationality of their fears. In order clearly to establish the phobic phenomena in patients with CAD, further in-depth studies are suggested.

## Heart-specific constructs

Psychosocial risk factors, such as anxiety and depression, are highly prevalent in patients with CAD and are often associated with adverse cardiovascular outcomes and adverse effects on treatment adherence (80, 86, 87).

Kinesiophobia has not previously been described in relation to CAD. There are, however, two related constructs that are worth mentioning in this context; heart-focused anxiety and cardiophobia. Heart-focused anxiety is defined as *“The fear of cardiac-related stimuli and sensations based upon their perceived negative consequences”* (107). This construct was originally conceptualised as a psychological problem in individuals with non-cardiac chest pain (108). Heart-focused anxiety pertains to the fear of heart-related events, sensations and functioning and not particularly in relation to fear of movement.

For certain individuals with elevated heart-focused anxiety, the focused attention on their heart when experiencing physiological responses may persist and become similar to phobic responses that are out of proportion to true danger (108). These individuals continue to believe that they are suffering from an organic heart problem, despite repeated negative medical investigations. In order to reduce anxiety, they seek continuous reassurance from medical facilities and avoid activities believed to bring out symptoms. This condition has been described as cardiophobia and is defined as *“repeated complaints of chest pain, heart palpitations and other somatic sensations accompanied by fears of having a heart attack and of dying”* (108).

*Table 4. Definitions of constructs related to kinesiophobia*

Fear	The usually unpleasant feeling that arises as a normal response to realistic danger ( <i>Marks et al., 1987</i> )
Anxiety	The apprehensive anticipation of future danger or misfortune accompanied by a feeling of dysphoria or somatic symptoms of tension ( <i>First et al., DSM-IV, 2004</i> )
Phobia	Fear of the situation that is out of proportion to its danger, can be neither explained nor reasoned away, is largely beyond voluntary control and leads to avoidance of the feared situation ( <i>Marks et al., 1987</i> )
Specific phobia	A circumscribed, persistent and unreasonable fear of a particular object or situation ( <i>First et al., DSM-IV, 2004</i> )
Heart-focused anxiety	The fear of cardiac-related stimuli and sensations based upon their perceived negative consequences ( <i>Eifert et al., 2000</i> )
Cardiophobia	Characterised by repeated complaints of chest pain, heart palpitations and other somatic sensations accompanied by fears of having a heart attack and of dying ( <i>Eifert et al., 1992</i> )

### 1.5.3 The Tampa Scale for Kinesiophobia – Heart

Only one questionnaire, the Tampa Scale for Kinesiophobia (TSK), has been specifically designed to measure kinesiophobia (109, 110). The TSK was originally designed on the basis of clinical experiences from a pain clinic in order to discriminate between non-excessive fear and phobia in patients with persistent musculoskeletal pain (111, 112). A Swedish translation of the TSK (TSK-SV) is available; it is reliable for patients with persistent low back pain (113). The present thesis reports on a modified, heart-specific, version of the TSK (TSK-SV Heart) for patients with CAD (114). This questionnaire was designed to screen for kinesiophobia and the associated fear of physical rehabilitation or the consequences of physical rehabilitation.



### **The four sub-dimensions of TSK-SV Heart**

We believe that some important aspects have been neglected in previous studies of kinesiophobia in which the TSK has been used. The focus has often been fear avoidance, which is essential but not sufficient for investigations of kinesiophobia in the sense Kori et al. (97) originally conveyed. The TSK was designed before the introduction of Vlaeyen's fear-avoidance model in 1995 (98). So, to provide better prerequisites to screen for the perceptions and consequences of kinesiophobia, we propose four concepts based on the framework presented by Kori et al. (97) and on the DSM (105). The DSM describes a framework for typical mental imaginings and beliefs that occur with phobia of an object: the subject's perceptions of the object, the subject's avoidance of the object and the consequences for the subject of having a phobic relationship with the object.

The four sub-dimensions of the TSK-SV Heart were defined as:

- Perceived danger of heart problem (Danger)
- Fear of injury (Fear)
- Avoidance of exercise (Avoidance)
- Dysfunctional self (Dysfunction)

Of these, "Danger" and "Fear" are perceived as beliefs and mental imaginings, while "Avoidance" and "Dysfunction" are behaviourally oriented constructs.

### **1.5.4 Occurrence of kinesiophobia**

The occurrence of kinesiophobia in patients with CAD has not previously been studied. However, one study has shown that fear of exercise correlates with poor quality of life for patients with an implantable internal cardiac defibrillator (115). High levels of kinesiophobia have been found in several other patient groups, such as patients with persistent low back pain (94, 98, 112, 116), fibromyalgia (112, 117), osteoarthritis (112), chronic whiplash-associated disorder (118), upper extremity disorders (112), overuse injuries (119), postpartum lumbopelvic pain (120), cancer survivors (121) and anterior cruciate ligament injuries (122). Increased levels of kinesiophobia have also been shown in the general population (123) and among health-care providers (124).

### **1.5.5 Kinesiophobia and rehabilitation**

Even though there have been great advances in the application of exercise as a prominent part of the rehabilitation in patients with CAD, in clinical

practice, old recommendations to avoid exercise and physical activity still appear to influence the patients in their daily living (125).

Kinesiophobia has been shown to have a negative influence on the outcome of rehabilitation in patients with chronic pain (94-96) and is consequently of importance in the clinical situation and of significance for physiotherapists. More specifically, kinesiophobia is associated with impaired physical performance, increased self-reported disability and may predict future occupational disability (96, 118, 126-128). In patients with persistent pain, findings have indicated that scores on the TSK were better predictors of disability levels than pain intensity or biomedical findings (94, 111).

However, the impact on kinesiophobia by rehabilitation outcomes in patients with CAD has not previously been investigated. The presence of kinesiophobia and an associated fear of physical rehabilitation or the consequences of physical rehabilitation may theoretically prevent successful cardiac rehabilitation. In the core components of cardiac rehabilitation, it is stressed that all cardiac rehabilitation programmes should contain interventions to reduce disability and promote an active lifestyle (129). Furthermore, this guideline supports readiness to change behaviour and evaluate barriers to increased physical activity (129). The impact on kinesiophobia in cardiac rehabilitation thus needs to be further investigated.

## **1.6 The physiotherapeutic perspective in exercise-based cardiac rehabilitation**

In cardiac rehabilitation, exercise is regarded as a central part, associated with evidence-based positive health benefits (30, 67, 68, 79). Many of the risk factor improvements occurring in cardiac rehabilitation can be mediated through exercise programmes (83). Physiotherapists therefore play a fundamental role in cardiac rehabilitation when it comes to prescribing individually tailored exercise programmes, based on necessary skills of exercise physiology and according to current international guidelines (29, 35).

To date, current recommendations for the treatment of CAD have basically focused on increasing the “quantity” of life (130). This biomedical perspective is clearly important, but I believe that the addition of an holistic perspective of health will provide more information to optimise the management of CAD. By asking the right questions, more people with disabilities can be identified and treated. So, to be able to capture the complexity of cardiac rehabilitation, my original biomedical perspective was

extended to include a bio-psycho-social perspective of health. Likewise, physiotherapy has preferably been described in an holistic view of the patient, dividing the human being into three distinct yet inter-related entities – a biological being, a psychological being and a social being – examining all three and then adding them together to make a whole (131).

My main perspectives of the impact of exercise and physical activity in the secondary prevention and cardiac rehabilitation of CAD were extended to include the concept of kinesiophobia, as a factor with a potential influence on cardiac rehabilitation. To date, the role of kinesiophobia in cardiac rehabilitation has not been extensively described and it would benefit from future studies. However, kinesiophobia has been theoretically defined in relation to physiotherapy in previous literature (132). A short overview is provided in this thesis to increase coherence.

The stem *kinesis* in the word “kinesiophobia” means motion or movement. Moreover, the word emotion stems from the Latin *movere*, which means to act. Interestingly, the concept of kinesiophobia combines motion and emotion in the same word. Movement from a physiotherapeutic perspective is a central, multidimensional concept (133-135). The way in which physiotherapists conceptualise movement is what differentiates them from other health-care professions (134). As a short background, Hislop defined the central concepts of physiotherapy as human motion and the internal relationship from the tissue level to the person level (135). Furthermore, Tyni-Lenné presented the concepts of movement prerequisite, movement ability and movement behaviour (133). In a similar way, Cott et al. described “The Movement Continuum Theory”, which incorporates physical and pathological aspects of movement with social and psychological considerations (134).

According to the World Confederation of Physical Therapy (WCPT), physiotherapy includes developing, maintaining and restoring maximum movement and functional ability throughout the lifespan. Functional movement is central to what it means to be healthy. Physiotherapy is concerned with identifying and maximising quality of life and movement to encompass physical, psychological, emotional and social well-being (136). However, the scope of physiotherapy is dynamic and responsive to the patients. It is therefore important to ensure that physiotherapy in practice reflects the latest evidence base and continues to be consistent with current health needs.

## 1.7 International Classification of Functioning, Disability and Health

To capture the complexity of cardiac rehabilitation from a bio-psycho-social perspective, the International Classification of Functioning, Disability and Health (ICF) (137) was used as a theoretical framework to organise the outcome measures in the methodological section as well as in the discussion of the results.

The ICF was designed to record and organise a wide range of information about functioning and health (137). In the clinical context, it is intended for use in needs assessment, rehabilitation and outcome evaluation (138). My main perspective in this thesis was to focus on the impact of physical activity and exercise in relation to kinesiophobia and cardiac risk markers. The ICF categories presented in this thesis were not comprehensive, but I believe this approach is a first step in new ways of understanding the personal consequences of CAD within the complexity of exercise-based cardiac rehabilitation. New directions in therapeutic interventions might be developed.

The International Classification of Diseases (ICD) – 10th Revision contains a standard classification of health conditions, including diseases, disorders and injuries. The ICF complements the ICD-10 as a framework for describing and organising information on functioning and disability, associated with health conditions (137). The ICD-10 and the ICF together provide a more meaningful, complete picture of health. In scientific research, the ICF assists by supplying a structure for interdisciplinary research and for making results comparable. In the ICF, the term *functioning* refers to all bodily functions, activities and participation, while *disability* is similarly an umbrella term for impairments, activity limitations and participation restrictions.

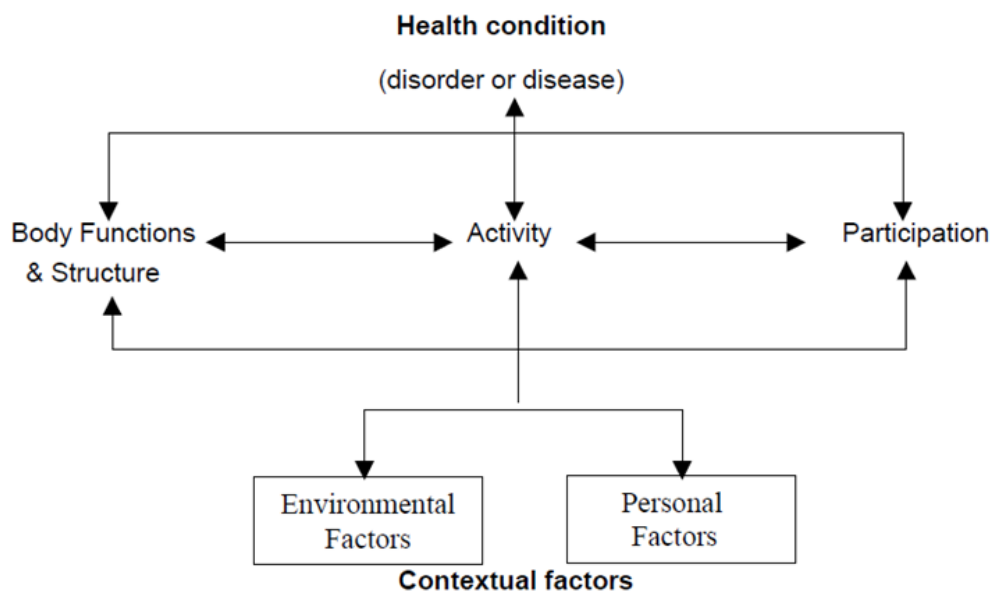
Functioning and disability are related to the following components of the ICF:

- The Body component includes a classification of body functions and body structures.
- Activities and participation contains all aspects of functioning from both individual and societal perspectives.
- Contextual factors include both personal and environmental factors. Environmental factors influence functioning and disability. Personal

factors, e.g. gender and age, are recognised but not classified in the ICF.

Under each of these components, there are hierarchically organised domains, which relate to physiological functioning, anatomical structure, actions, tasks, areas of life and external influences.

Figure 2 shows the ICF model and illustrates the dynamic interactions between the components.



*Figure 2. Adapted from WHO 2001. The International Classification of Functioning, Disability and Health (ICF). Interaction of the three levels of functioning classified by the ICF, including body functions and structures, activities and participation and contextual factors.*

## 2 AIM

The overall aim of this thesis was to study the impact of exercise and physical activity in relation to kinesiophobia and cardiac risk markers in patients with CAD.

The aims of the studies were:

- I. To evaluate the effects of high-frequency exercise before and after an elective PCI.
- II. To examine the level of physical activity and the association between physical activity and cardiac risk markers in patients with CAD.
- III. To investigate the validity and reliability of the Tampa Scale for Kinesiophobia Heart (TSK-SV Heart).
- IV. To describe the occurrence of kinesiophobia in patients with CAD and to explore the impact on kinesiophobia by clinical variables with an influence on rehabilitation outcomes.

## 3 PATIENTS AND METHODS

### 3.1 Study population

**Study I:** Thirty-seven patients with stable CAD from the waiting list for an elective PCI at Sahlgrenska University Hospital/Sahlgrenska (SU/S) were included. During the inclusion period between 2004 and 2006, 200 patients were available on the waiting list.

