Exercise training in patients awaiting liver transplantation and complex endovascular aortic aneurysm surgery

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Thesis submitted for the degree of Doctor of Medicine (Research)

Declaration

‘I, Clare Marie Morkane confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.'

Signature:

Abstract

Introduction:

Mounting evidence supports a relationship between physical fitness and perioperative outcomes. This thesis assesses the feasibility of a structured, preoperative exercise training programme in two high-risk surgical cohorts as two distinct studies: patients awaiting liver transplantation (LT) and fenestrated endovascular aortic aneurysm repair (FEVAR).

Methods:

Participants in the intervention arms for both studies performed thrice weekly directly supervised training sessions on a cycle ergometer for six weeks, individualised according to baseline fitness measured by cardiopulmonary exercise testing (CPET). Feasibility and acceptability outcomes were eligibility, recruitment, adverse events and adherence to exercise. The impact of training was assessed by repeat CPET after the intervention. In each study, changes in anaerobic threshold (AT) and peak oxygen-consumption (VO_2peak) were compared to those among a group of control participants. The effect of exercise on cardiorespiratory fitness, health-related quality of life (HRQL) and exercise enjoyment was assessed along with the impact on postoperative outcomes.

Results:

Predefined feasibility and safety outcomes were met by both studies. A high participant drop-out rate in the LT study was noted (13 of 33 patients across both cohorts) attributed to transplantation, clinical deterioration and delisting. All 23 patients awaiting FEVAR (11 in the exercise and 12 in the control arm)

completed the six week study period with a 97% compliance for exercise sessions in the intervention group.

No difference in AT was observed between intervention and control cohorts in either study. In patients awaiting LT, an increase in VO_2peak was demonstrated in the intervention group and a corresponding decrease in VO_2peak in controls from baseline to week six. No change in HRQL scores were observed in either cohort, likewise no difference in postoperative intensive care lengths of stay were seen.

Discussion:

These two studies demonstrate feasibility for the exercise intervention and will form the basis for further evaluation of similar interventions in future studies.

Impact statement

The two studies presented in this thesis have had an impact on both new scientific findings and clinical practice.

Impact on new scientific findings:

1) *Academic outputs*
    a. *Presentations*

The results of both studies have been presented at national and international conferences:

- *CM Morkane et al. An individualised, hospital-based prehabilitation programme for patients with cirrhotic liver disease awaiting transplantation surgery: a feasibility study. Oral presentation at International Liver Transplantation Society (ILTS), Toronto, May 2019.*

This oral presentation was awarded an ILTS Travel Award 2019.

- *CM Morkane et al. The feasibility of a structured, individualised exercise training programme for patients awaiting complex fenestrated endovascular aortic aneurysm repair at the Royal Free Hospital. Poster presentation at the Vascular Anaesthesia Society ASM, September 2018.*

As a consequence of my experience setting up and running prehabilitation programmes and the expertise I have gained conducting and interpreting cardiopulmonary exercise tests, I was invited to give the following lectures at conferences:

- Presentation at Acute & General Medicine Incorporating Anaesthesia and Critical Care 2019, 12th November- ExCeL London. '*Update on CPET and Prehabilitation'*

- Presentation at the TRIPOM (Trainees with an Interest in PeriOperative Medicine) section of EBPOM 3rd July 2019. '*Live CPET and interpretation'* and *'Exercise as the single most useful preoperative intervention'.*

- Cutting Edge London Aortic Symposium, *'Prehabilitation, exercise, sarcopenia and making our patients walk',* 11th October 2018, RSA House London.

b. Publication

The results of study number 1 were published in the journal *Transplantation*:

- *Clare M. Morkane, Orla Kearney, David Bruce, Clare Melikian, Daniel S Martin. An outpatient hospital-based exercise training programme for patients with cirrhotic liver disease awaiting transplantation: a feasibility study. Transplantation.* 2020 Jan;104(1):97-103

c. Collaboration and influence on future studies

Through dissemination of study findings at international conferences, interest has been generated, particularly in the field of prehabilitation prior to liver transplantation. I have helped to establish a collaborative relationship with the Birmingham transplant team and have built on the preliminary feasibility work reported in this thesis, using our shared experiences to develop a dual centre, randomised, controlled trial which has been fully funded by the National

Institute for Health Research (NIHR) Efficiency and Mechanism Evaluation (EME) programme (code: NIHR129318, award: £1,293,103.50).

This work has also had a local academic impact, motivating other clinicians to conceive and develop separate small, exercise-based interventions and studies. It has also raised the profile of cardiopulmonary exercise testing and its perioperative utility amongst clinicians.

Impact on clinical practice:

The adoption into clinical practice of preoperative exercise prior to abdominal aortic aneurysm surgery has been a very satisfying outcome. The encouraging results from this work and overall patient satisfaction have had a real impact at the Royal Free Hospital with a pathway for preoperative exercise supervised by physiotherapists established as a direct consequence.

On a personal level, the hundreds of hours spent supervising individual training sessions has afforded me a unique insight into patient motivation and empowerment. This is a position I am privileged to be in and is experience I will take forward into my future career.

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Abbreviations

AAA	Abdominal aortic aneurysm
AKI	Acute kidney injury
AT	Anaerobic threshold
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
CI	Confidence interval
CO	Cardiac output
CPET	Cardiopulmonary exercise test
DASI	Duke activity status index
DBD	Donation after brain death
DCD	Donation after cardiac death
DO_2	Oxygen delivery
ECG	Electrocardiogram
ERAS	Enhances recovery after surgery
ESLD	End-stage liver disease
EVAR	Endovascular aneurysm repair
FEVAR	Fenestrated endovascular aneurysm repair
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
Hb	Haemoglobin
HDU	High dependency unit
HIF	Hypoxia-inducible factor
HIT	High intensity training
HR	Heart rate
HRA	Health research authority
HRQL	Health related quality of iife
ICU	Intensive Care Unit
IQR	Interquartile range
LT	Liver transplant
MAC	Mid-arm circumference

MAMC	Mid-arm muscle circumference
NHS	National Health Service
NIHR	National Institute for Health Research
NVR	National Vascular Registry
PAES	Physical activity enjoyment scale
POSSUM	Physiological and operative severity score for the enumeration of mortality
RER	Respiratory exchange ratio
RFH	Royal Free Hospital
RPE	Ratings of perceived exertion
SD	Standard deviation
SVR	Systemic vascular resistance
TSF	Triceps skinfold thickness
TV	Tidal volume
VCO_2	Carbon dioxide production
VE/VCO_2	Ventilatory equivalents for carbon dioxide
VO_2 peak	Peak oxygen uptake
VO_2 max	Maximal oxygen uptake
WR	Work rate

Acknowledgements

I would like to thank the following people and organisations:

My supervisors Professor Daniel Martin and Professor Brian Davidson, who helped conceive and develop these studies and guided me throughout. I am indebted to Prof Martin for funding the cycle ergometer and for his encouragement, energy and continued support, both academically and clinically.

The UCL exercise physiology team, in particular Dr James Otto and Mr David Bruce whose expertise and teaching equipped me with the skills and knowledge to perform and interpret high quality exercise tests. David also played an integral role in the supervision of exercise training sessions; without him this work would not have been possible.

Miss Orla Kearney, specialist liver transplant dietitian, performed all the anthropometric assessments in study 1: exercise training for patients awaiting liver transplantation.

I am extremely grateful to the Vascular Surgery Charity at the Royal Free Hospital for funding the pedometers used in study 2: exercise training for patients awaiting complex endovascular aortic surgery.

The greatest debt of gratitude however, is owed to the patients who gave up their precious time to take part in this research and the physicians looking after them whose enthusiasm for this work and ongoing commitment to improving patient outcomes is truly inspiring. In particular I would like to thank Miss Tara Mastracci, clinical director of vascular surgery and lead for complex aortic surgery and Dr Rachel Westbrook, consultant hepatologist and transplant waiting list clinic lead.

Finally, I would like to dedicate this work to my late father, who passed away in May 2019; his steadfast encouragement and commitment to supporting my exploits both within and outside of clinical training will continue to motivate me throughout my career.

1. Introduction

1.1 Risk assessment

1.1.1 The high-risk surgical patient

The number of surgical procedures performed worldwide is increasing. Global estimates suggest 312 million major operations were performed in 2012, an increase of one-third over eight years (1). Postoperative mortality (death within 30 days of surgery) accounts for 7.7% of all deaths globally, making it the third greatest contributor to deaths after ischaemic heart disease and stroke (2). Patients who survive postoperative complications commonly experience functional limitation and reduced long-term survival (3). In the UK, approximately 1 in 10 people undergo a surgical procedure each year (4). Given this volume of activity, patient outcomes following surgery are a growing area of public health concern and hence an important research target (5, 6).

Estimating risk and putting into place processes and interventions to mitigate it has become an important focus of the field of perioperative medicine. High-risk patients are defined by a predicted hospital mortality of ≥ 5%; they account for approximately 10-15% of the surgical population, but suffer around 80% of postoperative deaths (7–9). Patients with a predicted hospital mortality lower than 5% should not however be viewed as 'low risk'. Most patients undergoing major general surgery will be at high risk of adverse postoperative outcomes hence objective, clinician-led assessment of risk is required on a case-by-case basis.

The surgical population in the developed world is ageing and with an increasing number of procedures being performed on high-risk patients there is a clear need to identify interventions that improve perioperative outcomes (8).

1.1.2 Exercise capacity and surgery

There is a consistent relationship between physical activity, physical fitness and good health. Cardiorespiratory fitness is inversely associated with mortality with no observed upper limit of benefit (10). Indeed, sedentary time is one of the strongest known predictors of adverse outcomes including all-cause mortality, cardiovascular disease, malignancy, musculoskeletal disease and metabolic disorders (11). Major surgical interventions are associated with a variety of perioperative cardiopulmonary, neuroendocrine and metabolic changes (12), known as the 'surgical stress response' due to an increase in tissue oxygen demands (table 1-1). The stress response to surgery is initiated by neuronal activation of the hypothalamic-pituitary-adrenal axis and results in overall catabolism (13). The magnitude and duration of the response is proportional to the surgical injury and development of perioperative complications.

Sympathetic nervous system activation
Endocrine stress response
- Pituitary hormone secretion
- Insulin resistance
Immunological and haematological changes
- Cytokine production
- Acute phase reaction
- Neutrophil and lymphocyte activation

Table 1-1: Systemic responses to surgery

Adapted from Desborough JP et al (13)

A patient's preoperative functional status plays a key role in their ability to withstand this stress (14). It follows that physical fitness is an important determinant of perioperative outcome: less fit patients have higher incidences of morbidity and mortality after major surgery. Physical fitness measures (such as cardiopulmonary exercise test outputs) were used as risk indices to guide perioperative care in early studies (15, 16). The American College of Cardiology/American Heart Association guidelines stratify patients according to exercise capacity, to target the use of preoperative investigations to patients who will benefit most (17).

Levels of physical activity amongst adults in the UK are declining. According to Public Health England data, one in four women and one in five men are classed as physically inactive – doing less than 30 minutes of moderate physical activity per week and as a population, we are 20% less active than we were in the 1960s (18). This 'physical inactivity epidemic' coupled with the complex interplay of comorbid disease, age, obesity and the physiological demands of complex surgery has focused attention on exercise capacity as a modifiable risk factor. Indeed, physical training programs or 'prehabilitation' as they have become known, have been proposed as an intervention to improve postoperative outcome.

1.1.3 Risk prediction tools

Identifying a patient as 'at risk' of perioperative morbidity and mortality aids in the comprehensive provision of information essential for shared decision-making between clinician and patient, facilitating a decision that is specific to an individual patient's condition and context. There are a number of ways of estimating risk for a general surgical patient. Simple risk indices based on clinical data have been devised but have limitations. Perhaps the earliest of these is the American Society of Anesthesiologists (ASA score) in 1963 (19). The ASA score involves subjective assessment of the patient and fails to take into account the surgery-specific risk. Other indices were constructed to predict specific events, for example the Lee's cardiac risk index was created to predict the risk of postoperative cardiac events, rather than all-cause mortality (20). A more recent risk prediction tool, the POSSUM score (Physiological and Operative Severity Score for the enUmeration of Mortality) requires intraoperative data (alongside preoperative parameters) that is not available at the point of pre-assessment for surgery (21).

Patient exercise capacity has historically been known as a good indicator of preoperative fitness and is a reliable predictor of perioperative and long-term cardiac events (17, 22). Global or local tissue hypoperfusion is a common feature in patients developing serious postoperative complications; usually as a result of inadequate cardiopulmonary function (23). It hence follows that dynamic assessment of cardiopulmonary fitness will form an important component of surgical risk prediction. Consensus American guidelines for preoperative practice state that patients who can demonstrate more than four metabolic equivalents (METs), equivalent to climbing two flights of stairs or running a short distance, can be considered safe to proceed to surgery without cardiac assessment (17). Simple exercise assessments, such as climbing two flights of stairs can be valuable in identifying patients at risk of postoperative cardiopulmonary complications (24). This is even more significant when cardiac symptoms limit exercise capacity. However, it has been widely acknowledged that determining functional status can be inaccurate or easily confounded (25). There is clear evidence that subjective, clinician assessment of patient fitness neither accurately identifies patients with poor cardiopulmonary fitness nor predicts postoperative morbidity and mortality (26). The patient-reported measure Duke Activity Status Index (DASI) (27) has been associated with prediction of 30-day myocardial infarction or death, and 30-day myocardial injury or death (26). The DASI is a standardised questionnaire correlated with gold standard measures of functional capacity.

Cardiopulmonary exercise testing (CPET), represents the gold standard for the determination of exercise capacity and cardiopulmonary reserve in the field of sports and exercise medicine (28, 29) and has been recognised as a tool to aid in preoperative risk assessment for more than 25 years (30).

1.2 Exercise and oxygen flux

The maximum limit of oxygen utilisation during exercise (VO_2max), can be defined as the maximum integrated capacity of the pulmonary, cardiovascular and muscular systems to uptake, transport and utilise oxygen respectively (31). Usually measured by an incremental exercise test on a treadmill or cycle ergometer, whilst assessing ventilation and the oxygen and carbon dioxide concentrations of the inhaled and exhaled air. VO_2max has become a cornerstone in clinical and applied exercise physiology as it coincides with the point of physical exhaustion (29), is the most commonly used measure of aerobic fitness and is highly reproducible (32).

The fundamental basis for quantifying oxygen transport, utilisation and mitochondrial energy production remain the same today as they did nearly 100 years ago when first described by the British physiologist Archibald Hill in 1924, who outlined four key factors determining VO_2max (33)

1. Arterial oxygen saturation
2. Mixed venous oxygen saturation
3. Arterial oxygen content
4. Circulation rate

These components comprise the Fick equation, which underpins the utility of functional exercise testing (34). At rest, the Fick equation (equation 1) states that oxygen uptake (VO_2) equals cardiac output times the arterial minus mixed venous oxygen content.

Equation 1

$$VO_2 = (SV \times HR) \times (CaO_2 - CvO_2)$$

Where SV is the stroke volume, HR is the heart rate, CaO_2 is the arterial oxygen content and CvO_2 is the mixed venous oxygen content. Because two individuals of quite different sizes may have the same absolute VO_2max value, VO_2max is often normalised for body weight and expressed as ml/kg/min. Adjusting for body weight allows for between-person comparisons (35).

Oxygen is carried in the blood in two forms: 1) dissolved in plasma (around 2% of the total) and 2) reversibly bound to haemoglobin (around 98% of the total). Hence arterial oxygen content is essentially dependent on oxygen carried by haemoglobin and is calculated using equation 2.

Equation 2

$$CaO_2 = (1.36 \times Hb \times SaO_2) + (0.003 \times PaO_2)$$

Where Hb represents the haemoglobin concentration, SaO_2 the arterial saturation, PaO_2 the arterial tension and 0.003 (ml/mmHg O_2/dL plasma) is the solubility coefficient of oxygen in human plasma. Hüfner's constant, 1.36, is the amount of oxygen (ml at 1 atmosphere) bound per gram of haemoglobin at physiological temperature and pH.

VO_2max is the maximal ability of a person to take in, transport and use oxygen, defining their aerobic capacity (34). In healthy people, a clear plateau in VO_2 represents VO_2max on maximal exertion; however, in clinical exercise testing, symptom limitation may prevent a clear plateau from occurring and many older adults are unable to satisfactorily complete a maximal exercise effort. In these scenarios, 'peak VO_2' (the highest value of VO_2 achieved during an incremental ramp test) is often used as an estimate of VO_2max (36).

1.3 Factors affecting maximal oxygen uptake

This is an impressively vast area of physiology and discussion in detail is not necessary for the purposes of this thesis in which exercise training, not testing, predominates. The following key factors affecting maximal oxygen uptake have been briefly summarised so as not to overlook their importance when considering the physiology of exercise:

Pulmonary factors

During exercise, ventilation might increase from resting values of around 5-6 litres/min to > 100 litres/min (37). At submaximal exercise intensities, ventilation increases linearly with work rate. In health, breathing capacity does not reach its maximum even during strenuous exercise and is not responsible for the limitation in oxygen delivery to muscles during high intensity exercise (38). Pulmonary limitations to VO_2max are evident in patients with certain pathologies including asthma or other types of chronic obstructive pulmonary disease. Likewise, a negative influence of smoking on VO_2max and a positive effect of giving up smoking on VO_2max have been reported (39, 40).

Haematological factors

Haemoglobin concentration is a fundamental determinant of convective oxygen carriage, hence acute manipulation of red blood cell mass has a dramatic effect on exercise capacity. Ekblom et al showed through experimental venesection, that a reduction in haemoglobin concentration precipitated a predictable fall in VO_2max and the subsequent re-infusion of blood resulted in restoration VO_2max (41, 42).

The pivotal roles of blood volume and total body haemoglobin as determinants of VO_2max are highlighted by the illegal practice of blood doping to improve performance in elite athletes (43). Both autologous blood transfusion and recombinant human erythropoietin (EPO), administered with the aim of increasing haemoglobin concentration and oxygen delivery, have been shown to improve VO_2max and hence performance (44–46). Other emerging strategies such as the use of hypoxia-inducible factor (HIFs) stabilisers/activators generated interest in the sporting world towards the end of the 1990s as interventions aimed at increasing total Hb mass. HIF stabilisers/activators are compounds that act by mimicking hypoxia and thereby stimulating EPO synthesis via the HIF pathway (45) and there is clear evidence of their abuse within elite sport to this day (47).

Cardiovascular factors

Cardiovascular factors are central and peripheral. Cardiac output (CO) is the key central factor. Regional distribution of CO occurs alongside steal of flow by respiratory muscles and vasodilation within muscles. Resting blood flow to muscle is usually 2-4 ml/100g muscle/min but might increase to nearly 100ml/100g muscle/min during maximal exercise (38). Muscle oxidative capacity and oxidative enzyme activity, alongside muscle capillary length which limits the surface available for peripheral oxygen diffusion, also impact on maximal oxygen uptake (48).

Tissue blood flow and oxygen extraction

The adequacy of tissue oxygenation depends on the rate of oxygen delivered to the tissues (oxygen delivery or DO_2) and the rate of oxygen consumed by the tissues (oxygen uptake or VO_2). Oxygen delivery is the product of CO and arterial oxygen concentration (CaO_2):

$$DO_2 = CO \times CaO_2$$

Tissue oxygenation is adequate when tissues receive sufficient oxygen to meet their metabolic demands. Factors impacting on oxygen transport will limit tissue uptake of oxygen. These factors include:

1. *Blood flow*

Decrease in cardiac output and/or hypovolaemia may affect blood flow with a limitation of oxygen transport by convection. When DO_2 is reduced, there are systemic and local responses that serve to redirect oxygen to areas of greatest metabolic demand, namely the brain and heart (49).

2. Oxygenation measures: CaO_2, PaO_2, haemoglobin oxygen affinity

The oxygen-haemoglobin dissociation curve (fig 1-1) describes the relationship between PaO_2 and oxygen saturation of haemoglobin. The affinity of haemoglobin for oxygen is decreased by an increase in CO_2, decreased pH, increased temperature and increased levels of 2,3-DPG; this facilitates the dissociation of oxygen from haemoglobin and is hence an adaptive mechanism for improved tissue oxygenation during exercise.

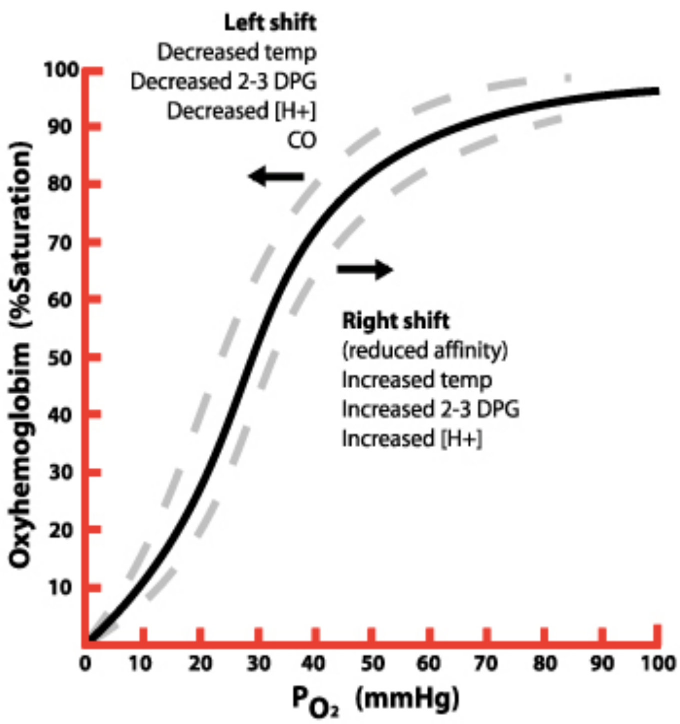


Figure 1-1 Oxygen-haemoglobin dissociation curve

From Anaesthesia UK (50)

3. Microcirculation structure and function

Capillary density determines the surface area for oxygen diffusion. Disorders of the microcirculation, for example sepsis or inflammatory states, can increase the heterogeneity of microcirculatory blood flow, creating a situation of both no and excessively high blood flow, resulting in microcirculatory or anatomical shunt (51, 52). This may predispose the tissue to the development of hypoxia. Furthermore, tissue diffusion limitation is perpetuated by severe hypoxaemia, when oxygen fails to diffuse into tissues as a result of reduced alveolar and arterial oxygen partial pressures (53).

4. Nutrition

Protein-caloric undernourishment also affects aerobic work capacity, as established by Barac-Nieto who demonstrated that VO_2max rises in severely malnourished patients as a normal nutritional status is restored (54).

5. Age

VO_2max generally decreases with age (55) and the extent to which this can be attributed to a reduction in cardiac reserve is not certain. Part of the age-related decline in maximum oxygen uptake can be attributed to peripheral circulatory factors such as a decrease in muscle mass, reduced ability to direct blood flow to muscles and ability of muscle to utilise oxygen (56).

1.4 Dynamic functional assessment and cardiopulmonary exercise testing

Exercise requires an increase in oxygen transport between the airway and mitochondria. Fig 1-2 illustrates the physiological mechanisms that must be coupled to achieve this gas exchange as described by Wasserman in 1997 (57). Exercise limitation is caused by any disease state that disrupts the normal gas exchange coupling. The perioperative period is a time of physiological stress, resulting in an increase in metabolic rate alongside neuroendocrine and inflammatory changes with consequent increase in tissue oxygen demand (58).

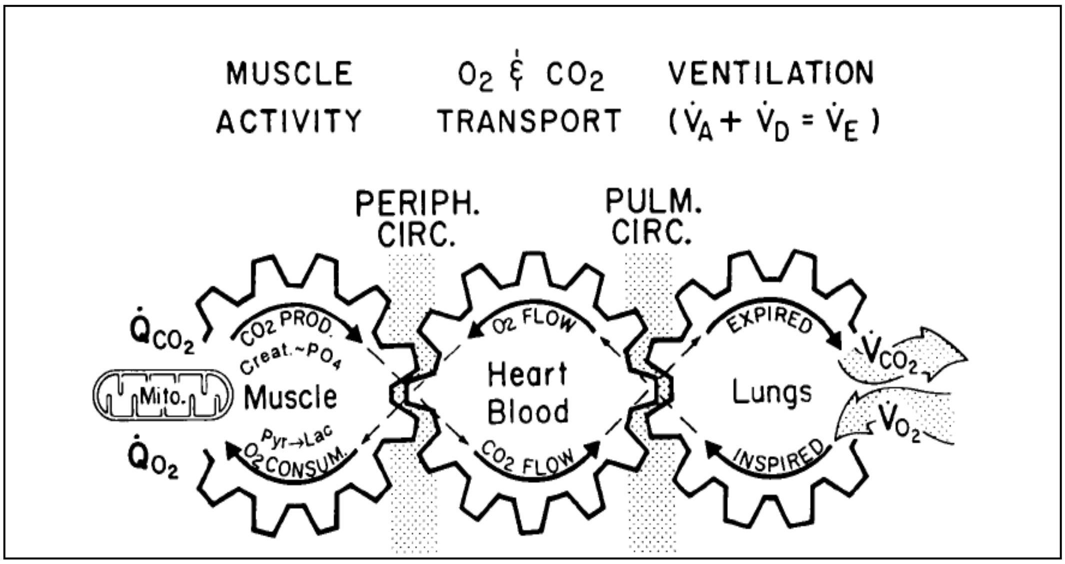


Figure 1-2 Diagnosing cardiovascular and lung pathophysiology from exercise gas exchange.

From: K Wasserman 1997 (57)

CPET is a safe and non-invasive tool that involves exercise on a cycle ergometer with simultaneous spirometry to provide indices of cardiorespiratory function. CPET directly measures or calculates several physiological variables, including ventilatory parameters, heart rate (HR) and inspired and expired gases. It is used in a variety of surgical settings to aid in the prediction of perioperative morbidity and mortality. The presence of abnormal exercise capacity and reduced physiological reserve identifies patients at increased risk of complications. There have been several previous reviews of CPET in non-cardiac surgery and all have concluded that CPET may be a strong predictor of postoperative outcomes (59–62).

The terms functional capacity, exercise capacity and exercise tolerance are generally considered synonymous and imply that a maximal exercise test has been performed on a cycle ergometer or treadmill, with maximal effort given by the subject (63). These terms are also used to express a patient's capacity to perform submaximal activities and generally reflect the ability to perform activities of daily living that require sustained aerobic metabolism (63). Whereas assessment of fitness relates the measured capacity to relevant age and sex population norms (64).

During exercise, the oxygen consumption above which aerobic energy production is supplemented by anaerobic mechanisms, causing a sustained increase in lactate and metabolic acidosis, is termed the anaerobic threshold (AT) (65). The AT has been shown to be a predictor of mortality from cardiopulmonary causes in patients undergoing major intra-abdominal surgery, with a value of <11 ml/kg/min considered the threshold for classifying patients as high risk (15). In 1999 Older et al published a prospective series of 448 patients over three years, assigning patients to postoperative care on the intensive care unit (ICU), high-dependency unit (HDU) or the ward based on CPET results. They showed that deaths due to cardiopulmonary causes were virtually all confined to patients who had at AT < 11ml/kg/min (fig 1-3) (15). AT was shown to be a good predictor of outcome for pancreatic, colorectal and intra-abdominal surgery when compared with other CPET variables in a 2016 systematic review (66).

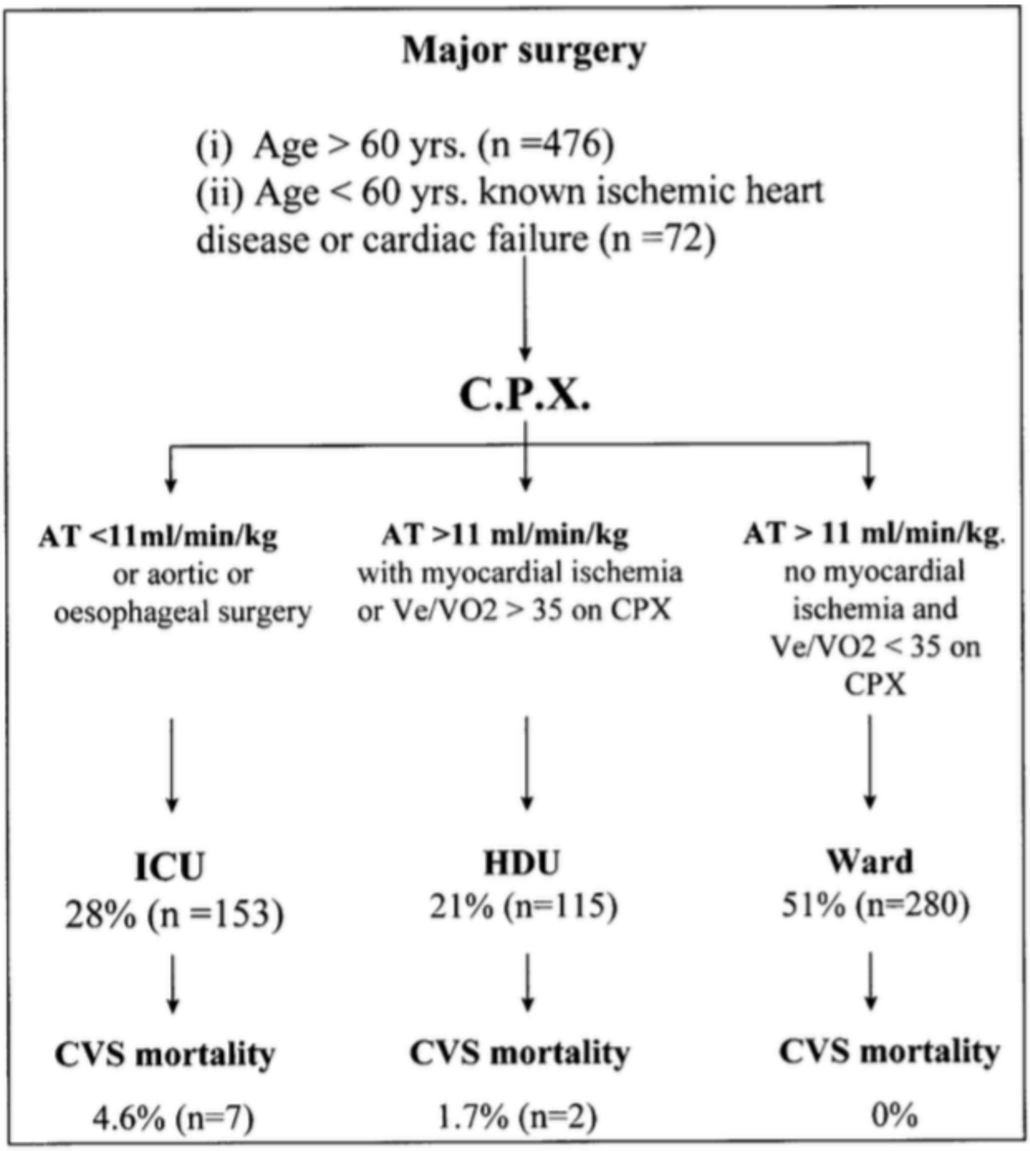


Figure 1-3 Flow chart showing postoperative triage site and outcome following major surgery.

From: Older et al. 1999 (15)

It has been shown that up to half of patients presenting for intra-abdominal, non-vascular surgery, do not have the prerequisite fitness, quantified using CPET, to be deemed at low risk of perioperative complications (67).

The relationship between minute ventilation (VE) and carbon dioxide production (VCO_2) can be characterised by the instantaneous ratio of ventilation to carbon dioxide production, known as the ventilatory equivalent for CO_2 (VE/VCO_2). In 2007 Carlisle and Swart proposed a method for predicting mid-term survival after aortic surgery, involving both a raised VE/VCO_2 as measured using CPET and the presence of one or more Lee's cardiac risk factors (68). This prospective study followed patients up for a median of 35 months.

Debate persists on the utility of exercise capacity assessment for preoperative cardiac risk assessment. The most recent 2016 systematic review by Moran et al. describes the role of CPET as a risk-assessment method in non-cardiopulmonary intra-abdominal surgery and defined cut-offs for VO_2 at AT and peak predicting specific postoperative outcomes (66). However, the study concludes that further research is needed to justify the ability of CPET to predict postoperative outcome in the majority of other abdominal surgical specialties: renal transplant, colorectal, upper gastrointestinal, and bariatric surgery. The 2018 METs study is a multicentre, international, prospective cohort study involving 1401 patients, which confirmed that formal assessment of cardiopulmonary fitness based on peak oxygen consumption during CPET, improved prediction of moderate or severe postoperative complications (26). Most of these events were, however, pulmonary complications, surgical site infections, unexpected critical care unit admissions, and re-operations. Peak oxygen consumption and AT were not associated with postoperative myocardial infarction or myocardial injury. These findings do contradict to some extent the emphasis of current ACC/AHA and ESC/ESA guidelines on functional capacity for cardiac risk evaluation in the preoperative setting (17, 69).

1.5 The impact of exercise on physiology

Physical exercise is associated with numerous physical health benefits including overall life expectancy and reduced risk of cardiovascular disease, obesity, stroke and cancer (70). There are many mechanisms by which our physiology adapts to exercise conditioning and the following is a synopsis of the major known effects of physical activity on principal factors associated with risk for poor cardiovascular health.

During exercise, increased CO results from an increase in stroke volume (SV) and heart rate (HR), which coupled with a transient increase in systemic vascular resistance (SVR), elevates mean arterial blood pressure (71). However, long-term exercise can promote a net reduction in blood pressure at rest (72); thought to be driven largely by a chronic reduction in SVR.

