CHAPTER 1

Introduction

For patients listed for open-heart surgery, avoiding postoperative adverse events and ensuring optimal recovery are the most important goals. Unfortunately, there is a risk that patients’ mental and physical health will deteriorate in the period before and immediately after cardiac surgery, resulting in an increased risk of complications in postoperative recovery and associated higher healthcare costs. To improve preoperative and postoperative care, a newly developed multidisciplinary cardiac rehabilitation programme has been implemented. This so-called ‘Heart-ROCQ programme’ begins when patients are added to the waitlist and continues postoperatively. The overall aim of this thesis is to assess the feasibility of the Heart-ROCQ programme and its effects on postoperative complications, physical functioning, and postoperative health-related quality of life (HR-QoL) in patients awaiting open-heart surgery.

CLINICAL CARE IN CARDIAC SURGERY AND PHYSICAL (IN-)ACTIVITY

Although the first open-heart surgeries only transpired in the early 1950s, cardiac surgery is now daily practice. More than 15,000 patients annually undergo coronary artery bypass grafting (CABG), valve, and/or aortic surgery in the Netherlands. In the pioneering era of cardiac surgery, the potential risk of death was as high as 200% using the ‘controlled cross-circulation’ technique.* After decades of improvement in both operative and postoperative care, the risk of mortality has significantly decreased to just 1.0–2.6%.

 Nonetheless, despite major improvements in survival rates, the incidence of postoperative complications is still high, which places a major burden on the healthcare system. Reported incidences range from seven to 18% for pulmonary complications, 12 to 34% for delirium, and 18 to 67% for arrhythmias. Moreover, two recently conducted multicentre studies among the Dutch population showed that despite average improvements, 27 to 56% of the patients do not improve or even decline in terms of HR-QoL after CABG or valve surgery. With more patients surviving the surgery, it is therefore important to reduce postoperative morbidity and improve functioning and well-being.

There are several explanations for the high morbidity rate following cardiac surgery. First, the average age of the patient group has increased over recent decades. Older patients tend to have more comorbidities and greater illness severity, resulting in a poorer preoperative status. Second, modifiable preoperative lifestyle risk factors such as obesity, diabetes mellitus, hypertension, and dyslipidaemia have steadily increased in this patient group over the years, and these lifestyle risk factors have potentially adverse effects on surgical outcomes.

Despite these observations, preoperative risk attenuation has not really been

* The ‘controlled cross-circulation’ technique refers to the technique in which another person was utilised as the ‘heart-lung machine’. As a result, two people, rather than one person, could potentially die from the surgery. In fact, none of those who ‘served as heart-lung machines’ died, and 63% of the patients undergoing the surgery survived.
addressed in recent decades. This lack of attention is remarkable because a patient’s preoperative status is a well-known predictor of cardiac surgery outcome, and several models based on preoperative status have already been applied in clinical practice. For example, the European System for Cardiac Operative Risk Evaluation (EuroSCORE) risk model, which is indispensable in daily surgical practice, predicts postoperative in-hospital mortality. This model is based on preoperative risk factors including modifiable risk factors, such as diabetes, poor mobility, and left ventricle function. A lower level of preoperative physical fitness is another modifiable risk factor, that has been associated with shorter event-free survival after cardiac surgery. In addition, Hulzebos and colleagues (2003) found a correlation between preoperative modifiable risk factors such as preoperative smoking, diabetes mellitus, and lung function, and the development of postoperative pulmonary complications. As these preoperative risk factors are potentially modifiable, it is possible that they can be reduced following therapeutic interventions, such as rehabilitation, physical medicine, and lifestyle interventions before surgery. Thus, improving cardiac patients’ preoperative status may prevent poor surgical outcomes and improve postoperative functioning and quality of life. In turn, such improvements may reduce the economic burden on the healthcare system.