**Studies II-IV:** A total of 332 patients with a confirmed diagnosis of CAD were recruited between 2007 and 2009 at SU/S, a median of six months (range 3-10) after hospital discharge. In all, 1,465 patients were screened for evaluation, i.e. were hospitalised for CAD during the time of the study. Of these, 1,112 patients fulfilled the inclusion criteria. The reasons for exclusion are shown in Figure 3. The main reason for exclusion was a delayed evaluation >10 months after hospital discharge, caused by a lack of organisational capacity. The effective participation rate among the patients who were contacted (n=402) was 83%. The inclusion and exclusion criteria in Studies I-IV are described in Table 5. A comparison between included and excluded patients is presented in Table 6.

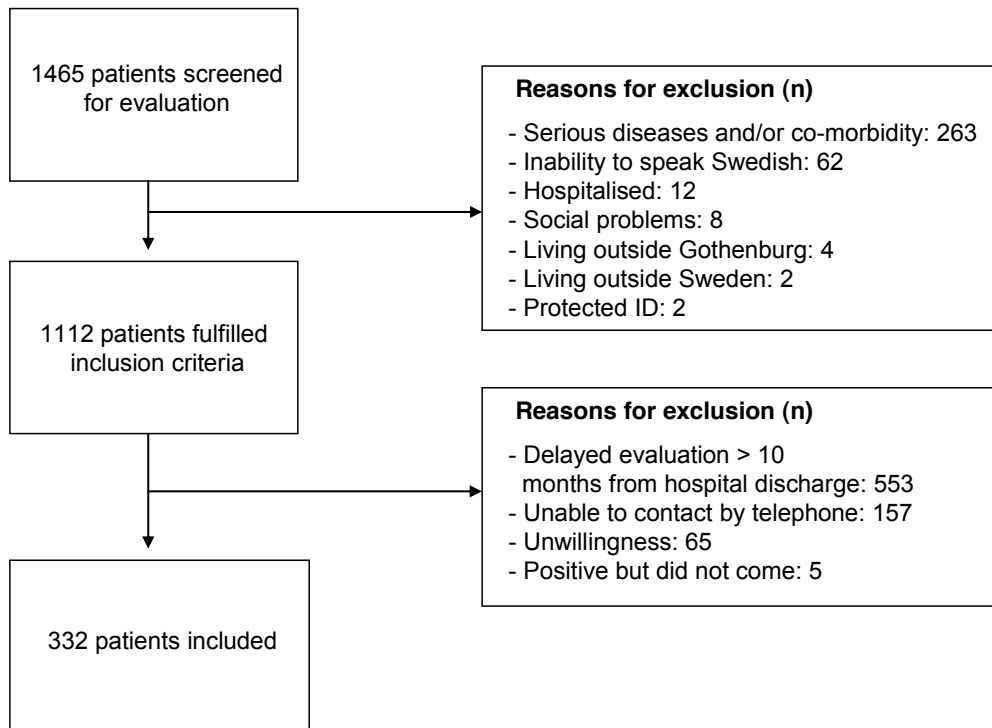


Figure 3. Flow chart of included patients in Studies II-IV

*Table 5. Inclusion and exclusion criteria in Studies I-IV*

	Inclusion criteria	Exclusion criteria
Study I	<ul style="list-style-type: none"> <li>– Coronary artery stenosis documented by angiography or previous CABG</li> <li>– Angina pectoris, CCS class I-III</li> </ul>	<ul style="list-style-type: none"> <li>– Serious diseases or disabilities interfering with regular exercise on a bicycle ergometer</li> <li>– Exercise <math>\geq 3</math> days/week</li> <li>– Inability to understand the Swedish language</li> </ul>
Studies II- IV	<ul style="list-style-type: none"> <li>– Principal diagnosis of CAD, documented by coronary angiography either prior to or at the time of hospitalisation</li> </ul>	<ul style="list-style-type: none"> <li>– Death during the hospital period</li> <li>– Serious diseases interfering with participation</li> <li>– Inability to understand the Swedish language</li> <li>– Time lapse <math>&gt; 10</math> months from hospital discharge</li> </ul>

CABG, coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; CAD, coronary artery disease



*Table 6. A comparison of included and excluded patients in Studies II-IV*

	Internal missing (included/excluded)	Included n=332	Excluded n=1133	p-value
Age (years)				
Mean±1SD		64±9	68±12	<0.001
Gender (%)				
Female		23	31	0.005
Tobacco use				
Smoking	0/136	19	26	0.008
Medical history (%)				
Angina pectoris	0/7	48	48	0.901
Diabetes	0/3	17	24	0.011
Myocardial infarction	0/8	30	30	0.892
Heart failure	0/9	6	11	0.012
Hypertension	0/6	47	45	0.573
Type of CAD	0/2			<0.001
STEMI		30	20	
Non-STEMI		16	30	
Unstable angina pectoris		37	18	
Stable angina pectoris		17	32	

SD, standard deviation; CAD, coronary artery disease; STEMI, ST-elevation myocardial infarction

## 3.2 Study design

Study I: Randomised controlled trial (RCT)

Studies II-IV: Descriptive, cross-sectional design

### 3.3 Procedure

**Study I:** After the medical recruitment process, the patients were contacted by a study nurse and asked to participate in the study. Patients were randomised using a 1:1 ratio to either exercise (n=21) or the control group (n=16). The study was designed to contain 60 patients. However, due to an upcoming absence of waiting time for elective PCI interventions during the study, it was difficult to include new patients who wanted to exercise prior to the PCI. We therefore had to stop the inclusion at 37 patients. The included patients were assessed on three different occasions.

*Test occasion one (T1):* At baseline, two months before PCI. T1 included a maximum exercise test, followed by measurements of HRQoL, muscle endurance tests and WHR after a few days.

*Test occasion two (T2):* One week after PCI. The tests that were performed were identical to T1, except for the maximum exercise test, which was accomplished three months after the PCI.

*Test occasion three (T3):* One week after the control angiography/PCI. The tests that were performed were equivalent to T1.

**Study II:** A study nurse contacted and informed the patients about the study by telephone. If the patient was interested, a visit to the study nurse was arranged. Patients were investigated with regard to blood sampling, blood pressure monitoring and a detailed history of smoking. In addition, a visit to a physiotherapist at the physiotherapy department was organised within the next few days and the patients were tested for muscle endurance, level of physical activity and WHR.

**Study III:** The TSK-SV Heart was tested according to the following procedure. The items from the original version of the TSK-SV were adapted to patients with CAD and subsequent analyses of validity and reliability were performed. The TSK-SV Heart was translated back and forth into English by a professional translator.

**Study IV:** A study nurse contacted and informed the patients about the study by telephone. If the patient was interested in participating in the study, a visit to a physiotherapist at the physiotherapy department was arranged within the next few days and tests with reference to kinesiophobia, HRQoL, anxiety and depression, WHR, muscle endurance and level of physical activity were conducted.

## 3.4 Intervention programme

### Aerobic exercise

The patients in the exercise group were asked to exercise at home on a bicycle ergometer (Monark 915E, Monark exercise AB, Varberg, Sweden) for 30 minutes (including a 10-minute warm-up and five-minute cool-down), five days a week for eight months. The patients exercised for two months before the PCI and six months after the PCI. The exercise intensity was designed according to the Borg RPE scale (13-15 on scale  $\approx$  60-80% of  $\text{VO}_{2\text{max}}$ ) (34). The patients in the exercise group were tested once a month during the intervention period at a submaximum level by a physiotherapist on a bicycle ergometer, to upgrade the intensity level. Twice a week, the patients were allowed to exchange cycling for an equivalent exercise such as jogging or swimming. The patients described their exercises in a training diary.

### Resistance exercise

In addition, resistance exercise with elastic bands (resistance exercise band, Jpm products, Hertfordshire, United Kingdom), including unilateral shoulder flexion, unilateral shoulder abduction and bilateral rowing, was performed three times a week. In addition, one set of maximum unilateral heel lifts was accomplished three times a week. The resistance of the elastic band was determined and adjusted after performing 10 repetitions maximum (33). The patients performed each exercise with three sets of 10 repetitions with an intensity level of 75% of 1 repetition maximum.

### Control group

Patients in the control group were asked to live as usual. The patients in both groups were invited to participate in the cardiac rehabilitation programme at SU/S, consisting of individually adapted group-based exercise twice a week. Each exercise session included aerobic exercise for 30 minutes (intensity 13-15 on Borg-scale) and resistance exercise (10-15 repetitions of 1-2 set of 8-10 different exercises). Two patients in the control group and none in the exercise group accepted this offer.

*Table 7. Overview of the exercise programme in Study I*

Aerobic exercise	Resistance exercise
F = 5 days/week I = 13-15 on Borg scale, i.e. 60-80% of $VO_{2max}$ T = 30 min M = continuous on bicycle ergometer (could be exchanged twice/week for equivalent exercise) P = submaximum ergometer bicycle test once a month to upgrade intensity level	F = 3 days/week I = 75% of 1 RM R = 10 repetitions per set D = 3 sets of three different upper body exercises P = determined and adjusted once a month after performing 10 RM  One set of maximum unilateral heel lifts was accomplished three times a week

F, frequency; I, intensity; T, duration; M, modality; P, progression; R, repetitions;  $VO_{2max}$ , maximum oxygen uptake; RM, repetition maximum

## 3.5 Measurements

The measurements are presented according to the framework of the ICF.

### 3.5.1 Body functions

#### Anxiety and depression

Anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS) (139). This scale is a 14-item self-report comprising seven anxiety and seven depression items, from which separate anxiety and depression scores are calculated. The items are scored on a four-point Likert scale, ranging from 0-3 points. The HADS has been widely applied and is considered reliable and valid for use in medical and primary care, including patients with CAD (140-142).

#### Cardiac risk markers

##### Body mass index

Body mass index (BMI) was calculated as the weight in kilograms divided by the height in square metres ( $kg/m^2$ ).

##### Oral glucose tolerance test

Hemocue Glucose 201+ was used for analysis (143). After an overnight fast, the patient drank 75g of glucose dissolved in water. Blood samples for

glucose measurements were obtained before and one and two hours respectively after glucose load.

#### **Serum lipids**

After an overnight fast, blood samples to measure total cholesterol, LDL-C, HDL-C and triglycerides were taken. Venous blood was analysed with an enzymatic photometric method, 505 nm at 37°C.

#### **Smoking**

Current smoking was defined as daily or occasional smoking. Ex-smoking status was confirmed by an expired carbon monoxide level of 10 ppm or less.

#### **Twenty-four-hour blood pressure and heart rate monitoring**

Blood pressure and heart rate were recorded every 20 min between 6 am and 10 pm and once an hour between 10 pm and 6 am. Spacelabs equipment was used (144).

#### **Waist-hip ratio**

The waist-hip ratio (WHR) was measured at the smallest section of the waistline. Hip circumference was measured over the widest part of the gluteal region. The WHR was calculated by dividing the waist circumference by the hip circumference (145).

#### **Maximum aerobic capacity**

A maximum exercise test on an electronically braked cycle ergometer (Schiller ERG 500S, Schiller AG, Baar, Switzerland) was performed, with watts as the marker of maximum aerobic capacity. The test was performed using a ramp protocol with a 10W increase every minute until exhaustion or signs of pronounced cardiac ischemia. Men started at 50W and women at 30W and a pedalling rate at 60 rates per minute was used. Subjective symptoms such as chest pain and fatigue were assessed with a 0-10 graded scale (Borg's Category Ratio Scale; CR-10 scale) (38). Exercise testing is a well-established, safe procedure that is frequently used in clinical practice. It has been considered to be an important tool after a coronary event to develop and modify the exercise prescription (146, 147).

#### **Muscle endurance**

Muscle endurance was evaluated by three clinical endurance tests, described in detail below. The reliability of these tests has been found to be good for patients with chronic heart failure (148).

#### **Unilateral isotonic heel lift**

The patients performed a maximum heel lift on a 10° tilted wedge, one lift

every other second, with pace held by a metronome (Taktell, Germany). The contralateral foot was held slightly above the floor and, for balance, the wall was touched with the fingertips. The number of maximum heel lifts was counted for each leg.

#### **Unilateral isotonic shoulder flexion**

The patients sat comfortably on a chair, with their back touching the wall, holding a dumbbell (2 kg for women and 3 kg for men) in the dominant hand. The patients were asked to elevate their shoulder from 0° to 90° flexion as many times as possible, using a pace of 20 contractions per minute kept by a metronome (Taktell, Germany).

#### **Bilateral isometric shoulder abduction**

The patients sat comfortably on a chair, with their back touching the wall and with a 1 kg dumbbell in each hand. They were asked to elevate both shoulders to 90° abduction and to hold this position as long as possible. The time in seconds the patients were able to keep their shoulders in 90° abduction was recorded. The patients were given one warning if their arms were descending from 90° abduction, before the test was stopped.

### **Kinesiophobia**

The Swedish version of the TSK-SV Heart was used to measure kinesiophobia (114). The TSK-SV Heart comprises 17 items assessing the subjective rating of kinesiophobia. Each item is rated on a 4-point Likert scale with scoring alternatives ranging from “strongly disagree” (score 1) to “strongly agree” (score 4). A total sum is calculated after the reversion of items 4, 8, 12 and 16. The total score varies between 17 and 68. A high value indicates a high level of kinesiophobia. A cut-off point of > 37 has been defined as a high level of kinesiophobia (111). The TSK-SV Heart includes four constructs; two behaviourally oriented constructs “Avoidance of exercise” (items 2, 4, 12, 14, 17) and “Dysfunctional self” (items 5, 6, 10, 15), relating to possible irrational perceptions and beliefs about rehabilitation, while two constructs are concerned with beliefs and mental imaginings, “Perceived danger of heart problem” (items 3, 8, 11, 16) and “Fear of injury” (items 1, 7, 9, 13). The TSK-SV Heart has been found to be sufficiently reliable and valid for patients with CAD (114).

