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Eccentric cycling in the immediate postoperative phase following coronary artery bypass surgery: A proof of concept study

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Eccentric cycling in the immediate postoperative phase following coronary artery bypass surgery: A proof of concept study

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Certification

I, Mathew Doyle, declare that this thesis, submitted in partial fulfillment of the requirements for the award of Masters by Research, in the school of Medicine, University of Wollongong, is wholly my own work unless otherwise referenced or acknowledged. This document has not been submitted for qualifications at any other academic institution.

Abstract

Background: Immobility and physical inactivity following coronary artery bypass graft (CABG) surgery can lead to significant functional decline, due to a combination of central haemodynamic and peripheral tissue changes. In the immediate post-operative recovery, there is opportunity for exercise interventions that target skeletal muscle health. Eccentric cycling describes the use of a motor-driven, self-pedalling bicycle ergometer to allow participants to resist the turning of the cycle wheel and thus perform repetitive muscle lengthening contractions. This exercise modality requires lower cardiorespiratory demand than workload-matched concentric exercises such as walking or traditional concentric cycling, while still engaging skeletal muscle. Outpatients with cardiorespiratory and other chronic disease have experienced clinical improvements following low-load eccentric cycling exercise, however there is a paucity of ergometers available for use in a hospital setting, where maintaining haemodynamic stability and minimising patient relocation is imperative. As such, eccentric cycling has not yet been studied in a hospitalised patient cohort, where its value in the immediate post-operative environment needs urgent attention

Aims: This thesis is comprised of two main objectives. First, to design and construct an eccentric cycle ergometer specifically tailored to deliver low loads to patients in an acute care hospital setting. Second, to investigate whether eccentric cycling, provided at the bedside, can be practically and safely performed in the acute recovery after cardiac surgery, by observing the heamodynamic and peripheral muscle oxygen utilisation characteristics, and compare peripheral skeletal muscle oxygenation to walking at hospital discharge.

Methods: In study 1, an eccentric cycle ergometer (125 W AC) was custom-designed and built to be used by hospitalised patients, to perform low workload eccentric cycling, using visual feedback (power). The completed mobile eccentric cycle ergometer was tested using eight (n=8) healthy adult participants in a laboratory setting. After confirmation of eccentric workload load capacity, study 2 enrolled hospital patients (age; 61.6±10.3 years, BMI; 28.6±6.2 m2; 23 males and 1 female) to perform repeated bouts of low-intensity eccentric cycling following uncomplicated CABG. Pre and postoperative heart rate, blood pressure, arterial and skeletal muscle oxygen saturation were collected using continuous 12-lead ECG, automated sphygmomanometry and near-infrared spectroscopy respectively. Participants performed 10-minute exercise sessions, under supervision, on up to three occasions, commencing from the third postoperative day until hospital discharge. Workload was self-prescribed based upon ratings of perceived exertion using a maximum of 4/10 as a cut off. Functional capacity was assessed using a 20-meter walk for gait speed performed at hospital discharge.

Results: In study 1, all participants completed the protocol in its entirety with no mechanical issues with the ergometer. Mean power output for the two eccentric workloads was 31.1±5.7 W and 56.6±8.8 W respectively. Heart rate (rest: 68±13bpm) and minute ventilation (rest: 12.4±3.5 L.min-1) increased incrementally with workload 1 (HR: 83±16bpm MV: 21.76±6.5 L.min-1, p<0.001 v rest) and workload 2 (HR: 94±14 bpm MV: 26.5±8.9 L.min-1, p<0.001 v rest) while peripheral arterial oxygen saturation (98±1%) and local muscle oxygen saturation of the quadriceps muscle (89±5%) was sustained for both workloads. Participants did not report any muscle soreness following the exercise. The

eccentric cycle ergometer performance was deemed reliable for the feasibility study in the post-operative CABG patient cohort.

In study 2, mean workload was assessed during consecutive eccentric cycling sessions, with a maximum of three eccentric cycling sessions performed prior to hospital discharge. The mean workload significantly increased during the second and third eccentric cycling sessions, albeit partly as a factor of increased cycling cadence. By the commencement of the third eccentric cycling session, cadence approached the pre-determined limit for safety (30 rpm) and was maintained over the duration of 10 minutes. Rate of perceived exertion increased in line with the workload, but was always retained at or below 4/10, over the course of the 10 minute bout. In session one, heart rate significantly increased from rest (87±11 bpm) to a maximum mean of 93±11 bpm ($P<0.05$) and this response was equivalent in session two and three (<10bpm despite increased workloads in those 10 min bouts). Muscle oxygen saturation was not disturbed from resting values by the eccentric workloads, maintaining a consistent tissue saturation index of 30-35% whilst arterial oxygen saturation was preserved (>95%).

Conclusion:

An eccentric cycle ergometer for the hospital environment was successfully designed and constructed and was able to deliver consistent low-workloads to a healthy adult population. Following transfer of this ergometer to a hospital setting, 24 patients performed repeated bouts of eccentric cycling using workloads up to 40 watts, with no significant change in skeletal muscle oxygenation despite increasing workloads. No adverse medical events were encountered during the eccentric cycling exercise. This is the first study of hospitalised patients performing eccentric cycling exercise. The potential for improved patient outcomes, including the attenuation of physical capacity loss, may now be addressed in a range of hospitalised patients with low physiologic reserve.

Abbreviations

6MWT – 6 minute walk test

6MWD – 6 minute walk distance

ACS - acute coronary syndrome

AF – atrial fibrillation

BMI – body mass index

BP – blood pressure

BPM – beats per minute

CABG – coronary artery bypass graft

CAD – coronary artery disease

COPD – chronic obstructive pulmonary disease

CPET – cardiopulmonary exercise test

CR – cardiac rehabilitation

DOMS – delayed onset muscle soreness

ECG – electrocardiogram

ERAS – enhanced recovery after surgery

HR – heart rate

ICU – intensive care unit

M – meter

NIRS – near-infrared spectroscopy

PAD – peripheral arterial disease

PCI – percutaneous coronary intervention

POD – postoperative day

ROM – range of motion

RPE – rating of perceived exertion

RPM - revolutions per minute

RR – respiratory rate

SpO2 – arterial oxygen saturation

TLX – task load index

W - Watts

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Presentations and publications

Publications

1. Doyle MP, Indraratna P, Tardo DT, Peeceeyen SCS and Peoples GE. Safety and efficacy of aerobic exercise commenced early after cardiac surgery: A systematic review and meta-analysis. Eur J Prev Cardiol. 2019, Vol. 26(1) 36–45. DOI: 10.1177/2047487318798924

2. Doyle MP, Brown M, Kemp L, McLennan P and Peoples GE. Eccentric cycling ergometer to address skeletal muscle dysfunction in hospitalised patients: ergometer design, construction and demonstration. *BMJ Innov* 2020;**0**:1–7. doi:10.1136/bmjinnov-2019-000403

Presentations:

Doyle MP. Early aerobic exercise after coronary artery bypass graft surgery: A systematic review. ANZSCTS Annual Scientific Meeting 2016, 6–9 November, Cairns Convention Centre Cairns, Queensland, Australia

Doyle MP. Characterisation of Skeletal Muscle Oxygen Kinetics After Cardiac Surgery. ANZSCTS Annual Scientific Meeting 2018, 8-11 November, Sofitel Noosa Pacific, Queensland, Australia. DOI: 10.1016/j.hlc.2019.02.044

Doyle MP. American Association of Thoracic Surgeons Annual meeting, 2020. New York, USA April 25-28. (presentation accepted not delivered due to COVID-19 pandemic).

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Conceptual overview

Cardiac surgery, in particular coronary artery bypass graft surgery (CABG) utilising cardiopulmonary bypass (CPB), has been safely and routinely performed since the 1960's [1,2]. Despite the established morbidity and mortality benefits of CABG, a degree of postoperative morbidity may relate not only to the underlying disease pathology but to the procedure itself.

For all patients who undergo CABG, functional capacity is reduced in the postoperative period. This may be either as a cause or consequence of their underlying cardiac disease [3]. This functional reduction following CABG may be accelerated in susceptible populations including the elderly, physically frail, chronically diseased, and previously physically inactive [4–6]. Although immobilisation and bed rest have been identified as significant contributors in reducing functional capacity [7–9], periods of bedrest and immobilisation are required in the immediate postoperative period after CABG. It is during these periods that much of the postoperative morbidity is encountered or at least initiated. Patients may also be subjected to several days of low mobility periods preoperatively if admitted to hospital with acute medical issues such as acute coronary syndrome, syncope or heart failure.

Regardless of the cause, patients that are restricted to bedrest (bed lying and sitting) are at risk of profound deconditioning and morbidity [10,11]. Decreased muscular strength, increased bone resorption, and lower total energy expenditure can ensue even short periods of bed rest [12].With this in mind, every effort should be made to minimise physical inactivity and, if possible, provide safe, effective exercises that can be performed by these patients whilst in hospital that aim to minimise the functional capacity lost whilst recovering from surgery.

Early mobilisation and exercise regimes following CABG have generally been restricted to respiratory exercises aimed at reducing pulmonary complications and mobilisation via ambulation. Mobilisation is usually commenced once patients have invasive monitoring removed and provided no other medical contraindications are present (such as continuous intravenous infusions). The aims of early mobilisation are twofold; to reduce the incidence of postoperative complications (particularly pulmonary), and to improve functional capacity [13,14]. Several studies have reported favourable results following the implementation of low to moderate intensity exercise regimes early in the post-operative period using walking and stationary cycling [15–17]. However these activities require staff with appropriate training in exercise prescription after cardiac surgery as well as supervision for patients performing the exercise. Additionally, these exercises may pose too great of a physiological demand for susceptible patients after major cardiac surgery. In such instances, patients have no available therapy to provide the muscles of ambulation with adequate stimulation to avoid functional decline. Eccentric exercise, specifically using lower limb cycle ergometry, has cardiopulmonary and metabolic characteristics that favour its use in patients with cardiovascular disease. The most noticeable and potentially favourable characteristic is the energy cost to produce the same absolute work rate is far less during eccentric contractions compared to concentric contractions. Since one of the earliest demonstrations of this physiologic phenomenon[18], these results have been consistently demonstrated across a wide range of workloads and patients. More recently, eccentric cycling has demonstrated improvement in physiologic parameters as well as the functional status of patients with several chronic disease states including heart failure [19] , chronic obstructive pulmonary disease (COPD) [20-21] and the elderly and frail [22, 23], improving outcomes such as leg strength, balance, quality of life and functional capacity. These results provide strong rationale to engage hospitalised patients in eccentric cycling. Furthermore hospitalised patients, particularly those that have undergone CABG, experience an acute derangement in functional capacity that could potentially be attenuated by lower limb skeletal muscle loading while avoiding cardiopulmonary stress. Despite how well suited eccentric cycling appears for patients following CABG, to date there are no reports of this exercise modality being assessed in any hospitalised patients.

Patients in hospital for whom eccentric cycling would be most beneficial are likely to be confined to their hospital bed space, due to physical capacity limitations and/or monitoring and treatment requirements. The use of a cycling ergometer is appealing for these patients as patients can remain semi-recumbent, minimising the baseline physical capacity require to commence participation. The use of a stationary cycling ergometer provides the additional advantage of being able to be performed in the patients' immediate bed area. A major barrier to the use of eccentric cycling for hospitalised patients is the lack of an ergometer with an appropriate design for mobile use in a hospital environment. Commercially-available eccentric ergometers are designed to deliver large workloads and the mechanical components required to perform these workloads make these ergometers too heavy, loud and immobile for use at the bedside. If an eccentric cycling ergometer could be constructed that is mobile and quiet, it could be deployed to multiple hospital bed spaces sequentially, allowing multiple patients to access eccentric cycling training. The workload capacity of such as ergometer would not need to be as large as that of ergometers designed for use in healthy populations.

This thesis aims to perform a series of studies that addresses the forementioned concepts of delivering eccentric to a unique group of hospitalised patients; those following CABG. This patient cohort provides a unique opportunity to identify the impact of eccentric cycling exercise on central haemodynamic and peripheral skeletal muscle physiology. In order to perform this assessment however, an ergometer appropriate for use in the hospital must first be designed and constructed. If eccentric cycling demonstrates similar characteristics to previous studies such as less oxygen consumption than walking for an equivalent workload (i.e.: at a lower metabolic “cost”) with low haemodynamic variation in patients, this could have implications for both usual postoperative care in cardiac surgery patients and the potential to expand into other cohorts of patients where inactivity and bed rest are a major determinant of morbidity during hospital admission.

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1. Background and rationale

1.1. Coronary artery bypass graft surgery

The global burden of cardiovascular diseases is rising and the number of people expected to undergo cardiac surgery is projected to follow [1]. The most common cardiac surgery performed both globally and in Australia is CABG [2]. CABG is the gold standard for coronary revascularisation due to obstructive coronary artery disease (CAD) for several indications including multi-vessel obstruction, left main coronary artery obstruction and diabetic patients [3]. Revascularization via CABG of anatomically-identified, haemodynamically-significant coronary artery stenosis improves prognosis, relieves symptoms, prevents ischaemic complications and improves functional capacity [4].

1.1.1. Technical overview of CABG

Coronary artery bypass graft surgery utilises arterial and/or venous autografts in order to provide conduits for surgical revascularisation of obstructed epicardial coronary arteries. Access to the heart is gained by dividing the sternum longitudinally (median sternotomy), with CPB utilised to both expose and protect the myocardium during surgery. Coronary artery bypass graft surgery requires mechanical oxygenation and ventilation to facilitate anaesthesia for the duration of surgery. The heart is arrested using a perfusate given directly into the aortic root and/or coronary sinus in order to minimise myocardial metabolic activity for the duration of surgery. At the completion of revascularisation the heart is weaned from CPB, often with the assistance of inotropic and/or vasoactive pharmacologic support. The sternum is reapproximated with stainless steel wire cerclage and the soft tissues of the wounds are approximated using absorbable sutures.

1.1.2. Physiologic impact of CABG

At the completion of surgery, following the restoration of myocardial blood flow, a degree of temporary myocardial dysfunction often ensues [2,3]. The use of CPB also results in a systemic inflammatory response induced from contact of the blood components with the artificial surface of the bypass circuit. Ischemia–reperfusion injury, endothelial dysfunction and endotoxemia occur as a result, and may contribute to postoperative complications including myocardial dysfunction and respiratory failure [3]. Coagulopathy can occur from a systemic inflammatory response from CPB causing platelet dysfunction as well as residual heparin effect at the completion of CPB. Consumption of clotting factors may also result from ongoing bleeding and may need to be replaced based on clinical assessment and biochemical assays. This culmination of physiologic alterations means patients are returned to the ICU being mechanically ventilated and closely monitored with invasive monitoring for several hours following surgery. Furthermore, mediastinal, pleural and/or pericardial drains are placed at the completion of surgery in order to drain residual fluid from the operative field. Both median sternotomy incision and the presence of drains can cause pain [4], leading to poor inspiratory effort and atelectasis with or without pulmonary consolidation, as well as local inflammation, which can in turn cause pericarditis and pericardial and/or pleural effusions. Following sternotomy, a period of precautionary upper limb movements and loading is also required to facilitate sternal bone union and to limit infection risk.

This description is not exhaustive but outlines some of the complex physiologic changes experienced by patients undergoing CABG. The sequalae of these physiologic events is, in most cases of uncomplicated CABG, a predictable postoperative clinical course.

1.1.3. Postoperative recovery

The postoperative recovery following CABG is unique in that it requires a period of complete immobility in the immediate postoperative hours. This time period is not fixed; it is determined by a combination of patient and the above-mentioned operative factors. This interval of bed rest can be almost inconsequential in cases of uncomplicated CABG performed in patients with minimal comorbidities. Some patient cohorts however are at higher risk of prolonged immobilisation and bed rest and, therefore, exposed to a range of complications associated with complete immobility. The postoperative care has been refined over decades and now the majority of elective patients are discharged from hospital approximately one week following surgery [5]. Some cardiac surgery centres have post-operative protocols to streamline the inpatient progression from intensive care admission to hospital discharge [6]. The use of these clinical pathways helps reduce hospital length of stay for uncomplicated CABG patients. Very recently, enhanced recovery after surgery (ERAS) guidelines have been published however mobilisation and exercise is not yet included in these recommendations [7].

1.1.4. Cardiac rehabilitation

Cardiac rehabilitation (CR) is the coordinated physical, social and psychological intervention for patients following cardiac surgery, that favourably influences the underlying risk factors [5]. As recently as the 1970's, patients were under strict advice to refrain from any strenuous activity for many weeks following CABG, with some practices advocating complete bed rest [21,22,29-31]. However, deleterious effects of physical inactivity following CABG have been identified and CR in the modern era is now obliged to include tailored exercise prescription for all patients following CABG, as this has produced irrefutable reductions in mortality, hospital admissions and improved functional and peak exercise capacity [8–11].

Cardiac rehabilitation consists of three distinct phases in order to provide patients with appropriate interventions during all stages of their postoperative recovery. Phase 1 encompasses the acute hospitalisation, while phases 2 and 3 are outpatient phases, focused on transitioning patients from a supervised program to lifestyle modification and long-term maintenance. Cardiac rehabilitation provides the following benefits and support for patients following CABG [12,13]:

i) Exercise capacity assessment and supervised aerobic exercise prescription and training.
ii) Improvement in functional capacity
iii) restoring quality of life following surgery
iv) education and counselling for medication adherence and lifestyle modification

These results and recommendations have been derived from outpatient CR, most of which have a predominant exercise component. Typically, this rehabilitation commences 4-6 weeks after surgery and is referred to as phase 2 CR [14,15]. While phase 2 CR has established strong benefits for morbidity and mortality reductions for patients after CABG, phase 1 or inpatient CR remains a relatively under-utilised and under-studied intervention. With this in mind, the current thesis has primarily focussed on designing a novel approach to exercising during phase 1 CR; the immediate postoperative recovery period following CABG.