Structural cardiac adaptations result in response to recurrent exercise. The heart undergoes adaptive remodelling with an increase in mass, predominantly through an increase in ventricular wall thickness, resulting in preservation or enhancement of contractile function (73). Exercise can also produce functional adaptations of the heart, which may increase cardiac output and reduce arrhythmia risk. Studies have shown that exercise-trained individuals have improved systolic and diastolic function (74). Likewise, animal studies show endurance exercise promotes enhanced cardiomyocyte contraction-relaxation velocities and force generation (75). Structural and functional adaptation also occurs in the resistance arterial vascular network. Repeated exercise leads to increased vascular density and greater vasodilatory capacity, enhancing perfusion (76).

Plasma lipids are key determinants of cardiovascular disease risk. Exercise has been shown to alter plasma lipid profiles and increase high-density lipoprotein (HDL) concentration (77). Likewise, exercise could directly impact the homeostasis of the arterial wall to halt the progression of atherosclerosis, contributing to the reduction in coronary artery disease seen in those with active lifestyles (78). Furthermore, exercise has been shown to decrease morbidity and mortality in patients with coronary artery disease. The increase in myocardial oxygen demand acts as a stimulus to increase coronary blood flow and thus myocardial oxygen supply, reducing myocardial infarction and angina (79). Additionally, exercise promotes collateralisation, increasing blood flow to ischaemic myocardium.

Hence when exercise is included alongside dietary modification and weight loss, a significant impact on cardiovascular disease incidence can result (77).

Exercise also improves mental health. In a recent cross-sectional US sample of 1,237,194 people, physical exercise was significantly and meaningfully associated with lower mental health burden (80). Individuals who exercised had around 1.5 fewer days of poor mental health in the past month than individuals who did not exercise. Positive effects of exercise have been shown on mental health outcomes (81), anxiety (82) and post-traumatic stress disorder (83). Indeed, most studies consider exercise an effective treatment for mild and moderate depression (84).

Ultimately, a fitter population is a healthier population.

1.6 The physical inactivity epidemic

Despite the multiple benefits of exercise and the impact of chronic health conditions (fig 1-4), alongside the modifiable nature of sedentary behaviour, physical inactivity remains a modern-day global public health problem. According to World Health Organization global data, around 23% of adults aged 18 and over were not active enough in 2010 (men 20% and women 27%) (85). Rates of physical inactivity are highest in Europe, the Americas and Western Pacific regions. As countries develop economically, levels of inactivity increase owing to the influence of technology, urbanisation and cultural values (86).

In the UK, physical inactivity is responsible for one in six deaths and is estimated to cost the UK £7.4 billion annually according to Public Health England data (87). The population in the UK is around 20% less active than in the 1960s and it is thought that around 1 in 3 (34%) men and 1 in 2 (42%)

women are not active enough for good health. Physical activity also varies with age and stage of life with older people generally being less active.

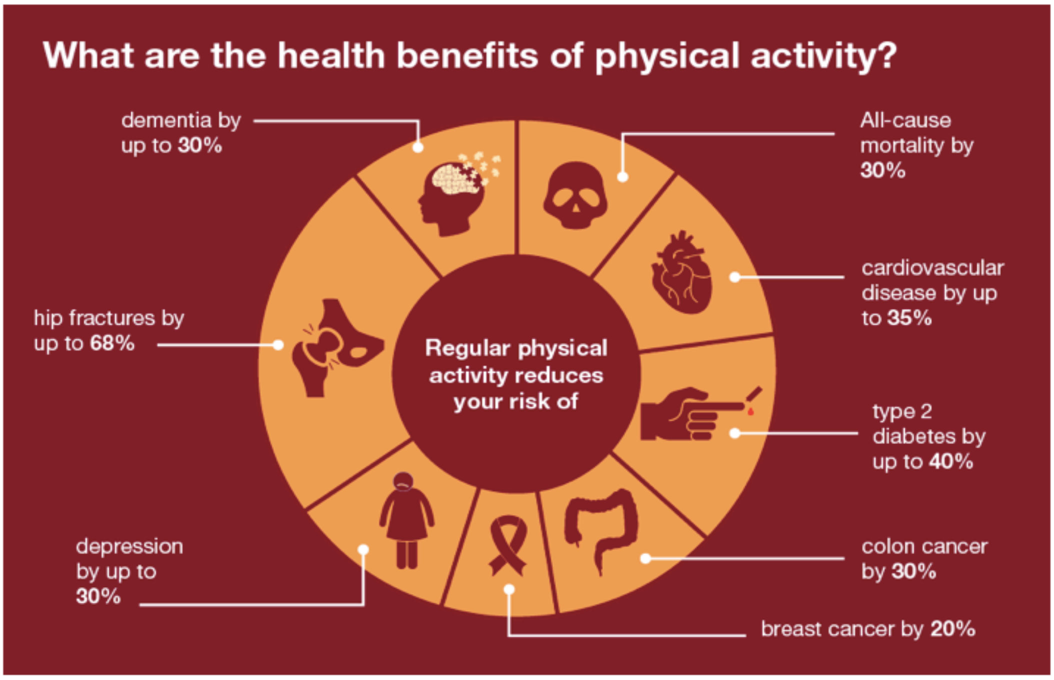


Figure 1-4 The health benefits of physical activity

From: Public Health England physical activity guidance 2015 (87)

1.7 Prehabilitation

Over the past decade, there has been a growing realisation that the success of surgery is not solely dependent on the procedure, but rather the patient's return to physical and psychological health (88). Optimisation of perioperative care has historically focused on attenuation of the surgical stress response and improved postoperative mobility and nutrition in the form of Enhanced Recovery After Surgery (ERAS) programmes (89). More recently this concept has been extended to the preoperative period, with the aim of optimising exercise capacity prior to surgery. This preoperative optimisation has been termed 'prehabilitation' with a key component being the prescription of exercise interventions (90). The prescription of exercise with the intention of therapeutic benefit has been shown to be effective in more than 25 chronic diseases (91), however, debate persists regarding the optimal period of exercise, the intensity, the type and the size of the impact on outcomes. In addition, objectively measured preoperative fitness relates to postoperative outcomes, with increased levels of fitness generally protecting against complications with long-term consequences (92).

Prehabilitation is the process of enhancing an individual's exercise capacity to enable them to withstand a forthcoming stressor (such as major surgery). The first article with a prehabilitation focus was published in 1946 (93) and described the rejection of men presenting for enlistment into the army on account of poor physical and mental conditioning. The same recruits were transformed by a two month programme of physical, nutritional, and educational interventions. The core concepts of multidisciplinary working to optimise physical performance, nutritional status and mental wellbeing form the basis of 21st century prehabilitation, with the goal of improving surgical outcomes.

The benefits of exercise interventions and prehabilitation programmes can be categorised into three distinct areas (94):

1) *Personal empowerment* and heightened sense of control, facilitating preparation for surgery and leading to improved quality of life
2) *Physical and psychological resilience* enhancing the ability to withstand surgical stressors and reduce burden on healthcare resources (for example reduced length of hospital stay)
3) *Long-term health* through positive health behaviour change

1.7.1 Components of a prehabilitation programme

It is common for a delay of several weeks between the decision to proceed to surgery and the surgery itself, which presents an opportunity to positively impact a patient's health behaviour. This timeframe, often between 4-8 weeks, allows interaction and engagement with essential members of the multidisciplinary team consisting of surgeons, anaesthetists, physicians, physiotherapists, dietitians and psychologists. Indeed, the benefits of a multidisciplinary approach are now clear, producing lifestyle modification through:

1) Medical optimisation
2) Physical activity
3) Nutritional advice
4) Psychological support

1.7.2 Prehabilitation: the evidence

Patients undergoing major surgery represent a diverse and challenging group with increasing population age and increasingly prevalent comorbidities (95, 96). The need to optimise patients undergoing high-risk surgery with the aim of improving clinical outcomes has been recognised around the world and evidence is accumulating to support preoperative exercise training as a means to improve fitness and postoperative outcomes (97). A number of systematic reviews have been published looking at the impact of preoperative exercise training in patients awaiting a variety of surgical procedures on a number of outcomes. A 2019 systematic review and meta-analysis by Hughes et al. (98), included 15 randomised controlled trials comparing outcomes of patients undergoing prehabilitation involving prescribed respiratory and exercise interventions prior to major abdominal surgery (mainly colorectal surgery). A significant reduction in overall and pulmonary morbidity (atelectasis determined by radiological evidence; lower respiratory tract infection defined according to positive microbiology and/or radiological evidence and respiratory failure requiring additional oxygenation and/or ventilation) was observed in the prehabilitation group. However, no difference in length of hospital stay or exercise capacity (as per 6 minute walk test) was demonstrated. The sample sizes were small with studies recruiting between 20 and 124 patients. The intervention in 11 studies was aerobic exercise, with the addition of resistance exercises in three of these. Six studies specifically included inspiratory muscle training in their intervention protocol. Patients randomised to control groups received ‘standard care’ as per the preoperative pathways of the recruiting institutions in nine studies. Patients in the control groups of the remaining six studies were provided with non-supervised activity promotion/instruction, diet supplementation or a similar intervention to the exercise group postoperatively. Blinding of patients in the exercise/intervention groups was not possible, so only single blinding was performed at best, with some studies being unblinded. The overall quality of the studies included was considered moderate. No reference was made to any cost benefit of reducing pulmonary complications.

An earlier systematic review conducted by Valkenet et al in 2011 (99) showed that preoperative exercise can be effective in reducing postoperative complications as well as hospital length of stay in patients awaiting joint replacement, cardiac and abdominal surgery. Twelve studies were included in the analysis, recruiting between 20 and 276 participants awaiting either CABG (coronary artery bypass grafting), joint replacement surgery (knee or hip) or major abdominal surgery. The intervention groups of four studies specifically involved inspiratory muscle training with the remaining eight studies implementing a number of exercise interventions including strength and stretching exercises and/or aerobic training, some directly supervised and others given instruction to exercise at home. Patients randomised to control groups predominantly received care defined as standard or usual preoperative care as per the institution. Three studies provided exercise advice leaflets/education and one study provided a sham intervention for control patients (inspiratory muscle training with no resistance). No subgroup analysis between different patient groups and their specific surgical interventions was performed. Studies assessing the impact of exercise prior to joint replacement surgery, did not find a difference in postoperative length of stay or complication rate. Whereas preoperative exercise was found to decrease hospital length of stay after cardiac surgery. The conflicting length of stay data can potentially be attributed to the heterogeneity of operative procedures included and variation in perioperative care protocols and clearly indicates that more work is required in order to benefit specific surgical populations.

A more detailed assessment of the impact of prehabilitation on patients awaiting major joint replacement was conducted in 2015 by Cabilan et al (100) Their systematic review analysed data from 17 studies conducted predominantly in orthopaedics (mainly hip or knee arthroplasty) and found that prehabilitation had no significant benefits in function, quality of life and pain, however, there was evidence for a reduction in admission to rehabilitation in this population. No surgery-specific outcomes were reported.

Marmelo et al (101) concluded that prehabilitation reduces the number of post-surgical complications in patients undergoing non-urgent cardiovascular intervention from analysis of eight studies. Another systematic review from Santa Mina et al (102) analysed data from 21 studies of preoperative exercise for patients undergoing colorectal, cardiac, orthopaedic and thoracic surgery. Compared to standard care, the majority of studies found that prehabilitation reduced postoperative pain, length of stay and improved physical function. This systematic review included 17 RCTs and four cohort/case-control designed studies, involving a median of 54 participants. Ten trials assessed supervised, facility-based interventions, four were home-based and seven utilised a combination of in-hospital and home-based exercises. The median intervention duration was 6 weeks (range 1-8 weeks). Aerobic exercise was the primary exercise modality in five trials with remaining studies utilising resistance/strength training in isolation or combination with aerobic exercise. Ancillary interventions including education and dietary supplementation were implemented in five studies. The moderate to poor methodological quality and significant risk of bias of the included trials demands caution in interpretation of findings

Overall, the main limitation of prehabilitation meta-analyses to date, is the heterogeneity of the included trials. The perioperative 'standard care' pathways, prehabilitation regimens and outcome measures vary markedly and methodological design often of low or moderate quality. Studies are generally small and inadequately powered to detect differences in postoperative clinical outcomes and frequently focus on establishing the feasibility of the exercise intervention. Many studies are non-randomised with high risk of bias. What is very clear from the large number of published papers aiming to address the impact of prehabilitation on a variety of outcomes following a number of surgical procedures, is that there remains no consensus on the optimal prehabilitation intervention, duration, frequency, intensity, degree of supervision and outcome measures of interest.

There has been a recent focus on the impact of prehabilitation on patients awaiting major cancer surgery. In particular, benefit of preoperative exercise has been demonstrated in patients with colon and rectal cancer (103–105) in terms of cardiorespiratory fitness, respiratory muscle endurance, fatigue and physical health perception. The benefits of structured exercise in patients requiring fitness-reducing neoadjuvant chemoradiotherapy (NACRT) have also been shown; with exercise returning fitness to baseline levels post NACRT (106). There are important clinical implications to these findings: patients who do not recover fitness post NACRT are at higher risk of adverse surgical outcomes on the basis of AT risk stratification cut-off points (107). Recent evidence from West et al. also suggests that exercise training may have direct anti-tumour effects, leading to augmented tumour regression following neoadjuvant chemoradiotherapy in locally advanced rectal cancer (108). A 2019 systematic review found evidence from eight RCTs (565 patients) that prehabilitation had beneficial effects on postoperative outcomes in patients undergoing major intra-abdominal cancer surgery (109).

The strength of evidence for a beneficial effect of prehabilitation on patients awaiting cancer surgery is such that following a 2017 Macmillan Cancer Support 'Evidence and Insight Review', it was agreed that prehabilitation should be incorporated into routine cancer care (94). This Macmillan review laid out the clear distinctions between prehabilitation and standard preoperative care as regards perceived patient benefit:

1) Wider wellbeing: prehabilitation as a multimodal process that looks at the person with cancer as a whole, taking into account their wider physical, psychological and psychosocial wellbeing.
2) Greater professional involvement: for physical activity there could be supervised exercise with a trained professional and possible continual professional involvement.

In healthcare generally, effective resource allocation and cost efficiency is of utmost importance. Robust health economic analysis is central to the success and widespread uptake of interventions such as preoperative exercise training and until very recently there was no real data to this effect. A secondary analysis of prehabilitation in patients who underwent major elective gastrointestinal or liver surgery, was reported by Barberan-Garcia et al in 2019 (110). Their original randomised, blinded controlled study showed improved physical fitness and a reduction in overall complication rate in the prehabilitation group (111). The cost consequence analysis revealed cost savings in the intervention group attributable to reduced short-term hospital use and readmissions. The prehabilitation programme, however, did not show significant cost savings at 30 days, hence results are encouraging but far from definitive. Fully capturing all the clinical benefits of an intervention such as prehabilitation is difficult as there is a complex relationship between function, quality of life and cost (112); hence application of health economic evaluation is not straightforward and more work in this area is required.

The optimal exercise regimen has yet to be defined (113). Shorter programmes may be ineffective, whilst longer programmes may lead to issues with compliance. Establishing the impact of prehabilitation on outcomes is essential; it is possible that patient selection and psychological conditioning have more of an impact than improved physiology. The effectiveness of preoperative exercise training might vary between surgical interventions as well as patient populations. For example, a patient with colorectal cancer potentially has a limited preoperative time span for exercise training and the addition of neoadjuvant chemotherapy may necessitate modification of the programme and targets. It is very likely that each specific patient population could need a specific programme in a specific time frame. Large scale, high-quality studies are needed to confirm early data and determine the frequency, intensity and duration of prehabilitation needed to produce optimal results.

Very little attention to preoperative optimization specifically prehabilitation programmes, has been given to niche, yet important surgical populations including those awaiting liver transplant and complex abdominal aortic aneurysm repair. These two high-risk patient groups will be discussed in detail in chapters 3 and 4.

1.8 Motivating patients to participate in exercise

Encouraging individuals to adopt and maintain health-promoting behaviours represents a global challenge (114). The preoperative period is considered a 'teachable moment' (115). During this time patients may be more receptive to altering their risk behaviours and achieve greater motivation and confidence in their ability to do so for the short preoperative period, yielding short-term health benefits (116). Patients may perceive this as more acceptable than the prospect of making permanent, long-term changes.

Enjoyment is both a predictor and outcome of physical activity participation (117, 118). Expected enjoyment can motivate the intention to exercise and predict ongoing participation (119). Conversely, the anticipation of negative emotions is associated with fewer/weaker physical activity intentions (120). Hence the experience of exercise enjoyment is an essential part of ensuring compliance and a sustainable change in behaviour. The physical activity enjoyment scale (PAES) is an 18-item measure (appendix 2), developed as an instrument to assess the extent to which an individual enjoys any given physical activity and has been well validated for this purpose (121).

Other important factors impacting on exercise adherence are perceived lack of control, self-esteem and quality of life. Chronic illnesses are likely to have a considerably negative impact on day-to-day quality of life. Quality of life is influenced not only by the primary disease but also by its management and disease-related complications. The eventual aim in the management of all chronic disease is to improve and sustain a reasonably good quality of life. Personal empowerment and taking control are essential to generate sustainable behavioural change and improve quality of life. It is increasingly acknowledged that prehabilitation should include psychological components (122). Patients not only need to prepare physiologically for the demands of surgery, but they also need to be mentally fit (123).

1.9 Liver transplantation and complex fenestrated endovascular aneurysm repair (FEVAR): high risk surgery

1.9.1 Two high-risk cohorts presenting very different challenges

The Royal Free Hospital (RFH) is one of seven liver transplant (LT) centres nationally and is also a tertiary referral centre for complex abdominal endovascular aortic aneurysm repair. Both liver transplant and major vascular surgery constitute two of the highest risk surgical specialties and patients present unique and complex challenges to the multidisciplinary team.

Patients awaiting LT are deconditioned and burdened with frailty and multi-morbidity. Decompensated liver failure has multi-system sequelae, resulting in diuretic-resistant ascites, encephalopathy, muscle wasting and many patients have unique cardiorespiratory pathophysiology, including a high prevalence of cirrhotic cardiomyopathy, portopulmonary hypertension and hepatopulmonary syndrome (124). All these factors impact on their compliance and engagement with exercise programmes and may modulate their physiological response to, and clinical benefit from, exercise, making them a particularly challenging cohort to optimise preoperatively, hence their inclusion in this research.

Patients with abdominal aortic aneurysms present a different set of challenges. The vast majority are elderly, frail and frequently suffer cardiovascular co-morbidity. Risk factors for ischaemic heart disease, including smoking, hypertension and diabetes, are features associated with patients requiring major aortic aneurysm surgery and further contribute to the development of peripheral vascular disease (PVD) and exercise-restricting intermittent claudication. All of these issues can limit a patient's conformity with and indeed their physical ability to partake in preoperative exercise training.

1.9.2 Liver transplantation

In the 2018/2019 financial year 1003 liver transplants were performed in the UK and 124 of these were at the RFH (125), at a minimum cost of £80,000 per procedure. Part of this substantial cost is the treatment of postoperative complications. In an analysis of 551 patients who underwent liver transplantation at the RFH from 1999 to 2008, 67% developed at least one significant postoperative complication. These complications led to a longer intensive care unit and hospital length of stay, an increased frequency of graft failure, higher mortality at three months, and increased costs. A single postoperative complication costs the NHS approximately £10,000. Furthermore, complications also lead to long-term morbidity and a reduced quality of life for patients. The prediction of early postoperative mortality is therefore of particular importance in the liver transplant population.

There is a large body of evidence highlighting the negative clinical consequences of the reduced exercise capacity in cirrhosis (126). Patients awaiting liver transplantation surgery are frequently deconditioned with severe functional impairment (127); this impairment worsens as liver function deteriorates (128). In addition to this, the complex multi-system nature of liver cirrhosis means that malnutrition, muscle wasting, muscle weakness, cirrhotic cardiomyopathy, anaemia and pulmonary gas exchange impairment also frequently affect patients and impact on postoperative outcomes. Previous studies have demonstrated the importance of cardiopulmonary reserve in this cohort of patients; a VO_2 at AT value < 9.0 ml/kg/min has been shown to reliably predict an increased perioperative mortality risk (129).

Current management of end-stage liver disease (ESLD) focuses on treating complications and tends to neglect aspects such as functional disability and frailty, both of which are potentially reversible with targeted interventions(130). Physical activity is one such intervention and there is increasing emphasis on the potential benefit of exercise in patients with cirrhosis (131, 132) and attention is turning to patients with end-stage disease awaiting transplantation (133). Patients awaiting LT have previously been considered 'too sick to exercise' due to their general frailty and disease-related complications such as ascites and encephalopathy. Unlike other chronic diseases such as heart failure or chronic obstructive pulmonary disease, liver failure is a multisystem disorder of considerable complexity. It is perhaps for this reason that there is such scarcity of data related to exercise training in patients with end-stage liver disease and why progress in this population lags behind other surgical specialties. Indeed, the utility of formal incremental exercise training in this unique cohort has yet to be demonstrated. It is therefore crucial to understand the limitations and difficulties of exercise training in patients with ESLD prior to large-scale evaluative research. The literature on exercising prior to liver transplant is reviewed in Chapter 3.

1.9.3 Complex endovascular aneurysm repair

Abdominal aortic aneurysms that occur above or around the renal arteries are more complex to manage as the renal blood flow must be maintained. While open surgery with re-implantation of the renal arteries was the traditional approach to repairing these complex AAA, endovascular aneurysm repair techniques (EVAR) have revolutionised operative management. According to the 2020 UK National Vascular Registry (NVR), 2,577 elective complex AAA repairs were performed between January 2017 and December 2019, of which 2,306 were endovascular and 271 were open surgical repairs (134). Data indicated in-hospital mortality rates of 14.0 and 2.7 per cent for open and endovascular elective complex abdominal aortic aneurysm repair respectively, with non-fatal postoperative complications several times more common (134, 135).

The RFH is a centre for vascular surgery and endovascular aortic aneurysm repair in particular, performing 50 fenestrated EVARs involving the renal arteries in 2017 and 42 in 2018.

Aneurysm repair, both open and endovascular, carries a high risk in patients with complex aortic aneurysms who may have poor exercise capacity due to deconditioning and comorbidity. Surgical repair results in the surgical stress response of neuroendocrine, metabolic and inflammatory changes that lead to an increase in global tissue oxygen uptake of up to 50% (58). Many of the risk factors for AAA, such as smoking, hypertension, obesity and advancing age are associated with coronary artery disease (136). Low aerobic fitness represented by VO_2peak <15ml/kg/min and reduced ventilatory efficiency consistent with a VE/VCO_2 >42 have been shown to be independent predictors of reduced survival post open and endovascular aortic surgery (137). Patients with aneurysms that have a high risk of rupture may still have to be considered for treatment even if they have substantial co-morbidity. However, if improvement in their cardiopulmonary fitness could be achieved before surgery this could lead to a reduction in postoperative complications as has been demonstrated with other disease processes.

Attention is turning to ways in which patients can be optimised from a cardiopulmonary fitness point of view. One of the main conclusions of the UK-based EVAR 2 study back in 2005 was that vascular teams should be focusing on techniques to improve patient fitness before surgery (138). Indeed, the waiting time for major elective vascular interventions such as EVAR, presents an ideal opportunity to optimise patient fitness and potentially improve perioperative outcomes. The vascular surgery team at the RFH were engaged and motivated to support the work contained within this thesis, with a view to the development of a prehabilitation pathway aimed at improving the preoperative fitness of local vascular patients.

The existing evidence base pertaining to preoperative exercise training for patients awaiting AAA surgery is discussed in chapter 4.

1.10 In-hospital exercise

An ‘in-hospital’ approach to exercising patients was chosen over community/at-home or gym-based alternatives. A hospital-based exercise programme allows close supervision by clinicians and access to emergency care in the event of a complication; given the high-risk nature of the two patient cohorts it was decided this modality represented the safest option. The inconvenience of travelling to and from the hospital three times per week is a potential limitation of this modality, however, patients in both groups (especially those awaiting LT) are used to travelling to the RFH for frequent appointments; hence this burden was considered minimal. It was decided all travel costs incurred would be reimbursed from the study budget.

1.11 Summary of introduction and thesis plan

Physical fitness has benefits in almost every context of health and disease, and there is mounting evidence confirming the relationship between physical fitness and improved perioperative outcomes. In accordance with the American College of Sports Medicine (ACSM) guidelines for the management of people with chronic diseases and disabilities, exercise training is a key recommendation for patients with chronic disease (139). There is an emerging evidence base for the benefits of exercise in chronic diseases including heart failure (140), depression (141) and as part of a programme of pulmonary rehabilitation for lung diseases such as COPD (chronic obstructive pulmonary disease) (142)

Patients with end-stage cirrhotic liver disease awaiting liver transplantation and those with vascular disease necessitating complex endovascular aortic aneurysm repair, represent two distinct patient groups with unique and challenging pathophysiology. As patients with ESLD spend an average of 152 days on the liver transplant waiting list in the UK (143), there is ample time for preoperative optimisation of exercise capacity with a structured exercise programme. Likewise, the median time from assessment to surgery for all patients requiring repair of complex AAA was 132 days (79-197) between 2015 and 2017 (144); again, offering an ideal and natural window for a prehabilitation programme.

1.11.1 Overall aim

The two feasibility studies described within this thesis were designed to determine whether it is possible to engage patients awaiting LT and FEVAR in a programme of intense supervised aerobic exercise, in a hospital setting over a period of six weeks.

I also wanted to understand fitness levels in these two high risk patient cohorts and see if measures of cardiopulmonary fitness as determined by CPET could be improved when compared to a group of matched patients not involved in an exercise programme.

1.11.2 Clinical Studies

Clinical data presented in this thesis are derived from that recorded in patients at a single centre: The RFH London.

This thesis will refer to each study in the following manner:

- ***Study 1:*** The feasibility of an outpatient, hospital-based exercise training programme for patients with cirrhotic liver disease awaiting transplantation surgery

- ***Study 2:*** The feasibility of an outpatient, hospital-based exercise training programme for patients awaiting complex fenestrated endovascular aortic aneurysm repair.

Both studies were conducted over an 18 month period, from August 2016 until January 2018.

All patients enrolled in these studies had been reviewed by a consultant anaesthetist as part of the pre-assessment/work-up for surgery process. All additional relevant preoperative treatments and investigations had been completed and patients deemed 'fit-for-surgery' before being assessed for eligibility and approached to take part in these studies.

1.11.3 Plan of Investigation

1. The feasibility of preoperative exercise training programmes in patients awaiting liver transplant and complex endovascular abdominal aneurysm repair
2. The impact of an individualised training programme on exercise physiology
3. The impact of exercise training on anthropometric parameters in patients with cirrhotic liver disease awaiting LT
4. The impact of exercise training on daily activity in patients with abdominal aortic aneurysms awaiting FEVAR
5. The impact of exercise training on health-related quality of life
6. Impact of exercise on surgical outcomes including ICU and hospital length of stay and mortality

2 General Methods.

This chapter will provide an overview of the procedure for:

1) Testing exercise capacity using CPET
2) The exercise training programme involving individualised interval training on an electromagnetically braked, cycle ergometer.

Specific variation in methodology between the two studies is described in chapters 3 and 4.

2.1 Ethical approval

Ethical approval for study 1 was granted by London Bromley Research Ethics Committee (16/LO/0762). Health Research Authority (HRA) approval was not required as the timing of the research ethics application preceded the need for it (submission was prior to the 31st March 2016).

Ethical approval for study 2 was granted by London Chelsea Research Ethics Committee (16/LO/0788). HRA approval was necessary for this study given the timing of the application, which was granted.

Local NHS permission (Research and Development approval) to proceed and recruit patients at the Royal Free London NHS Foundation Trust was granted for both studies (Royal Free reference for study 1 was 9735 and study 2 was 9756).

2.2 Cardiopulmonary Exercise Testing (CPET)

In order to enable construction of individualised training programmes and quantify performance throughout and following exercise training, exercise capacity was measured using CPET. The primary aim of CPET was to determine individual oxygen consumption at AT and peak and to assess the power outputs at which these were achieved.

All CPETs were carried out in a single centre: the RFH, London and supervised by the primary researcher.

2.2.1 Cardiopulmonary exercise testing equipment

All CPETs were performed using a stationary, electronically braked cycle ergometer (Corival, Lode, Gronigen, the Netherlands) and a breath-by-breath analysis CPET system (Cortex, Leipzig, Germany). The latter measured oxygen and carbon dioxide concentration along with gas flow via a turbine connected to a tight-fitting facemask. The Cortex software directly measures breath-by-breath concentrations of oxygen and carbon dioxide. It then integrates gas flow and concentration data to calculate the following pulmonary and gas exchange variables:

- Oxygen uptake (VO_2)
- Carbon dioxide production (VCO_2)
- Minute ventilation (V_E)
- Respiratory exchange ratio (RER)
- Ventilatory equivalents for oxygen (V_E/VO_2) and carbon dioxide (V_E/VCO_2)
- End-tidal partial pressures of oxygen and carbon dioxide ($P_{ET}CO_2$ and $P_{ET}O_2$)
- Tidal volume (V_T)

Non-invasive blood pressure measurement, peripheral oxygen saturation (SpO_2) and 12-lead electrocardiogram (ECG) monitoring were continually recorded throughout all tests.

Prior to every CPET, appropriate calibration measurements were undertaken:

- Ambient pressure and temperature.
- Oxygen cell calibration with ambient air (20.93% O_2 and 0.03% CO_2) and 4% CO_2/16% oxygen/nitrogen calibration gas (certified values 16.17% O_2, 3.99% CO_2, BOC, UK). Maximum error: ± 0.05% for O_2, ± 0.02% for CO_2.
- Flow-volume sensor calibration: 3 litre syringe, three computer generated flow rates: 0.5 l/s, 1.0 1/s, 3.0 l/s (maximum error: ± 100 ml).

2.2.2 Exercise testing subject preparation

Prior to CPET, patients were asked to refrain from caffeine and fasted for 1.5 hours before the test. A full medical and exercise history was taken prior to the first CPET and basic measurements including weight, height and blood pressure were recorded before every test. All patients underwent spirometry (forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) prior to testing in order to calculate predicted maximal values for ventilatory capacity. A point of care haemoglobin concentration was taken prior to each test (HemoCue, Radiometer, Copenhagen, Denmark).

American Thoracic Society (ATT) and the American College of Chest Physicians (ACCP) guidelines were adhered to throughout testing (28). Contraindications to CPET are listed in Table 2-1.

Absolute	**Relative**
Acute myocardial infarction (3 to 5 days) or unstable angina	Left coronary stenosis or equivalent
Uncontrolled arrhythmias causing symptoms or haemodynamic compromise	Moderate stenotic valvular heart disease
$SpO_2 \leq 85\%$ on room air (patient should be exercised with supplemental oxygen)	Severe arterial hypertension at rest (>200 mmHg systolic, >120 mmHg diastolic)
Thrombosis of lower extremities	Tachyarrhythmias or bradyarrhythmias
Active endocarditis, myocarditis or pericarditis	High degree atrioventricular block
Symptomatic severe aortic stenosis	Hypertrophic cardiomyopathy
Uncontrolled heart failure	Significant pulmonary hypertension
Acute pulmonary embolism or pulmonary Infarction	Advanced or complicated pregnancy
Pulmonary oedema	Electrolyte abnormalities
Acute non cardiopulmonary disorder that may affect performance or be aggravated by exercise (i.e. infection, thyrotoxicosis)	Orthopaedic impairment that compromises exercise performance
Mental impairment with the inability to cooperate	
Uncontrolled asthma	

Table 2-1: Absolute and relative contraindications to cardiopulmonary exercise testing as per ATS/ACCP guidelines

From: American Thoracic Society; American College of Chest Physicians 2003 (28)

2.2.3 Incremental exercise test protocol

Subjects performed an incremental ramp test to exhaustion on an electromagnetically braked cycle ergometer and CPET system (fig. 2-1). Once optimal bicycle seat height was established for each participant at baseline CPET, this height was measured and kept constant for subsequent tests for the duration of the study. Likewise, each patient wore the same size facemask for every test they performed (small, medium or large sizes available). Appropriate exercise intensity (incremental wattage ramp test, 10 to 20 Watts/min) was chosen depending on the sex, age and physical fitness of the participants in order to obtain a test duration of approximately 10 minutes (145).

Wasserman equations were used to help guide the determination of the work rate increment (146):

1. VO_2 (ml/min) = 150 + (6x weight(kg))
2. Peak VO_2 (ml/min) *Males* = height (cm) – age (years) x 20
3. Peak VO_2 (ml/min) *Females* = height (cm) – age (years) x 14
4. Work rate increment (W/min) = (Peak VO_2 – VO_2 Unloaded) / 100)

Exercise increments (the wattage ramp) remained the same for each individual throughout the study.

Resting baseline measurements were recorded for three minutes, followed by three minutes of unloaded pedalling (zero external watts applied to the braking system) with subsequent initiation of incremental ramp as previously described (147). Participants were asked to maintain a steady cycling cadence of 60 revolutions per minute (rpm); some freedom around pedal speed was allowed by the electronically braked ergometers. The ramped component of the test generally lasted between 4 and 10 minutes. The test was terminated when the subject could not maintain a constant cadence of 55 - 65 rpm despite encouragement and/or where symptoms (e.g., leg pain/fatigue or shortness of breath) precluded continuation of exercise. Full criteria for stopping the tests are based on ATS/ACCP guidelines (28) and are presented in Table 2-2. Following cessation of exercise, a three minute period of unloaded pedalling was undertaken, during which time full physiological monitoring was continued, prior to dismounting the bike. Figure 2-2 depicts the sequence of events required to perform a CPET.