### **Restenosis**

In Study I, a coronary angiography was performed at T1. A control angiography was performed at T3. In the event of a significant restenosis, ad-hoc PCI was performed. The stenosis was considered significant if the

diameter of the tightest part of the stenosis was  $< 50\%$  of the mean diameter of the proximal and distal reference segments.

### **3.5.2 Activities and participation**

The level of physical activity was measured with the following three tests over the seven-day period.

#### **Activity diary**

Patients recorded daily physical activity in a diary constructed by the authors. Each day, the patients noted the type of activity, duration (minimum bout of 10 minutes) and intensity according to the RPE scale constructed by Borg (38). Physical activity was classified into total general activity, low level of activity ( $\text{RPE} \leq 11$ ), medium level of activity ( $\text{RPE} 12-13$ ) and high level of activity ( $\text{RPE} \geq 14$ ), according to guidelines from the ACSM (34).

#### **International Physical Activity Questionnaire**

The short form of the International Physical Activity Questionnaire (IPAQ) was administered (149). This questionnaire comprises nine items that provide information on the time spent walking, during moderate- and vigorous-intensity activity as well as sedentary activity. Total weekly physical activity was estimated by weighting the reported minutes per week within each activity by a metabolic equivalent (MET) energy expenditure estimate assigned to each category of activity. One MET is defined as a  $\text{VO}_2$  of  $3.5 \text{ mL} \times \text{kg}^{-1} \times \text{min}^{-1}$ , which corresponds to the resting metabolic rate (150). The IPAQ form can also be classified as a categorical variable, identifying three levels of physical activity (1=low, 2=medium, 3=high). The IPAQ has been shown to be reliable and valid in an international study conducted in 12 countries (149) and the criterion validity is acceptable for use in healthy Swedish adults (151). In addition, it has been suggested that the IPAQ successfully estimates  $\text{VO}_{2\text{max}}$ , as well as submaximum exercise testing in college-aged males and females (152).

#### **Pedometer**

The patients were asked to wear a hip-borne pedometer (Keep walking LS 2000, Keep Walking Scandinavia AB, Kalmar, Sweden) for seven consecutive days. The result was converted to average steps per day (total steps during a week/7). The pedometer used in this thesis has been shown to be one of the most accurate and suitable for research (153).

### **3.5.3 Personal factors**

#### **Gender and age**

Gender and age were used in descriptive characteristics in all studies, as well as in comparisons between groups (Study IV). However, gender or age perspectives were not a direct focal point in this thesis.

### **3.5.4 Health-related quality of life**

#### **Short-Form 36**

Health-related quality of life (HRQoL) was measured using the Short-Form-36 (SF-36) (154). The SF-36 is a generic, psychometrically sound instrument, comprising 36 items across eight dimensions: physical functioning (PF), role limitations due to physical problems (RP), bodily pain (BP), general health perceptions (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (RE) and mental health (MH). The responses to each question within a dimension are combined to generate a score from 0 to 100, with higher scores indicating better health. In addition, the questionnaire comprises two distinct higher-ordered factors related to physical health (PF, RP, BP, GH) and mental health (VT, SF, RE, MH). The SF-36 has been widely used in various countries with different population groups (155). The Swedish version of the SF-36 has shown good reliability and construct validity across general populations (156). Furthermore, the SF-36 has established reliability and validity for patients with CAD (157).



*Table 8. Description of the variables used in Studies I-IV*

Variables	Measures	Study			
		I	II	III	IV
Body functions					
Anxiety	Hospital Anxiety and Depression Scale			•	•
Body mass index	Body weight/body length <sup>2</sup>		•		
Depression	Hospital Anxiety and Depression Scale			•	•
Kinesiophobia	Tampa Scale for Kinesiophobia Heart			•	•
Maximum aerobic capacity	Maximum exercise test	•			
Muscle endurance	Shoulder flexion, heel lift right, heel lift left, shoulder abduction	•	•	•	•
Oral glucose tolerance test	Oral intake of 75 g glucose		•		
Restenosis	Coronary angiography	•			
Serum lipids	Total cholesterol, LDL-C, HDL-C, triglycerides		•		
Smoking			•	•	•
Twenty-four-hour blood pressure	Blood pressure recording		•		
Twenty-four-hour heart rate	Heart rate recording		•		
Waist-hip ratio	Waist circumference/hip circumference	•	•		•
Activities and participation					
<i>Level of physical activity</i>					
METs x min/week	International Physical Activity Questionnaire		•	•	•
Minutes/week	Activity diary		•		•
Steps/day	Pedometer		•		•
Personal factors					
Gender	Men/women, n (%)	•	•	•	•
Health-related quality of life	Short-Form 36	•		•	•

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; MET, metabolic equivalent

## 3.6 Psychometrics

Psychometrics is the field of study concerned with the theory and technique of psychological measurement. The field focuses primarily on the construction and validation of measurement instruments (158). Most abstract constructs must be defined as a function of multiple dimensions or interrelated concepts. It is important to remember, however, that all constructs, such as kinesiophobia, have been operationally defined by researchers (97). In research and clinical practice, it is important to use psychometrically sound instruments (159). For clarity, reliability and validity are described in two different sections in this thesis. In addition, the statistical analyses will be presented in relation to each method.

### 3.6.1 Reliability

The usefulness of measurements in clinical research depends on the extent to which the data can be relied upon as accurate (158, 159). The first prerequisite is reliability, or the extent to which a measurement is consistent and free from error. Reliability is basically a question of the ability of a test to yield the same result under similar test conditions, i.e. the repeatability of observations (158-160). Reliability is based on the theory of measurement error, defined as the difference between the true value and the observed value (158, 161). Measurement error can be a combination of systematic errors and random errors. The focus of reliability is the degree of random error that is present within a measurement. As random errors diminish, the observed score moves closer to the true score and the measurement is subsequently more reliable (158, 159, 161). For this reason, reliability is a ratio of the true score variance to the total variance, yielding the reliability coefficient ranging between 0 and 1. The measurements of reliability included in relation to the TSK-SV Heart in this thesis were stability over time, internal consistency and composite reliability, briefly described below.

#### Stability over time

The reliability of a test over time is known as test-retest reliability (160). This method involves the re-administration of a test to the same group on a second occasion. If the two sets of scores are highly correlated, random error may be minimal (162). The time interval between tests must be carefully considered, i.e. intervals should be far enough apart to avoid learning or memory effects but close enough to avoid genuine changes in the measured variable (158, 161). Stability in the response variable and the intended purpose of the test must be assumed. For example, trait measures are intended to have high test-retest reliability, but state measures are not (158, 159). In the present thesis,

an interval of two weeks between administrations of the TSK-SV Heart was used.

### Statistical analyses

For the analysis of test-retest reliability, the Intraclass Correlation Coefficient (ICC) was calculated (158). This index reflects both correlation and agreement, by estimating the average correlation between all possible ordering of pairs. Moreover, a Bland-Altman plot of the difference against mean of test-retest values was performed. This analysis included calculations of limits of agreement equal to the mean difference  $\pm$  twice the standard error (163).

### Internal consistency

Internal consistency describes estimates of reliability on the average correlation among items within a test (158-160). In general, it is desirable to see some relationship between items, especially if the scale score is added up.

### Statistical analyses

To measure internal consistency, Cronbach's alpha statistics were calculated for the 17 items in the TSK-SV Heart (164). Cronbach's alpha can be written as a function of the number of test items and the average inter-item correlation between the items (158, 159, 162). If the inter-item correlations are high, the items measure the same unidimensional latent construct. However, it must be noted that Cronbach's alpha says nothing about multiple-factor item structures (159, 165).

Internal consistency was also examined by the item-total correlation coefficient, measuring how each individual item is correlated with the total score, omitting that item from the total. If a questionnaire is homogeneous, these correlations are expected to be high (158, 160).

### Composite reliability

In addition to the analysis of internal consistency, it is advantageous to estimate the composite reliability of factor (construct) measurement (166). Composite reliability is a ratio of true composite variance (latent variables) to observed composite (items) variance of scores (162, 166). In this approach, the reliability coefficient is independent of the underlying dimensionality of the composite. The scale used for analysis could be assumed to be non-congeneric (non-homogeneous scale). Basically, this means that a single reliability measure can be calculated for different subscales (166). Consequently, this method provides an approach for the point and interval estimation of the reliability of a general structure composite that may involve more than a single source of latent variability (162, 166).

### Statistical analysis

Composite reliability was analysed according to a procedure, described by Raykov and Shrout (1997), for a scale with different subsets of items.

## 3.6.2 Validity

Measurement validity relates to the extent to which an instrument measures what it is intended to measure (158-160). Validity places the emphasis on the objectives of a test and the ability to make inferences from the test result. Validity is not a universal characteristic of an instrument. It must be evaluated in the context of the intended purpose of the test and in relation to a specific population (158-160). In other words, the use to which an instrument is put rather than the instrument itself is validated (159). Measurement inferences are difficult to verify and establishing validity is therefore not as straightforward as determining reliability. Validity is a characteristic that an instrument has to some degree or other (158, 160). Dealing with abstract constructs, the investigation of test validity remains ongoing. In order properly to assess the validity of a test, a set of findings have to be taken into account (158, 159). To investigate the validity of the TSK-SV Heart in this thesis, face validity, content validity and construct validity were investigated.

### Face validity

Face validity indicates that an instrument appears to test what it is supposed to (158-160). Usually, the judgement of face validity is performed by the people who are going to administer the questionnaire (158). The advantage of established face validity is the increased motivation and acceptability of the respondents, which is important in order to answer questions with accuracy and honesty (158-160). Face validity is the weakest form of validity and it cannot be considered sufficient. There is no standard for judging it or determining “how much” face validity an instrument has (158-160). In the current thesis (Study III), 10 patients with CAD and five experts (physiotherapists with experience of working with patients with CAD within cardiac rehabilitation) were asked to give their opinion of the face validity of the TSK-SV Heart.

### Content validity

Content validity implies that the items that make up an instrument adequately sample the universe of content that defines the variable being measured (158). An instrument is suggested to have content validity if it contains every part of the variable being studied and reflects the relative importance of each part. Content validity therefore also requires that an instrument is free from the influence of factors that are irrelevant to the purpose of the measurement

(158-160). The assessment of content validity is usually made by a panel of experts who review the instrument and determine whether the items satisfy the content domain (158). Content validity, in the present thesis (Study III), was assessed by five experts (physiotherapists with experience of working with patients with CAD within cardiac rehabilitation). They reviewed the TSK-SV Heart through a pre-printed form.

### **Construct validity**

Construct validity establishes the ability of an instrument to measure an abstract construct and the degree to which the instrument reflects the theoretical components of the construct (158, 162). The construct under investigation in this thesis was kinesiophobia measured by the TSK-SV Heart. Furthermore, construct validity determines whether a supposed measure of a construct correlates in the expected ways with measures of other constructs (159). Construct validation provides evidence to support or refute the theoretical framework behind the construct and is an ongoing process. There is no single, definitive test of construct validity. Instead, numerous research approaches relating to particular facets are suggested. Moreover, the relative importance of these facets depends on the context, content and goals of measurement (158, 160, 162).

In this thesis, construct validity was investigated in two phases. Firstly, the TSK-SV Heart was conceived as a theoretical concept with four sub-dimensions. A model for this concept was based on a second-order confirmatory factor analysis (CFA). In addition, the proposed four-factor model was compared with a frequently used two-factor model (167) based on 11 items (168). Secondly, four composite constructs were created and used separately as dependent variables in multiple regressions on nine sets of independent variables. These sets comprised demographics (gender, age), medical focus (cardiac rehabilitation, heart failure and muscle endurance), physical activities, health-related quality of life, anxiety and depression. The CFA method will be described briefly below.

### **Confirmatory factor analysis**

The method of CFA analyses a priori measurement model in which both the number of factors and their correspondence with the indicators are clearly specified (162). The goal of CFA is to see how well proposed factors explain the data (159). Hierarchical CFA describes at least one construct as a second-order factor that is not directly measured by any indicator. This exogenous (independent) second-order factor is presumed to have direct effects on the first-order factors, which have indicators.

Basically, three steps of CFA were performed in this thesis: (a) screening for influential cases, (b) tests of the second-order model and (c) revising the model.

The choice of the second-order CFA model was based on a hierarchy of constructs of kinesiophobia. The four constructs (Danger, Avoidance, Fear and Dysfunction) were first-order latent indicators to the construct of kinesiophobia and were at the same time superior constructs of the 17 items of the TSK-SV Heart. Moreover, the first-order latent (reflective) variables were assumed to be uncorrelated in the model, as were the residuals of the items within each construct. The following items were included in each of the constructs: Danger (3,8,11,16), Fear (1,7,9,13), Avoidance (2,4,12,14,17) and Dysfunction (5,6,10,15). The factor loadings for the first-order constructs were controlled for type 1 errors using a Bonferroni correction at the 5% significance level (169).

### *Model fit*

Maximum likelihood estimation, which calculates the probability of obtaining the observed data, was performed. The estimates are the ones that maximise the likelihood that the data were drawn from this population (162). A number of fit calculations were employed in testing the fit of the proposed model to the empirical data.