1.2. Phase 1 cardiac rehabilitation (Exercise in the immediate postoperative period)

In the modern era patients are actively encouraged to become ambulant following surgery as soon as it is medically safe to do so. Phase 1 CR aims to minimise morbidity associated with inactivity and foster early postoperative discharge by maximising physical function [6,7]. The coordinated application of exercise and education regarding cardiac risk factors whilst patients remain in hospital following CABG typically consists of physiotherapy-prescribed respiratory exercises [16] plus an exercise program usually consisting of stationary cycling or walking. Postoperative physiotherapy regimes have traditionally included respiratory exercises aimed at reducing pulmonary complications and gradual walking progression until independent stair climbing can be achieved. The use of respiratory exercises, primarily with the goal of reducing pulmonary postoperative complications, has not demonstrated clinically significant benefits [17]. Exercise in the immediate postoperative period on the other hand, with either walking or stationary cycling, has emerged as safe and effective option for improving functional and ventilatory capacity following cardiac surgery [18]. It should be noted that these exercises primarily utilise concentric skeletal muscle contractions. Typically, patients who have undergone uncomplicated CABG will progress to supervised walking within two to three days after surgery.

The progression from chair sitting to walking however may be particularly challenging for patients with pre-existing reduced functional capacity. Walking requires adequate lower limb strength, balance and a metabolic capacity of at least double that of sitting quietly in a chair [19]. Furthermore the patients that are likely to find this progression most challenging are the same patients that are likely to experience higher rates of postoperative complications and morbidity; those with heart failure, respiratory disease, obese and frail patients. If the return to independent mobilisation is prolonged either by the pre-existing patient morbidity or postoperative complications, further functional decline can follow. As the return to independent mobilisation is prolonged either by baseline characteristics of the patient or postoperative complications, further functional decline may ensue making the return to independence even more elusive. An exercise modality that improves balance, strength and other functional domains without the haemodynamic demands of walking would be ideal for these patients.

1.2.1. Systematic review

As part of the background of this thesis, a systematic review and meta-analysis was performed investigating the safety and efficacy of exercise when commenced within the first week following CABG [18]. Current recommendations prohibit strength-based exercise being performed within this timeframe. Therefore only aerobic or functional-based exercises were included.

The electronic databases Medline, ProQuest, Web of Science, ScienceDirect and Cochrane Central Register of Controlled Trials were searched from their dates of inception to July 2017. The search terms 'cardiac surgery' or 'heart surgery' or 'heart valve surgery' or 'coronary artery bypass' or 'CABG' were combined with 'early' and (‘rehabilitation’ or ‘exercise’ or ‘mobilization’ or ‘physiotherapy’) as both keywords and MeSH terms. This was supplemented by manually searching the reference lists of key reviews and all potentially relevant studies. Selected studies included those reporting outcomes of aerobic exercise training commenced within two weeks following cardiac surgery. Aerobic exercise was defined as physical activity that induces a steady and sustainable increase in aerobic metabolism when performed at intensity below anaerobic threshold. Non-comparative studies required the intensity of the exercise to be clearly defined according to established physiologic exercise intensity measures (rate of perceived exertion (RPE), metabolic equivalents (METs), percentage of actual or calculated maximum heart rate or volume of oxygen uptake or calculated workload, such as power output in watts). Studies comparing exercise interventions with other care required the difference in exercise intensity to be clearly defined. Isolated walking programmes were only included for analysis if walking intensity was deemed to exceed simple ambulation. Simple postoperative mobilization was also excluded, as an aerobic workload suitable for the purpose of this review is not consistently induced. Studies that performed isolated respiratory exercises were also excluded. Efficacy analysis was performed if functional or metabolic capacity were assessed following an aerobic exercise intervention. Studies reporting on postoperative adverse events and mortality following prescribed exercise were included for safety analysis. All publications were limited to those involving human subjects and written in English. Studies with fewer than 10 patients in an intervention cohort were excluded.

Baseline characteristics and intervention details were presented as raw values (%) or mean ± standard deviation unless otherwise indicated. Pooled values for clinical outcomes were reported as mean ± standard deviation or as otherwise specified. Meta-analysis was performed by combining results of outcome variables. Data were summarized as standard mean difference with overall weighted mean presented where appropriate. I^2 statistic was used to estimate the percentage of total variation across studies, due to heterogeneity rather than chance. An I^2 value of greater than 50% was considered substantial heterogeneity. If there was substantial heterogeneity, the possible clinical and methodological reasons for this were explored qualitatively. A random-effects model was used to take into account the possible clinical diversity and methodological variation amongst studies. Specific analyses considering confounding factors were not possible because raw data were not available. All p-values were two sided. A significant difference was defined as $p < 0.05$.

The systematic review identified eight studies in which aerobic exercise commenced within the first week after surgery [6,16,20–25]. Relevant reported outcomes included functional and aerobic capacity testing utilising a 6-minute walk test (6MWT) and/or cardiopulmonary exercise testing measuring peak oxygen uptake or anaerobic threshold, heart rate variability and functional milestones. The modality of exercise prescribed was either walking, stair climbing or stationary concentric cycling. Seven of the eight studies reported on adverse outcomes during inpatient exercise, and adverse event rates were not significantly different to control group (when control groups were included as a comparison)(fig 1.1). The study characteristics and exercise intervention summaries are presented in tables 1.1 and 1.2.

Table 1.1: Summary of studies that have implemented aerobic exercise during the immediate postoperative period following CABG

Author	Year	Location	Period	Study Type	Exercise patients	Total patients	Intervention Duration
Borges	2016	Brazil	2015	Randomized	15	34	<1 week
Hirschhorn	2012	Australia	2008-2009	Randomized	64	64	<1 week
Mendes	2010	Brazil	NR	Randomized	24	47	<1 week
VanDerPejil	2009	Netherlands	2000-2001	Randomized	246	246	<1 week
Stein	2009	Brazil	NR	Randomized	10	20	<1 week
Hirschhorn	2008	Australia	2004-2005	Randomized	61	92	<1 week, 4 weeks
				Total	420	503	

Table 1.2: Summary of intervention protocols for studies that have implemented aerobic exercise during inpatient recovery after CABG

Intervention Duration	Study	Year	Aerobic Exercise Intervention						Outcome
			Mode	Frequency	Intensity	Time (mins)	Commence (POD)	Completion	
< 1 week (immediate)	Borges	2016	Cycling	Twice daily (ICU) Daily (ward)	NR	5-20	1	Hospital D/C	6MWT
	Hirschhorn	2012	Cycling Walking	Twice daily	RPE 3 – 4	10	3	Hospital D/C	6MWT
	Mendes	2010	Walking	Daily	2 – 4 METS	5 – 10	1	Hospital D/C	HRV
	Stein	2009	Walking	Twice daily	RPE 7/10 *	> 9	2	POD 7	6MWT
	Hirschhorn	2007	Walking	Twice daily	RPE 3 – 4	3 – 10	1	Hospital D/C	6MWT
	Van Der Pejil	2004	Walking Walking	Twice daily Daily	1 – 3.5 METS	< 20	1 1 – 3	POD 6	Functional milestones

In summary, this systematic review identified a total of 420 patients who performed CON aerobic exercise in the immediate postoperative period following CABG. Concentric aerobic exercise sessions were performed for 3–20 min and utilised either concentric cycling or flat level walking. Four studies reported outcomes of the 6MWT for exercise commencing during inpatient recovery, completed at hospital discharge [6,16,21,24]. Overall pooled mean distance walked during the 6MWT at hospital discharge by the exercise intervention group was 420±89m compared with 341±81m in the usual care group. Three studies were included in a meta-analysis comparing 6-minute walk distance (6MWD) at hospital discharge [16,21,24]. There was a statistically significant increase in the 6MWD at hospital discharge for patients who performed aerobic concentric exercise following CABG compared with those who received usual care (419±88m vs. 341±81 m, mean difference 69.5 m, 95% confidence interval (CI) 39.2–99.7 m, $p<0.001$; Figure 1.2). In the two studies that did not measure 6MWD, those performing high frequency aerobic exercise reached most functional milestones significantly earlier than those performing low-frequency exercise [6] and aerobic exercise significantly improved cardiac autonomic function assessed by heart rate variability, compared with usual care [23].

Study or Subgroup	Early Exercise Events	Early Exercise Total	Usual Care Events	Usual Care Total	Weight	Odds Ratio M-H, Random, 95% CI
Adachi 2001	0	34	0	23		Not estimable
Borges 2016	0	15	0	19		Not estimable
Hirschhorn 2007	4	61	4	31	74.1%	0.47 [0.11, 2.04]
Mendes 2010	0	24	0	23		Not estimable
Stein 2009	1	10	3	10	25.9%	0.26 [0.02, 3.06]
Takayama 2000	0	13	0	15		Not estimable
Total (95% CI)		**157**		**121**	**100.0%**	**0.41 [0.12, 1.42]**
Total events	5		7			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.17$, df = 1 (P = 0.68); $I^2 = 0\%$
Test for overall effect: Z = 1.41 (P = 0.16)

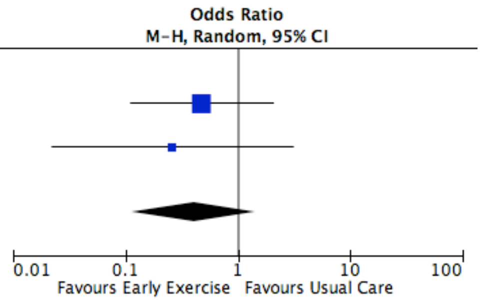

Figure 1.1 Adverse events comparing immediate and early aerobic exercise training to usual care

Study or Subgroup	Early Exercise Mean	Early Exercise SD	Early Exercise Total	Usual Care Mean	Usual Care SD	Usual Care Total	Weight	Mean Difference IV, Random, 95% CI
Borges 2016	348	84	15	292	73	15	28.8%	56.00 [-0.32, 112.32]
Hirschhorn 2007	444	84	31	377	90	31	48.7%	67.00 [23.66, 110.34]
Stein 2009	415	78	10	323	67	10	22.5%	92.00 [28.27, 155.73]
Total (95% CI)			**56**			**56**	**100.0%**	**69.46 [39.22, 99.69]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.71$, df = 2 (P = 0.70); $I^2 = 0\%$
Test for overall effect: Z = 4.50 (P < 0.00001)

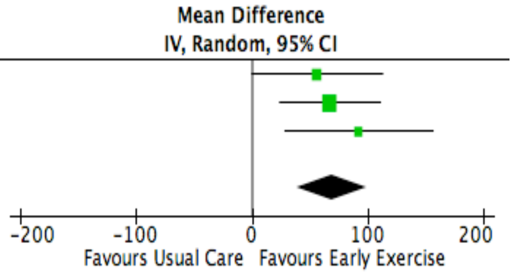

Fig 1.2: 6-minute walk distance (m) at hospital discharge comparing aerobic concentric exercise therapy during inpatient recovery after CABG to usual care

There are several key points to be taken from the abovementioned study results. Firstly and perhaps most importantly, almost all authors reported few to no increases in adverse postoperative events. From a safety perspective, this is critical in considering any form of exercise in the early postoperative period. If there are to be any benefits gained for patients performing exercise during this time, the benefits must not be outweighed by any potential risks or complications. There was one exception; atrial fibrillation (AF) rates described by Macchi [23] were significantly higher in the early rehabilitation group compared to the late rehabilitation group. They address this in their discussion, noting that this increase in new onset AF between the groups could well be accounted for by the fact that new AF post-CABG occurs in over 30% of patients within the first three postoperative days (POD) and less than 5% after POD six [26]. Given that no other studies have shown that AF or any other atrial or ventricular arrhythmias are significantly more common with early postoperative aerobic exercise, the likelihood of the exercise intervention itself being causative to the increased rate of new onset AF is unlikely. No other study identified a significant increase in AF rates in an exercise intervention group compared to a control group, regardless of the intervention. Other postoperative complications including pulmonary complications (pleural effusion, pneumonia, atelectasis), wound infection, cardiac events including malignant ventricular arrhythmias and death were not increased in any exercise group in any study.

Secondly, these studies mostly included only patients who had undergone uncomplicated surgery, with few-to-no comorbidities. This likely misrepresents the population of patients undergoing CABG in modern clinical practice, as they are more likely to be older with multiple comorbidities. The exercise interventions described in the studies above, as well as those performed in the future, should aim to include as many complex patients as is safe to do so, as these patients are most likely to experience longer hospital admission and therefore longer period of immobility and greater functional decline.

Finally, the use of alternative modes of exercise to improve functional capacity has been explored in some of these populations. Hirschhorn [6] are the only group to have compared walking to another concentric aerobic exercise modality in the early postoperative period. Stationary concentric cycling showed similar improvements in functional capacity at hospital discharge compared with walking, with no difference in postoperative complications [6]. Regardless of the exercise modality (cycling or walking), exercise in the early postoperative period following CABG improves functional capacity and some parameters of respiratory function, while not demonstrating any increase in adverse peri-operative events. The improvements in functional outcomes are evident at hospital discharge and may persist until the commencement of phase 2 CR. This under-utilised stage of CR is an opportunity to provide both usual standard practice of exercise whilst also exploring new more innovative ways of targeting the needs of the patient during the hospital stage of recovery.

1.3. Eccentric exercise as a novel approach during Phase 1 cardiac rehabilitation

1.3.1. Background

Eccentric muscle contractions are an essential component of human movement, occurring during stair descent, bending forwards or lowering a weight. The muscle producing the force lengthens as it contracts, resulting in a negative amount of net work done by the contracting muscle. This is in contrast to concentric contractions whereby the muscle shortens as it contracts and a positive net amount of work is performed. Most human movements require both concentric and eccentric muscle contractions to facilitate stable, smooth and safe range of motion: the muscle group performing the work typically undergoes concentric contraction while the antagonising muscle group provides stability and control by providing an opposing eccentric force. The use of eccentric exercise as a training modality has historically been utilised by athletes, primarily for strength training. The application of heavy loads that overwhelm the ability of muscles to shorten as they contract can result in greater strength gains compared to isolated concentric training alone [27]. This property has facilitated the inclusion of eccentric exercise training in various rehabilitation settings including tendinopathy, soft tissue injury and following anterior cruciate ligament surgery [27,28]. Most recently, continuous submaximal eccentric exercise has begun to be explored as an alternative exercise modality to traditional concentric exercise modalities. Downhill walking and eccentric cycling are examples of such exercise. Downhill walking requires the quadriceps to lengthen during contraction to overcome gravity. Similarly, eccentric cycling utilises a motor-driven ergometer to drive the pedals in a reverse direction while the user applies force to the pedals in order to resist the backwards-turning motion. Exercises such as downhill walking or eccentric cycling using a stationary ergometer have been investigated in rehabilitation populations, primarily for the profound reduction in metabolic cost compared to concentric equivalent workloads [29–31]. These physiologic properties, discussed in more detail in over the next sections, been recognised in modern literature as attractive for patients requiring rehabilitation and those with cardiorespiratory limitations [32,33]. These same authors acknowledge there is a need to further explore low-load eccentric loads, particularly in critically-ill patients. The studies undertaken as part of this thesis encompass these recommendations.

1.3.2. Eccentric cycling

Traditional stationary cycling using an ergometer (stationary exercise bike) predominantly utilises concentric contractions, whereby force is produced via skeletal muscle shortening to perform “positive” work [34]. Alternatively, cycle ergometers may be modified in order to induce predominantly eccentric “negative” contractions [35–38]. There are multiple studies using eccentric cycling ergometers for training amongst varying populations. Healthy participants can perform workloads several-folds higher using eccentric exercise compared to concentric exercise, with identical oxygen consumption [39–41]. These eccentric training groups improved leg strength significantly more than their concentric counterparts. Furthermore, eccentric cycling has demonstrated improvement in the functional status of patients with several chronic disease states including heart failure [42–44], COPD [45–49]and the elderly [50–52]. Leg strength, balance, quality of life and functional capacity have all been positively affected with the application of eccentric cycling in these populations. The most recent advances in eccentric loading indicate that even low load eccentric endurance activities that do not necessarily cause significant muscle soreness or discomfort can still induce physiologic and functional benefits, especially in pathology groups and those with extremely low exercise tolerance [53–55]. The efficacy of a similar approach to patients following CABG shows great potential.

1.3.3. Beneficial Mechanisms

There are several unique properties of eccentric exercise that make it an attractive application in a rehabilitation setting, particularly for patients following CABG. The primary metabolic property of eccentric cycling, as discussed above, is that the energy requirements for eccentric contractions at a given workload are significantly less than that required for concentric contractions at the same workload [34,37,56,57]. Based on this unique property, equivalent workloads can be achieved at a lower cardiorespiratory cost compared to other concentric exercises that have traditionally been used in rehabilitation (walking and concentric cycling). While understanding of the oxygen-sparring mechanism is not yet complete, lower muscle activation and lower utilisation of cellular energy are important cellular processes contributing to the low oxygen demand [57,58]. This is further supported by increased efficiency of glucose utilisation [55] and increased fat utilisation [58], as well as a lesser degree of tissue desaturation during eccentric contractions [40,58]. A greater contribution of elastic components in the muscle-tendon complex during eccentric actions has been proposed, thus increasing the potential of force production at reduced energy expenditure [29]. Endothelial function is unperturbed during acute bouts of eccentric exercise [59]. Furthermore, eccentric contractions are associated with greater contractile force production per muscle fibre and less muscle fibre recruitment than concentric contractions with equivalent workloads [56] thereby producing greater muscular hypertrophy and strength gains than can be induced by concentric muscular contractions [60]. Yet such an approach of eliciting the very high workloads is questionable for patients immediately following CABG based on potential adverse outcomes.

1.3.4. Adverse Effects of Eccentric Exercise

Eccentric training has been approached with caution and often avoided due to a fear of delayed onset muscle soreness (DOMS) and muscle damage which has been associated with high intensity eccentric work. Eccentric exercise at high workloads has been linked with intracellular muscle damage, elevated plasma creatine kinase levels, impaired glycogen resynthesis and an acute inflammatory response [61–64]. Additionally, eccentric work is often associated with transient muscle soreness, temporary strength loss, joint stiffness and reduced range of motion (ROM) [61,65]. This soreness can occur at lower exercise intensities than that required to elicit the physiological muscle damage described above.

However, eccentric work does not always elicit DOMS or muscular damage. In fact, repeated exposure to a particular ECC movement may attenuate or eliminate the aforementioned adverse responses completely [38,62,65]. Furthermore, when performed at low loads, both DOMS and myofibrillar damage may be avoided completely [38,66].

1.3.5. Eccentric cycling in patients with low physiologic reserve

There were three broad groups of patients identified in the literature that have been studied using continuous eccentric cycling: patients with respiratory disease, patients with heart failure and the elderly.