Currently, little attention is paid to improving patients’ physical or mental status in cardio-thoracic clinical care, especially before surgery and up to six weeks after surgery. Before cardiac surgery, the majority of patients are registered on a waitlist for several weeks, during which they receive no regular clinical or preventive guidance. However, during this waiting period, patients are commonly advised not to engage in too much physical exertion, since they may have recently experienced a cardiac event or have an increased risk of sudden cardiac death. Both events are considered contra-indications for exercise. However, recent studies indicate that light to moderate exercise can be safely performed by patients awaiting CABG, but the literature is sparse, and no standard guidelines exist for preoperative aerobic exercise. From the point of view of patients, who often know little about the limits of safe exercise, it is difficult to know which exercises they can and cannot do. However, even if patients are cognisant of the existence of safe exercise, they often believe that physical activity is undesirable and may experience mental barriers, such as anxiety, to engaging in physical activity. One study among patients with coronary artery disease showed that 20% had kinesiophobia (i.e., fear of movement). In sum, patients awaiting cardiac surgery who experience mental barriers to exercise tend to adopt sedentary and physically inactive lifestyles, resulting in further declines in muscle strength, physical functioning, and well-being.

Unfortunately, patients also often remain physically inactive after cardiac surgery. In the hospital immediately after surgery (eight to 11 days on average), patients spend 90% of their time sitting or lying down, which further reduce physical fitness. In-hospital physical inactivity has been associated with a longer hospital stay and rehospitalisation. Following discharge from hospital, patients are not immediately encouraged to be physically active in the Netherlands, as the outpatient cardiac
rehabilitation programme only begins four to six weeks after surgery\textsuperscript{29,32}. During this period in particular, between hospital discharge and the beginning of cardiac rehabilitation, patients continue to show low levels of physical activity because patients experience pain, fatigue, anxiety, and low confidence or even fear (i.e., kinesiophobia) in their ability to exercise or be physically active\textsuperscript{33,34}. Thus, during the preoperative waiting time and the first weeks after surgery, patients demonstrate high levels of physical inactivity, sedentariness, and bed rest, which negatively impact their preoperative and postoperative physical and mental status.

The waiting period before and the initial weeks immediately after cardiac surgery are often overlooked as appropriate rehabilitation-oriented times to become more physically and mentally fit, as well as to encourage a physically active and healthy lifestyle before and after the operation. For this reason, the majority of this thesis (\textit{chapters 4 to 7}) focuses on the implementation and effects of a cardiac rehabilitation programme during these periods. However, knowledge about the physical impacts of cardiac surgery is required to enhance the development of effective interventions. Therefore, \textit{chapters 2 and 3} focus on understanding and measuring the physical impacts of cardiac surgery. In these chapters, the focus is mainly on muscle strength, which is a key element of physical fitness.

**MUSCLE STRENGTH**

Muscle strength, the force generated by the contraction of a muscle or muscle groups, is essential to perform daily activities such as walking, climbing stairs, and rising from a chair\textsuperscript{35,36}. The inability to perform daily activities can negatively affect an individual’s state of health. Loss of skeletal muscle strength is related to the risk of falling, cognitive impairment, decline in HR-QoL, and increased mortality\textsuperscript{37,38}. Muscle strength is therefore an essential element of body function in the International Classification of Functioning, Disability and Health (ICF) model. The ICF model provides a common framework for health outcome measurement in rehabilitation and general healthcare and is endorsed by the World Health Organisation (WHO) as a common language that helps standardise and compare the evaluation of healthcare interventions\textsuperscript{36,39}. For persons aged 60 years and older, who represent the main cardiac surgical population, preventing declines in muscle strength is therefore critical for maintaining independent daily functioning and a satisfactory quality of life.

Few studies on the consequences of changes in muscle strength before and after cardiac surgery have been conducted, yet they are needed to increase our understanding of the impact of surgery on muscle strength\textsuperscript{40}. Furthermore, such studies will help define the subgroups that experience the highest impact from surgery on muscle strength. This knowledge is needed to better tailor interventions to the individual. In this thesis, the hand-held dynamometer was used to evaluate grip strength over time in patients undergoing CABG. This grip strength test measures isometric muscle strength and has prognostic value for all-cause death, cardiovascular disease, HR-QoL, and postoperative complications after cardiac surgery\textsuperscript{41–43}. In this thesis, a latent class growth mixture modelling (LCGMM) was used to determine subgroups
based on changes in weight-normalised grip strength before and after CABG (chapter 2). Subsequently, we examined the prognostic value of weight-normalised grip strength on postoperative HR-QoL in these identified subgroups.

A muscle group that is essential for daily activities (e.g., walking and climbing stairs) are the knee extensors. Measuring knee extensor strength will provide an additional value, along with grip strength, to obtain a better understanding of changes in overall muscle strength. A muscle strength test measuring knee extensor strength is therefore important to evaluate rehabilitation interventions such as the Heart-ROCQ programme for patients undergoing cardiac surgery. Unfortunately, knee extensor strength is often not measured in clinical studies, possibly because the existing devices used to test muscle strength are not always suitable for accurately measuring the high forces of this muscle group. Consequently, a portable device to measure the isometric muscle strength of the knee extensors in clinical studies was developed and tested in this thesis (chapter 3).