1. A  $\chi^2$  test with maximum likelihood parameter estimation robust to non-normality was used (MLMV estimator mean- and variance-adjusted maximum likelihood). The  $\chi^2$  statistic is a goodness-of-fit measure that investigates the magnitude of the discrepancy between the sample covariance matrix and the estimated covariance matrix (170). A large, statistically significant value of the  $\chi^2$  in relation to its degrees of freedom indicates a poor model fit. However, it must be noted that the  $\chi^2$  statistic is sensitive to sample size (162).
2. Approximate fit indices were reported to supplement a failed  $\chi^2$  test. These were the comparative fit index (CFI) and root mean square error of approximation (RMSEA). The CFI is an incremental fit index, while RMSEA is a measure of the discrepancy per degree of freedom for the model. For a good fit between the hypothesised model and the observed data, cut-off values that are frequently suggested are close to 0.95 and 0.06 for the CFI and RMSEA respectively (170).
3. In addition, factor determinacy, reflecting the correlation between the estimated and true factor score, was reported (171).

### *Influential cases*

In order to enhance external validity, a model-based selection of influential cases was made (172). Each case was tested with respect to its contribution to model fit. If the removal of a case improved the model  $\chi^2$  fit by at least 3.8, it was classified as an influential case.

## **3.7 Statistical analyses**

Data were computerised and analysed using the Statistical Package Software for the Social Sciences (SPSS version 11.5-20.0, Chicago, IL, USA). In Study II, adjusted correlations between steps/day and cardiac risk markers were analysed using Statistical Analysis Software (SAS 9.2, North Carolina, USA). The computation of composite reliability and the CFA model in Study III was performed with Mplus, version 6, (Muthén & Muthén, Los Angeles, CA, USA). All the tests were two sided and considered statistically significant if  $p < 0.05$ . An overview of the statistical methods used in this thesis is presented in Table 9.

### **Descriptive statistics**

Descriptive statistics were used for demographic data. Continuous variables (ratio and interval data) were presented as median and inter-quartile range (IQR) in Studies I and II. In Study I, data for the SF-36 were presented as the mean  $\pm$  one standard deviation (1SD). The normal frequency distributed ratio and interval data were presented as the mean  $\pm$  1SD, in Studies III and IV. A complementary median and IQR were presented for skewed data (skewness  $>2$ ) in Study IV. For nominal data (categorical variables), absolute or relative numbers (%) or both were described in all studies.

### **Differences within and between groups**

In Study I, Wilcoxon's rank sum test was used for comparisons of paired observations within each study group (exercise and control group), while differences between groups were tested with a Mann-Whitney U-test. A sample size calculation was performed for watts ( $\beta$ -value of 0.80 and  $\alpha$ -value of 0.05). The least mean difference was set at 11 watts and the mean SD at 9 watts. Data were analysed both according to an intention-to-treat (ITT) design (last value carried forward) and with a per protocol analysis. In Study IV, differences between a high versus a low level of kinesiophobia were tested with a Student's t-test for interval data and Pearson's chi-square for independence for nominal data. For comparisons between included and excluded patients in Studies II-IV (reported in the thesis), a Fisher's exact test and a Mann-Whitney U-test were used for categorical and continuous data respectively.

*Table 9. Overview of the statistical methods used in this thesis*

Statistical methods	Study			
	I	II	III	IV
<b>Descriptive statistics</b>				
Mean (1SD)	•		•	•
Median (inter-quartile range)	•	•		•
Proportions (absolute numbers and/or %)	•	•	•	•
<b>Differences within and between groups</b>				
Wilcoxon's rank sum test	•			
Mann-Whitney U-test	•	•		
Student's t-test				•
Pearson's chi-square test for independence				•
<b>Power calculation</b>	•			
<b>Association</b>				
Spearman's rank order correlation		•		
Spearman's partial rank order correlation		•		
Binary logistic regression				•
<b>Reliability</b>				
Composite reliability			•	
Cronbach's alpha			•	
Item-total correlation coefficient			•	
Intraclass Correlation Coefficient			•	
Bland-Altman plot			•	
<b>Validity</b>				
<i>Confirmatory factor analysis:</i>				
Maximum likelihood parameter estimation (MLMV):				
$\chi^2$ -statistic			•	
Comparative fit index (CFI)				
Root mean square error of approximation (RMSEA)				
<i>Construct validity related to external measures:</i>				
Regression analysis			•	

SD, standard deviation; MLMV, mean- and variance-adjusted maximum likelihood



## Correlation

In Study II, the association between steps/day and baseline characteristics was tested using the Mann-Whitney U-test and Spearman's rank order statistic for categorical variables and continuous variables respectively. Correlations with cardiac risk indicators were assessed using Spearman's partial rank order correlation, where adjustments were made for characteristics univariately associated ( $p < 0.05$ ) with both pedometer steps/day and the variable in question. The correlations were interpreted according to Cohen ( $\rho$  0.10 to 0.29 = small,  $\rho$  0.30 to 0.49 = medium,  $\rho$  0.50 to 1.0 = large) (173). Correlations between the measures of physical activity (pedometer, IPAQ and activity diary) were included in the thesis to be able to discuss the validity of the measurements.

## Binary logistic regression

In Study IV, binary logistic regression analyses were performed with the dichotomised TSK ( $> 37$  defined as a high level of kinesiophobia) as the dependent variable and the observed 42 clinical variables (ICF variables) as independent variables. The independent variables consisted of 16 categorical (nominal and ordinal) and 26 continuous variables. The regression analyses were performed in two steps. Firstly, using a likelihood ratio test, the difference can be analysed between a full model (including all 42 variables) and a reduced model, by omitting a variable from the full model. If the difference had a p-value of  $< 0.10$ , the corresponding variable was selected for further analysis. Secondly, the selected variables were included in a final model. This model was subjected to different analyses of the detection of influential cases, estimation of parameters and different model of fit.

## Missing value analyses

Internal missing refers to missing values in the data set, i.e. incomplete cases. A few missing values, such as less than 5% on a single variable, in a large sample, may be of little concern (162). This is especially true if the reason for missing values can be ignored, which means that it is not systematic. On the other hand, a systematic data loss pattern means that incomplete cases differ from cases with complete records for some reason, rather than randomly (162). Pairwise deletion refers to cases that are excluded only if they have missing data for variables involved in a particular analysis. This method was used in all the analyses in Study II, descriptive statistics in Study III and for pairwise differences between high and low levels of kinesiophobia in Study IV. Multiple imputation methods that take advantage of the structure in the data were used in Studies III and IV. In Study III, the choice of MLMV estimation of the CFA model was combined with an expectation maximisation algorithm (Little's missing completely random (MCAR) test)

(174). In Study IV, by using multiple imputations, all cases could be used in the regression analyses. This imputation procedure was based on a combination of two methods: a monotone method for data with a monotone pattern of missingness and an iterative Markov Chain Monte Carlo (MCMC) method for data with an arbitrary missing pattern (162).

## **3.8 Ethical considerations**

Informed written consent was obtained from all participants prior to participation in the study and they were allowed to withdraw at any point without giving a reason. The regional ethical review board in Gothenburg approved the research protocols (number of approved protocols: 524-02 and 099-07).

## 4 RESULTS

The main findings from Studies I-IV are presented.

### 4.1 High-frequency exercise before and after an elective PCI (Study I)

The exercise programme was well tolerated and there were no serious adverse events. The adherence rate for the prescribed exercise programme remained high. Eighteen of the twenty-one patients in the exercise group completed the trial. Three withdrew from the study: one due to restless leg syndrome, another underwent coronary artery bypass grafting (CABG) instead of a PCI and the third withdrew because of lack of motivation to exercise. All sixteen patients in the control group completed the study. The ITT and per protocol analyses revealed no differences in significance level.

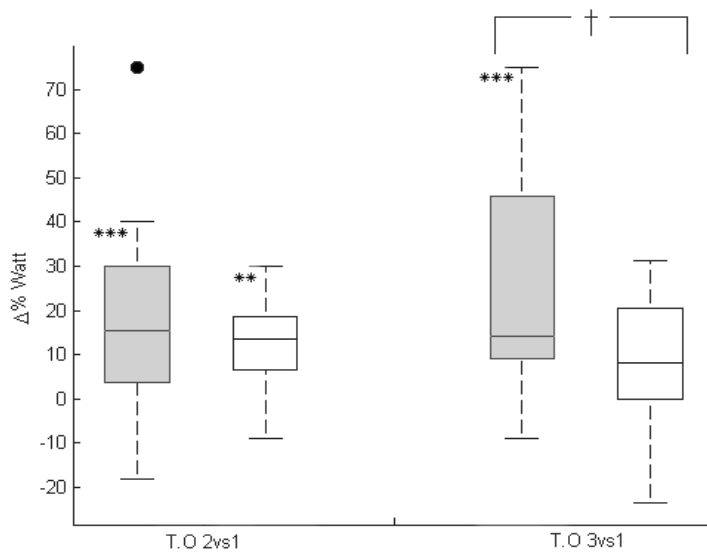


Figure 4. T1: Two months before PCI; T2: Three months after PCI; T3: Six months after PCI. Changes in maximum aerobic capacity achieved after exercise. Filled bars, exercise group (n, 21 before exercise period and n, 18 after exercise period). Empty bars, control group (n, 15 before control period and n, 16 after control period). Data are given as box plots, in which the box encompasses the 25th to 75th percentile, the middle line is the median. Whiskers represent the 10th and 90th percentile and dots are values outside this range. \*\*  $p \leq 0.01$ , \*\*\*  $p \leq 0.001$  within-group comparison with baseline in patients with PCI, †  $p \leq 0.05$  in difference between groups; T.O, test occasion

## Primary effect variable

### *Maximum aerobic capacity*

The exercise group showed a significant ( $p \leq 0.05$ ) improvement at T3 compared with the control group. There was a significant ( $p \leq 0.001$ ) improvement at T2 in both groups ( $p \leq 0.01$ ). At T3, there was a significant ( $p \leq 0.001$ ) improvement in the exercise group but not in the control group (Figure 4).

## Secondary effect variables

### *Muscle function*

Compared with the control group, there was a significant improvement in the exercise group regarding shoulder flexion ( $p \leq 0.01$ ), shoulder abduction ( $p \leq 0.01$ ) and heel lift in the right leg ( $p \leq 0.05$ ) at T3. The ability to perform heel lift in the left leg did not change significantly compared with the control group after the exercise period (Figure 5).

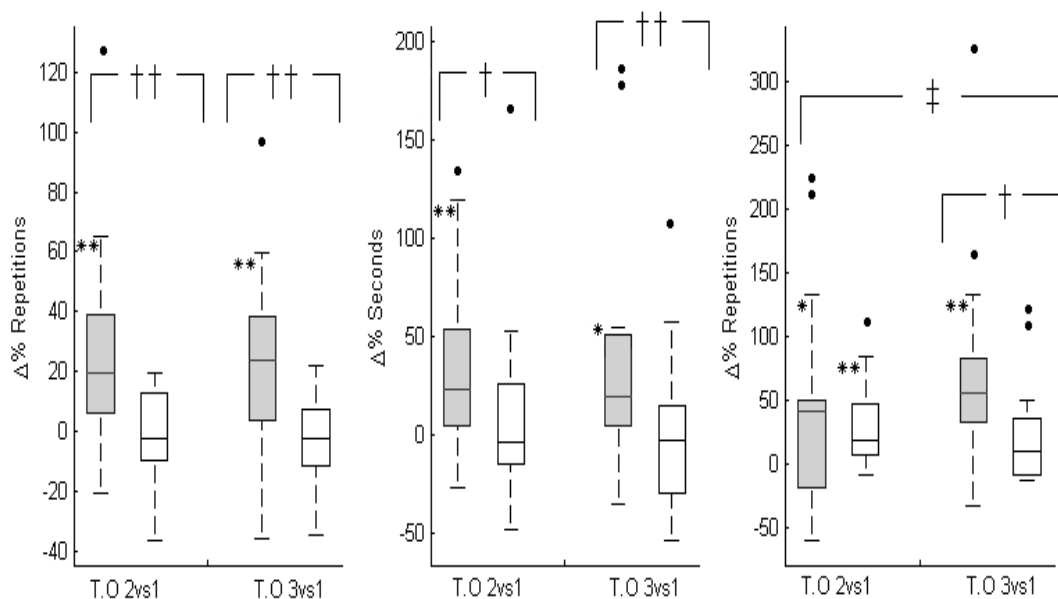


Figure 5. T1: Two months before PCI; T2: One week after PCI; T3: Six months after PCI. The change in shoulder flexion (repetitions), shoulder abduction (seconds) and heel lift (repetitions right) after exercise. Filled bars, exercise group ( $n$ , 21 before exercise period and  $n$ , 18 after exercise period). Empty bars, control group ( $n$ , 15 before control period and  $n$ , 16 after control period). Data are given as box plots, in which the box encompasses the 25th to 75th percentile, the middle line is the median. Whiskers represent the 10th and 90th percentile and dots are values outside this range. \*  $p \leq 0.05$ , \*\*  $p \leq 0.01$ , within-group comparison with baseline in patients with PCI, †  $p \leq 0.05$ , ††  $p \leq 0.01$  in difference between groups, ‡  $p \leq 0.001$  in difference between T.O 2 vs. 1 and T.O 3 vs. 1 in the exercise group; T.O: test occasion

### *Health-related quality of life*

All dimensions of HRQoL, apart from physical role limitations within the control group, improved significantly within the exercise and control group at T3. There was a significant improvement ( $p \leq 0.05$ ) for physical role limitations in the exercise group compared with the control group at T3.

### *Waist-hip ratio and restenosis*

There was a significant improvement ( $p \leq 0.05$ ) in WHR in the exercise group at T3 (0.95 (0.89-0.99)) compared with T1 (0.96 (0.91-1.01)). There were no significant differences between the groups in WHR and rate of restenosis.