Chest pain suggestive of ischaemia
Ischaemic ECG changes (significant ischaemia >1mm ST depression in chest leads or >2mm ST depression in limb leads or ECG pattern consistent with myocardial infarction or evolving ischaemic changes)
Complex ectopy
Second or third degree heart block
Fall in systolic blood pressure >20 mmHg from the highest value during the test
Hypertension (>250 mmHg systolic, >120 mmHg diastolic)
Severe desaturation ($SpO_2 \leq 80\%$) when accompanied by signs and symptoms of hypoxia
Sudden pallor, dizziness or faintness
Loss of coordination or mental confusion
Signs of respiratory failure

Table 2-2: ATS/ACCP indications for exercise termination

From: American Thoracic Society; American College of Chest Physicians 2003 (28)

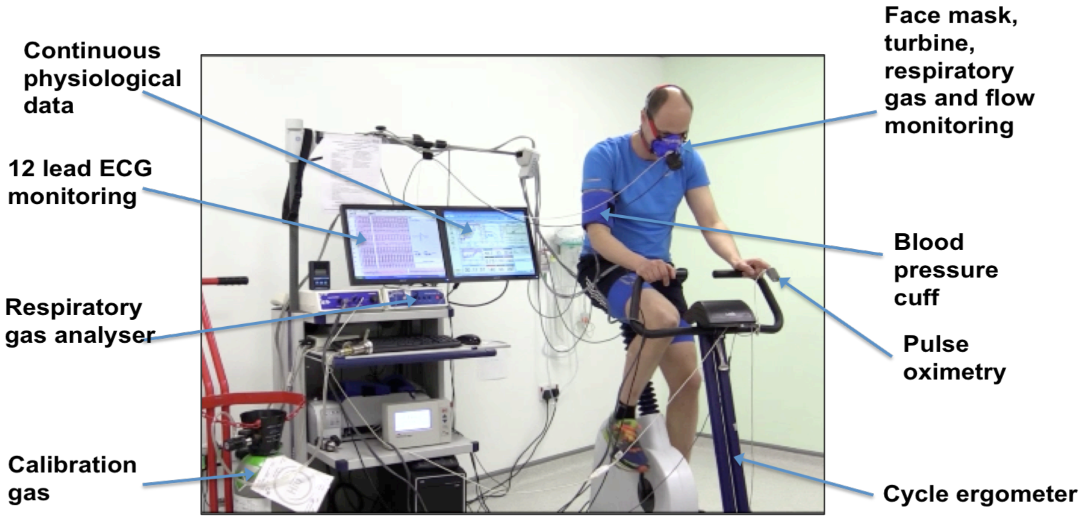


Figure 2-1 Cardiopulmonary exercise test apparatus at the RFH

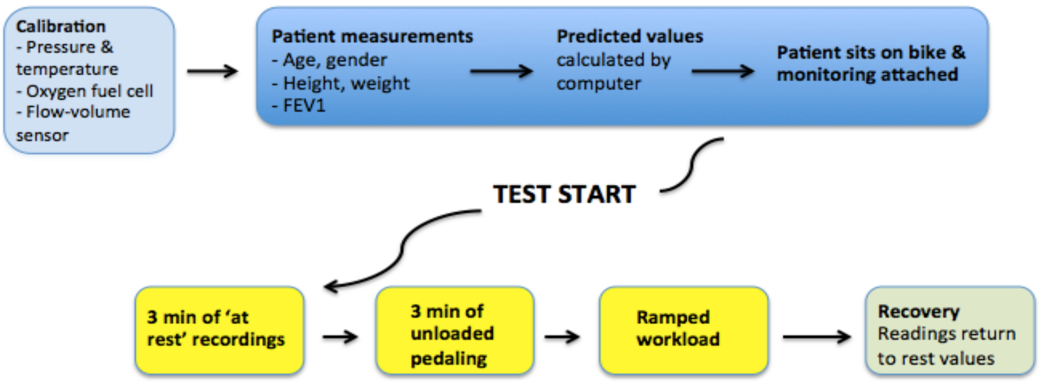


Figure 2-2 Conduct of cardiopulmonary exercise testing

2.3 Data analysis and interpretation

CPET physiological data were recorded continually, exported into an Excel spreadsheet and also expressed visually as the standard nine-panel plot (fig. 2-3). The nine-panel plot allows 15 measures to be described on nine graphs and several formats have been described in the literature; the format chosen by this institution is the UCLA (University of California, Los Angeles) layout, which is automatically produced by the Cortex software.

The VO_2 at AT was measured as ml/kg/min. AT was determined by modified V-slope technique (148) and confirmed with the ventilatory equivalents, RER, $P_{ET}O_2$ and $P_{ET}CO_2$ responses using the methods described by Whipp (149). AT was identified as the breakpoint in the VCO_2-VO_2 relationship from the line of unity ('line of one') during the incremental stage of the exercise test (fig. 2-4).

VO_2peak was calculated as the average VO_2 for the individual breaths taken in the final 20 seconds of the exercise test; a compromise between the inclusion of sufficient data to overcome breath-by-breath fluctuations whilst capturing any underlying physiological changes in VO_2.

12 lead ECG recordings were continually analysed and assessed for ischaemia and arrhythmias (Pathfinder SL. Spacelabs Healthcare, Hertford UK). ST segment neutrality was gauged from the baseline ECG trace of each patient. ST segment depression was assessed in lead II and defined as abnormal when depression of 0.1 mV or more occurred (28)

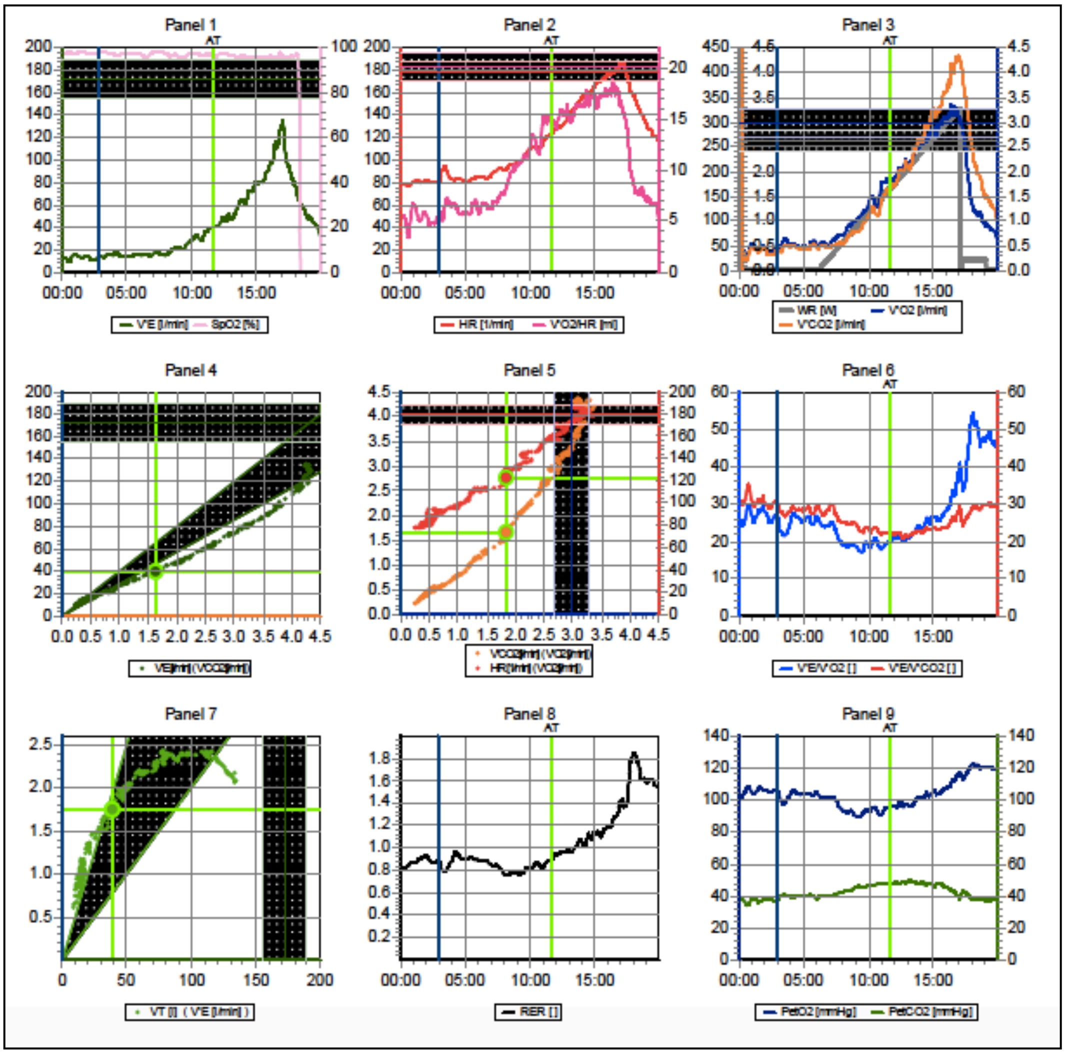
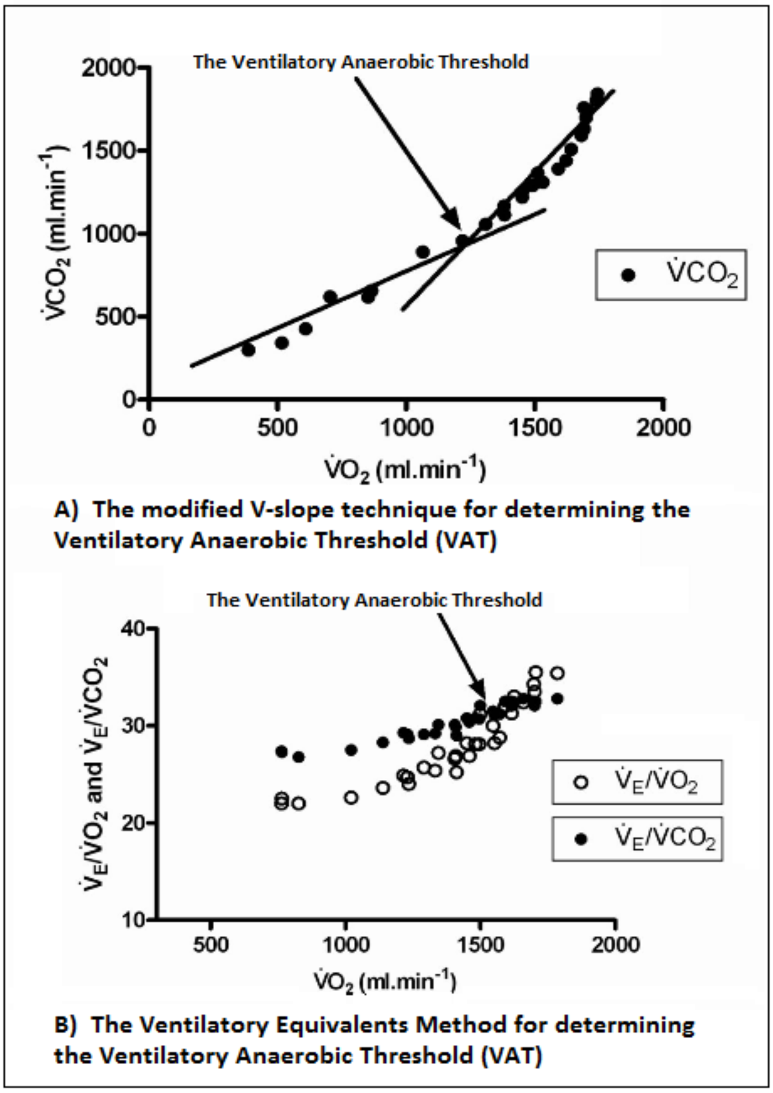


Figure 2-3 The standard UCLA nine panel CPET plot

Panels 2,3,5 relate to the cardiovascular system, panels 1,4 and 7 are pertinent to ventilation and panels 6, 8 and 9 display ventilation/perfusion relationships.



A) The modified V-slope technique for determining the Ventilatory Anaerobic Threshold (VAT)

B) The Ventilatory Equivalents Method for determining the Ventilatory Anaerobic Threshold (VAT)

Figure 2-4 Methods for determining the anaerobic threshold

A. The modified V-slope technique: AT is the point at which the two regression lines explaining VCO_2 as a function of VO_2 intersect. It is expressed as the VO_2 where the residual sum of squares is minimised.

B. The ventilatory equivalents method. AT is the point at which the V_E/VO_2 begins to increase without an accompanying increase in V_E/VCO_2 and is expressed as the VO_2.

From: NL Jones 1997 (150)

Normal ranges and predicted values for CPET measures quoted in this thesis are those used routinely at the RFH in the clinical interpretation of CPETs and are outlined in Table 2-3.

Variable	**Predicted Value**	**Range**
VO_2 max (ml/min)	Based on gender, age, height	Lower limit of normal < 80% predicted
Resting VO_2 (ml/min)	150 + (6 x weight in kg)	250 -300 (larger in obese individuals)
Peak heart rate (bpm)	220- age or 210 – (0.65 x age)	Max HR > 90% predicted
Oxygen pulse (ml/beat)	(Predicted VO_2max) ÷ (predicted max HR)	80% predicted (~ 15 ml/beat in men; ~ 10 ml/beat in women)
Minute ventilation (L/min)		Peak Exercise: 70-80% of MVV
Maximum tidal Volume	60% of the FVC	
VE/VCO_2 (early exercise)		25-35
VE/VO_2 (early exercise)		25-35
VD/VT		0.25-0.35 at rest Should decrease with exercise
$P_{ET}CO_2$ (mmHg)		38-42 (Should decline after ventilatory threshold)
$P_{ET}O_2$ (mmHg)		95-100 (Should rise after ventilatory threshold)
SpO_2 (%)		> 95% (Should remain constant with exercise)
Respiratory exchange ratio	Rest: 0.8 Peak Exercise: > 1.15	Rest: 0.6-1.0 Peak Exercise: 1.1-1.3

Table 2-3: Normal values and ranges used at the RFH for CPET interpretation, in line with ATS/ACCP recommendations

Adapted from American Thoracic Society; American College of Chest Physicians 2003 (28)

2.3.1 Procedure for data checking

Given that the interpretation of AT has considerable scope for inter-observer variability and hence potential reporting error, all CPETs were reported by two independent assessors: the primary researcher and a second experienced operator. The second operator, an exercise physiologist with more than 5 years of experience independently performing and interpreting CPETs, was blinded to all participant details, study allocation, test date and test number. He was provided with anonymised raw data in 'MSTEST' file format for interpretation on the cortex software and asked to interpret the position of the AT as per his usual approach. An average of the reported values given by both interpreters was then calculated.

A procedure was put in place to handle the event where AT was felt to be uninterpretable or not present. A third expert, blinded to all patient and study allocation details as above was asked to interpret the AT position.

Bland-Altman plots were generated to assess inter-observer agreement and look for the presence of proportional bias in the assessment of AT.

2.4 Exercise training programme

2.4.1 Exercise training frequency

Patients in both liver transplant and complex vascular cohorts were asked to attend a supervised exercise training programme three times per week for six weeks.

2.4.2 Exercise training intensity

An aerobic interval exercise training programme, incorporating moderate and severe intensities was used. Individualised exercise training intensities were derived from the baseline (week 0) CPET. The protocol for this interval training regimen was developed and described by the Southampton-based Fit-4-Surgery team (151). This group has extensive experience studying the effects of preoperative exercise training in patients who have undergone neo-adjuvant chemoradiotherapy (152, 153).

Moderate-intensity exercise is defined as a power output equivalent to 80% of the oxygen uptake at AT

Severe-intensity exercise is at a power output half-way between AT and VO_2 peak (termed 50%Δ).

Power intervals were calculated for each subject as follows:

Moderate-intensity exercise: (work load at AT –2/3 of work ramp) × 80 %

Severe-intensity exercise: ((work load at VO_2 Peak- work load at AT –2/3 of work ramp) × 50 %) + work load at AT

Each exercise session included a five minute warm-up and cool-down consisting of unloaded pedalling.

Exercise training intensities for each patient were modified following a CPET at the mid-point (week three) of the exercise programme. Moderate and severe training intensities were informed by measured work rates at AT and VO_2 Peak in an identical manner to that described above. The absolute power output for subsequent training sessions was adjusted according to the outcome of this CPET.

All CPET measures were derived and reported by two independent assessors; where there was disagreement of ≥ 10%, the opinion of a third assessor was sought as described above.

2.4.3 Training time

The first two training sessions consisted of 30 minutes of exercise with patients performing the interval exercise training protocol for 20 minutes with a five minute warm-up and cool down either side. The interval exercise training phase comprised four repeated bouts of moderate (4x3 min intervals) and severe (4x 2 min intervals) intensity.

Following week one, the time of each exercise training session increases to 40 minutes with a five minute warm up and cool down. The interval exercise training phase consisted of alternating moderate- and severe-intensity intervals. The 40 minute programme consisted of alternating six sets of three minute intervals at moderate intensity and six sets of two minute intervals at severe intensity.

Figure 2-5 illustrates the training programme overview for each patient; each session individualised to patient specific CPET measures.

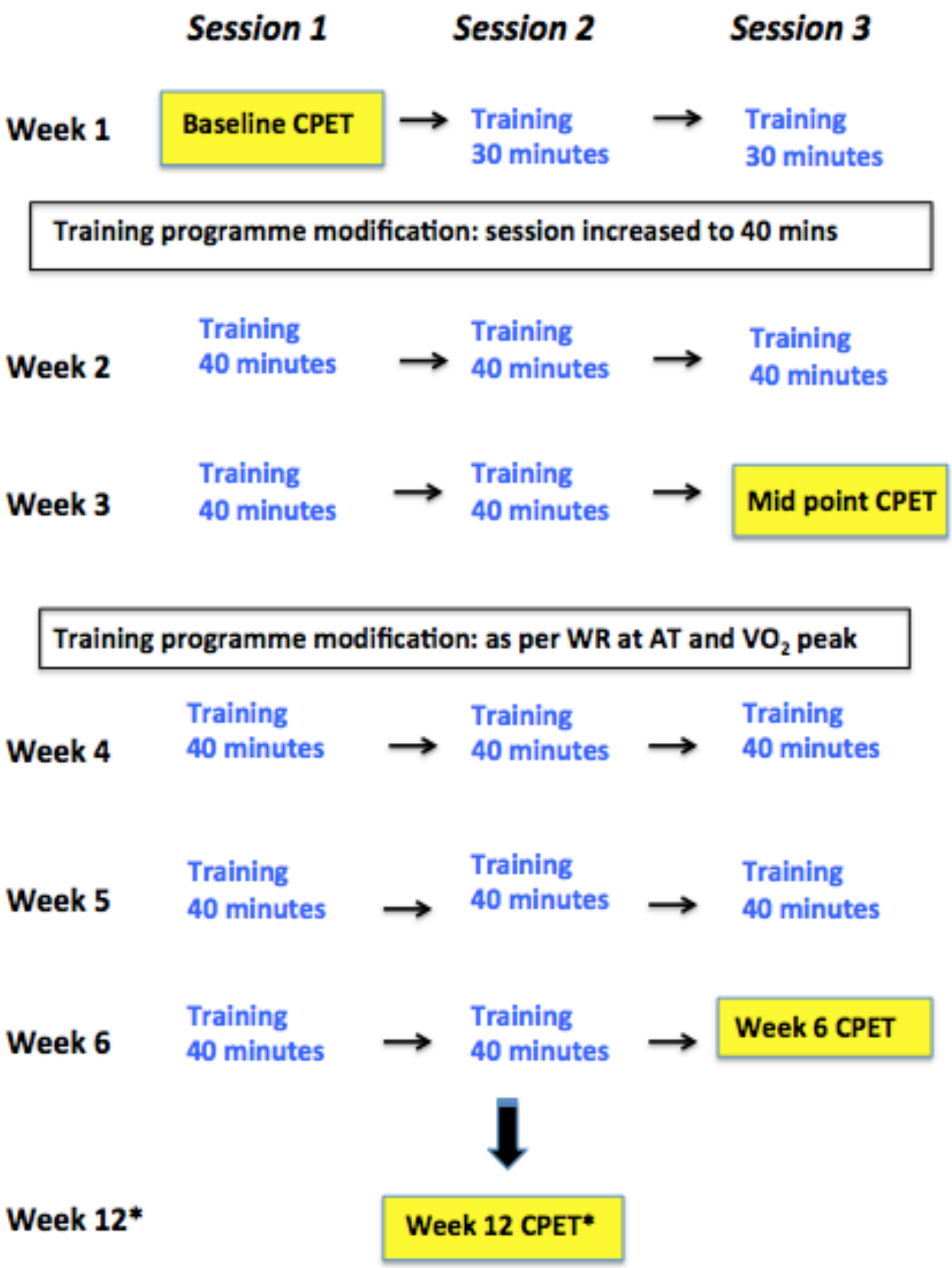


Figure 2-5: Exercise training programme schematic

* Week 12 CPET: study 1 only

2.4.4 Training type

The exercise training programme was conducted on a computer-controlled, electromagnetically braked, cycle ergometer (Optibike Ergoselect 200; Ergoline, GmbH, Bitz, Germany) (fig. 2.6). Heart rate was continuously recorded from the R-R interval (Polar FT7, Warwick, UK).

The training programme was preloaded on to a chip-and-pin card that executes the moderate and severe interval intensities automatically onto the screen displayed on the cycle ergometer (fig. 2.7)

Figure 2-6: Exercise training cycle ergometer

(Optibike Ergoselect 200; Ergoline, GmbH, Germany)

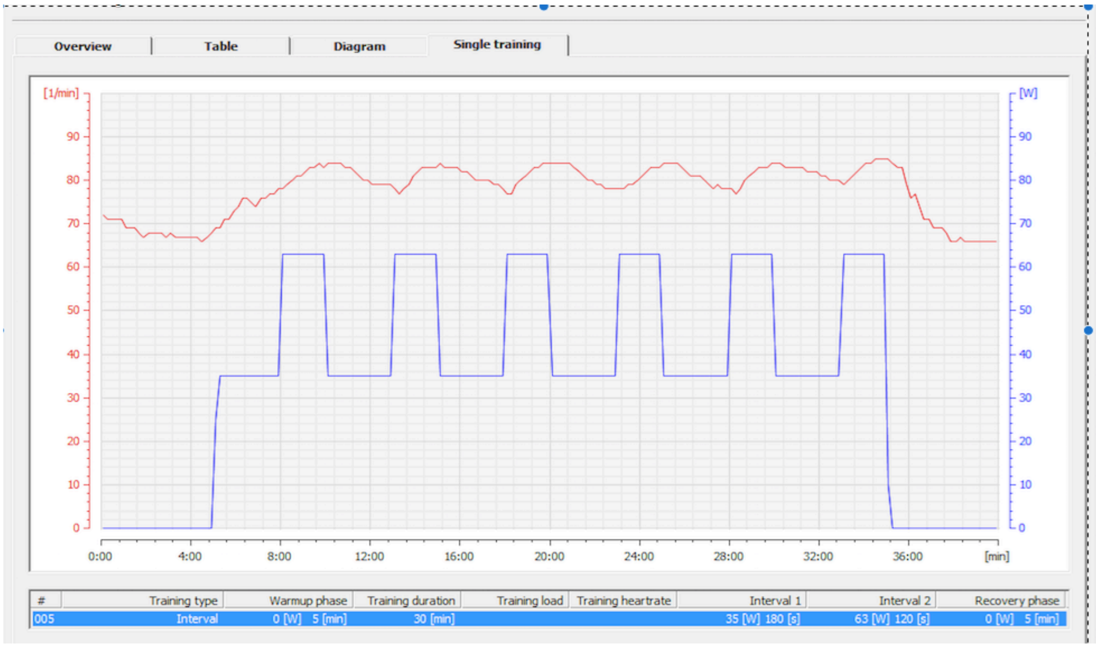


Figure 2-7 Screen shot of a 40 minute exercise session, similar to that displayed on the cycle ergometer.

Power (W) and heart rate (beats/min) depicted on the y-axis and time (min) is shown on the x-axis. The blue square wave line is the individualised training profile, and the red line is heart rate.

2.4.5 Exercise supervision

All exercise training sessions took place at the RFH and were supervised by one of two members of staff: the primary researcher or a clinical exercise physiologist. Both were trained in resuscitation/life support.

2.5 Health-related quality of life assessment

Evidence on patients' health-related quality of life (HRQL) can be obtained using patient-reported outcome measures (PRO). HRQL was measured using the EuroQol five dimensions, five levels (EQ-5D-5L) questionnaire (154) (appendix 3) which is recommended by NICE (National Institute of Clinical Excellence) to inform cost-utility analyses of healthcare interventions (155). The EQ-5D has been NICE's preferred measure of health-related quality of life in adults since 2008 (156). The questionnaire consists of 2 pages – the EQ-5D-5L descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive system assesses the following 5 dimensions: *mobility, self-care, usual activities, pain/discomfort* and *anxiety/depression*. The labels for all 5 dimensions follow the format *'no problems,' 'slight problems,' 'moderate problems,' 'severe problems,'* and *'unable to'/ 'extreme problems'.* A 5 digit health state profile is produced that represents the level of reported problems on each of the five dimensions of health, e.g.EQ-5D-5L health state 21143 represents a patient who indicates slight problems on the mobility dimension, no problems on the self-care and usual activities dimensions, severe pain or discomfort and moderate problems on the anxiety/depression dimension(157). These health states can be converted into a single index value using one of the standard EQ-5D-5L value sets; in this thesis the value set for England has been used(158). These value sets represent the preferences of the general population and are anchored on 11111 = 1 (representing full health) and 0 equating to death. The minimum value of this self-reported measure is -0.285 (for the worst health state, 55555) with 5.1% of the 3,125 health states described by the EQ-5D-5L as being worse than dead (158).

The EQ VAS records the respondents' self-rated health on a 20 cm vertical, visual analogue scale with endpoints labelled '100 = the best health you can imagine' and '0 = the worst health you can imagine'. This information can be used as a quantitative measure of health as judged by the individual respondents. The EQ VAS scores are self-reported and are therefore not representative of the general population. The most attractive features of the EQ-5D instrument include its brevity and the fact that it is cognitively simple. In addition, it is available in more than 150 official languages and offers several population weights (e.g., different value sets for the UK, France, Germany, Netherlands, Denmark, Spain, Japan, USA) (159)

The EQ-5D-5L questionnaire was administered at baseline assessment for all participants and after six weeks of exercise training in the intervention group or at the time of the week six CPET in the control group.

2.6 Physical Activity Enjoyment Scale (PAES)

Patients enrolled into the exercise group in both studies provided an overall rating of enjoyment of the exercise programme, using the PAES questionnaire (121), appendix 2. PAES is one of the most widely used measures of patient-reported enjoyment in the field of exercise psychology (160). This questionnaire was completed at a single time point: the end of the third week of exercise training. Respondents were asked to rate 'how you feel at the moment about the physical activity you have been doing' using a 7-point bipolar rating scale. Eleven items are reverse scored. Higher PAES scores reflect greater levels of enjoyment. The maximum score on this tool is 126.

3 Study 1: *The feasibility of an outpatient hospital-based exercise training programme for patients with cirrhotic liver disease awaiting transplantation*

3.1 Introduction

3.1.1 Liver transplantation background

In the past 30 years, significant progress has been made in the management of almost all chronic disorders, the one glaring exception being liver disease with a mortality rate that has increased by 400% since 1970 (161) (fig. 3-1). Liver disease constitutes the third commonest cause of premature death in the UK (161); around two-thirds of these deaths are due to alcohol with the majority of the remainder resulting from obesity and viral hepatitis (143). Liver transplantation is the only curative treatment for ESLD; the goal of the procedure being to prolong survival and improve quality of life.

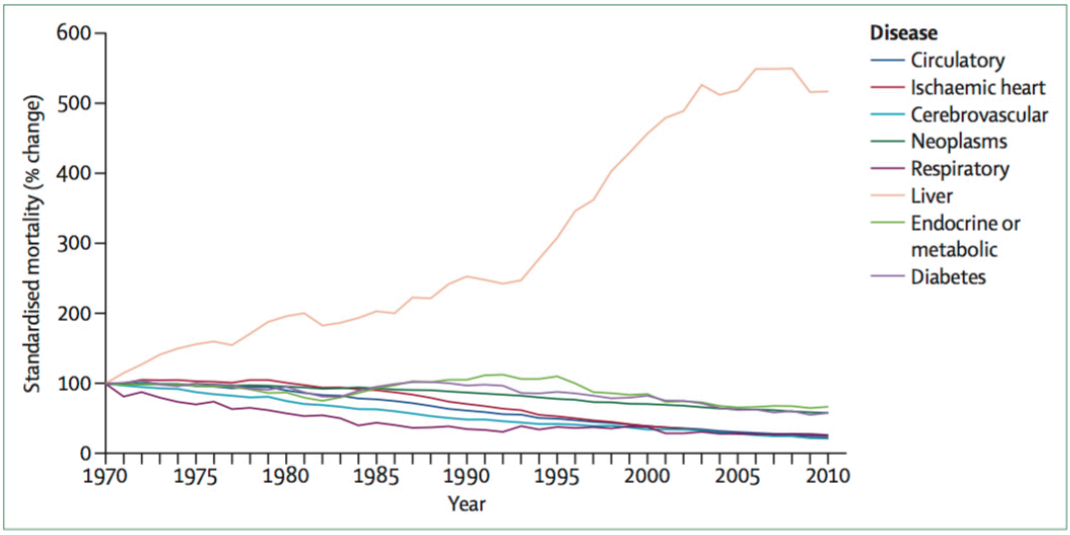


Figure 3-1 Standardised UK mortality rate data illustrating the risk of premature death from liver disease

From: Williams et al 2014 (161)

The first human liver transplant in the United Kingdom was performed in 1968 by Sir Roy Calne (143, 162). There are now seven designated liver transplant units covering the UK, between them performing 8740 LTs over the last 10 years (125).

Patients with ESLD have unique cardiorespiratory pathophysiology including a high prevalence of cirrhotic cardiomyopathy, portopulmonary hypertension and hepatopulmonary syndrome (163). Many are deconditioned and burdened with frailty and multimorbidity. These extremely frail patients must not only survive their illness for an undefined period on the waiting list but must prepare themselves for one of the most physiologically challenging operations known in order to benefit from organ transplantation.

Improving physical activity in this cohort could therefore increase their chance of survival on the waiting list until a donor organ becomes available, increase their likelihood of a successful outcome with liver transplantation and lead to improved long-term survival once discharged from hospital.

Attention is turning towards the development of effective exercise/lifestyle intervention programmes for patients awaiting LT, where involvement of a liver multidisciplinary team is essential, particularly in respect to tailored physical and nutritional intervention. Indeed, time spent on the waiting list prior to LT provides an ideal window of opportunity to optimise recipient fitness through prehabilitation.

3.1.2 Cirrhotic liver disease

Cirrhosis is a progressive chronic liver disease characterised by diffuse fibrosis, severe disruption of the intrahepatic venous flow, portal hypertension and liver failure (164). The course of cirrhosis is divided into distinct stages: compensated and decompensated liver disease. 'Compensated' cirrhosis defines the period between the onset of cirrhosis and the first major complication. After a variable period of time, liver function progressively deteriorates and from a clinical point of view, patients may develop ascites, jaundice, variceal haemorrhage, hepatic encephalopathy, cardiopulmonary dysfunction and renal failure. This phase is referred to as 'decompensated' cirrhosis (165–167) and a survival of only 3-5 years is associated with this period (168).

Patients with cirrhosis and portal hypertension are at an increased risk of developing circulatory dysfunction with consequent multi-organ failure (fig 3-2). As the disease progresses, the circulation becomes hyperdynamic, and signs of cardiac, pulmonary, and renal dysfunction are observed.

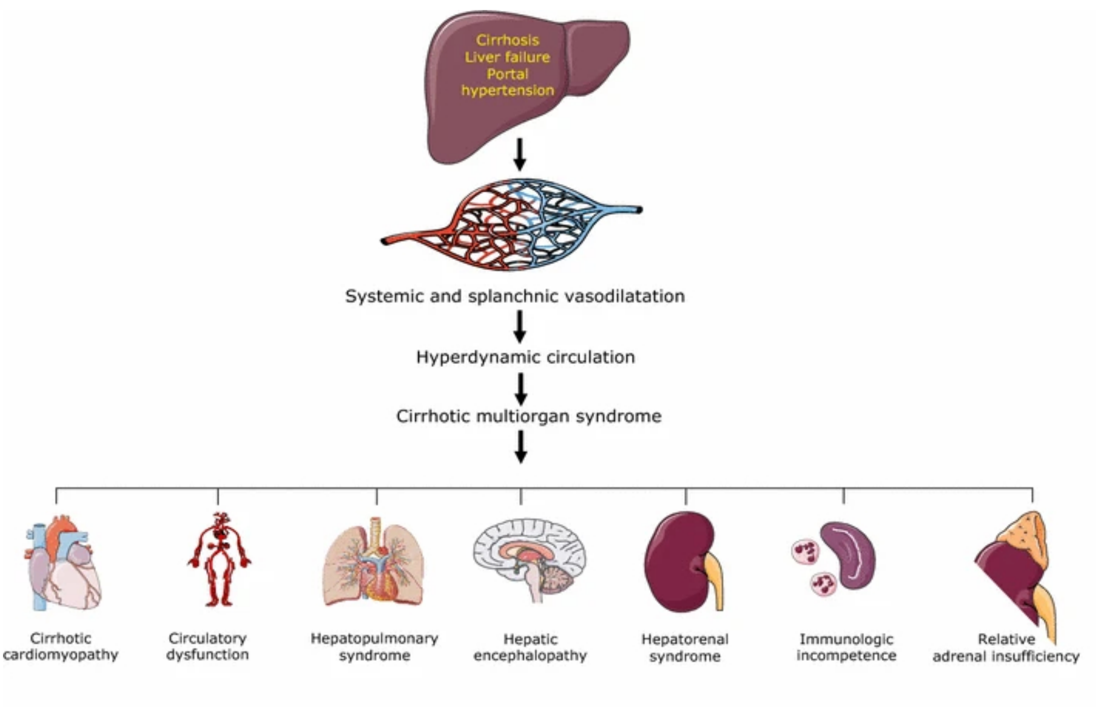


Figure 3-2 development of multiorgan dysfunction secondary to cirrhosis and portal hypertension.