Respiratory disease, specifically COPD, results in reduced exercise capacity due to ventilatory limitations and skeletal muscle weakness and fatigue [67]. Exercise is a critical component of treatment for patients with severe COPD, improving exercise tolerance and reducing dyspnoea [67]. While traditional aerobic exercise such as walking and concentric cycling can improve symptoms and functional capacity, patients with severe disease may be limited by breathlessness at low workloads, hence the skeletal muscle stimulus may not be enough to produce favourable adaptations [48,68]. Since the very first demonstration of feasibility of eccentric training in patients with severe COPD, patients performed eccentric cycling workloads several-fold higher than concentrically matched cycling counterparts [45,46,69]. Eccentric cycling has been at least as efficacious, if not better than concentric exercise in improving exercise tolerance, dyspnoea and lower limb strength, for a lower metabolic cost [46,48].

Eccentric exercise has also been investigated in elderly and frail patients. Ageing can affect a patients capacity to perform activities of daily living without undue fatigue [31]. This functional decline is multifactorial however loss of skeletal muscle and function (sarcopaenia) is a primary contributor. Exercise training reduces the muscle dysfunction seen with sarcopaenia [70,71] . Tailored eccentric exercise programs for elderly patients improve physiologic outcomes such as aerobic capacity and strength, as well as clinical variables such as falls risk, functional capacity, and quality of life [53,54]. Continuous eccentric cycling again has only relatively recently been investigated in this population. The physiologic properties of eccentric muscle contractions make this exercise modality well suited to frail patients [31,51,52]. Most studies reported on muscle strength and functional capacity, which both improve following several weeks of eccentric cycling training.

Metabolic cost was lower compared to concentric exercise in all comparisons. Furthermore, muscle soreness could be almost completely avoided by commencing training at low workloads, guided by rate of perceived exertion (RPE), while still incrementing the training loads over the ensuing weeks [52]. Studies on eccentric cycling in the elderly have primarily recruited patients with good levels of physical function. No studies have yet endeavoured to perform eccentric cycling for patients with high frailty scores. The development of a mobile ergometer capable of delivering low-moderate eccentric workloads, together with the low oxygen costs of eccentric cycling provides further support for exploring the potential improvements in physiologic and clinical outcomes for frail patients.

The final group of patients with chronic low physiologic reserve are those with heart failure. Heart failure is a broad term used to describe a clinical spectrum of patients with myocardial dysfunction from a variety of aetiologies [72]. Symptoms are similar to those of both frailty and severe respiratory disease, being dyspnoea and exertional fatigue [72]. Complex neurohormonal and vasogenic mechanisms result in a systemic syndrome that includes skeletal muscle dysfunction [73–75]. Exercise training, as in most chronic disease, provides symptom amelioration as well as quality of life improvement and mortality reduction [10,13,76,77]. Again, the usual exercise modalities for exercise therapy are walking and concentric cycling, with strength training and high-intensity interval training being applicable when patients are selected appropriately. Of all the chronic illness, continuous eccentric exercise using eccentric cycling is perhaps best suited to patients with heart failure as it targets the organ often most debilitated (skeletal muscle) while protecting the primary organ of pathology (heart).

Several groups have investigated the feasibility and then impact of eccentric cycling in patients with chronic, stable heart failure; When matched for RPE, functional outcomes are equivalent between eccentric cycling and concentric cycling [43,44,78]. However this improvement comes at a significantly lower cardiorespiratory demand in those patients performing eccentric cycling [43,44]. Similarly, when workload is matched for power output, oxygen consumption is 13% lower [42]. The study included in chapter three of this thesis is one of the first to investigate muscle saturation responses to eccentric in patients with acute cardiac disease.

1.3.6. Eccentric Exercise in patients with CAD

Eccentric cycling training studies have been performed in patients with CAD. A systematic review of the literature identified four studies investigating the effects of eccentric exercise on various outcomes in patients with CAD [36,79–81]. All four studies were performed in patients with stable CAD. All studies randomised small patient cohorts to either eccentric or concentric exercise. A total of 51 patients were analysed across the four studies, although Steiner and Meyer performed separate studies on the same patient cohort.

Meyer and Steiner [36,79]randomised 13 patients with revascularized CAD to either eccentric or concentric cycling over a period of eight weeks. All patients had undergone previous percutaneous coronary intervention (PCI) (eccentric cycling = 6, concentric cycling = 3) or CABG (eccentric cycling = 2, concentric cycling = 1). They performed 30 minutes of cycling exercise at either 60% of their peak oxygen uptake and/or 85% of peak heart rate (HR). Training intensity was gradually increased to avoid muscle soreness and was capped at the end of week five. Cadence was self-selected by the patients and average cadence was 55 revolutions per minute (RPM) and 80 RPM for the eccentric cycling and concentric cycling participants, respectively. Central venous access was gained via a pulmonary artery catheter placed in the left cubital vein and central haemodynamic measures including right heart and left filling pressures and pulmonary artery oxygen saturation were recorded during subsequent exercise sessions. Throughout the training period, no significant difference was observed in RPE (mean RPE score 9-10 throughout training period for both groups) or the peak HR (64% week 1, 75% week 8) between the eccentric cycling and concentric cycling training groups. The eccentric cycling group achieved a markedly greater power output than the concentric cycling group (357±6 W vs 97±21 W: $P < 0.005$), while oxygen consumption was lower for the eccentric cycling group than the concentric cycling group (oxygen uptake approximately 1500ml/min for CON cycling and 1100ml/min ECC cycling, data presented in graph and exact values not obtainable). AT steady-state exercised, mean arterial blood pressure and capillary wedge pressure was similar between the two groups whilst the eccentric group demonstrated a lower stroke volume index, cardiac index, stroke work, arterial-venous oxygen difference and blood lactate levels. Following the training period, the eccentric group experienced an increase in left ventricular function whilst the CON group did not (ejection fraction: eccentric group 57±7 % to 62±6%, concentric group 65±8% to 63±2%; $p < 0.05$). No diastolic parameters were significantly affected in either group. Peak power output improved significantly in both groups whilst only the eccentric group experienced a significant increase in oxygen consumption.

In 2010, Gremeaux randomised 15 patients to either eccentric or oncentric cycling, within six weeks after PCI for acute coronary syndrome (ACS) (eccentric cycling = 8, concentric cycling = 7). All patients received optimal medical therapy including B-blockade, angiotensin converting enzyme inhibitors, antiplatelet agents and statins.

Patients performed 15 exercise sessions (one session per day, three days per week). Exercise sessions were identical with the exception of the cycling ergometer workout. At the beginning and completion of the exercise program, patients completed a symptom-limited cardiopulmonary exercise test on a cycle ergometer, a 6MWT and a 200m fast walk. Strength was also assessed via maximal isometric knee extension and ankle flexion. Following the 15 exercise sessions, all patients experienced a significant improvement in symptom-limited VO2, peak workload, 6MWD and knee extensor maximal voluntary contraction ($p<0.01$), regardless of the exercise intervention. There was no significant differences between the eccentric and concentric cycling groups for any outcomes, with the exception of ankle plantar flexion strength being significantly more increased in the eccentric cycling than the concentric cycling group after the five weeks of training ($p<0.05$). One patient from the eccentric group required readmission to an acute care hospital for a psychiatric illness, otherwise there were no adverse outcomes including DOMS, arrhythmias or cessation of the exercise program due to any cause.

Zoll and coworkers performed muscle biopsies in order to determine the molecular mechanisms for structural and functional modifications after concentric and eccentric exercise in twelve male patients with stable CAD. Patients participating in CR were randomly assigned to either a eccentric or concentric training program consisting of 30 minutes of either eccentric or concentric cycling or a stationary ergometer, three days a week for eight weeks. Muscle biopsies were obtained from vastus lateralis prior to and at the completion of the training program. They found a reduction in mitochondrial volume density in the eccentric group compared to the concentric group, with a concomitant reduction in the expression of mitochondrial biogenesis factor Tfam and mitochondrial respiratory chain component COX-4. Genes coding for contractile properties were also reduced in the eccentric group compared to the concentric group. Insulin-like growth factor 1 mRNA was increased in both groups following training. While the details of the assay performed for transcript factor analysis is beyond the scope of this thesis, the authors conclude that muscle tissue reacts specifically and differently to the combination of mechanical and metabolic stresses induced by eccentric and concentric training in patients with CAD.

Importantly, these studies did not identify any adverse events that require participants to cease the eccentric exercise training. A single patient across the four study cohorts experienced a benign arrhythmia that required pharmacologic treatment. No other adverse events were reported, and no participants were required to cease the exercise intervention for any reason. Furthermore, all studies reported equivalent or improved aerobic and/or functional outcomes with eccentric training compared to concentric exercise performed at the same workloads. Central haemodynamics during eccentric exercise behaved similarly to concentric exercise, with some parameters in the eccentric training groups such as stroke volume index and blood lactate having less change from resting levels than their concentric counterparts. This remained unchanged throughout the course of 20 minutes of exercise, once patients achieved steady-state.

Eccentric exercise using a stationary cycling ergometer is attractive for patients following CABG, not only due to the abovementioned physiologic properties of eccentric muscle contractions but an appropriately-designed cycle ergometer could be manoeuvred throughout the ward environment and brought to the participant, negating the requirement of participants to move around and facilitating close supervision and monitoring if required. The results of the background literature review are reassuring for the application of early eccentric exercise in patients following CABG. The cardiovascular responses are significantly lower when workloads are performed eccentrically compared to concentric exercise, even at relatively demanding workloads. If the workload is down-titrated to a gentle or mild level, muscle recruitment and therefore strength improvements may be facilitated with little to no increase in cardiovascular demand. Taken together these data provide a strong rationale for a trial that tests the feasibility, safety and physiologic response to eccentric cycling in patients following CABG.

1.4. Summary

Coronary artery bypass graft surgery provides patients with therapeutic treatment for coronary artery diseases. A degree of postoperative morbidity, particularly functional decline, is associated with CABG. Although several studies have examined the effects of mobilisation and various physical activities in the early postoperative period, management and prevention of postoperative complications remains highly varied. Patients who are frail and deconditioned prior to surgery may not be able to return to their usual level of mobility so soon after CABG surgery. This cohort are at risk of further deconditioning and disuse atrophy of major muscle groups within days of bed rest and physical inactivity. This group in particular may receive the most benefit from eccentric cycling exercise therapy. Eccentric cycling poses to be an effective alternate exercise strategy in the immediate postoperative period for patients following CABG, due to the low metabolic demand. However a paucity of appropriate ergometers have prevented this therapy in even being considered for patients in the hospital environment.

For those undergoing CABG, the immediate postoperative period (phase 1 CR) can potentially contribute specialised exercise stimulus to the skeletal muscle, whilst maintaining cardiopulmonary stability and patient safety. This series of studies included the overarching objective to develop and pilot a unique form of skeletal muscle contraction, via eccentric cycling, at the hospital bedside and in doing so demonstrate its potential for improved outcomes for patients following CABG.

1.4.1. Aims and Hypotheses

The thesis comprises of two studies. The first study (Chapter 2) was a developmental process that included the construction of an eccentric cycle ergometer with design features specific for use in a hospital environment, followed by healthy participants performing eccentric workloads on this ergometer and their physiologic responses recorded. The second study (Chapter 3) was a pilot study that transitioned this ergometer to the hospital environment and patients following coronary artery bypass graft surgery performed repeated bouts of eccentric cycling early in their postoperative recovery. Specifically aims and hypothesis for each study were as follows:

1.4.2. Study 1: Eccentric cycle ergometer development.

Aim: To design and construct an eccentric cycle ergometer that can be used in the immediate bedspace of a hospital bedside and assess the performance of this ergometer using healthy participants performing two bouts of eccentric cycling exercise.

Hypothesis: An eccentric ergometer would be designed to suit the practical needs of hospitalised patients, which include mobility, reliability and workload reproducibility.

1.4.3. Study 2: Post-operative eccentric cycling feasibility following coronary artery bypass surgery.

Aim: To demonstrate the safe application of bedside eccentric cycling for patients following CABG patient during acute recovery in hospital.

Hypothesis: Providing low load eccentric cycling is practically achievable, safe in terms of cardiopulmonary stability, and physiologically relevant in terms of the potential to elicit a progressive exercise stimulus to the peripheral skeletal muscle of the lower limbs.

If outcomes such as functional capacity can be positively impacted with the addition of a safe, physiologically tailored, ward-based eccentric cycling exercise protocol, this may warrant further investigation for safety in a wider array of hospital inpatient populations with conditions requiring hospitalisation and mobility restrictions.

There may be potential impact for all patients following not just cardiac surgery, but many major surgeries as well as other hospitalisations that render patients unable to walk. Whether mobility restriction is due to disease, intervention or safety requirements such as needing to stay at the bedspace for monitoring purposes, eccentric cycling may provide a bridging exercise from patients inactively sitting out of bed to being able to meet the aerobic, strength and coordination demands of returning to walking. While many short-admission patients may easily make this transition, patients undergoing major surgery and recovering from lengthy hospital admissions may benefit from this type of exercise intervention.

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2. Eccentric cycle ergometer construction and demonstration for the hospital bedside.

2.1. Introduction

One of the great challenges in the management of patients in acute care hospitals, including those undergoing major surgery including cardiac surgery, is the prevention of functional capacity decline associated with periods of immobility and bedrest [1-3)]. Up to 50% of patients will experience a decline in functional capacity following hospital admission, with the incidence increasing in elderly patient's and in those with chronic disease [4-6)]. A significant proportion of elderly or frail patients are unable to participate in any continuous mobilisation exercises, as the energy cost of performing these exercise poses too great of a physiologic demand [7]. This may be due to a pre-morbid state of low energy availability exacerbated by acute illness, or a period of immobility during admission. Furthermore, the energy cost of movement increases with age as well as comorbidity and chronic illness [8,9]. Herein lies a challenge; to provide an exercise modality with low metabolic demands for exercise-intolerant patients.

As outlined in Chapter 1, skeletal muscle responds to tension in a dose-dependent manner. Concentric muscle contractions are characterized by force generation during muscle shortening. In contrast, eccentric muscle contractions generate force during an active lengthening of the muscle. Eccentric muscle contractions provide a unique stimulus to skeletal muscle, accompanied by a significant difference in maximal force production and metabolic cost [10]. The metabolic cost of performing a given workload using eccentric contractions is less than half of that required to produce the same workload using concentric contractions [11-13]. This unique property of low metabolic cost for a given workload is an established physiologic phenomenon of eccentric contractions and forms the basis of its potential utility in hospitalised patients.

Stationary cycling has been used as a means of providing continuous stimulus to lower limb musculature in patients with reduced physiologic reserve, in both inpatient and outpatient settings. It can limit the loss of functional capacity, as well as improve muscle strength and quality of life during hospital admission [6,14-17]. Due to the nature of the contractions being primarily concentric however, the physiologic requirements to perform these activities may be too demanding, particularly in patients with low physiologic reserve such as the elderly, frail or those with chronic disease. Stationary eccentric cycling can overcome these prohibitive physiologic demands as metabolic requirements for equivalent workloads are only one-third required for concentric exercise [18]. Eccentric cycling has demonstrated improvements in exercise capacity in outpatient settings for patients with poor exercise tolerance and low cardiopulmonary reserve [19-24]. The ergometers used to deliver eccentric cycling in these settings are often large, immobile and noisy; impractical if not implausible for use in a hospital setting. Herein lies an opportunity for an eccentric cycling ergometer to be developed for hospitalised patient use, so eccentric exercise can translate into the acute care environment.

The aim of this study was to construct an eccentric cycling ergometer for specific use in a hospital ward environment. Furthermore, this phase of the thesis aimed to demonstrate the capacity of this custom-designed ergometer to deliver continuous eccentric cycling workloads by reporting physiological outcomes of healthy participants.

2.2. Methods

2.2.1. Subjects

Ten healthy subjects, seven male and three female, with a median age of 33.9 years (range 20 – 64 years) participated in the study. Subjects were recruited from the university campus via verbal request. Ten subjects were chosen based on sample sizes used in similar studies in the literature. Prior to participation, all subjects were screened for musculoskeletal, respiratory and cardiovascular conditions that may be exacerbated during the study. Written informed consent was obtained prior to participation and all protocols were approved by the University of Wollongong Human Research Ethics Committee.

2.2.2. Eccentric Cycle Ergometer Construction

A Monarch arm crank ergometer (Rehab Trainer 881E, Monarch, Netherlands) was retrofitted to create the custom-made eccentric cycle ergometer. The base frame (1m x 1m) was constructed using aluminium and included four small wheels, one in each corner, with a locking mechanism to prevent movement during ergometer use. The base frame had a flat desk attached at the rear of the ergometer, to provide a surface for equipment such as a personal computer and data monitoring equipment to be used by researchers while participants are performing the exercise. The handles previously used for arm cranking were replaced with standard Monarch foot pedals (Monarch, Netherlands).

The Rehab Trainer 881E (Monarch, Netherlands) was internally fitted with a 240 V, 0.125 kW asynchronous electric motor and gearbox (GPG 90mm, Gonzalez Motors) to facilitate one directional eccentric cycling. The motor and all gearing systems were contained within the original Monarch Rehab Trainer housing. The motor system was governed by an AC speed controller (6-200W) (Samgold Electric Co. LTD, Shanghai, China), with a safety cut-out switch ("deadman switch") incorporated into the circuit. The cadence range was set from 0 to 45 RPM.

Eccentric workload was measured using instrumented (0-1000W ± 2.5%) bicycle cranks (SRM, PowerCrank, Jülich, Germany) that allowed power (W) and cadence (RPM) to be recorded (1Hz) using a cycle computer (Garmin Edge 520, Garmin, USA) as previously described in the laboratory setting (22). This power meter was also internally built into the Monarch arm crank, and in-line with the drive chain to the motor, thus allowing instantaneous force production (each revolution) to be relayed to the power monitor. This monitor was mounted on base-frame table, facing the patient, to enable real-time biofeedback. The design features of the ergometer are depicted in figures 2.1a and 2.1b.

Fig 2.1a: Eccentric cycle ergometer. Retro-fitted Monarch Rehab Trainer modified by the internal inclusion of a 125 W asynchronous motor and SRM power meter in line with the externally visible pedals.