## 4.2 Physical activity and cardiac risk markers (Study II)

### Level of physical activity

The median value for the pedometer was 7027 steps/day. The total amount of physical activity registered by the IPAQ was 1616 METs x min/week. The median self-rated amount of physical activity in the activity diary was 530 min/week. For further details, see Table 10.

*Table 10. Description of physical activity in patients with coronary artery disease (n=332)*

Variable	Internal missing	Median (25th-75th percentile)
Steps/day (pedometer)	19	7027 (4553-9356)
METs x min/week (IPAQ)		
Total	26	1616 (924-3147)
Vigorous	25	0 (0-400)
Moderate	26	240 (0-1080)
Walking	26	792 (358.9-1386)
Sitting (min/week) (IPAQ)	78	2100 (1418-2940)
Category 1/2/3 (IPAQ) (%)	21	18.7/56.5/24.8
Min/week (activity diary)		
Total	38	530 (290-884)
High intensity	39	75 (0-210)
Moderate intensity	40	158 (40-360)
Low intensity	41	120 (0-390)

Internal missing, pairwise deletion was used for missing data; MET, metabolic equivalent; IPAQ, International Physical Activity Questionnaire; Category IPAQ, 1=low level of physical activity, 2=medium level of physical activity, 3=high level of physical activity; activity diary, high intensity  $\geq 14$  on Borg's rate of perceived exertion (RPE) scale, moderate intensity 12-13 RPE, low intensity  $\leq 11$  RPE

### Correlations between the measures of physical activity

This result is only presented in the thesis. The correlation between pedometer steps/day and total METs x min/week (IPAQ) was  $\rho=0.44$ ,  $p<0.001$ . The correlation between pedometer steps/day and min/week (activity diary) was  $\rho=0.19$ ,  $p<0.01$ . The correlation between METs x min/week (IPAQ) and min/week (activity diary) was  $\rho=0.45$ ,  $p<0.001$ .

## Association between physical activity and cardiac risk indicators

The statistically significant adjusted correlations between pedometer steps/day and risk markers were generally low ( $r$  ranging from 0.19 to 0.25). For more details, see Table 11.

*Table 11. Selected results from the associations between steps/day and cardiac risk indicators for patients with coronary artery disease (n=313)*

Risk indicator	Adjusted correlation (rho-value)
Waist-hip ratio	-0.03
Body mass index	-0.21***
<i>Serum lipids (mmol/l)</i>	
Cholesterol	0.06
Low-density lipoprotein	0.08
High-density lipoprotein	0.19***
Triglycerides	-0.19***
Oral glucose tolerance test after 120 min (mmol/l)	-0.23***
<i>Twenty-four-hour blood pressure (mmHg)</i>	
Systolic blood pressure during day	0.04
Systolic blood pressure during night	-0.05
Diastolic blood pressure during day	0.03
Diastolic blood pressure during night	-0.09
<i>Twenty-four-hour heart rate (HR/min)</i>	
Heart rate during day	-0.10
Heart rate during night	-0.17**
Heart rate total	-0.13*
<i>Muscle endurance</i>	
Shoulder flexion (n.o)	0.25***
Shoulder abduction (s)	0.19***
Heel lift right (n.o)	0.22***
Heel lift left (n.o)	0.19***

Actual number of steps/day were used in p-value calculations \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ ; rho, Spearman's rank correlation; oral glucose tolerance test, no previous diabetes; n=252; n.o, number of

## 4.3 The validity and reliability of the TSK-SV Heart (Study III)

### Validity

#### *Face and content validity*

The patients with CAD and the panel of experts agreed that the TSK-SV Heart appeared to have face validity. On the whole, the experts considered the TSK-SV Heart to have content validity.

#### *Construct validity related to factorial structure*

The exclusion of the five influential cases improved the model fit for the second-order CFA model. The first-order latent residuals were constrained to be equal, as they were fairly small and had similar values. The model fit was not significantly impaired by this constraint. The factor with the reversed items largely improved the model fit. Moreover, one ad-hoc modification was performed based on calculations of modification indices. The correlation (0.26) between the residuals of items 4 and 17 was set free. As these items both relate to the benefit of physical activity, the modification appeared reasonable. The final model had an acceptable fit:  $\chi^2(113, n=327)=145.98$ ,  $p=0.020$ ; ratio  $\chi^2/df=1.29$ ; CFI=0.95, RMSEA=0.030 (90% CI:0.013-0.043). The factor loadings of the second-order model are shown in Table 12.

### Reliability

Composite reliability was computed as 0.77. Internal consistency assessed with Cronbach's alpha was 0.78. The results for the corrected-item total correlation coefficients are presented, with higher values indicating better consistency with the total score: values between 0-0.20 (items 4, 8, 16), values between 0.20-0.40 (items 5, 7, 12, 13, 17). All other items had values of  $> 0.40$ . The TSK-SV Heart was stable over time (ICC 0.83 95% confidence interval 0.73- 0.89). Moreover, a Bland-Altman plot showed that the mean difference between the test and re-test scores was close to zero. Either skewness or kurtosis for test and re-test was significant. These findings were confirmed in the Bland-Altman plot.



*Table 12. Standardised factor loadings (FL) for second- and first-order latent variables (n=327)*

	FL	S.E.	t-value (FL/S.E.)	Two - tailed p-value
SECOND ORDER				
<i>Kinesiophobia</i>				
Danger	0.960	0.019	50.330	0.000
Fear	0.935	0.031	29.983	0.000
Avoidance	0.953	0.021	45.229	0.000
Dysfunction	0.973	0.014	69.056	0.000
FIRST ORDER				
<i>Perceived danger for heart problem</i> (Danger)				
Item 3	0.631	0.045	13.942	0.000
Item 11	0.565	0.051	10.985	0.000
Item 8	0.110	0.061	1.812	0.070
Item 16	0.087	0.063	1.371	0.170
<i>Fear of injury</i> (Fear)				
Item 9	0.556	0.055	10.063	0.000
Item 1	0.499	0.054	9.258	0.000
Item 7	0.319	0.065	4.927	0.000
Item 13	0.315	0.058	5.389	0.000
<i>Avoidance of exercise</i> (Avoidance)				
Item 2	0.659	0.051	12.829	0.000
Item 14	0.692	0.045	15.407	0.000
Item 17	0.357	0.064	5.575	0.000
Item 4	0.090	0.061	1.480	0.139
Item 12	0.295	0.069	4.287	0.000
<i>Dysfunctional self</i> (Dysfunction)				
Item 5	0.308	0.060	5.126	0.000
Item 6	0.607	0.043	14.062	0.000
Item 10	0.677	0.042	16.046	0.000
Item 15	0.766	0.035	22.015	0.000
METHOD FACTOR (orthogonal to all factors)				
<i>Reversed items</i>				
Item 4	0.532	0.095	5.625	0.000
Item 8	0.344	0.082	4.207	0.000
Item 12	0.565	0.102	5.513	0.000
Item 16	0.184	0.077	2.407	0.016

S.E., standard error; for a description of the statements of item 1-17 in the TSK-SV Heart, please see the appendix

*Construct validity related to external measures*

The regression analysis with the four constructs of the TSK-SV Heart as dependent variables is presented in Table 13.

*Table 13. Regression analyses showing the change in explained variance of a dependent construct when a separate independent variable set was removed from the model*

Independent variable sets	Dependent variable							
	Perceived danger for heart problem (R <sup>2</sup> = .237)		Fear of injury (R <sup>2</sup> = .199)		Avoidance of exercise (R <sup>2</sup> = .242)		Dysfunctional self (R <sup>2</sup> = .405)	
	R <sup>2</sup> change	p	R <sup>2</sup> change	p	R <sup>2</sup> change	p	R <sup>2</sup> change	p
1 Gender, Age	.031 (13.1%)	.002	.001	.903	.010	.143	.003	.468
2 Smoking	.002	.341	.013 (6.5%)	.024	.002	.397	.003	.226
3 Cardiac rehabilitation	.003	.311	.002	.419	.026 (10.7%)	.001	.004	.136
4 Heart failure (previous,present)	.001	.828	.011	.117	.005	.390	.018 (4.4%)	.010
5 Flexion, Abduktion	.011	.139	.006	.368	.014 (5.8%)	.067	.013 (3.2%)	.040
6 IPAQ categories (L vs M&H), Pedometer	.001	.912	.009	.335	.003	.729	.013	.113
7 SF36: Physical (PF RP BP GH)	.055 (23.2%)	.000	.014	.244	.020 (8.3%)	.090	.069 (17.0%)	.000
8 SF36: Mental (VT SF RE MH)	.005	.727	.021 (10.6%)	.094	.014	.224	.010	.260
9 HADS: Anxiety, Depression	.010	.135	.034 (17.1%)	.002	.008	.197	.017 (4.2%)	.012

The percentage (change/total) of a significant ( $p < 0.01$ ) change in  $R^2$  is noted within parentheses. Figures in bold are significant at  $p < 0.05$ . IPAQ, International Physical Activity Questionnaire; M, medium level of physical activity, H, high level of physical activity; pedometer, mean/steps day; SF-36; Short-Form 36; PF, physical functioning; RP, role limitations due to physical problems; BP, bodily pain; GH, general health perceptions; VT, vitality; SF, social functioning; RE, role limitations due to emotional problems; MH, mental health; HADS, Hospital Anxiety and Depression Scale

## 4.4 The impact on kinesiophobia by clinical variables (Study IV)

### Occurrence of kinesiophobia

A high level of kinesiophobia was present in 20% of the patients. In the total study population, the score ranged from 17-59, with a mean value of 30.8 and a median at 29.

### Summary of pairwise differences between high and low levels of kinesiophobia

#### *Medical variables*

Patients with a high level of kinesiophobia were found to have a significantly higher presence of previous history of myocardial infarction ( $p<0.05$ ), CABG ( $p<0.05$ ), diabetes ( $p<0.01$ ) and hypertension ( $p<0.05$ ), compared with patients with a low level of kinesiophobia. Furthermore, patients with a high level of kinesiophobia experienced more complications in hospital, in terms of heart failure ( $p<0.05$ ) and atrial fibrillation ( $p<0.05$ ).

#### *Body functions*

Patients with a high level of kinesiophobia had a larger waist-hip ratio ( $<0.05$ ), reported lower muscular endurance for all tests ( $p<0.01$ ) and displayed significantly higher degrees of anxiety and depression ( $p<0.001$ ), compared with the group with a low level of kinesiophobia.

#### *Activities and participation*

The group with a high level of kinesiophobia had a significantly lower attendance at cardiac rehabilitation ( $p<0.05$ ), compared with the group with a low level. In terms of measurements of physical activity, patients with a high level of kinesiophobia reported a significantly lower degree of physical activity with the pedometer (mean steps/day) ( $p<0.01$ ), IPAQ total weekly physical activity (METs x min/week) ( $p<0.01$ ), IPAQ vigorous- ( $p<0.05$ ) and moderate- ( $p<0.05$ ) intensity activity and IPAQ categorical ( $p<0.05$ ), compared with patients with a low level of kinesiophobia.

*Personal factors*

There were no differences between the groups in relation to gender, age and current smoking.

*Health-related quality of life*

Patients with a high level of kinesiophobia reported significantly ( $p < 0.001$ ) poorer health-related quality of life on all dimensions of the SF-36.

**Binary logistic regression**

Ten variables were selected for the final regression model. The logistic regression coefficients (logged odds) were significant for seven of the 10 variables. Regression coefficients for each predictor involve estimating the difference in the odds of the target outcome for a one-point difference in the predictor, holding other predictors constant (162, 175, 176).

The following five independent variables reduced the odds of fear of physical rehabilitation or fear of consequences of physical rehabilitation (figures in parentheses denote the amount of change): SF-36: GH (-4.3%), SF-36: PF (-1.8%), attendance at cardiac rehabilitation (-56.7%), previous history: heart failure (-88.3%), while an increase from a medium to a high level of activity reduced the odds of a high level of kinesiophobia (-80.2%). The following two independent variables increased the odds: HADS: anxiety (19.2%) and complications in hospital: heart failure (418.7%). See Table 14 for further details.

*Table 14. Binary logistic regression coefficients with a high level of kinesiophobia (TSK-SV Heart >37) as the dependent variable in patients with coronary artery disease (n=327)*

Independent variables	B	Std. Error	Wald	Sig	Exp(B)	Lower 95% CI for Exp(B)	Upper 95% CI for Exp(B)
Intercept	.989	.999	.979	.322			
Abduction	-.006	.006	1.114	.291	.994	.984	1.005
SF36_GH	-.044	.011	16.981	.000	.957	.938	.977
HADS_anxiety	.176	.053	11.022	.001	1.192	1.075	1.322
SF36_PF	-.018	.009	4.428	.035	.982	.965	.999
Smoke=yes	-.513	.489	1.100	.294	.599	.229	1.562
Smoke=no	.000						
IPAQ_category=L	.798	.659	1.464	.226	2.221	.609	8.093
IPAQ_category=M	1.649	.606	7.419	.007	5.204	1.584	17.099
IPAQ_category=H	.000						
Rehab=yes	-.837	.393	4.532	.033	.433	.200	.936
Rehab=no	.000						
Prev-heart-fail=yes	-2.149	.836	6.611	.010	.117	.023	.600
Prev-heart-fail=no	.000						
Heart-fail=yes	1.646	.566	8.451	.004	5.187	1.710	15.736
Heart-fail=no	.000						
CABG2=yes	.635	.508	1.562	.211	1.887	.697	5.109
CABG2=no	.000						

Abduction; muscle endurance: isometric shoulder abduction; SF36\_GH, Short Form-36: general health; HADS\_anxiety, Hospital Anxiety and Depression Scale; SF36\_PF, Short Form 36: physical functioning; smoke=yes/no, smoking; IPAQ\_category=L,M,H, International Physical Activity Questionnaire: Category Low, Medium, High; Rehab=yes/no, cardiac rehabilitation; prev-heart-fail=yes/no, previous history of heart failure; heart-fail=yes/no, complications in hospital: heart failure; CABG2=yes, interventions in hospital: coronary artery bypass grafting



## 5 DISCUSSION

The main findings in the present thesis are discussed according to the aims and clinical implications.