From Møller & Bendtsen 2015 (169)

The cardiovascular disturbance in cirrhosis is characterised by decreased vascular reactivity alongside endothelial and autonomic dysfunction (170). The term 'cirrhotic cardiomyopathy' (CCM) denotes a chronic cardiac dysfunction with a blunted inotropic and chronotropic response to stress, impaired diastolic relaxation and prolongation of the QT interval (171). The pathogenesis includes impaired function of beta-receptors, altered transmembrane currents and overproduction of cardiodepressant factors, such as nitric oxide, cytokines and endogenous cannabinoids (172).

Patients with cirrhosis have a higher frequency of pulmonary diseases associated with immune dysfunction such as pneumonia (173). Specific pulmonary dysfunction related to liver disease involves diffusion abnormalities and the development of hepatopulmonary syndrome (HPS) and portopulmonary hypertension (PoPH) (table 3-1). HPS generally presents with insidious onset of dyspnoea, platypnoea (dyspnoea on standing), orthodexia (hypoxia on standing), clubbing and cyanosis (174) whereas PoPH involves progressive fatigue, exertional dyspnoea, dependent oedema and syncope (175).

The pathogenesis of PoPH is not completely understood but one proposed mechanism suggests that the high cardiac output in chronic liver disease causes pulmonary vascular wall stress, triggering dysregulation of vasoactive, proliferative and angiogenic mediators (176). This leads to intimal fibrosis, hypertrophy of smooth muscle cells and in situ thrombosis (177). The hallmark of HPS is intrapulmonary vasodilatation, resulting in arterial deoxygenation by three mechanisms: ventilation/perfusion mismatch, intrapulmonary shunting and limitation of oxygen diffusion (176).

Hepatopulmonary syndrome	Portopulmonary hypertension
Presence of liver disease	Presence of liver disease and portal hypertension
$P_{A\text{-}a}O_2$ > 2 kPa	MPAP > 25mmHg
Positive contrast enhanced TTE	PVR>240 dyn s cm^{-5} LAP < 15mmHg

Table 3-1 Diagnostic criteria for hepatopulmonary syndrome (HPS) and portopulmonary hypertension (PoPH)

Adapted from Møller & Bendtsen 2015 (169)

$P_{A\text{-}a}O_2$ = Alveolar-arterial oxygen content, MPAP = mean pulmonary arterial pressure, PVR = pulmonary vascular resistance, LAP = left atrial pressure, TTE = trans-thoracic echocardiography

Circulatory changes also impact on renal function. Renal failure is common in cirrhosis and denotes a spectrum of renal dysfunction from acute kidney injury (occurring in approximately 20% of hospitalised cirrhotic patients (178)) and chronic kidney disease to full-blown hepatorenal syndrome (HRS) (179). HRS is a functional prerenal failure that is unresponsive to volume expansion in patients with chronic liver disease and ascites. Arterial vasodilatation in the splanchnic circulation, triggered by portal hypertension, plays a central role in the pathogenesis of declining renal function in cirrhosis and is secondary to increased production of vasodilators such as nitric oxide (180). The prognosis of HRS is poor with LT the only effective treatment (181).

3.1.3 Chronic liver disease risk scoring and selection for liver transplantation

The process of determining patient eligibility for adult elective LT is based primarily on risk of death without a transplant and specific criteria are determined by NHS Blood and Transplant (NHSBT) policy (182). The model for End-Stage Liver Disease (MELD) Score (figure 3-3), originally developed as a method of predicting the outcome of chronic liver disease, has been widely used for prioritizing liver donor allocation since the early part of the 21st century. Incorporation of serum sodium was found to improve predictive accuracy and in 2008 the UK Liver Transplant Units jointly developed a new scoring system, United Kingdom Model for End-Stage Liver Disease (UKELD) Score, for selecting cirrhotic patients for liver transplantation (183) (figure 3-4).

Model for End-Stage Liver Disease (MELD) Score
MELD = 3.78×ln[serum bilirubin (mg/dL)] **+ 11.2×ln[INR]** **+ 9.57×ln[serum creatinine (mg/dL)]** **+ 6.43**
If the patient has been dialyzed twice within the last 7 days, then the factor for serum creatinine used should be 4.0

Figure 3-3: Model for End-Stage Liver Disease (MELD) Score

United Kingdom Model for End-Stage Liver Disease (UKELD) Score
UKELD = 5.395 × ln(INR) **+ 1.485 × ln(creatinine)** **+ 3.13 × ln(bilirubin)** **– 81.565 × ln(Na)** **+ 435**

Figure 3-4: United Kingdom Model for End-Stage Liver Disease (UKELD) Score

Higher MELD and UKELD scores equate to higher one-year mortality risk without liver transplant. A UKELD score of ≥49 indicates a 9% one-year mortality risk without transplantation and is the minimum score required to be added to the UK LT waiting list in patients with chronic liver disease or liver failure (182).

Liver transplant recipients are increasingly older and have more cardiovascular comorbidities than ever before (184). Rising MELD scores at the time of transplant and aggressive organ utilization reflect the escalating risk profiles of LT candidates. Likewise, a decline in liver graft quality may be negatively impacting LT outcomes. Efforts to increase the donor pool have included adding older donors and donors with fatty livers plus accepting donation after cardiac death (DCD) to the standard donation after brain death (DBD) (185).

3.1.4 Indications for liver transplantation

The aetiologies of liver failure requiring transplantation vary in different parts of the world. In the West, the most common indications for LT due to ESLD are alcohol-related liver disease and hepatitis C virus (HCV) (186). Indications for LT (excluding causes of acute liver failure) are detailed in table 3-2.

Cirrhosis from chronic liver disease	Alcoholic liver disease Non-alcoholic fatty liver disease Chronic hepatitis B infection Chronic hepatitis C infection Autoimmune hepatitis Cryptogenic liver disease
Cholestatic liver diseases	Primary biliary cirrhosis Primary sclerosing cholangitis Secondary biliary cirrhosis
Malignant diseases of the liver	Hepatocellular carcinoma Carcinoid tumour Epithelioid hemangioendothelioma
Metabolic liver diseases	Wilson's disease Hereditary hemochromatosis Alpha-1 antitrypsin deficiency Cystic fibrosis Glycogen storage disease Crigler-Najjar syndrome Galactosemia Type 1 hyperoxaluria Familial homozygous hypercholesterolemia Haemophilia A and B
Vascular diseases of the liver	Budd-Chiari syndrome Veno-occlusive disease
Miscellaneous	Adult polycystic liver disease Severe graft-versus-host disease Amyloidosis Sarcoidosis Caroli's disease

Table 3-2: Indications for liver transplantation (excluding causes of acute liver failure)

Adapted from Varma et al. 2011 (187)

3.1.5 Malnutrition, frailty and anthropometric assessment

Cirrhosis is a state of accelerated starvation demonstrated by a rapid post-absorptive physiology (188) and malnutrition is a frequent burden; reported in more than 50% of patients with decompensated liver disease (189). Malnutrition in cirrhosis has been linked to increased mortality, independent of disease severity (190, 191). The malnutrition of ESLD, better defined as protein-energy malnutrition (PEM), is multifactorial (table 3-3), however the major determinants are abnormal nutrient and caloric intake, decreased intestinal absorption and metabolic disturbances (192).

Physical deconditioning and decreased skeletal muscle mass (sarcopenia) result from the combined effects of impaired dietary intake, altered macronutrient and micronutrient metabolism, chronic inflammation and low physical activity (193). The prevalence of sarcopenia in patients with cirrhosis varies within the literature, ranging from 40-70% (194) and there is significant data supporting its prognostic significance (195, 196). Sarcopenia is independently associated with both waiting list and post-liver transplant mortality (197, 198); similarly it is associated with a higher rate of infection and longer hospital stay (199, 200), hepatic encephalopathy (201), poor quality of life and increased healthcare cost (202). The frailty syndrome is the end result of prolonged sarcopenia and physical deconditioning which is in turn associated with a higher rate of complications and is an independent predictor of lower survival in cirrhosis and in patients undergoing liver transplantation (203). Frailty is thought to be reversible with emerging data in the field of prehabilitation and lifestyle intervention programmes (203–206). However, there are few studies in patients with cirrhotic liver disease regarding treatment (203).

More recently, in addition to undernutrition, ESLD in patients who are overweight or obese are increasingly being observed due to the rising prevalence of cirrhosis secondary to non-alcoholic fatty liver disease.

Decreased intake	Metabolic alterations
• Anorexia/early satiety, nausea • Ascites • Altered mental status/encephalopathy • Frequent hospitalisations	• Increased/decreased metabolic rate • Glucose intolerance/insulin resistance • Postprandial gluconeogenesis • Reduced glycogen stores • Elevated leptin and TNF-alpha • Increased protein requirements and protein degradation • Decreased bile salt and increased fat malabsorption
Decreased absorption	**Iatrogenic factors**
• Inadequate bile flow • Pancreatic insufficiency • Bacterial overgrowth	• Overzealous dietary restrictions • Frequent paracentesis • Diuresis (micronutrient losses), lactulose

Table 3-3: Aetiologies of malnutrition in cirrhosis

Adapted from Kerwin and Nussbaum 2011 (192)

Difficulties in the accurate assessment of nutritional status in patients with cirrhosis are widely recognised, given that many of the markers associated with malnutrition are intrinsically affected in liver disease (e.g., albumin and lymphopenia). Therefore, skeletal muscle evaluation provides an objective means to determine nutritional status (193, 207). The RFH Global Assessment Data Collection Form (appendix 4) has been externally validated (208) as a nutritional assessment method specifically for this patient population and is used in routine clinical practice in transplant centres across the UK. The data collection form encompasses measures of body mass index (BMI), mid-arm muscle circumference (MAMC), hand-grip strength combined with details of dietary intake. This tool is validated (208) and well accepted as providing a semi-structured, algorithmic construct to provide a nutritional assessment scheme for use in patients with cirrhosis specifically. Evaluated individuals are classified as adequately nourished, moderately malnourished (or suspected to be), or severely malnourished.

Malnutrition is correlated with clinical severity of liver disease (209), hence in ESLD an aggressive, early approach to ensure adequate nutritional repletion is central to maintaining remaining hepatic liver function and improving the patient's metabolic reserves and outcomes after LT (210, 211). Timely nutritional assessment and intervention for patients on the LT waiting list may improve post-transplant outcomes (212), making dietitians integral members of the liver transplant team.

3.1.6 Transplant outcomes and exercise capacity

The one- and five- year survival rates for adults following their first liver transplant in the UK is 93.8% and 81.3% respectively as per the 2017/2018 NHS Blood and Transplant (NHSBT) annual report (213). In comparison, one- and five- year patient survival rates *from listing* for adults going onto the waiting list for their first transplant were 84% and 71% respectively. This >10% mortality rate on the waiting list can be accounted for by a number of factors including a shortage of organs and physical deterioration. The complex multi-system nature of liver cirrhosis means that malnutrition, muscle wasting, muscle weakness, cirrhotic cardiomyopathy, anaemia and pulmonary gas exchange impairment conspire to result in progressive overall physical deconditioning and frailty. Given these challenges, it could be argued that improving the quality and length of life of patients who would benefit from LT is hence one of the greatest priorities in the field of transplant medicine.

Liver transplantation surgery itself has a significant early postoperative morbidity and mortality rate (167); likely related to the patient's pretransplant condition alongside the quality of the donor organ (214). Patients with the highest MELD scores (>24) have a higher risk of post-operative complications, reflecting a significant increase in ICU costs and hence overall transplant costs (215). A recent study from the liver transplant team at King's College London, showed that the need for renal replacement therapy (RRT) was associated with an ICU stay greater than 3 days and the median ICU cost of those receiving RRT was £32,400 compared with £3,600 for those not requiring it (216). However, despite the utility of MELD and UKELD at predicting mortality without transplantation, they do not consistently predict post-transplant survival.

The physiological demands of liver transplantation surgery highlight the limitation of cardiac reserve and cardiovascular complications are a major cause of postoperative morbidity and mortality (217). Studies have shown low aerobic capacity and anaerobic threshold to have predictive value as regards early postoperative complications after LT (129, 218). Peak oxygen consumption (VO_2 peak) measured during CPET is inversely correlated with both MELD and Child-Pugh scores. A VO_2 peak of <60% of predicted has been shown to be independently associated with an increased 100 day mortality following liver transplantation (independent of disease severity: MELD and Child-Pugh score) (218). AT is the CPET variable most consistently associated with liver transplant outcomes (66). Measurement of AT does not require maximal patient effort and so is less likely to be confounded by volitional factors. The optimal AT for survival has been defined to be >9.0 mL/kg/min (129). Patients with good cardiopulmonary reserve (according to pre-transplantation CPET derived measures) have a higher survival rate and use fewer critical care resources postoperatively. In this respect, AT is a measure of functional decline, which may be driven by disease severity. Despite this knowledge, current management of ESLD tends to focus heavily on preventing and treating complications (such as encephalopathy), rather than targeting therapies to improve exercise capacity.

3.1.7 Ongoing assessment and the importance of exercise

Prognostication of patients with cirrhosis is complex, depending on more than just the severity of liver disease. Scores such as MELD and Child Pugh can assist with prognostication, yet by focusing on physiological parameters they fail to completely capture the elements contributing to a patient's clinical status.

Evidence is increasing to support an important role for physical functioning in patient outcomes (203). Preventing medical deterioration and physical deconditioning whilst awaiting transplantation is central to achieving optimal perioperative outcomes. Patients on the transplant waiting list must be constantly reviewed for a number of reasons (219). Firstly, in the event that treatment for complications and/or the underlying disorder is successful, clinical improvement can result and LT becomes unnecessary. Similarly, individuals can acutely and rapidly deteriorate, and regular, meticulous multidisciplinary input is required to help prevent this and/or intervene before the clinical situation becomes irretrievable.

Patients with chronic liver disease are being considered for liver transplant at a more advanced age and have more cardiovascular comorbidities than ever before (184). The use of more marginal donor organs including those from DCD donors have increased the risk profiles of LT candidates. At the RFH, a dedicated transplant waiting list clinic is in operation. All patients awaiting LT are seen every six weeks by the specialist liver transplant team which includes review by a consultant hepatologist, anaesthetist, liver transplant dietician and addiction specialist nurse as required. Review in this clinic provides the opportunity to recognise and intervene on a number of issues including physical deconditioning and malnutrition. Patients are encouraged to exercise as a standard of care, but to date patients are not provided with individualised exercise plans/prescriptions and a physiotherapist is not involved in this outpatient setting. As the median interval between listing and transplantation is 152 days for adults awaiting their first elective transplant (143), there is ample time for preoperative optimisation of exercise capacity with a structured exercise programme.

3.1.8 Existing evidence base: prehabilitation and cirrhotic liver disease

There is currently limited data to determine the effects of exercise in patients with cirrhosis; a potential consequence of historical, now disproved safety concerns (220, 221). A recent meta-analysis sought to assess the effects of exercise on cirrhotic patients (222), revealing only four small, randomised studies with 81 patients included. Reported outcomes included an improvement in VO_2 peak (223), exercise capacity (223–225) quality of life (225), reduced fatigue (223) and hepatic venous pressure gradient (HVPG) (226). Likewise, a 2018 Cochrane review on physical exercise for people with cirrhosis included only six small randomised controlled studies with a total of 173 participants diagnosed with Child-Pugh stage A or B cirrhosis; no trials involved decompensated patients with stage C cirrhosis/ end-stage disease awaiting LT (126). Primary outcomes of the trials again focused on exercise capacity and included muscle strength (227) VO_2 peak (223, 228), quality of life (225, 226), change in muscle mass (223–225) and HVPG (226). Results concluded that physical exercise had no effect on exercise capacity or quality of life and the only beneficial effect on anthropometric assessments was detected when analysing mid-arm circumference. The review involved a large proportion of patients with Child-Pugh A cirrhosis and none of the included trials specifically included patients with sarcopenia or malnutrition. Authors concluded that future trials should focus on patients with Child C cirrhosis and reduced muscle strength/mass.

3.1.8.1 Literature review search strategy

A comprehensive literature review of both randomised and non-randomised trials was performed in 2016, prior to starting the current study, which revealed a dearth of studies exclusively dedicated to studying the impact of exercise on patients with end-stage cirrhotic liver disease prior to LT (table 3-5).

The search strategy aimed to locate published studies only. An initial limited search of MEDLINE was undertaken to identify articles on the topic (table 3-4). Text words in the titles and abstracts were used to develop a search strategy.

Search	Query	Records retrieved
# 1	Liver transplantation [MeSH Terms] OR liver transplant [Title/Abstract] OR cirrhosis [MeSH Terms] OR cirrhosis [Title/Abstract]	70,838
# 2	Prehabilitation [MeSH Terms] OR exercise [MeSH] prehabilitation [Title/Abstract] OR exercise [Title/Abstract] OR physical activity [Title/Abstract] OR lifestyle intervention [Title/Abstract]	164,861
# 3	# 1+ 2	152

Table 3-4: MEDLINE search conducted August 2016

Literature sources included the Cochrane Central Register of Controlled Trials in the Cochrane Library, MEDLINE (from 1946) and EMBASE (from 1980). Searches were limited to studies on humans. A review of references included in primary studies and published systematic reviews was performed. No search for conference proceedings was performed and no language limitations were imposed.

3.1.8.2 Literature review results

Of the 152 records retrieved, a total of five studies (four RCTs and one prospective cohort study) specifically assessing the impact of exercise training on patients with cirrhosis were identified (table 3-5). The majority of the studies excluded were review articles/editorials and case studies. Other exclusions included studies on paediatric patients and articles investigating exercise performance without an exercise/prehabilitation intervention. Trials looking at physical activity following liver transplantation were also excluded as were studies on living organ donors. Other excluded trials focused on the analysis of exercise electrocardiography and were experimental studies assessing the physiological responses to exercise in cirrhotic patients.

Of the five studies identified, all were small (enrolling between 9 and 23 patients). In addition, all but one of the five studies described in table 3-5 involve clinically stable, predominantly compensated cirrhotic patients with Child-Pugh A or B disease and specifically exclude patients with decompensated and ESLD to whom LT is indicated.

The physical exercise intervention in each of the studies varied in type, intensity and duration. The different types of exercise performed included aerobic exercise involving cycling on an ergometer and/or treadmill walking/walking exercises of varying intensities, kinesiotherapy and flexibility, muscle building/resistance training and stretching either in isolation or as combinations. Duration of exercise varied between 8 and 14 weeks. The exercise intervention in all five studies was supervised at an institution by specialists. Two studies had a particular focus on nutrition; Macias-Rodriguez et al 2016 (226), included ‘nutritional therapy’, determining caloric and protein intake and limiting sodium. Whereas Roman et al, 2014 (225) administered 10g/day of leucine during their 12 week exercise intervention with the aim of increasing muscle mass in cirrhotic patients. A lack of a standardised approach to exercise in cirrhotic liver disease limits direct, detailed comparisons between these studies, enabling a systematic review but without combinable data for metanalysis.

Only one trial specifically assessed the feasibility and impact of exercise prior to LT. This prospective pilot study by Debette-Gratien et al in 2015 (229), investigated the feasibility of a 12-week personalised APA (adapted physical activity) programme, involving training on a cycle ergometer and muscle building activities on a weight bench. Thirteen patients were enrolled with eight completing the programme. There was no control group for comparison. The primary objective was to show acceptability of a programme of APA in patients awaiting LT. Acceptability was primarily defined as safety and the authors concluded that this particular intervention was indeed safe for patients with ESLD; no other pre-defined acceptability criteria were stated. Impact of APA on aerobic capacity (specifically VO_2 peak), muscle strength and quality of life before LT was also assessed, but no post-operative clinical outcomes were reported.

Knowledge pertaining to the field of exercise training prior to LT is still at an early stage. Only one cohort study assessing the impact of exercise prior to LT pre-dates this current study (229). Methodological flaws were evident, notably the small sample size and lack of a control group and this study did not incorporate specific nutritional assessment/intervention. It is well established that a combination of exercise and dietary supplementation is optimal to improve aerobic capacity and function prior to surgery (230) and nutritional therapy is particularly important in LT (211).

There is no real evidence that a prehabilitation programme prior to LT can improve postoperative clinical outcomes. There is considerable scope for further evaluation to ensure the compliance of patients with ESLD and define the optimal prehabilitation programme to keep patients well on the liver transplant waiting list.

Author, year	Study design and duration Disease severity	Intervention and comparator group details	Associated interventions	Outcome measures	Study conclusions
Roman, 2014 (225)	RCT, 12 weeks CP-A = 82% MELD 7-13	Exercise & leucine vs leucine Int: n=8, supervised moderate exercise Cont: n=9	All patients received leucine (10g/day)	- Impact on exercise capacity (6MWT and 2 min step test) - Muscle mass - HRQL	Moderate exercise and leucine supplementation improve exercise capacity, thigh circumference and HRQL
Zenith, 2014 (223)	RCT, 8 weeks CP-A = 84% MELD 10	Exercise vs standard care Int: n=9, supervised exercise 3x/week Cont: n=10	No	Change in VO_2 peak	Eight weeks of supervised exercise on an ergometer, improved VO_2 peak and muscle mass and reduced fatigue.
Debette-Gratien, 2015 (229)	Cohort, 12 weeks ***Patients awaiting LT*** MELD = 13-21	Supervised exercise n=13 2x/week adapted physical activity programme (APA)	No	- Feasibility - Aerobic capacity - Muscle strength - HRQL	Improvement in VO_2 peak, maximum power, 6MWT and knee extensor strength seen relative to baseline.

Roman 2016 (224)	RCT, 12 weeks CP-A = 5.4 +/- 0.2 MELD 8 +/- 0.4	Moderate exercise vs sham relaxation Int: n=14, supervised exercise 3x/week Comparator: 1hr supervised relaxation sessions 3x/week (n=9)	No	- Changes in functional capacity (as assessed by CPET) - Muscle mass	Moderate exercise improves functional capacity and increases muscle mass.
Macias-Rodriguez, 2016 (226)	RCT, 14 weeks CP-A 64% MELD 7-14	Aerobic and resistance training Int: n= 11, 40 supervised sessions Cont: n=11	All patients received nutritional therapy according to the Harris-Benedict equation.	- Effect on HVPG - HRQL	Training on a cycle ergometer alongside resistance training and nutritional therapy decreases HVPG and improves nutritional status.

Table 3-5 Clinical trials looking at the impact of exercise in patients with cirrhosis

Int = intervention, cont = controls, CP = Child-Pugh score, HRQL = health-related quality of life, HVPG = hepatic venous pressure gradient, BCAA (branched-chain amino acids), 6MWD = 6 minute walk distance, ISWT = incremental shuttle walk test, MELD= model for end-stage liver disease

3.2 Specific aims:

To engage patients with cirrhotic liver disease on the LT waiting list, in a programme of intense supervised aerobic exercise in a hospital setting over a period of six weeks. This single centre study was designed to determine the issue of feasibility and to compare changes in cardiopulmonary fitness as assessed by CPET, to a group of matched patients not involved in an exercise programme.

The purpose of this study was to provide information to justify and power a trail on efficacy and costs.

3.3 Study Objectives:

3.3.1 Primary Objective:

An assessment of the feasibility of formalised interval exercise training in patients awaiting liver transplantation.

3.3.2 Secondary Objectives:

a) Evaluation of the effectiveness of exercise training in this patient cohort using objective fitness measures provided by CPET
b) Comparison of changes in CPET measures with a group of standard care patients, matched for age, gender and disease severity (MELD score) to the exercise group, not undergoing formalised exercise training.
c) Objective assessment of nutritional status using anthropometric measurements at baseline and week six.
d) Measurement of changes in HRQL brought about by a formalised training programme.

e) Post-operative outcomes: intensive care and hospital length of stay, postoperative morbidity assessed using the Clavien-Dindo classification.
f) Assessment of exercise enjoyment using the PAES.

3.4 Hypothesis

3.4.1 Primary hypothesis

A structured six week exercise training programme alongside nutritional advice is feasible and can improve CPET indices of cardiopulmonary function.

3.5 Outcome measures

The primary outcome was feasibility of formalised exercise training in this complex cohort. Feasibility and acceptability outcomes were: recruitment, absence of adverse events and adherence to exercise as defined by:

a. Absence of exercise-related serious adverse events
b. Recruitment: >50% recruitment rate of patients meeting eligibility criteria
c. Compliance with exercise: >66% exercise sessions completed.

Feasibility criteria are by definition, context specific and very dependent on the characteristics of the population in question. Given the marked lack of research and knowledge in the field of perioperative exercise for patients with ESLD awaiting LT, it was difficult to set these pre-defined feasibility outcome measures. We based feasibility on the following criteria: recruitment, adherence to protocol and drop out rate, using our knowledge of the local LT population including waiting list times and transplant rates etc. Compliance with exercise was of particular importance given the need for physiological adaptation to exercise potentially impacting postoperative outcomes.

Cardiopulmonary fitness, as assessed by CPET, was defined as oxygen uptake at anaerobic/lactate threshold (VO_2 at AT) and peak oxygen uptake (VO_2 peak).

Nutritional status was defined using changes in specific arm anthropometric parameters: MAC (mid-arm circumference), MAMC and handgrip.

3.6 Study 1 specific methodology

3.6.1 Study design

This single centre prospective matched cohort study assessed the feasibility of a six week, structured, outpatient, hospital-based prehabilitation programme in patients awaiting LT. The study ran for a period of 18 months from August 2016 to January 2018 at the RFH, London. I aimed to recruit 15 patients into the exercise group and 15 matched control patients. All eligible patients were approached to take part.

3.6.2 Inclusion Criteria

- Diagnosis of cirrhotic liver disease
- Eligible for liver transplantation at the RFH
- Aged over 18 years
- Competent to give consent

3.6.3 Exclusion Criteria:

- Non-cirrhotic liver disease
- Fulminant hepatic failure
- Emergency liver transplantation
- Contraindication to exercise training or testing (according to the American Thoracic Society and the American College of Chest Physicians guidelines) (28)

- Receiving waiting list care/follow-up in satellite clinics remote to the RFH (live a significant distance from London)
- Refusal or inability to provide informed consent
- Prisoners

3.6.4 Patient identification, screening and recruitment

All potentially eligible patients were identified from the liver transplant waiting list held by the liver transplant coordinators at the RFH. This is standard practice for the screening of potential participants for research in this centre. Once patients were formally listed for liver transplantation, they were approached with written information about the trial at their initial waiting list outpatient clinic appointment or by post. Patients were then contacted by telephone to provide additional information about the trial and confirm eligibility. If the patient chose to participate in the study an initial research visit was organised when written, informed consent was obtained and baseline measurements including CPET and nutritional assessment were performed.

The study was limited to cirrhotic patients given the high prevalence of physical inactivity, compounded by multiple other factors including malnutrition and decreased hepatic protein synthesis alongside cardiac and skeletal muscle deconditioning and the potential for an exercise intervention to limit decline.

Given that the primary aim of this study was feasibility, formal randomisation was not considered necessary and the study was not designed to detect differences in outcomes. The ‘standard care’ cohort of patients (no exercise programme) were matched to those in the exercise group according to specific demographic criteria: age, gender and disease severity (MELD score). Once patients were matched, allocation to study arms was a function of geographical location and logistical ability to commit to attending hospital three times per week.

3.6.5 Assessment of fitness

Using the methodology described in chapter 2, serial CPETs were used to objectively assess change in cardiopulmonary fitness at the following time points: baseline (week 0), at the midpoint of exercise training to guide exercise prescription (week three; exercise group only), at the end of the six week exercise programme (week six) and a final CPET at week 12. The week 12 CPET was included to determine change in exercise capacity following cessation of exercise six weeks prior.

Self-reported activity status was assessed at baseline using the Duke activity status index (DASI) score (27) (appendix 1).

3.6.6 Intervention group:

Following the baseline CPET, patients were asked to attend thrice weekly, supervised, hospital-based exercise training sessions for six weeks. Sessions were held at the RFH (London) and patients travelled from home for each appointment. Each training session consisted of 40 minutes (including 5 min warm-up and 5 min cool-down) of interval training on an electromagnetically braked cycle ergometer (Optibike Ergoselect 200; Ergoline, GmbH, Bitz, Germany). The exercise training intensities were formulated according to an individual's CPET data at weeks 0 and 3 and altered according to measured work rates at VO_2 for AT and VO_2 peak in the manner described in chapter 2. A summary flow chart representing the study protocol is presented in figure 3-5.

3.6.7 Control/usual care group:

A comparator 'usual care' group was created by selecting patients matched to those in the exercise group according to age, sex and MELD score (the same inclusion and exclusion criteria were applied to both groups). These patients underwent CPET at baseline, six and 12 weeks but no exercise programme was initiated. Once patients were matched, allocation to study groups was based on geography and logistics; the patient living furthest from the hospital was allocated to the control group to avoid any logistical issues in thrice weekly hospital visits.

These patients were given general advice about the importance of keeping active but no structured exercise advice, as per the standard practice of the liver transplant department at that time.

3.6.8 Follow up assessment:

All participants were invited to a follow up CPET at 12 weeks after baseline if they were still awaiting transplantation. The purpose of this was to determine any alteration in level of cardiopulmonary fitness from week six to 12. Patients were encouraged to keep active following completion of the six week exercise training period, but not provided with structured training sessions.

3.6.9 HRQL and PAES self-reported measures

Health-related quality of life was assessed using the EQ-5D-5L questionnaire (154) at baseline and weeks six and 12 and exercise enjoyment was assessed using physical activity enjoyment scale (121) as per general methods section (chapter 2).

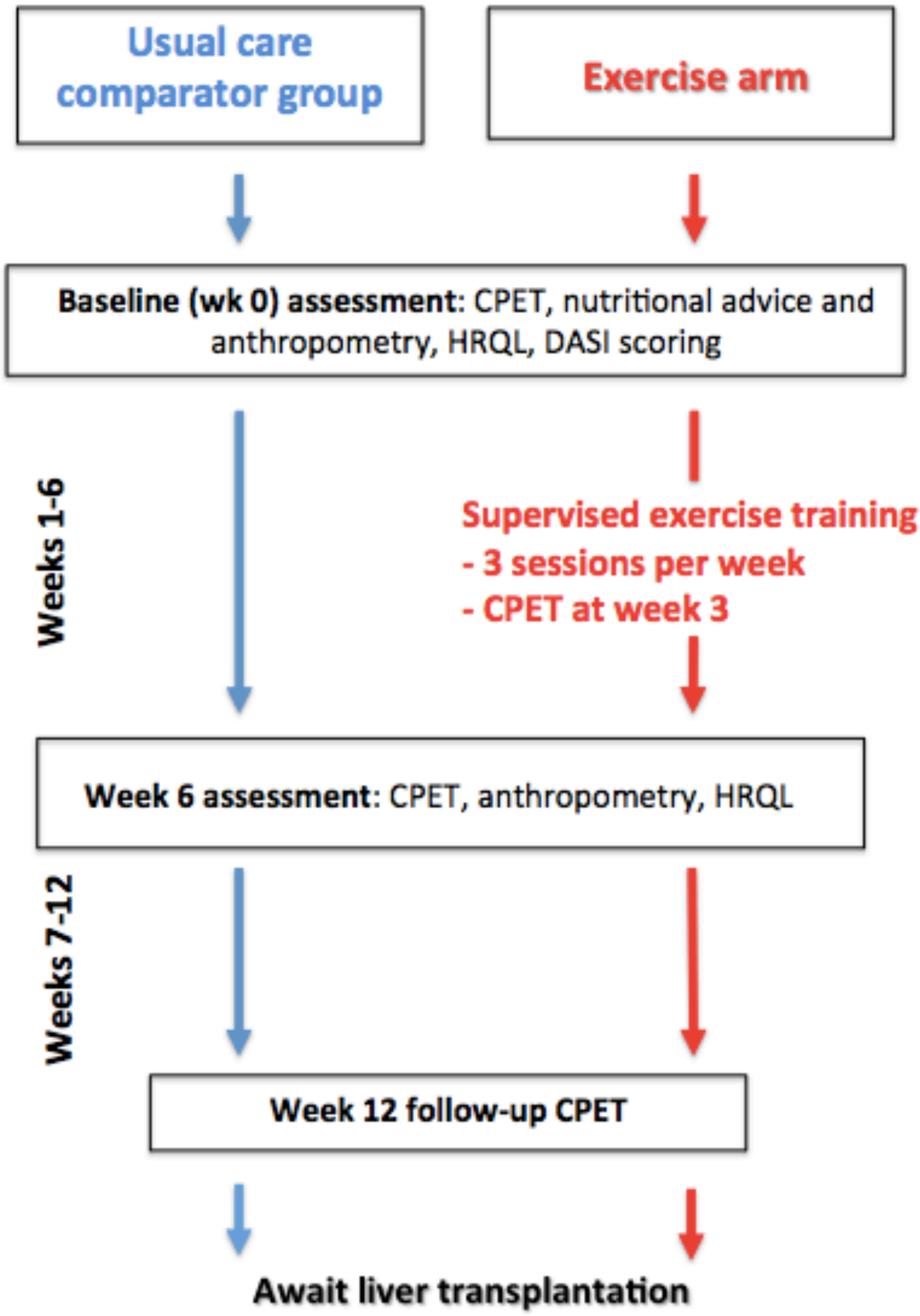


Figure 3-5: Protocol flow diagram for study 1: the feasibility of an outpatient hospital-based exercise training programme for patients with cirrhotic liver disease awaiting transplantation

3.7 Anthropometric assessment & nutritional status in LT patients

Nutrition is an integral part of LT perioperative patient care and given that protein-energy malnutrition is almost universally present in patients suffering from ESLD (231), incorporating nutritional assessment and advice into a study looking at the feasibility of exercise was considered essential. Adaptation to exercise requires appropriate nutritional support and measuring anthropometry at baseline and 6 weeks, allows the assessment of body composition and any potential impact of exercise.