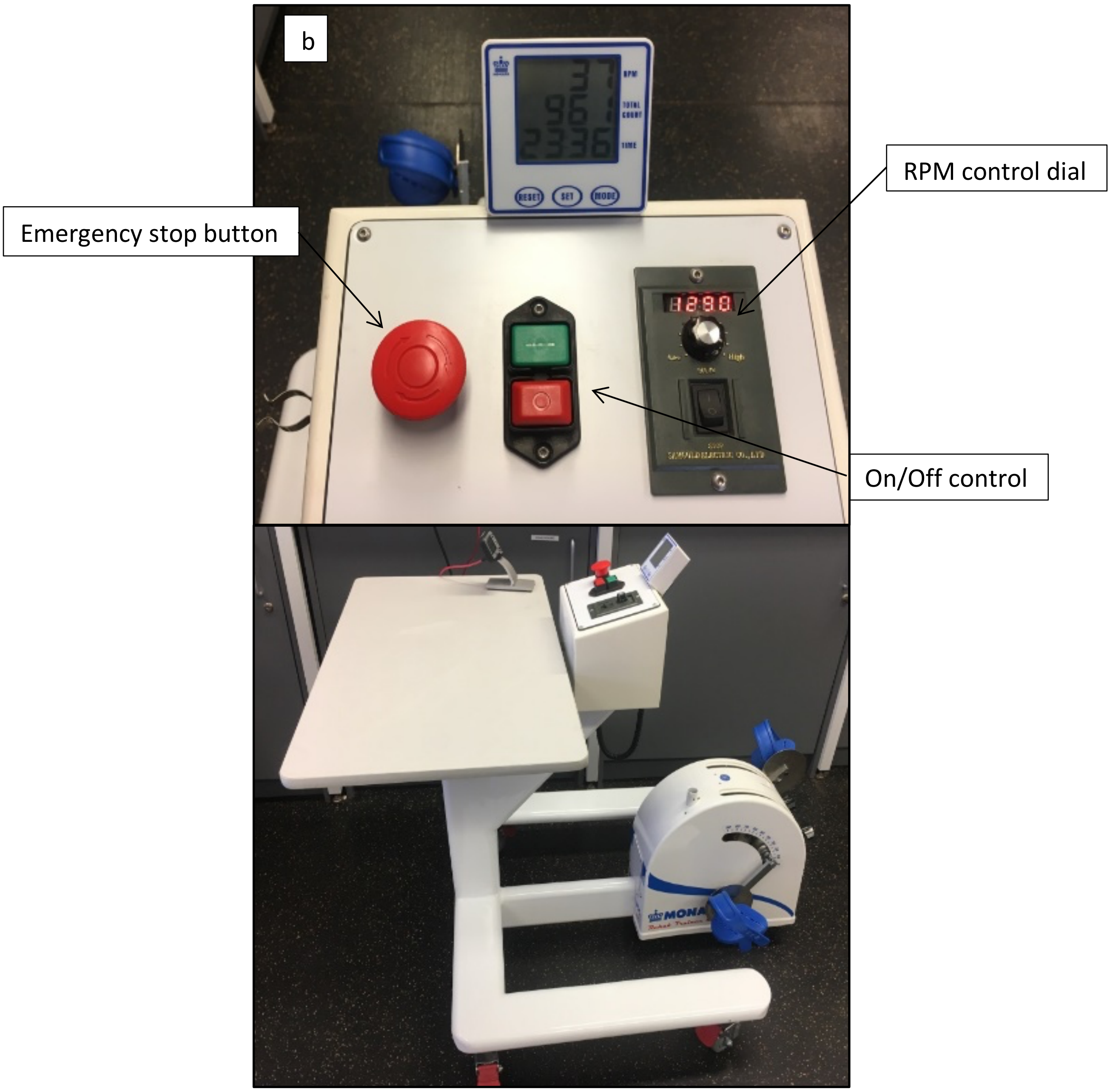

Fig 2.1b: Eccentric cycle ergometer. Control panel (on, off, emergency stop, revolution speed) and trolley mounted to mobile eccentric cycle ergometer

2.2.3. Experimental standardisation

Subjects were asked to rest in a seated position for a minimum of 5 minutes prior to commencing the study. All testing was conducted at a similar time of day between 0900 and 1700 hours in a room where temperature was controlled at an average of 22^{o}C. The same group of investigators performed all testing in order to avoid inter-tester variation.

2.2.4. Experimental design

After the completion of the screening and pre-procedural rest period was completed, all subjects performed a stepped-protocol of eccentric cycling. Two separate workloads were performed by all participants. A lower workload was performed first and then repeated prior to performing the higher workload. The higher workload was aimed to be twice the lower workload; however this was not always attainable by each participant. Participants used optical feedback via the power-meter display to ensure a constant workload was achieved. Each workload was performed for five minutes and then followed by a five minute rest period. The rest period was performed seated in the chair directly opposite the eccentric ergometer.

2.2.5. Measurements

Participant height was measured using a stadiometer (Advantage Medical, IL, USA) and body mass using electronic scales (Presier, DVM-Medical Supplies, Canberra, Australia). A resting (seated) blood pressure (OMRON, DVM-Medical Supplies, Canberra, Australia) was measured following 10 minutes of seated rest.

Power output was monitored second-by-second throughout the eccentric cycling protocol using a power-meter, with data being remotely supplied from the power cranks. Workload was maintained by each subject based on live feedback displayed on the power meter, with each participant instructed to alter eccentric force and cadence respectively in order to achieve the desired total workload.

Heart rate was obtained continuously using ventricular depolarisation (Vivid iq, GE, Australia). A standard 3-lead ECG arrangement was used for all participants to capture ventricular depolarisation. Three disposable electrodes were located on the participant's torso to record the ECG (lead 1, 1000 Hz). All data were collected over the whole five-minute exercise period. Mean values were calculated using data from the final three minutes of each period. Data from the first two minutes of each work and rest period were recorded but not included in the final mean calculations as we assumed this first two minutes is required to achieve a steady physiologic state.

Expired gas samples were collected during the four five-minute sampling periods. Mean and standard deviation were calculated form the final three minutes of each workload and the initial rest period. Standard respiratory parameters; tidal volume (L), breathing frequency (breaths.min-1) and expired gas composition (%) was measured using mixing chamber gas analysis, with the 2900c Metabolic Measurement Cart (SensorMedics Corporation, Yorba Linda, CA, USA). The system was calibrated using ambient temperature (^{o}C), pressure (mmHg) and humidity (%) as measured by a wet/dry bulb thermometer and barometer located in the testing room. Oxygen and carbon dioxide gas analysis was calibrated using alpha gas standards (15.97% oxygen, 4.03% carbon dioxide, balance Nitrogen). The system was calibrated for volume using a 3.012 Litre calibration syringe. Subjects inspired room air through a one-way valve (Hans Rudolf inc, Shawnee, KS, USA) and expired directly into the metabolic measuring cart.

Arterial saturation was continuously measured on the index finger using near infrared spectronomy (NIRS). This data was collected using Powerlab systems (AD instruments, Australia). Muscle tissue oxygen saturation (SmO2) was recorded continuously (2 Hz) on the anterior surface of the thigh (vastus lateralis), mid-way between the anterior superior iliac spine and the patella at 90 degrees of hip and knee flexion at a frequency of 2 Hz using a NIRS device (Moxy Monitor, Fortiori Design, Minnesota, USA). The NIRS device measures the amount of light reaching two detectors from one emitter at four wavelengths in a diffuse reflectance configuration, with the detectors spaced at 12.5 and 25 mm from the emitter [25] Muscle oxygen saturation was calculated using software incorporated into the Moxy Monitor, applying a Monte-Carlo model to generate optical ray-trace data, incorporating expected measurements of various tissue layers using pre-established values [25].The emitter and detectors were aligned in the direction of muscle fibres and a light-shield fitted around the device. Muscle tissue saturation was recorded to the nearest percent and data was exported to Microsoft excel for analysis on a personal computer (Dell Latitude, E7250, USA, 2017).

2.2.6. Statistical analysis

Subject demographic data including age, height, mass and BMI were reported as mean ± SD. All other experimental data was reported as mean ± SEM. Variance of physical attributes was presented as mean ± SD, as standard deviation is used to describe the variation in measurements of a variable within a sample population. Standard error of the mean was used for the physiological measurements as it more appropriately describes the precision of a sample mean. A two-way ANOVA was used to determine if any difference in physiologic variables were present between the two workloads performed by each participant. A one-way ANOVA was used to determine any difference in physiologic variables between either workload performed and the rest period.

Data was confirmed as normally distributed using the Shapiro-Wilko test. A repeated measures analysis of variance (2-way ANOVA) was used to determine interactions between conditions. A post-hoc Bonferroni test was used to determine the all-pairwise comparison of means. Alpha was set at $P<0.05$..

2.3. Results

All participants completed the ECC cycling protocol in full. The ergometer was able to maintain workloads to allow protocol completion for all 10 participants, with all workloads being achieved and sustained without interruption. No mechanical or ergonomic issues were encountered during any of the exercise sessions, including the ergometer motor, wheel locking mechanisms, pedal straps, emergency stop switch and ergometer positioning. The eccentric cycle ergometer was successfully manoeuvred around the laboratory, including through standard width doorframes.

2.3.1. Power output

The mean power output for the lower workload was 31.1±5.7 W (range 25-35W), while the mean higher workload was 56.6±8.8 W (range 50-65W). The inter-workload variability of each outcome was not significantly different for any variable measured.

2.3.2. Central cardiorespiratory and metabolic

The mean resting HR was 68±13 beats per minute, which increased significantly during both workloads ($p<0.05$). Mean HR during the first (83±16 bpm) and second (94±14 bpm) workloads did not differ significantly. Minute ventilation (rest; 12.4±3.5 L/min, workload 1; 21.76±6.5 L/min, workload 2; 26.5±8.9 L/min), VO2 (rest; 0.31±0.05 L.min-1, workload 1; 0.64±0.23 L/min, workload 2; 0.82±0.27 L/min) and VCO2 (rest; 0.28±0.06 L.min-1, workload 1; 0.56±0.2 L/min, workload 2; 0.73±0.27 L/min) also increased significantly from rest during both workloads, with no significant difference between each workload. Resting arterial oxygen saturation was 98±1% and did not differ significantly during either workload (workload 1; 97±2%, workload 2; 97±1%, $p=0.69$). Heart rate and ventilation variables all returned to resting levels during the 5 minute rest period following each ECC cycling workload. A summary of HR and metabolic responses can be found in Table 2.

2.3.3. Peripheral skeletal muscle

The mean oxygen saturation index of the vastus lateralis at rest was 88.8±5.2%. There was no significant difference in muscle tissue oxygen saturation index when ECC cycling was commenced either within bouts of the same ECC workload, between workloads or compared to resting baseline (Table 2).

Table 2.1: Heart rate and metabolic responses of participants (n=10) at rest and during two eccentric cycling workloads (30, 60 W).

	Rest	Workload 1 (30 W)		Workload 2 (60 W)	
		Trial 1	Trial 2	Trial 1	Trial 2
Actual workload (W)		30±7	32±5	56±10	57±9
Heart rate (b/min)	68±13*	83±14	84±19	93±16	95±13
Minute ventilation (L/min)	12.4±3.5*	21.7±6.3	21.7±7.0	26.4±9.1	26.6±8.8
VO_2 (L/min)	0.31±0.05*	0.64±0.22	0.63±0.23	0.82±0.27	0.81±0.27
VCO_2 (L/min)	0.28±0.06*	0.56±0.19	0.56±0.21	0.72±0.28	0.73±0.27
RER	0.89±0.12	0.86±0.09	0.88±0.06	0.86±0.06	0.88±0.06
SaO2 (%)	98±1	97±1	97±2	97±1	97±1
TSI (%)	89±5	87±12	87±11	86±15	86±14

VO_2 (L/min): oxygen consumption, VCO^2(L/min): carbon dioxide production, RER: respiratory exchange ratio, SaO2(%): arterial oxygen saturation, TSI (%): muscle tissue saturation index. Data presented as mean±SD. *P<0.05 rest versus workload 1 and workload 2.

2.4. Discussion

This study describes the first eccentric cycling ergometer designed and constructed that can be rapidly deployed to the bedside in a hospital setting. The effectiveness of the ergometer to deliver consistent low load eccentric cycling, with expected physiological responses to these workloads, was demonstrated in healthy subjects. The effectiveness of this small, mobile and quiet design provides opportunity in the hospital setting to achieve muscle lengthening contractions in those patients most at risk of poor mobility and bedrest disuse.

This study did not intend to compare concentric and eccentric cycling physiology in terms of the lower cardiopulmonary and metabolic demand of the latter. Nonetheless, it was important that when the achievement of eccentric workloads was executed by the healthy participants, their physiological responses were meaningful and relevant. To demonstrate this, mean HR increased significantly from rest during both workloads (table 2). Furthermore, minute ventilation also increased incrementally with workload. Although these HR and ventilatory responses to continuous eccentric cycling loads increased incrementally with workload, even at low workloads [18,26], the slope of this relationship was flat compared to incremental concentric cycling [27]. Patients with severe exercise intolerance have been studied at eccentric workloads as low as 10 W [28-30]. The physiologic response to low-load ECC cycling are similar at these low loads, with HR and ventilatory responses significantly less than that for concentric cycling at equal workloads [28,29]. The workloads performed by participants in this study are some of the lowest studied in the current eccentric cycling literature, particularly in healthy subjects. It was important to demonstrate that the eccentric ergometer could deliver low workloads as this was a requirement of the ergometer for the study performed in chapter 3 of this thesis. The participants, demonstrated a workload-dependent increase in HR and whole-body oxygen consumption, although as predicted due the unique slope of these responses with muscle lengthening contractions, the second rise in cardiopulmonary and metabolic response was not significantly different from the initial lower workload.

While each participant demonstrated a workload-dependent increase in muscle activity, cardiopulmonary and metabolic demand, tissue oxygen saturation of the contracting skeletal muscle remained unperturbed. This is in agreement with others, who have shown tissue oxygen saturation remained stable in the quadriceps muscle during continuous eccentric cycling, at workloads approaching 200 W [12,31,32]. The capacity of the eccentrically contracting skeletal muscle to generate force with no change in net muscle oxygen saturation, combined with the abovementioned cardiometabolic profile, make continuous eccentric cycling an ideal exercise modality for patients with reduced functional or physiological reserve [20,21,33,34].

The application of eccentric cycling has remained isolated to patients and participants outside the hospital setting. One limitation to the introduction of eccentric cycling to hospitalised patients is the lack of an ergometer appropriate for the hospital environment [35]. The design of most commercially available eccentric ergometers makes them difficult to use in the acute care setting. They are large, immobile machines, designed for relatively permanent placement within a fixed environment, typically a gymnasium [30,36-38]. Furthermore, these ergometers usually require cycling in an upright seated position. The motors used in these machines, while capable of very high workloads (>500W) for healthy adults and elite athletes, are inappropriately noisy for an inpatient setting and require large workspaces to be used in. Based on these limitations, there were several design features deemed essential for an ergometer specifically constructed for hospital inpatients (See Fig 3.1 in chapter 3). The ergometer was to be for semi-recumbent use. This achieves two purposes: the recumbent position provides a supported chair for the participant, removing the requirement for trunk stabilisation that exists in upright cycling. This further reduces the overall energy requirement for the exercise, isolating the energy expenditure to only the working lower limbs. Second, it allows the ergometer to be used by all patients in a hospital setting, provided they can sit out of bed in a standard bedside chair (See Fig 3.1 in chapter 3). The portability of the ergometer was also considered crucial for hospital use. The manoeuvrability of the ergometer allows it to be securely positioned in front of a patient whilst they sit in a bedside chair, while also being easily moved from one bed space to another. Patients are often in shared rooms and may be restricted to their immediate bed space, either due to care requirements such as cardiac monitoring, the nature of the acute illness or deconditioning from periods of immobility. The portability of the ergometer allows it to be in the immediate bed space, potentially allowing patients to continue to receive haemodynamic monitoring or intravenous treatment whilst performing eccentric cycling (See Fig 3.1 in chapter 3).

There is a paucity of available literature to guide workload capacity required for an ergometer for hospitalised patients. Concentric cycle ergometry has been prescribed in critically ill and post-surgical patients, however the majority of studies use RPE or other patient determined outputs to set exercise intensity [14,16]. The maximum capacity of the ergometer in this study was set to 100 W. Literature supports loads within this range being able to provide enough stimulus to evoke positive skeletal muscle adaptations in exercise-intolerant populations [21,29,30]. Furthermore, this range allowed the use of a relatively small motor, keeping both the size and noise levels of the ergometer to well within practically acceptable ranges. Despite the small motor size, all participants in this study completed both the lower and higher workloads without any mechanical issue (workloads of up to 80 W were performed by participants during single participant study, results not shown). The novel construction of this ECC ergometer makes it easily deployable to the bedside whilst the engine design is capable of delivering smooth external work to provide resistive force generation. Importantly, these outcomes are achieved whilst also maintaining low noise production. This creates an exciting opportunity to deliver continuous eccentric cycling in the hospital setting.

2.5. Conclusions

This chapter describes the development and demonstration of an eccentric cycling ergometer appropriate for the inpatient hospital environment. Furthermore, the efficacy of this ergometer to deliver constant, low-load eccentric workloads in healthy adult subjects has been demonstrated. Given the suitability of low-load eccentric exercise, that emphasises the duration of the stimulus for hospitalized patients, research questions focussed on safety, acceptability and optimal eccentric loading in various acute illnesses requiring hospitalization are now possible. The deployment of this prototype to the frail and post-surgical patients, who are likely to experience the most pronounced reduction in functional capacity from short periods of immobility and bed rest, is urgently required and now possible. It was therefore logical to implement this eccentric cycle ergometer in patients following cardiac surgery and forms the next chapter of this thesis.