High-frequency exercise improved maximum aerobic capacity and muscle function in patients treated with PCI, which may have clear advantages when it comes to preventing the progress of CAD. This result confirms already existing strong evidence of the beneficial effects of exercise in patients with CAD. However, are we taking full advantage of the documented value of exercise for this target group in clinical practice?

A relatively high level of physical activity was found, six months after the cardiac event. In addition, there was a weak, yet significant association between physical activity and several cardiac risk markers. Based on the results of the present thesis and according to previous literature, which dose of physical activity should we recommend to patients with CAD in order to achieve established health benefits?

The results of this thesis support the reliability and validity of the TSK-SV Heart questionnaire for measuring kinesiophobia in patients with CAD. From a rehabilitation perspective, it is desirable to have a psychometrically sound questionnaire to identify high levels of kinesiophobia in patients with CAD. However, is the TSK-SV Heart the optimal questionnaire to detect kinesiophobia in patients with CAD?

Finally, a high level of kinesiophobia was found in 20% of patients with CAD, six months after the cardiac event. Moreover, an impact on kinesiophobia was identified by several important clinical findings with an impact on rehabilitation outcomes. The potential impact on kinesiophobia by clinical variables in cardiac rehabilitation is further discussed.

### **5.1.1 Are we taking full advantage of the documented value of exercise in patients with CAD?**

The results of the present thesis show that a home-based exercise programme improved maximum aerobic capacity and muscle function in patients treated with elective PCI, compared with a control group. This result is in line with others (18, 19). A systematic review has recently suggested that home- and centre-based cardiac rehabilitation appeared to be equal in their benefits in

terms of mortality, morbidity, benefits in terms of risk factors, quality of life and costs (177). The trials included in this review were, however, limited to patients with stable CAD, following myocardial infarction or PCI.

Available research has concluded that patients treated with PCI represent one group with poor attendance at exercise-based cardiac rehabilitation and treatment adherence (11, 178). In overall terms, few practice recommendations are currently available when it comes to increasing uptake and adherence to exercise-based cardiac rehabilitation (90). It has, however, been suggested that a patient-centred approach, including coping strategies targeting barriers to adherence, enhances the level of success (90, 92, 179). More research is needed to focus on the long-term maintenance of exercise. Turning the focus on patients treated with PCI, one study has shown that these patients were less likely to receive cardiac rehabilitation compared with patients treated with CABG (180). In addition, patients treated with acute PCI were more likely to attend cardiac rehabilitation in comparison to patients treated with elective PCI (180). The mechanisms for a low attendance rate among these patients may include a short hospital stay, thereby reducing the opportunity for arranging sufficient referral to cardiac rehabilitation (92). From clinical experience, short sick leave makes it difficult for these patients to participate in traditional hospital-based cardiac rehabilitation programmes. It has been hypothesised that patients who work full or part time and who perceive time constraints are more likely to take advantage of home-based cardiac rehabilitation (177). A home-based exercise programme may therefore represent an alternative to broaden access and participation.

It is extremely important to take all the influencing factors in the individual patient with CAD, such as aetiology, medical history, risk factor analysis, fitness level and psychological factors, into consideration when designing an optimal exercise programme. The choice of participating in a centre-based or home-based programme should reflect the preference of the individual patient (177). One study including the patient perspective has reported that supervised exercise may motivate in ways that are lacking in unsupervised exercise at home (181). In addition, some patients with CAD were worried about exercising on their own and found direct supervision reassuring (181). This result is also important to consider in relation to the discussions of the potential impact of kinesiophobia in cardiac rehabilitation.

The exercise programme in this thesis was initiated two months before and one week after PCI. A recent meta-analysis has concluded that starting exercise early (from one week post myocardial infarction) and with a



duration longer than three months had the greatest beneficial effects on left ventricular remodelling (182). Every week that exercise was delayed required an additional month of exercise to accomplish the same level of benefit in left ventricular remodelling. There is a need to emphasise these results within cardiac rehabilitation settings.

Fostering long-term adherence to exercise after completing cardiac rehabilitation programmes is essential in order to sustain long-term cardiovascular risk reduction benefits, but this often remains a challenge. There are few studies that address this issue. Findings from a systematic review, however, have suggested that behavioural strategies, such as self-monitoring and goal setting, were more successful in exercise behaviour adherence after cardiac rehabilitation than cognitive strategies, including enhancement of self-efficacy (183). Physiotherapists are in a unique position to support behavioural change among patients in relation to exercise after completing exercise-based cardiac rehabilitation, using a bio-psycho-social perspective of health. Additional studies are needed to evaluate clinical applications.

In conclusion, encouraging patients with CAD to participate in exercise-based cardiac rehabilitation must be a top priority. Increasing health-care providers' awareness of the benefits of exercise-based cardiac rehabilitation may be effective in increasing uptake and adherence in patients with CAD. Results from future studies should extend the traditional alternatives to hospital-based cardiac rehabilitation and give patients with CAD a choice in line with their preferences. Offering different alternatives to exercise-based cardiac rehabilitation may have an impact on uptake and adherence in individual cases.

### **5.1.2 Which dose of physical activity should we recommend to patients with CAD?**

The dose of physical activity necessary to achieve health benefits, in terms of positive effects on cardiac risk markers in patients with CAD, is as yet unclear. The results from the present thesis suggest highly significant, yet weak, associations between pedometer steps/day and HDL-C, muscle endurance, triglycerides, glucose tolerance, BMI and 24-h heart rate, indicating the possibility of positive effects of physical activity on these parameters. However, in current literature, the physical activity doses required to achieve specific health benefits in patients with CAD are not well established and would benefit from future research.

When comparing the results of exercise or physical activity intervention studies, the extreme heterogeneity between the available studies in terms of study design, exercise interventions, exercise intensity, duration and frequency must be considered. In addition, the terms “physical activity” and “exercise” are often used interchangeably in the literature, even though they are not synonymous, which possibly confuses the results. Moreover, it is important to consider the individual differences in response to the same exercise programme, representing a strong genetic component for improvement in cardiovascular and metabolic variables (26). Future research is needed to distinguish the components of physical activity and exercise that are associated with better specific outcomes in patients with CAD.

Consequently, giving patients with CAD clinically meaningful advice in terms of goals of a total number of steps per day is complex. Exercise prescription is probably more complex than this and requires an individualised exercise prescription for specific exercise volume, based on tests of physical fitness. More attention needs to be paid to assessing the health benefits of physical activity when intensity is measured relative to the individual’s fitness and not as an absolute value (32). These suggestions are strengthened by a recent systematic review which concludes that the effectiveness of exercise referral schemes for increasing physical activity, fitness, or health indicators remains uncertain (184).

On the other hand, it is indicated that exercise intensity represents the most critical factor for successful aerobic exercise (26). In healthy adults, higher intensities of exercise have been found to be more effective for improving  $VO_{2max}$  than lower intensities, when the volume of exercise was controlled for (185). Similar findings also refer to patients with CAD (186). Two recent reviews have concluded that high-intensity interval exercise in cardiac rehabilitation may induce significant physiological adaptation, in terms of improved cardiorespiratory fitness, endothelial function, left ventricular morphology and function, as well as improving quality of life, to a greater extent than moderate-intensity continuous exercise (186, 187). These findings are important, as  $VO_{2max}$  has been noted as the single best predictor of death among patients with CAD (85). However, based on methodological limitations in these studies, it may be premature to draw conclusions about the effectiveness of high-intensity interval exercise as compared to moderate continuous training in the cardiac rehabilitation of patients with CAD. It is likely that both modalities of exercise will produce positive health benefits, as long as they are individually adapted.

Furthermore, studies have attempted to define the threshold intensity for improving cardiorespiratory fitness as a percentage of  $VO_2$  reserve ( $VO_2R$ ).

A review of exercise studies in healthy subjects has supported the use of 45% of  $\text{VO}_2\text{R}$  as the minimal effective exercise intensity for fit subjects (188). Individuals with baseline aerobic capacities below  $40 \text{ mL} \times \text{min}^{-1} \times \text{kg}^{-1}$  obtain improvements in  $\text{VO}_{2\text{max}}$  with intensities as low as 30% of  $\text{VO}_2\text{R}$ . However, no threshold intensity has been identified in a similar review of exercise studies in patients with CAD, where the lowest intensity studied was approximately 45% of  $\text{VO}_2\text{R}$  (189). Whether exercise intensities below this value may be an effective stimulus, especially in deconditioned patients with CAD, must be determined in future studies.

The research focus in cardiac rehabilitation has basically been to study the effects of aerobic exercise. The exercise programme in Study I in this thesis, however, included both aerobic and resistance exercise, as recommended in the secondary-prevention exercise guidelines for patients with CAD (29, 35, 36). A meta-analysis has concluded that combined aerobic and resistance exercise is more effective than aerobic exercise alone in patients with CAD in improving body composition, strength and some indicators of cardiovascular fitness (190). In addition, an increase in muscle strength may lead to a reduction in blood pressure, as occlusion of the intramuscular vessels begins at a lower percentage of one repetition maximum, thereby reducing after-load (61).

Further research is required to determine optimal modalities and doses of exercise to provide the greatest health benefits for patients with CAD. So far, however, clinicians should recognise that there are no supportive data for the efficacy of advice such as “go home and walk”. Based on current knowledge, patients with CAD are recommended to participate in individually tailored exercise-based cardiac rehabilitation in order to achieve established positive health benefits.

### **5.1.3 Is the TSK-SV Heart an optimal questionnaire for detecting kinesiophobia in CAD?**

The results of the present thesis have provided introductory support for the TSK-SV Heart as a reliable questionnaire to detect kinesiophobia in patients with CAD. Furthermore, its face, content and construct validity were established. From a secondary-prevention point of view, it is desirable to have a self-report measure to identify high levels of kinesiophobia in this target group, as early recognition may facilitate the appropriate treatment for these patients. It is, however, interesting to discuss some aspects.

The four concepts we hypothesised, based on the framework presented by Kori et al. (97) and on the DSM (105), add theoretical prerequisites for a comprehensive evaluation for screening for the consequences of kinesiophobia. The focus in previous studies of kinesiophobia in which the TSK has been used has often been reduced to fear avoidance, which is essential but not sufficient for the measurement of kinesiophobia in the sense Kori et al. have conveyed (97). The two alternative tests in this thesis of the frequently used two-factor model with 11 items from the reduced version of the TSK (168) did not dispute the construct validity of the proposed four-factor model. In addition, methodological considerations can be raised, as the majority of previous studies were performed using exploratory factor analyses (EFA) (191). Given the lack of a priori hypothesis, EFA tests unrestricted factor models resulting in ad-hoc theories which attempt to interpret the clearest factor solution. This has contributed to various factor models of the TSK. In contrast, using confirmatory factor analysis (CFA), as in this thesis, a more meaningful a priori specification reflects the hypotheses. An evaluation of model fit determines how well the hypothesised model fits the data (162).

Moreover, regression analyses revealed fairly distinct features for each of the four constructs in the present thesis. It was advantageous from a theoretical point of view that only the behavioural constructs (Avoidance and Dysfunction) were associated with medical states and physical activity. If irrational perceptions and beliefs are held about rehabilitation, it is most reasonable that they are not tied to real-state circumstances. In contrast, the constructs related to beliefs and mental imagining (Danger and Fear) were characterised by bodily oriented perceptions (Danger) and by anxiety and depression (Fear) respectively. As it is a short screening test, the TSK-SV Heart is unable safely to screen for kinesiophobia in patients with CAD. However, if phobic imaginings are present, high ratings are required for more factors than just fear avoidance. For example, patients with high ratings for Dysfunction should receive attention, as they may have a view of self-preventing successful rehabilitation, especially if they also hold a belief that a heart problem is dangerous. In general, a group with phobic imaginings has high estimates in all four concepts. However, as always, the screening must be followed by a more detailed diagnosis.

In this thesis, a cut-off score of  $>37$  for a high level of kinesiophobia was used, which followed the original operational definition presented by Vlaeyen et al. (192), in order to make our results comparable. However, in clinical application for patients with CAD, the issue of cut-off values needs to be further analysed. Clearly, the alternative score with regard to the four sub-

dimensions of kinesiophobia based on a more detailed case analysis should be given priority in future research, to allow for the more effective screening and treatment of kinesiophobia. Identifying sub-groups of patients according to these underlying constructs of the TSK-SV Heart would create an opportunity for more targeted interventions to treat kinesiophobia and improve activity and exercise.

For clinical purposes, the TSK has been found to be an appropriate tool for identifying patients with high levels of kinesiophobia (96). The TSK, and thus the TSK-SV Heart, lack sensitivity, however, and do not tell us exactly what patients are fearful of. Being diagnosed with cardiac disease may increase the probability of experiencing a life-threatening cardiac crisis (193). However, the nature of the perceived threats may differ between different patient groups in relation to kinesiophobia. For example, in patients with chronic musculoskeletal pain, the catastrophic misinterpretation of pain leads to a fear of situations and movements associated with their pain (96, 97). The mediating attribute between the cardiac disease and the feared consequences of specific physical activities must be elaborated on, however. Future in-depth studies are suggested for this purpose.