3.7.1 Nutritional status and dietary advice

The components of a detailed nutritional assessment include evaluation of: muscle mass, global assessment tools and a detailed dietary intake assessment (188). Nutritional assessment was performed and then dietary advice was given by the same specialist liver transplant dietitian at baseline (prior to first CPET) and at week six for all patients in both the intervention and control groups. All assessments were made on the day of and just prior to the corresponding CPET. The anthropometric measures used and nutritional advice provided were standard care for every patient on the LT waiting list at RFH. These dietitian-led sessions were, however, standardised to take place at baseline and week 6 for all patients in study 1 so as not to be a source of bias/confounding factor.

The RFH Global Assessment Data Collection Form has been evaluated as a nutritional assessment method specifically for this patient population and encompasses measures of BMI, MAC, MAMC, triceps skinfold thickness (TSF) and hand-grip strength combined with details of dietary intake (208).

All patients in the LT waiting list are asked to keep a food diary and record everything they are eating, enabling the assessment of usual recent dietary intake at every dietitian appointment. At each dietitian assessment during the study, appetite was subjectively categorised as good, fair, or poor using this self-reported diet history. Assessment included quality and quantity of food and nutritional support supplements, dietary restrictions and barriers to eating, fluids, sodium in diet and the number and timing of meals. These data were used to provide an overall impression of the adequacy of the diet in relation to estimated daily requirements, for energy (35-40 kcal/kg/day) and protein (1.2-1.5 g/kg/day) (196, 232–234). Intakes were categorised as *adequate* if they met estimated requirements, *inadequate* if they did not meet estimated requirements but exceeded 500 kcal/d, or negligible if they provided fewer than 500 kcal/d (208)

As per the standard of care provided to all patients on the LT waiting list, practical dietary advice was then given to each participant. There was particular emphasis on an increase in protein intake (focused discussion on specific sources including animal protein (meat) and vegetable protein (beans, peas etc)), decreasing added salt (for example by avoiding pre-prepared, processed supermarket meals) and eating as many fruits and vegetables as possible. Given that frequent feeding can help prevent accelerated starvation and related proteolysis (188), patients were encouraged to split food into three main meals (breakfast, lunch and dinner) and 3 snacks (mid-morning, mid-afternoon and late evening). Particular emphasis was given to the late evening snack as this is a strategy for minimising nocturnal fasting. Eating an adequate number of calories and protein is more important than avoiding specific types of food, hence the need for a varied diet that the patient actually enjoys and will be sustainable was highlighted.

3.7.2 Anthropometric assessment

Height and weight were recorded at each assessment and an estimated dry weight was determined by the specialist LT dietitian using clinical assessment of oedema, previously documented weights, ascitic volumes removed at paracentesis and published guidelines (235). BMI was calculated from the estimated dry weight and height (208).

MAC and TSF were measured on the nondominant arm using Holtain/Tanner Whitehouse skinfold callipers (Holtain, Crymych, UK) and a tape measure. MAMC was then calculated as per the formula:

MAMC = MAC – (TSF x 0.3142) (236)

The average of 3 measurements was used. MAMC and TSF measurements were compared with published standards (237) and MAMC expressed in relation to the 5th percentile, for the appropriate age and gender category (208).

All measurements were made at baseline immediately prior to the first CPET and then repeated at week six before the CPET was performed.

3.8 Clinical data collection

Data, including patient demographics and the underlying disease types alongside laboratory results, were prospectively collected at the time of recruitment and baseline assessment. The MELD/UKELD scores were calculated at the time of recruitment as was length of time on the liver transplant waiting list.

At the time of transplant, donor variables required for calculating the donor risk index (DRI) (238), which is used as a metric for donor organ quality, were collated. Postoperative outcome measures including morbidity and intensive care and hospital length of stay were collected retrospectively.

3.9 Statistical Analysis

Statistics were calculated using IBM SPSS Statistics, Version 24.0. Armonk, NY: IBM Corp. Continuous data were examined for normality using the Shapiro-Wilk test. Continuous data are presented as median with interquartile range (IQR) or mean with standard deviation (SD)/ 95% confidence intervals (CI) for normally distributed data and categorical data as number (percentage). Mann-Whitney analyses for independent samples or Wilcoxon for dependent samples (continuous, non-normal distribution), *t* test analyses (continuous, normal distribution), and chi-square analyses (categorical) were used to compare the demographic and CPET variables of patients in both the exercise and control groups and are presented as absolute values (with percentage). Comparisons across grouped variables were made using analysis of variance (ANOVA) with Tukey's post-hoc test for comparisons of pairings within a group. All tests were two tailed, and significance was taken as $p<0.05$.

3.9.1 Sample size:

The primary outcome measure of this study was feasibility of the exercise intervention, therefore no sample size calculation was performed

3.10 Results

3.10.1 Feasibility outcome measures

3.10.1.1 Recruitment

A total of 140 patients were listed for liver transplantation over the study period, of which 61 met inclusion/exclusion criteria and were approached to take part in the study. Thirty-three patients were recruited (16 to the exercise and 17 to the control arm), representing a 54% recruitment rate (fig. 3-6). The predefined recruitment target of >50% of patients meeting eligibility criteria was met.

Twenty patients (61%) completed the initial six week study period (9 out of 16 in the exercise arm and 11 out of 17 in the control group). Of the 13 patients that did not complete this first six weeks, five were transplanted (38%), five deteriorated (38%), two (15.4%) were delisted and one patient withdrew from exercise sessions due to pre-existing knee pain (see figure 3-6 for study recruitment flow diagram). Causes of deterioration leading to study removal were obstructive cholangiopathy, pneumonia, fluid overload (n=2) and faecal impaction with need for hospitalisation. The reasons for delisting were new HCC (hepatocellular carcinoma) outside of transplant criteria and relapse of alcohol dependence.

Of the 20 patients completing the initial six weeks of the study, five (25%) failed to go on to complete the 12 week follow-up CPET; transplantation being the primary reason for this with three (60%) patients receiving an organ. One patient withdrew from the control arm as she did not want to do a third CPET and one patient in the control arm deteriorated due to profound decompensation of his cirrhotic liver disease necessitating hospitalisation.

No patients withdrew from the exercise arm of the study due to non-clinical reasons such as inconvenience or dislike of the exercise intervention.

3.10.1.2 Compliance with exercise sessions

A total of 240 training sessions over six weeks were available to the 16 recruited patients and 162 of these were attended (67.5%). The seven patients who were withdrawn from the exercise arm (after transplantation, deterioration or pre-existing knee pain) completed an average of 4.5 exercise sessions.

The pre-defined compliance target of >66% completed exercise sessions was met.

When considering the nine patients who finished the six week exercise intervention, compliance with the prescribed exercise training was high, with

127 out of the overall total of 135 individual exercise sessions available (94%) completed.

3.10.1.3 Safety

No adverse incidents related to exercise training were reported.

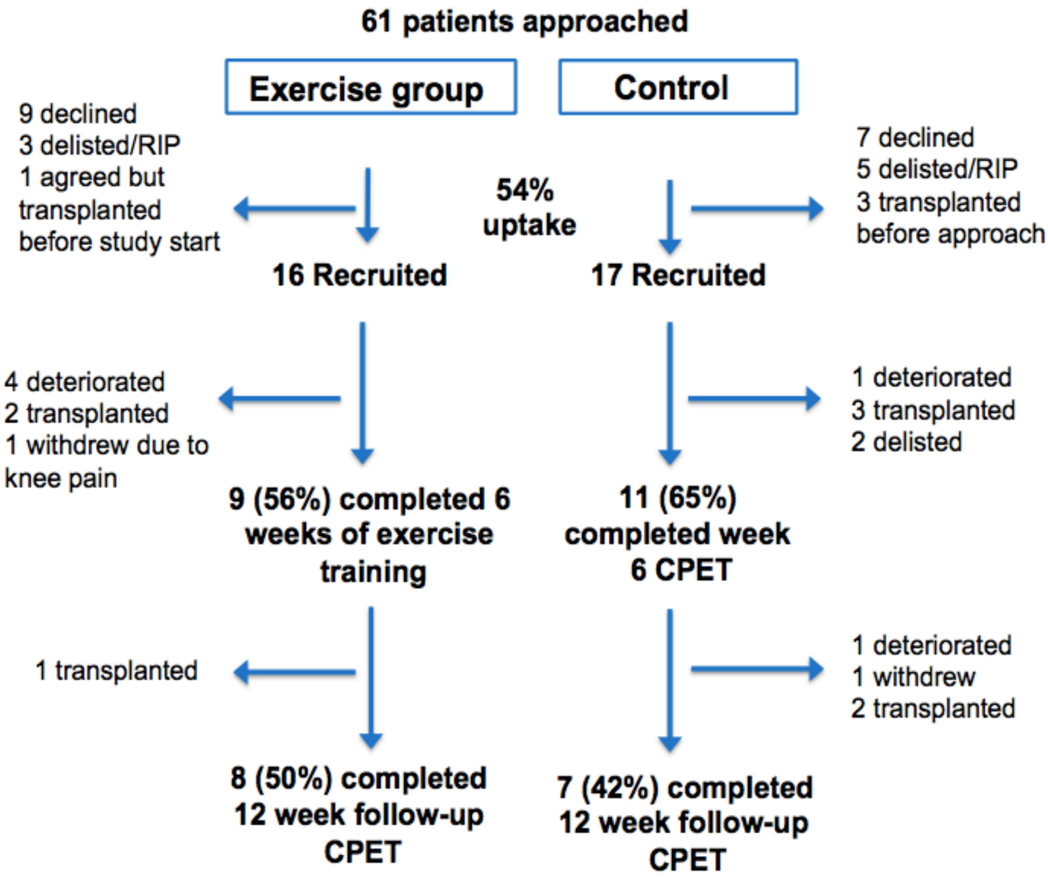


Figure 3-6 Study 1 patient recruitment and retention flow diagram

3.10.2 Demographic/baseline data

The baseline demographic data of all consenting patients are presented in table 3-6. There were no significant differences in baseline demographics and disease severity (in terms of MELD and UKELD scores) between groups. The majority of patients (n=25, 75%) recruited required regular diuretics to control the formation of ascites and of these, six patients underwent regular paracentesis for diuretic-resistant ascites. The use of non-cardioselective β-blockade, predominantly propranolol and carvedilol, recommended for primary prophylaxis of variceal haemorrhage in cirrhosis (239) was seen in 19 patients (57.6%).

There was a higher proportion of diuretic use in the exercise group (94% vs 59%) and the incidence of diuretic-resistant ascites (hence the need for regular paracentesis) was higher in the exercise group (25% vs 12%).

The mean (SD) haemoglobin in the exercise group was 108.6 (20.8) g/l versus 117.6 (19.8) g/l in controls (p=0.21). Baseline laboratory values are shown in table 3-7; no significant differences in albumin, sodium, creatinine, bilirubin or international normalised ratio (INR) values between groups were found.

	Exercise (n=16)	**Usual care (n=17)**
Age (years) Mean (CI)	**55.6** (51.4-59.8)	**55.6** (51.6-59.7)
Sex No. (%) female	**2** (12.5)	**3** (17.6)
MELD Mean (CI)	**13.7** (11.2-16.1)	**13.2** (11.3-15.1)
UKELD Mean (CI)	**52.9** (51.5-54.4)	**52.2** (50.6-52.0)
Use of diuretics No. (%)	**15** (93.8)	**10** (58.8)
Diuretic-resistant ascites No. (%)	**4** (25.0)	**2** (11.8)
Use of β blockers No. (%)	**10** (62.5%)	**9** (52.9%)
DASI Median (IQR[range])	**43.5** (32[18-58])	**36.7** (23[19.9-58])
METS Median (IQR[range])	**8.1** (3.9[5-10])	**7.3** (2.8[5-10])
Aetiology: • **Alcohol related** No. (%)	**6** (37.5)	**6** (35.3)
• **Viral hepatitis** No. (%)	**5** (31.3)	**1** (5.9%)
• **NASH** No. (%)	**2** (12.5)	**3** (17.6)
• **Cholestasis** No. (%)	**3** (18.7)	**6** (35.3)
• **Autoimmune hepatitis** No. (%)	**0**	**1** (5.9)

Table 3-6 Baseline demographic, clinical and physiological data of the two patient cohorts

	Exercise (n=16)	**Usual care (n=17)**	**p-value**
Haemoglobin (g/l) Mean (SD)	**108.6** (20.8)	**117.6** (19.8)	0.21
Albumin (g/l) Mean (SD)	**33.4** (6.5)	**33.7** (5.4)	0.70
Sodium (mmol/l) Mean (SD)	**136.7** (4.3)	**137.8** (3.6)	0.41
Creatinine Mean (**SD**)	**78.3** (18.1)	**77.7** (17.1)	0.93
Bilirubin Median (IQR)	**27.5** (26.3)	**44** (38)	0.55
International normalised ratio Median (IQR)	**1.3** (0.18)	**1.2** (0.15)	0.38

Table 3-7 laboratory data of all recruited patients at baseline

3.10.3 Cardiopulmonary exercise test data

CPET measures at baseline and at weeks six and 12 are displayed in table 3-8. The mean (SD) predicted VO_2 peak at baseline was 65% (±9.5) of expected in the exercise group and 69% (±15.7) in the controls. This predicted value is calculated using patient gender, age and height and is a formula used in the clinical interpretation of CPETs (table 2-3).

There was an increase in VO_2 peak in the exercise group from a mean (SD) of 16.2 (± 3.4) ml/kg/min at baseline rising to 18.5 (±4.6) ml/kg/min at week six (p=0.02). Patients were also able to generate more power on the ergometer with peak workload rising from a mean (SD) of 117 (±26) W at baseline to 134 (±26) W at week six (p=0.006). However, by week 12 (six weeks after exercise cessation) the mean VO_2 peak reduced to 17.4 (±3.0) ml/kg/min (p=0.15).

In the control group, mean (SD) VO_2 peak decreased from 19.0 (± 6.1) ml/kg/min at baseline, to 17.1 (±6.0) at week six (p=0.03). Mean AT at baseline was 13.0 (±3.5) ml/kg/min and 11.8 (±3.2) ml/kg/min at week six (p=0.25). Peak power generated on the ergometer decreased from 128 (±51) W at baseline to 114 (±53) W at week six (p=0.07). Figure 3-7 illustrates the change in AT and peak across both intervention and comparator groups at baseline, weeks 6 and 12.

Haemoglobin concentration did not change significantly for individuals in both groups across the study period. Of the nine patients completing the exercise intervention, mean (SD) haemoglobin at baseline was 114 (19.5)g/l and 112 (13.7)g/l at week six (p=0.32). The 11 control participants completing the week six CPET had a mean (SD) haemoglobin at baseline of 123 (20.1)g/l and 118 (24.4)g/l at week six (p=0.08).

There was no significant relationship between baseline haemoglobin, age, UKELD or MELD when correlated against change in VO_2 peak and AT from baseline to week six.

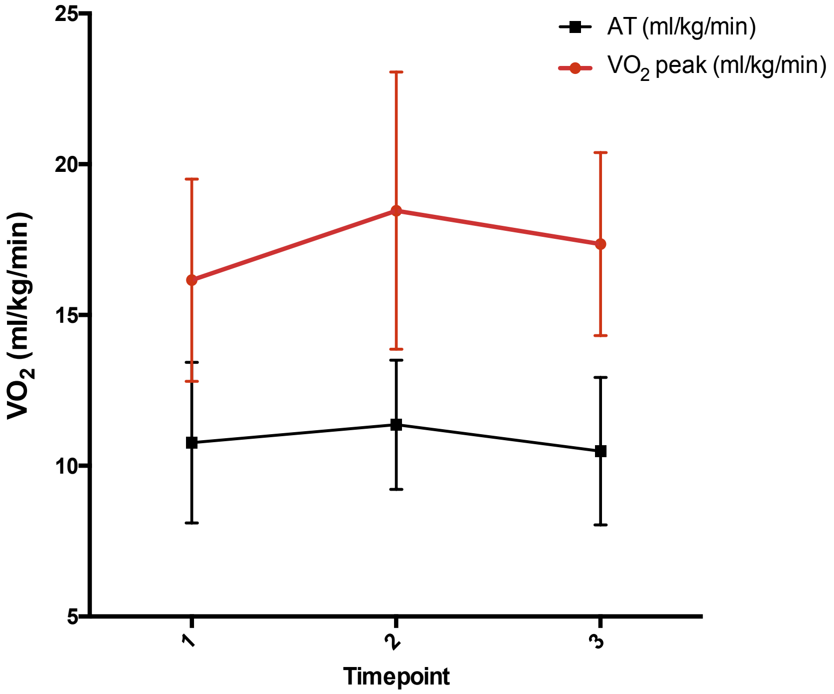
As regards the specific ventilatory CPET measures, there was a significant increase in mean (SD) VE/VCO_2 (ratio of ventilation to CO_2 output) at VO_2 at AT in the control group, rising from a baseline value of 30.9 (4.0) to 33.6 (4.5) at week six (p=0.002). There were no significant changes in ventilatory efficiency across the study period in the exercise group.

	Exercise group (n=9)			Usual care (n=11)		
	Wk 0	**Wk 6**	**Wk 12**	**Wk 0**	**Wk 6**	**Wk 12**
Weight (kg) Mean (SD)	**99.9** (23.8)	**101.8** (23.6)	**100.6** (23.9)	**84.0** (20.2)	**85.9** (19.9)	**86.1** (14.8)
VO_2 at AT (ml/kg/min)♯ Mean (SD)	**10.9** (2.6)	**11.4** (2.1)	**10.5** (2.4)	**13.0** (3.5)	**11.8** (3.2)	**12.6** (2.7)
VO_2 at AT (L/min) Mean (SD)	**1.07** (0.3)	**1.14** (0.3)	**1.02** (0.2)	**1.07** (0.3)	**1.04** (0.3)	**1.02** (0.3)
VO_2 at peak (ml/kg/min)♯ Mean (SD)	**16.2** (3.4)	**18.5** (4.6)*	**17.4** (3.0)	**19.0** (6.1)	**17.1** (6.0)*	**18.4** (7.4)
VO_2 at peak (L/min) Median (IQR)	**1.38** (0.61)	**1.71** (0.89)*	**1.79** (0.56)	**1.53** (0.97)	**1.32** (0.80)*	**1.57** (0.56)
% predicted VO_2 peak Mean (SD)	**65.4** (9.5)	**74.6** (24.5)*	**67.9** (11.0)	**69.1** (15.7)	**61.0** (12.9)*	**60.7** (22.0)
O_2 pulse at peak Median (IQR)	**11** (8)	**14.1** (8.3)	**13.3** (5.7)	**13.7** (6.2)	**12.5** (6.2)	**13.3** (9)
% predicted O_2 pulse Median (IQR)	**80** (26.5)	**101.5** (51)	**83** (20.3)	**98** (25.3)	**86** (29)	**74** (33)
VE/VCO_2 at AT Mean (SD)	**32.8** (4.5)	**34.2** (4.4)	**34.5** (4.0)	**30.9** (4.0)	**33.6** (4.5)*	**32.9** (4.1)
Maximum heart rate (bpm) Mean (SD)	**124** (24)	**128** (20)	**131** (10)	**121** (19.9)	**114** (23)	**122** (12)
Peak workload (W) Mean (SD)	**117** (26)	**134** (26)*	**134** (25)	**128** (51)	**114** (53)	**127** (57)
Haemoglobin (g/L) Mean (SD)	**114.6** (19.5)	**112.3** (13.7)	**108** (14.4)	**125.1** (19.9)	**117.7** (24.4)	**125.0** (22.0)

Table 3-8 CPET measures at baseline week six and week 12 in both cohorts. AT = anaerobic threshold, VO_2 peak = peak oxygen consumption, VE/VCO_2= ratio of ventilation to carbon dioxide output.

* Denotes a significant difference from baseline (p= <0.05).

♯ dry body weight was used for ascitic patients a)



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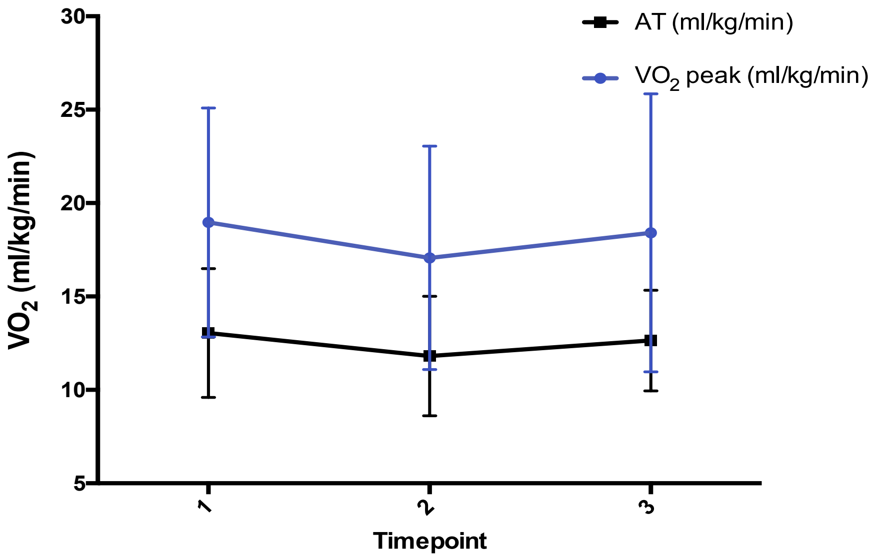


Figure 3-7 CPET measures
Timepoints 1 = baseline, 2 = week six, 3 = week 12

a) *Exercise group:* mean (SD) serial VO_2 at AT and peak (ml/kg/min) at baseline and weeks six and 12 (n=9)

b) *Usual care group:* mean (SD) serial VO_2 at AT and peak (ml/kg/min) at baseline and weeks six and 12 (n=11)

3.10.4 Inter-rater variability in anaerobic threshold reporting

Figure 3-8 shows a Bland-Altman plot illustrating the inter-rater variability in anaerobic threshold interpretation for baseline, week 6 and week 12 CPETs.

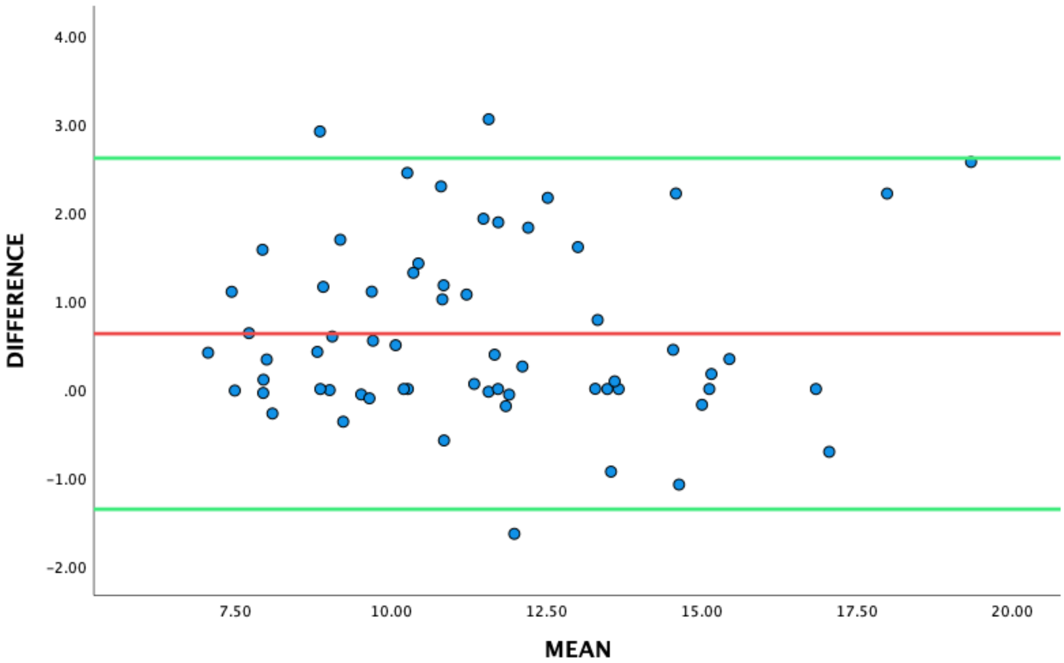


Figure 3-8 Bland-Altman plot displaying observer variability in reporting of anaerobic threshold

Red line: mean inter-rater difference (0.63)

Green lines: upper and lower 95% confidence intervals (2.61, -1.36)

There was no significant linear relationship between inter-rater difference and mean AT ($p=0.93$) confirming that there was no proportional bias.

3.10.5 Nutritional assessment

The anthropometric measures (as per the RFH global assessment tool) at baseline and week six assessments, are displayed in table 3-9. There is baseline imbalance apparent between groups; intervention patients have a higher BMI (30.9 vs 27) and greater MAMC and MAC at baseline than controls. There was no overall change in BMI (dry weight) in either group across the study period. An increase in mean (SD) handgrip strength from 26.4 (±7.5) kg at baseline to 29.4 (±6.4) kg at week six was observed in the exercise group (p=0.05), whilst handgrip in the control group was 29.1 (±10.7) kg at baseline and 30.5 (±13) kg at week six (p=0.80). There was no change in MAC over the six-week study period in either group. The mean (SD) MAMC in the exercise group was 29.5 (±5.9) cm at baseline and 28.9 (±4.5) cm after six weeks of training (p=0.6), indicating no difference in mid arm muscle mass across the study period. The mean (SD) MAMC in the control group also did not change significantly with values of 24.2 (±3.3) cm at baseline and 23.5 (±3.7) cm at week six (p=0.16).

	Exercise (n=9)			**Usual care (n=11)**		
	Wk 0	**Wk 6**	**P Value**	**Wk 0**	**Wk 6**	**P Value**
BMI (dry weight) Mean (SD)	**30.9** (5.6)	**31.1** (5.5)	0.38	**27** (4.6)	**26.9** (3.8)	0.86
Handgrip (kg) Mean (SD)	**26.4** (7.5)	**29.4** (6.4)	0.05	**29.1** (10.7)	**30.5** (13)	0.80
MAC (cm) Mean (SD)	**35.4** (7)	**35.7** (6.9)	0.59	**30.2** (3.7)	**30** (3.5)	0.75
MAMC (cm) Mean (SD)	**29.5** (5.9)	**28.9** (4.5)	0.60	**24.2** (3.3)	**23.5** (3.7)	0.16
TSF (cm) Mean (SD)	**18.8** (10.6)	**21.5** (9.8)	0.27	**18.4** (9.2)	**22.5** (11.2)	0.21

Table 3-9 anthropometric parameters at baseline and week six in both the exercise and control groups.

BMI = body mass index, MAC = mid-arm circumference, MAMC = mid-arm muscle circumference, TSF = triceps skinfold thickness

3.10.6 Operative and postoperative data

Of the 20 patients that completed the six week study period, 16 had received their liver transplants with one patient still on the waiting list one year after the end of the study. Two patients (one in the exercise and one in the control group) were delisted as they clinically improved hence no longer met transplantation criteria and one control patient went on to be delisted due to profound decompensation and deterioration. The mean time to transplant with respect to completion of the six-week exercise training period was 165 (118) days in the exercise group and 192 (211) days in the controls. There were no significant differences in donor liver quality as assessed by the donor risk index (DRI) (238) in either group (table 3-10).

Post-transplant outcome data are presented in table 3-10. There were no deaths in the postoperative period and indeed up until six months after transplantation in either group. The median (IQR) hospital length of stay for the index transplant admission in the exercise group was 13 (6) days and 30 (13) days in the control group, a difference of 17 days (p=0.02).

Postoperative complications were scored as per the Clavien-Dindo (CD) classification (240, 241). The grade of most severe complication at 30 days was a median of 3a in both groups. Acute kidney injury (AKI) was the most frequent complication, with a total of six patients (three patients in both exercise and control groups, 43% and 33% respectively) requiring renal replacement therapy on the ICU postoperatively. Other complications included hospital acquired pneumonia (one control group patient requiring re-intubation), sepsis necessitating prolonged intubation, wound infections/collections requiring drainage and acute rejection. One patient in the exercise group developed a pulmonary embolus without haemodynamic compromise.

	Exercise (n=7)	Usual care (n=9)	P=value
Donor risk index Mean (SD)	**1.5** (0.34)	**1.62** (0.26)	0.24
Duration of ICU stay (days) Median (IQR)	**2** (4)	**4** (5.5)	0.77
Hospital length of stay (days) Median (IQR)	**13** (6)	**30** (13)	0.02
6 month survival Number (%)	**7** (100)	**9** (100)	
Clavien-Dindo grade Median (range)	**3a** (1-4b)	**3a** (1-4b)	
Number (%) of patients with CD grade 2 or more complications	**5** (71)	**8** (89)	

Table 3-10 Post transplant clinical data

3.10.7 Physical activity enjoyment

The PAES questionnaire was completed at the end of the third week of exercise training by patients in the intervention group. Of the 11 patients completing 3 weeks of exercise training, the mean (SD) physical activity enjoyment scale score was 94.6 (13.9), out of a maximum of 126.

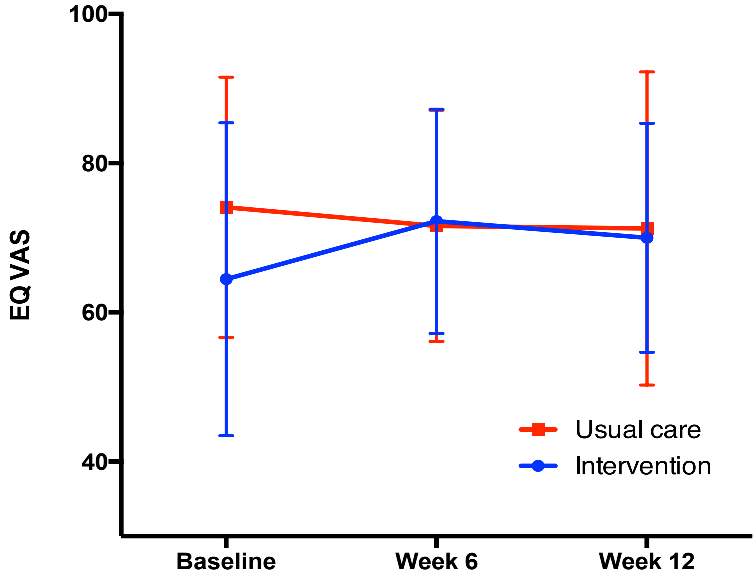
3.10.8 Health-related quality of life assessment: EQ-5D-5L

Health-related quality of life measures as assessed by the EQ-5D-5L self-reported measure at baseline, week six and week 12, for both the EQ-VAS and index values are shown in table 3-11. Responses to the question ‘we would like to know how good or bad your health is TODAY’ on the 0-100 EQ-VAS, returned higher mean (SD) values at baseline in the control group (74.1 (±17.4) vs 64.4 (±21.0)). The EQ-VAS responses in the control group essentially remained the same at weeks six and 12. Mean (SD) EQ-VAS responses in the exercise group were 64.4 (±21) at baseline and 72.2 (±15.0) after six weeks of exercise (p=0.14). The EQ-5D-5L index values followed almost identical trends with control responses remaining the same over the 12-week study period. Median (IQR) exercise group index values were 0.78 (±0.25) at baseline, rising to 0.87 (0.12) at the end of the exercise programme (p=0.40). Figure 3-9 illustrates EQ-VAS responses and index values for both intervention and comparator groups at baseline, weeks 6 and 12.

	Exercise (n=9)			**Usual care (n=11)**		
	Wk 0	**Wk 6**	**Wk 12**	**Wk 0**	**Wk 6**	**Wk 12**
EQ VAS Mean (SD)	**64.4** (21.0)	**72.2** (15.0)	**70** (15.4)	**74.1** (17.4)	**71.6** (15.5)	**71.3** (21.0)
EQ-5D-5L index values Median (IQR)	**0.78** (0.25)	**0.87** (0.12)	**0.82** (0.37)	**0.89** (0.16)	**0.88** (0.14)	**0.86** (0.20)

Table 3-11 EQ VAS self-rating and EQ-5D-5L index values

No significant differences between time points for either cohort a)



b)

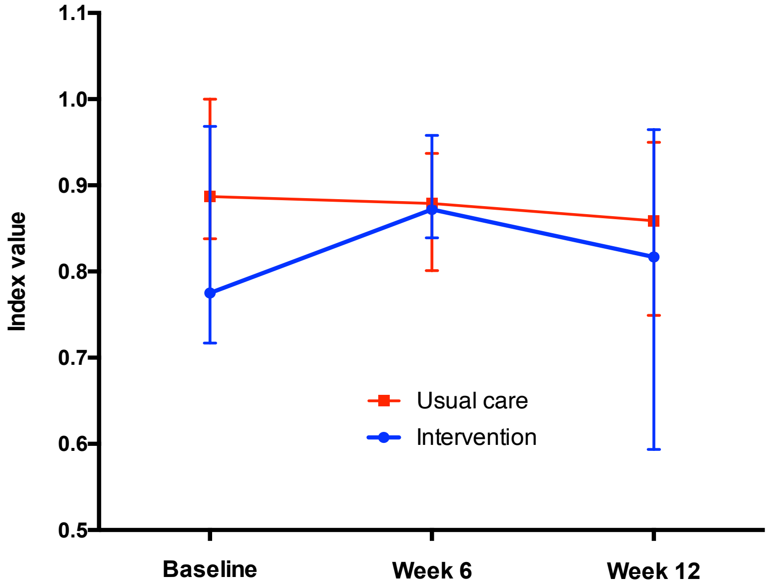


Figure 3-9 EQ-5D-5L index values and VAS data for both intervention and usual care groups

a) Mean (SD) EQ-VAS data at baseline and weeks 6 and 12

b) Median (IQR) EQ-5D-5L index values at baseline and weeks six and 12

3.11 Discussion

3.11.1 Feasibility and safety

This study demonstrated that it was safe and feasible to engage patients with decompensated cirrhotic liver disease awaiting LT surgery in an intense, supervised exercise programme comprised of three sessions a week in a hospital outpatient clinic for a total of six weeks.