**CURRENT CARDIAC REHABILITATION**
Cardiac rehabilitation is a key component on the continuum of postoperative clinical care to restore physical fitness. According to the WHO, rehabilitation is a set of interventions designed to optimise functioning and reduce disability in individuals with health conditions in interactions with their environments. Cardiac rehabilitation aims ‘to favourably influence the underlying cause of cardiovascular disease as well as to provide the best possible physical, mental, and social conditions’. Postoperative multidisciplinary outpatient cardiac rehabilitation programmes, including physical therapy and psychological counselling, are recommended throughout the world. Typically, a postoperative cardiac outpatient rehabilitation programme, as is common in the Netherlands, consists of physical therapy twice a week for six weeks. A physical therapy session generally consists of 30 minutes of cycling and 30 minutes of sports and games, relaxation therapy, or resistance training. In addition, four educational sessions may provide knowledge and information regarding risk factors and the requirements for a healthy lifestyle. A study in the Netherlands found that patients who followed outpatient cardiac rehabilitation programmes as part of standard care obtained substantial survival benefits for up to four years after cardiac surgery. In addition, participation in postoperative cardiac rehabilitation outpatient programmes is associated with lower levels of kinesiophobia, reduced hospital admissions, and improved HR-QoL.

**PREHABILITATION AND REHABILITATION SOON AFTER CARDIAC SURGERY**
Prehabilitation is an intervention that commences before cardiac surgery and is intended to optimise a patient’s preoperative mental and physical health status, with the aim of reducing the risk of postoperative morbidity. Despite the limited number of randomised controlled trials, the effects of prehabilitation have been reviewed in other different surgical patient groups, such as orthopaedic, oncological,
and abdominal surgeries\textsuperscript{54–62}. In lung cancer surgery, prehabilitation (i.e., 1–2 weeks, 3–10 times per week, including inspiratory muscle, resistance, and aerobic exercise training) was effective in reducing postoperative complications and length of hospital stay\textsuperscript{62}. However, in patients undergoing other oncological surgeries the evidence was too limited to draw conclusions concerning its effectiveness\textsuperscript{62}. Other reviews among different patient groups also concluded prehabilitation had promising effects, but they also noted the limited amount of available data and emphasised the need for large, high-quality controlled trials\textsuperscript{54,58–61}.

In cardiac surgery, prehabilitation studies have mainly focused on the effects of single component interventions, and on inspiratory muscle training (IMT) in particular\textsuperscript{4,63}. During IMT, inspiratory muscles were trained using an inspiratory threshold-loading device\textsuperscript{18}. In patients listed for CABG following preoperative IMT, declines in pulmonary postoperative complications and shorter hospital stays have also been reported\textsuperscript{4,63}. The advantage of IMT is that it is safe and feasible in high-risk patients\textsuperscript{64}. However, an obvious disadvantage of IMT is that it only targets the inspiratory muscles and no other essential parts of the body are involved.

Alternative training modalities that comprise the whole body and may also be feasible during prehabilitation are aerobic exercise and resistance training. Both training modalities are, in addition to IMT, included in the Heart-ROCQ programme owing to their benefits. Moreover, similar to effective preoperative rehabilitation programmes in cancer patients, the Heart-ROCQ programme consists of a combination of different training modalities, including aerobic bicycle exercise training to improve physical fitness and resistance training to improve muscle strength and power\textsuperscript{62}.