The reversed items (items 4, 8, 12 and 16) in the TSK-SV Heart did not function as intended. This finding may be related to the absence of a specified mediating object in these items, reducing the affective relevance for the patients. The lack of systematic answers to these items resulted in low factor loadings on the corresponding factor in the CFA. This result is in line with previous psychometric findings of the TSK, showing low factor loadings for the four reversely scored items (123, 167, 194). However, the content of these four items does seem relevant for the theoretical framework of kinesiophobia and the experts did not find the items difficult to interpret. For this reason, we do not suggest that the reversed items should be excluded from the TSK-SV Heart. On the contrary, we propose that they should be further examined in future studies.

In conclusion, the results included in this thesis provide introductory support for the TSK-SV Heart as a reliable, valid questionnaire for detecting kinesiophobia in patients with CAD. Future research is needed to further examine and advance the TSK-SV Heart and to establish the clinical applicability for patients with CAD.

### **5.1.4 What is the impact on kinesiophobia by clinical variables in cardiac rehabilitation?**

The results in the current thesis show that several important clinical findings with an impact on rehabilitation and prognosis for patients with CAD were found to be associated with a high level of kinesiophobia.

Kinesiophobia was found to be present in 20% of patients with CAD. This is lower than, for example, patients with chronic musculoskeletal pain, in which 50% of the patients reported a high level of kinesiophobia (98, 116, 195). Recently published norm data for the TSK have demonstrated that patients with low back pain obtained higher scores on the TSK compared with patients with fibromyalgia, osteoarthritis and upper extremity disorders (112).

One interesting result in the present thesis was that anxiety increased the odds of a high level of kinesiophobia. This finding makes sense, as anxiety is the primary affective component of phobias and there is strong evidence to suggest the influence of anxiety on kinesiophobia for patients with chronic pain (96, 100, 105). Furthermore, patients with high levels of kinesiophobia in our study showed significantly higher degrees of depression, compared with patients with low levels of kinesiophobia. This result is consistent with the results of previous studies and in accordance with the theories of the fear-avoidance model (96, 98, 100, 196). In addition, two dimensions of the SF-36 reduced the odds of a high level of kinesiophobia. A negative association between quality of life and kinesiophobia has been shown in previous studies (115, 121). One important reason to promote interest in the evaluation and management of psychological factors in cardiac rehabilitation is the strong link between adverse cardiac events and a negative effect on treatment adherence (80). So far, this link has not been investigated with regard to kinesiophobia. There is therefore a need for future research to investigate the mediation roles of several cognitive and emotional factors influencing kinesiophobia and to further establish the impact on rehabilitation outcomes.

Complications, such as heart failure, during the acute hospital stay were found to be a significant predictor of developing a high level of kinesiophobia. Patients with heart failure, after a coronary event, often receive medical information about impaired functioning of the heart. Studies have suggested that patients' fear of movement may be fed by health-care providers' knowledge and perception of how harmful physical activity can be (100, 124, 197). It is not surprising that fearful patients receiving information regarding exercise and physical activity accompanied by caution may respond with more avoidance behaviours. The results of a study of patients

with back pain concluded that practitioners with high scores for fear avoidance were more likely not to provide clear information about activities which may have a negative influence on treatment practice (197). In addition to the detrimental consequences of inadequate advice, it is also plausible that the threatening diagnosis of cardiac disease may activate fear, especially if patients perceive danger in relation to their disease. A recent study has suggested that patients hold incorrect beliefs and misconceptions about heart disease, which may have an important effect on a patient's physical and psychological outcomes (198). Consequently, patients are in need of clear, consistent advice about how to continue with physical activity and exercise after a cardiac event. Improving health-care providers' knowledge of and adherence to current exercise prescription guidelines in patients with CAD is therefore a matter of great concern (29, 35, 36).

In the present thesis, patients with high levels of kinesiophobia performed less well in all muscle endurance tests, compared with patients with low levels of kinesiophobia. These results are in line with studies of patients with chronic pain, showing that muscle performance has been found to be negatively related to kinesiophobia (98, 199, 200). In patients with CAD, improved muscular strength will favourably change body composition and reduce the cardiovascular demand at a fixed submaximum aerobic exercise load and is therefore beneficial (201). In addition, our results show that an increase from a medium to a high level of physical activity significantly reduced the odds of developing high levels of kinesiophobia. On the other hand, there were no significant differences between the groups in terms of low-intensity activities and self-reported activities in the activity diary. These results are supported by previous studies of patients with chronic musculoskeletal pain (116, 196). By replacing these feared activities with less feared alternatives, it is possible that the general level of physical activity was not affected. So far, these findings suggest the possibility that patients with CAD avoid specifically feared high-intensity activities. With the objective of secondary prevention in CAD, including moderate to vigorous exercise, exercise-based cardiac rehabilitation with the aim of improving  $VO_{2max}$ , is associated with significant health benefits (30, 35, 67, 68, 79). Future studies must therefore further examine the impact of kinesiophobia on physical activity and exercise in patients with CAD.

Interestingly, attendance at exercise-based cardiac rehabilitation reduced the odds of high levels of kinesiophobia. This is interesting from a treatment perspective. Graded exposure *in vivo* to situations the patients have identified as dangerous has proven to be a successful treatment in patients with anxiety disorders, including phobia (202). Given the similarities between

kinesiophobia and specific phobia, a similar exposure-based treatment has been developed for application in patients with kinesiophobia (203). This treatment has been found to be successful in patients with chronic pain (100, 204, 205). For patients who fear that certain activities will increase bodily harm, a cognitive behavioural treatment approach has been suggested (100, 206). There is a need for future studies to show whether this treatment may also be applicable to patients with CAD. It would be interesting to elaborate on the idea of matching treatment to specific patient characteristics (207) in relation to the four sub-dimensions of the TSK-SV Heart, together with potential moderators affecting the treatment, such as therapist skilfulness and competence.

In the light of these findings, showing that an impact on kinesiophobia was identified in relation to clinical variables with an influence on rehabilitation outcomes in patients with CAD, kinesiophobia needs to be considered in the cardiac rehabilitation of patients with CAD and given priority in future research.

### **5.1.5 Methodological considerations**

The majority of the patients included in this thesis were male, of Swedish origin and without major co-morbidities, which is consistent with many other studies of patients with CAD (29). Furthermore, ST-elevation myocardial infarction was more frequent among the included patients, while stable angina pectoris was more frequent among the excluded patients in Studies II-IV. Meta-analyses have concluded that most studies of exercise-based cardiac rehabilitation in patients with CAD are conducted on low-risk, middle-aged men following myocardial infarction or PCI (67, 68, 79). It would be interesting to discuss whether the patients who would benefit most from exercise interventions and secondary-prevention surveys are excluded from the trials. There are no physiological reasons why patients who are female or older should not obtain the same benefits from exercise or physical activity interventions (26), despite less clear scientific evidence for these groups (67, 68, 79). Studies have reported that the significant benefits of exercise on physical fitness, muscle strength, quality of life, cardiac risk markers, anxiety and depression also relate to older patients with CAD (208, 209). In addition, a meta-analysis has concluded that gender or age distribution in samples was not related to physical activity, suggesting that interventions are equally effective for men and women across different ages (55). Finally, few studies mention the ethnic origin of their participants (67, 68, 79). The focus on the Swedish language in the present thesis excluded immigrants, which might be a potential limitation in the generalisation of the results. In overall terms,



there is a need for future research to design studies in patients across the range of coronary artery disease diagnoses, genders, ages and ethnicities.

Randomised controlled trials constitute the highest hierarchical form of evidence-based medicine when evaluating treatment effects, by eliminating bias. It is important to collect a representative sample, as inferences about the population are made from the results (175). In Study I, patients with serious diseases interfering with exercise on a bicycle ergometer had to be excluded. The choice to exclude patients already performing regular exercise ( $\geq 3$  times/week) originates from exercise physiology. If a patient is already performing exercise at a certain level, no further improvements can be achieved. It is important to consider the baseline fitness level, as patients with reduced exercise capacity generally obtain greater improvements in physical fitness after exercise (26). One major strength of the study was therefore the lack of baseline differences between the groups. It is also worth mentioning that fitness may vary substantially among patients performing identical exercise programmes because of individual and genetic influences (26). The sample size in the study was somewhat small, but, as a power calculation for the primary effect variable was performed, it is reasonable to believe that the results are true. However, it is possible to discuss whether the study was underpowered to be able to show differences for the secondary endpoint variables. Additional larger studies are needed for this purpose. Furthermore, block randomisation would have been useful to keep the different groups balanced at all times.

In the present thesis, the ITT design in Study I was not correctly specified from the start, according to the up-to-date definition of ITT: *“All patients are allocated to each arm of the treatment regimen and analysed together as representing that treatment arm, whether or not they received or completed the prescribed regimen”* (210). A recent study has emphasised that authors use the ITT concept quite differently (210). Another generally used definition of ITT is: *“the analysis of all available subjects as randomised, while ignoring missing data”*. Based on the first definition, it would be more correct to define the approach in Study I as per protocol, as only the patients who adhered to the exercise protocol were analysed at T3. Even though the ITT design is considered to be the most appropriate approach, it has been suggested that the addition of per protocol analysis may better reflect the effectiveness of treatment effects in clinical practice. The recommendation is to analyse RCT studies using both methods (211). The data in Study I were therefore calculated according to both ITT analysis and per protocol analysis. The absence of differences in the level of significance using the two methods was probably due to a few missing data.

The observational study may more accurately reflect clinical practice. In the absence of randomisation, however, internal validity may be affected by selection bias and confounding (158, 175, 212). In the present thesis, confounding was controlled for by multivariate statistics. The observational studies (II-IV) were conducted with the aim of including consecutive patients hospitalised with CAD, representative of usual clinical practice in order to obtain external validity. However, due to a lack of organisational capacity within the hospital to call all patients within six months after hospitalisation, patients with delayed evaluation (>10 months from hospital discharge) were excluded. It is important to highlight, however, that patients were excluded in strict order in relation to their hospitalisation. Furthermore, the effective participation rate among the patients who were actually contacted was 83%. It is always possible, however, that patients with a greater interest in their own health are more likely to attend this kind of study. Because of cross-sectional data design, it is difficult to make casual inferences. For this purpose, future longitudinal studies are needed (158, 175).

### **5.1.6 How do the selected endpoint variables affect the results?**

The results of the present thesis must be discussed in relation to the selected endpoint variables. These variables were mainly chosen in relation to clinical experience and a careful review of previous research. Potential omitted variables that account for some unique proportion of total criterion variance can always bias the analyses (162). However, it is unrealistic to be aware of and be able to measure all relevant variables.

In rehabilitation, outcomes have often been related to improvements in impairments and pathologies. However, death and re-infarction are less likely to be reduced as a single result of any added intervention. They are therefore not suggested to be the only endpoints to be evaluated in order to measure the effectiveness of exercise interventions (29). The importance of systematically assessing symptoms and functional impairments to optimise the management of CAD has been highlighted (29). Internationally accepted and evidence-based ICF core sets for chronic ischemic heart disease (IHD) (equivalent to CAD) have been developed to define the typical spectrum of IHD-related changes in body functions, activity limitations and restrictions in participation (130). These core sets can serve as guidance in the multidisciplinary assessment of patients with IHD. As a short comparison between these core sets and the variables included in this thesis, categories from the body functions, such as exercise tolerance functions, muscle endurance functions and emotional functions, were well represented. Most of

the measures in the component activities and participation in the present thesis belong to the categories of looking after one's health and recreation and leisure. The inclusion of these categories is in line with the ICF core sets. However, future research should include additional aspects of activities and participation, such as family relationships, intimate relationships and employment, in relation to the selected endpoint variables. Finally, the ICF core set for IHD has a broad representation of the component of environmental factors, while such variables were inconclusive in the present thesis. More focus on variables from this component, such as attitudes and social support, are suggested in future studies. The concept of HRQoL used in this thesis is a comprehensive measure, which includes several domains of the ICF. It is therefore not specifically classified. Please refer to the reference for a comprehensive review of ICF categories included in the ICF core set for IHD (130).

A discussion of selected endpoint markers in relation to the results in this thesis will be presented according to the ICF.

## **Body functions**

### **Cardiac risk markers**

In overall terms, it is important to note that the benefits of the secondary prevention of CAD will be optimised when a comprehensive approach to risk factor reduction is made (213). Some possible influencing variables that may have been omitted will be briefly discussed.

### *Diet*

Diet is a possible confounder of the association between physical activity and cardiac risk markers. As discussed previously, diet in combination with physical activity is suggested to produce the most promising results regarding weight reduction and could therefore affect BMI and WHR (51, 54).

Moreover, a meta-analysis has shown that diet and diet in combination with exercise were superior to exercise only for improving triglycerides, LDL-C and cholesterol in primary prevention (70). Further investigation is needed to determine whether these findings also refer to patients with CAD. A recent systematic review concludes that there is a lack of studies of dietary interventions in patients with CAD containing an appropriate follow-up (>12 months) (214). Discussing the potential effects of all available diets in relation to cardiac risk markers in more detail is beyond the scope of this thesis.

### *Inflammatory markers*

As reported earlier, exercise appears to play an important role in endothelial function. Atherosclerosis is recognised as a dynamic chronic inflammatory process in the vessel wall (3, 215). So, studying inflammation markers in the present thesis would have been of interest. A recent meta-analysis has confirmed that exercise is associated with reduced inflammatory activity in patients with CAD, as indicated by lower C-reactive protein (CRP), fibrinogen and interleukin-6 (IL-6) (216). The association between physical activity and inflammatory markers is less clear and must be further investigated. A cross-sectional study, however, suggested that a high level of physical activity is associated with lower levels of inflammatory markers (217). In addition, a recent review study indicated strong evidence of an inverse relationship between physical activity and markers of systemic inflammation (74). The effects of exercise on inflammation markers have been less established in randomised trials, however, with conflicting results in healthy populations and among patients with CAD. Further research is needed to clarify the effect of exercise on systemic inflammation, independent of other factors, such as weight loss and co-morbid conditions.