Feasibility and acceptability outcomes were pre-defined as:

a. Absence of exercise-related serious adverse events
b. Recruitment: >50% recruitment of patients meeting eligibility criteria
c. Compliance with exercise: >66% exercise sessions completed

No serious adverse events related to the exercise programme were observed both during the intervention and in the following six weeks. There were no adverse events specifically related to CPET testing in either group. A recruitment rate of 54% (as per figure 3-8) was demonstrated, meeting the pre-determined threshold of > 50%. These recruitment rates are consistent with recent literature reporting exercise training in cirrhotic liver disease (223, 242).

The >66% threshold for compliance with the prescribed exercise training was fulfilled, with 162 sessions attended out of a total of 240 sessions available to the 16 recruited intervention patients (67.5%). When specifically considering the 9 patients finishing the six week exercise programme, 127 out of the overall total of 135 exercise sessions (94%) were completed. No patients withdrew from the exercise arm of the study due to non-clinical reasons such as inconvenience or dislike of the exercise intervention.

Patients were allocated to the exercise group based on the distance they lived from the hospital; it is perfectly reasonable to assume that compliance would be far less were patients to have lived further away. One of the main reasons

79 out of 140 patients listed for LT during the study period did not meet inclusion/exclusion criteria was geographical – they lived outside the London area and received care whilst on the waiting list in satellite clinics as far away as Portsmouth and Bristol. Given that many patients awaiting LT nationally live a substantial distance from their transplant centre, an in-hospital exercise intervention may not be appropriate for all of them due to the logistics of travel. Supervised hospital-based exercise is also resource intensive, particularly in terms of staff time and input. So, whilst an in-hospital approach to exercise is feasible, it is not pragmatic and exploring home- and community-based exercise approaches should be explored in the LT cohort.

Even though the recruitment target was achieved, the final sample for analysis was diminished by the fact that 8/33 patients underwent LT between the initial CPET and completion of the week 12 CPET. This finding is important for informing the sample size calculations of future RCTs and also highlights the potential need to investigate the efficacy of exercise training at the point of entry onto the LT waiting list, rather than recruiting those well-established on the waiting list.

3.11.2 Differences in exercise capacity between both groups

This study was not designed or powered to detect differences in secondary outcomes. It is also important to bear in mind the high risk of false positives with multiple variables being analysed in a small cohort. I did observe an increase in VO_2 peak in patients who underwent the exercise programme, which declined six weeks after cessation of the programme. This suggests exercise has the potential to improve aerobic fitness but that this gain is lost and deconditioning occurs once exercise stops. I would hence propose that future trials incorporate a design that allow exercise to be continued up until the point of surgery, with the hypothesis that continuing exercise may lead to further improvements in exercise capacity.

A decline in VO_2 peak was observed in a matched control group, suggesting that this patient group becomes progressively more unfit over time, probably as a result of their underlying disease and lack of exercise. Serial MELD calculations throughout the study period would have provided evidence for deterioration in liver disease and should be considered as an addition to future research in this field.

The increase in VO_2peak that resulted from the exercise intervention demonstrated in this study, is supported by other research. A recent pilot study by Zenith et al. showed an increase in VO_2peak following eight weeks of exercise in patients with compensated cirrhosis, compared to a matched control group (223). A further 2015 pilot study confirmed that an increase in VO_2peak was observed after 12 weeks of adapted physical activity (APA) in patients awaiting LT, however, this study did not involve a control group for comparison (229). Roman et al. 2016 reported an increase in VO_2peak that did not reach statistical significance following a 12-week exercise programme (224). There are, however, intrinsic issues surrounding the use of VO_2peak data. This value is the point of maximal *volitional* work rate and hence is influenced by factors impacting patient effort and motivation including lack of sleep, boredom/mood and time pressures (i.e., desire to complete a test to catch a train), raising some concerns in relation to repeatability in patient groups. Despite this concern, studies have previously confirmed the highly reproducible nature of VO_2peak on repeated CPETs pre- and post- training in adults (243), however a learning effect is possible with sequential testing and this should be considered, but very difficult to measure and account for. In contrast, AT measurement is independent of subject motivation and can be safely achieved during sub-maximal exercise.

No difference in AT was observed across the study period in either group. A signal towards a decrease in AT between weeks one and six was demonstrated in the control group with a mean baseline value for VO_2 at AT of 13.0 (±3.5) ml/kg/min and 11.8 (±3.2) ml/kg/min at week six ($p=0.25$). This fits with the pattern observed with VO_2peak and progressive deconditioning in the absence of exercise. Previous studies reporting the impact of exercise training on CPET variables in patients with cirrhosis, have not reported AT data.

As regards inter-rater variability in the interpretation of AT as described by the Bland Altman plot (fig 3-8), no proportional bias was demonstrated. The mean inter-rater difference was 0.6 which is a small difference, unlikely to have a significant clinical impact. The degree of data spread around the mean is minimal and is put into context when compared to published work. Abott et al (2018) described inter-rater reliability of preoperative CPET interpretation in a cross-sectional study of 28 observers (244). Different statistics were used in this paper, indeed inter-rater reliability was measured using intra-class correlation coefficients. On inspection of their published plots, the spread of data as regards the interpretation of AT in particular appears greater than that reported here.

Ultimately, it was not possible to demonstrate a meaningful improvement in exercise capacity with this exercise intervention in the context of such a small sample size. Further investigation is required to establish the impact of exercise training on CPET measures (in particular the AT) in patients with decompensated cirrhosis awaiting LT.

The high patient drop-out rate after week six in the control group introduces bias and greatly limits the ability to interpret and make conclusions based on 12 week CPET data. The patients that left the study early due to deterioration and transplantation generally had lower VO_2 at AT and peak at baseline and week six, meaning the apparent increase in both values at week 12 are difficult to interpret.

A significant increase in mean (SD) VE/VCO_2 at VO_2 at AT in the control group was demonstrated, rising from a baseline value of 30.9 (4.0) to 33.6 (4.5) at week six (p=0.002). There were no significant changes in ventilatory efficiency across the study period in the exercise group. This control group finding is very difficult to explain; implying improved ventilatory efficiency without intervention and is not consistent with the cardiovascular CPET data. Given that this study was not powered to detect a difference in physiological outcomes, false positives are likely and caution should be exercised when interpreting the data.

It is important to note that both study cohorts were anaemic at baseline; the mean (SD) haemoglobin in the exercise group was 108.6 (20.8) g/l versus 117.6 (19.8) g/l in controls (p=0.21). This factor alone has been shown to contribute to impaired physical performance through a reduction in oxygen-carrying capacity.

3.11.3 Differences in anthropometric measures

There was a trend towards improvement in handgrip strength in the exercise group after six weeks of training, suggesting that lower limb exercise may have a systemic impact, potentially increasing strength in the arms. Handgrip strength has previously been shown to be a strong predictor of overall muscle mass (245). However, no corresponding increase in mid arm muscle mass was demonstrated and indeed TSF measurements indicate a trend towards an increase in subcutaneous fat in the exercise group after six weeks of training. Whilst skeletal muscle evaluation provides an objective means to determine nutritional status in patients with ESLD, the collection of anthropometric data is subject to measurement error which may play a pivotal role in both assessment and interpretation of nutritional status. Indeed, observer error resulting in imprecision is recognised as a source of error in the nutritional literature (246). Skinfold thicknesses in particular are difficult measurements to make with precision and accuracy without rigorous training and even then can be prone to large variations. I aimed to reduce observer error by taking the average of three readings for each measurement. The same experienced but unblinded observer was responsible for every anthropometric assessment on all 33 patients ensuring consistency in measurement technique, but potentially introducing bias given the need for repeated measurements.

It is also important to take into consideration the fact that the groups did not appear to be balanced in terms of baseline anthropometric data; patients in the exercise group were heavier at baseline with larger arm circumference and stronger handgrip. This is a likely consequence of the cohort matching design (anthropometric measures were not used in cohort grouping) or insufficient sample size for statistical comparison. Given that this study was not powered to detect differences in anthropometric data, no firm conclusions can be drawn from these data.

Muscle ultrasound to specifically measure lower limb muscle thickness was considered as an additional assessment of body composition and impact of exercise, however due to logistics, financial constraints and clinical commitments of colleagues with the relevant expertise, I decided not to include this in the study protocol, Other more reliable and accurate means of body composition assessment such as cross-sectional imaging, DEXA (dual energy x-ray absorptiometry) or under water/hydrostatic weighing should be considered for appropriately funded future research.

3.11.4 Differences in enjoyment and HRQL between groups

This study demonstrated that it was feasible to motivate patients to attend hospital three times a week and participate in an aerobic exercise training programme whilst awaiting LT. The high PAES result indicates a positive signal towards overall patient enjoyment of the exercise modality and the programme itself.

No significant benefit to psychological health in terms of HRQL as assessed by the EQ-5D-5L was demonstrated. Both the self-reported EQ-VAS and the population-generalisable EQ-5D-5L index value, showed almost identical trends with values rising after six weeks of exercise and then falling back towards baseline by week 12. Values in the control group did not change across the 12 week study period.

There was baseline imbalance between groups given that both EQ-VAS and EQ-5D-5L scores were higher at baseline in the standard care group. This baseline imbalance is likely to be a consequence of the cohort matching process; the absence of formal randomisation allows unmeasured confounding variables to bias the data.

Whilst conclusions cannot be drawn from this underpowered data, it is important to consider the possibility that the generic EQ-5D-5L measure may not be a clinically meaningful test in this complex cohort of patients.

3.11.5 Training regimen and patient feedback

Informal feedback was obtained from patients during an evening focus group/patient and public involvement (PPI) group. This evening meeting was carried out after completion of the study and was designed to stimulate discussion regarding future LT prehabilitation research and understand the needs of this particular patient group on the LT waiting list. This focus group involved 12 of the 20 patients (60%) completing the six week study period (both intervention and control participants).

Patients were asked specifically about ‘motivators to exercise’ and participants from both intervention and control groups said that whilst awaiting LT, it was motivating to set themselves a weekly challenge and then strive to beat it. Exercise group participants also commented that having structure, targets and regular contact with the study team was motivating. There was also specific feedback from patients that being educated about exercise and really understanding how exercise helps with postoperative recovery was reported to be motivating. Of note, four patients had enrolled in a local gym following completion of the study period as they were motivated to continue exercising having perceived real personal benefit.

A particular focus of this meeting was a discussion around the barriers to sustainable activity change; also, to appreciate what patients considered to be the benefits of exercise personally. Several patients discussed the role of pre-existing sedentary lifestyle as a mental barrier to exercise and it was also clear that distance to travel into hospital for supervised exercise had been an issue for several patients. As regards the perceived benefits for individuals, a few patients noticed an improvement in their cognitive function (a lifting of the 'brain fog' as described by one gentleman) and patients also felt that they felt tougher mentally and physically, which was something they had only been able to appreciate retrospectively, having now recovered following LT.

Overall, patients felt challenged by the exercise programme and considered that the design provided the right level of physical exertion for them personally. No one commented that the sessions were too easy, confirming that the training programme was appropriate for this population. The informal feedback was very positive and suggested that I had begun to take steps towards changing attitudes and perceptions around exercise.

As regards future research in this field, all patients felt exercise was important and further research should be pursued. The concept of randomisation was put forward and patients said they would be willing to be randomised into control vs intervention groups.

3.11.6 Study limitations

This study has a number of major methodological limitations: participants were not randomised, there was no observer blinding and the sample size was not powered to detect differences in physiological or postoperative outcomes. All these factors increase the chance of confounding and a type 2 error in the presented data.

This matched cohort trial design is not without challenges. There is potential for selection bias intrinsic in a matched cohort methodology; indeed, motivated, fitter patients are more likely to consent to take part and comply with training sessions. A geographical bias was also introduced by using the distance lived from the RFH as a criterion for study eligibility and group allocation. Baseline differences in groups are likely without formal randomisation.

I recognise that a randomised trial design would have been optimal to address the question of feasibility and inform powering of a large, definitive study. The main reason for not utilising an RCT approach was an inability to secure adequate funding. Nevertheless, this work has gone on to form the basis of a successful grant application to run a large multi-centre RCT as discussed further in chapter 5. Having highlighted the limitations as regards logistics and intervention delivery with hospital-based exercise, the future ExaLT (Home-based EXercise and motivAtional programme before and after Liver Transplantation) trial will utilise a home-based approach to exercise in patients awaiting LT.

Whilst safety and feasibility are demonstrated, the notable drop-out rate of participants, with 13 patients (39.4%) in total (seven in exercise and six in control) failing to complete the six week study period, is a significant issue. Five of these patients were transplanted shortly after recruitment, which is an inherent, unpredictable risk specific to the study population. Likewise, attrition due to patient medical deterioration is also not an unexpected finding given the comorbid nature of the cohort. The design and powering of a future RCT would crucially need to take into account the proportion of patients expected to be transplanted or die/be removed from waiting list prior to completion of the exercise training programme. One way of addressing this is to aim to recruit patients at entry to the LT waiting list, rather than patients who have been listed for many months.

When considering drop-outs, it is important to note that no patients in the exercise cohort dropped out because they were physically or logistically unable to complete the programme. This demonstrates that the amount of exercise prescribed was tolerable to all patients.

The reporting of postoperative outcomes in an underpowered study is also a limitation and caution with interpretation of results should also be exercised. It is likely that none of the clinical end points will be altered with any single intervention in the context of such a small sample size. Also importantly, postoperative outcomes following LT are highly multifactorial. Future research should be appropriately powered. A 17 day difference in hospital length of stay between exercise and control groups (median stays of 13 and 30 days respectively) was demonstrated in this study. For comparison, a 2016 study reported a UK average hospital length of stay of 24.8 days (95%CI: 24.2 to 25.5) in a series of 3772 adult patients (247). Attributing this significant reduction to preoperative exercise in the context of an inadequately powered trial would be inappropriate, particularly given the lag time from completion of exercise to transplantation. A difference in hospital length of stay of the magnitude seen here is highly unlikely to be attributable to our intervention and may be a consequence of biased group assignment. Despite attempts to match groups, there may be other significant baseline differences unaccounted for in the cohort allocation process. However, the difference in length of stay is a promising association that merits further research.

3.11.7 Strengths and weaknesses in relation to other studies

Existing liver transplant literature demonstrates consistently that malnutrition adversely impacts upon post-transplant morbidity and mortality (196, 248–250); and a clear association between low cardiopulmonary reserve and 90-day post-transplant mortality has been shown (129). To date, evidence for preoperative exercise in patients with cirrhosis awaiting LT is extremely limited, inadequately powered to detect improvements in markers of physical fitness or postoperative outcomes and lacking nutritional intervention or standardisation (229, 242). This present feasibility study, whilst also underpowered, demonstrates that a preoperative exercise training programme alongside structured nutritional advice is feasible and may aid in improving certain markers of cardiopulmonary fitness. It follows that close attention to nutrition and physical optimisation on the liver transplant waiting list may translate into improved postoperative outcomes and hence prehabilitation for patients awaiting LT is an important ongoing research target. Our collaborative interdisciplinary approach sets a precedent for future studies to build upon and a multi-centre study to assess efficacy is now required.

4 Study 2: *The feasibility of an outpatient, hospital-based exercise training programme for patients awaiting complex fenestrated endovascular aortic aneurysm repair at the RFH*

4.1 Introduction

4.1.1 Abdominal aortic aneurysms

An AAA is defined as a full thickness dilatation of the abdominal aortic diameter of ≥ x1.5; in men, this is taken to mean 3 cm or greater (251). They are found in 5.0–7.5% of men and 1.5–3.0% of women aged 65 years or over (252). Across the UK more than 4000 AAA repairs were performed in 2017 (253). AAAs usually remain asymptomatic until they rupture, which can result in catastrophic haemorrhage and a substantial mortality rate (up to 80%) (136). Risk factors for AAAs include increasing age, male sex, smoking, and low HDL-cholesterol levels. Familial associations exist and although susceptibility genes have been described, robust genetic studies have failed to discover causative gene mutations.

The risk of AAA rupture increases with increasing aneurysm diameter (fig 4-1), reaching around 30% for AAA >7 cm in diameter. The NHS has run a AAA screening programme for men aged 65 years since 2009 (254) which aims to detect aneurysms before they become symptomatic and rupture, given that elective open surgical or endovascular repair is the most effective treatment for preventing aneurysm-related rupture and death. However, elective AAA repair is also responsible for more perioperative deaths than any other general or vascular surgical procedure (255).

The UK's National Institute of Clinical Excellence (NICE) 2020 guidelines for the diagnosis and management of abdominal aortic aneurysms (256) stipulate that elective AAA repair should be considered if the aneurysm is:

- symptomatic

- asymptomatic and 5.5 cm or larger
- asymptomatic, larger than 4.0 cm and has grown by more than 1 cm in 1 year.

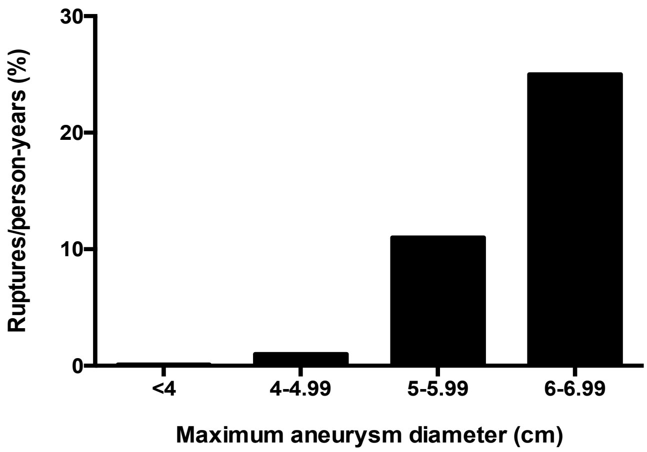


Figure 4-1 Risk of AAA rupture per year based on size at latest ultrasound

Data derived from: Reed et al. 1997 (257)

Aneurysms can occur at various locations along the aorta. The term 'complex aneurysm' refers to those occurring above or around the origins of the renal arteries.

4.1.2 Complex endovascular AAA repair

Open surgical repair was first reported in 1962 and remains the treatment with the best long-term results. However, open surgical repair is unsuitable for some people with an unruptured AAA because of their anaesthetic risk and/or medical comorbidities. The surgical management of AAAs has been revolutionised by minimally invasive endovascular repair (136). Three principal randomised controlled trials for AAA (258–260) have demonstrated reduced 30-day mortality in patients undergoing EVAR compared to open surgical repair. However, the longer-term advantages are not so clear as EVAR is associated with more frequent complications which may necessitate further procedures. Indeed, the total mortality benefit demonstrated in these randomised trials was lost (catch-up mortality) after 2-5 post-operative years (261, 262). EVAR also has higher net costs than open repair.

Endovascular procedures are increasingly being performed instead of open surgery for complex aneurysm repair thanks to advancing endovascular technology, the most common of which are (134):

- Fenestrated EVAR (FEVAR): a graft that has fenestrations to allow the passage of blood vessels from the aorta
- Branched EVAR (BEVAR): separate grafts are deployed on each blood vessel after the main graft is fitted
- Thoracic endovascular aneurysm repair (TEVAR)

Collectively these procedures are known as 'complex endovascular repairs'.

The access sites are the two femoral arteries (fig 4-2) and the procedure can be performed under either general or regional anaesthesia depending on aneurysm morphology and certain patient factors (including the ability to lie still).

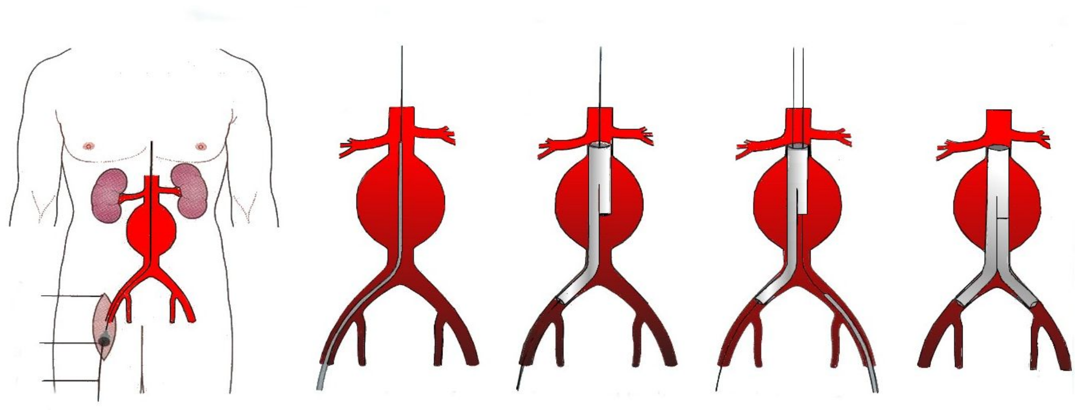


Figure 4-2 technique of introduction and deployment of the endograft

From I Droc et al 2012 (263)

According to 2020 NVR annual report data, a total of 73 vascular units across the UK performed complex aortic procedures between January 2017 and December 2019, 89% (n=2,306) of cases were endovascular, with just over half being fenestrated repairs (134).

4.1.3 Comorbid disease

Patients presenting for AAA surgery are getting older; relatively fit octogenarians with large AAAs are no longer an exception (264). Advancing age is associated with multiple comorbidities, reduced exercise capacity and an increased risk of postoperative complications (265). According to the 2018 NVR report, 85% of patients who underwent endovascular repair of their complex AAA were over the age of 65 years, 76% had hypertension and 81% were a current or ex-smoker (144). Indeed, cardiovascular risk factors are the most common comorbidities linked to long-term mortality in patients undergoing vascular surgery. Ischaemic heart disease was responsible for > 25% of deaths, compared with <6% for early surgical or aneurysm specific complications, in the large UK-based EVAR 1 and 2 trials (266). The European Society for Vascular Surgery recently reported that up to 70% of patients with peripheral arterial disease or abdominal aneurysm had multi-site vascular disease (267).

Surgery can induce a marked decline in exercise capacity (particularly in the elderly), which has detrimental effects on general health and quality of life. By improving the physical condition of patients with an individualised preoperative exercise programme, it may be possible to improve clinical postoperative outcomes alongside HRQL measures and lead to sustainable behavioural changes.

The need for advice from other specialists results in delays from initial assessment to surgery for complex AAA repairs. The 2016 NVR annual report found that over a quarter of patients having a complex open repair required specialist opinion from a physician in cardiology, respiratory medicine or nephrology (268). Another reason for longer waiting times can be the need for a non-conventional, bespoke endovascular device to be designed and manufactured; the average delivery time being 67 days (268). These delays provide a natural and predictable opportunity for a structured exercise programme prior to surgery.

4.1.4 Assessing surgical risk in vascular patients

Elective aortic surgery carries significant risk. Data from the 2020 NVR annual report indicated in-hospital mortality rates of 2.7% for complex endovascular aneurysm repair (134).

The aim of electively operating on unruptured AAAs is to prolong survival, but the health of patients, especially those with significant comorbidity, can deteriorate following major surgery (68). Accurate risk stratification is of paramount importance, primarily to fully equip patients with accurate quantification of the risks and benefits to enable them to make a truly informed decision. A number of models are currently available for assessing perioperative risk in AAA repair including the Physiological and Operative Severity Score for the enUmeration of Mortality (POSSUM) (269) and Vascular Biochemistry and Haematology Outcome Model (VBHOM) (270). However, these models lack sensitivity and specificity for the general AAA population and have not been adopted widely. The AAA and National Surgical Quality Improvement Program (NSQIP) scores are accepted as more sensitive, specific and reliable predictors of in-hospital mortality following AAA repair.

The AAA Score (271) was developed to assess risk of in-hospital mortality following AAA repair and was based on data from 8088 open and endovascular operations and published in 2015.

The value of exercise capacity variables as measured by CPET in identifying those at risk of postoperative pulmonary complications after AAA is also recognised. Nugent et al were amongst the first to describe the value of VO_2 at peak in identifying postoperative risk after open AAA repair (272). A VO_2 at peak of <20 ml/kg/min was associated with an increased risk of postoperative complications in this small retrospective study. Others have shown that AT has utility in the prediction of duration of ICU and hospital length of stay (273) and mid-term outcomes (30 day mortality) (274), following elective AAA repair (both open and endovascular). Likewise, a VE/VCO_2 of < 43 is associated with improved 30 day and mid-term survival (68). The routine use of CPET for the preassessment of patients with AAA is controversial. A 2012 systematic review of CPET in vascular surgery (275) concluded that a paucity of good quality data at that time precluded the recommendation for routine adoption of CPET in risk stratifying patients undergoing high-risk vascular surgery. However, the 2020 NICE guidelines on AAA diagnosis and management stipulates that CPET should be considered when assessing patients for elective repair of AAA, if it will assist in shared decision-making (256).

4.1.5 Activity tracking

Walking is considered to be an ideal form of physical activity to promote and maintain health status in the general population (276) and pedometers have been widely used in clinical research for the assessment and management of physical activity in a number of conditions including diabetes, osteoporosis and obesity (277–279). Pedometers are simple and inexpensive body-worn motion sensors that can supply valuable information on the number of steps taken, distance travelled, time spent in activity and provide an estimate of energy expenditure (280). These devices can both assess and motivate physical activity behaviours.

A value of 10,000 steps/day is often associated with a healthy level of physical activity (281, 282). This value dates back to the 1960's when Japanese walking clubs embraced a pedometer manufacturer's nickname for their product: manpo-kei (translated to 'ten thousand steps meter') (283). Table 4-1 illustrates indices used to classify pedometer-determined physical activity in healthy adults.

Steps/day	Activity zone
≥12,500	Highly active
10,000 – 12,499	Active
7500 – 9,999	Somewhat active
5,000 – 7,499	Low activity
< 5000	Sedentary

Table 4-1 Steps/day and activity zone groupings

Adapted from Tudor-Locke and Bassett 2004 (284)

By tracking activity using wearable pedometers, an assessment of any potential impact of exercise training on day-to-day activity compared with controls can be made.

Daily activity was monitored in the vascular cohort (study 2) as the comorbidities present in patients with AAAs all contribute significantly to a sedentary lifestyle. Patients are frequently elderly with cardiac comorbidity including ischaemic heart disease/angina and it is not uncommon for patients with AAA to have coexisting lower limb vascular disease that can limit walking. It was deemed important to assess the impact of an exercise programme on day-to-day activity and hence potential sustainable behaviour changes.

4.1.6 The risks of exercise in patients with AAAs

Research has shown that the incidence of exercise-induced hypertension (and hypotension) is higher in AAA patients than in age-matched adults (285). Safety concerns revolve around the combined impact of excessive rises in systolic blood pressure and heart rate leading to aneurysm rupture, which is a physiologically catastrophic insult carrying a mortality of about 75% (286).

Hence early trials focused on safety and establishing that the presence of an AAA is not a contraindication to physical activity. Importantly, no increase in AAA growth rates and serious clinical incidents e.g. ventricular tachycardia and aneurysm rupture with exercise were demonstrated in theses initial trials (285, 287, 288). Aneurysm sizes in this early work were small (around 4 cm) but recent research has also confirmed that it is possible to exercise patients with large AAAs (> 5.5 cm) at moderate to high intensities safely (289, 290). Tew et al, 2017 showed preoperative high intensity interval training (HIT) involving short bursts (2-4 min intervals) of vigorous exercise (on a cycle ergometer) interspersed with periods of low intensity recovery was acceptable and safe in 27 patients with large AAAs (290).

Concerns still exist regarding excessive SBP rises in patients with very large AAAs and safety guidelines exist with respect to maximal exertion/stress testing. In our centre patients with AAAs > 8 cm in diameter are excluded from CPET and stress echocardiography and for this reason an AAA diameter > 8 cm is an exclusion criterion for this study. It has been suggested that SBP should not rise above 180 mmHg for AAA patients engaging in vigorous aerobic exercise (e.g., running or cycling (291, 292))

4.1.7 Current evidence base for exercise training in the infra-renal cohort

Despite evidence demonstrating the beneficial effects of exercise in patients with cardiorespiratory disease (293–295), there is a paucity of research examining the effects of exercise initiatives on patient fitness prior to elective AAA repair. A 2015 systematic review of preoperative exercise in AAA surgery identified just five trials (296) that showed beneficial effects on various physical fitness variables and good patient compliance (70-94%), using programmes lasting between 2 and 12 weeks.

4.1.7.1 Literature review search strategy

A comprehensive literature review of both randomised and non-randomised trials assessing the impact of exercise training on patients awaiting infra-renal aortic aneurysm repair was performed whist planning the current study in 2016.

The search strategy aimed to locate published studies only. An initial limited search of MEDLINE was undertaken to identify articles on the topic (table 4-2). Text words in the titles and abstracts were used to develop a search strategy.

Search	Query	Records retrieved
# 1	Aortic aneurysm [MeSH Terms] OR aortic aneurysm [Title/Abstract]	29,974
# 2	Prehabilitation [MeSH Terms] OR exercise [MeSH] prehabilitation [Title/Abstract] OR exercise [Title/Abstract] OR physical activity [Title/Abstract] OR lifestyle intervention [Title/Abstract]	164,861
# 3	# 1+ 2	76

Table 4-2 MEDLINE search conducted June 2016

Literature sources included the Cochrane Central Register of Controlled Trials in the Cochrane Library, MEDLINE (from 1946) and EMBASE (from 1980). Searches were limited to studies on humans. A review of references included in primary studies and published systematic reviews was performed. No search for conference proceedings was performed and no language limitations were imposed.

4.1.7.2 Literature review results

A total of five studies (four RCTs and one cohort) assessing the impact of exercise training on patients with AAAs were identified (table 4-3). Three studies included patients with small aneurysms under surveillance and without indication for surgery and the remaining two studies included AAA patients awaiting surgical repair.

Articles excluded from this review included articles/editorials and case studies. Other exclusions were articles investigating exercise performance without an exercise/prehabilitation intervention. Trials looking at physical activity following aortic surgery or that did not involve a preoperative exercise intervention were excluded. Other excluded trials focused on assessing the physiological responses to exercise in patients with aortic aneurysms and CPET in the assessment and work-up of AAA patients.

The five studies identified in this literature review are small with sample sizes ranging from 20 to 140 patients, with heterogeneous patient populations, non-comparable exercise therapy programmes (utilising both supervised and community-based interventions) and methodological flaws. One study (Dronkers et al 2008) focused specifically on inspiratory muscle training as opposed to an aerobic exercise training intervention (297); plus, despite having a randomised design, the control group comparison was rendered almost useless as the usual care group was significantly older than the intervention group. The remaining four studies implemented a continuous moderate-intensity exercise regimen varying in duration from six weeks to three years.

Three of the five studies assessed the impact of exercise on patients with small AAAs < 5.5 cm under surveillance only with no indication for surgical repair

(288, 298, 299). These early studies primarily focused on establishing safety and compliance. Data on the first 57 patients included in the 2014 study by Myers et al (299) assessing the impact of exercise training on patients with small AAAs under surveillance, were also reported in a separate 2010 preliminary assessment (287), hence the exclusion of this initial paper in table 4-3.

Of the two studies involving patients with larger aneurysms awaiting surgery (the target population of this current study), both involved methodologies markedly different from that reported in this thesis. Dronkers et al 2008 investigated the impact of inspiratory muscle training (as opposed to aerobic activity) over two weeks. Barakat et al 2014 assessed aerobic and resistance training but specifically in patients awaiting infrarenal aneurysm repair only and did not include a control group. The current feasibility study was hence justified.

The lack of definitive evidence for the utility and cost-effectiveness of preoperative exercise in AAA surgery is highlighted by the 2020 NICE guidance on AAA management, which clearly identifies prehabilitation as a future research target. Further work is required to establish the clinical and cost effectiveness of preoperative exercise programmes and the optimal form it should take (256). Likewise, the 2019 Royal College of Anaesthetists Guidelines for the Provision of Anaesthesia Services (GPAS) highlights the implementation of prehabilitation programmes as an area for future research (300).

Author, year	Participant criteria Study design and duration	Intervention and comparator group details	Assessment of fitness	Outcome measures	Study conclusions
Dronkers, 2008 (297)	AAA awaiting surgery RCT, at least 2 weeks	Int: n=10 Inspiratory muscle training 6 days/wk for 2 weeks (15 min sessions) Cont: n=10, usual care		Postoperative pulmonary complications. Compliance.	Reduced incidence of atelectasis
Kothmann, 2009 (288)	AAA <5.5cm under surveillance RCT, 6 weeks	Int: n=17 2x weekly supervised cycling (30 minutes) Cont: n=8	CPET	Improvement in AT: minimum clinically important difference (MCID) was determined as 2 ml/kg/min	Improvement in AT of 1.1 ml/kg/min in exercise group (lower than the MCID) NNT of 5
Myers, 2014 (299)	AAA < 5.5cm under surveillance RCT, up to 3 years	Int: n= 72 supervised exercise, at home exercise, or a combination of both. Activity goal: mean energy expenditure of 2000 kcal/wk Cont: n= 68 Regular care	CPET: baseline, 3, 12, 24 and 36 months. MET-hours per week (from telephone interviews)	Impact of exercise training on AAA growth rates. Safety. CPET responses. Weekly average energy expenditure.	Exercise training did not influence AAA growth rates. Exercise is safe and effective. Increase in exercise time and perceived METS. No AAA-related or other adverse events occurred.