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3. Eccentric cycling at the bedside immediately after cardiac surgery

3.1. Introduction

As outlined in chapter one, many patients undergoing coronary artery bypass graft surgery (CABG) experience reduced functional capacity, either as a consequence of their underlying cardiac disease or other comorbidity[1]. Functional capacity is negatively impacted immediately following CABG [2,3] and the goals of exercise in the early postoperative period are to avoid immobility and pulmonary complications and limit the impact of functional losses at hospital discharge [4,5]. These functional reductions may be accelerated in susceptible populations including the elderly, frail and chronically diseased [6–8]. Although immobilisation and bed rest have been identified as significant contributors in reducing functional capacity [9–11], periods of bed rest and complete immobilisation are often required in the immediate postoperative period following CABG. This interval of bed rest may be inconsequential in many cases of uncomplicated CABG. However, elderly and frail patients are at higher risk of prolonged immobilisation and bed rest and, therefore, exposed to a range of morbidities such as decreased muscular strength, increased bone resorption and lower total energy expenditure [12]. Physiological sequelae of immobility can include a reduction in plasma volume, which therefore reduces cardiac preload, stroke volume, cardiac output, and ultimately, maximal oxygen consumption [8,13].

The goals of phase 1 or inpatient CR are to minimise morbidity associated with inactivity and foster early postoperative discharge by maximising physical function [14,15]. Traditional physiotherapy has focused on respiratory exercises to improve outcomes at discharge from hospital however the efficacy of these is uncertain [16,17]. Exercise such as walking and concentric cycling, which are classified as positive work, have emerged as safe and effective options for improving functional and ventilatory exercise capacity after cardiac surgery, as demonstrated in the meta-analysis performed as part of chapter 1 [18]. As also discussed in detail in previous chapters, these exercise modalities primarily utilise concentric muscle contractions, whereby the contracting muscle shortens to perform work. These muscle contractions elicit the greatest gain in relative oxygen consumption and thereby increase cardiorespiratory exertion [19–23]. This can render these forms of exercise more challenging for many high-risk, frail or elderly patients that undergo CABG.

As opposed to positive work, eccentric muscle contractions perform negative work as skeletal muscle fibres lengthen during contraction. Activities such as walking downhill or downstairs utilise such contractions; the muscles of the anterior thigh contract as they lengthen to control knee flexion against gravity during each step. Similarly, eccentric muscle contractions predominate during eccentric cycling, whereby a motorised cycling machine drives the pedals in a reverse direction and the cyclist pushes against or resists the turning pedals (see fig 2.1 and 2.2 in chapter 2).

Continuous eccentric contractions such as those performed during eccentric cycling are characterised by several unique physiological responses. Most notably, at a given workload, the oxygen requirement is at least half that of concentric cycling [22] and potentially four to five times lower than concentric contractions [21,24]. Furthermore, eccentric contractions display modified neural innovation [25] with low overall metabolic demand [26]. When performed at workloads several fold higher than concentric cycling, eccentric cycling elicits less of an alteration of cardiopulmonary physiological variables [27] such as heart rate or peripheral oxygen saturation of the skeletal muscle [28,29]. Based on these physiologic phenomenon, eccentric exercise, in particular eccentric cycling, has the potential to be an excellent alternative exercise for patients with limited cardiopulmonary reserve.

To date, eccentric cycling for CR has focussed on patients with stable chronic disease and their longer term management [30–33]. Nonetheless, there is increased recognition for employing eccentric cycling in cohorts experiencing critical illness and therefore in settings such as hospitals [34]. For the acute post-operative CABG patient, who experiences an acute reduction in physiological reserve, the opportunity to mechanically stimulate the skeletal muscles of the lower limb with a low energy demand creates opportunity for repeated bouts at the bedside, particularly if the eccentric cycling ergometer can be brought to the patient in their bedspace.

To begin to overcome the challenge of delivering eccentric cycling to hospitalised patients, a mobile eccentric cycling ergometer for inpatient rehabilitation at the bedside was constructed as described in the previous chapter. This eccentric cycling ergometer is unique in terms of being easily movable with a low impact on floor space, low noise production and has an engine capacity to deliver consistent, low-load eccentric workloads. In this environment, workload prescription based on maximal aerobic power is neither feasible or appropriate given the acute physiologic derangement and decompensation many hospitalised patients experience as well as a lack of maximal or submaximal exercise testing. This creates an opportunity to explore options for patient-centred eccentric exercise progression using principles such as perceived exertion.

Rating of perceived exertion (RPE) scales such as the Borg scale are widely used for self-assessment of whole-body exertion during physical activity. Studies investigating RPE responses to eccentric cycling have demonstrated incremental increases in RPE with workload, although lower compared to concentric equivalent [35]. Similarly, to metabolic demand, RPE is lower when compared to equivalent concentric workloads [22,28,36]. Eccentric workloads have been successfully implemented using RPE guided eccentric exercise prescription in heart failure patients with low functional capacity, demonstrating physiological adaptations beneficial for independent living [37] . Similarly, COPD patients have shown significant self-progression using eccentric cycling over several weeks, which also supports the concept of supervised workload management [31]. It is of great interest to determine if the same principles can be applied in the acute setting of phase 1 CR.

The overall aim of this study was to observe the responses and progression of post-operative CABG patients who were provided an opportunity take part in acute phase 1 CR using the eccentric cycle ergometer. On the basis that workload management could be delivered using medically supervised low RPE, it was hypothesised that this would have minimal central and peripheral physiological alterations while providing an opportunity to progressively increase eccentric workload over several sessions in hospitalised patients immediately following CABG surgery.

3.2. Methods

3.2.1. Study design

This study was a cohort description and subsequent analysis of the physiological responses to repeated bouts of eccentric cycling in patients following CABG. During the post-operative hospital stay, enrolled patients (n=24) were provided with the opportunity to engage in up to a maximum of three eccentric cycling sessions using a custom-built ergometer, secured by their hospital bedside. Each eccentric cycling session was clinically supervised and had a duration of a maximum of 10 minutes. Eccentric cycling workload was governed by RPE. When possible, patients also completed walking assessment on discharge from their hospital stay. All participants completed a medical screening questionnaire and provided written, informed consent to the procedures and publication of data approved by the Sydney local health district Human Research Ethics Committee (#X18-0282 & HREC/18/RPAH/395, approved on 16th November 2018) in accordance with the guidelines laid down in the Declaration of Helsinki.

3.2.2. Participants

All adult patients undergoing isolated CABG, with normal left ventricular function were considered for inclusion. Patients were screened for potential inclusion and provided informed consent prior to undergoing surgery. Following surgery, patients were enrolled in the study once they had left the ICU and transitioned to the postoperative ward.

3.2.3. Exclusion Criteria

Patients were excluded from the study if any of the following postoperative outcomes were encountered: reoperation for any cause, unplanned concomitant cardiac surgery at time of CABG, mechanical ventilation greater than 48 hours, cardiogenic shock requiring mechanical support, inotropic or vasopressor support required for greater than 24 hours, new onset neurologic deficit post-surgery, severe ventricular dysfunction demonstrated on postoperative echocardiogram (left ventricular ejection fraction less than 35%), mediastinal drains remaining in situ, active infection or sepsis, postoperative pulmonary complication (large pleural effusion on chest X-ray, tachypnoea, productive cough, fever, pneumothorax, large consolidation or interstitial infiltrate on chest x-ray considered causative for an increase in respiratory rate or drop in oxygen saturation, pulmonary embolus), sternotomy wound instability or the requirement of the use of a sternal vest or binder.

3.2.4. Eccentric Cycling:

An eccentric cycling ergometer was custom designed and constructed for use in postoperative patients as described in the previous chapter. Patients were seated in a recumbent position in a bedside chair which provided back support. The ergometer was positioned directly in front of the patient, their feet placed on the pedals and the pedal crank rotated so one leg was in the most extended position of the pedal stroke. Small additional ergometer positioning adjustments were made to ensure the extended knee did not reach maximal extension during the pedal stroke. The ergometer was secured in position using the wheel locks. A demonstration of the ergometer positioned at the patient bedspace is given in fig 3.1.

3.2.5. Familiarisation

Patients performed familiarisation prior to engaging in active eccentric cycling exercise. This consisted of a demonstration of the ergometer including the safety mechanisms. Patients then performed 2 minutes of supervised low-load eccentric cycling on the ergometer in order to familiarise themselves with the reverse motion of the pedals and the concept of eccentric force application. Patients were instructed not to apply any force to the pedals for the first two minutes of the first eccentric cycling exercise bout. The RPM was then incrementally increased over the next 2 minutes, to a maximum of 30 RPM as patients were comfortable and as physiologic and RPE responses permitted. The following variables were monitored during the familiarisation session: HR, heart rhythm, BP, RR and SpO2. Perceived exertion was kept below 4 out of 10 on the modified Borg scale of perceived exertion [38], which corresponds to “light activity”.

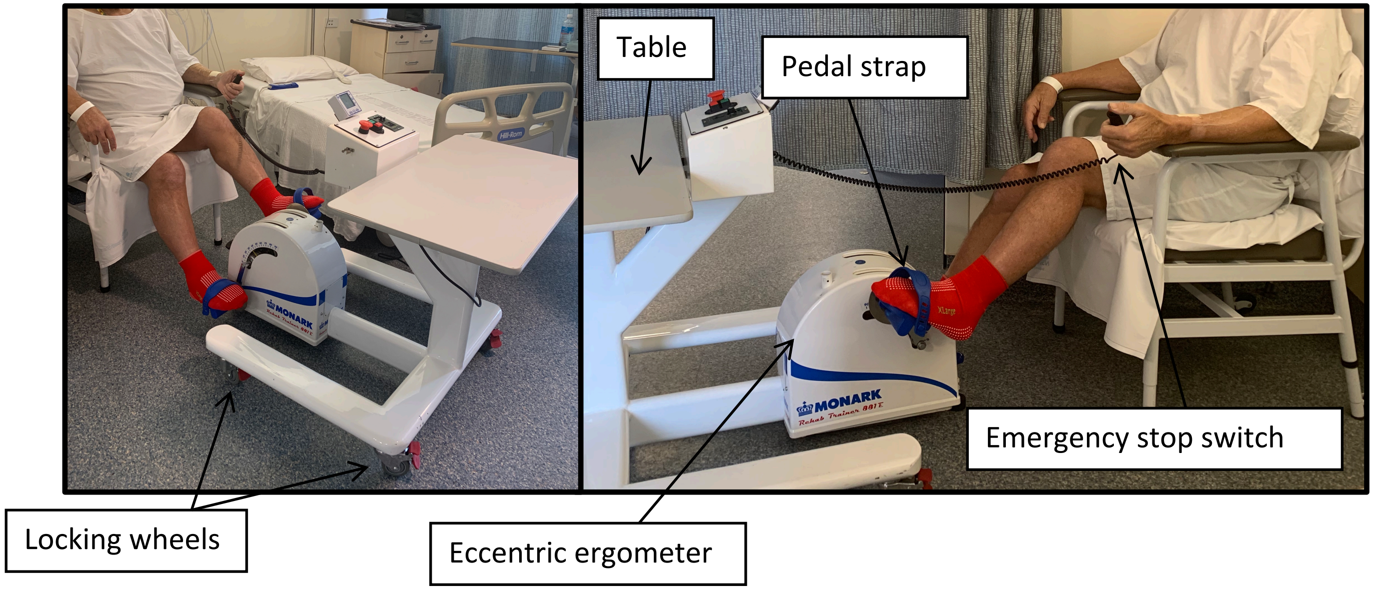

Fig 3.1: Eccentric cycling ergometer in the hospital setting: The eccentric cycle ergometer is easily manoeuvred around the ward environment and positioned at the feet of the patient sitting in a bedside chair. The wheels of the ergometer trolley can be locked in order to secure the ergometer position. The patient holds an emergency stop switch for the duration of the exercise. Portable computing and other equipment can be used during the eccentric cycling on the table mounted to the ergometer, facilitating easy monitoring and research use.

3.2.6. Exercise sessions

Patients commenced ECC cycling on the first POD following ICU discharge. All Patients were commenced on live 3-lead ECG telemetry. Patients were seated in a hospital-provided bedside chair and the ergometer positioned and secured. Following a resting period of five minutes, baseline physiologic measurements were performed and confirmation of understanding of the modified Borg scale of exertion was established. A verbal confirmation of patient understanding of ergometer function and its safety mechanisms was obtained immediately prior to exercise commencement.

The exercise sessions commenced with a warm-up phase of ECC cycling, with the cycle ergometer workload set at 10-30 W, depending on whether any prior ECC cycling had been performed. Patients were instructed to engage the ergometer by pressing and holding the safety switch for the duration of the ECC cycling. Ergometer speed (RPM) began at 20 for the initial ECC cycling session or five below the RPM performed on the previous ECC cycling session for subsequent sessions. Perceived exertion was kept at one to two over the first two minutes which equates to “very light”. Workload and/or RPM were reduced if the RPE exceed two in the initial two minutes of all ECC cycling sessions. At the completion of the first two minutes, all vital signs, RPE and total workload (W) were recorded. Workload was incrementally increased five to 10 W over the remainder of the ECC cycling sessions every two minutes, provided RPE remined at four or lower. All vital signs, RPE and workload were assessed at two minute intervals. If patients reported an RPE equal to or greater than four, RPM and workload were reduced to the previous level to maintain an RPE of less than four. Once a RPE of four was reached, no further increases in workload were performed for the remainder of the

EC session. Vital signs, RPE and total workload were continued to be recorded every two minutes. Each ECC cycling session was a total of 10 minutes. At the completion of the 10 minutes of exercise, a two-minute cool-down period was performed, with RPM and workload returned to the starting levels for this two-minute period.

At the completion of the ECC cycling, patients were monitored for a further 15 minutes seated in the bedside chair. Vital signs were recorded 15 minutes after the completion of the ECC cycling exercise. Patients performed ECC cycling on consecutive weekdays following their first ECC cycling bout, for a maximum of three bouts or until hospital discharge.

3.2.7. Monitoring and measurements

All patients were monitored for the duration of the ECC cycling sessions using real-time cardiac telemetry. Heart rate and SpO2 were recorded using NIRS pulse oximetry. Blood pressure was recorded using an automatic blood pressure monitor (Omron healthcare, Japan). Muscle oxygen saturation of the lower limb musculature was measured using a NIRS device (Moxymonitor©, USA). The RPE was recorded using the modified Borg Scale [38].

Eccentric workloads were measured in Watts (W), using strain gauge technology (SRM power meter) to allow instantaneous biofeedback to the user via a cycle computer (Garmin Edge 520, Garmin©, USA) as previously described [23,39].

On the day of hospital discharge, patients performed a 10 m walk test for assessment of gait speed. Gait speed (m/s) was recorded over a 10 m distance. Patients were instructed to walk at their preferred maximum comfortable walking speed around a hospital corridor (approximately 50 m in total distance). A 10 m section of the corridor was marked out. Timing was commenced once the leading foot crossed the start line and concluded when the leading foot crossed the 10 m line.

Overall perceived workload was measured using the NASA task load index (TLX). This is a validated, subjective multidimensional assessment tool, designed to assess perceived cognitive workload across six domains (mental demand, physical demand, temporal demand, overall performance, effort and frustration level) [40,41]. Overall perceived workload was recorded after the final ECC cycling exercise bout, prior to hospital discharge. Patients were asked to answer the questionnaire while considering all three ECC cycling bouts. Nonetheless, the response was most closely aligned to their last ECC cycling session. The questionnaire asks patients to subjectively assess the overall mental, physical and temporal demands of the task, as well as identifying any frustration and total effort.

3.2.8. Statistical analysis

This study was a within-cohort analysis. Clinical description of the cohort was implemented based upon patient records. Eccentric cycling and physiological responses were analysed using a mixed-effects model (session x time), where a reduced sample size from session 1-3 was deemed random, which was confirmed by inspection of the residual plots. Where significant difference was reported, a multiple comparison analysis (session x time) with Tukey post hoc was conducted to determine where the significant interaction occurred. Eccentric cycling and physiological data was expressed as mean (95% CI). Alpha was set at 0.05.

3.3. Results

3.3.1. Surgical

Twenty-four patients (age; 61.6±10.3 years, BMI; 28.6±6.2 m2; 23 males and 1 female) performed ECC cycling following uncomplicated CABG. On-pump CABG was performed in 87.5% of cases. Mean CPB and cross-clamp times were 88.9±26.3 and 69.3±22.3 mins respectively. The mean number of grafts performed was 2.75±1.0, with 62% of patients receiving more than one arterial graft. Pre-existing hypertension, diabetes mellitus and chronic renal insufficiency were present in 67%, 58% and 17% of patients respectively. Patient anthropometric details and operative characteristics are summarised in table 3.1.

Postoperative medical therapy included single-antiplatelet use in every patient, while 54% of patients received dual antiplatelet therapy. Beta-blocker and statin therapy was initiated in 92% and 100% of patients respectively. Individualised postoperative medical therapy is summarised in table 3.2.

Postoperative complications included pleural effusion (n=2; 8%), respiratory tract infection requiring antibiotics (n=5; 21%) and urinary tract infection (n=3; 13%). There were no cases of sternal wound infection or mechanical dehiscence. No stroke or transient ischaemic attacks were encountered. Atrial fibrillation occurred in five patients (21%), with all patients being medically cardioverted prior to hospital discharge. No arrhythmia's were encountered during the eccentric cycling bouts. Clinical postoperative outcomes are summarised in table 3.