Aerobic exercise and resistance training are already standard in postoperative outpatient cardiac rehabilitation programmes. In contrast, there are no specific guidelines for these training modalities while awaiting cardiac surgery. There has been little research into the feasibility and effects of prehabilitation programmes that include aerobic exercise and/or resistance training (Table 1.1). This lack of research may also be due to hesitancy in offering training modalities that comprise the whole body to patients who are considered at risk during exercise. Despite these risks, the prehabilitation programmes, consisting of aerobic exercise or resistance training, that have been provided to patients awaiting CABG have shown no increases in adverse event rates\textsuperscript{21–23,65}. Moreover, these studies have shown that these programmes may have the potential to improve HR–QoL and the distance walked in the six-minute walk test (Table 1.1)\textsuperscript{21–23}. However, HR–QoL was not improved in the prehabilitation group in two studies and two other studies showed no improvements in exercise performance\textsuperscript{21–23,65}. These inconsistent results may be due to differences in the training characteristics of the studied prehabilitation programmes, such as type, intensity, length, and frequency\textsuperscript{22,65}. Evaluating such training characteristics is essential for acquiring knowledge about the feasibility and working mechanisms of any such prehabilitation programme. Therefore, this thesis presents detailed information concerning the characteristics of the aerobic exercise and resistance training sessions conducted by patients who were scheduled for cardiac surgery (chapter 4).
INTRODUCTION

Since the aforementioned prehabilitation studies mainly focused on the effects of prehabilitation in patients who underwent CABG, in this thesis we also investigated the short-term effects of the prehabilitation phase of the Heart-ROCQ-pilot programme in patients undergoing higher risk surgeries, such as valve, aortic, or combined procedures (chapter 5). Chapters 4 and 5 describe data from the pilot study of the Heart-ROCQ programme, which was implemented in February 2015 at the Center for Rehabilitation at the University Medical Center in Groningen (UMCG), the Netherlands.

In addition, this thesis presents detailed information about the feasibility of aerobic exercise and resistance training soon after surgery because, as with prehabilitation, little is known about cardiac rehabilitation that commences soon after surgery (chapter 4). This knowledge gap may be explained by the fact that bed rest has traditionally been seen as an important part of postsurgical treatment. Furthermore, active (clinical) cardiac rehabilitation soon after surgery may not have been promoted to protect patients from the presumed potential risks. However, a rehabilitation programme that considers patient limitations but focuses on safe and feasible resistance exercises could promote higher fitness levels. Indeed, a recent review suggested that early cardiac rehabilitation including aerobic exercise training can be safely provided soon after cardiac surgery and can show greater improvements in functional and aerobic capacity than in patients following usual care. It should be noted that the review in question included randomised controlled trials with small sample sizes (total group size < 75 patients) and low-risk patients. Another review showed trends towards greater improvements in physical and functional recovery following resistance training after median sternotomy, without an increase in adverse events. However, these results were not statistically significant, possibly because of a lack of power.

In summary, well-designed studies with larger sample sizes to acquire sufficient power in more high-risk patients are needed to show the feasibility and safety, as well as the short- and long-term benefits of cardiac rehabilitation before and soon after surgery. In May 2017, we initiated the Heart-ROCQ PROBE study to evaluate the effects of the final Heart-ROCQ programme compared with a regular Dutch postoperative outpatient cardiac rehabilitation programme. A description of the design of the Heart-ROCQ PROBE study can be found later in this thesis (chapter 6). This thesis also presents the interim results of this study (chapter 7).

THESISAIMSANDOUTLINE

This thesis has three different aims that form the cornerstones and initiation of the Heart-ROCQ PROBE study, with the overall aim of improving cardiac rehabilitation before and after cardiac surgery to prevent postoperative complications and improve postoperative HR-QoL. The first aim of this thesis was to investigate muscle strength as a predictor of postoperative HR-QoL by examining the time course of muscle strength, using grip strength, in individuals before and after cardiac surgery. Considering the importance of leg function in daily life, a clinical testing device to measure...
the isometric muscle strength of the knee extensors was developed and evaluated in a healthy age–matched cohort. The second aim was to evaluate the preparation or pilot phase of the Heart–ROCQ programme. More specifically, the aim was to determine the feasibility and benefits of the Heart–ROCQ–pilot programme, a pre- and postoperative cardiac rehabilitation programme, on surgical outcomes in patients undergoing elective cardiac surgery. Third, this thesis aimed to initiate a trial to compare the final Heart–ROCQ programme with standard care and to analyse its interim results.

An outline of the thesis is presented in the following paragraphs. Chapters 2 and 3 focus on the prognostic value of changes in muscle strength before and after cardiac surgery. Chapter 2 identifies distinct trajectories of muscle strength in patients undergoing CABG and explores their prognostic value in HR-QoL after CABG. In chapter 3, the test–retest reliability of the Q-Force II, an isometric knee extension testing device, is examined.