Barakat, 2014 (301)	AAA awaiting infrarenal surgery Cohort, 6 weeks	Int: n= 20 6 wk supervised exercise programme 3x/wk, aerobic and resistance training	CPET	Change in exercise capacity as compared to baseline values (VO_2 at peak and AT).	Significant improvement in VO_2 at peak and AT following 6 weeks of exercise training.
Tew, 2012 (298)	AAA 3-5 cm under surveillance RCT, 12 weeks	Int: n=11 supervised exercise, 3x/wk moderate-intensity endurance exercise (treadmill, walking and cycle ergometry) Cont: n=14 Encouragement to exercise only	CPET	Safety: frequency of adverse events/change in AAA size Exercise capacity: VO_2 at peak and AT. HRQL: SF-36 Markers of vascular risk (e.g., BP, HR)	No adverse clinical events occurred. Ventilatory threshold increased in the exercise group, no significant difference in VO_2 peak. No significant changes in HR, BP, exertion, RER.

Table 4-3 Clinical trials looking at the impact of exercise in patients with abdominal aortic aneurysms

AT = anaerobic threshold, Int = intervention, cont = controls, HIT = high-intensity training, HRQL: health-related quality of life, BP = blood pressure, HR = heart rate, APACHE II = acute physiology and chronic health evaluation II

4.2 Study Objectives:

4.2.1 Primary Objective:

An assessment of the feasibility of formalised interval exercise training in patients awaiting complex endovascular AAA repair.

4.2.2 Secondary Objectives:

a) Evaluation of the effectiveness of exercise training in this patient cohort using objective fitness measures provided by CPET.
b) Comparison of fitness changes to a group of standard care patients, matched for age, gender and AAA score to the exercise group, not undergoing formalised exercise training.
a) Measurement of changes in HRQL brought about by a formalised training programme.
b) Objective assessment of impact on daily activity levels.
c) Postoperative outcomes: intensive care and hospital length of stay, postoperative morbidity, assessed using the Clavien-Dindo classification.
d) Assessment of exercise enjoyment using the PAES questionnaire.

4.3 Hypothesis

4.3.1 Primary hypothesis

In comparison to a control group (usual care, no formal exercise training), a structured six week exercise training programme would be feasible in patients awaiting FEVAR and that fitness and daily activity can be improved.

4.3.2 Secondary hypothesis

An in-hospital exercise training programme compared with a usual care control group will result in psychological health benefits in terms of HRQL as assessed using the EQ-5D-5L self-reported measure.

4.4 Outcome measures

The primary outcome was feasibility of formalised exercise training in this complex cohort. Feasibility and acceptability outcomes were: recruitment, outcome completion, adverse events and adherence to exercise as defined by:

a. Absence of exercise-related serious adverse events
b. Recruitment: >50% recruitment rate of patients meeting eligibility criteria.
c. Compliance with exercise: >66% exercise sessions completed

Cardiopulmonary fitness, as assessed by CPET, defined by VO_2 at AT and VO_2peak.

4.5 Study 2 specific methodology

4.5.1 Study design

This single centre prospective matched cohort study assessed the feasibility of a six week, structured, outpatient, hospital-based prehabilitation programme in patients awaiting FEVAR. The study ran for a period of 18 months from August 2016 to January 2018 at the RFH, London. I aimed to recruit fifteen patients into the exercise group and fifteen matched control patients.

4.5.2 Patient identification, screening and recruitment

All potentially eligible patients were identified from a list of those awaiting aortic surgery, held by the vascular coordinators and surgeons at the RFH. This is standard practice at the RFH for the screening of potential participants for research. Once patients were formally listed for FEVAR, they were approached with written information about the trial at their initial outpatient clinic appointment with a consultant anaesthetist, or by post. Patients were then contacted by telephone to provide additional information about the trial and confirm eligibility. If the patient chose to participate in the study an initial research visit was organised when written, informed consent was obtained and baseline measurements including CPET were performed.

Given that the primary aim of this study was feasibility, formal randomisation was not considered necessary and the study was not designed to detect differences in outcomes. The 'standard care' cohort of patients (no exercise programme) were matched to those in the exercise group according to specific demographic criteria: age, gender and AAA score. Once patients were matched, allocation to study arms was a function of geographical location and logistical ability to commit to attending hospital three times per week.

4.5.3 Inclusion Criteria

- Listed for fenestrated/juxtarenal AAA repair at the RFH
- Aged over 18 years
- Able to perform exercise on a bicycle ergometer

4.5.4 Exclusion Criteria:

- Contraindication to exercise training or testing (according to the American Thoracic Society and the American College of Chest Physicians guidelines) (28)
- Refusal or inability to provide informed consent
- Emergency AAA repair
- AAA > 8 cm (cut-off in our centre for CPET testing and stress echocardiography)
- Conservative management of AAA
- Prisoners

4.5.5 Assessment of fitness

Using the methodology described in chapter 2, serial CPET was used to objectively assess change in cardiopulmonary fitness across the following time points: baseline (week 0), at the midpoint of exercise training to guide exercise prescription (week three; exercise group only) and at the end of the six week study period (week six).

Self-reported activity status was assessed at baseline using the DASI score (27) (appendix 1).

4.5.6 Intervention group

Following a baseline CPET, patients were asked to attend thrice weekly, supervised in-hospital exercise training sessions for six weeks. Each training session consisted of 40 min (including 5 min warm-up and 5 min cool-down) of interval training on an electromagnetically braked cycle ergometer (Optibike Ergoselect 200; Ergoline, GmbH, Bitz, Germany). The exercise training intensities were formulated according to an individual's CPET data at weeks 0 and 3, and altered according to measured work rates at VO_2 for AT and VO_2peak in the manner described in chapter 2. A summary flow chart representing the study protocol is presented in figure 4-3.

4.5.7 Control/usual care group

A comparator 'usual care' group was created by selecting patients matched to those in the exercise group according to age, sex and AAA score. These patients underwent CPET at baseline and week six, but no in-hospital exercise was initiated. Once patients were demographically matched, allocation to study groups was based on geography and logistics; the patient living furthest from the hospital was allocated to the control group to avoid any logistical issues in thrice weekly hospital visits. These patients were given general advice about the importance of keeping active but no structured advice, as per the standard practice of the complex vascular surgery department. Other standards of care for the work-up of complex vascular patients include smoking cessation advice where applicable and referral to the smoking cessation team if patients were agreeable.

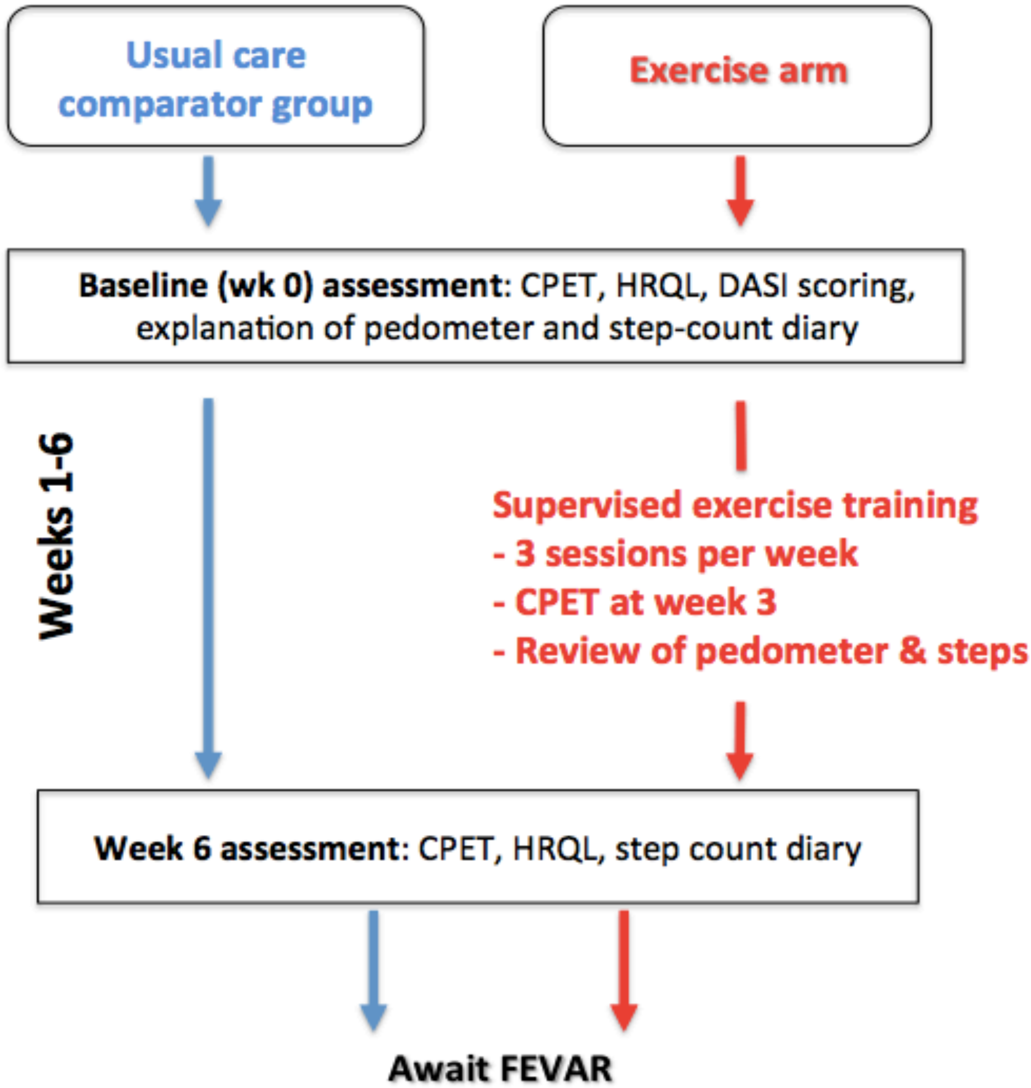


Figure 4-3 Protocol flow diagram for study 2: the feasibility of an outpatient, hospital-based exercise training programme for patients awaiting complex fenestrated endovascular aortic aneurysm repair at RFH.

4.5.8 HRQL and PAES self-reported measures

Health-related quality of life was assessed using the EQ-5D-5L questionnaire (154) at baseline and week six and exercise enjoyment was assessed using PAES tool (121) as per general methods section (chapter 2).

4.5.9 Pedometers and daily activity tracking

All patients were given a pedometer to monitor day-to-day activity. The Competitive Sport Xtreme (CSX) P341 3D pedometer with clip device (Fig 4-4) was specifically chosen for this cohort because it is simple to use and has a large, easy-to-read interface displaying daily step count (important for elderly patients who may be visually impaired). It is also economical; the £17 cost per device means patients could keep the pedometers they were given after cessation of the study and continue to use them. The step count re-sets to zero at midnight and there is a recall function enabling the review of steps taken over the last week. Identical instructions were given to each participant on how the device works and where to wear it (on the waistband/belt). Patients were not set a specific step count target to aim for. All patients were asked to record the number of steps taken every day before going to bed. They were given a very simple step count diary in which to record this data. This diary was collected at the end of the six-week study period.

Pedometer output also included distance walked, hence the set-up of each device required an assessment of stride length, performed during the initial meeting. Each patient was asked to walk 10 steps with their normal stride; the distance from start to finish was measured in centimetres and the total divided by 10. This final individual stride distance was entered into the pedometer to ensure a degree of accuracy in measuring distance walked. Patients in the intervention group were asked to remove their devices prior to each exercise session to remove this confounding factor and ensure a true assessment of usual daily activity.

Figure 4-4 CSX P341 3D Pedometer given to all recruited patients

4.6 Clinical data collection

Data, including the patient demographics and the underlying disease types alongside laboratory results, were prospectively collected at the time of recruitment and baseline assessment. The AAA scores were calculated at the time of recruitment. Postoperative outcome measures including morbidity and intensive care and hospital length of stay were collected retrospectively.

4.7 Statistical Analysis

Statistics were calculated using IBM SPSS Statistics, Version 24.0. Armonk, NY: IBM Corp. Continuous data were examined for normality using the Shapiro-Wilk test. Continuous data are presented as median with IQR or mean with SD/ 95% CI for normally distributed data and categorical data as number (percentage). Mann-Whitney analyses for independent samples or Wilcoxon for dependent samples (continuous, non-normal distribution), *t* test analyses (continuous, normal distribution), and chi-square analyses (categorical) were used to compare the demographic and CPET variables of patients in both the exercise and control groups and are presented as absolute values (with percentage). Comparisons across grouped variables were made using analysis of variance (ANOVA) with Tukey's post-hoc test for comparisons of pairings within a group. All tests were two tailed, and significance was taken as $p<0.05$.

4.7.1 Sample size:

The primary outcome measure of this study was the feasibility of training patients in this manner, therefore no sample size calculation was performed

4.8 Results

4.8.1 Recruitment and retention

A total of 61 patients were listed for FEVAR over the 18 month study period. Following screening for inclusion/exclusion criteria, 43 patients met inclusion/exclusion criteria and were approached to take part in the study, of whom 23 were recruited (11 to the exercise and 12 to the control arm), equating to a recruitment rate of 53% (fig. 4-5).

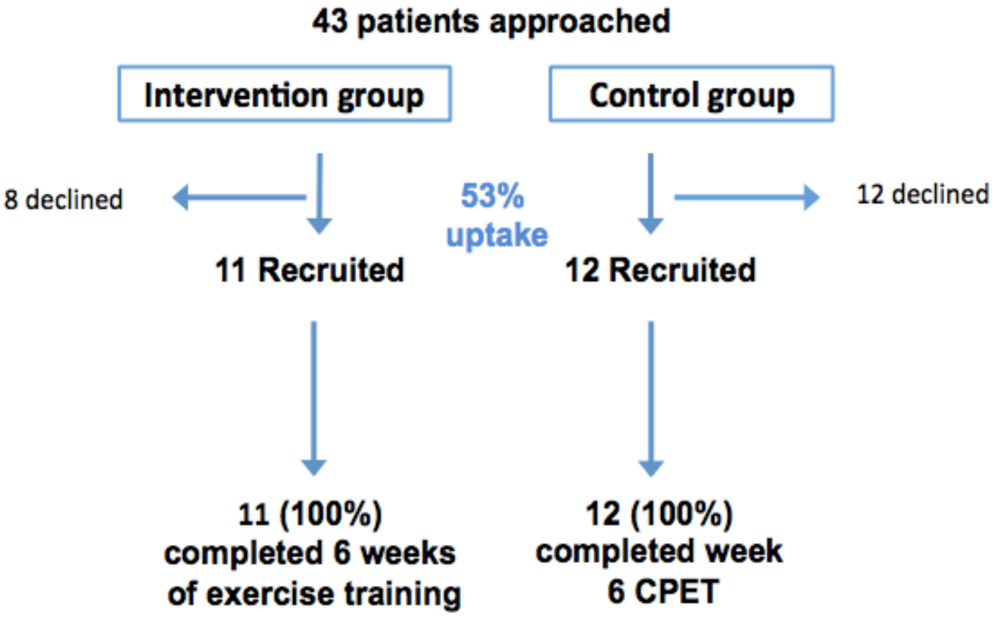


Figure 4-5 Study 2 recruitment and retention flow diagram

The commonest reason for refusal to take part in the study was logistical in that patients were unwilling to travel potentially long distances to the study centre three times per week for 6 weeks. All patients in both groups completed the study.

4.8.2 Demographic data

There were no differences in baseline demographic data between groups (table 4-4). Twenty-one patients were male (91%). Self-reported activity as reflected in the DASI score was slightly higher in the control group at baseline, with a mean (95% CI) value of 39.1 (32.1-46.1) compared with 37.65 (29.0-46.3) in the exercise group (p=0.77). The median (IQR) aneurysm diameter was 57 (±10) mm in the exercise group and 60 (±5) mm in the control group.

Sixty-four percent (n=7) of patients in the exercise group and 33% (n=4) in the usual care group had a history of ischaemic heart disease and around one quarter of all participants in each group were taking beta-blockers. Seventythree percent (n=8) of patients in the exercise group and 83% (n=10) in the usual care group were current or ex-smokers. Table 4-5 shows laboratory data at study recruitment. Mean haemoglobin was 138 g/l in both groups.

	Exercise (n=11)	Usual care (n=12)
Age (years) Mean (95% CI)	**74.5** (70.0 – 79.1)	**74.3** (70.0 – 78.7)
Sex No. (%) male	**10** (91)	**11** (92)
AAA Size (mm) Median (IQR)	**57** (10)	**60** (5)
AAA score Median (IQR)	**1.1** (0.6)	**1.0** (0.9).
DASI Mean (95% CI)	**37.65** (29.0 – 46.3)	**39.1** (32.1 – 46.1)
METS Mean (95% CI)	**7.37** (6.3 – 8.4)	**7.54** (6.7 – 8.4).
Beta-blocker usage No. (%)	**3** (27.3)	**3** (25)
Background: - **Smoker/ex-smoker** No. (%)	**8** (73)	**10** (83)
- **Hypertension** No. (%)	**7** (63.6)	**6** (50)
- **Ischaemic heart disease** No. (%)	**7** (63.6)	**4** (33.3)

Table 4-4 Demographic and background information for all recruited patients at baseline

	Exercise (n=11)	Usual care (n=12)	p-value
Haemoglobin (g/l) Mean (SD)	**138.0** (9.0)	**138.1** (13.7)	0.98
WCC (x10^9/l) Mean (SD)	**7.9** (1.3)	**8.1** (2.0)	0.77
Sodium (mmol/l) Mean (SD)	**140.8** (2.3)	**141.4** (2.7)	0.58
Creatinine Mean (SD)	**100.5** (30.9)	**92.0** (22.2)	0.45

Table 4-5 baseline laboratory data of all recruited patients

4.8.3 Compliance with exercise sessions and surgical timing

Compliance with the prescribed exercise training was high with 160 out of the overall total of 165 exercise sessions (97%) completed by the 11 patients in the exercise group.

No surgical delays occurred because of the exercise programme. Of the 23 study participants, four patients had a delayed operation. The two main reasons for delays were a lack of intensive care beds for postoperative care on the day of surgery and delays in receipt of the bespoke fenestrated aortic grafts tailored to each patient's specific vascular anatomy.

4.8.4 Cardiopulmonary exercise test data

CPET data, as presented in table 4-6, showed that patients in the control group were slightly fitter at baseline in terms of VO_2 peak with a median (IQR) of 13.7 (4.1) ml/kg/min in the exercise group and 16.0 (4.2) ml/kg/min in the control group, but this difference was not significant (p=0.3). As regards trends in oxygen consumption data over the course of the study, a signal towards improvement in VO_2peak in the exercise group was shown with a median (IQR) of 13.7 ml/kg/min (4.1) at baseline rising to 16.0 ml/kg/min (4.8) at week six (p=0.07). Patients were also able to generate more power on the ergometer with peak workload rising from a mean (SD) of 79 (±29) W at baseline to 134 (±96.3) W at week six ($p=0.004$). There was no significant difference in median [IQR] VO_2 peak in the control group, which decreased from 16.0 (4.2) ml/kg/min at baseline to 15.1 (5.8) ml/kg/min at week six. Likewise, the mean (SD) peak workload in the control group was 95.2 (33.1) W at baseline and 88.5 (38.2) W at the end of the study period.

The median (IQR) AT was 10.5 ml/kg/min (1.8) at baseline and 11.6 ml/kg/min (2.6) after six weeks of exercise training ($p=0.14$). In the control group, median AT at baseline was 10.6 ml/kg/min (1.8) and 11.0 ml/kg/min (2.1) at week six ($p=0.42$).

As regards specific ventilatory CPET measures, there were no changes in VE/VCO_2 (ratio of ventilation to carbon dioxide output) at VO_2 across the study period in either group. Mean haemoglobin concentration did not change for individuals in either group across the study period.

	Exercise (n=11)			**Usual care (n=12)**		
	Week 0	**Week 6**	**P Value**	**Week 0**	**Week 6**	**P Value**
Weight (kg) Mean (SD)	**80.0** (13.0)	**79.8** (13.3)	0.58	**83.9** (16.1)	**82.8** (15.5)	0.03
VO_2 at AT (ml/kg/min) Median (IQR)	**10.5** (1.8)	**11.6** (2.6)	0.14	**10.6** (4.0)	**11.4** (2.1)	0.42
VO_2 at AT (L/min) Mean (SD)	**0.88** (0.2)	**0.94** (0.2)	0.08	**0.99** (0.3)	**0.99** (0.3)	0.96
VO_2 at peak (ml/kg/min) Median (IQR)	**13.7** (4.1)	**16.0** (4.8)	0.07	**16.0** (4.2)	**15.1** (5.8)	0.43
% Predicted VO_2 peak Mean (SD)	**68.7** (11.6)	**81.5** (27.9)	0.05	**72.1** (16.5)	**73.0** (19.8)	0.68
VO_2 at peak (L/min) Mean (SD)	**1.16** (0.3)	**1.30** (0.4)	0.05	**1.30** (0.4)	**1.32** (0.4)	0.68
O_2 pulse at peak Mean (SD)	**10.3** (2.0)	**11.0** (3.1)	0.13	**11.2** (3.0)	**10.9** (3.1)	0.42
% predicted O_2 pulse Mean (SD)	**89.2** (14.1)	**94.2** (23.3)	0.22	**90.5** (19.6)	**86.1** (18.4)	0.29
VE/VCO_2 at AT Mean (SD)	**34.7** (2.4)	**34.8** (3.2)	0.84	**35.5** (6.2)	**34.8** (5.2)	0.48
Maximum heart rate (bpm) Mean (SD)	**112.7** (14.5)	**118.6** (13.3)	0.05	**117.3** (22.1)	**119.1** (20.2)	0.68
Peak workload (W) Mean (SD)	**79.3** (29.0)	**96.3** (25.3)	0.004	**95.2** (33.1)	**88.5** (38.2)	0.14
Haemoglobin (g/L) Mean (SD)	**138.0** (9.0)	**136.6** (12.4)	0.64	**138.1** (13.7)	**136.4** (12.9)	0.44

Table 4-6 CPET measures at baseline and week six in both the exercise and control groups.

4.8.5 Inter-rater variability in anaerobic threshold reporting

Figure 4-6 shows a Bland-Altman plot illustrating the inter-rater variability in anaerobic threshold interpretation for baseline and week 6 CPETs.

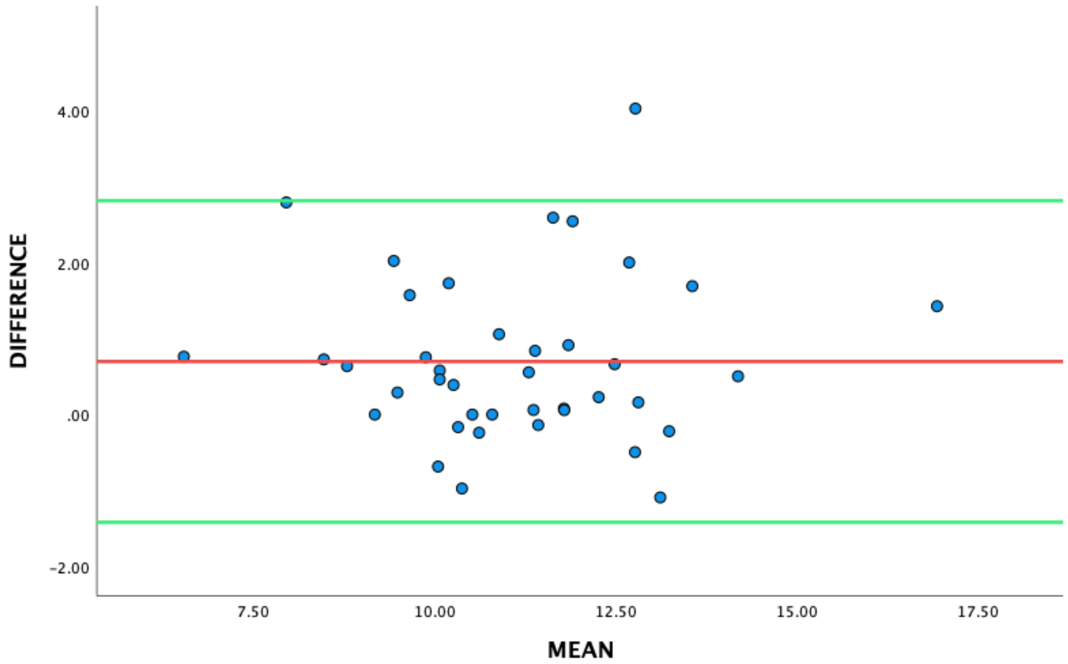


Figure 4-6 Bland-Altman plot displaying observer variability in reporting of anaerobic threshold

Red line: mean inter-rater difference (0.70)

Green lines: upper and lower 95% confidence intervals (2.82, -1.42)

There was no significant linear relationship between inter-rater difference and mean AT (p=0.9) confirming that there is no proportional bias.

4.8.6 Postoperative data

Postoperative outcome data are presented in table 4-7. Perioperative complications were scored as per the Clavien-Dindo classification (240, 241).

The median grade of most severe complication at 30 days was just 1 in both groups with a range of 1-3b in the exercise group and 1-5 in the usual care group. The most frequent postoperative complication was AKI (two patients in the exercise group and three controls); every case resolving without renal replacement therapy. One patient in the control group was readmitted to the ICU with chest sepsis and another required a prolonged period of vasopressor postoperatively. One exercise group participant developed a femoral artery pseudoaneurysm necessitating surgical intervention.

Patients in the exercise group stayed a median of 1 day longer on the ICU than usual care patients (p=0.12), however patients in both groups were discharged from hospital at a median (IQR) of 3 (3) days. There were no deaths in the postoperative period and up until six months after surgery in the exercise group. One patient in the usual care group died on the fifth postoperative day following a massive stroke thought to be secondary to cholesterol emboli. A second patient died within six months of surgery, but after discharge and from a cause unrelated to the operation.

	Exercise (n=11)	**Usual care (n=12)**	**P value**
Duration of ICU stay (days) Median (IQR)	2 (1)	1 (0)	0.12
Hospital length of stay (days) Median (IQR)	3 (3)	3 (3)	0.75
6 month survival Number (%)	11 (100)	10 (83)	
Clavien-Dindo grade Median (range)	1 (1-3b)	1 (1-5)	0.97
Number of patients with post-operative complications	3	5	

Table 4-7 Post FEVAR clinical data

4.8.7 Impact on physical activity: pedometer data

Daily step count (as per pedometer diary data) did not change significantly across the study period in either the exercise or usual care groups and revealed a low to sedentary level of daily activity. Step counts in the 11 intervention patients were higher than controls even at baseline and showed a signal towards increasing; rising from a median (IQR) of 6016 (3762) steps per day in week one to 6465 (4515) steps per day in week six (p=0.07) in the exercise group (table 4-8). Daily step counts in the control group decreased from a median (IQR) of 4779 (2899) steps in week one to 4347 (4430) steps in week six.

Group	Week 1	Week 6	Change, % change	P value
Intervention (n=11) Median (IQR)	6016 (3762)	6465 (4515)	+ 449 (7.5) *	0.07
Control (n=12) Median (IQR)	4779 (2899)	4347 (4430)	- 432 (9) *	1.0

Table 4-8 Daily step count at week one versus week six in both study groups

* Absolute change (no brackets) and relative (percentage) change (in brackets) at week six from baseline within the groups.

Figures 4-7 and 4-8 illustrate the median (IQR) step counts week-by-week for the six week study period.

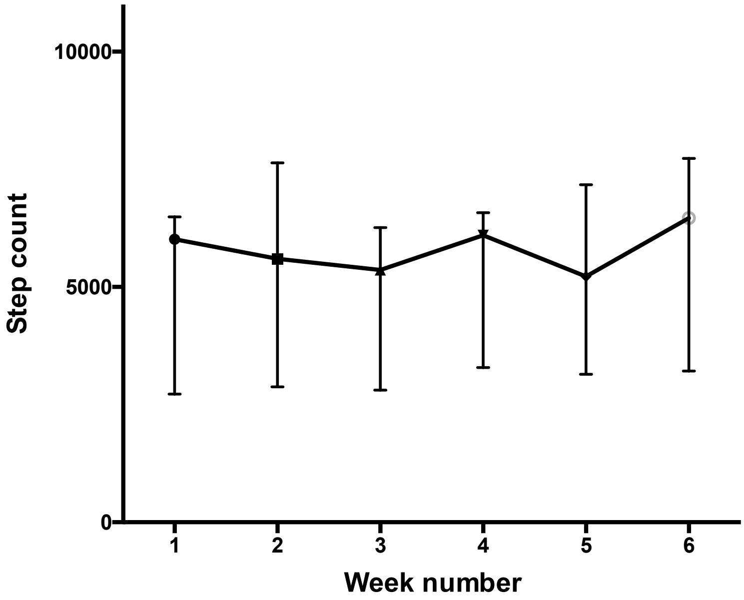


Figure 4-7 Median (IQR) step count for the 11 patients who underwent the exercise intervention over the six week study period.

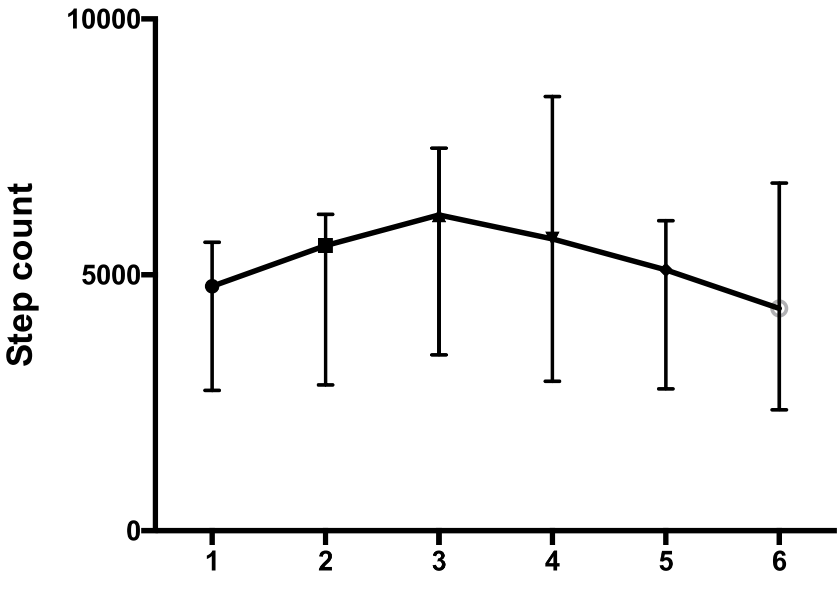


Figure 4-8 Median (IQR) step count for the 12 control patients from weeks one to six.

4.9 Complications related to exercise

No complications or adverse events were encountered in patients undergoing exercise training during the study period.

4.10 Physical activity enjoyment scale

The exercise group also provided an overall rating of enjoyment of the exercise programme, using the PAES questionnaire (121). For the 11 patients completing 3 weeks of exercise training, the mean (SD) physical activity enjoyment scale score was 102.3 (11.1), out of a maximum of 126.

4.11 Health-related Quality of life

Health-related quality of life measures as assessed by the EQ-5D-5L self-reported measure at baseline and week six, for both the EQ-VAS and index values are shown in table 4-9. Responses to the question 'we would like to know how good or bad your health is TODAY' on the 0-100 EQ-VAS, did not change from baseline to week six in the exercise group; median (IQR) EQ-VAS responses in intervention patients were 80 (±20) at baseline and after six weeks of exercise (p=0.59). However, perceived health did show a trend towards improvement in the control group with median (IQR) reported values rising from 70 (±30) at baseline to 90 (±25) at week six. The EQ-5D-5L index values for both groups essentially remained the same over the six week study period.

	Exercise (n=11)			Usual care (n=12)		
	Wk 0	**Wk 6**	**P Value**	**Wk 0**	**Wk 6**	**P Value**
EQ VAS Median (IQR)	**80** (20)	**80** (20)	0.59	**70** (30)	**90** (25)	0.09
EQ-5D-5L index values Median (IQR)	**0.88** (0.11)	**0.92** (0.18)	0.61	**0.93** (0.21)	**0.92** (0.31)	0.13

Table 4-9 EQ VAS self-rating and EQ-5D-5L index values

4.12 Patient feedback

All 23 study participants were asked to provide feedback on their experiences of both activity tracking and the exercise intervention (when applicable) via an anonymised postal questionnaire sent to them after their surgery. Patients were asked to score a series of statements on a visual analogue scale from 1 to 10. Twelve (52%) of patients returned responses. Patients in the exercise arm found the training programme enjoyable, returning a mean score of 9/10 to the question ‘I found the exercise programme enjoyable’. A mean score of 9.4/10 was given to the question ‘I found the exercise programme motivating’ and 100% of patients would recommend the exercise programme to a friend. Enjoyment of the exercise modality and the programme itself is also reflected in the top quartile PAES result.

All study participants were asked specifically about ongoing pedometer use and 8 out of 12 (66.7%) patients were still using their pedometer to track their daily activity following surgery; returning a mean score of 9.2/10 to the question ‘did you find the pedometer helpful in encouraging you to exercise?’.

4.13 Discussion

4.13.1 Feasibility and safety

This study demonstrated the feasibility and safety of a hospital-based, outpatient exercise training programme for elderly, comorbid patients awaiting complex endovascular abdominal aortic aneurysm repair.

As per study 1, feasibility and acceptability outcomes were pre-defined as:

a. Absence of exercise-related serious adverse events
b. Recruitment: >50% recruitment rate of patients meeting eligibility criteria.
c. Compliance with exercise: >66% exercise sessions completed

All pre-specified feasibility and acceptability outcomes were met given the 53% recruitment rate, absence of exercise-related adverse events and 97% of exercise sessions completed. All 11 patients in the exercise group completed the six week study period and final CPET with no drop-outs, injuries or adverse events encountered. All 12 usual care patients also completed the week six CPET; even those who travelled significant distances to the study centre were not deterred from attending.

A target study population of 30 was planned, however only 23 patients were recruited. The initial target was ambitions given the number of patients listed for FEVAR over the study period (n=61) with only 43 meeting eligibility criteria.