Table 3.1: Patient characteristics (n=24) and surgical details for patients who performed eccentric cycling during inpatient recovery following CABG

Patient	Age	Sex	Height	Mass	BMI	HTN	DM	CVA	CRF	PVD	smoke	Surgery	Grafts	Art	CPB	XC
1	62	M	170	62	21.5	✓	✓	-	-	-	-	CABG	3	1	57	47
2	50	M	197	114	29.4	✓	✓	-	-	-	✓	CABG	2	2	70	55
3	56	M	175	65	21.2	-	✓	-	-	-	-	CABG	2	2	77	63
4	71	M	175	90	29.4	✓	✓	-	-	-	-	CABG	3	2	105	80
5	59	M	188	85	24.0	-	-	-	-	-	✓	CABG	4	2	100	75
6	74	M	160	68	26.6	✓	-	✓	✓	-	-	CABG	4	2	120	96
7	51	M	170	66	22.8	-	-	-	-	-	-	CABG	2	2	90	75
8	61	M	176	83	26.8	✓	-	-	-	-	-	CABG	3	2	83	69
9	52	M	165	107	39.3	✓	✓	-	✓	-	✓	CABG	4	3	134	118
10	77	M	170	97	33.6	✓	-	-	-	-	-	CABG	3	1	75	60
11	79	M	177	99	31.6	✓	-	-	-	-	-	CABG	3	1	125	75
12	63	M	174	79	26.1	✓	✓	-	-	-	✓	OPCAB	1	1	-	-
13	68	M	157	56	22.7	✓	✓	-	-	✓	-	OPCAB	1	1	-	-
14	57	M	186	74	21.4	✓	✓	-	✓	-	✓	CABG	4	0	75	60
15	36	M	175	122	39.8	✓	✓	-	-	-	✓	CABG	2	2	60	45
16	48	M	180	87	26.9	✓	✓	-	✓	-	✓	CABG	3	2	110	85
17	73	F	152	49	21.2	-	-	-	-	-	✓	CABG	3	1	80	55
18	72	M	165	68	25.0	✓	-	✓	-	-	-	OPCAB	1	1	-	-
19	69	M	164	71	26.4	-	-	-	-	-	-	CABG	5	2	75	60
20	64	M	167	100	35.9	-	-	-	-	-	✓	CABG	3	2	65	50
21	58	M	169	79	27.7	-	✓	-	-	-	✓	CABG	2	2	57	42
22	54	M	178	132	41.7	-	✓	-	-	-	✓	CABG	3	2	129	112
23	63	M	184	117	34.6	✓	✓	-	-	-	-	CABG	2	1	55	38
24	62	M	175	91	29.7	✓	✓	-	-	-	-	CABG	3	2	125	95

Footnotes: CABG-coronary artery bypass graft surgery using cardiopulmonary bypass; OPCAB-off pump coronary artery bypass graft surgery; Grafts-total number of distal anastomosis; arterial-total number of distal anastomosis performed using an arterial conduit; XC-cross clamp time (minutes); CPB-cardiopulmonary bypass time (minutes).

Table 3.2: Postoperative medical therapy and adverse events in patients who performed eccentric cycling following CABG

Patient	BB	Statin	Antiplatelet	DAPT	ICU LOS	LOS	DC Hb	AF	Pleural Effusion	Pneumonia	UTI	sternal	CVA/TIA
1	✓	✓	✓	-		9	89	-	-	-	✓	-	-
2	✓	✓	✓	✓	4	8	103	-	-	✓	-	-	-
3	✓	✓	✓	✓	3	8	101	-	✓	✓	-	-	-
4	✓	✓	✓	-	4	8	85	✓	-	-	-	-	-
5	✓	✓	✓	✓	2	5	95	-	-	-	-	-	-
6	✓	✓	✓	-	4	7	92	✓	-	-	✓	-	-
7	✓	✓	✓	✓	2	5	99	-	-	-	-	-	-
8	✓	✓	✓	✓	2	6	78	✓	-	-	-	-	-
9	-	✓	✓	-	2	5	75	-	-	-	-	-	-
10	✓	✓	✓	✓	2	7	94	-	-	✓	-	-	-
11	✓	✓	✓	-	1	6	120	✓	-	-	-	-	-
12	✓	✓	✓	✓	1	4	115	-	-	-	-	-	-
13	✓	✓	✓	✓	2	7	130	-	-	-	-	-	-
14	✓	✓	✓	-	3	9	75	-	-	-	-	-	-
15	✓	✓	✓	✓	2	6	140	-	-	-	-	-	-
16	✓	✓	✓	-	4	6	94	-	-	-	-	-	-
17	✓	✓	✓	-	2	9	110	-	✓	-	-	-	-
18	-	✓	✓	-	3	6	124	-	-	✓	-	-	-
19	✓	✓	✓	-	2	7	108	-	-	-	-	-	-
20	✓	✓	✓	-	2	5	119	-	-	-	-	-	-
21	✓	✓	✓	✓	3	6	129	-	-	✓	✓	-	-
22	✓	✓	✓	✓	2	8	108	✓	-	-	-	-	-
23	✓	✓	✓	✓	2	4	103	-	-	-	-	-	-
24	✓	✓	✓	✓	4	7	100	-	-	-	-	-	-

Footnotes: CABG-coronary artery bypass graft surgery using cardiopulmonary bypass; OPCAB-off pump coronary artery bypass graft surgery; BB-beta blocker; Statin-acetyl CoA reductase inhibitor; DAPT-dual antiplatelet therapy. ICU-intensive care unit; LOS-length of stay; DC Hb-serum Haemoglobin on day of hospital discharge; AF-atrial fibrillation; UTI-urinary tract infection; Sternal-sternal instability from any cause including mechanical sternal dehiscence or deep sternal wound infection; CVA/TIA-cerebrovascular accident/transient ischaemic attack

3.3.2. Eccentric cycling

In summary, a total of 56 ECC cycling sessions were completed within the first week following CABG. All 24 patients completed an initial ECC cycling exercise bout, with 20 patients completing two ECC cycling sessions and 12 patients completing three ECC cycling sessions. As patients recovered from surgery they were discharged from hospital according to the supervising medical team instructions, therefore not all participants had an adequate length of stay to allow all three eccentric cycling sessions. Eccentric cycling workload progressively increased both within the cycling sessions and across the three sessions (fig 3.2). All patients commenced session one by performing passive ECC cycling (ie: ECC cycling with a negative workload of zero), with 46% (n=11) of patients progressing to perform at least 10W of work by completion of the first bout. Mean workload during session two (mean workload = 9.2±7W, mean maximum workload = 14±4W) and three (mean workload=14.1±8W, mean maximum workload 20.5±10W) also significantly increased, albeit partly as a factor of increased cycling cadence. By the commencement of the third ECC cycling session, cadence was approaching the pre-determined limit for safety (30 rpm) and this cadence was maintained over the duration of 10 minutes (fig 3.2). As such, the increasing ECC cycling workload, independent of cadence, was an outcome of increased torque production as patients applied increased force on the pedals. Rate of perceived exertion increased as workload increased over the course of the 10-minute bout (fig 3.2). The RPE remained below the pre-determined safety limit of four out of 10 in all but five occurrences where RPE was elevated to four. These exercise bouts were either terminated if patients exhibited other physiologic signs of increased exertion (increased HR/BP/RR, n=2), or workload was reduced with a resultant decrease in RPE (n=3). Over the duration of each of the ECC cycling bouts, mean RPE increased over the duration of 10 min ($P<0.05$) as workload increased. The RPE exertion did not differ significantly between each of the three sessions (fig 3.2).

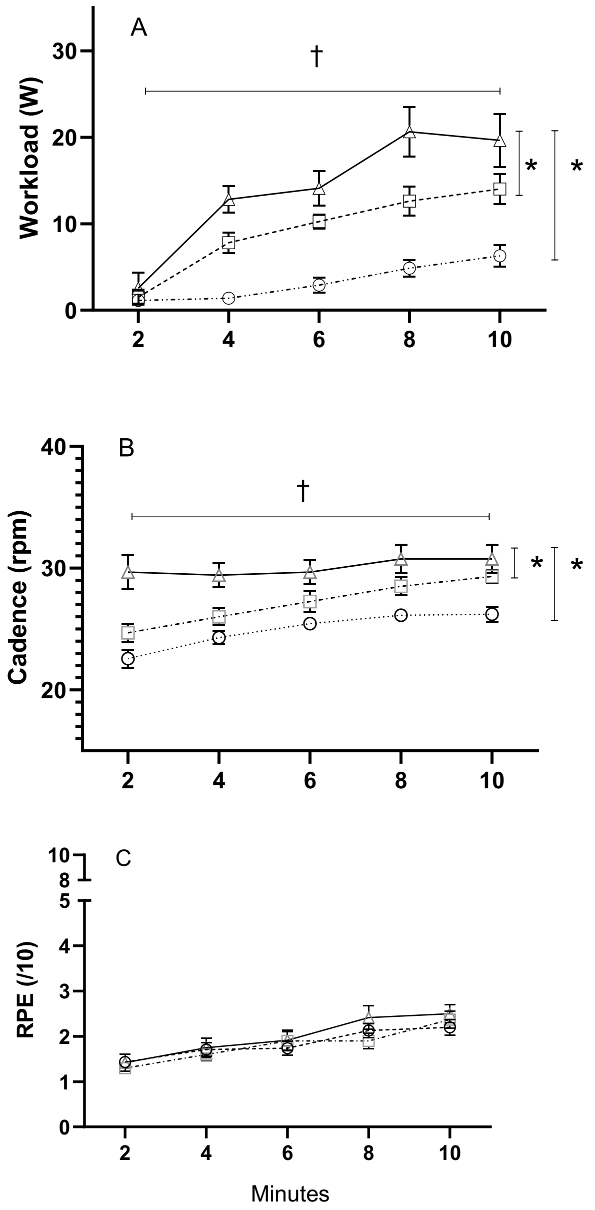

Fig 3.2: Workload (W), Cadence (RPM) and RPE (/10) for eccentric cycling exercise sessions 1, 2 and 3. Session 1 (○ n=24), session 2 (□ n=20) and session 3 (Δ n=12) each for a duration of 10 minutes. Multiple comparison analysis (session x time) with Tukey post hoc conducted where a significant interaction was identified.

† p<0.05 time independent of session.

** p<0.05 for session 1 and session 2 compared to session 3.*

Heart rate significantly increased from rest during session one from a resting mean of 87±11 bpm, to a maximum mean of 93±11 bpm ($P<0.05$). This elevation was less than 10 bpm on average and rapidly returned to resting values during the recovery period. Although a similar response occurred during session two and three, there was no session effect detected (Fig 3.3). Furthermore, the HR response to increasing workload tended to be attenuated during the second and third ECC cycling bouts. For the current study, there was no interaction of time and ECC cycling session for either arterial or muscle oxygen saturation and both remained relatively undisturbed. The muscle oxygen saturation values were less than 50% and were observed to be highest in the post-contractile recovery period (and significantly increased from rest in the recovery from session two)(Fig 3.3). The muscle oxygen saturation and peak power performed during each ECC cycling is presented in table 3.3. Aural temperature also remained steady throughout each session and was not affected by the increased EC workload (Fig 3.4).

3.3.1. Hospital Discharge

Following inpatient recovery, all patients met medical and allied health criteria for discharge home. Thirteen patients performed a timed 10-meter walk on the day of hospital discharge. Mean gait speed was 1.27±0.28 m/s (range 0.79-1.83m/s). During this walk, patients experienced a significant drop in oxygen saturation of the calf muscle from 31.3±8.1% at rest to 8.4±7% maximum desaturation during walking ($p<0.05$)(Fig 3.5).

The NASA-TLX questionnaire was also performed at hospital discharge. There was a large spread of responses across all six questions. The results of the NASA-TLX questionnaire are given in figure 3.6.

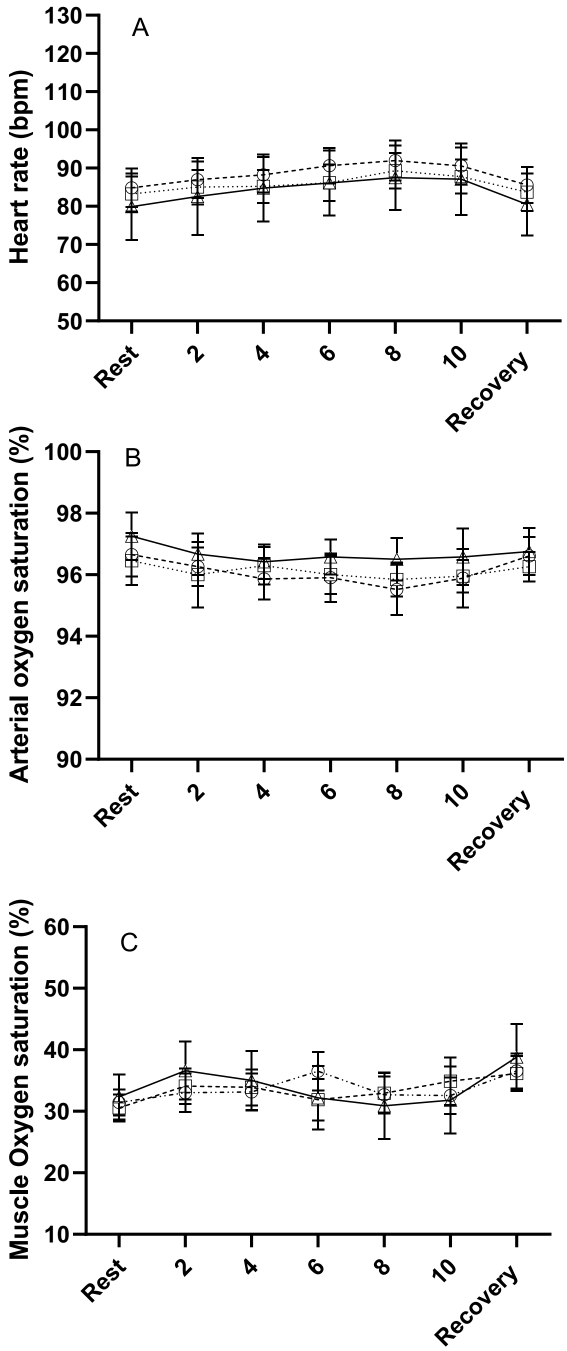

Fig 3.3: Heart rate (HR), Arterial oxygen saturation (%) and Muscle oxygen saturation (%) for eccentric cycling exercise sessions 1, 2 and 3.

Session 1 (○ n=24), session 2 (□ n=20) and session 3 (Δ n=12) each for a duration of 10 minutes and recovery. No significant interactions for multiple comparison analysis (session x time).

Table 3.3: Skeletal muscle oxygen saturation during rest, maximum workloads and recovery, associated with peak workload and during recovery.

Patient	No of EC sessions	Eccentric cycling session 1				Eccentric cycling session 2				Eccentric cycling session 3			
		Resting TSI	max workload TSI	Recovery TSI	Max workload	Resting TSI	max workload TSI	Recovery TSI	Max workload	Resting TSI	max workload TSI	Recovery TSI	Max workload
1	3	22	0	38	8	18	0	25	10	-	-	-	10
2	1	33	33	-	10				-				
3	2	20	19	28	2	34	32	42	10				
4	3	30	18	38	10	24	15	29	10	26	16	28	20
5	2	42	41	41	15	44	51	47	25				
6	3	22	29	-	0	32	37	40	0	27	30	-	5
7	2	50	54	55	10	28	-	-	20				
8	3	33	25	56	12	25	13	32	20	20	10	39	30
9	1	16	9	15	10								
10	3	20	8	13	3	10	3	13	15	17	9	10	20
11	2	39	41	44	5	31	36	45	20				
12	2	51	50	51	0	34	41	41	10				
13	1	49	51	-	5								
14	3	16	13	16	0	25	27	28	20	18	8	20	25
15	3	39	40	46	0	43	61	56	15	45	56	64	20
16	2	20	38	31	0	31	38	31	12				
17	1	25	-	-	5	20	10	16	10	41	36	48	10
18	1	40	31	60	10								
19	3	34	41	39	10	41	42	50	30	52	48	58	40
20	2	41	41	46	0	42	35	46	10				
21	3	32	34	42	10	30	34	36	15	28	25	30	25
22	3	26	13	18	10	23	13	26	15	38	31	41	20
23	2	32	28	37	10	21	26	26	15				
24	3	26	23	26	10	27	29	36	10	44	52	50	20

EC – eccentric cycling, TSI – tissue oxygen saturation of the skeletal (vastus lateralis) muscle

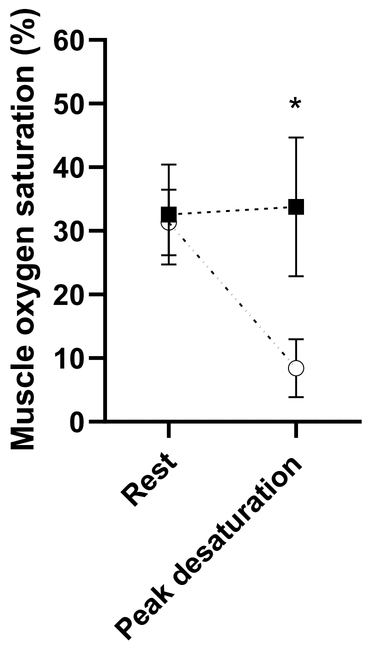

Fig 3.4: Muscle oxygen saturation (%) during final eccentric cycling exercise session versus discharge walk in participants that performed repeated bouts of eccentric cycling following CABG.

Twelve (12) participants at rest and then either in response (peak desaturation) to corridor walking (20 m) (○) at the gastrocnemius muscle or eccentric cycling (10 min) (■) at the vastus lateralis muscle. Repeated measure ANOVA (condition x time) and where a significant interaction occurred a Tukey's post hoc analysis was conducted.

** $p<0.05$ for eccentric cycling versus walking at the point of peak de-saturation*

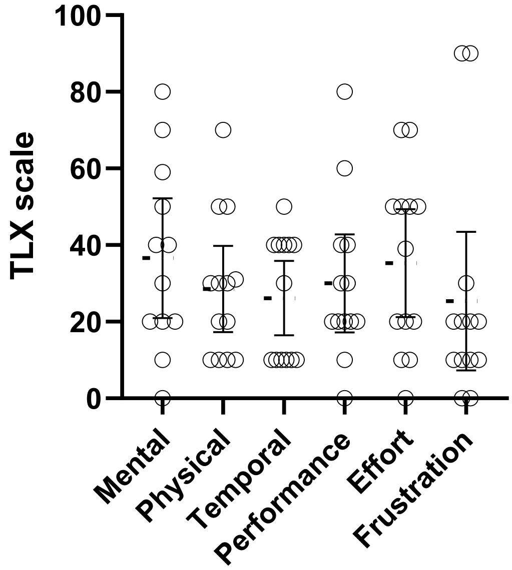

Fig 3.5 Task load index scale reported by participants (n=13) after completing final eccentric cycling exercise bout (either two or three eccentric cycling sessions) considering eccentric cycling experience as a whole.

3.4. Discussion

Eccentric cycling has demonstrable evidence for its capacity to mechanically load skeletal muscle whilst being uncoupled from cardiopulmonary demand [19,42], as has been extensively outlined in earlier chapters of this thesis. As a mode of exercise for medical rehabilitation, there is no doubt that its application for the outpatient or community dwelling patient with stable chronic disease is valuable, albeit still challenging from limited choice of commercially available ergometers. This current study, using an eccentric ergometer specifically designed to deliver negative workloads for hospital inpatients, provides the first account of eccentric cycling being performed in such cohort. Furthermore, patients performed eccentric cycling in the immediate post-operative stage following CABG, arguably where the most rapid maladaptive changes to the skeletal muscle are experienced. This study demonstrates a number of key outcomes that are the basis for eccentric cycling to be considered an alternative exercise modality during inpatient or phase 1 CR, with mechanisms that support its utilisation in a broader patient cohort with low physiologic reserve.