Chapters 4 and 5 concern the preparation or pilot phase of the Heart–ROCQ programme. In chapter 4, we study whether the Heart–ROCQ–pilot programme is feasible for patients undergoing cardiac surgery. More specifically, we investigate the compliance and the ability of elective cardiac surgical patients to increase their training load before and immediately after surgery. In chapter 5, the potential short–term postoperative benefits for in–hospital acquired complications and unintended consequences of the preoperative phase of the Heart–ROCQ–pilot programme are evaluated using a (partly) historical group.

Based on the results of the pilot studies for the Heart–ROCQ–pilot programme, we initiated a prospective randomised, open, blinded endpoint (PROBE) trial to compare the final Heart–ROCQ programme with a regular Dutch postoperative outpatient cardiac rehabilitation programme. Chapter 6 describes the design of this so–called Heart–ROCQ PROBE study, and chapter 7 discusses the first interim results of the impact of the Heart–ROCQ programme on the primary composite outcome compared to usual operative care. Finally, a summary of the findings of this thesis and future perspectives are presented in chapter 8.
<table>
<thead>
<tr>
<th>STUDY</th>
<th>n</th>
<th>PATIENTS</th>
<th>WAIT TIME</th>
<th>DURATION</th>
<th>MODALITY</th>
<th>FREQUENCY</th>
<th>INTENSITY</th>
<th>TIME (MIN)</th>
<th>PRE- AND POSTOPERATIVE OUTCOMES</th>
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<tbody>
<tr>
<td>Arthur 2000&lt;sup&gt;21&lt;/sup&gt;</td>
<td>249</td>
<td>Low-risk CABG</td>
<td>11 weeks</td>
<td>8 weeks</td>
<td>Walking, stretching, cycling, arm ergometry, stair climbers&lt;sup&gt;3&lt;/sup&gt;</td>
<td>2 x p/wk</td>
<td>40–70% functional capacity</td>
<td>90 min</td>
<td>↓ Length of stay ↑ HR-QoL = Exercise performance = Anxiety = Health services utilisation = Social support</td>
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<tr>
<td>Rosenfeldt 2011&lt;sup&gt;65&lt;/sup&gt;</td>
<td>117</td>
<td>CABG and/or valve</td>
<td>10 weeks</td>
<td>2 weeks</td>
<td>Stretching, cycling, walking, arm ergometry&lt;sup&gt;3&lt;/sup&gt;</td>
<td>2 x p/wk</td>
<td>60% expected HRmax</td>
<td>60 min</td>
<td>= HR-QoL = Length of stay = Atrial fibrillation</td>
</tr>
<tr>
<td>Sawatzky 2014&lt;sup&gt;22&lt;/sup&gt;</td>
<td>17</td>
<td>CABG</td>
<td>~11 weeks</td>
<td>8 weeks</td>
<td>Walking, cycling&lt;sup&gt;3&lt;/sup&gt;, resistance exercise&lt;sup&gt;3&lt;/sup&gt;, stretching&lt;sup&gt;3&lt;/sup&gt;</td>
<td>2 x p/wk</td>
<td>85% of VO2peak</td>
<td>60 min</td>
<td>↑ Six-minute walk distance = Physical activity = HR-QoL = Depression = Anxiety = CE-SE</td>
</tr>
<tr>
<td>Steinmetz 2020&lt;sup&gt;23&lt;/sup&gt;</td>
<td>230</td>
<td>CABG</td>
<td>2.5 to 3 weeks</td>
<td>2 weeks</td>
<td>Cycling, breathing exercises, coordination exercises</td>
<td>3 x p/wk</td>
<td>70% of VO2peak</td>
<td>35–65 min</td>
<td>↑ Six-minute walk distance ↓ TUG time ↑ HR-QoL&lt;sup&gt;5&lt;/sup&gt; = Exercise performance</td>
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<sup>1</sup> All trials compared the intervention to standard care and did not report whether the exercise was monitored and/or adjusted when considered necessary; <sup>2</sup> Total group; <sup>3</sup> Intervention included additional modules for psychological support<sup>21, 65</sup>, smoking cessation<sup>46</sup>, or education sessions<sup>22</sup>; <sup>4</sup> Two out of eight participants participated in these modalities; <sup>5</sup> Significant improvements observed only in preoperative period. CE-SE: cardiac exercise self-efficacy; HR-QoL: health-related quality of life; TUG time: time to perform the timed-up-and-go test.
CHAPTER 1

References


INTRODUCTION


CHAPTER 1