An absence of untoward events occurring during exercise is consistent with the existing literature on exercise training in abdominal aortic aneurysm disease. All but one of the published studies reviewed reported zero adverse consequences of exercise in this cohort (287, 290, 297) and indeed exercise training has been shown not to influence AAA growth rates (287, 299). Kothmann et al. in 2009, did report one serious event associated with exercise:

a cardiac arrest (ventricular fibrillation) during an exercise session in a patient with previous coronary artery bypass grafting, but good reported exercise capacity at study enrolment (288). The weight of available evidence certainly supports the conclusion that, overall, it is safe to exercise patients with AAAs. Tew et al. in 2017 have gone so far as to demonstrate the safety and feasibility of high-intensity training despite the high-risk nature of this patient population (290). It is important to note the presence of safety criteria (such as a systolic blood pressure > 180 mmHg) triggering power output reduction and limitation of exercise progression in this study. The safety of CPET conduct itself also needs to be taken into account. As previously highlighted in 3.10.2, the measurement of VO_2peak depends on encouraging participants to reach volitional exhaustion, raising safety concerns around high-risk individuals with cardiac comorbidity. AT measurement is, however, achieved at sub-maximal levels of exercise. No safety concerns were raised during the maximal exercise tests in the present study.

The recruitment rate observed in this study equalled or bettered that reported in existing literature (287, 290).

4.13.2 Exercise capacity

This study was not designed or powered to detect differences in secondary outcomes and exercise training did not significantly improve aerobic capacity among our small sample of patients. A signal towards an increase in VO_2peak in patients who underwent the exercise programme was seen, with VO_2peak trending downwards between baseline and week six in the usual care group. There was also a significant increase in the peak workload generated from baseline to week six by patients in the exercise group, indicating an increase in exercise capacity. These results should be interpreted with caution given the small sample size and the high risk of type 1 error with multiple variables being analysed in such a small cohort. Ventilatory efficiency remained unchanged across the study period with no significant changes in VE/VCO_2 at AT in either group, suggesting no effect of exercise on ventilatory efficiency.

Modest, non-significant increases in VO_2peak have also been shown in the existing prehabilitation literature. Myers et al, in 2010, reported a baseline VO_2peak of 18.5 ml/kg/min prior to a programme of home exercise training, rising only to 20.0 ml/kg/min at 1 year in patients with small AAAs under surveillance (287). Data reported by Barakat et al. 2014 contradicts these findings, reporting significant increases in both VO_2peak and AT in a cohort of 20 patients following six weeks of exercise training (301). Kothmann et al conducted a small, randomised pilot study in patients under AAA surveillance and demonstrated an increase in AT of 10% in patients completing a six week exercise intervention compared with controls. This difference was lower than a predetermined 'minimum clinically important difference' of 2 ml O_2/kg/min (288). These studies are not appropriately powered to detect small changes in cardiorespiratory parameters and properly powered studies are required to definitively address this area.

Inter-rater variability in the interpretation of AT was described in a Bland Altman plot (fig 4-6) and no proportional bias was demonstrated. The mean inter-rater difference was 0.7 which similarly to Study 1 represents a small difference, unlikely to have a significant clinical impact.

4.13.3 Differences in step counts between groups

Step-count data revealed a sedentary level of daily activity in the control group. Interestingly, step counts were generally > 1000 steps/day higher in the exercise cohort even at baseline. This may be a consequence of a degree of performance bias as patients in the intervention group received more contact with the study team, potentially enhancing motivation to perform and 'please' clinical and research staff. This is a limiting factor inherent in utilising the real-time feedback provided by pedometer devices. Also, the matched cohort methodology generates the potential for selection bias: motivated, fitter patients are more likely to consent to take part in the exercise group and comply with training sessions.

No significant differences in daily activity between weeks one and six were demonstrated in either group according to pedometer data. There was a signal towards an overall increase in daily activity in the exercise group at week 6 compared to baseline step counts. Whereas patients in the control group were walking a median of 432 fewer steps per day at week six, despite an initial increase in activity. There was marked variation in the number of steps each patient walked as highlighted by the wide IQRs. This spread of data is a function of the lack of statistical power and caution should be exercised when interpreting results. Further investigation is required to establish the impact of exercise training on daily activity in patients awaiting complex AAA repair.

4.13.4 Enjoyment and HRQL

No significant benefit to psychological health in terms of HRQL as assessed by the EQ-5D-5L was demonstrated. The HRQL data were inconclusive and difficult to explain. A trend towards improvement in the self-reported EQ-VAS perceived health was evident in the control group whilst responses from the exercise group remained the same over the six week study period. The population-generalisable EQ-5D-5L index values did not change between baseline and week six in either group. The generic EQ-5D-5L measure may not be a clinically meaningful test in this particular cohort of patients. The tool plays an important role in economic evaluations, but its utility in detecting meaningful change in health status in certain populations is not always clear (302). The use of a condition-specific measure to ensure adequate estimates of effectiveness would have been beneficial, alongside the EQ-5D-5L. Elderly patients awaiting complex vascular surgery with multiple comorbidities will likely require a validated tool specifically designed to accommodate their specific medical and physiological issues. It may also be the case of course, that exercise genuinely did not make this cohort of patients happy!

Tew et al. in 2017 also assessed the impact of exercise on HRQL using the EQ-5D-5L measure. No significant differences in EQ-VAS and EQ-5D-5L utility scores between baseline and week five following four weeks of HIT training were found (290). Likewise, no substantial changes were reported in eight quality of life domains following a 12 week programme of moderate-intensity endurance exercise, as assessed by Tew et al. in 2012 (298).

4.13.5 Postoperative data

There was a very low rate of significant postoperative complications; the median Clavien-Dindo grade being 1 for each group. The one postoperative death within six months was in a control patient and was the unfortunate consequence of a direct complication of the surgical procedure itself. A stroke secondary to cholesterol emboli is a rare complication of endovascular intervention and could not have been predicted or prevented with improved patient fitness. There was no difference in hospital length of stay, with patients in both groups staying a median (IQR) of 3 (3) days in total. Again, this study was not powered to detect differences in postoperative outcomes so an absence of a difference between these endpoints is not surprising.

There are few existing studies reporting postoperative outcomes in this patient cohort. An RCT led by Barakat et al. in 2016 and involving 124 patients did report a significantly shorter length of stay and fewer postoperative complications following six weeks of preoperative supervised exercise compared with controls, in patients undergoing both open and endovascular aneurysm repair (12).

Overall, the findings of this study have clear implications for ongoing investment in prehabilitation programmes and inter-disciplinary collaboration consistently throughout the preoperative phase. Further large randomised controlled trials are required to assess the effectiveness and optimal design of preoperative exercise interventions for patients awaiting FEVAR.

Following completion of study 2, the decision was taken by the multidisciplinary team to implement preoperative exercise as a standard of care for patients awaiting FEVAR surgery. Vascular physiotherapists now oversee twice-weekly group sessions for vascular patients awaiting complex endovascular aneurysm surgery. Data on the success of this initiative is awaited but as per the initial study it is well accepted by those involved in the prehabilitation of these patients that they relish the opportunity to improve their fitness in the run-up to major surgery.

4.13.6 Patient feedback

Study participants were engaged and empowered by the opportunity to improve the preoperative pathway and help future patients prior to FEVAR surgery. Anecdotally, attitudes towards exercise and activity appeared to change in patients taking part in the exercise arm. Patients focused on the amount of work they were doing on the exercise bike and were motivated by improvements at the week 3 CPET. They were keen to report to the research and clinical teams their progress with step-counts and daily activity.

As demonstrated by the feedback questionnaire, the majority of patients in the exercise arm found the training programme enjoyable and 100% of patients would recommend the exercise programme to a friend. Enjoyment of the exercise modality and the programme itself is also reflected in the high PAES results.

The majority of patients continued to use their pedometer following surgery, finding it helpful in encouraging them to exercise. This suggests that some patients may be gaining ongoing, sustainable changes in their attitudes towards exercise and benefitting from a device that allowed self-monitoring of walking activity, motivating them to achieve goals for steps. This motivation for walking due to pedometer use is consistent with the current literature (303).

The regular contact with healthcare professionals and close supervision of the exercise appeared to be very reassuring and made patients feel supported. The rapport developed between study participants and exercise supervisors was notable.

4.13.7 Study limitations

This study has a number of limitations. Participants were not randomised, there was no observer blinding and the study was not powered to detect differences in physiological or clinical outcomes. There are therefore high risks of bias and type 2 error inherent in this data.

The main methodological limitation is the absence of formal randomisation to inform design of a large, definitive study. Similar to study 1, funding and resource limitations precluded conducting a larger, randomised controlled trial. A matched group design was adopted as a pragmatic approach to minimise baseline differences on key confounding variables between small groups. However, unlike a randomised design, this approach cannot be assumed to minimise the influence of unmeasured confounding variables.

There are several limitations with using pedometer data to measure activity. Firstly, there are intrinsic sources of error with the pedometer itself. Undercounting at slow speeds is a problem that afflicts most step counters. At 54 m/min (2mph) many devices begin to undercount steps (304). Likewise, double counting of steps can occur when devices are jostled or exposed to mechanical vibrations. The risk of double counting was mitigated by instructing patients to wear the device on their waist band and avoid putting it in a pocket and wearing around their neck for example. Secondly, it is important to consider the fact that physical activity is a behaviour as opposed to other stable health indicators such as body composition. There are naturally occurring changes in behaviour on a daily, seasonal and yearly basis (305). Activity trackers allow automatic feedback to patients, enhancing motivation to perform and please clinical and research staff, which in the context of this study is a potential source of bias.

The inability of the intervention to continue past six weeks is a further limitation. Delays in surgery occurred for unpredictable reasons; most commonly due to a lack of ICU beds essential for postoperative care, but also delays in receipt of bespoke grafts and emergency aortic procedures taking precedent. Patients who were keen to continue supervised exercise right up until the day of surgery were unable to do so within the remit of the study. This situation occurred four times and, in each case, patients were referred to a physiotherapist working within the trust who was responsible for supervising group cardiac rehabilitation sessions. Patients completing this study could join twice/week sessions with a combination of resistance and aerobic 'circuit'-type activity in a group, in the gym local to the study centre. This arrangement was pre-agreed with the vascular surgery team and taken up by two patients.

4.13.8 Strengths and weaknesses in relation to other studies

The present study is consistent with the existing vascular prehabilitation literature in demonstrating the safety of, and patient compliance with, structured preoperative exercise in frail, elderly patients awaiting AAA repair. To date, the majority of evidence for preoperative exercise in patients awaiting AAA surgery is limited to observational trials that are inadequately powered to detect improvements in markers of physical fitness or postoperative outcomes. A proportion of the existing literature has also focused on patients with smaller aneurysms under surveillance (288, 298, 299). The present study sought to add to the existing literature by recruiting patients with aneurysms > 5.5 cm in diameter, specifically awaiting high-risk fenestrated endovascular aneurysm repair. However, it is also underpowered for both physiological and postoperative outcomes, and further research is required to definitively assess the effectiveness of preoperative exercise in patients with complex AAAs.

5 Discussion

5.1 Overall discussion

Physical fitness has benefits in almost every context of health and disease, and exercise has been shown to be effective in improving the health and well-being of almost every patient group it has been applied to (306). In an era of substantial NHS resource limitation, delivering interventions (particularly those that can be delivered by the existing workforce) that reduce the risk of complications for patients undergoing major surgery (such as liver transplantation and complex aortic aneurysm repair) cannot be underestimated. Complications of high-risk surgery include cardiac, respiratory and kidney failure which may require prolonged support in intensive care, delayed functional recovery, and a long hospital stay, all of which place a significant burden on NHS resources. Increased health and social care support costs can result in the longer term. Hence, interventions that reduce the risk of complications are likely to reduce immediate and long-term costs to the NHS and improve patient quality of life.

Patients with better cardiorespiratory fitness and exercise capacity experience fewer postoperative complications and better long-term outcomes (307). In the high-risk surgical population, the interval between approval for surgery and the operation itself offers an opportunity to intervene to improve fitness and potentially improve postoperative outcomes, but the impact of exercise on post-operative outcomes in both patients awaiting liver transplantation and complex endovascular aortic aneurysm surgery remains to be proven.

The research contained within this thesis has provided feasibility evidence for a direct improvement in clinical care and positive changes for the patient. I have shown it is possible to motivate frail, comorbid patients awaiting either LT or FEVAR to attend hospital three times per week and take part in supervised exercise sessions. Despite the methodological issues discussed in chapters 3 and 4, I have gained a wealth of insight into patient needs, expectations and motivational factors.

There are consistent themes that emerged from the informal feedback patients were asked to provide following cessation of both studies. Patients found exercise enjoyable, motivating and would recommend it to others. From an anecdotal point of view, patients became empowered to improve their own fitness; relishing the opportunity to impress their clinical teams. They became determined to improve their step count/peak work rate with some even perceiving improvement in their clinical condition; notably the improvement in cognitive function/lifting of the 'brain fog' described by one gentleman with ESLD. These are areas that should be explored further in future work.

Having demonstrated that intense aerobic exercise training is feasible in these two high-risk patient cohorts, urgent follow up research is required in this area as clear questions remain: are measurable improvements in preoperative fitness possible and do they translate into better postoperative outcomes? The incidence of cardiopulmonary complications, mortality and duration of hospital/intensive care stays are important targets for improvement after any preoperative intervention. Preoperative exercise has the potential to change risk stratification prior to surgery and highlight those at greater risk. Large scale RCTs are in progress to help definitively answer this question in a variety of surgical specialties. The Wessex Fit-4-Cancer Surgery Trial (WesFit) (308) is one such example. However, there is a pressing need to address these questions in complex, high risk patient groups previously deemed 'unsuitable' for exercise training, such as LT and complex vascular patient cohorts. Exercise is likely to be of particular benefit in frail/sedentary patients, indeed, real gains may lie purely in enabling sedentary patients to just walk a little. Assumptions cannot be made simply by transferring findings from other patient cohorts. There are a number of specific factors impacting on exercise behaviour and indeed success of an exercise intervention, which need to be considered. These are outlined in table 5-1.

Preoperative factors:
- Co-morbidities - Level of frailty - Demographics (age/sex) - Usual activity
Operative factors:
- Cancer surgery - Magnitude of surgery - Solid organ transplantation with immunosuppression

Table 5-1 Perioperative factors that may influence the outcome of an exercise intervention.

5.1.1 Lessons learnt and what I would do differently with the benefit of hindsight

1. *Methodology and feasibility criteria*

Difficult decisions had to be made in planning this research, leading to subsequent compromises. The biggest of which was the design of the studies. As already discussed in chapters 3 and 4, matched cohort designs can lead to selection bias and do not take into account unmeasured variables/confounds, hence there is potential for real differences between groups. Randomisation should balance groups and even in the face of small recruitment targets and funding issues, could have been implemented. Allocation to groups using a more rigorous minimisation process could have been utilised for these small studies, avoiding selection bias and is certainly what I would investigate using were I to have this time again.

The feasibility criteria used in both these studies were not rigorous. Feasibility criteria generally are context specific, hence there are no agreed/accepted outcomes resulting in the real risk of subjective, random targets being set by researchers. If I were to run these studies again, I would follow a methodological framework such as that described by Lancaster et al in the study design process (309) and include participant eligibility and retention components, particularly given the drop-out rate in study 1. More consideration to the individual LT and vascular populations should have been given instead of keeping feasibility outcomes the same for both groups. Slower recruitment for the vascular study should have been anticipated given the lower number of surgical procedures performed in comparison to LT and recruitment targets lowered.

2. *Standardisation of motivation in the conduct of each CPET*

An important feature of CPET is the requirement for the participant to put in a maximal effort, with a submaximal effort potentially invalidating results. Verbal encouragement is commonly used to motivate an individual's engagement with the task and commitment to effort and is recommended in several exercise testing guideline (310–312). The verbal motivation given to each patient was not standardised as part of the study protocol prior to beginning to the study, hence is a source of unconscious bias particularly with repeated tests supervised by an unblinded observer. I would standardise the words used and number of times they are said in future to ensure the same encouragement is given to each patient.

3. *Use of UK CPET consensus guidelines*

Since these studies were conducted, UK CPET consensus clinical guidelines on organisation, conduct and interpretation of tests have been published by Levett et al and the Perioperative Exercise Testing and Training Society (POETTS) in 2018 (311). CPETs conducted in the context of research such as this would hence adhere to these recommendations (as opposed to the American ATS/ACCP guidelines (310)).

5.1.2 Unanswered questions and future investigations

1. Pragmatic, community-based exercise interventions

These studies have demonstrated that a supervised regimen of in-hospital, outpatient exercise training sessions is feasible and may be beneficial to patients. However, this model is neither scalable nor likely to be cost effective. Patients on the LT waiting list in particular, are dispersed across a large geographic area, meaning supervised, in-hospital exercise is likely to be excessively costly and time-consuming for patients who must travel long distances to their treating centre. A modified approach to training patients in their local hospital, a local gymnasium or within their own home could be viable alternatives and may yield marked cost-saving benefits, but the efficacy of such approaches has yet to be categorically proven and further research is required. Delivering an effective community-based exercise programme that can be monitored and objectively evaluated is therefore an important avenue for future research.

Ensuring optimal uptake and adherence to unsupervised programmes in the community is critical to realise meaningful improvements in health and wellbeing, hence patients should be involved in the design of ongoing research in this area. Modification of our design with the input of patients could result in a deliverable intervention that will have a tangible effect on long-term outcomes.

Feasibility studies play an important role in health research, providing information for the planning and justification of RCTs (313). The experience gained from running study 1 has gone on to form the basis of a research collaboration between RFH London and the Queen Elizabeth University Hospital Birmingham resulting in the award of a National Institute for Health Research (NIHR) Efficacy and Mechanism Evaluation (EME) grant to run a dual-centre RCT (code: NIHR129318, award: £1,293,103.50). The ExaLT

(Home-based EXercise and motivAtional programme before and after Liver Transplantation) trial has been designed and powered to address the following specific research question: does a home-based exercise and theory-based motivation support programme delivered before and after LT improve quality of life in LT recipients compared with a standard of care approach using patient advice leaflets? I was part of the original discussions between centres and my work highlighted our centre's ability to recruit patients awaiting LT to a study involving a complex behavioural intervention and promote adherence in the preoperative period. The Royal Free Hospital was able to demonstrate credibility in exercising patients with decompensated cirrhosis hence this initial feasibility data was key to achieving the grant.

2. *Finding the optimal training programme design and duration*

The physiological response to exercise is dependent on the intensity, duration and frequency of the exercise as well as the environmental conditions (314). Future research is needed to determine and optimise these factors plus identify the type of exercise needed to minimise (and possibly reverse) physical frailty and improve hard clinical outcomes (i.e., survival and hospitalisation) in patients with both ESLD and AAAs. In particular, studying the impact of resistance exercise alongside aerobic training is an emerging area of future investigation.

The optimal type of exercise (aerobic versus strength) and the duration of maximal benefit in cirrhotic patients and those with vascular disease is yet to be categorically determined. A greater understanding of the dose-response relationship of exercise and outcomes is required. Questions such as 'does a gradual increase in physical activity delay or reverse muscle loss and contractile dysfunction?' should be addressed in the design of future research.

Delays to the date of surgery itself are common given the other pressures on a resource-limited NHS and exercise programmes should be flexible and allow patients to continue exercising right up until the week of surgery to ensure the full benefit perioperatively.

Fitness may be improved further by increasing the length of the exercise intervention beyond six weeks. Existing evidence in elderly people suggests that regular aerobic exercise for 12 weeks significantly improves fitness (315, 316).

3. *Understanding the specific impact of the unique pathophysiology*

Severe chronic liver disease contributes to high levels of sedentary behaviour (317) and also has direct pathophysiological effects on the cardiovascular and respiratory systems, resulting in poor aerobic capacity. The related syndromes of portopulmonary hypertension, hepatopulmonary syndrome and cirrhotic cardiomyopathy are prevalent in, and unique to, this patient cohort (318). A greater understanding of the mechanisms by which exercise can improve aerobic function in these patients could increase the effectiveness of exercise programmes in the future.

4. Patient-centred clinical outcome measures and cost effectiveness

Multi-centre RCTs, adequately powered to detect differences in patient-centred outcomes are required. Future trial design should focus on linking improvements in physiological measures, such as cardiovascular performance and muscle mass and/or function to improved clinical outcomes (reduced risk of decompensation and encephalopathy in patients awaiting LT, infection, hospital readmissions, decreased length of hospital stay, improved survival, quality of life). Measuring the incidence and impact of postoperative complications may contribute to demonstrating the clinical value of prehabilitation.

Future research should include a robust health economic analysis given the importance of cost efficiency and appropriate resource allocation in the NHS.

Fully capturing all the benefits of prehabilitation in a cost analysis is challenging, given the complex relationship between fitness and quality of life and the multifactorial nature of long-term surgical outcomes. Work is only just beginning in this area.

5. *Biological markers of performance*

Elucidating the biological pathways that lead to clinical improvements and how these relate to exercise type and dose are crucial concepts to include in the design of future clinical trials. Considering the clinical significance of sarcopenia in predicting outcomes in cirrhosis and vascular disease, understanding muscle biological abnormalities and underlying mechanisms is a priority for future research. Indeed, there is evidence that the pathophysiology of sarcopenia in severe liver disease differs from that in other populations (319), involving unique metabolic and molecular abnormalities, and the mechanisms by which exercise may lead to improvements in skeletal muscle performance in this cohort are yet to be explored.

6. *Utilising technology and activity tracking devices in delivery of prehabilitation programmes*

Technological progress has fostered the development of wearable devices for 'self-tracking' of physical activity and certainly, patients in study 2 relished the opportunity to improve their step-counts with a pedometer with >60% still using them after surgery. There are many prospects for self-tracking in everyday health (320) and this wearable sensor technology is importantly not affected by self-report. Such technology can be used to investigate the precise association between the actual frequency, duration and intensity of activity on postoperative outcomes. However, research is needed to investigate the use of tracking technology for use in complex patient cohorts such as those awaiting LT and FEVAR and to contribute to an understanding of the scope of tracking technology and nuances related to digital health engagement (321).

Following the success of study 2, the vascular team began to investigate other scalable and cost-effective ways to integrate and advocate preoperative exercise as a standard of care at RFH. The team considered utilising a smart phone application and structured guidance and enlisted the expertise of the company Medopad who worked closely with the department of vascular surgery and anaesthesia to put together a very simple smartphone application. We designed an 'app' that patients could use to track activity, motivate themselves and source information on topics including exercise advice, smoking cessation and surgery specifics for both the patient and their relatives. Progress was hampered however by the fact that only around 50% of this particular patient cohort own smartphones. Certainly, there is emerging evidence for digital health solutions and this area presents exciting future avenues for investigation (322).

7. Heart rate recovery

Heart rate recovery (HRR) is commonly defined as the decrease of heart rate at one minute after cessation of exercise (323) and is a powerful prognostic factor for all-cause mortality and death associated with coronary artery disease (324). HRR has been shown to be attenuated by beta-blockade and hence has diminished utility in beta-blocked patients (325, 326). Likewise, it performs less well in current smokers (325). HRR data following exercise was originally considered in the plan of investigation, however 58% of patients in the LT group and in the complex vascular surgery group were taking beta-blockers so this avenue of analysis was not pursued.

8. Health-related quality of life

No differences in patient reported HRQL were shown in either study following exercise. Despite the EQ-5D-5L being one of the most frequently used generic, preference-based measures in clinical studies of quality of life (302), there are issues with its utility in these two unique patient cohorts. Apart from the reliability and validity of an instrument, its responsiveness to detect clinical change is a critical property. If an instrument is not sensitive to clinical changes, it will fail to detect benefits or harms of interventions or treatments (302). To address this issue, validated condition-specific measures could be used to measure effectiveness in future clinical studies.

9. <u>Psychological/motivating factors and lasting behavioural changes</u>

Perhaps the most challenging goal of a successful preoperative exercise programme is achieving lasting behaviour change. Empowering patients to make exercise and nutrition a routine part of their day postoperatively is essential for meaningful long-term health benefit on a population scale. Therefore, promoting and sustaining increased physical activity in our patients should be goals for all healthcare professionals. We all know physical activity is modifiable and yet why are clinicians still failing to recommend exercise? There are numerous public health drives, programmes and strategies aimed at empowering people to increase their daily activity and yet sedentary behaviour remains one of the widest-reaching public health concerns.

Motivation to engage and adhere to exercise remains a challenge in all chronic medical conditions and is crucial in achieving ongoing benefits from exercise. Common psychological barriers to exercise include low self-efficacy (competence) and a lack of individual support. To promote behavioural change towards exercise, NICE recommends that interventions target recognised determinants of behaviour that are theoretically grounded (327). However, the efficacy of these theory-based behavioural therapies has yet to be tested in patients awaiting LT and FEVAR. Future large-scale RCTs should address behavioural therapy and sustainable attitude change towards exercise.

A detailed understanding of the factors that determine ongoing patient engagement with complex interventions is required. Anecdotally, it can be said that the attitudes of study participants towards exercise changed in a positive way following their participation in the exercise programme, with several taking up local gymnasium memberships and using activity-tracking devices. Understanding the psychological processes through which an exercise intervention motivates patients to adopt and sustain positive changes in exercise behaviour will guide future studies in this area.

Psychological input and assessment are of huge importance in the field of transplantation in particular. Given the severity and progressive nature of chronic liver disease, there is likely to be significant impact on quality of life (328) and prevalence of anxiety and depression disorders (329–331). Clinical psychologist input should be considered in the design of future large-scale research.

Personalising exercise recommendations will be an important feature of future research in order to identify what format of exercise will best motivate patients and enable maximum benefit perioperatively. Likewise, it is important to recognise the contribution of nutritional optimisation and psychological wellbeing for both the adherence and the response to the physical training stimulus (88). There are notable physical and mental barriers to exercise therapy in co-morbid, frail patients with chronic diseases. Evidence is lacking on how to tailor exercise and behavioural techniques to unique patient populations such as those awaiting LT. Expert input from exercise physiologists helping to test fitness and prescribe exercise in every major surgical centre may be a particularly beneficial future avenue of exploration.

6 Appendices

6.1 **Appendix 1:** Duke activity status index scoring sheet

Hitaky MA et al 1989 (27)

DUKE ACTIVITY STATUS INDEX DATA ENTRY SHEET

PATIENT NAME ....PATIENT DOB..........................

HOSPITAL NUMBER...

Item	Activity	PLEASE CIRCLE CORRECT ANSWER	
1	Can you take care of yourself (eating dressing bathing or using the toilet)?	YES	NO
2	Can you walk indoors such as around your house?	YES	NO
3	Can you walk a block or two on level ground?	YES	NO
4	Can you climb a flight of stairs or walk up a hill?	YES	NO
5	Can you run a short distance?	YES	NO
6	Can you do light work around the house like dusting or washing dishes?	YES	NO
7	Can you do moderate work around the house like vacuuming sweeping floors or carrying in groceries?	YES	NO
8	Can you do heavy work around the house like scrubbing floors or lifting and moving heavy furniture?	YES	NO
9	Can you do yardwork like raking leaves weeding or pushing a power mower?	YES	NO
10	Can you have sexual relations?	YES	NO
11	Can you participate in moderate recreational activities like golf bowling dancing doubles tennis or throwing a baseball or football?	YES	NO
12	Can you participate in strenuous sports like swimming singles tennis football basketball or skiing?	YES	NO

6.2 **Appendix 2:** Physical activity enjoyment scale (PAES) questionnaire

Kendzierski D, DeCarlo K 1991 (121)

Please rate how you feel *at the moment* about the physical activity you have been doing?

*I enjoyed it	1	2	3	4	5	6	7	I hated it
I feel bored	1	2	3	4	5	6	7	I feel interested
I dislike it	1	2	3	4	5	6	7	I like it
*I find it pleasurable	1	2	3	4	5	6	7	I find it unpleasurable
*I am very absorbed In this activity	1	2	3	4	5	6	7	I am not at all absorbed in this activity
It's no fun at all	1	2	3	4	5	6	7	It's a lot of fun
*I find it energising	1	2	3	4	5	6	7	I find it tiring
It makes me Depressed	1	2	3	4	5	6	7	It makes me happy
*It's very pleasant	1	2	3	4	5	6	7	It's very unpleasant
*I feel good physically whilst doing it	1	2	3	4	5	6	7	I feel bad physically whilst doing it
*It's very Invigorating	1	2	3	4	5	6	7	It's not at all invigorating
I am very frustrated by it	1	2	3	4	5	6	7	I am not at all frustrated by it
*It's very gratifying	1	2	3	4	5	6	7	It's not at all gratifying
*It's very exhilarating	1	2	3	4	5	6	7	It's not at all exhilarating
It's not at all stimulating	1	2	3	4	5	6	7	It's very stimulating
*It gives me a strong Sense of accomplishment	1	2	3	4	5	6	7	It does not give me any sense of accomplishment
*It's very refreshing	1	2	3	4	5	6	7	It's not at all refreshing
I felt as if I would rather be doing something else	1	2	3	4	5	6	7	I felt as if there was nothing else I would rather be doing

* Item is reverse scored (i.e., 1=7, 2=6……6=2, 7=1)

6.3 **Appendix 3:** EuroQol EQ-5D-5L questionnaire

Herdman M et al 2011 (154)

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ☐

I have slight problems in walking about ☐

I have moderate problems in walking about ☐

I have severe problems in walking about ☐

I am unable to walk about ☐

SELF-CARE

I have no problems washing or dressing myself ☐

I have slight problems washing or dressing myself ☐

I have moderate problems washing or dressing myself ☐

I have severe problems washing or dressing myself ☐

I am unable to wash or dress myself ☐

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ☐

I have slight problems doing my usual activities ☐

I have moderate problems doing my usual activities ☐

I have severe problems doing my usual activities ☐

I am unable to do my usual activities ☐

PAIN / DISCOMFORT

I have no pain or discomfort ☐

I have slight pain or discomfort ☐

I have moderate pain or discomfort ☐

I have severe pain or discomfort ☐

I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION

I am not anxious or depressed ☐

I am slightly anxious or depressed ☐

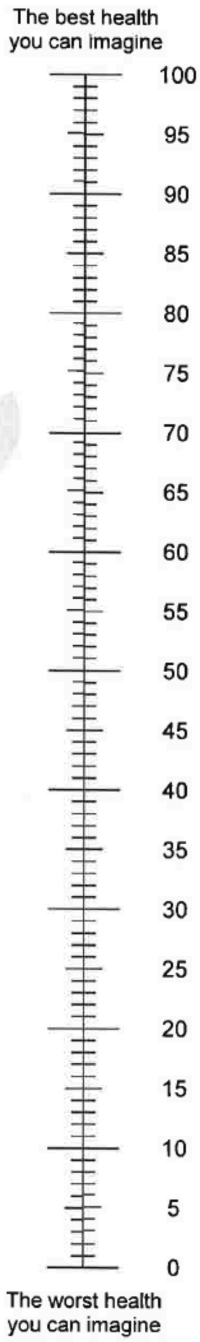
I am moderately anxious or depressed ☐

I am severely anxious or depressed ☐

I am extremely anxious or depressed ☐

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = [ ]



6.4 **Appendix 4:** RFH global assessment data collection form

Morgan MY et al 2006 (208)

RFH Global Assessment Data Collection Form

Patient Name ....

Age .... years

Sex: male / female

CLINICAL INFORMATION

Diagnosis	....
Anorexia	absent / mild / moderate / severe
Nausea	absent / mild / moderate / severe
Vomiting	absent / mild / moderate / severe
Difficulty in mastication	absent / mild / moderate / severe
Dysphagia	absent / mild / moderate / severe
Indigestion	absent / mild / moderate / severe
Food-related abdominal pain	absent / mild / moderate / severe
Bowel frequency	.... times daily
Stool consistency / colour	....
Infections	yes / no dates ....
Renal dysfunction	absent / mild / moderate / severe
Hepatic encephalopathy	absent / mild / moderate / severe
GI tract bleeding	absent / mild / moderate / severe
Weight loss	..................kg, ...%
Physical activity	working as usual .... working sub-optimally .... not working .... ambulatory .... bedridden ....
Fatigue	absent / mild / moderate / severe

DIETARY INTAKE

Appetite	good / fair / poor
Early satiety	absent / mild / moderate / severe
Taste changes	absent / mild / moderate / severe
Recent dietary intake	....
Estimated requirements	....kcal
Dietary restrictions	....
Nutritional supplements	none / oral / enteral / parenteral
Nutrient intake	adequate / inadequate / negligible

PHYSICAL STATUS

Subcutaneous fat stores	**good / fair / poor**
Muscle wasting	**absent / mild / moderate / severe**
Peripheral oedema	**absent / mild / moderate / severe**
Ascites	**absent / mild / moderate / severe**

ANTHROPOMETRIC

Height	**………………….. m**	
Weight	**……………………kg**	
Estimated dry weight	**……………………kg**	
BMI (dry weight)	**……………………kg/m^2**	
Arm used for anthropometric measurement	**L R**	**halfway measurement……………………**
MAC	**……………………cm**	
TSF	**……………………mm**	
MAMC	**……………………cm**	
MAMC 5th% ile (26)	**……………………cm**	
MAMC in relation to 5th % ile	**above / below**	
Handgrip	**……………………kg**	

SUMMARY

BMI:	**≥ 20 ……**	**<20……**	
MAMC:	**≥5th%ile ……**	**<5th% ile……**	
Nutrient intake:	**adequate ……**	**inadequate ……**	**negligible ……**

Refer to algorithm

Interim nutritional category:

Well nourished

Moderately malnourished (or suspected of being so)

Severely malnourished

Subjective override:

None / decrease / increase

Global nutritional category:

Well nourished

Moderately malnourished (or suspected of being so)

Severely malnourished

X:\Clinical services\Liver service\Liver Assessment tools\OLTx Nut. Ass. collection.doc

6.5 **Appendix 5:** Publication in Transplantation

Morkane C et al 2020 (332)

Original Clinical Science—Liver

An Outpatient Hospital-based Exercise Training Program for Patients With Cirrhotic Liver Disease Awaiting Transplantation: A Feasibility Trial

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