First, eccentric cycling was able to be safely performed, albeit at low workloads, on up to three occasions in the early postoperative period following uncomplicated CABG. No adverse events were experienced during the exercise bouts, including no arrythmias. Importantly, no patients encountered sternal wound complications or neurologic events. Overall incidence of postoperative AF was also similar to patients receiving usual care following cardiac surgery [43,44]. The importance of avoiding adverse events and the eccentric cycling being well tolerated by participants in the early postoperative period cannot be overemphasised, particularly when patients are engaging in a novel form of exercise. The meta-analysis undertaken as part of the first chapter of this thesis demonstrated patients who perform low to moderate intensity aerobic exercise within the immediate days following cardiac surgery have improved functional capacity at hospital discharge with no increase in adverse events. Studies included in this meta-analysis commenced exercise as early as the first POD and used traditional concentric bedside cycling and walking as modes of early postoperative exercise. We chose not to perform eccentric cycling on patients in the ICU to provide a margin of safety of at least 48 hours after CABG as haemodynamic changes are more common in this initial period [45]. In our institution, patients are usually transitioned to the postoperative ward on the second POD following uncomplicated CABG, meaning the third POD is often the first opportunity for patients to commence ward-based exercise. In the institution in which this study was performed, supervised walking is the only modality of postoperative exercise. The first eccentric cycling bout was commenced within five days of undergoing CABG, with the mean time to commencement of 3.4±0.9 (median=3) days. This alone is a novel outcome; prescribing eccentric muscle loading in patients immediately following major cardiac surgery and ICU discharge. Previous studies investigating eccentric cycling in patients with CAD have all been done in outpatients with stable symptoms, including post-revascularisation [46,47]. These studies showed patients with CAD were able to eventually perform high eccentric workloads and improve skeletal muscle structure contributing to strength gains. No adverse events were experienced by any patients during eccentric cycling in the postoperative patients in study 2 of this thesis, or in any studies in the literature on eccentric cycling in patients with CAD.

Second, the favourable physiological uncoupling of the cardiopulmonary system from the skeletal muscle loading allowed repeated, continuous loading of the peripheral skeletal muscle of the lower limbs with a significant increase in negative workload as the number of bouts increased, while maintaining minimal change to the muscle oxygen saturation of the skeletal muscle. There was a small but significant increase in heart rate during eccentric cycling from rest. These minor observable perturbations in heart rate may be explained by several mechanisms, including an increase in cardiac output from increased muscle blood flow, or the repeated mechanical stretching during contraction of the lower limb muscle fibres during the eccentric cycling [48]. That is, a graded response to skeletal muscle mechanical and metabolic stimuli evoke elevations in cardiac output and ventilation. These HR responses to eccentric cycling have been demonstrated previously in other cardiac pathology cohorts such as patients with CAD and heart failure [30,47]. While our study did not have a mode-specific concentric exercise comparison, the muscle oxygen saturation response of eccentric cycling was compared to short distance walking at hospital discharge. Notably, muscle oxygen saturation remained undisturbed during eccentric cycling while there was a clear reduction in muscle oxygen saturation during walking. While this exercise was not matched for absolute workload, this observation supports uncoupling of eccentric cycling from oxygen-requiring mechanisms [49] and a lower metabolic demand compared to walking.

The focus of the first eccentric cycling bout was largely familiarisation with the eccentric cycling ergometer and ensuring patients could complete the 10 minutes with no complication. As a result, mean workload performed during the first eccentric cycling bout was less than 5 W and the mean maximum workload performed during the first eccentric cycling bout was between 5-10 W. Workload then increased incrementally over the remaining two eccentric cycling bouts. After three eccentric cycling bouts, the mean workload had increased over three-fold. While overall negative workloads were low, they are not without potential benefit. The avoidance of immobility alone may provide skeletal muscle with enough stimulus to prevent acute muscle breakdown [9,50]. Furthermore, patients requiring mechanical ventilation have shown functional improvements with workloads similar to those performed by our patients in the first eccentric cycling bout [51]. Patients with severe COPD also experienced significant improvements in exercise tolerance after performing negative workloads as low as 25 W[31]. Whether the results in this second experimental study of this thesis represent a true improvement in exercise capacity or whether this is a result of familiarisation with eccentric cycling mechanics is unclear. There is a familiarisation process for individuals who are naïve to eccentric cycling that may mean metabolic responses to initial workloads are higher [22,26] or the ability to consistently achieve a pre-determined negative workload is limited [23]. Familiarisation may occur in as little as 3-4 eccentric cycling exercise sessions [26]. We were unable to perform a familiarisation exercise session in patients prior to undergoing surgery as patients were enrolled in the study following surgery. Introduction to and familiarisation with both eccentric cycling and the ergometer may be warranted prior to surgery as a means of eliminating this process from the postoperative exposure. Results from the TLX assessment in study 2 demonstrate a wide spread in self-reported levels of task demand. Those patients who experienced high feelings of frustration or task difficulty may improve following a period of familiarisation. The logistics of familiarising pre-operative CABG patients is a challenge, but stable outpatients may be able to perform at least one familiarisation eccentric cycling session. It would be of great interest to identify workloads performed at a given RPE prior to undergoing CABG, compared to the immediate postoperative period. Whether the decline in functional capacity, as demonstrated by the meta-analysis performed as part of chapter 1, is mirrored in patients who perform negative workloads following surgery could also be a focus of future investigation.

The delivery of repeated bouts of eccentric cycling was able to be performed and negative workload progressively increased up to three-fold, with RPE remaining below "moderate" throughout the workload increase. This physiologic phenomenon of lower RPE for a given workload is unique to eccentric cycling [22,35] and make it an attractive exercise choice for patients following CABG. Rate of perceived exertion has been assessed during both eccentric and concentric cycling, with some recent groups prescribing eccentric exercise intensity based on RPE [52,53]. Our choice to limit RPE to "moderate" is less than used in similar patients performing eccentric bedside cycling [3,54]. We elected to use this lower RPE target as muscle soreness, damage and dysfunction can occur when high eccentric workloads are performed [55,56]. This unfavourable effect of eccentric cycling can be completely avoided by using low negative workloads with low RPE [57,58]. Furthermore, targeting exercise intensity to physiologic variables in patients after CABG is not appropriate as haemodynamic variable such as heart rate and blood pressure can be impacted by multiple postoperative factors which include the physiologic stress of surgery, fluid status and pain. Furthermore, the use of beta-blockers, while indicated in optimal medical therapy following CABG, may limit the incremental increase in HR required to meet metabolic demands during aerobic activity.

It is also worth considering what haemodynamic changes, if any, may be displayed by similar patients if they were to perform concentric cycling. Only two studies are available that describe patients performing concentric cycling within the first week after cardiac surgery [3,59]. Both studies used traditional concentric stationary cycling (positive workloads) with a bedside cycling ergometer. Neither study reported the positive workloads that were performed, although it is likely these workloads were low as patients commenced the exercise on the third POD, at an RPE of 3-4. Both studies reported an increase in functional capacity at hospital discharge, as measured by the 6MWT. Similarly, critically ill patients who performed concentric cycling demonstrated improved functional capacity at hospital discharge compared with controls [51]. In patients with stable, treated CAD, when workload was matched for oxygen consumption, patients were able to perform four times the absolute workload doing eccentric cycling compared with concentric cycling, with no significant difference in HR or mean arterial pressure [47]. In another cohort of patients with heart failure, patients performing concentric cycling had a significantly higher HR compared to eccentric cycling when working at a similar RPE [53]. Given the low workloads performed in this study, it is uncertain if changes in haemodynamics may be experienced by patients if concentric cycling was performed instead. There may be cases of individual variability. However, it may be hypothesised from the work of Meyer and colleagues that, if matched for workload, patients performing concentric cycling would display higher myocardial oxygen demand given cardiac index, left ventricular stroke volume and stroke index are all higher compared to eccentric cycling [47]. This is undesirable in patients with CAD, as increased myocardial oxygen demand may lead to coronary ischaemia. This adds further support as eccentric cycling being a preferable exercise modality to concentric cycling for patients with CAD.

Muscle oxygen saturation in the quadriceps did not change at any workload performed during eccentric cycling in our study. While there was not a concentric cycling group for comparison, 11 patients performed a walking assessment including a timed 20-meter walk on the day of their hospital discharge. Muscle tissue oxygen saturation of the calf muscle was recorded during this walk. The calf muscle contracts concentrically during walking to plantar flex the ankle and create forward propulsion with the foot fixed on the ground during midstance to push off. The aim of including this walk as a single assessment prior to leaving hospital was to observe the oxygen saturation of the calf muscle performing concentric contractions during the essential functional activity of comfortable walking. We also wanted to identify the gait speed of patients leaving hospital with the aim of comparing this, combined with muscle oxygenation, to other literature.

All patients experienced a significant drop in calf muscle oxygen saturation during the walk. As already acknowledged, the walking and eccentric cycling were not matched for any physiologic parameter. However, patients were instructed to walk at a comfortable pace during the walk. One other study in the literature has compared concentric cycling and walking in patients following cardiac surgery [3]. This study found no difference in 6MWD at hospital discharge when patients performed either concentric cycling or walking training at an RPE of 3-4 out of 10 in the week after cardiac surgery.

While there is robust data demonstrating an association between preoperative gait speed and postoperative morbidity and mortality [8,60], literature on gait speed in patients following cardiac surgery is limited. Nevertheless, the walking speeds achieved by the patients in our study at hospital discharge are like those in other limited studies [61]. In an attempt to determine whether walking speeds performed by our patient cohort at hospital discharge are similar to other cardiac surgical patients in Australia, a separate cohort of 11 patients in an unrelated study had gait speed and calf muscle oxygen saturation assessed, prior to CABG and at hospital discharge following CABG. These patients had a mean gait speed of 0.57±0.3 m/s at hospital discharge following uncomplicated CABG. While not statistically assessed (due to heterogeneity and lack of matching), these walking speeds are similar to those performed by the patients in our study who performed eccentric cycling after CABG. Indeed, both results are significantly lower than those of healthy older community-dwelling adults [62] and patients prior to undergoing cardiac surgery [63]. Low walking speeds are likely to improve as patients recover from surgery and progress through outpatient cardiac rehabilitation [64,65] and discharge gait speed has not been associated with any poor medium- or long-term outcomes. However, the mean resting muscle oxygen saturation of the calf muscle in the abovementioned cohort of 11 patients that did not perform eccentric cycling after cardiac surgery was 45.5±16.8 % after CABG, while the patients in study 2 of this thesis who performed eccentric cycling, mean resting TSI was 31±11 %. This is lower than expected; preoperative cardiac surgical patients and healthy community-welling older adults had a mean resting calf muscle saturation of 70.4±15.4% vs 62.2±11.9% (P=0.14)[66]. Tissue saturation dropped significantly during walking after CABG (mean maximum desaturation in the separate 11 patient cohort 8.0±8.1% [66] and mean maximum desaturation in this study 8.4±7%). This significant decrease in muscle oxygen saturation while walking suggests that the oxygen requirements of the calf muscle during comfortable walking is metabolically demanding. While there are no other studies assessing oxygen saturation of the lower limb musculature in cardiac surgical patients, patients with PAD display similar tissue saturation characteristics to our patients. That is, the degree of desaturation during exercise is greater in patients with PAD than healthy controls [67]. Furthermore, a very recent review of exercise interventions in patients with PAD reported an increased time to maximum desaturation during walking, although the absolute desaturation values did not change after interventions [68]. Based on this and in conjunction with our study results showing no change in muscle oxygen saturation during eccentric cycling at an RPE of less than 4 out of 10, where in contrast muscle desaturation during comfortable walking does occur, it should be considered that eccentric cycling may be a better-suited exercise modality for patients with low resting muscle saturation from any cause. Further research into these various pathology groups is warranted and the application of the eccentric cycling ergometer used in this study may help facilitate these studies

3.5. Limitations

This study is a small cohort observational study, with quasi-experimental design. It was not powered to elicit a significant statistical difference in any measured variable; therefore all conclusions should only be considered hypothesis-generating. There is a large gender-imbalance with male patients over-represented. This reflects the gender difference seen in the clinical workload at the time this study was performed.

3.6. Conclusions

In low-risk patients with normal ventricular function following uncomplicated CABG, eccentric cycling performed in the immediate postoperative period was safe, while being able to deliver negative workloads with little change in haemodynamics. Furthermore, this study showed workload could be incrementally increased over three exercise bouts with perceived exertion remaining below moderate and no change in skeletal muscle oxygen requirements. Given the small change in haemodynamic variables experienced by patients performing eccentric cycling in our study, future studies may consider introducing eccentric cycling earlier in the postoperative recovery period, including whilst in the ICU. Given the immediacy of preceding cardiac surgery, and the requirement for a well-tolerated and uneventful postoperative recovery, the lowest-possible workloads should be chosen that facilitate these goals. Workloads for patients with normal biventricular function may be able to be prescribed at higher intensities in future studies. Finally, there should be consideration for applying eccentric cycling to other patient cohorts who may experience either low functional capacity and/or low resting tissue saturation, as the skeletal muscle loading in eccentric cycling can be performed with minimal impact on central and peripheral haemodynamics as well as being well-tolerated with low perceived exertion.

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4. Final discussion and recommendations

The studies described in this thesis were performed in an attempt to address a clinical need that was both personally identified by the author and recognised in recent literature [1,2]. Coronary artery bypass graft surgery is the most common cardiac surgery performed across the globe [1]. As extensively outlined in the first chapter, the intraoperative physiological insult and postoperative critical care requirement significantly impacts mobility and functional capacity in the immediate postoperative phase. This impact on ambulation is heightened in susceptible populations [2]. Furthermore, these same at-risk populations are more likely to have pre-existing skeletal muscle dysfunction [3]. The meta-analysis study [4] performed and summarised as a part of Chapter 1, demonstrated that implementation of exercise therapy in the early postoperative phase safely improves functional capacity at hospital discharge. This is the first review of its kind and provides high-quality evidence supporting exercise in the immediate postoperative period.

The age and medical complexity of patients undergoing CABG in the modern day may preclude some patients from participating in common postoperative exercise that primarily utilise concentric muscle contractions, as the physiologic requirements of postoperative exercise therapies such as walking and concentric cycling may be too demanding. The relatively recent application of eccentric exercise for patients with low physiologic reserve has demonstrated the utility of this exercise modality in being able to deliver a stimulus to the peripheral skeletal muscle that can improve strength [5,6], aerobic and functional capacity [7], while minimising muscle soreness [8], muscle damage [9] and metabolic demand [10]. These physiologic characteristics of eccentric exercise make it well-suited to many patient cohorts with functional limitations, however eccentric exercise has not yet been investigated in any hospitalised patients prior to this study.

One potential barrier to performing eccentric exercise in an acute-care hospital may be the lack of appropriate equipment. As described in the Chapter 2 of this thesis, commercially available eccentric cycling ergometers are typically designed to be used in a static position and deliver high loads. To overcome this barrier, an eccentric cycling ergometer was designed and constructed with specific features to support its use in an acute care hospital. In the first experimental study of this thesis, healthy participants performed two steady state workloads using this custom-designed ergometer. The ability of the ergometer to deliver consistent workloads was demonstrated, in controlled experimental conditions, with healthy adults. The ergometer design also met several requirements for use in a hospital setting, specifically mobility, low noise production and applicability to the individual bed space. With an eccentric ergometer now available, that could be used for multiple patients in a cardiac surgical recovery ward, a second experimental study was performed (Chapter 3).

As a form of feasibility, patients with normal ventricular function and otherwise deemed low-risk for cardiac surgery performed eccentric cycling workloads at their bedside, following uncomplicated CABG. These patients were able to perform repeated days of eccentric cycling with increasing workloads while keeping rate of perceived exertion below "moderate". Furthermore, perhaps most importantly for the primary objective of this thesis, a small increase cardiorespiratory demand was experienced during eccentric exercise. Skeletal muscle oxygenation was undisturbed by the process of increasing the workload within and between sessions. Clinically, there were no increase in adverse events rates compared to usual postoperative care.

Overall, this thesis describes the identification of a clinical patient population with specific physiologic restrictions, outlines the development and testing of a cycling ergometer that can deliver eccentric loads, by the bedside, to this vulnerable patient group and performed a pilot study to demonstrate the combined feasibility and safety of both the ergometer and eccentric cycling. This thesis discusses not only the development of the ergometer specifically constructed for this population, but also the application of eccentric cycling in a patient cohort not previously studied. The development of this eccentric cycling ergometer and application of this novel exercise modality was well tolerated, while also demonstrating a favourable physiologic response-profile for post-cardiac surgical patients.

Early mobilisation is an essential component of postoperative recovery following cardiac surgery. In the ICU setting invasive haemodynamic monitoring, intravenous infusions and supplemental oxygen requirements are examples of necessary support that patients often require in the immediate postoperative setting that are barriers to performing any exercise other than bed-based movements. However critical care in the modern day recognises the importance of early mobilisation and every effort is made to free patients from ambulation-restricting treatments [11,12]. As demonstrated by the meta-analysis performed in the first chapter however, there are few studies investigating exercise in the immediate postoperative period following cardiac surgery. Despite the safety of these interventions and the positive impact on functional capacity, medical, nursing and allied health staff have been anecdotally noted to have concerns about over-exertion in the immediate postoperative period. Patient expectations are associated with outcomes after CABG [13] and as such, patients with a fear of over-exertion may also avoid engaging in postoperative exercise. In addition to these psychological barriers, simple exercise such as walking can pose significant physiological demands on patients in the immediate postoperative period, even if the activity would usually be of little physiological significance. As an example, the small and separate cohort of comparative patients in chapter 3 that had lower limb muscle oxygenation assessed during walking before and after CABG, demonstrates the impact of CABG on the physiologic cost to working skeletal muscle performing comfortable walking immediately following surgery (See appendix fig 5.1). This acute decompensation in skeletal muscle oxygenation may be linked to clinical and functional consequences such as the reduction in functional capacity at hospital discharge seen in many patients after cardiac surgery [14,15].