### *Kinesiophobia*

The fear-avoidance model has been suggested as an explanatory model for the chronification of pain (100) and variables included in this model have consequently often been used in relation to kinesiophobia (96, 100, 127). It would have been interesting to study some of these variables, such as catastrophising, anxiety sensitivity and disability, in relation to avoidance behaviour in patients with CAD. In addition to measuring the fear associated with avoidance behaviour in patients with pain, several other factors have been suggested to be important, such as motivation, self-efficacy and the emotional state of the patient (218). These variables could also be taken into account in relation to patients with CAD. A recent review supports the theory that the fear-avoidance model needs to be conceptually expanded and further tested to provide sufficient clinical utility (218). It is therefore suggested that more interest should focus on related measures to extend our knowledge of the constructs of Dysfunction and Danger.

### *Maximum aerobic capacity*

According to the principle of specificity, patients improve what they practise (26). It should therefore be noted that the patients in Study I both exercised and were tested on a bicycle ergometer. Peak oxygen uptake is the gold standard in assessments of maximum aerobic capacity and it would have been advantageous to use an ergospirometry test (26, 219). In Studies II-IV, maximum aerobic capacity was not investigated. Being able to compare

physical fitness with measures of physical activity, cardiac risk markers and kinesiophobia would have strengthened the results. However, this was not possible within the framework of the present study.

### **Activities and participation**

The methodological challenge of measuring physical activity is well known in the literature and will be briefly discussed in relation to the chosen measurement instruments in this thesis (219-222).

The pedometer has been suggested as a sufficiently valid and inexpensive option for measuring physical activity (153, 219, 220). However, pedometers are not designed to capture the intensity, pattern, or type of physical activity and are considered to be less valid during slow walking and also in patients with obesity (219, 220, 222). Other objective physical activity assessment methods include accelerometry and heart rate monitoring (219, 222). The accelerometer is sensitive to change in three planes (vertical, horizontal and mediolateral), while the pedometer is limited to capturing movement in the vertical plane. Accelerometry therefore has the advantage of monitoring the intensity of movement and the opportunity to assess the energy expenditure (219, 223). However, in terms of convergent validity, pedometers correlate (median  $r = 0.86$ ) with different accelerometers and, moreover, pedometers correlate with time in observed activity ( $r=0.82$ ) (223).

Self-reports can provide important contextual information that is not available from pedometers and accelerometers. Furthermore, they are easy to apply to large epidemiological studies (221, 222). These measures are frequently used due to their practicality, low cost and low participant burden (222). However, self-report methods entail a risk of over- or underestimating true physical activity, as well as issues of recall and response bias (222).

The correlation between direct measures and self-reports is generally low to moderate. Self-report measures have been found to be both higher and lower than directly measured levels of physical activity (222). A review has found a median correlation of  $r=0.33$  between pedometer and different self-reports, varying depending on the self-report instrument that is used (223). A Swedish study has shown a correlation of  $r=0.34$  between IPAQ and accelerometry (151). These results can be compared with the association between the pedometer and the IPAQ ( $\rho=0.44$ ) and between the pedometer and the activity diary ( $\rho=0.19$ ) in the present thesis. The activity diary used here was not tested for reliability and validity, which probably explains the low association with the pedometer.

Assessing sitting time is an important new area in epidemiology, in addition to the measurements of physical activity. Sedentary behaviour has been shown to be a distinct risk factor for multiple health outcomes, including mortality (224). The sitting question in the IPAQ has acceptable reliability and validity (225). However, in the present study, this question was affected by high rates of internal missing and possible recall bias. The use of advice measures, such as accelerometers, eliminates these problems, but, on the other hand, this is expensive. To date, only a few studies have used device measures for this purpose (224).

In conclusion, the selection of an appropriate physical activity measurement depends on the purpose of the study, the methodological considerations and also, to a great extent, the project budget. Based on the discussion above, a combination of objective and subjective measurement approaches is suggested for the best measurement of physical activity.

## **Personal and environmental factors**

Gender and age perspectives are discussed elsewhere in this thesis.

## **Health-related quality of life**

The reason for choosing a generic HRQoL instrument (SF-36) was to make our results comparable with other research. The SF-36 has been widely used across different countries and populations (155). The heterogeneity of outcome measures precluded a meta-analysis of HRQoL in relation to exercise-based cardiac rehabilitation (79), which highlights the importance of using validated instruments, such as the SF-36 (157). On the other hand, the question of whether generic HRQoL measures lack sensitivity to change in connection with cardiac treatment, in comparison with disease-specific measures, has been discussed (226).

### **5.1.7 Gender perspective**

The gender perspective was not a direct focus of this thesis. However, it is interesting briefly to discuss the results from this angle. When it comes to CAD, it is well known that men have a higher prevalence than women (1), which possibly explains why the patients included in this thesis were predominantly male. Furthermore, the incidence of total CAD in women lags behind that of men (1). Consequently, since patients with serious co-morbidities were excluded from this thesis, the older patients and women would clearly be more likely to be affected.

In all, none of the studies revealed any significant differences between men and women, in relation to the selected endpoints. Stratified analyses with

regard to gender were not focused on, however. Swedish register data have illustrated that more men than women with CAD are physically active (91). Another study has confirmed that men with CAD reported higher levels of physical activity than women (227). However, there were no differences between men and women regarding steps/day, as measured with the pedometer in this thesis. This result is in line with another Swedish study of patients with CAD, showing no gender differences in involvement in physical activity (228). Consequently, gender aspects relating to physical activity in CAD need to be studied in more detail.

There were no gender differences regarding the occurrence of kinesiophobia in the present thesis. In contrast, some studies of patients with chronic musculoskeletal pain indicate higher levels of kinesiophobia among men (98, 112, 116, 195). Since a specific phobia is regarded as part of general anxiety disorders, it is interesting to note that women run a greater risk than men of developing most anxiety disorders (103). In CAD, higher prevalence rates for anxiety have also been found among women, compared with men, and this trend is consistent across western and eastern cultures (229). In addition, a recent review has concluded that there is a higher prevalence of fear among women with regard to dental treatment, fear of injections and snakes, for example. Moreover, women reported higher prevalence rates of spider phobia and phobia of enclosed spaces (230). The gender perspective of kinesiophobia in patients with CAD requires further explanation.

### **5.1.8 Clinical implications**

The results of the present thesis suggest that high-frequency exercise in patients before and after treatment with elective PCI can improve maximum aerobic capacity and muscle function. This home-based exercise programme was well tolerated and can therefore be suggested as an alternative to traditional hospital-based exercise programmes to broaden access and participation. It is always important, however, to perform physical fitness testing before starting an exercise programme, to be able to prescribe individually based exercise according to guidelines (29, 35). Furthermore, additional fitness testing by a physiotherapist with skills in exercise physiology is warranted throughout the exercise programme to upgrade the intensity level. The positive effects of exercise-based cardiac rehabilitation are scientifically established (30, 67, 68, 79). The real challenge for the future, however, must be to further extend the effectiveness of a variety of exercise programme approaches within cardiac rehabilitation, designed to increase accessibility, uptake and long-term adherence for the individual patient.

In the present thesis, there was a weak, yet significant, association between physical activity and several cardiac risk markers in patients with CAD. These results may indicate a positive effect of physical activity on these risk factors. However, based on current literature, the physical activity doses required to achieve positive effects on cardiac risk markers in the secondary prevention of CAD are unclear. This area would benefit from future interventional studies, including a long-term follow-up, before clinical implications can be formulated. Based on the literature so far, patients with CAD are recommended to participate in exercise-based cardiac rehabilitation, in favour of a more general recommendation to increase the level of physical activity. Exercise prescription is more complex than this and needs to be individually based in order to achieve established health benefits (26, 29, 35).

The results of the current thesis indicate that a high level of kinesiophobia was present in 20% of patients with CAD, six months after their cardiac event. From a secondary-prevention point of view, it is desirable to identify high levels of kinesiophobia in patients with CAD, as recognition may facilitate the appropriate treatment for these patients. The significance of using a psychometrically sound questionnaire for this purpose must be highlighted (159, 160). The present thesis has provided introductory support for the TSK-SV Heart as a reliable, valid questionnaire for measuring kinesiophobia in patients with CAD. Moreover, several important clinical variables with an impact on rehabilitation outcomes were found to be associated with a high level of kinesiophobia. Although these are the first, introductory results on this topic, it is theoretically possible that the presence of kinesiophobia and associated fear of physical rehabilitation may prevent successful cardiac rehabilitation. Future studies should therefore extend this knowledge and design optimal treatment interventions for patients with high levels of kinesiophobia, with the overall target of enhancing levels of physical activity and exercise.

Taken as a whole, kinesiophobia needs to be considered in cardiac rehabilitation in patients with CAD and would benefit from future research. Moreover, the improved implementation of exercise-based cardiac rehabilitation could prove to be a powerful tool for long-term efficacy and positive effects on outcome, such as reducing mortality, morbidity and increasing quality of life for patients with CAD.





## 6 CONCLUSIONS

- High-frequency exercise in patients before and after treatment with elective PCI improved maximum aerobic capacity and muscle function. The exercise programme was well tolerated and can be used as an alternative to traditional hospital-based exercise programmes.
- A relatively high level of physical activity was found among patients with CAD, six months after the cardiac event.
- There was a weak, yet significant, association between physical activity (steps/day) and HDL-C, muscle endurance, triglycerides, glucose tolerance, BMI and 24-h heart rate, indicating potential positive effects of physical activity on these parameters.
- Introductory support was found for the TSK-SV Heart as a reliable, valid questionnaire for measuring kinesiophobia in patients with CAD.
- The construct validity of a four-factor model of the TSK-SV Heart was acceptable.
- A high level of kinesiophobia was present in 20% of patients with CAD, six months after the cardiac event.
- An impact on kinesiophobia was identified by clinical variables with an influence on rehabilitation outcomes and prognosis, representing all the components of the ICF, medical variables and health-related quality of life in patients with CAD. In the light of these findings, kinesiophobia needs to be considered in the cardiac rehabilitation of patients with CAD.

## 7 FUTURE PERSPECTIVES

Several ideas for future research have arisen during the work on this thesis.

- The TSK-SV Heart must be further tested and developed in relation to patients with CAD.
- The further establishment of the impact on kinesiophobia in cardiac rehabilitation and the design of a treatment intervention should be prioritised in future studies.
- It would be interesting to explore the patient perspective in relation to kinesiophobia and CAD in future qualitative studies.
- The effects of physical activity in the secondary prevention of CAD need to be further explored.
- Further research is required to determine optimal modalities and doses of exercise to provide the greatest health benefits for patients with CAD.
- Studies in relation to physical activity and exercise with greater focus on variables representing all components of the ICF are suggested.
- Evaluations are needed to investigate the effectiveness of a variety of exercise programme approaches within cardiac rehabilitation, designed to increase accessibility, uptake and long-term adherence for the individual patient.

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## 10 APPENDIX

Tampaskalan för kinesiofobi – svensk version hjärtbesvär (TSK-SV Heart)  
(Originalversion Tampa Scale for Kinesiophobia av Miller RP, Kori SH, Todd DP, 1991)

(Denna version något modifierad för att passa patienter med kranskärslssjukdom)

Nedan följer olika erfarenheter som andra patienter delgivit oss. Var vänlig och ringa in lämplig siffra från 1-4 för varje påstående. Läs och besvara varje påstående så gott Du kan.

		Håller inte alls med			Håller med helt
1.	Jag är rädd för att jag kan skada mig under fysisk aktivitet/träning.	1	2	3	4
2.	Om jag försökte vara fysiskt aktiv/träna så skulle mina hjärtbesvär öka.	1	2	3	4
3.	Min kropp säger mig att jag har någon allvarlig åkomma.	1	2	3	4
4.	Mina hjärtbesvär skulle troligen lindras om jag var fysiskt aktiv/tränade.	1	2	3	4
5.	Människor tar inte mitt medicinska tillstånd tillräckligt allvarligt.	1	2	3	4
6.	Mina hjärtbesvär har försvagat mig kroppsligen för resten av mitt liv.	1	2	3	4
7.	Hjärtbesvär beror alltid på kroppslig skada.	1	2	3	4
8.	Bara för att någonting framkallar obehag i bröstet behöver det inte betyda att det är farligt.	1	2	3	4
9.	Jag är rädd för att jag skulle kunna skada mig själv oavsiktligt.	1	2	3	4

## Appendix

10.	Genom att vara försiktig med onödiga rörelser kan jag förhindra att hjärtbesvären förvärras.	1	2	3	4
11.	Jag skulle inte ha mina hjärtbesvär om det inte var något farligt på gång i min kropp.	1	2	3	4
12.	Även om jag har hjärtbesvär klarar jag mig bättre om jag är fysiskt aktiv/tränar.	1	2	3	4
13.	Hjärtbesvären säger mig när jag skall sluta vara fysiskt aktiv/träna, så att jag inte skadar mig själv.	1	2	3	4
14.	Det är verkligen inte säkert för en person med mina besvär att vara fysiskt aktiv/träna.	1	2	3	4
15.	Jag kan inte göra samma saker som andra eftersom det är för stor risk att få hjärtbesvär.	1	2	3	4
16.	Även om någonting orsakar mig mycket hjärtbesvär så tror jag faktiskt inte att det är farligt.	1	2	3	4
17.	Ingen ska behöva vara fysiskt aktiv/träna när hon eller han har hjärtbesvär.	1	2	3	4

Svensk originalversion för patienter med kranskärslsjukdom (2011)

Maria Bäck (maria.m.back@vgregion.se), Bengt Jansson, Åsa Cider, Johan Herlitz, Mari Lundberg