These forementioned barriers to exercise all stand to be overcome with an intervention that can provide skeletal muscle loading to the lower limb at the hospital bedside, with minimal change to cardiorespiratory and metabolic parameters. Multiple stationary concentric cycling ergometers are used in current practice, including several that are compact and appropriate for use at the hospital bedside. These ergometers however utilise concentric muscle contractions and, as such, have physiologic limitations associated with oxygen dependent muscle contractions. As described in chapter one, eccentric cycle ergometry has physiologic characteristics that appear to be well suited to patients with low physiologic reserve. Yet, as highlighted in recent literature, this exercise modality has not yet transitioned to the hospital or postoperative environment. When this project was initially envisioned, no commercially available ergometer could be identified that was appropriate for the hospital environment. Detailed in chapter two, ergometer size, motor noise and manoeuvrability were some of the concerns with available ergometers. As the ergometer was only required to deliver relatively low loads, a manoeuvrable and quiet eccentric cycle ergometer was successfully designed and constructed. This novel ergometer consistently delivered up to 100 Watts of negative work during eccentric cycling. This ergometer is the first of its kind and can be deployed to any hospital patient bedspace and deliver consistent ECC workloads. This has essentially opened the door for multiple future studies in various hospitalised patients, including critical care and non-ambulatory patients.

The studies in this thesis were initially designed and proposed based on the most pronounced physiologic principle that underpins continuous, low-load eccentric cycling; that is, the oxygen requirement for performing negative workloads is significantly lower than what is required to perform the same workloads using concentric contractions. This physiologic phenomenon has been consistently demonstrated since the often-cited "original" eccentric cycling work by Abbot in 1952[16]. Multiple studies following this demonstration have matched workloads between eccentric and concentric cycling while investigating various physiologic parameters such as oxygen consumption, heart rate, and cardiac output [17–20]. Since the early demonstrations of equivalent workload at lower metabolic cost, attention has moved towards eccentric cycling for training populations with low physiologic reserve. Patients with cardiac [10,21], respiratory [6,22,23] and metabolic disease [24]as well as frailty syndromes [7,25] have all improved exercise capacity with lower oxygen demand than concentric exercise . The increasing number of studies investigating eccentric exercise in patients with various chronic disease states is reflected by multiple reviews written recently [26–30]. These reviews provide an up to date account of the mechanisms, physiologic and clinical outcomes of patients with chronic cardiorespiratory disease and frailty, who have undergone acute and chronic training programs utilising eccentric exercise. Despite the growing interest in and recognition of the unique physiologic properties of eccentric exercise. Until now however, it had not yet transitioned to the hospital environment.

Patients that have undergone CABG provide a unique opportunity to explore both the physiologic response to eccentric cycling in a group of patients with an acute reduction in functional capacity, as well as the potential impact of eccentric on functional outcomes. As outlined in chapter one, patients undergoing CABG experience acute physiological changes in the several days immediately following surgery, including variability in haemodynamic parameters such as HR and BP. Optimal medical therapy includes antiarrhythmics such as b-blockers and antihypertensive medications [31,32], which are commenced at various timepoints following surgery depending on patient clinical progress and haemodynamics.

While aerobic exercise such as bedside cycling and walking improve functional capacity following CABG, these exercises utilise primarily concentric muscle contractions. As described in chapter one, continuous concentric exercises have a linear increase in oxygen requirement and heart rate as workload increases [33]. While no studies identified in the meta-analysis performed in chapter 1[4] reported any increase in adverse advents including arrhythmia, the patients recruited were low risk. Haemodynamic variables were not reported in any study.

In experimental study 1, healthy participants performing two low workloads of 30W and 60W, experienced a small but statistically significant increase in heart rate from rest, but not between workloads, which is indicative of the low heart rate to external workload slope which occurs during eccentric cycling [33]. Similarly, in patients in the immediate days after CABG, heart rate increased from rest in all eccentric cycling bouts. However, this increase was only a mean of six bpm. This is congruent with other studies that report a heart rate increase when performing eccentric cycling, although not as pronounced as con cycling when compared to workload-matched exercise [9,17,18,33]. Experimental studies one and two in this thesis further affirm this blunted heart rate response to eccentric cycling, even in patients who have experienced both an acute physiologic insult and pharmacotherapy that impacts on central haemodynamic regulation.

Hospitalised patients, particularly those in critical care environments can experience rapid loss in skeletal muscle function and mass due to immobility or acute illness [34]. The prospect of having an exercise modality that loads skeletal muscle with little to no alteration on cardiopulmonary or metabolic demand can provide patients with a potential remedy to muscle dysfunction from immobility, dis-use and maladaptation. Other patient groups that experience skeletal muscle dysfunction include patients with heart failure [35], peripheral vascular disease [36]and diabetics [37]. Analysis of muscle oxygenation using NIRS is a non-invasive technique to assess overall balance of oxygen delivery and oxygen consumption in the area of interest of skeletal muscle [38]. In study two, healthy participants were able to perform increasing eccentric cycling workloads with no reduction in muscle oxygen saturation of the quadriceps coupled with minimal change in heart rate or blood pressure. These results were able to be almost completely translated to patients less than 72 hours after major cardiac surgery, with these patients performing workloads up to 40W during the course of the postoperative hospital stay, with no significant change in muscle oxygen saturation. This observation is supported by others, whereby matched external workload during eccentric and concentric cycling, demonstrates muscle oxygen saturation is less disturbed during eccentric cycling[39]. The assumption then follows that higher absolute workloads could be performed using eccentric cycling than concentric cycling, with equivalent working muscle oxygen saturation, and this has also been demonstrated during continuous eccentric cycling [40]. Patients after CABG are a unique patient population in that they often experience a significant drop in haemoglobin following surgery. As haemoglobin concentration is a component of oxygen delivery [41], postoperative anaemia may contribute to exercise intolerance experienced by these patients. Despite this reduced capacity in oxygen delivery, the CABG patients in the second experimental study did not experience any drop in tissue saturation during eccentric cycling, even as workload increased over the bouts. Nevertheless, when these patients performed a walking exercise at hospital discharge, muscle tissue oxygen saturation dropped suddenly and significantly. Acknowledging, while these two activities were not matched for workload or perceived exertion, RPE did not exceed four out of 10 during eccentric cycling and instructions given to patients performing the walking were to walk at a comfortable or usual pace, so it is unlikely that these same patients would have perceived the exertion in excess to that of the eccentric cycling. This large drop in muscle tissue oxygen saturation during walking and after CABG was also seen in eleven patients that performed a comfortable walk prior to surgery and again at hospital discharge [42]. The drop in muscle oxygen saturation of the calf muscle was significantly more following surgery when compared to preoperative walking, with some patients not showing any desaturation prior to surgery and then subsequently experiencing desaturation to less than 10% (Appendix fig 5.1). Clearly, the relative physiologic demand of walking on the muscles of the lower limb is much greater than eccentric cycling for patients following CABG. The mechanisms behind this sudden change in calf muscle saturations were not the focus of this study and remain an area for future investigation. Nonetheless, it is clear that skeletal muscles of the lower limb can perform negative workloads with no change to muscle oxygen saturation, while concentric exercise caused large desaturations in the calf muscle. This adds to the appeal of eccentric cycling as an exercise modality for patients with skeletal muscle dysfunction.

Another important consideration from this study is that while the absolute workloads were low, they were prescribed according to RPE. Workload was able to be increased with repeated days of eccentric cycling, with RPE remaining constant. While RPE was limited to moderate as a safety feature for the study, patients were still able to sustain eccentric muscle contractions whilst maintaining haemodynamic stability with no reduction in muscle tissue oxygen saturation. Perceived exertion has only recently been investigated as a means of eccentric exercise prescription [43], however it has been recorded in several studies of patients performing eccentric including healthy participants [39] and those with chronic cardiorespiratory disease [44–46]. Given the favourable safety profile of eccentric cycling in study 2 (chapter 3), future studies may allow RPE to extend to higher ratings, and presumably therefore higher mechanical workloads.

A potential limitation from study 3 is whether the workloads performed by patients are enough to stimulate structural or architectural adaptations traditionally sought from exercise prescription. Studies on patients with severe exercise limitations such as COPD have shown that even extremely low initial loads can provide enough stimulus to improve functional outcomes while also being able to up-titrate workloads and avoid muscle injury [23,44]. Whether workloads as low as those performed by these hospitalised patients are enough to induce muscular adaptations to the loads was not yet the focus of research; it must be reiterated that this study was a feasibility study, aiming to demonstrate the safety of this exercise modality and its potential applicability to hospitalised patients. It is also important to recognise that the overall goal for many hospitalised patients is to deliver a stimulus to the skeletal muscle that enables patients to avoid or at least limit muscle dysfunction associated with acute illness and immobility. Passive cycling using an ergometer for bedbound or unconscious patients has been used in cases of critically-ill patients in ICU as a means of avoiding complete immobility [47–49]. Minimal to no haemodynamic changes were seen during the passive cycling bouts in these patients. However this should not be confused with active efforts to apply force, however small the workload, in order to actively stimulate the skeletal muscle and not simply avoid immobility. The ability to engage meaningful lower limb contractile activity is achieved with the use of bedside eccentric cycling, while minimising the metabolic requirements associated with concentric force application.

There are several key considerations to come from the studies performed in this thesis. As identified in the background research, the impact of appropriately-prescribed, tailored exercise therapy of any sort for patients after CABG should not be under-estimated. Improvements in functional capacity after as little as three days of exercise therapy may allow patients to return to independent ambulation and associated activities of daily living sooner than if exercise was not performed. Loading the skeletal muscle of the lower limbs is a critical component of preventing acute muscle dysfunction and loss of muscle mass in patients with critical illness. Exercise immediately following CABG does this with minimal risk to patient safety. Cardiac surgical units should ensure all patients with the physiologic reserve to engage in aerobic exercise such as walking or stationary cycling are given this opportunity following CABG and other forms of cardiac surgery.

Following the demonstration of patient safety and the feasibility to conduct eccentric cycling at the bedside from studies 2 and 3 in this thesis, there are several important studies that should now take place. In doing so, a number of limitations of the current thesis can also be addressed. First, the introduction of a formal control group should be considered. Direct comparison of concentric and eccentric cycling in the postoperative period following CABG, including systematic assessment of oxygen delivery constituents such as haemoglobin concentration, is the logical next step. Workload prescription in this population should be done with caution and, given this thesis provides the first account of eccentric in post-CABG patients, RPE is likely the most appropriate means of ensuring workloads are limited to ensure safety. Haemodynamic responses to workloads should be investigated in greater detail, including increasing RPE limitations. Assessment of muscle oxygen saturation during rest, standing and walking over sequential postoperative days could serve as assessment of a control group of patients receiving usual care (standard physiotherapy) following CABG. The comparison of concentric and eccentric cycling on physiologic outcomes such as muscle oxygenation and clinical outcomes such as gait speed should be high priority of future research.

Clinical studies can often be confounded by non-standardised variables. In critically ill and postoperative patient cohorts, controlling for pharmacotherapy, fluid balance and comorbidities is unlikely to be achieved, even in a large, randomised trial. Nevertheless, these limitations should be embraced as part of the complex nature of research in critically-ill patients, and not a barrier to further investigation. Larger trials should be powered appropriately to ensure primary outcomes can be confidently assessed even in such heterogenous cohorts.

Eccentric cycling as a therapy to avoid immobility and disuse atrophy of skeletal muscle should be explored in a wider spectrum of hospitalised patients, including those with reduced left ventricular function, prolonged ICU stay and the elderly. The ergometer constructed in chapter 2 provides a means of delivering consistent eccentric loads to practically any bedspace in a hospital. Each of the abovementioned patient cohorts has its own metabolic and skeletal muscle abnormalities that may be addressed in some part by eccentric cycling.

With an established pre-operative baseline and the opportunity to engage extended eccentric cycling during the post-operative hospital stay, describing the changes in muscle architecture would be the most obvious underpinning mechanism to explore. This is on two accounts, given acute bed rest itself is a driver of muscle atrophy in period of disuse [50], and in contrast eccentric muscle stimulus encourages positive adaption to the arrangement of those muscle fibres [51]. The proposed next study in CABG patients would monitor and document the muscle architectural via non-invasive ultrasound, including changes during the course of surgery for both those with and without the opportunity to engage in daily post-operative eccentric cycling. Finally, given that those characteristics to muscle architecture such as muscle fibre length and angle are components of muscle function [52,53], targeted physical capacity assessments should be coupled with muscle structural observations to determine the underpinning mechanism of improved patient outcomes when leaving hospital.

In conclusion, this thesis both responds to and echo's the observations and conclusions of several other authors, commenting on the utility of eccentric cycling and the potential for its application in populations with low physiologic reserve [54,55]. Patients with skeletal muscle dysfunction from chronic disease or frailty may not have the physiologic reserve to perform traditional forms of concentric rehabilitation exercise. Eccentric cycling using a stationary ergometer is exceptionally well suited for these patients, due to the reduced metabolic cost of performing negative work. There is a mounting body of evidence that supports its use in patients with various chronic disease states. This thesis includes the first study to investigate the safety and feasibility of eccentric cycling in hospitalised patients with an acute drop in both skeletal muscle function and physiologic reserve following major cardiac surgery. Patients with an acute decompensation in physiologic reserve i.e.: those following CABG, safely performed eccentric cycling with minimal change to both haemodynamic variables and local muscle oxygenation. With the development of an ergometer that is now tailored for hospital use, many other hospitalised patient cohorts may now be considered for eccentric cycling.

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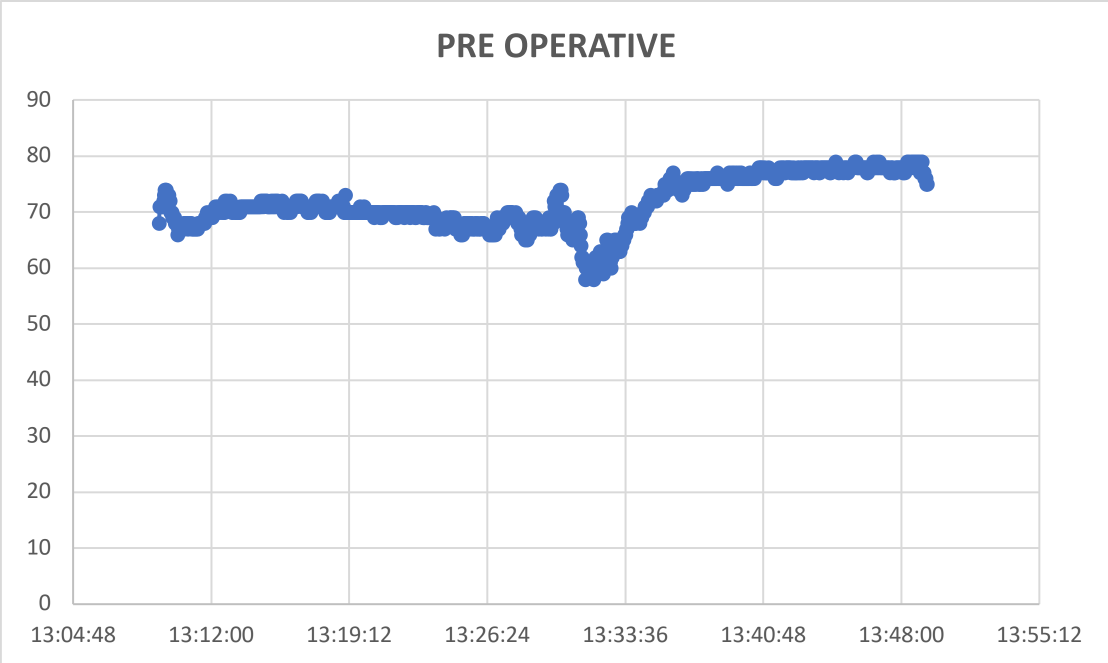
Appendix



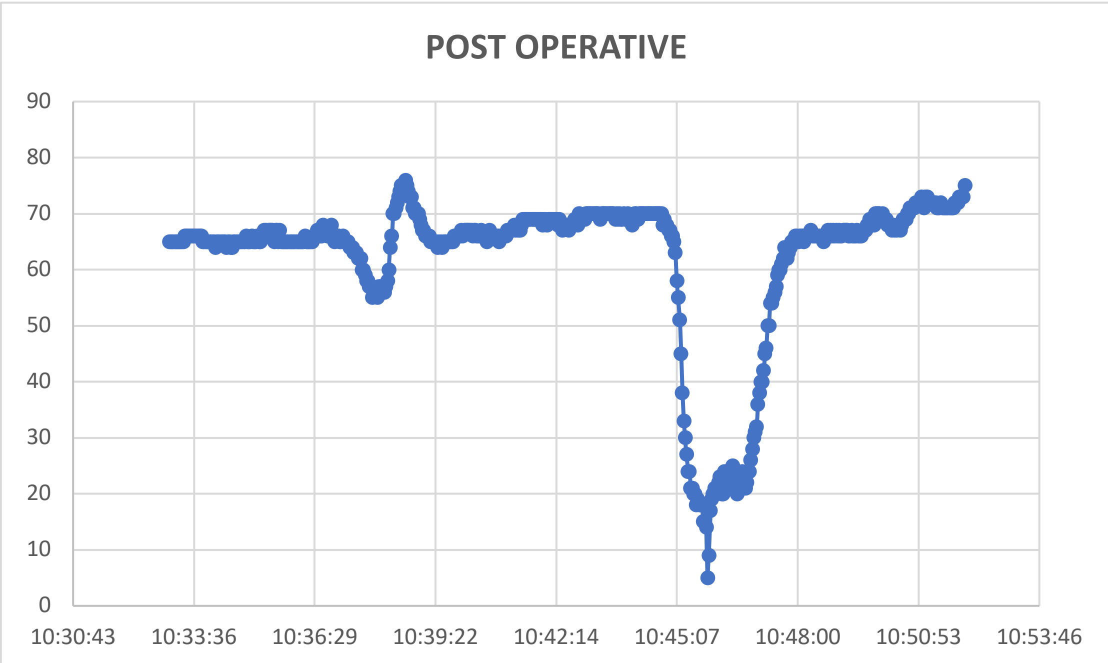


Figure 5.1: Skeletal muscle oxygenation during comfortable walking approximately 50 m on the day prior to CABG, and at hospital discharge following CABG in a 55 year old woman with hypertension as her only comorbidity, demonstrating the sharp and severe drop in muscle oxygen saturation following surgery.